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SEARCH FOR NOVEL THERAPEUTIC TARGETS FOR NEURODEGENERATIVE DISEASES VIA GENOMIC APPROACHES

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Abstract

Neurodegenerative diseases are chronic, progressive disorders primarily affecting the Central Nervous System. They represent a serious global healthcare issue, and the majority of currently available treatments are symptomatic or palliative. The Mesio-Temporal Lobe Epilepsy (MTLE) syndrome is an intractable neurodegenerative disease characterized by the recurrence of spontaneous focal seizures in mesial temporal structures of the limbic system of the brain and often associated with hippocampal sclerosis (HS). Clinical management of MTLE is challenging, since it is associated with pharmacoresistance and is the most common type of epilepsy referred for resective surgery.

The aim of this study was to characterize the molecular mechanisms implicated in MTLE pathogenesis and progression, in order to identify novel therapeutic targets for MTLE, through genomic approaches. To achieve this goal, whole genome expression analysis with microarrays was performed on an experimental model that simulates human MTLE, obtained by intrahippocampal kainate (KA) injection in the mouse, at three time points representing distinct stages of MTLE. A multi-level bioinformatical analysis and data mining approach followed, in order to characterize the molecular changes that may affect epileptogenesis and disease progression, and identify central regulatory molecules that may control the observed changes and can serve as candidate therapeutic targets for MTLE. The analysis resulted in the identification of multiple significantly changed genes and molecular pathways at each KA-MTLE stage interrogated, and provided leads for further investigation. Accordingly, additional steps were taken to assess the role of NAPDH oxidase complex in epileptogenesis. Furthermore, global transcriptomic analysis was applied and on hippocampal samples from patients with MTLE-HS, inorder to elucidate the molecular mechanisms associated with this prominent histopathological feature of MTLE. This study provides a comprehensive analysis of hippocampal expression profile during the course of MTLE development and progression, and interrogates novel candidate therapeutic targets for MTLE.

Περίληψη

Οι νευροεκφυλιστικές παθήσεις είναι χρόνιες, σταδιακά επιδεινούμενες διαταραχές που προσβάλλουν κυρίως το Κεντρικό Νευρικό Σύστημα. Αποτελούν ένα σοβαρό πρόβλημα υγείας παγκοσμίως, ενώ η πλειονότητα των διαθέσιμων θεραπευτικών προσεγγίσεων είναι συμπτωματικές ή παρηγορητικές. Το σύνδρομο της Επιληψίας του Έσω Κροταφιαίου Λοβού (ΕΕΚΛ) είναι μια δυσίατη νευροεκφυλιστική πάθηση που χαρακτηρίζεται από αυθόρμητες επαναλαμβανόμενες εστιακές κρίσεις στις έσω κροταφικές δομές του μεταιχμιακού συστήματος του εγκεφάλου, και συνδέεται συχνά με σκλήρυνση του ιπποκάμπου (ΣΙ). Η κλινική αντιμετώπιση της ΕΕΚΛ αποτελεί μια πρόκληση, καθώς εμφανίζει ανθεκτικότητα στη φαρμακευτική αγωγή και είναι ο τύπος επιληψίας που παραπέμπεται συχνότερα για χειρουργική αντιμετώπιση.

Ο σκοπός της παρούσας μελέτης ήταν ο χαρακτηρισμός των μοριακών μηχανισμών που εμπλέκονται στην παθογένεση και την εξέλιξη της ΕΕΚΛ, ώστε να εντοπιστούν νέοι υποψήφιοι θεραπευτικοί στόχοι, με προσεγγίσεις γονιδιωματικής. Για το σκοπό αυτό, πραγματοποιήθηκε ανάλυση της έκφρασης ολόκληρου του γονιδιώματος με μικροσυστοιχίες σε ένα πειραματικό μοντέλο που προκύπτει με μικροέγχυση καϊνικού οξέος (ΚΑ) στον ιππόκαμπο και προσομοιάζει στο ανθρώπινο σύνδρομο, σε τρία χρονικά σημεία που αντιστοιχούν σε διακριτά στάδια της ΕΕΚΛ. Ακολούθησε εντατική βιοπληροφορική ανάλυση και εξόρυξη δεδομένων, για το χαρακτηρισμό των μοριακών αλλαγών που ενδέχεται να σχετίζονται με την παθογένεση και την εξέλιξη της ΕΚΚΛ, και τον εντοπισμό κεντρικών ρυθμιστικών μορίων που μπορεί να ελέγχουν τις παρατηρούμενες αλλαγές και μπορούν να αποτελέσουν υποψήφιους θεραπευτικούς στόχους για την ΕΕΚΛ. Η ανάλυση οδήγησε στην ανακάλυψη πολυάριθμων σημαντικά αλλαγμένων γονιδίων και μοριακών μονοπατιών σε κάθε στάδιο του συνδρόμου που μελετήθηκε, ένω προέκυψαν ευρήματα που έχρηζαν περαιτέρω διερεύνησης, και πραγματοποιήθηκαν επιπρόσθετα πειράματα για τη διερεύνηση του ρόλου του συμπλόκου της οξειδάσης NAPDH στην παθογένεση της ΕΚΚΛ. Επιπροσθέτως, πραγματοποιήθηκε ανάλυση της έκφρασης ολόκληρου του γονιδιώματος σε δείγματα ιππόκαμπου ασθενών με ΕΕΚΛ-ΣΙ, για το

χαρακτηρισμό των μοριακών μηχανισμών που σχετίζονται με αυτό το ιστοπαθολογικό εύρημα της ΕΕΚΛ. Η παρούσα μελέτη αποτελεί μια λεπτομερή ανάλυση του προφίλ έκφρασης του ιππόκαμπου κατά τη διάρκεια της παθογένεσης και εξέλιξης του συνδρόμου της ΕΕΚΛ, και εξετάζει νέους υποψήφιους θεραπευτικούς στόχους για την πάθηση αυτή.

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1. INTRODUCTION

1.1. NEURODEGENERATIVE DISEASES

Neurodegenerative diseases (NDs) are a group of chronic, progressive disorders primarily affecting the Central Nervous System (CNS). NDs are typically characterized by the gradual loss of physiological neuronal function or structure in discrete areas of the CNS that may ultimately result in neuronal cell death. Neurodegeneration can affect the nervous system on multiple levels, leading to the development of a systemic disease. Neuronal loss causes patients to suffer from various dysfunctions, such as impaired movement coordination, mobility disorders, memory loss and speech impairment [1-3].

NDs represent a major global healthcare problem, with Western countries being more severely affected due to the ageing population. NDs affect mostly adults and can last for decades, causing long term suffering to patients and their families [4]. According to the European Brain Council, the total annual cost of NDs was estimated at €147 billion in 2010 (incl. dementias, epilepsy, MS and PD) [5]. Currently, 16% of the European population is over 65, and this figure is expected to reach 25% by 2030. With the continuous increase in the proportion of elderly people, these costs are becoming a real burden to the society [6].

Current treatments for NDs are mostly palliative or treat the symptoms rather than the cause, hence providing only relief instead of cure. Extensive research has been undertaken to interrogate the biological basis of NDs, leading to the identification of a substantial number of pathological mediators. The findings to date support that NDs can be triggered by misfolded protein aggregation, glutamate, reactive oxygen and nitrogen species, auto-antigens etc., whilst a sustained inflammatory response is believed to be a critical mechanism responsible for the progressive nature of neurodegeneration and inflammation [7-11]. However, these findings have yet to be successfully translated in effective therapeutic interventions. The drugs currently used to treat ND are largely inefficient [12] and clinical trials undertaken have often met with failure [13].

Examples of intractable debilitating NDs include Alzheimer disease (AD)[14], Parkinson disease (PD), Huntington's disease (HD)[15], Motor Neuron

Disease (MND), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS) [16], depression[17], and some forms of epilepsies associated with cell loss, such as Mesio Temporal Lobe Epilepsy (MTLE)[18].

1.2. EPILEPSY

1.2.1 Epilepsy and epileptic seizures

Epilepsy is a group of chronic neurological disorders characterized by recurrent, unprovoked seizures [19], resulting from the high- frequency, synchronized activity of groups of CNS neurons, in one or more brain structures. The definition accepted by International League of Epilepsy (ILAE) describes a seizure as the “transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”[20]. Focal seizures occur within networks limited to one hemisphere and can be either discretely localized or more widely, whilst generalized seizures occur in and rapidly engage bilaterally distributed networks [21].

Epileptic seizures manifest as episodes of involuntary movement that range from brief, nearly undetectable events to severe and prolonged convulsions. These episodes may be accompanied by loss of consciousness and control of bowel or bladder function, and can result in physical injuries that may occasionally be as severe as broken bones. The duration of epileptic seizures is typically <1 minute, whilst the frequency can vary from <1 per year to several per day (WHO, Epilepsy Fact Sheet, February 2017).

Despite common belief, the occurrence of a single seizure does not signify epilepsy (up to 10% of people worldwide have one seizure during their lifetime). An individual is diagnosed with epilepsy only if any of the following criteria are met:

- at least two unprovoked (or reflex) seizures occurring >24 hours apart;
- one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
- diagnosis of an epilepsy syndrome [22]

Although the genetic background appears to play a critical role in epilepsy, the molecular mechanisms underlying the disease remain unknown for the most part [23]. Due to the poor understanding of the disease etiology, the different types of epilepsy and epileptic syndromes are not yet categorized according to their biological basis. Instead, they are currently classified by specificity as electroclinical syndromes, non-syndromic epilepsies with structural-metabolic causes, and epilepsies of unknown cause, and further organization within these divisions can be based on natural classes (e.g., specific underlying cause, age at onset, associated seizure type)[21].

1.2.2 Epilepsy consequences on patients and society

Epilepsy is the most common serious neurological disorder worldwide, with no age, racial, geographic or socio-economic boundaries. Anyone may experience an epileptic seizure at any point during their life. Globally, an estimated 2.4 million people are diagnosed with epilepsy each year, and approximately 50 million people currently live with epilepsy worldwide [24] .It is estimated that the proportion of the general population with active epilepsy (i.e. continuing seizures or with the need for treatment) at a given time is between 4 and 10 per 1000 people. (WHO, Epilepsy Fact Sheet, February 2017). More specifically, in Europe, the prevalence of epilepsy is 8.2 per 1,000 people, with approximately 6 million people in Europe currently having epilepsy, and 15 million people estimated to have had epilepsy at some time in their lives [25]. Furthermore, prevalence studies in low- and middle-income countries show much higher figures (e.g. 11.3 per 1,000 people in Africa) in comparison to the high-income countries [26].

Epilepsy and epileptic syndromes have a detrimental effect on both quality of life and life expectancy. Specifically, epilepsy diagnosis changes drastically the patient’s lifestyle, since they have to live a life of uncertainty, never knowing when and where a seizure may occur, whether they may lose consciousness without warning and if ultimately their seizures can be controlled. Their employability and ability to operate a vehicle are greatly compromised, and their emotional and psychological state is affected by the

realization of the extent of the adjustments that need to be made in their everyday life (e.g. avoid intense stimuli that can contribute to seizure manifestation). Furthermore, epilepsy can cause memory impairment, learning deficiencies and loss of concentration, tiredness and sleepiness, whilst in many occasions the patients are stigmatized and are the victims of discriminations, predominantly due to misconceptions about the disorder in their workplace or sociocultural context. The psychosocial problems that are faced by the person render them vulnerable to depression and anxiety disorders [27, 28].

Epilepsy patients are also highly likely to present with numerous accompanying pathologies and neurological disorders, which are described as physical comorbidities of epilepsy. Some representative examples of such comorbidities include cardiac, respirational and gastrointestinal disorders, strokes, dementia, migraines[29], psychosis and schizophrenia [30]. It has been suggested that the manifestation of such disorders further perplexes epilepsy diagnosis and/or affects epilepsy prognosis, while increasing healthcare needs, compromising quality of life. The etiology of these pathologies lies within a plethora of interacting genetic and environmental factors, and it is believed that their effective management may facilitate epilepsy therapy [29].

Notably, epilepsy patients have been also reported to have a significantly higher risk of death throughout their life, and especially during the first 2 years following diagnosis. Moreover, standardized mortality rates were found to be especially high in younger patients and in patients with symptomatic epilepsies, whilst persistent seizures were shown to be strongly related to increased mortality [31].

1.2.3 Epilepsy treatment

The heterogeneity of the disease, in conjunction with the lack of diagnostic and therapeutic biomarkers impose a challenge for the clinical management of epilepsy [32]. Epilepsy treatment includes administration of symptomatic anti-seizure medication (antiepileptic drugs, AEDs); whilst on occasion the

surgical resection (lobectomy) of the brain section that generates the seizures is essential. However, despite the significant improvements in AEDs and the developments in surgical treatment of epilepsy accomplished in the recent years, only up to 70% of the patients may become seizure free (about 60% with the first drug and a further 10% after further attempts). Currently available AEDs have proved to be ineffective, since over 30% of the patients are resistant to treatment (continue to suffer from seizures) [33, 34], which is strongly associated with increased mortality rates [31]. Furthermore, the medications used have severe side effects on the person's cognitive function (e.g. consciousness impairment, memory loss) [33, 34], that affect patients' quality of life, as well as tolerability, compliance, and long-term continuation of the treatment [35].

Beyond the profound need for an efficient therapeutic strategy to battle a disease with such a significant impact on the quality of life of a sizeable proportion of the world population, the economic burden of epilepsy on the healthcare systems worldwide should be also considered. In specific, it has been reported that the treatment cost of an epilepsy patient appears to be increased by 60 to 95%, when compared to the treatment cost of patients with conditions such as acute heart attack, cardiac arrest and endocranial hemorrhage [36]. Moreover, in an approximately 30% of epilepsy patients where the seizures cannot be controlled with the use of a single AED (monotherapy), additional treatment with multiple medications is required, without being clear yet if these medications are more efficient and cost effective [37].

The need for the discovery of improved medications is thus apparent.

1.3. MESIO TEMPORAL LOBE EPILEPSY SYNDROME

Ours study is focused on a focal epilepsy type that affects the temporal lobe (Temporal Lobe Epilepsy, TLE), and is a diagnostically distinct type defined as MTLE. MTLE is a syndrome -or, as recently redefined, a "constellation" [21]- characterized by the recurrence of focal seizures in mesial temporal structures of the limbic system of the brain (hippocampus, amygdala) and is one of the most common types of intractable focal epilepsy [38, 39].

Epilepsies with seizures of focal origin constitute approximately 60% of adult epilepsies, and MTLE represents an important challenge to clinicians, being the most common type of epilepsy referred for resective surgery and very common pharmacoresistant epilepsy at the same time [40]. Specifically, the resistance rates to AED treatment range from 30% to as high as 80% in some clinical trials [41]. As an optimum solution to stop the recurrence of seizures, partial surgical resection of the temporal lobe (lobectomy) can be performed upon the determination of the seizure focus within the temporal lobe through extensive tests, in a specific subset of pharmacoresistant patients.

MTLE is a type of epileptic syndrome of unknown etiology, that lacks a specific pattern regarding the age of onset, and manifests in otherwise healthy individuals, whilst the precise diagnosis requires advanced neuroimaging techniques and deep electroencephalography (EEG) recordings [40].

1.3.1 MTLE syndrome clinical features

Some of the clinical features that are typical of the recurrent focal seizures of MTLE are the “auras”, epigastric or abdominal in specific, loss of consciousness, amnesia, aphasia, automations such as chewing and other motor symptoms, as well as confusion after the end of the seizure [42]. These symptoms are associated with focal discharges, according to deep EEG recordings [43]. The frequency of focal seizure can vary in MTLE, and can be as high as 40 or 50 times per day.

With regards to the symptoms’ intensity, the typical focal seizures in MTLE are mild and non-convulsive. Under no circumstances will uncontrolled generalized convulsive activity be observed as a result of the focal seizures[42]. This feature obstructs diagnosis, since a focal seizure cannot be detected based on obvious symptoms, and requires the performance of deep EEF recording or/and simultaneous assessment of cognitive function via oral tests instead.

1.3.2 Epileptogenesis: development of MTLE syndrome

In most clinical cases, the MTLE syndrome seems to be triggered by an initial insult in the brain in early childhood [44, 45]. This insult often includes

recurrent complex febrile seizures before one year of age or the manifestation of an epileptic seizure of more than 10 minutes (*Status epilepticus, SE*), but it can also be attributed to brain damage due to injury, intracranial infections or ischemic episodes[38, 46].

The initial traumatic insult triggers many- mostly unknown- molecular mechanisms, thus causing functional alterations and damages in the affected brain structures during the period that follows, without them being accompanied by evident clinical symptoms. This latent period spans several years, ultimately resulting in the manifestation of sudden, spontaneous, focal seizures originating from mesio temporal limbic brain structures, such as the hippocampus and the endorhinal cortex [38, 39]. The age of onset of the first spontaneous seizure is typically prepubescence or during puberty, between 10 and 14 years of age.

1.3.3 MTLE Histopathology and the role of hippocampus

The typical histopathological findings and functional alteration characterizing TLEs in general are mainly associated with the hippocampal structure. According to Positron Emission Tomography (PET), the structures showing the larger decrease in metabolic activity are localized within the lateral and mesial temporal regions, whilst the extent of the decrease is associated with the severity of hippocampal pathology [47]. Surgical resection of the hippocampus and the amygdala improves this phenomenon in the remaining regions of the temporal-limbic system [48], whilst the presence of sclerosis in the surgically resected mesial temporal lobe has been associated with positive surgical outcome [49] and a decrease or absence of seizures 2 years post-surgery [50]. Furthermore, intracranial electroencephalographic (EEG) recordings from patients with TLE and hippocampal sclerosis (HS) have shown that the seizures originate from the sclerotic hippocampus [51], thereby highlighting the significance of this structure in disease pathogenesis.

Regarding MTLE in particular, HS seems to be a substantial histopathological finding based on which MTLE patient hippocampi are often discriminated from those with other types of TLE, such as mass-associated temporal lobe epilepsy (MaTLE) or paradoxical temporal lobe epilepsy (PTLE) [52, 53]. HS

is manifested with a decrease in the hippocampal structure size (atrophy), accompanied by neurodegeneration with loss of granular neurons in CA1, CA3 and CA4 regions, granule cell dispersion (GCD) in the dentate gyrus (DG), along with aberrant mossy fiber (MF) sprouting in the internal molecular layer of the hippocampus (Figure 1.1). Furthermore, morphological and functional alterations are observed in hippocampal glial cells, with the process of astrogliosis being the most well-characterized among them [55, 56]. In addition, it must be noted that neuronal loss and gliosis have also been observed in the endorhinal, to a lesser extent, independently of hippocampal sclerosis [57].

All of the alteration described above, and/or combinations thereof, are seemingly implicated in the perpetuation and the progression of MTLE syndrome throughout the patient's lifespan.

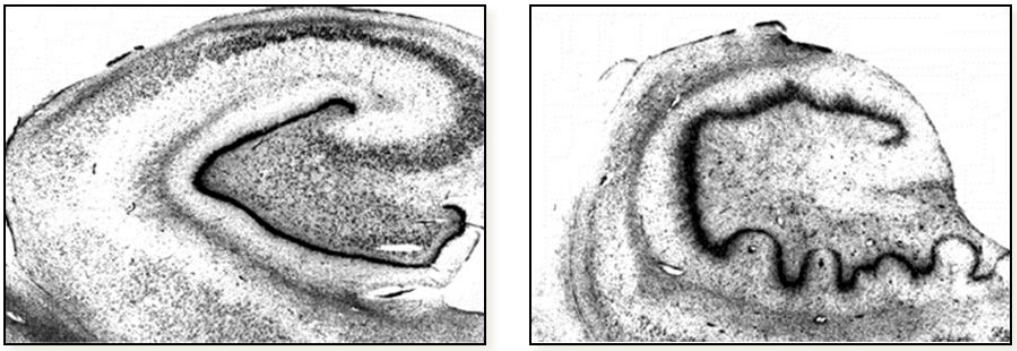


Figure 1.1. *Morphological alterations in the sclerotic hippocampus in MTLE. Left: non-epileptic, non -sclerotic autopsy hippocampal tissue, right: resective tissue with MTLE-HS (Loup et al, 2002).*

1.4. ANIMAL MODELS

1.4.1 The necessity of animal model studies

The range of biological evidence available for human MTLE are limited to the pathological alterations observed in the hippocampi of MTLE patients derived from resective surgery or autopsies, and in the study of cerebrospinal fluid samples (CSF). Such an approach imposes a series of limitations with regards to the conclusions that can be drawn, such as the inability to outline the temporal pattern of the histopathological changes in the hippocampus, the restriction of the study to the chronic disease essentially excluding the early disease stages, and the inability to assess the molecular effects of a compound on the tissue studied. In order to delineate the mechanism of the pathological alterations' establishment, and to assess new pharmacological interventions on specific tissues, one would have to study the tissue in different disease stages with biopsy collections, which is impossible to implement in humans.

Thus, the use of experimental animal models that simulate the human disease proves to be extremely valuable, since they enable the unobstructed observation and intervention, aiming to the better understanding of the pathology interrogated. To date, a range of experimental rat and mouse models have been engaged for the study of MTLE syndrome, with the most prevalent being those resulting from pilocarpine or kainic acid (KA) administration, or upon electrical stimulation [18, 55].

1.4.2 The KA-MTLE mouse model

Over the last decade, only a few rat and mouse models with recurrent focal seizures in the temporal lobe have been developed that are characterized by in-depth EEG and are suitable for MTLE studies, based on their similarities with the human disease. Such models result from topical intra-hippocampal KA administration or continuous electric stimulation, causing an initial *SE* with milder symptoms from those induced by e.g. systemic pilocarpine or KA administration [58-60], which lasts for several hours and ends spontaneously, without the need to be disrupted by pharmacological intervention (e.g. diazepam injection) for the animal to survive.

A similar KA-induced MTLE mouse model has been also developed and characterized by our collaborator Dr. A. Depaulis (INSERM, Université Grenoble Alpes). Specifically, MTLE is induced by a unilateral microinjection of KA in the right dorsal hippocampus of the mouse [58, 61]. In this model, the initial mild non-convulsive focal *SE* is followed by a latent period of two weeks, during which the spontaneous paroxysmal hippocampal discharges progressively develop, along with hippocampal sclerosis including neuronal loss in CA1, CA3 and hilus regions, gliosis, mossy fiber sprouting and GCD in the Dentate Gyrus (Figure 1.2) [58, 62]. Moreover, typical *in vivo* intracellular discharge recordings have been recently provided for this model [63]. Simulating the pattern of human MTLE seizures, the seizures recorded in these mice were limited mostly to the hippocampus and rarely exhibited generalizations, whilst they were associated with mild behavioral symptoms (chewing, head nods etc.)[58].

For these reasons we selected the KA-MTLE mouse model as the most relevant for human MTLE studies, and more specifically to be utilized for the delineation of MTLE underlying pathogenetic mechanisms and the identification of novel therapeutic targets.

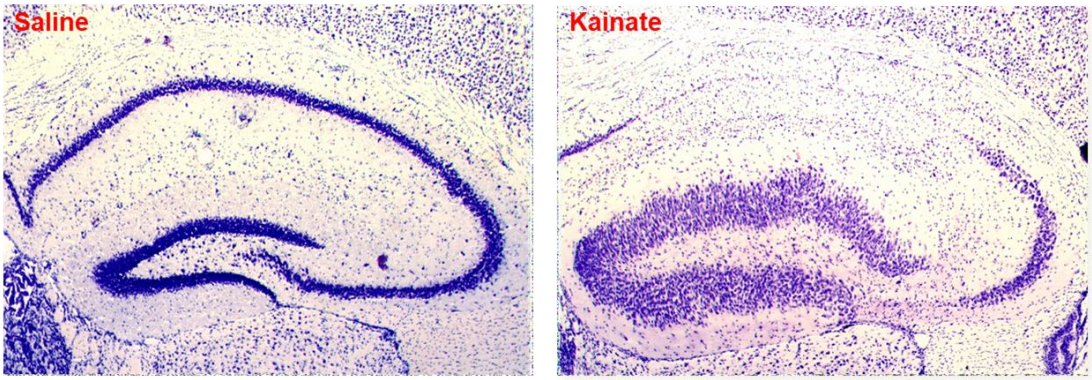


***Figure 1.2**. Morphological alterations induced by KA injection into the dorsal hippocampus at 3 weeks post-injection. Left: saline-injected (control), right: KA-injected [58].*

1.5. INTRODUCTION TO OMICS

The completion of the Human Genome Project in 2001, a major scientific achievement, also signified the beginning of a true revolution in the analytical methodologies available to researchers. The advances in technology during the years that followed allowed for the development of powerful tools for large scale, high throughput analyses in multiple sectors of biological research that are now referred to by the suffix "-omics". The term "omics" is used to describe a novel approach in biology research that aims at the collective quantification and characterization of very large numbers or even the sum of biological molecules of a specific category, such as genes, transcripts, proteins or metabolites. In biomedical research, "omics" approaches (e.g. genomics, transcriptomics, proteomics, metabolomics, lipidomics, glycomics, etc.) are extensively used today towards delineating the molecular mechanisms that change in a biological system, typically in the context of human disease development and progression, or in response to different treatments [64, 65] (Figure 1.3).

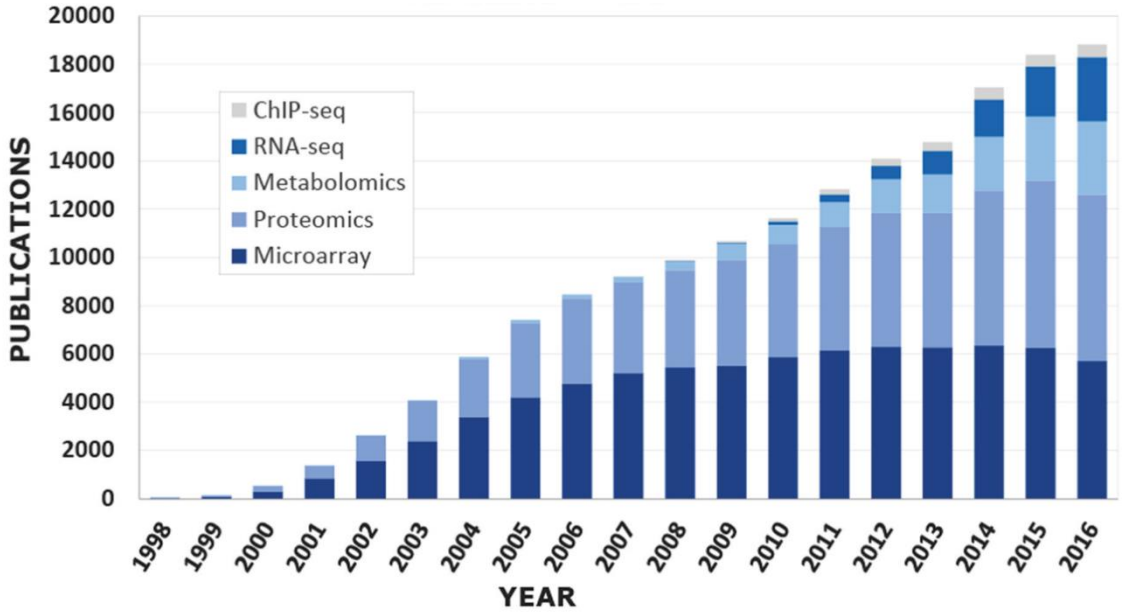


Figure 1.3. *Annual number of publications available on PubMed, representative of the use of omics approaches in biomedical research over the past 20 years [66].*

1.5.1. Genomics

The term “Genomics” describes the study of an organism’s entire genome, including interactions of the gene comprising the genome with each other, and with the surrounding environment [67]. Genomics is one of the most widely used approaches in biomedical research, for the investigation and understanding of human physiology, the pathogenetic mechanisms of human diseases, the identification of diagnostic and prognostic biomarkers, the discovery of novel therapeutic targets, as well as the development of predictive markers for personalized medicine [68-73].

The establishment of Genomics has been enabled by the development of innovative techniques for large scale analysis of the genome, thus allowing for the transition from the single gene/transcript analysis to the parallel characterization of thousands of genes/transcripts, in a single experiment [74, 75]. The first such approach was this of microarrays, and it opened the way for the “Genomics era” with tens of thousands of publications since [76-79] (Figure 1.3). Microarrays, together with the more recently developed method of Next Generation Sequencing, are transforming biomedical research with major immediate and long-term implications for the clinical practice.

1.6. MICROARRAYS

Microarrays are a revolutionary technology, enabling the analysis of the whole genome in a single hybridization. More specifically, thousands of genes can be studied simultaneously on a 1 cm^2 glass surface [74-76]. Different types of microarrays have been developed, each one for a different application, such as DNA resequencing, single nucleotide polymorphism or copy number change detection, global DNA methylation studies, gene expression analysis, splice variant detection, non-coding RNA measurements, and more.

The global gene expression analysis with microarrays enables the assessment of gene expression during various developmental stages/time points or in different tissues, the comparison of pathological and physiological conditions, the analysis of cell and organism responses to pharmaceutical compounds administration or under various physiological conditions, amongst other applications [74-78].

1.6.1 Microarray technology

The term “microarrays” describes small slides made of glass, plastic or silicone, onto which arrays of millions of DNA fragments (probes) representative of known or unknown genes have been bound. These slides serve to hybridize DNA or RNA samples isolated from tissues/cells of interest, following labeling with appropriate fluorescent dyes [77, 80]. The fluorescence intensity corresponding to each array probe set depends from the quantity of the labeled target-molecule specifically hybridized to the probe set, and is associated with the sequence or the quantity of the DNA or RNA fragments in question, respectively [77, 79, 80].

Microarrays fall under several different categories, depending on the manufacturing technique used (e.g. inkjet printing, photolithography, electrical field, microbeads), the type of DNA fragments used as probes (e.g. oligonucleotides or cDNA), and the intended use [77, 80, 81].

In the present study we used Affymetrix GeneChip® microarrays (http://www.affymetrix.com). Affymetrix GeneChip® microarrays are produced with i*n situ* photolithographic synthesis of up to 300.000 of distinct oligonucleotides (25 bases/each) directly onto glass slides (Figure 1.4).

In Affymetrix GeneChip® expression arrays, the levels of each transcript are measured by a group of 11 to 20 oligonucleotide pairs (probe pairs), which is referred to as “probe set”. Probe sets interrogating the expression of the same transcript are distributed in various locations on the surface, to guard against local defects of the array. Each probe set consists of an oligonucleotide with a sequence perfectly complementary to that of the target transcript (Perfect Match-PM), and a “negative control” oligonucleotide with a partially complementary sequence containing a single base change (A-T or G-C) in the sequence position 13 (Mismatch-MM). This single central mismatch strongly destabilizes the hybridization of the target transcript. This design allows for measurements with increased specificity and reproducibility.

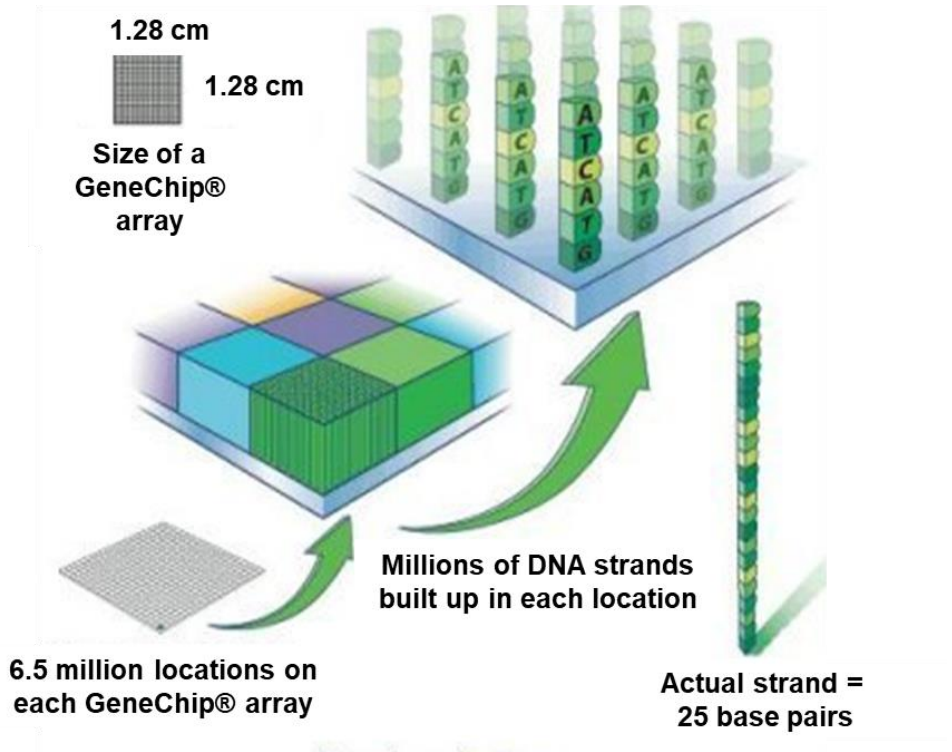


Figure 1.4: *Affymetrix GeneChip® oligonucleotide microarray.*

In parallel, high quality and purity total RNA is extracted from each cell or tissue specimen, processed through reverse transcription and in vitro transcription reactions, to yield cDNA and biotin-labeled cRNA, respectively.
The cRNA from biological sample is hybridized to a different microarray, and multiple biological replicates (≥4) are employed in order to achieve statistical significance.
The millions of measurements obtained from microarrays studies are analyzed with advanced bioinformatical, statistical and mathematical methods, due to their size and complex nature.

1.6.2. Bioinformatical analysis of microarray data

Microarrays produce a large volume of data, in the orders of hundreds of gigabytes, which has to undergo extensive bioinformatical analysis in order for the data to be translated into meaningful biological observations. The type of bionformatical tools and the steps of data analysis vary between projects depending on the type of microarrays used and the biological questions posed. The bioinformatical analysis strategy applied in the present study was selected based on the biological questions posed (i.e. the delineation of MTLE pathogenesis and the identification of novel therapeutic targets), and the type of arrays used (i.e. Affymetrix GeneChip® expression arrays). The principle behind each of the key steps is presented below.

1.6.2.1 Microarray data preprocessing

In order to reduce the technical variation and eliminate any sources of noise in microarray data, a number of preprocessing steps are necessary, prior to differential expression analysis. These steps aim to convert the raw measurements obtained in the form of scanned hybridization images to measures of biological meaning for further statistical and bioinformatical analyses [82].

1.6.2.1.1 Signal detection and processing

Each microarray is scanned by a laser scanner and each hybridized probe emits a fluorescence signal (Figure 1.5). The fluorescence intensity is relative to the quantity of the target molecule hybridized to the probe, and thus corresponds to the expression level of the respective mRNA in the sample

interrogated. Consequently, the raw data from a microarray experiment are in the form of a scanned image of the hybridized target mRNAs to the probes.

During the first step of signal processing any potential null measurements are addressed. A null measurement can occur when a probe set emits zero fluorescence (signal intensity=0), or when the intensity of the fluorescence emitted is lower than the background fluorescence. In this step, the ratio of positive/null measurements for each gene is calculated, as a measure of confidence for the presence of gene expression, whilst null measurements can be removed. A mathematical correction follows, in order to subtract the background signal from the signal of each probe set in order to obtain a more representative measurement of the expression levels [83].

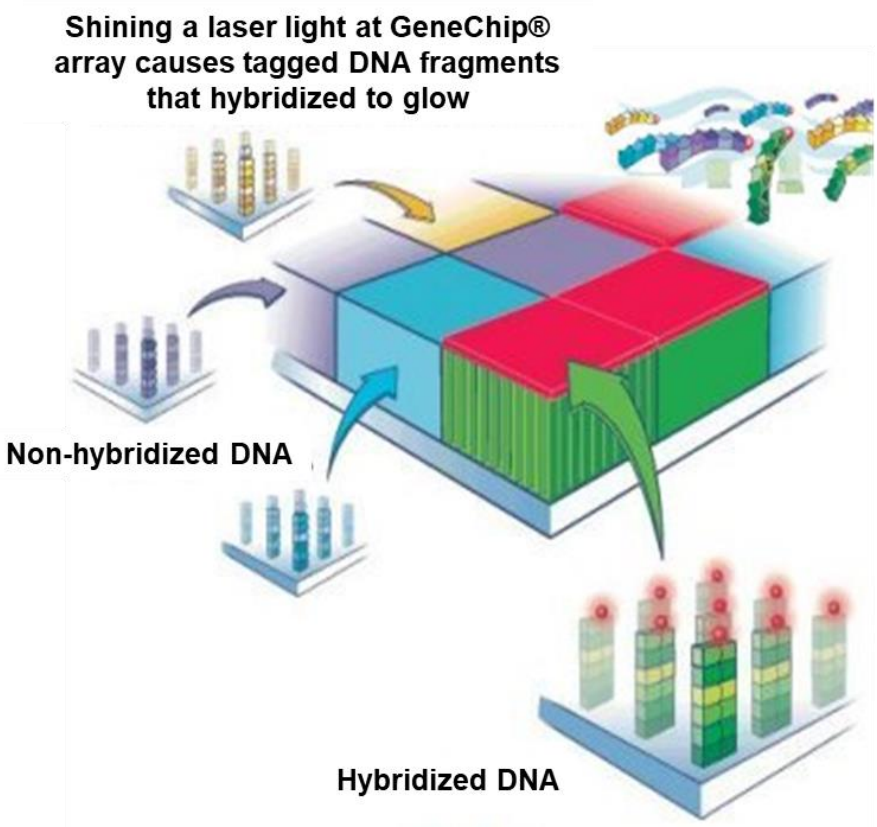


Figure 1.5: *Signal detection in Affymetrix GeneChip® microarray.*

1.6.2.1.2 Sample comparability and normalization

In order to ensure linearity and hence comparability of measurements across different arrays, the correlation coefficient (R) for the multiple microarrays used in each study is calculated. The R value is between –1 and 1; the larger the absolute value of R, the stronger the correlation between the arrays compared.

A key step in the microarray data preprocessing is the normalization process. In array studies, two types of variation are expected: interesting variation and obscuring variation. In gene expression studies, large differences in the expression levels of particular transcripts between the test sample and the control sample account for interesting variation. However, the observed expression levels also include variation introduced during the experimental process, which could be classified as obscuring variation with no biological meaning. The purpose of normalization is the minimization of non-biologically originating variations on the biological data of the experiment, and is essentially a type of systematic error removal process. In the case of microarrays, potential sources of errors include experimental conditions affecting labeling and hybridization processes, scanner errors, manufacturing abnormalities in the array, as well as human error etc. Sources of errors are multiplicative and may strongly affect probe set intensities (i.e. true expression levels), especially if the genes are moderately expressed. When the errors are minor, they can be compensated for through bioinformatical normalization.

The main concept of normalization is that the expected mean intensity ratio between the sample and the respective control equals 1, since only 10-20% of a cell's genes are expressed in a given point in time. The process includes mathematical processing of the results, until the expected mean value is achieved. Although normalization entails a considerable risk of removing variations of biological origin along with the systematic errors, it is an imperative step to ensure the comparability of different probe sets within and across microarrays [83-85].

1.6.2.1.3 Summarization

In Affymetrix GeneChip ® microarrays multiple probes are used to quantify the same target sequence. Specifically, a probe set consisting of 11-20 probe pairs is used to measure the expression levels of a given transcript, and summarization of the 22-40 measurements from a probe set is performed to give a single estimate of the expression of the target transcript [82].

1.6.2.2 Detection of differential gene expression

1.6.2.2.1 Calculation of gene expression changes

The change in gene expression is calculated as the ratio of the probe set signal intensity in the test sample/array, to the intensity of the respective probe set in the control sample/array. In the case that the expression of a given gene has not changed, the signal intensity ratio is equal to 1. When a gene is overexpressed, the ratio is >1, whilst for underexpressed gene the ratio is <1. However, in most cases, the distribution of intensity ratios appears to be extremely asymmetric: the overexpressed genes are represented by values between 1 and infinity (in theory), whilst for the underexpressed genes the ratio values are between 0 and 1. For the normalization of this distribution asymmetry, these values can be either logarithmized, or calculate a Fold Change instead. For values >1, the Fold Change is calculated as the ratio of the signal intensity, and for values <1 the Fold Change equals the inverted ratio of signal intensity (1/intensity ratio)[83].

1.6.2.2.2 Determination of statistically significant gene expression changes

Upon completion of all the above analysis steps, robustness of differential expression is evaluated by combining fold change with statistical validation. A mathematical analysis for the identification of statistically significant gene expression changes. This includes the comparison of the intensity levels of each probe set across the investigated groups of samples. The comparison can be performed with approaches based on regularized t-test [86] for two conditions, Analysis Of Variance (ANOVA) [87] for more than two conditions, or the Wilcoxon rank-sum test, and requires multiple measurements for each

gene within the experiment. Another widely used method is Significance Analysis of Microarrays (SAM) [88]. Inevitably, each approach presents with distinct advantages and limitations, as described in the scientific literature [89].

1.6.2.3. Biological interpretation of microarray results

After determination of the statistically significant gene expression changes between the sample groups compared in a study, the data needs to be organized in subcategories of manageable size in order to effectively decode the biological information contained. This can be achieved via approaches such as clustering genes based on the observed expression patterns or their functional classification [90, 91].

1.6.2.3.1 Cluster analysis

Clustering approaches represent different ways to cluster points in multidimensional space, and aim to extract the fundamental patterns of gene expression inherent in the data obtained from microarray experiments [92]. Cluster analysis is commonly used in microarray studies, to group both genes and samples. In specific, cluster analysis can be used to classify genes into groups according to the degree of their expression profile similarity. The resulting clusters suggest the correlation and/or co-regulation of the respective genes, indicating that they may serve common biological roles. It has been shown that clustering can group together efficiently genes of known similar function, and expression patterns observed in whole genome-expression studies can be indicative of the status of cellular processes. Moreover, co-expression of genes of known function with poorly characterized or novel genes may provide insight into the currently unknown functions of the latter [93]. Lastly, clustering samples enables the comparison of the expression profiles of different samples for the detection of sample groups with similar expression profiles. This approach proves to be valuable in certain study designs, such as the classification of patients with similar clinical presentation, in subgroups with different risk or possible therapeutic output [94].

Comparison analyses have shown that the performance of a clustering algorithm may vary significantly depending on the characteristics of the dataset analyzed and thus different types of clustering may accommodate different types of experimental data [94]. Some examples of broadly used clustering methodologies in microarray datasets include hierarchical clustering, K-means clustering, model-based clustering, Principal Component Analysis (PCA) and Self-Organizing Maps (SOM)[95].

1.6.2.3.2 Functional analysis

Although clustering analysis has proven to be a useful methodology in microarray analysis, it provides minimal information on the functional correlation between the differentially expressed genes. Extraction of functional information from microarray expression data can be a challenging process, that requires extensive data mining in multiple scientific databases (e.g. with sequence-based annotations, protein-protein interactions, experimental evidence on gene functions etc.), and effective integration of the retrieved information. To this aim, sophisticated bioinformatical software and advanced online search tools that rely on robust gene functional annotations and scientific literature are utilized. These tools enable the application of a number of comprehensive analytic methodologies for datasets derived from whole genome expression studies. These methodologies are exemplified by three popular types of analysis, implemented in our study: functional categorization of the differentially expressed genes according to Gene Ontology, mapping the genes to well characterized molecular pathways, and prediction of central regulatory molecules that may account for the observed transcriptomic changes and the associated altered biological functions.

Gene Ontology classification

Functional classification of genes is typically performed according to the Gene Ontology™ database (www.geneontology.org). The Gene Ontology (GO) Consortium GO defines concepts/classes (“GO terms”) used to describe gene function, and how these functions are related to each other (“relations”). GO classifies gene functions along three aspects: Molecular Function (molecular level activities performed by gene products), Cellular Component (the

subcellular structure where a gene product performs a function), and Biological Process (larger processes made up of the molecular activities of multiple gene products). The GO database is constantly revised and enriched as biological knowledge accumulates. [96]. Importantly, in the GO approach for functional classification a GO term can have more than one parent term, and a gene can be associated with more than one GO term, allowing for each gene to be categorized on the basis of the full set of its GO features. In order to facilitate this type of analysis for gene expression dataset, a great number of bioinformatic data mining software and online platforms have been developed, including DAVID [97], GOEAST [98], g:Profiler [99] and geneXplain [100], amongst many others.

Molecular pathway analysis

Pathway analysis have been utilized for over a decade to gain insight into the underlying biology of differentially expressed genes, as it reduces complexity and has increased explanatory power [101]. Knowledge base–driven pathway analysis involves mapping of the differentially expressed genes into pre-designed molecular pathways included in a database. These molecular pathways are curated based on published scientific evidence and known molecular interactions, and cover a wide spectrum of complex biological functions. Consequently, pathway analysis can provide information on which well-characterized cell signaling and metabolic pathways are changed in the biological system of the study. A variety of data mining tools have been developed to enable this type of analysis, including the commercially available software Ingenuity Pathway Analysis (IPA) [102], and the publically available KEGG international database [103].

Prediction of central regulators

Prediction of central regulators in gene expression data involves the identification of common pivotal molecules participating in signal transduction sequences upstream of the significantly changed genes of the study, which renders them likely to control multiple of these genes and their associated functions. This type of analysis is complementary to functional classification and pathway analyses, by pinpointing central regulators for the observed biological functions and pathways that change in the phenotype/condition

studied. An alternative approach for the identification of central regulators is based on the sequence-based prediction of the transcription factors that could possibly orchestrate the observed gene expression changes. This type of analysis is performed via transcription factor binding site prediction within the promoters of the differentially expressed genes of the study, so as to predict the transcription factors that act as central regulators in the biological system of the study, In both cases, the information obtained on the possible interactions of the upstream regulators with their target genes, as well as with other regulators, can provide testable hypothesis for gene regulatory networks and enable the discovery of candidate therapeutic targets. The prediction of upstream central regulators in transcriptomics data can be implemented with the aid of software such as geneXplain[100], EXplain [104], and IPA [102].

Reaching the end of this section, it should be noted that most of the data mining bioinformatical analysis methods that work towards the unbiased identification of molecular mechanisms associated with the studied condition, may overlook valuable biological information, due to inherent flaws of the algorithms used. Consequently, it is essential to supplement these types of automated analysis with manual data mining in the scientific literature [105], in order to validate and enrich the results obtained from bionformatical analyses.

1.6.3 Microarray applications in the characterization of pathogenetic mechanisms of disease

Microarrays were first described in 1995, and have been the basic tool in tens of thousands of publications in the international scientific community since [106-111]. These publications cover almost the full spectrum of human disease, including cancer, cardiological, neurological, rheumatological and many more [112-119].

Some representative microarray applications are exemplified by studies conducted by researchers of our group, where gene expression profiles were utilized for the investigation of intractable diseases, on multiple levels. For example, the use of microarrays for the identification of global gene expression changes in patient skeletal muscle tissue samples led to the discovery of distinct molecular signatures in the case of inflammatory myopathies, which can be utilized for more effective disease classification and more accurate diagnosis [120]. A similar analysis of nemaline myopathy samples identified different subcategories, with distinct gene expression signatures, histological status and prognosis [121]. At the level of deciphering disease pathogenesis gene expression analyses in patient samples with nemaline myopathies (NMs) [122], or Duchene Muscular Dystrophy (DMD) [123], uncovered relevant molecular pathways that explained, at least in part, the molecular basis of the pathology and pinpointed new therapeutic targets. Beyond human specimens, microarrays are equally used for the study of animal models. In this context our team applied gene expression microarrays in various mouse models of human disease. For example, a mouse model carrying one of the human mutations causing NM provided valuable information on the molecular mechanisms impaired in different skeletal muscles at different stages of the disease [124], thus expanding the overall understanding of NM pathogenesis. A study in a mouse model of diet-induced obesity, deciphered the effects of CNTF in skeletal muscle gene expression, ultimately showing that it exerts an overall beneficial effect on metabolism, thereby suggesting its potential use in novel antiobesogenic treatments [125].In the field of cardiovascular research, studies in a transgenic mouse model expressing human PLN provided valuable insight in the downstream

effects of this protein in the cardiac remodeling process, thus improving our understanding of key biological mechanisms implicated in heart failure [126].

1.6.4 Microarray studies in MTLE

Microarray technology has also emerged as a valuable partner in the investigation of pathogenetic mechanisms and the identification of therapeutic targets in the case of neurodegenerative diseases. Specifically, in MTLE, microarrays have employed for the whole genome expression analysis of human samples [127-131], as well as animal models of the disease [132-138]. However, despite these efforts, no promising therapeutic targets for MTLE pathogenesis have been brought to light yet. The selection of an appropriate animal model is considered as a serious limiting factor, since some studies were performed in animal models obtained by systemic KA administration [132, 134, 135] or pilocarpine administration [136], which are known to cause long lasting *SE* and can lead to symptoms that are not typical of human MTLE, such as. generalized seizures with convulsions [18]. An additional factor that may contribute to the unsuccessful therapeutic target discovery during MTLE pathogenesis, is the time point(s) investigated in a study, with regards to the time course of MTLE. In the case of studies performed in human samples [127-131], which are obtained from partial hippocampectomy in patients suffering from chronic MTLE, the findings possibly represent the consequences of MTLE development and progression, as well as the effects of recurrent seizures. On the other hand, the majority of studies in experimental models of MTLE are conducted in tissue samples collected during seizures, either during the initial SE or after the occurrence of spontaneous seizures. Consequently, it is possible that some of the observed expression changes may be due to neuronal hyperexcitation, which is typical of these two time points. For example, in a study performed in the same experimental model of MTLE examined in our study, microarrays were employed for the investigation of global gene expression changes during KA-induced SE (6 hours post KA) and in chronic MTLE (15 days, 6 months post KA). [137]. Furthermore, the biological interpretation of transcriptomics data in the studies mentioned is usually limited to cluster analysis and/or functional

annotation of the differentially expressed genes, and lack additional levels of regulatory network analysis that could potentially aid the identification of putative therapeutic targets.

The limiting factors mentioned were taken into consideration during the design of the experiments and multi-level bioinformatics approach of our study. Accordingly, we aim to provide a more comprehensive microarray analysis of MTLE pathogenesis and progression, and work towards the discovery of novel candidate therapeutic targets.

1.7. Aim of the study

The aim of our study was to characterize the molecular mechanisms implicated in MTLE pathogenesis and progression, in order to identify novel therapeutic targets for MTLE. To this aim, we utilized an experimental model of MTLE obtained by intrahippocampal KA injection in the mouse [58, 139] that simulates human MTLE [18], and a cohort of patient samples with MTLE-HS. Whole genome expression analysis with microarrays was performed on the KA-MTLE hippocampi at three time points representing distinct stages of MTLE development and progression, and on hippocampal samples from patients with established MTLE with hippocampal sclerosis. Multi-level bioinformatical analysis and data mining followed, in order to characterize the molecular changes that may affect epileptogenesis and disease progression. The analysis was extended to the level of central regulatory molecules that may control the observed changes, aiming to pinpoint novel candidate therapeutic targets for MTLE, whilst we performed additional experiments, in an effort to validate the hypotheses formed during the course of the study.

2. MATERIALS AND METHODS

2.1. LABORATORY EXPERIMENTS

2.1.1 Animal samples

KA-MTLE mouse model

The mouse model for MTLE was obtained by unilateral intrahippocampal microinjection of kainate (KA;1 nmol/50 nL) in C57BL/6J, 2- month old, male mice, and was used in parallel with saline-injected animals as controls (n= as previously described [58, 62, 140].The animals were decapitated at 1 day, 3 days or 30 days post injection, their brain was rapidly removed from the skull at 4°C, the hippocampus was dissected and snap frozen in liquid nitrogen. These experimental procedures were carried out in the laboratory of our collaborator Dr A. Depaulis at the Grenoble Institute for Neuroscience (INSERM), Université Grenoble Alpes, France.

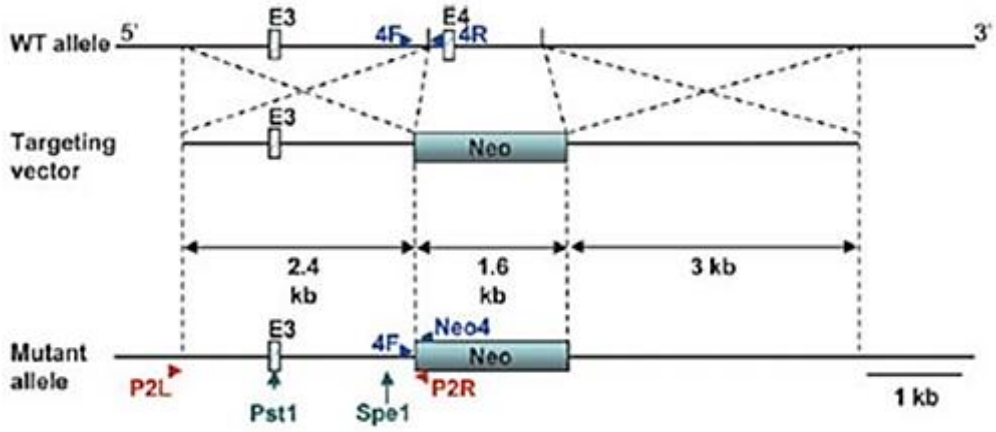
KA-MTLE NOX4 knock out mouse model

The KA-MTLE NOX4 knock out mouse model was developed by our collaborator Dr. V. Duveau and his team (SynapCell, France). In specific, a HindIII fragment containing the Exon 4 (85bp) in the wild type NOX4 allele was replaced with a pGK-neo cassette (1.6kb) in C57BL/6J mice (Figure 2.1). The KA-injected NOX4 knock out mice and wild type controls were sacrificed at 30 days post KA injection, and hippocampal samples animals were obtained as described above.

Chronic Valproate treatment in the KA-MTLE mouse model

KA-MTLE mice (C57BL/6J strain, 2 months old, males) were treated with a single intraperitoneal injection of the anticonvulsive drug Valproate at 3 hours post KA, followed by continuous administration of Valproate for 28 days post KA, using saline treated KA-MTLE mice as controls. At 30 days post KA injection, hippocampal tissue samples from both groups of animals were obtained as described above. The chronic Valproate treatment animal experiments were performed by our collaborator Dr. V .Duveau and his team in SynapCell, France.

A



B

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0001 ATGGCGGTGT CCTGGAGGAG CTGGCTGGCC AACGAAGGGG TTAAACACCT CTGCCTGCTC ATTTGGCTGT
0071 CCCTAAACGT TCTACTTTTC TGGAAAACCT TCCTGCTGTA CAACCAAGGG CCAGAATACT ACTACATTCA
0141 CCAAATGTTG GGCCTAGGAT TGTGTTTAAG CAGAGCATCT GCATCTGTCC TGAACCTCAA CTGCAGCCTC
0211 ATCCTTTTAC CTATGTGCCG GACAGTCCTG GCTTATCTTC GAGGATCACA GAAGGTCCCT AGCAGGAGAA
0281 CAAGAAGATT GTTGGATAAA AGCAAGACTC TACACATCAC ATGTGGTGTA ACTATCTGTA TTTTCTCAGG
0351 TGTGCATGTA GCCGCCCACT TGGTGAATGC CCTCAACTTT TCAGTGAACT ACAGTGAAGA TTTCCTTGAA
```

Figure 2.1. *A. Schematic representation showing targeting cassette used for generation of NOX4-knock-out mice [141]; B. The nucleotide sequence of Exon 4 of the wild type NOX4 allele, marked with blue font.*

Chronic Apocynin treatment in the KA-MTLE mouse model

KA-MTLE mice (C57BL/6J strain, 2 months old, males) were treated with the NADPH oxidase inhibitor Apocynin in drinking water, using tap water as control, for 28 days post KA injection. Hippocampal tissue samples from both groups of mice were obtained at 30 days post KA injection as described above. The Apocynin chronic treatment animal experiments were performed in the laboratory of our collaborator Dr A. Depaulis at the Grenoble Institute for Neuroscience (INSERM), Université Grenoble Alpes, France.

2.1.2 MTLE patient samples

For transcriptomic analysis of human MTLE, appropriate human hippocampal tissue samples were selected from a human brain tissue bank created by our collaborator Dr. S. Hamelin at INSERM, Université Grenoble Alpes, France

(Table 2.1). The samples were provided through the epilepsy surgery program of the University Hospital (Hôpital Michallon, Grenoble, France). The samples included in this analysis were obtained from adults that received mesio-temporal lobe resection (hippocampus included), and were operated in Grenoble (2014-2016).The resective tissues from hippocampal regions were collected by a neurosurgeon and immediately frozen for future analysis.

2.1.3 RNA extraction

The hippocampal samples obtained from:

i. KA- and saline-injected animals at 1, 3 and 30 days post injection (n=30, 5 biological replicates/ treatment/ time point) by Dr A. Depaulis (INSERM, University Joseph Fourier, France);
ii. KA-injected NOX4 KO and WT KA-MTLE animals at 30 days post KA injection (n=8, 4 biological replicates /genotype) by Dr. V .Duveau (SynapCell, France);
iii. KA-injected animals subjected to chronic treatment with Apocynin or tap water (n=8, 4 biological replicates/ treatment) by Dr A. Depaulis (INSERM, University Joseph Fourier, France);
iv. KA-injected animals subjected to chronic treatment with Valproate or saline (n=8, 4 biological replicates/treatment) by Dr. V .Duveau (SynapCell, France); and
v. MTLE patients that received resective surgery for epilepsy treatment (n=17) by Dr. S. Hamelin (INSERM, Université Grenoble Alpes, France)

were shipped to Athens under appropriate conditions, and were further processed in our laboratory.

Total RNA was extracted from all samples with a modified TRIzol^{TM} reagent (Invitrogen) protocol. Specifically, 1mL of TRIzol^{TM} reagent was added to each frozen hippocampal sample and homogenized while on wet ice. The homogenized tissue mix was centrifuged at 13.000 rpm for 10 minutes (4^{o}C); the supernatant was collected and incubated at room temperature for 5 minutes.

Table 2.1. *Human MTLE samples demographics and histopathological features. M: male; F: female; MTLE: Mesio Temporal Lobe Epilepsy; HS: Hippocampal Sclerosis; HS ILAE Type: type of HS according to International League of Epilepsy classification; MRI: HS presence/absence according to Magnetic Resonance Imaging; FS: Febrile Seizures.*

Sample ID	Gender	Age	Surgery Date	Histopathological features
14D0100.7	M	54	20/05/14	Human MTLE; HS ILAE Type 1 (MRI) no FS
14D0088.4	F	43	1/7/2014	Human MTLE; HS ILAE Type 1 (MRI) with FS
14D0118.5	F	21	5/8/2014	Human MTLE; HS ILAE Type 1 (MRI) no FS
14D0120.3	M	64	27/08/14	Human MTLE; HS ILAE Type 1 (MRI) with FS
14D0134.1	M	31	7/10/2014	Human MTLE; HS ILAE Type 1 (MRI) with FS
14D0141.4	M	19	9/10/2014	Human MTLE; HS ILAE Type 1 (MRI) with FS
15DO041.3	M	47	11/6/2015	Human MTLE; HS ILAE Type 1 (MRI) with FS
16DO004.5	M	31	19/01/16	Human MTLE; HS ILAE Type 1 (MRI) no FS
16DO034.5	M	49	14/04/16	Human MTLE; HS ILAE Type 1 (MRI) with FS
15DO067.1	F	31	11/8/2015	Human MTLE; HS ILAE Type 1 (MRI) with FS
14D0128.3	F	63	3/9/2014	Human MTLE; HS ILAE Type 2 (MRI) with FS
16DO013.6	F	41	3/1/2016	Human MTLE; HS ILAE Type 2 (MRI) with FS
15D0013.1	F	34	19/02/15	Human MTLE; no HS (MRI), no FS
14DO026.1	F	46	16/01/14	Human MTLE; no HS (MRI), no FS
14DO086.1	F	40	15/04/14	Human MTLE; no HS (MRI), no FS
14D0117.5	M	49	26/08/14	Human MTLE; no HS (MRI), no FS
15DO029.4	F	39	21/04/15	Human MTLE; no HS (MRI), no FS

200 µL of chloroform (4^{o}C) was added to the mix, followed by incubation at room temperature for 3 min, and centrifugation at 13.000 rpm for 15 minutes (4^{o}C), and then the RNA-containing aqueous phase was collected. RNA was precipitated by the addition of 250 µL of isopropanol and 250 µL of high salt solution (0.8 M sodium citrate, 1.2 M NaCl), followed by 10 minute incubation at room temperature, and centrifugation at 13.000 rpm for 10 minutes (4^{o}C). The RNA pellet was washed once with 500 µL of EtOH 75%, centrifuged at 13.000 rpm for 5 minutes (4^{o}C), the EtOH was removed, and the pellet was air-dried and resuspended in nuclease-free H_2O. The extracted RNA was quantified by Qubit (Invitrogen), the RNA integrity of the obtained samples was assessed by gel electrophoresis on 1% agarose gels (0,5x TBE buffer, 90 Volts, ~25 minutes), and contamination was assessed by performing spectrophotometer absorbance measurements at 230 nm, 260nm and 280 nm. For the microarray analyses of the study, only high quality RNA samples with 28S/18S rRNA ratios close to 2 on 1% agarose gels, and with absorbance ratios 260 nm/280 nm and 260 nm/230 nm between 1.9 and 2.1, were utilized.

2.1.4 Microarray Experiments

Microarray analysis of the KA-MTLE mouse model

The RNA obtained from the KA- and saline-injected hippocampi at 1, 3 and 30 days post injection was labeled according to the recommended Affymetrix protocols for target preparation (Figure 2.2), and was hybridized to Affymetrix GeneChip™ Mouse Gene 1.0 ST Array. This array interrogates >26,000 transcripts, representative of >21,000 well annotated genes (Entrez gene count), with >770,000 distinct probes. Specifically, it covers 26,166 RefSeq transcripts throughout the entire mouse genome, including 24,582RefSeq coding transcripts with well-established annotation (NM), 1,229 RefSeq non-coding transcripts with well-established annotation (NR), 279 RefSeq coding transcripts with provisional annotation (XM), 76 RefSeq non-coding transcripts with provisional annotation (XR), and ~8 long intergenic non-coding transcripts (lincRNAs).

Microarray analysis of the NOX4 KO KA-MTLE mouse model

The RNA from KA-injected NOX4 knock out and wild type KA-MTLE hippocampi at 30 days post KA was labeled according to the recommended Affymetrix protocols for target preparation (Figure 2.2), and hybridized to Affymetrix GeneChip™ Mouse Gene 2.0 ST Array. This array interrogates >35,000 transcripts, representative of >26,500 well annotated genes (Entrez gene count), with >698,000 distinct probes. Specifically, it covers 35,240 RefSeq transcripts throughout the entire mouse genome, including 26,191 RefSeq coding transcripts with well-established annotation (NM), 3,391 RefSeq non-coding transcripts with well-established annotation (NR), 1,946 RefSeq coding transcripts with provisional annotation (XM), 3,712 RefSeq non-coding transcripts with provisional annotation (XR), and ~2,000 long intergenic non-coding transcripts (lincRNAs).

Microarray analysis of the human MTLE samples

The RNA obtained from human hippocampal tissue samples was labeled according to the recommended Affymetrix protocols for target preparation (Figure 2.2), and was hybridized to Affymetrix GeneChip™ Human Gene 1.0 ST Array. This array interrogates >36,000 transcripts, representative of >21,000 well annotated genes (Entrez gene count), with over 760,000 distinct probes spanning the entire human genome. Specifically, it covers 36,079 RefSeq transcripts, including 32,020 RefSeq coding transcripts with well-established annotation (NM), 2,967 RefSeq non-coding transcripts with well-established annotation (NR), 579 RefSeq coding transcripts with provisional annotation (XM), 513 RefSeq non-coding transcripts with provisional annotation (XR), and ~ 466 long intergenic non-coding transcripts (lincRNAs).

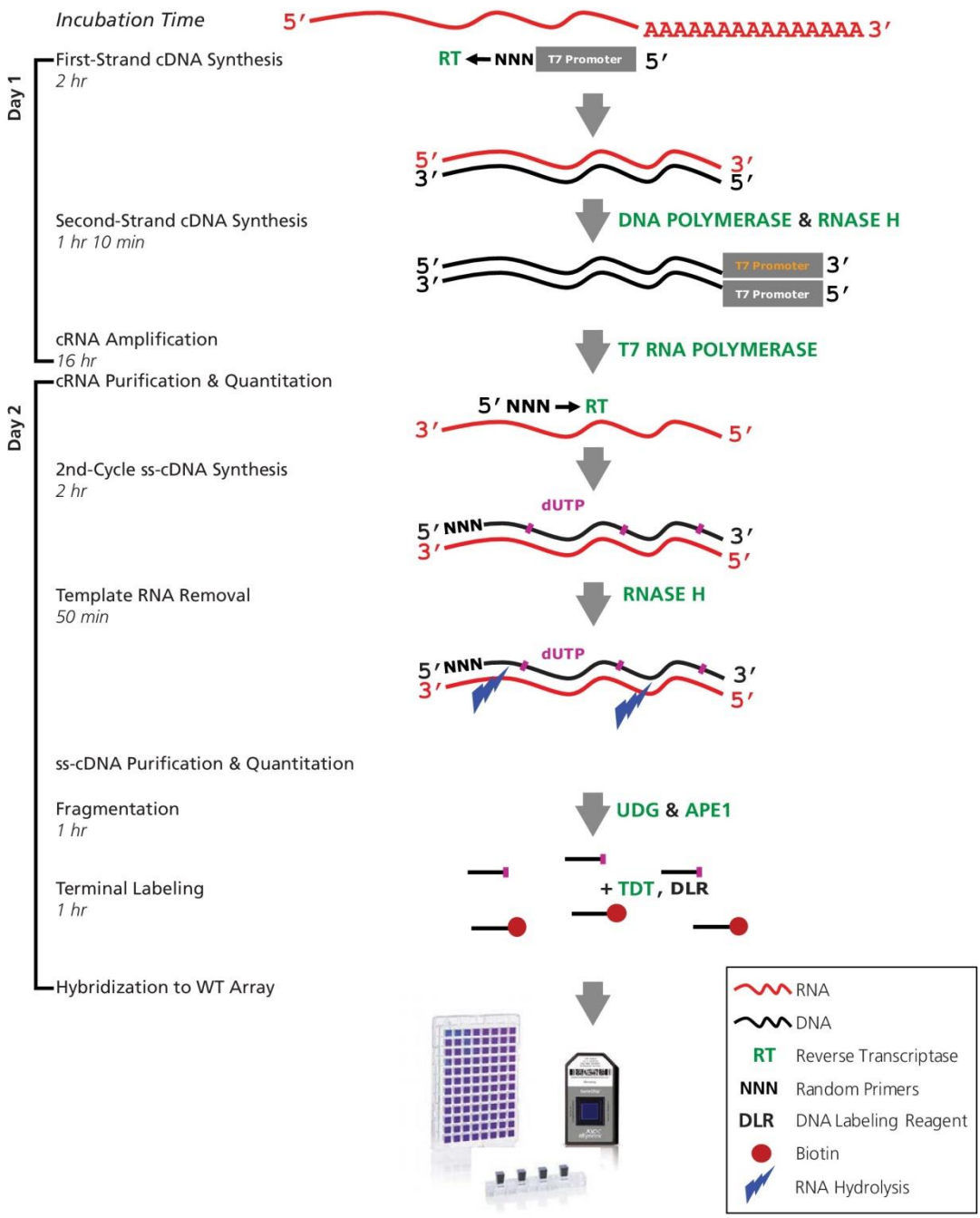


Figure 2.2. *Overview of Affymetrix target preparation protocol for hybridization to GeneChip® Whole Transcript (WT) Expression Arrays, using the WT Plus Reagent kit.*

2.1.5 RT-qPCR in Apocynin- and Valproate-treated samples

In order to assess the expression of NOX related genes in the hippocampus of KA-MTLE by RT-qPCR, we designed appropriate primer sets for twelve NOX related genes (Cyba, Cybb, Ncf1, Ncf2, Ncf4, Nox1, Nox4, Mpo, Prdx6, Rac1, Rac2, Pu.1) and one housekeeping gene (Gapdh) (Table 2.2). The RNA from KA-injected animals that received Apocynin treatment or tap water (n=8, 4 biological replicates /treatment), and Valproate treatment or saline (n=8, 4 biological replicates /treatment), was used as a matrix for cDNA synthesis that was subsequently analyzed with qPCR reactions.

***Table 2.2**. Primer sets sequences used for the interrogation of NOX-related gene expression by RT-qPCR, in KA-MTLE mouse hippocampi subjected to chronic treatment with Apocynin or Valproate.*

Gene	Forward primer sequence	Reverse primer sequence
Cyba	GTCATGGGGC AGATCGAG	ACCACTGTGT GAAACGTCCA
Cybb	CTTTCTCAGG GGTTCCAGTG	TGCAGTGCTA TCATCCAAGC
Gapdh	CGTCCCGTAG ACAAAATGGT	TTGATGGCAA CAATCTCCAC
Mpo	CTCCTCACCA ACCGCTCC	TGCTCTCGAA CAAAGAGGGT
Ncf1	CTATCTGGAG CCCCTTGACA	TCCTCTTCAAC AGCAGCGTA
Ncf2	GCAGTGGCCT ACTTCCAGAG	CTATCAGCTG GTTCCCACGA
Ncf4	TTTCTGACTAC CCACAGCCAT	TGAAGCCTCT CTTCTCCTCG
Nox1	TTACACGAGA GAAATTCTTG GG	GGACAGCAGA TTTCGACACA
Nox4	CTGGAAAACC TTCCTGCTGT	TCAGGACAGA TGCAGATGCT
Prdx6	CCAACTTTGA GGCCAATACC	GGTGCACACT GGGGTAAAGT
Pu.1	AGCGATGGAG AAAGCCATAG	TGCAGCTCTG TGAAGTGGTT
Rac1	AGATGCAGGC CATCAAGTGT	TCTCCAGGAA ATGCATTGGT
Rac2	CATCAGCTAC ACCACCAACG	AGGTTCACCG GCTTACTGTC

In specific, for the Valproate treated mice and saline treated controls, cDNA was prepared from 1μg of RNA with Superscript II (Invitrogen) reverse transcriptase reactions in MJ Dyad PCR machine (Bio-Rad). The cDNA template synthesis was performed according to the recommended Invitrogen protocol in a total reaction volume of 20 μL. For each sample, 1μg of total RNA template was added to 10mM dNTPs mix, 300ng random primers and Nuclease Free H_2O, in a total reaction volume of 13 μL, in a 0.5ml PCR Eppendorf tube, and the preparation was incubated at 65°C for 5 minutes in the thermocycler. After the incubation, 4 μL of 5x Buffer and 2 μL of 0.1 M DTT were added, in a total reaction volume of 19 μL, and the preparation was then incubated at 25°C for 2 minutes in the thermocycler. In the next step of the process, 1 μL of Superscript II reverse transcriptase enzyme (Invitrogen) was added, in a total reaction volume of 20 μL, and was followed by incubation at 25°C for 10 minutes, at 42°C for 50 minutes, and finally at 70°C for 15 minutes, in the thermocycler. The cDNA templates obtained were stored at -20°C for use in future analyses.

For the qPCR reactions, 1:40 dilutions of the cDNA templates were prepared. According to the recommended Invitrogen protocol, 2,5 μL of cDNA template was added to a mix of 5 μL of Platinum SYBR Green qPCR SuperMix-UDG (Invitrogen), 0.25 of forward primer, 0.25 μL of reverse primer, and Nuclease Free H2O in a total reaction volume of 10 μL. The samples were analyzed in triplicate reactions on a real time PCR machine (Sacace Technologies) with the following cycling parameters: denaturation for 3 minutes at 95^{o}C; 50 cycles of 3 seconds at 95^{o}C; and 20 seconds at 60^{o}C. The detection of the desired qPCR amplicon was ensured by melting curve analysis (6 second incubations from 65^{o}C-95^{o}C every 0.5^{o}C), and the cycles to threshold (Ct) were recorded.

The RT-qPCR experiments for Apocynin-treated mice and the respective control animals receiving tap water were performed by our associate Dr. D. Arvanitis in our lab (Molecular Biology Division, Biomedical Research Foundation of Academy of Athens, Greece) according to the protocol described above.

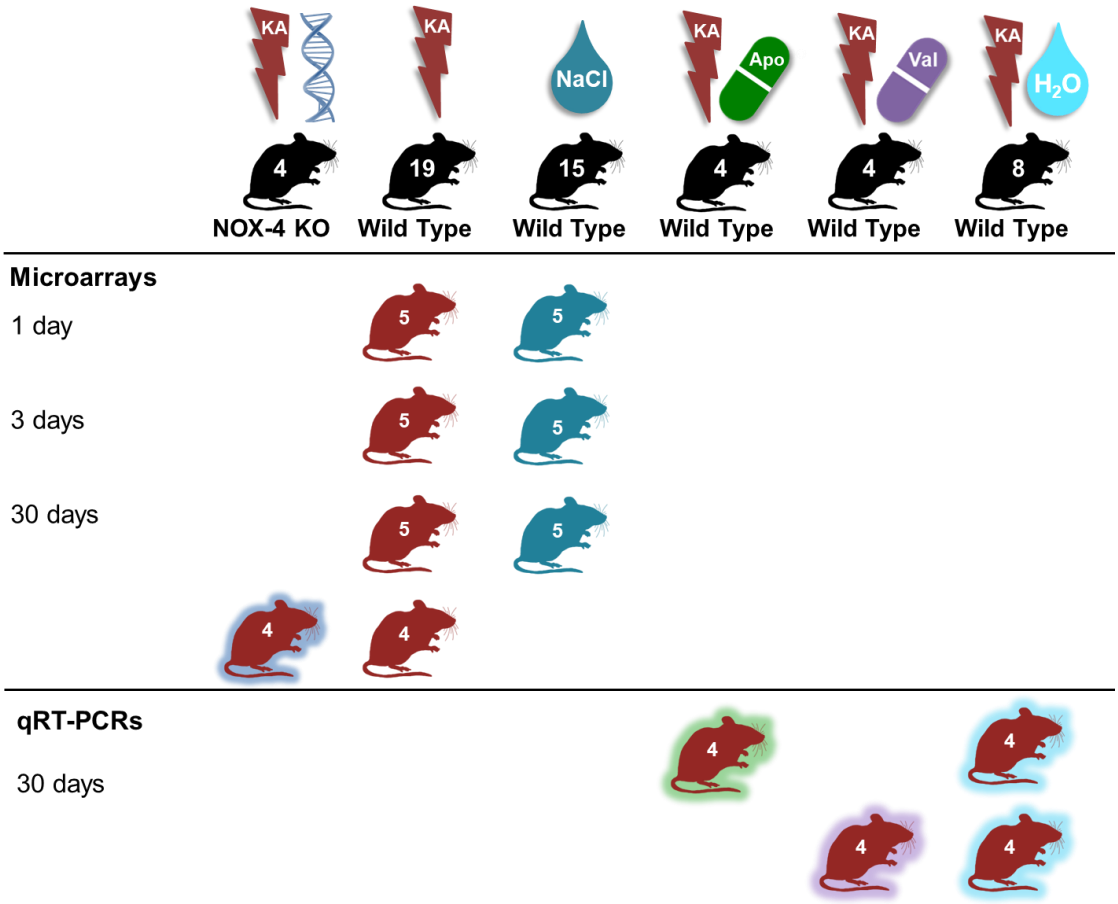


***Figure 2.3**. Overview of experiments conducted using the KA-MTLE mouse model. A total of 54 animals were used: 35 wild type mice and 4 NOX4-KO animals injected with KA; 15 wild type mice injected with saline. Microarray analyses were performed on hippocampal samples from 15 KA- and 15 saline-injected wild type mice as controls (5 mice/treatment/time point; 3 time points: 1 d, 3d, 30d post injection);, hippocampal samples from 4 KA-injected NOX4-KO mice with 4 KA-injected wild type mice as controls (30 days post injection). qRT-PCR analyses. were conducted on hippocampal samples from 4 KA-injected, Valproate-treated wild type mice with 4 KA-injected, tap water-treated wild type mice as controls; hippocampal samples from 4 KA-injected, Apocynin-treated wild type mice with 4 KA-injected, tap water-treated wild type mice as controls (30 days post injection).*

2.2. BIOINFORMATICAL AND STATISTICAL ANALYSIS

2.2.1 Microarray results processing

The raw microarray results obtained from the analysis of the KA-MTLE mouse model at 1, 3, 30 days post injection, the KA-MTLE NOX4 knock out model at 30 days post KA injection, and the human MTLE samples were processed with Partek® Genomics Suite® software. In specific, the workflow “Gene expression” was utilized for each of the above sets of experiments, and preprocessing of the data was performed with RMA (Robust Multi-array Average). The analysis included transformation of the scanned array images to numerical values, evaluation of quality controls for each experimental step of the protocol (e.g. labeling, hybridization, data quality) background correction on the PM values, log2 transformation of the data, quantile normalization of the numerical values with RMA algorithm, median polish summarization, and annotation of the array probe set IDs.

2.2.2 Determination of significant gene expression changes in microarrays

For the identification of statistically significant gene expression changes, ANOVA analysis was applied to all microarray datasets obtained in this study. Power analysis was also performed for each dataset interrogated, to facilitate the determination of the appropriate fold change threshold according to the sample size of each experiment.

For the KA-MTLE model at 1, 3, 30 days post injection, the following power analysis parameters were used: Effect Size from 1.25 to 3 by step 0.25, Sample Size from 8 to 60 by step 6, Significance 0.01, Power 0.8. Accordingly, 2-fold and 0.01 FDR-adjusted p-value thresholds were applied to determine the significant gene expression changes between KA- and saline-injected groups, at 1, 3 and 30 days post injection.

ANOVA analysis with a range of FDR-adjusted p-value and fold change thresholds (FDR-adjusted p-value <0.05,<0.01; fold change >2, >1.75, >1.5) was used to compare NOX4 knock out and WT animals, at 30 days post KA injection. Power analysis was applied with the following parameters: Effect

Size from 1.25 to 3 by step 0.25, Sample Size from 5 to 16 by step 1, Significance 0.01, Power 0.8.

In the case of human MTLE samples, the power analysis parameters used are as follows: Effect Size from 1.25 to 3 by step 0.25, Sample Size from 5 to 34 by step 4, Significance 0.01, Power 0.8. For this set of samples, a range of additional analysis steps were pursued in order to compare different sample groups. These steps included comparison of subgroups with distinct histopathological features, i.e. hippocampal sclerosis (HS vs. non HS), febrile seizures (FS vs. non FS), focal cortical dysplasia (FCD vs. non FCD), epilepsy side (Right vs. Left). When outlier samples were suspected, the analyses were repeated after omitting them. A range of different statistical thresholds were applied for each of the above analyses in order to have a better appreciation of the data (ANOVA, FDR adjusted p-value < 0.01, 0.05; fold change >2, >1.75, >1.5).

2.2.3 Statistical analysis of RT-qPCR results

For the Valproate and Apocynin set of RT-qPCR experiments, each individual sample was analyzed in two repeats of triplicate reactions, for a total of four samples per group (n=16, 4 biological replicates/ treatment). Relative quantitation was then performed with the comparative Ct method, using Gapdh as reference gene for normalization purposes. Accordingly, delta Ct (ΔCt), delta-delta Ct (ΔΔCt), and $2^{-\Delta\Delta Ct}$ were calculated versus the Gapdh internal control expression. The ΔCt values were then expressed relatively to the control samples that served as baseline for each set of comparisons (Apocynin vs. tap water, Valproate vs. saline). The statistical significance threshold for this analysis was set at $p<0.05$.

2.2.4 Biological Interpretation of significant gene expression changes

The lists with the significantly changed genes obtained from the statistical analysis of microarray results were subjected to bioinformatical analysis for the biological interpretation of the results. The analysis steps included functional classification to Gene Ontologies using the geneXplain software (http://genexplain.com/), molecular pathway analysis, interaction network

generation and upstream regulator analysis with the Ingenuity Pathway Analysis (IPA) software (https: //www. qiagenbioinformatics. com/products /ingenuity-pathway-analysis/), and *in silico* microRNA prediction based on the miRwalk platform (http://mirwalk.umm.uni-heidelberg.de/).

2.2.4.1 Functional classification to Gene Ontologies (geneXplain)

The lists of the significantly changed genes for each set of experiments performed during the course of this PhD were subjected to functional classification, via the tool “Mapping to ontologies”, that is available by the geneXplain platform [142]. The genes were classified according to Gene Ontology (GO) Biological Process (BP), Cellular Component (CC) and Molecular Function (MF), and at the same time the enriched GO terms for each GO category were identified. In each GO category, the observed “Hits”, the “Expected hits” by random chance, and the p-value are calculated for each GO term. The measure of statistical significance in this analysis, the p-value, is an expression of the likelihood of the observed number of “Hits” being determined by random chance, and the applied threshold was <0.05.

The “Level” of each GO term corresponds to the specification level of the process/ function/ topology it describes. The genes mapped in a Level 1 category e.g. Biological Process are subcategorized in more than one Level 2 sub-categories e.g. “metabolic process”, and this level 2 category includes multiple level 3 sub-categories e.g. “biosynthetic process”, “catabolic process” etc. As such, genes classified in enriched upper level categories (>5) mirror specific biological functions that are overrepresented in our dataset, and can often provide complementary information with molecular pathway analysis.

2.2.4.2 Ingenuity Pathway Analysis – Core analysis

The lists of the significantly changed genes and proteins for each set of experiments of the study were subjected to “Core Analysis”, that is available by the Ingenuity Pathway Analysis (IPA) software. More specifically, IPA Core Analyses were performed for the differentially expressed genes between KA- and saline-injected mice at 1, 3, 30 days post injection, and the significantly changed proteins obtained from proteomics analysis of the same sample

groups by our collaborator Dr. A. Vlachou (Proteomics Facility, BRFAA). Furthermore, it was applied for the differentially expressed genes between the HS and non-HS human MTLE samples.

IPA Core Analysis allows the interpretation of experimentally derived datasets in the context of biological processes, pathways and molecular networks. Core Analysis results in the identification of significantly changed Canonical Pathways, Biological Functions and Diseases, Networks, Upstream regulators and Regulator Effects for a given dataset.

Pathway and Function analysis

In specific, the “Canonical Pathways” and “Biological Functions and Diseases” features of Core Analysis identify the most significant biological functions, diseases, metabolic and signaling pathways, represented in the given dataset, and display them in order of significance, as determined by p-value. In determining which Functions and Pathways are most statistically significant for each given dataset, IPA compares the Functions/Pathways associated with the Functions/Pathways Eligible molecules in the dataset against functions associated with all possible molecules in the designated Reference Set, The Functions/ Pathway Eligible molecules are molecules from the given dataset that have been designated by the user as being of interest (e.g. they meet the thresholds of statistically significant expression change), and have at least one functional annotation or disease association in the Knowledge Base. The application allows the user to select the set of molecules to be used as the Reference Set (i.e. the complete universe of endogenous chemicals) for the analysis statistical calculations, with Ingenuity Knowledge Base serving as the recommended Reference Set for Core Analysis of datasets with <2000 identifiers (i.e. gene/protein IDs).

The significance value associated with “Canonical Pathways” and “Biological Functions and Diseases” analyses for each given dataset is a measure of the likelihood that the association between a set of genes in our experiment and a given process or pathway is due to random chance, and is expressed as p-value. The p-value is calculated with the right-tailed Fisher‘s Exact Test, where the p-value for a given function is calculated by considering: 1) The

number of Functions/Pathways Eligible molecules that participate in that annotation; 2) The total number of Knowledge Base molecules known to be associated with that function; 3) The total number of Functions/Pathways Eligible molecules; 4) The total number of genes in the Reference Set. In the right-tailed Fisher's Exact Test, only over-represented functions or pathways --those that have more Functions/Pathways Eligible molecules than expected by chance, are significant. Under-represented functions or pathways ('left-tailed' p-values) which have significantly fewer molecules than expected by chance are not shown. An additional measure of significance of the relationship between the genes/proteins in the dataset and the canonical pathways they are mapped to is provided by the “Ratio”. The “Ratio” is the number of the genes/proteins in the dataset analyzed, divided by the total number of the genes/proteins participating in the pathway examined.

Core Analysis was applied to the datasets of our study using the following settings: Reference set: Ingenuity Knowledge Database; Relationship to include: Direct and Indirect, Includes Endogenous Chemicals; Confidence: Experimentally Observed; Networks: Interaction networks; Data sources: All; Species: All; Tissues and Cell Lines: All; Mutation: The statistical significance threshold used for this analysis is p-value <0.05. The statistically significant “Canonical Pathways” obtained from the analysis indicated which well-characterized cell signaling and metabolic pathways are most relevant in each of our datasets, whilst the statistically significant “Biological Functions and Diseases” indicated the biological and disease processes that are most relevant to the genes in our datasets.

Upstream Regulator analysis

The IPA “Upstream Regulator” analysis is a feature of IPA Core Analysis and aims to identify the cascade of upstream transcriptional regulators that can explain the observed gene expression changes in a given dataset. The Upstream Regulator analysis is based on prior knowledge of expected effects between transcriptional regulators and their target genes stored in the Ingenuity knowledge base. The analysis examines how many known targets of each transcription Regulator are present in the given dataset and also

compares their direction of change (activated or inhibited. For each potential transcriptional regulator two statistical parameters are computed: the overlap p-value and the Z-score. The purpose of the overlap p-value is to identify transcriptional regulators that are able to explain observed gene expression changes. The overlap p-value measures whether there is a statistically significant overlap between the dataset genes and the genes that are regulated by a transcriptional regulator. It is calculated using Fisher's Exact Test, and significance is generally attributed to p-values <0.01. Since the regulation direction ("activating" or "inhibiting") of a molecule is not taken into account for the computation of overlap p-values, the underlying network also includes findings without associated directional attribute, such as protein-DNA (promoter) binding. Z-score represents experimentally observed transcription events associated to a direction which can be activating or inhibiting according to the literature. In our study, the Upstream Regulator analysis was utilized for the prediction of key regulatory molecules that may account for the observed expression changes in each of the datasets, and could possible serve as candidate therapeutic targets on occasion.

The "Regulator Effects" analytic, provided by IPA in the context of Upstream Regulator analysis, explains how predicted upstream regulators might cause increases or decreases in phenotypic or functional outcomes downstream. Each Regulator effects network includes an upstream regulator with a group of target genes/proteins associated with a specific downstream biological function/disease and are already statistically significant, due to being derived from the statistically significant results of upstream and downstream analyses in IPA. They are ranked according to "Consistency Score", which helps to prioritize smaller networks built on nodes with consistent relationships, meaning that the observed/predicted direction of node activity/expression is consistent with the direction one would expect based on the findings from the Ingenuity Knowledge Base. The Regulator Effects analytic was utilized in our study to provide insight into the possible causes and effects of differentially expressed genes that were identified as key upstream regulators in each of our datasets.

2.2.4.3 Ingenuity Pathway Analysis -Comparison analysis

The “Core Analysis” results for the transcriptomics data derived from the KA-MTLE mouse model at 1, 3, 30 days post KA injection were then subjected to “Comparison analysis”, so as to facilitate the identification of time point-specific and persistent molecular changes during the time course of KA-MTLE studied. Moreover, the results of “Core analysis” for the proteomics of the KA-MTLE mouse model were also compared to the results of transcriptomics “Core analysis” at each time point interrogated, in an effort to provide a more comprehensive molecular profile of the KA-MTLE hippocampus. In a similar fashion, the “Core analysis” results obtained from the transcriptomic analysis of the human MTLE samples (HS vs. no HS) were subjected to “Comparison analysis” with the “Core Analysis” results for the metabolomic data obtained from the same sample groups, aiming to provide a better understanding of the molecular events characterizing the sclerotic hippocampus.

2.2.4.5 microRNA analysis (miRWalk)

For the identification of possible microRNA-mRNA interactions that underlie the observed transcriptomic changes, the “Validated module” of the online miRWalk 2.0 platform was utilized [143]. Accordingly, the official NCBI Gene symbols corresponding to the significantly changed transcripts (fold change>2, FDR adjusted p-value<0.01) at 1, 3, and 30 days post KA were submitted to the “Validated gene-microRNA interaction information retrieval system”, which performs elaborate data mining across the PubMed scientific literature, to retrieve experimentally validated microRNA-mRNA interactions for the input set of transcripts. Furthermore, the “Predicted target module” feature of miRWalk was also used for the analysis of the same transcriptomic dataset. For this analysis, the platform utilizes multiple miRNA and gene databases to predict microRNA-mRNA interactions in a given dataset of microRNAs or genes, based on complementary sequence information. Lastly, in order to explore the possible associations of microRNAs obtained from the previous steps with tissues of interest (e.g. CNS); we utilized the “Validated information on organ-miRNA interactions” tool, which facilitates the

identification of organ-associated microRNAs, according to published experimental data.

3. RESULTS

3.1. KA-MTLE MOUSE MODEL

3.1.1 Statistically significant changes in global gene expression of the KA-MTLE mouse hippocampus

In order to understand the molecular mechanisms implicated in the pathogenesis of MTLE, the first part of this Thesis focused on the Bioinformatical and Statistical analysis of global transcriptome data from the hippocampus of KA-MTLE mice. To this aim, ANOVA analysis was applied for the comparison of KA- versus saline injected hippocampi at each of the three post-injection time points of the study (1, 3 and 30 days). To determine the appropriate fold change threshold according to the sample size of the experiment, power analysis was performed. As shown in Figure 3.1, fold changes greater than 1.75 are appropriate for the sample size of, the present study. Accordingly, thresholds of fold change$\leq$2 and FDR-adjusted p-value<0.01 were applied to determine the significant gene expression changes between KA- and saline- injected groups, at 1, 3 and 30 days post injection.

The analysis resulted in the identification of 577 significantly changed transcripts representative of 449 genes at day 1 (Appendix 1), 762 transcripts representative of 729 genes at 3 days (Appendix 2), and 597 significantly changed transcripts representative of 542 genes at 30 days post-injection (Appendix 3). Interestingly, across all three time points, the majority of the significantly expressed transcripts are over-expressed, with considerably less being underexpressed. Specifically, at 1 day 455 probe sets (~78%) were over- and 122 were under-expressed, with the fold changes of individual probe sets ranging from 13.36 (Inhba, inhibin beta-A) to -3.70 (Lct, lactase). At 3 days post-injection, 674 probe sets (~88%) were over- and 88 were under expressed, with a fold change range of 12.21 (Spp1, secreted phosphoprotein 1) to -3.73 (Akr1c18, aldo-keto reductase family 1, member C18). In a similar fashion, at 30 days 489 probe sets (~82%) were over- and 108 were under-expressed, and the fold changes at this time point ranged from 15.53 (Cst7, cystatin F /leukocystatin) to -3.80 (Affymmetrix Probe Set ID: 10342598) (Figure 3.2).

Cross comparison of the three lists with statistically significant changed probe sets revealed that 140 probe sets were consistently changed at 1, 3, 30 days, whereas 229 changed probe sets were common between 1 and 3 days, 359 probe sets were changed at both 3 and 30 days and 177 probe sets were changed at both 1 and 30 days. Lastly 313, 316 and 203 probe sets were uniquely changed at 1, 3 and 30 days, respectively (Figure 3.3).

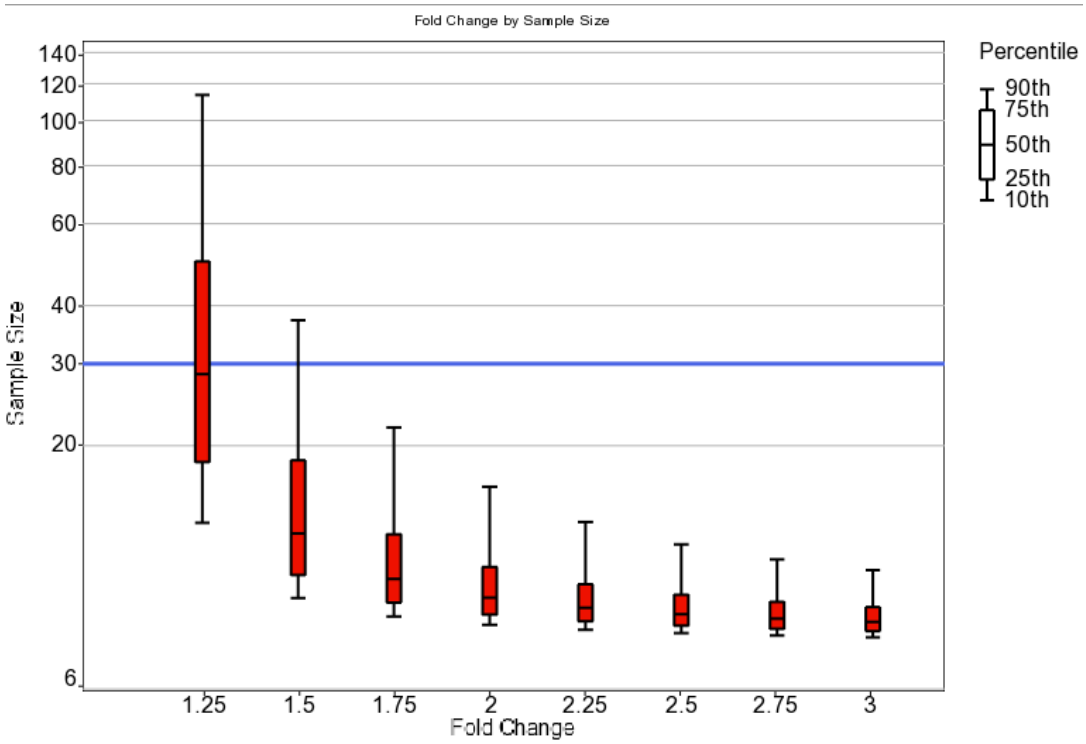


***Figure 3.1**. Power analysis for the determination of the appropriate fold change threshold, at 1, 3, and 30 days post injection in the KA-MTLE mouse model.*

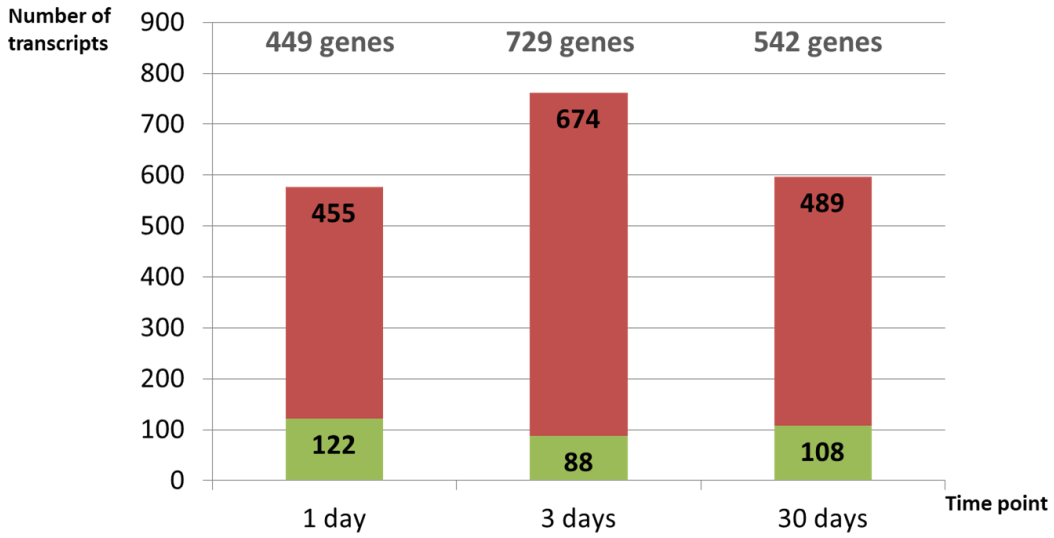


Figure 3.2. *Statistically significant changes in gene expression across the three time points of the study (1, 3, 30 days). 2-fold and 0.01 FDR thresholds, red=over-expressed probe sets, green=under-expressed probe sets*

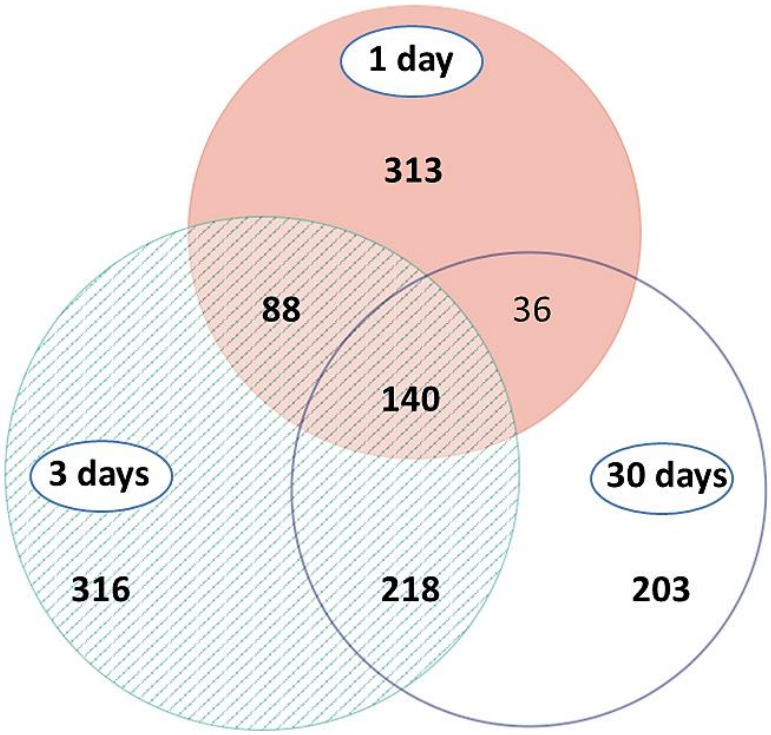


Figure 3.3. *Probe set expression change overlap between the three time points of the study (1, 3, 30 days). Over- and under-expressed probe sets are grouped together. Venn diagram designed with eulerAPE tool.*

3.1.2 Functional enrichment analysis: classification to Gene Ontologies

The lists of the significantly changed genes for each time point of the study were subjected to functional classification, according to the Gene Ontology (GO) categorization system. The analysis was performed using the tool “Mapping to ontologies” (geneXplain platform), with a statistical significance threshold $p<0.05$, as described in the Methods section (Chapter 2.2.4.1). The enriched GO terms for each of the three GO types of categories were identified, i.e. Biological Process (BP), Cellular Component (CC) and Molecular Function (MF). For the purposes of this study, the analysis was focused on the enriched Biological Process categories of each time point. The analysis resulted in the identification of the enriched BPs for all GO levels. In order to identify more specific biological functions that are overrepresented in our dataset, we focused on enriched upper level categories (level >5) (Methods, Chapter 2.2.4.1).

3.1.2.1. Time point: 1 day

The first step of the GO classification analysis through the geneXplain platform includes the conversion of the unique Affymetrix probe set IDs of the input list, to Ensembl gene IDs. 554 out of the 577 significantly changed probe sets were matched to their respective Ensembl gene IDs, and were included in the next steps of the analysis, that resulted in the identification of enriched GO Biological Processes. At the next level of the analysis, we focused on enriched Biological Processes that may be relevant to KA-MTLE manifestation and progression, and the accompanying histopathological symptoms, for each of the three time points of the study. These processes were selected due to their relevance to neuronal network development and function, and glial- and leukocyte-mediated immune and inflammatory responses, including oxidative stress mediated by NOX enzymes.

Enriched Biological Processes associated with neuronal network development and function at 1 day

Some of the most populated (>10 genes) upper level (>5) GO BP categories were related to CNS development, including neuron differentiation and

neurogenesis. In specific, at day post injection, several significantly genes were implicated in “positive regulation of neurogenesis” (↑Aspa, ↑Bcl11a, ↑Bdnf, ↑Bmp2, ↑Cdh4, ↑Clcf1, ↑Lif, ↑Sox11, ↑Tnfrsf12a), as well as “neuron projection development” (↑Areg, ↑Bdnf, ↑Btg2, ↑Cd44, ↑Gdnf, ↑Npy, ↑Tnc) and “regulation of neuron projection development” (↓Bcl11a, ↓Inpp5j, ↓Plk5, ↑Cdh4, ↑Klk6, ↑Lif, ↑Sphk1, ↑Spp1, ↑Tnfrsf12a, ↑Vim), four of which are implicated in “negative regulation of neuron projection development” (↓Bcl11a, ↓Inpp5j, ↑Spp1, ↑Vim). Moreover, BPs related to cytoskeletal organization appear enriched: “regulation of cytoskeleton organization” includes genes (↓Inpp5j, ↑Capg, ↑Cav1, ↑Clic4, ↑Ctgf, ↑Dlg1, ↑Edn1, ↑Efna5, ↑Nes, ↑Plek, ↑Tac1), with seven of them implicated specifically in the “positive regulation of cytoskeleton organization” (↑Cav1, ↑Ctgf, ↑Dlg1, ↑Edn1, ↑Nes, ↑Plek, ↑Tac1).

Other upper level enriched BPs that were related to neuronal-specific functions at that 1 day time point involved synaptic transmission. Specifically, nineteen genes were classified into “regulation of synaptic transmission”, with four of them implicated in “regulation of glutamatergic synaptic transmission” (↓Grm1, ↓Grm2, ↑Npy2r, ↑Ptgs2). In addition, six genes were categorized to the “regulation of neurotransmitter transport and secretion” (↓Grm2, ↑Gdnf, ↑Grm8, ↑Pdyn, ↑Sphk1) and another five in the BP “regulation of neuronal synaptic plasticity” (↓Bcan, ↑Arc, ↑Bdnf, ↑Egr2, ↑Vgf). Furthermore, the BP “neuropeptide signaling pathway” appeared enriched, with twelve genes (↓Npy2r, ↓Ntsr2, ↑Gal, ↑Galr1, ↑Gipr, ↑Glra2, ↑Npy, ↑Pdyn, ↑Penk, ↑Sorcs3, ↑Sstr2, ↑Tac1).

Enriched Biological Processes associated with glial development and function at 1 day

The glial-related enriched BPs included several categories implicated in regulation of glial cell proliferation, differentiation and migration. One of the upper level (>5) categories populated with more than 5 genes was “regulation of gliogenesis” (↑Bmp2, ↑Clcf1, ↑Lif, ↑Sox11, ↓Aspa) and “glial cell differentiation” (↑Egr2, ↑Fgf2, ↑Lif, ↑Stat3, ↑Vim). Interestingly, many glial-related genes were specifically categorized in astrocyte-related categories, i.e. “positive regulation of astrocyte differentiation” (↑Bmp2, ↑Clcf1, ↑Lif), “astrocyte differentiation” (↑Stat3, ↑Vim), “astrocyte cell migration” (↑Ccl2,

↑Ccl3), whilst none microglial-specific upper level category appeared to be enriched, under the conditions of this analysis.

Enriched Biological Processes associated with inflammatory and immune responses at 1 day

A wide range of upper level BPs related to immune and inflammatory responses was found to be enriched at 1 day. Specifically, “positive regulation of inflammatory response” was populated by eight genes (↑Ccl3, ↑Il33, ↑Osmr, ↑Pla2g4a, ↑Ptgs2, ↑Serpine1, ↑Tac1, ↑Tgm2) and “positive regulation of immune response” by thirteen genes. Interestingly, the significantly changed genes implicated in immune response regulation are sub-categorized into “regulation of adaptive immune response” (↑Cd44, ↑Clcf1, ↑Fcgr2b, ↑Hspa1b, ↑Il33, ↑Pvr) and “positive regulation of innate immune response” (↑Dusp4, ↑Fos, ↑Irf7, ↑Map2k3, ↑Mapkapk2, ↑Pvr, ↑Rps6ka3). Moving into more specific mechanisms, several BPs were related to leukocyte chemotaxis and migration. In specific, the enriched upper level BPs include “positive regulation of leukocyte chemotaxis” (↑C3ar1, ↑Ccl2, ↑Ccl3, ↑Cxcl10, ↑Edn1, ↑Serpine1, ↑Thbs1, ↑Thbs4), “positive regulation of neutrophil, macrophage, and granulocyte chemotaxis” (↑C3ar1, ↑Ccl2, ↑Edn1, ↑Thbs1), as well as “positive regulation of leukocyte migration” (↑C3ar1, ↑Ccl2, ↑Ccl3, ↑Cxcl10, ↑Edn1, ↑Serpine1, ↑Thbs1, ↑Thbs4). Moreover, the BP “phagocytosis” was also enriched (↑Ccl2, ↑Cd14, ↑Cd93, ↑Icam5, ↑Itgav, ↑Tgm2), with three of the genes implicated in “positive regulation of phagocytosis” (↑Fcgr2b, ↑Itgav, ↑Pros1).

Enriched Biological Processes associated with Reactive Oxygen Species at 1 day

The upper level enriched categories related to ROS include “response to reactive oxygen species” and specifically “response to hydrogen peroxide” (↑Areg, Dusp1, Fosl1, Hmox1, Pla2g4a, Sphk1). In addition, three more genes were associated with “superoxide metabolic process” (↑Cybb, Edn1, Sh3pxd2b) with the two of them specifically related to “superoxide anion generation” (↑Cybb, Edn1).

3.1.2.2. Time point: 3 days

The 762 significantly changed probe sets were matched to 771 Ensembl gene IDs, which were the input for the next steps of the GO classification analysis.

Enriched Biological Processes associated with neuronal network development and function at 3 days

At 3 days, no BPs related to neurogenesis and/or neuron differentiation appeared to be enriched unlike the 1 day time point. However, neuron projection development remains an enriched BP in the 3 day time point. Specifically, “regulation of neuron projection development” is represented by thirteen genes (↓Robo1, ↑Cd24a, ↑Grn, ↑Itgb1, ↑Klk6, ↑Lgals1, ↑Lyn, ↑Pmp22, ↑Rbpj, ↑Rhoc, ↑Spp1, ↑Tnfrsf12a, ↑Vim), five of which fall specifically under the subcategory “negative regulation of neuron projection development” (↑Lgals1, ↑Pmp22, ↑Rbpj, ↑Spp1, ↑Vim). There are only a few overlapping genes between 1 day and 3 day time points in these categories, and specifically ↑Klk6, ↑Spp1, ↑Tnfrsf12a and ↑Vim .

One of the most populated upper level categories with forty three genes is “cytoskeleton organization”. More specifically, “regulation of cytoskeleton organization” is populated by twice as many genes as at 1 day (22 genes), with only a few genes in common between time points. At 3 days, components of “regulation of cytoskeleton organization are classified in distinct upper level enriched categories: thirteen genes in “regulation of actin cytoskeleton organization” (↑Arpc1b, ↑Capg, ↑Ctgf, ↑Gpr65, ↑Hck, ↑Myo1f, ↑Nckap1l, ↑Nox4, ↑Plek, ↑Rhoc, ↑Sdc4, ↑Serpinf2, ↓Tac1) and eight genes in “regulation of microtubule cytoskeleton organization” (↑Cav1, ↑Ccnb1, ↑Cenpe, ↑Ckap2, ↑Ect2, ↑F630043A04Rik, ↑Racgap1, ↑Tpx2).

In comparison with the previous time point, less enriched upper level BPs related to other neuron specific functions are reported. Specifically, there are no synaptic function-related BPs, and there are less genes classified into the “neuropeptide signaling pathway” category (↑Cd97, ↑Ecel1, ↑Eltd1, ↑Emr1, ↑Gal, ↑Glra1, ↑Penk, ↑Sstr2, ↑Tac1) with three new genes changed at 3 days only (↑Cd97, ↑Ecel1, ↑Eltd1). On the other hand, “regulation of neuron

apoptosis" appears to be enriched in this time point (↑Axl, ↑C5ar1, ↑Ccl3, ↑Clcf1, ↑Egln3, ↑Gpx1, ↑Hmox1, ↑Itga1, ↑Lgmn, ↑Prkcc, ↑Rhoc).

Enriched Biological Processes associated with glial development and function at 3 days

The glia-related enriched upper level BPs at 3 days included "glial cell development" (↑Cd9, ↑Itgam, ↑Kcnj10, ↑Lyn, ↑Vim) and "glial cell migration" (↑Ccl2, ↑ Ccl3, ↑Hexb, ↑Tspo, ↑Vcan), with three of the genes specifically related to "astrocyte cell migration" (↑Ccl2, ↑Ccl3, ↑Hexb) and another two to "positive regulation of glial cell proliferation" (↑Lyn, ↑Tspo). Interestingly, the only upper level microglia-specific category that appears to be enriched at 3 days is "microglial cell activation" (↑Cx3cr1, ↑Tlr1, ↑Tlr2, ↑Tlr4, ↑Tlr7), whilst all five genes also fall under the BP "microglial cell activation involved in immune response".

Enriched Biological Processes associated with inflammation and immune responses at 3 days

All of the inflammation and immune response-related upper level categories described at 1 day ("inflammation", "innate and adaptive immune response", "leukocyte chemotaxis and migration", "phagocytosis"), were further enriched, whilst several new categories emerged as well. The new upper level enriched BPs include "positive regulation of leukocyte and mononuclear cell proliferation" with eighteen genes (↑Cd24a, ↑Cd74, ↑Cd86, ↑Cdkn1a, ↑Clcf1, ↑Csf1, ↑Fgf10, ↑Igfbp2, ↑Il13ra1, ↑Kitl, ↑Lyn, ↑Myd88, ↑Nckap1l, ↑Pnp, ↑Ptprc, ↑Tac1, ↑Tlr4, ↑Vcam1), "positive regulation of leukocyte mediated immunity" with nine genes (↑C3, ↑Cd24a, ↑Fcer1g, ↑Fcgr1, ↑Fcgr3, ↑H2-D1, ↑H2-K1, ↑Pnp, ↑Ptprc), "macrophage activation involved in immune response" with seven genes (↑Cx3cr1, ↑Sbno2, ↑Tlr1, ↑Tlr2, ↑Tlr4, ↑Tlr7, ↑Tyrobp5) and "complement activation, classical pathway" with six genes (↑C1qa, ↑C1qb, ↑C1qc, ↑C3, ↑Serping1).

Enriched Biological Processes associated with Reactive Oxygen Species at 3 days

In the 3 day time point, many more upper level enriched categories related to ROS and NOX are observed, in comparison with 1 day. The main categories

are “response to reactive oxygen species” and “positive regulation of reactive oxygen species metabolic process”, whilst the components of these categories are classified to subcategories according to the different ROS species involved in each one. Superoxide-specific categories include “superoxide anion generation” (↑Cyba, ↑Cybb, ↑Ncf1, ↑Nox4) that is populated exclusively by genes encoding for components of the NAPDH oxidase enzymic complex, and “regulation of removal of superoxide radicals” (↑Fbln5, ↑Nfe2l2). Hydrogen peroxide-related BPs included “cellular response to hydrogen peroxide” (↑Axl, ↑Cdk1, ↑Ect2, ↑Gpx1, ↑Gpx3), “hydrogen peroxide metabolic process” (↑Cyba, ↑Cybb, ↑Gpx1, ↑Gpx3, ↑Ncf1) and its subcategory “hydrogen peroxide biosynthetic process” (↑Cyba, ↑Cybb, ↑Ncf1).

3.1.2.3. Time point 30 days

The 597 significantly changed probe sets found at 30 days post injection were matched to 567 Ensembl gene IDs, which were included into the next steps of the GO classification analysis.

Enriched Biological Processes associated with neuronal network structure and function at 30 days

In contrast to the 3 days results, neurogenesis- and neuron differentiation-related upper level BPs appeared to be enriched at 30 days. The BP “regulation of neurogenesis” consists of nineteen genes, seven of which were specifically implicated in “negative regulation of neurogenesis” (↓Slit1, ↑Adcyap1, ↑Bdnf, ↑Lrrk2, ↑Sema3a, ↑Spp1, ↑Tgfb1).

Neuron projection development remains an enriched BP at 30 days. Specifically, “regulation of neuron projection development” is represented by fifteen genes (↓Robo1, ↓Slit1, ↓Epha3, ↓Islr2, ↓Plk5, ↓Camk1d, ↑Adcyap1, ↑Gfap, ↑Grn, ↑Klk6, ↑Lrrk2, ↑Lyn, ↑Sema3a, ↑Spp1, ↑Vim), six of which are implicated in the “positive regulation of neuron projection development” (↓Camk1d, ↓Epha3, ↓Plk5 ↑Adcyap1, ↑Grn, ↑Lyn), in contrast to the 3 day time point, where the “negative regulation of neuron projection development” was enriched instead. Only a few genes in these categories overlapped between the 3 day and 30 day time points (↓Robo1, ↑ Grn, ↑Klk6, ↑Lyn, ↑Spp1, ↑Vim).

At 30 days, the enriched upper level BPs related to the cytoskeletal changes are decreased compared to the 3 day time point, and are more reminiscent of the 1 day time point, in terms of the number of genes included. Specifically, “regulation of cytoskeleton organization” includes fourteen genes, the thirteen of which are more specifically classified as related to the “regulation of actin cytoskeleton organization”(↑Arhgap6, ↑Arpc1b, ↑Capg, ↑Csf1r, ↑Ctgf, ↑Efna5, ↑Epha3, ↑Gpr65, ↑Myo1f, ↑Nckap1l, ↑Plek, ↑Serpinf2, ↓Tac1) Interestingly, this category shares nine genes with the previous time point, with Hck, Nox4, Rhoc, Sdc4 changed only at 3 days, and Arhgap6, Csf1r, Efna5, Epha3 changed only at 30 days.

In contrast to the previous time point, many synaptic transmission- related changes are observed at 30 days. Specifically, twelve genes are categorized into the upper level BP “regulation of synaptic transmission” (↓Grm1, ↓Nos1, ↓Drd5, ↓Npy2r, ↑Tac1, ↑Htr2a, ↑Adcyap1, ↑Bdnf, ↑Gfap, ↑Htr2c, ↑Pdyn, ↑Vgf), whilst four of them are specifically implicated in “regulation of glutamatergic synaptic transmission” (↓Grm1, ↓Npy2r, ↑Adcyap1, ↑Htr2a,). The “neuropeptide signaling pathway” category remains changed, and is populated by twelve genes (↓Tac1, ↓Npy2r, ↓Lphn2,↑Adcyap1, ↑Cartpt, ↑Emr1, ↑Hcrtr2, ↑Nmbr, ↑Pdyn, ↑Penk, ↑Sorcs2, ↑Sorcs3) with only three common genes between the two time points (↑Emr1, ↑Penk, ↑Tac1).

Glia

“Glial cell development” remains an enriched upper level category since 3 days’ time point, represented by mostly the same genes with the exception of astrocyte marker Gfap (↑Cd9, ↑Gfap, ↑Itgam, ↑Lyn, ↑Vim). Most of the glial-related BPs described at 3 days are also represented by a few genes only in this time point: “positive regulation of glial cell proliferation” (↑Gfap, ↑Lyn), “astrocyte development and differentiation” (↑Gfap, ↑Vim), “astrocyte cell migration” (↑Ccl3, ↑Hexb), “microglial cell activation involved in immune response” (↑Cx3cr1, ↑Tlr1, ↑Tlr2, ↑Tlr7).

Inflammation and immune response

All of the inflammation and immune response categories described at 1 and 3 days remain enriched at 30 days post injection. According to these data, both inflammatory and innate and adaptive immune responses remain activated and the processes of “leukocyte chemotaxis”, “macrophage chemotaxis”, “neutrophil chemotaxis” “leukocyte migration”, “macrophage migration” and “neutrophil migration” persist, along with “phagocytosis”, which is further enriched. Interestingly, one of the BPs that showed significant increase in the number of genes is the “complement activation classical pathway” which is now represented by nine genes (↑C1qa, ↑C1qb, ↑C1qc, ↑C1ra, ↑C1rb, ↑C1s, ↑C4b, ↑Serping1), five of which are in common with the previous time point (↑C1qa, ↑C1qb, ↑C1qc, ↑C3, ↑Serping1).

NOX-ROS

In the 30 day time point, most of the NOX and ROS related categories observed at 3 days are populated with far less genes. The only upper level GO Biological Process enriched category is “regulation of reactive oxygen species metabolic process” (↑Fbln5, ↑Nfe2l2, ↑Rac2, ↑Tgfbr2, ↑Thbs1), whilst both “superoxide anion generation” and “hydrogen peroxide biosynthetic process” are represented by the same NOX genes (↑Cyba, ↑Cybb, ↑Ncf1), and “regulation of removal of superoxide radicals” (↑Fbln5, ↑Nfe2l2) remains exactly as reported at 3 days.

3.1.3 Ingenuity Pathway Analysis: Significantly changed Canonical Pathways

The lists of significantly changed genes for the three time points of the study (1, 3, 30 days) were subjected to “Core Analysis” via Ingenuity Pathway Analysis (IPA) software, as previously described in Methods section (Chapter 2.2.4.2).

3.1.3.1. Time point: 1 day

At 1 day post-injection, the analysis was applied to the list of 577 significantly changed probe sets. 432 of the 577 probe sets were successfully annotated, and subsequently mapped to known molecular pathways registered in IPA knowledge database (“Canonical pathways”). Core Analysis mapped the analyzed genes to 72 significantly changed Canonical pathways ($p<0.05$), populated with one to eighteen genes each (Appendix 4), Accordingly, the Canonical Pathway populated by the greatest number of genes is “G-Protein Coupled Receptor Signaling” (Grm2, Htr1a, Rgs7, S1pr3, Grm3, Adcy1, Stat3, Htr2b, Dusp1, Pde7b, Rgs2, Grm1, Pde6b, Grm8, Rgs4, Dusp4, Adra1a, Prkar2a) (Figure 3.4), and is followed by “cAMP-mediated signaling” with 15 genes (Grm2, Htr1a, Rgs7, S1pr3, Grm3, Adcy1, Stat3, Dusp1, Pde7b, Rgs2, Pde6b, Grm8, Rgs4, Dusp4, Prkar2a) (Figure 3.5).

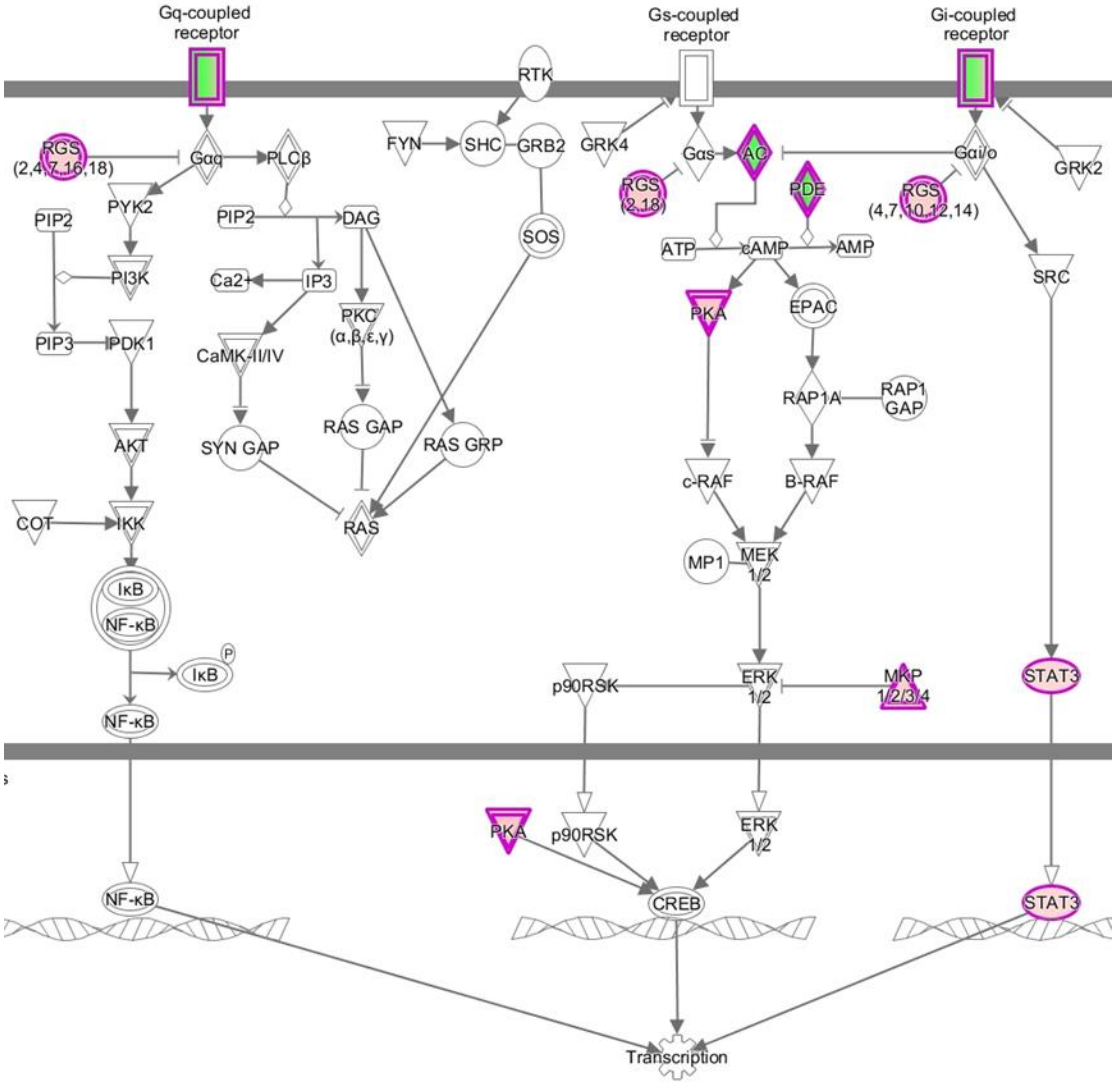
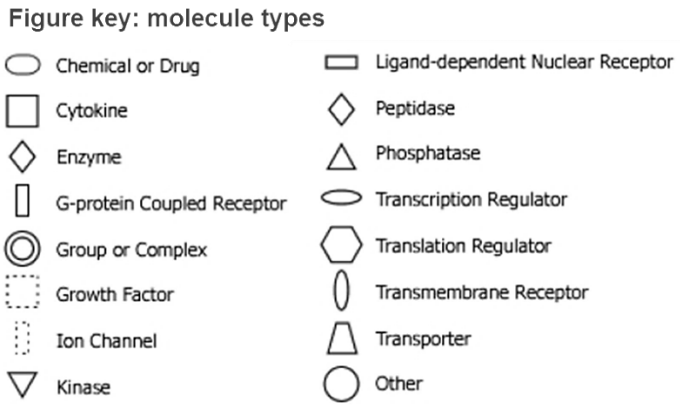


***Figure 3.4**. G-Protein Coupled Receptor Signaling Canonical Pathway at 1 day post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill=overexpression, green fill=overexpression).*



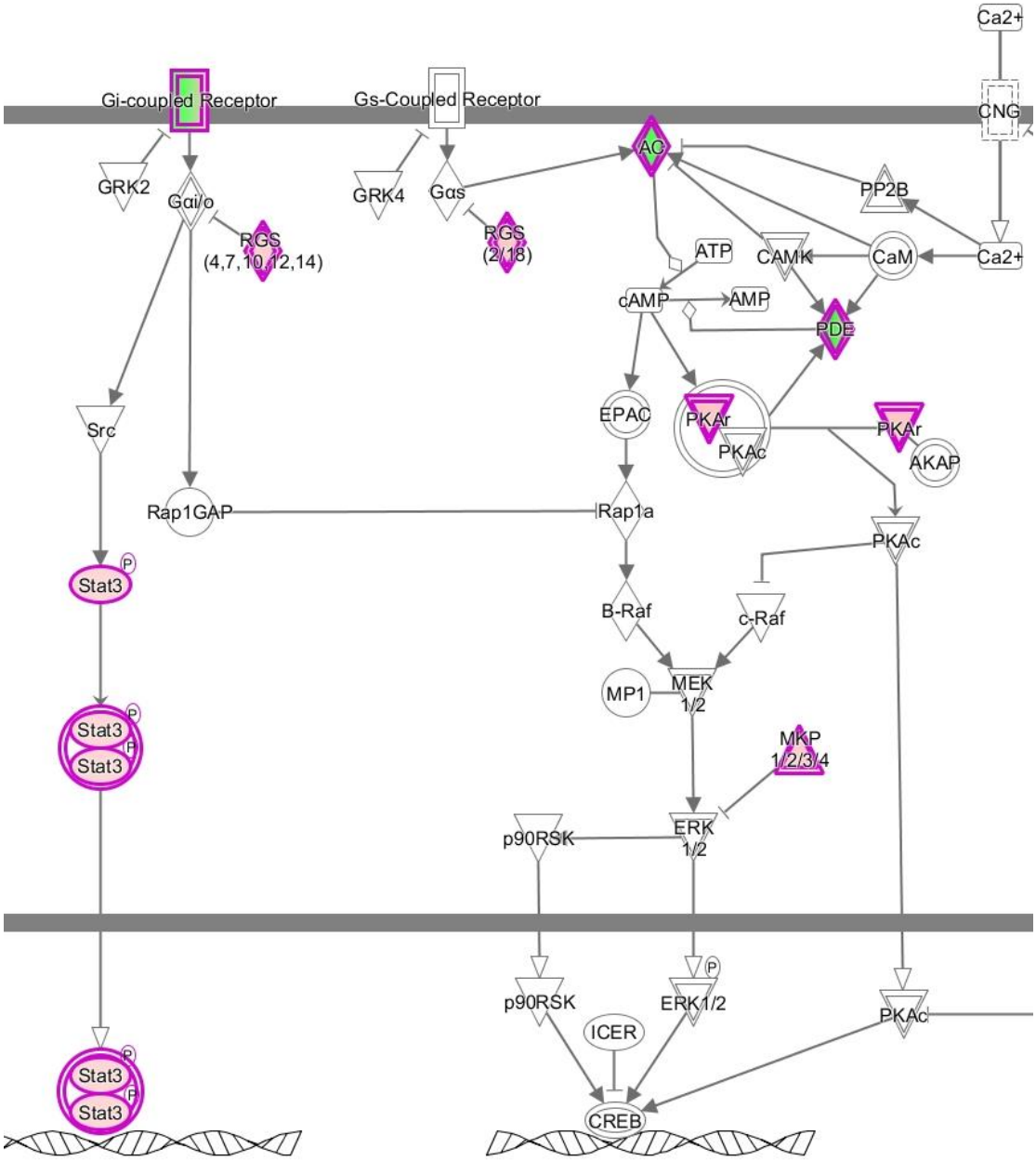


Figure 3.5. *cAMP-mediated signaling Canonical Pathway at 1 day post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill=overexpression, green fill=overexpression).*

The top significantly changed Canonical Pathway as determined by p-value, is “IL-10 Signaling” (Figure 3.6). It encompasses ten significantly changed genes (Fos, Stat3, Fcgr2b, Socs3, Cd14, Blvrb, Map2k3, Hmox1, Il33). Interestingly, several other immune and inflammatory-response-related pathways were found to be significantly changed at 1 day as well (Figure 3.7). Specifically, these include interleukin signaling pathways such as the pro-inflammatory “IL-6 signaling” pathway which is populated by eight genes (↑Fos, Hspb1, Stat3, Socs3, Cd14, Map2k3, Il33, Mapkapk2) (Figure 3.8), and “Il-17 signaling” encompassing six significantly changed genes (↑Cxcl10, Ccl2, Ptgs2, Map2k3, Timp1, Mapkapk2). Other cell-specific functions include “Granulocyte Adhesion and Diapedesis” (↓Cldn10, ↑Ccl2, Hspb1, Cxcl10, C5ar1, Ccl2, Ccl9, Msn, Ccl3l3, Itga5, Il33) and “Phagosome Formation” (↑Fcgr2b, Plce1, Msr1, Fcrls, Rhoj, Rnd3, Itga5, Fcgr3a/Fcgr3b).

Amongst the top Canonical pathways there were multiple G-protein associated molecular pathways, in line with the functional classification results for this time point. Specifically, besides “G-Protein Coupled Receptor Signaling” (Figure 3.4), these pathways include “Gαi Signaling” (↑S1pr3, Grm8, Rgs7, Prkar2a, Rgs4, Stat3, Cav1, ↓ Grm3, Grm2, Adcy1, Htr1a), “Gαq Signaling” (Htr2b, Rgs7, Arhgef25, Rgs2, Grm1, Rgs4, Rhoj, Hmox1, Rnd3, Adra1a), “Glutamate Receptor Signaling” (↑Grm8, ↓Grm1, Grm2, Grm3, Homer2) (Figure 3.9) and “Synaptic Long Term Potentiation” (↑Grm8, Prkar2a, Plce1, ↓Grm1, Grm2, Grm3, Adcy1).

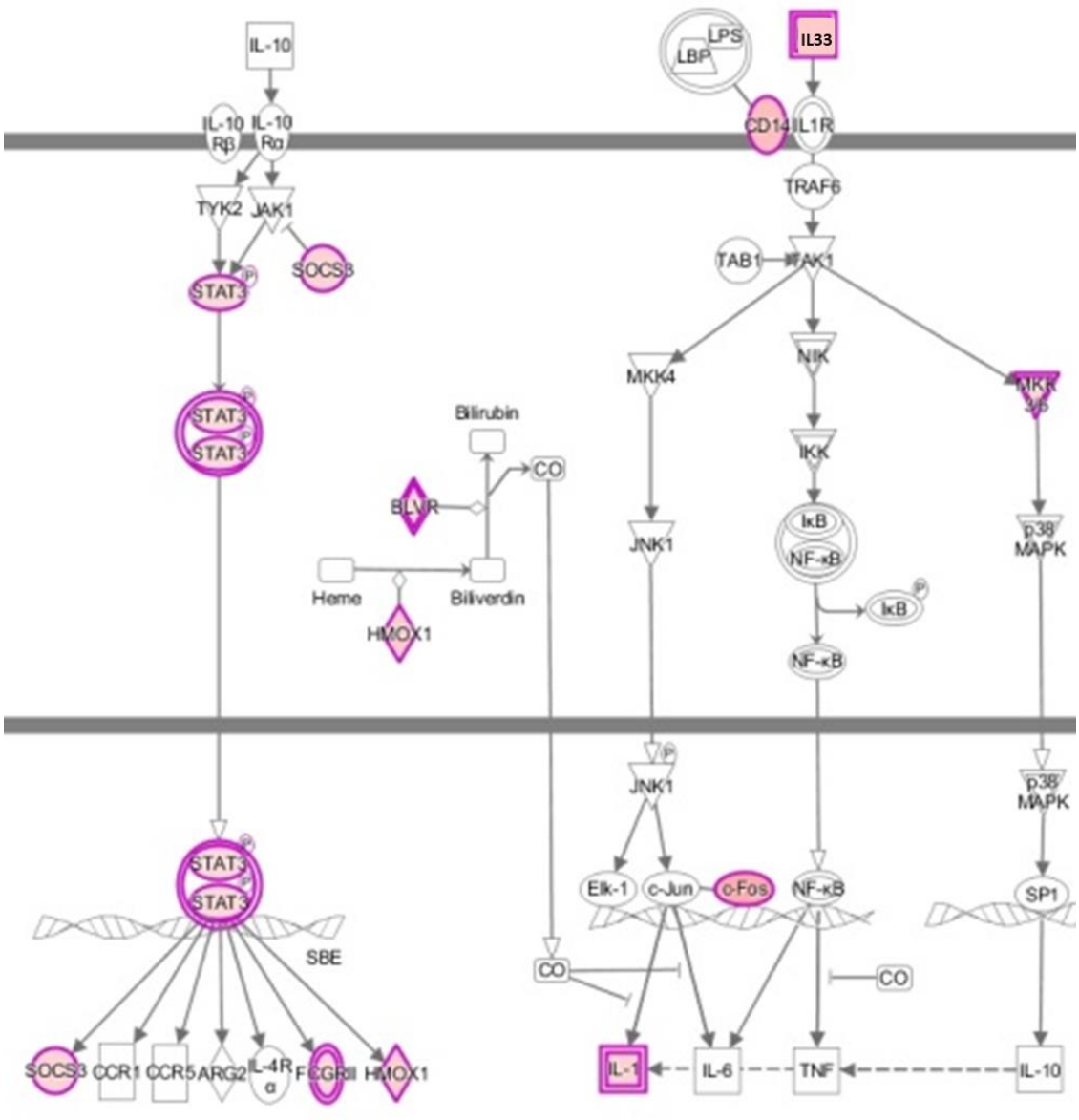


Figure 3.6. *IL-10 Canonical Pathway at 1 day post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill=overexpression).*

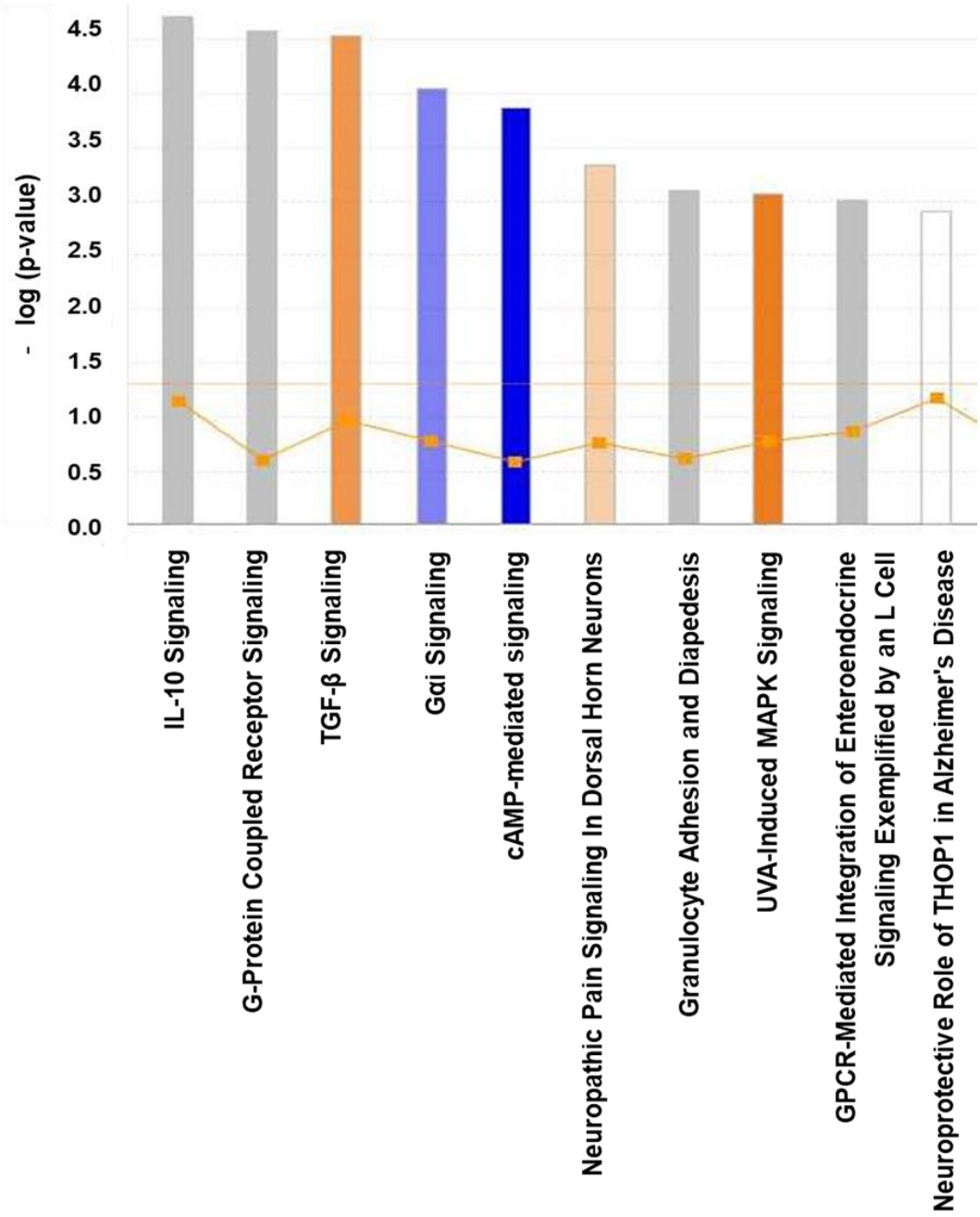


Figure 3.7. *Top 10 statistically significant changes in Canonical pathways at 1 day post injection, according to Ingenuity Pathway Analysis. The pathways are ranked by descending –log (p-value) (y-axis), the threshold of statistical significance (p-value<0.05) is marked by the horizontal yellow line.The yellow square inside each bar represents the ratio of the number of the genes in the list mapped to a pathway to the total number of genes that are included in the pathway, according to IPA software.*

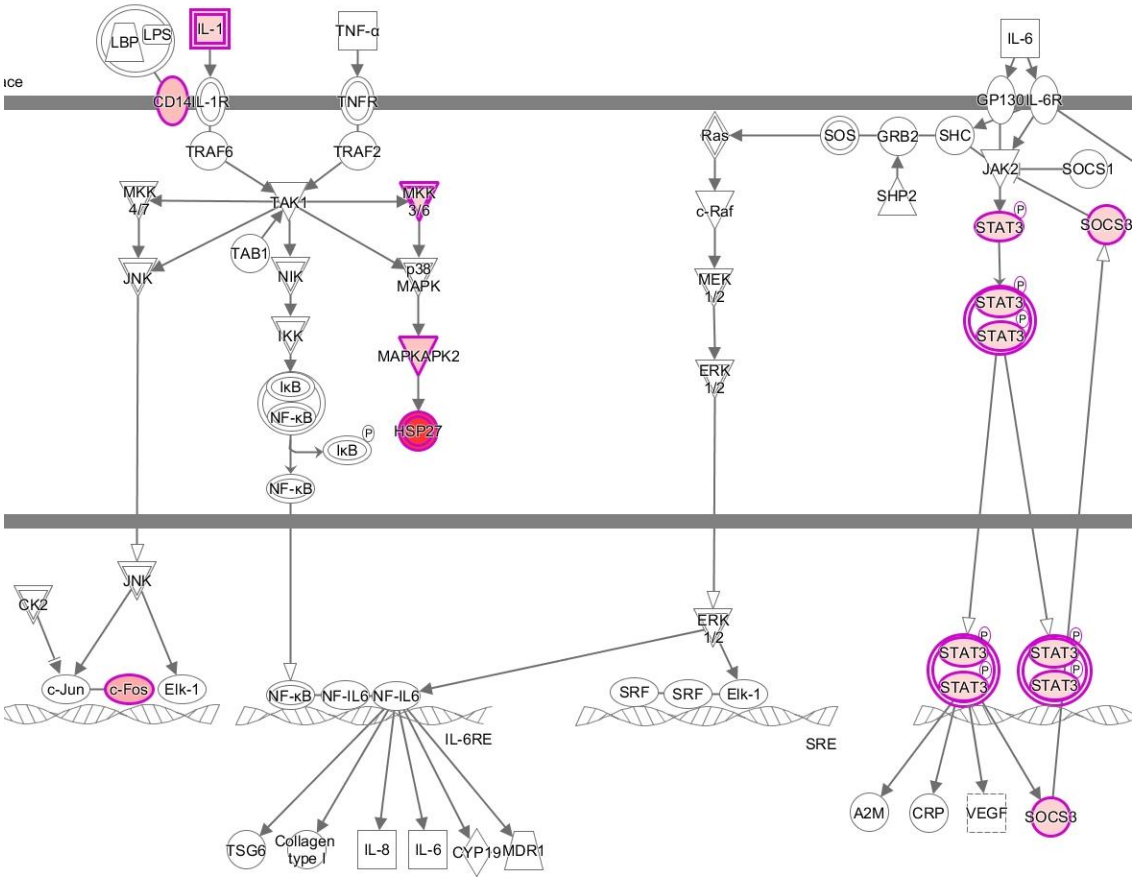


***Figure 3.8**. IL-6 Canonical Pathway at 1 day post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill=overexpression).*

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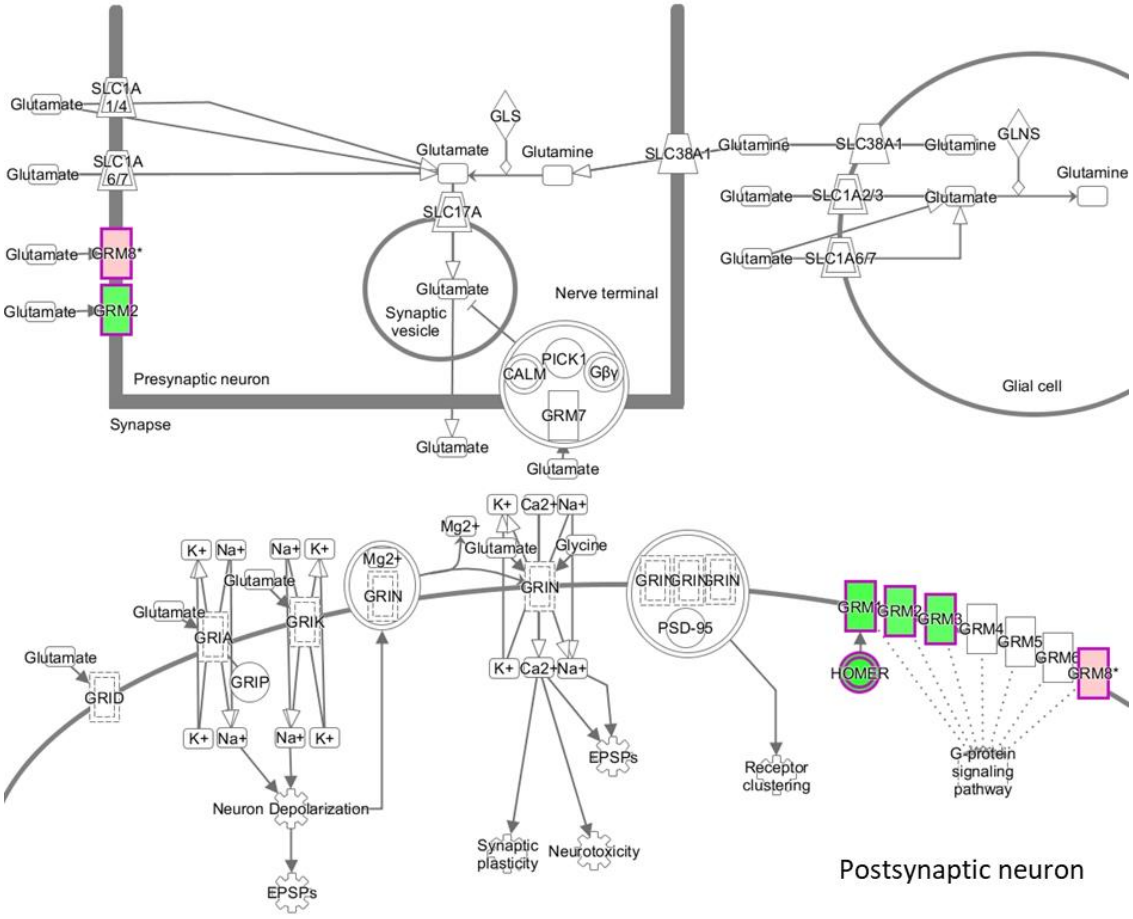
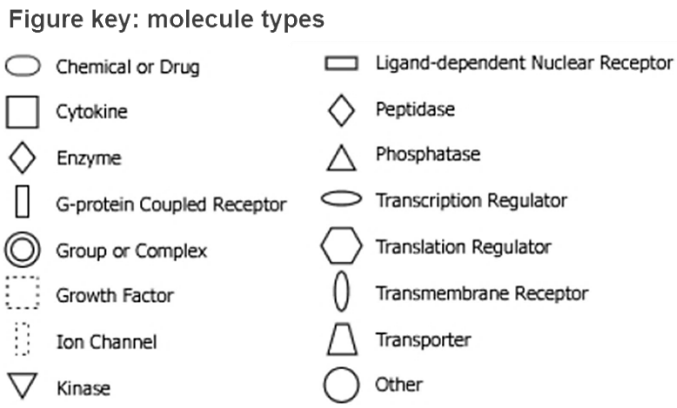


***Figure 3.9**. Glutamate Receptor Signaling Canonical Pathway at 1 day post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill=overexpression green fill= overexpression).*



3.1.3.2. Time point: 3 days

In the intermediate time point of our study on the KA-MTLE mouse model, at 3 days post-injection, 732 of the 762 probe sets were successfully annotated and included in the analysis. According to IPA “Core Analysis”, 128 significantly changed pathways were identified (Appendix 5). The Canonical Pathway with greatest number of genes is “Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis” with twenty four significantly changed genes (Myd88, Socs3, Tnfrsf1a, Fcgr1a, Tlr1, Plce1, Fgf2, Il16, Vcam1, Mapkapk2, Pik3cg, Tlr4, Stat3, Fn1, C5ar1, Ccnd1, Ccl2, Csf1, Tlr13, Rras, Tlr2, Il33, Prkcg, Fcgr3a/Fcgr3b), followed by “Leukocyte Extravasation Signaling” with twenty two genes (Itgam, Jam2, F11r, Itga6, Ncf1, Ezr, Msn, Timp4, Itgb2, Rac2, Cd44, Vav1, Vcam1, Pik3cg, Itga1, Mmp19, Itgb1, Timp1, Cybb, Itga5, Cyba, Prkcg) (Figure 3.10) and “Phagosome formation” with twenty genes (Fcgr1a, Tlr1, Rhoc, Plce1, Msr1, Fcer1g, Fcrls, Rhoj, Fcgr2a, Pik3cg, Tlr4, Fn1, Fcgr2b, Inpp5d, Itgb1, Tlr13, Itga5, Tlr2, Clec7a, Prkcg, Fcgr3a/Fcgr3b) (Figure 3.11).

Interestingly, the top significantly changed IPA Canonical Pathways based on p-value at 3 days include mostly inflammatory-and immune response- related pathways (Figure 3.12), that share multiple genes and are also amongst the pathways with the largest number of genes in this time point.

Specifically, the top pathway is “Phagosome formation” (Figure 3.10), followed by the “Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses” (Eif2ak2, Oas1, C3, Myd88, Tlr1, C1qb, Ddx58, C3ar1, Oas1b, C1qa, Pik3cg, Tlr4, C1qc, Irf7, C5ar1, Ifih1, Tlr2, Clec7a, Ptx3, Prkcg) (Figure 3.13), and “Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes” (Hck, Fcgr1a, Ncf1, Ezr, Fyb, Pld4, Rac2, Arpc1b, Hmox1, Vav1, Fcgr2a, Pik3cg, Lcp2, Inpp5d, Prkcg, Lyn, Fcgr3a/Fcgr3b) (Figure 3.s 14, 15). “TREM1 Signaling” follows with fifteen significantly changed genes (Myd88, Tlr1, Naip1 , Tlr4, Lat2, Stat3, Fcgr2b, Itgb1, Tyrobp, Ccl2, Tlr13, Itga5, Tlr2, Cd86), while ten genes are mapped to “Complement System” pathway (Itgam, C1qc, C3, C5ar1, C1qb, Itgb2, Serping1, Cfh, C3ar1, C1qa) (Figure 3.16).

“Dendritic Cell Maturation” is the sixth most changed pathway, populated by twenty genes (Myd88, Tnfrsf1a, Hla-Dqa1, Hla-Dqb1, Fcgr1a, Plce1, Fcer1g, Trem2, Fcgr2a, Pik3cg, Tlr4, Irf8, Hla-A, Fcgr2b, Stat1, Tyrobp, Tlr2, Cd86, Il33, Fcgr3a/Fcgr3b), and is followed by “Granulocyte Adhesion and Diapedesis” with twenty genes (Ccl2, Itgam, Tnfrsf1a, Cxcl10, Itga6, Ezr, Msn, Itgb2, Ccl3l3, Vcam1, Hspb1, Itga1, Mmp19, C5ar1, Itgb1, Ccl2, Cxcl16, Sdc4, Itga5, Il33) (Figure 3.17), and “Caveolar-mediated Endocytosis Signaling” with thirteen genes (Itgam, Itgb5, Itgav, Flna, Itga6, Cd48, Itgb2, Cav1, Itga1, Hla-A, Itgb1, Flnc, Itga5). “Acute Phase Response Signaling “ follows with twenty genes (Tf, C3, Myd88, Socs3, Tnfrsf1a, Serpinf1, Cp, Rbp1, Serpina3, Hmox1, Pik3cg, Osmr, A2m, Stat3, Fn1, Serpinf2, Serpine1, Serping1, Rras, Il33) (Figure 3.18), and “Agranulocyte Adhesion and Diapedesis” is the tenth most significantly changed pathway, with twenty genes (Ccl2, Tnfrsf1a, Cxcl10, Itga6, Ezr, Msn, Myl9, Itgb2, Ccl3l3, Vcam1, Itga1, Fn1, Mmp19, C5ar1, Itgb1, Ccl2, Cxcl16, Sdc4, Itga5, Il33). Interestingly, eighteen of these genes are also mapped to “Granulocyte Adhesion and Diapedesis” (Ccl2, Tnfrsf1a, Cxcl10, Itga6, Ezr, Msn, Itgb2, Ccl3l3, Vcam1, Hspb1, Itga1, Mmp19, C5ar1, Itgb1, Cxcl16, Sdc4, Itga5, Il33).

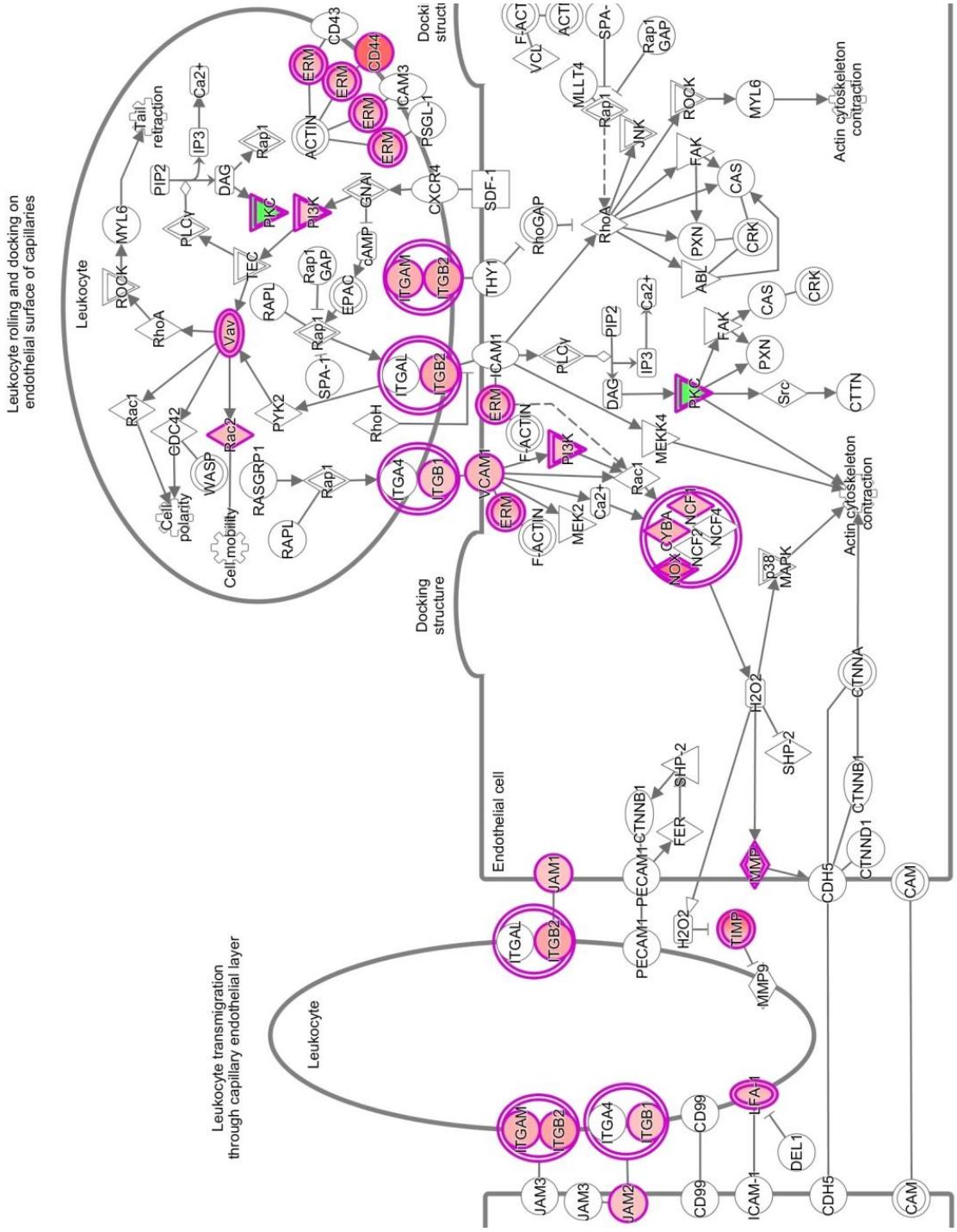


Figure 3.10 *.Leukocyte extravasation signaling Canonical Pathway at 3 days post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill= overexpression, green fill=underexpression).*

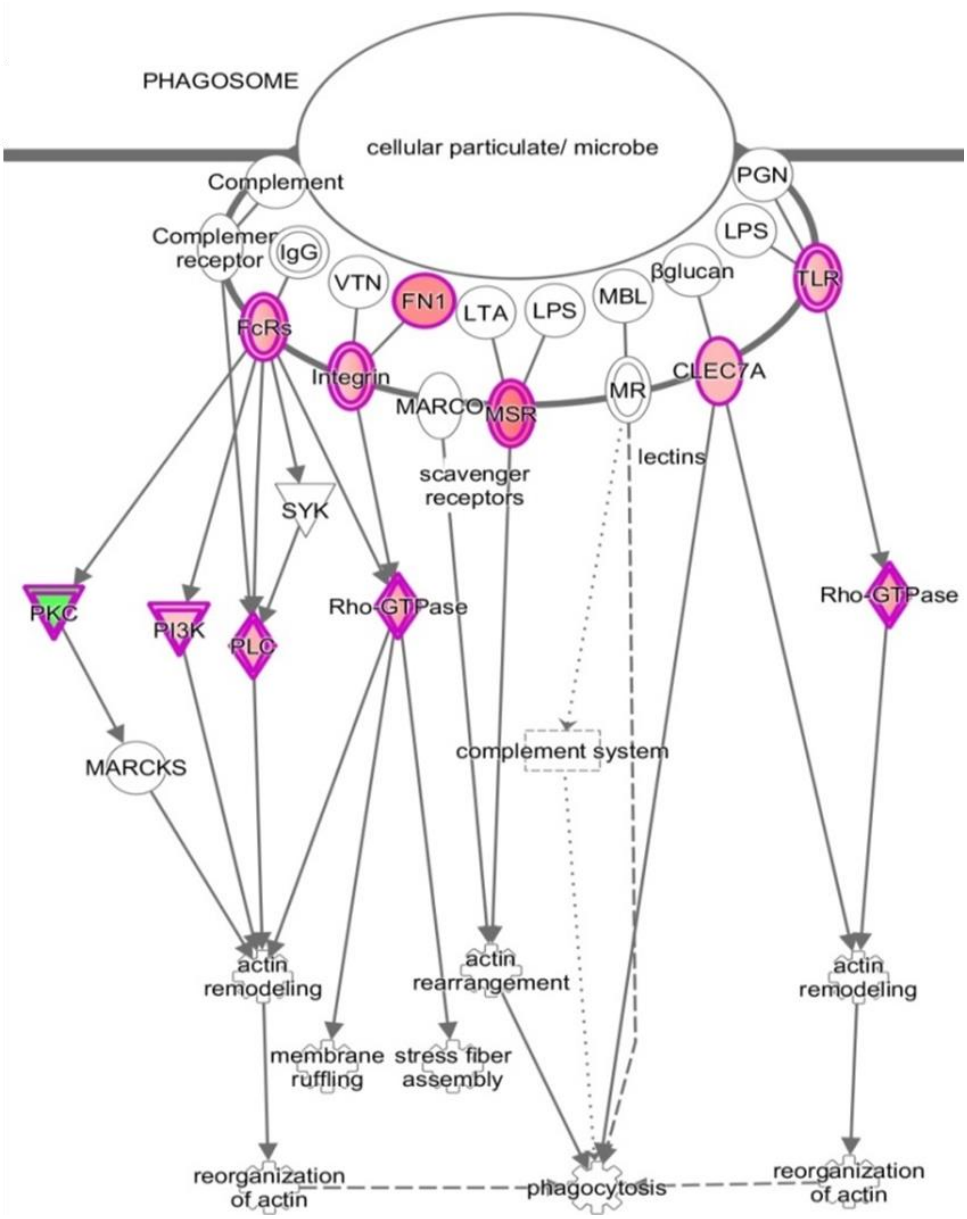
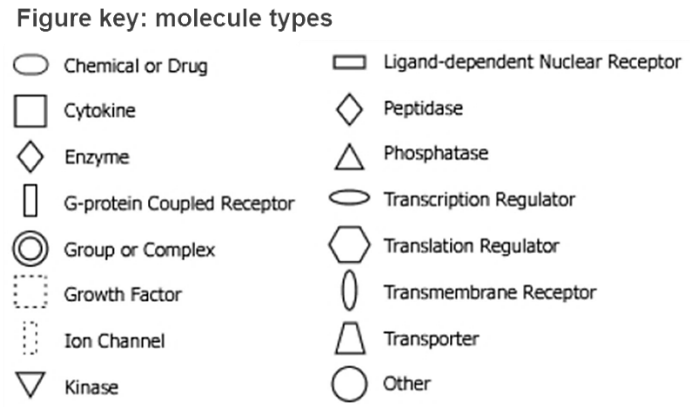


Figure 3.11. *.Phagosome formation Canonical Pathway at 3 days post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill= overexpression, green fill=underexpression).*



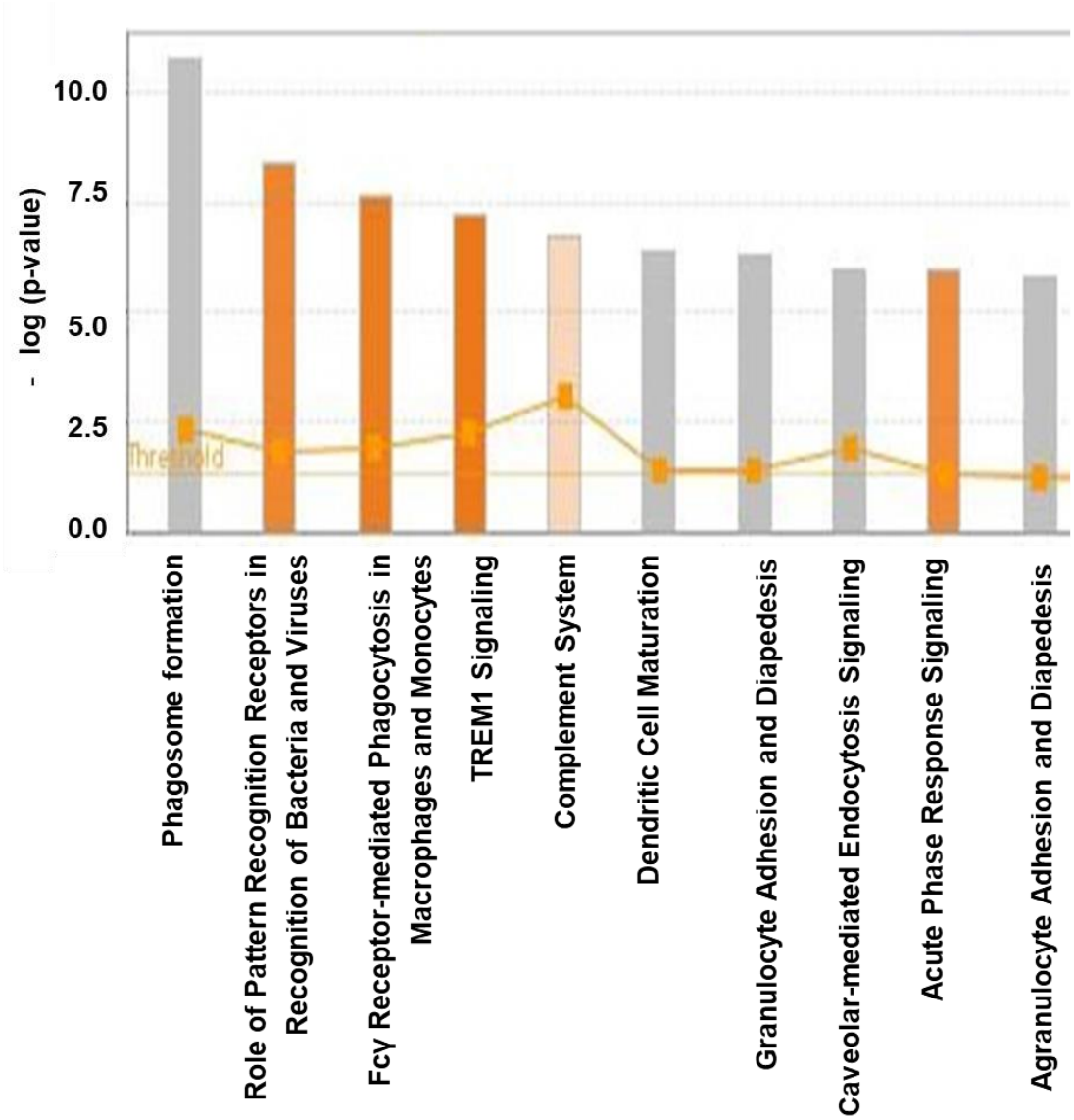


Figure 3.12. *Top 10 statistically significant changes in Canonical pathways at 3 days post injection, according to Ingenuity Pathway Analysis. The pathways are ranked by descending –log (p-value) (y-axis), the threshold of statistical significance (p-value<0.05) is marked by the horizontal yellow line.The yellow square inside each bar represents the ratio of the number of the genes in the list mapped to a pathway to the total number of genes that are included in the pathway, according to the IPA software.*

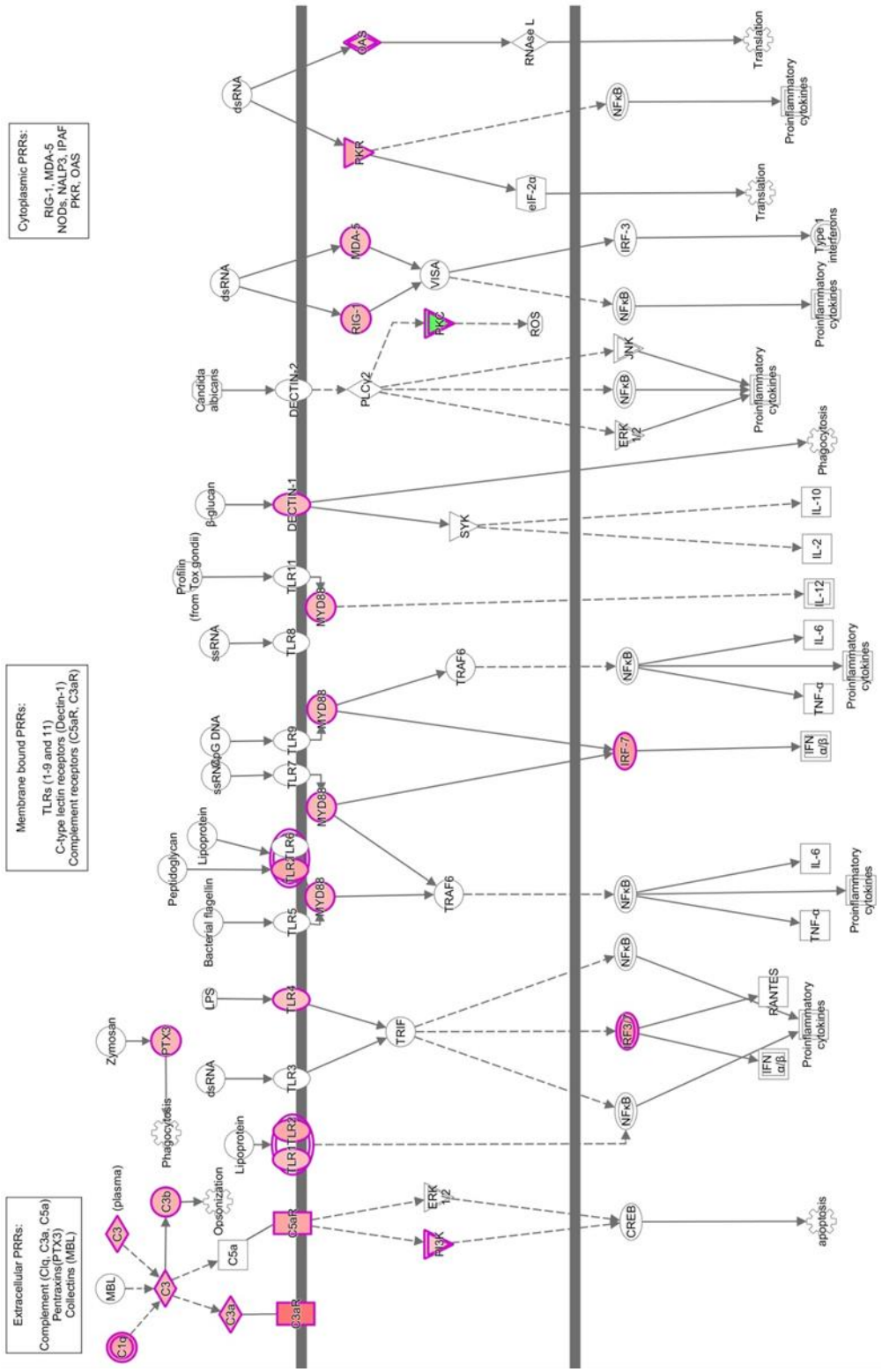


***Figure 3.13**. Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses Canonical Pathway at 3 days post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill= overexpression, green fill=underexpression).*

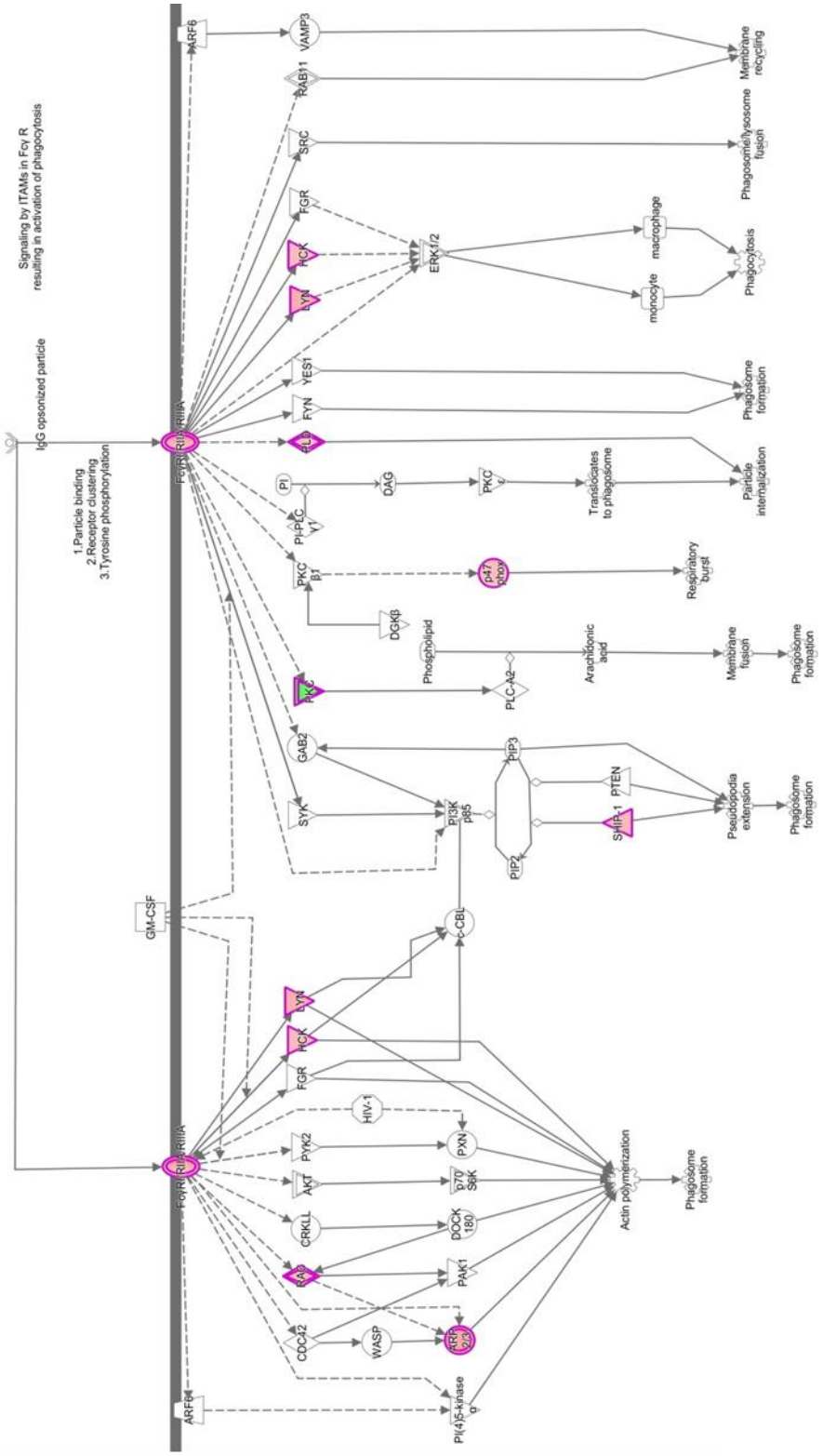


Figure 3.14. *Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes Canonical Pathway at 3 days post injection (part 1/2).Image generated via IPA software (bold outline=gene with significantly changed expression, red fill= overexpression, green fill=underexpression).*

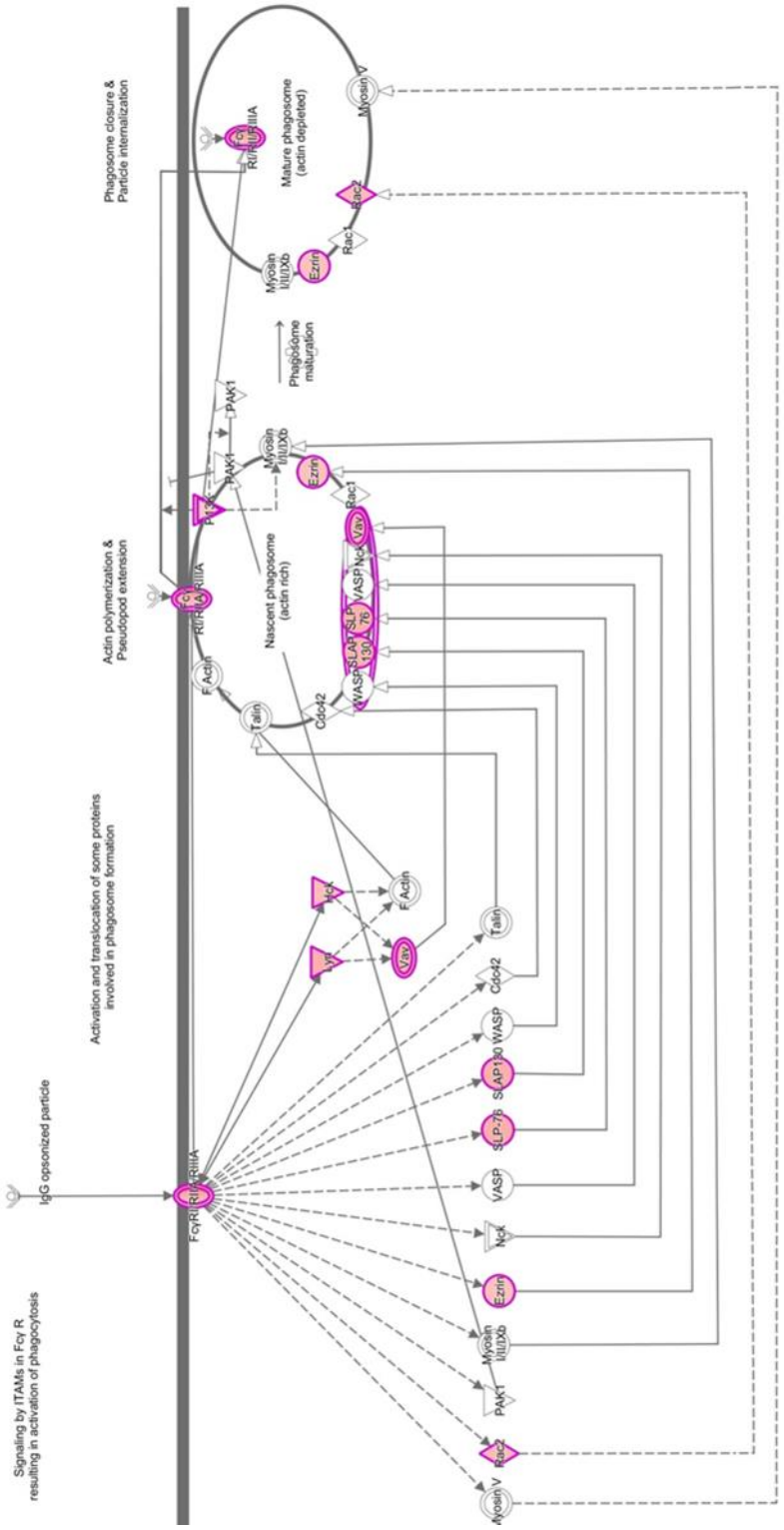


Figure 3.15. *Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes Canonical Pathway at 3 days post injection (part 2/2).Image generated via IPA software (bold outline=gene with significantly changed expression, red fill= overexpression, green fill=underexpression).*

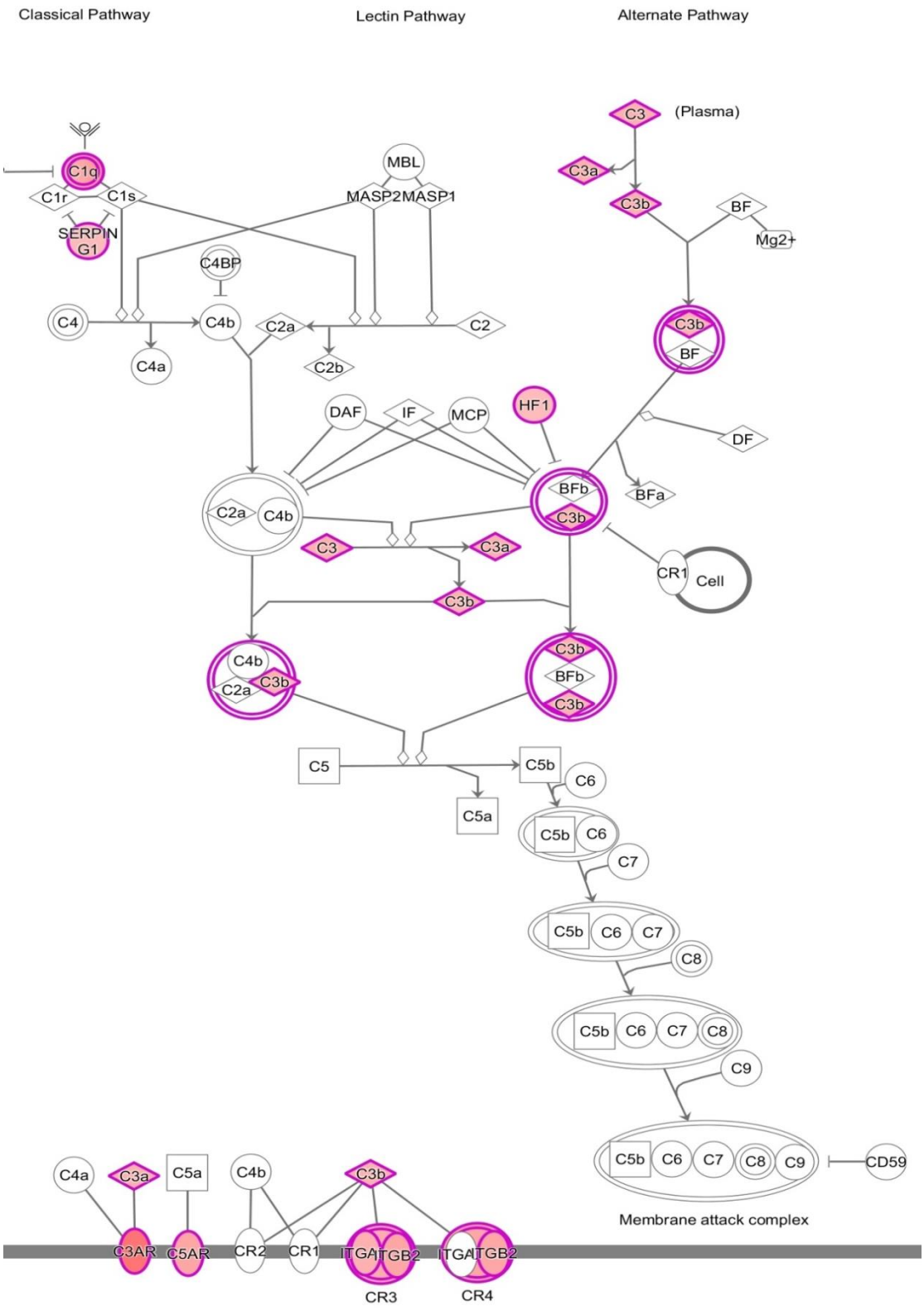


Figure 3.16. *Complement system Canonical Pathway at 3 days post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill= overexpression).*

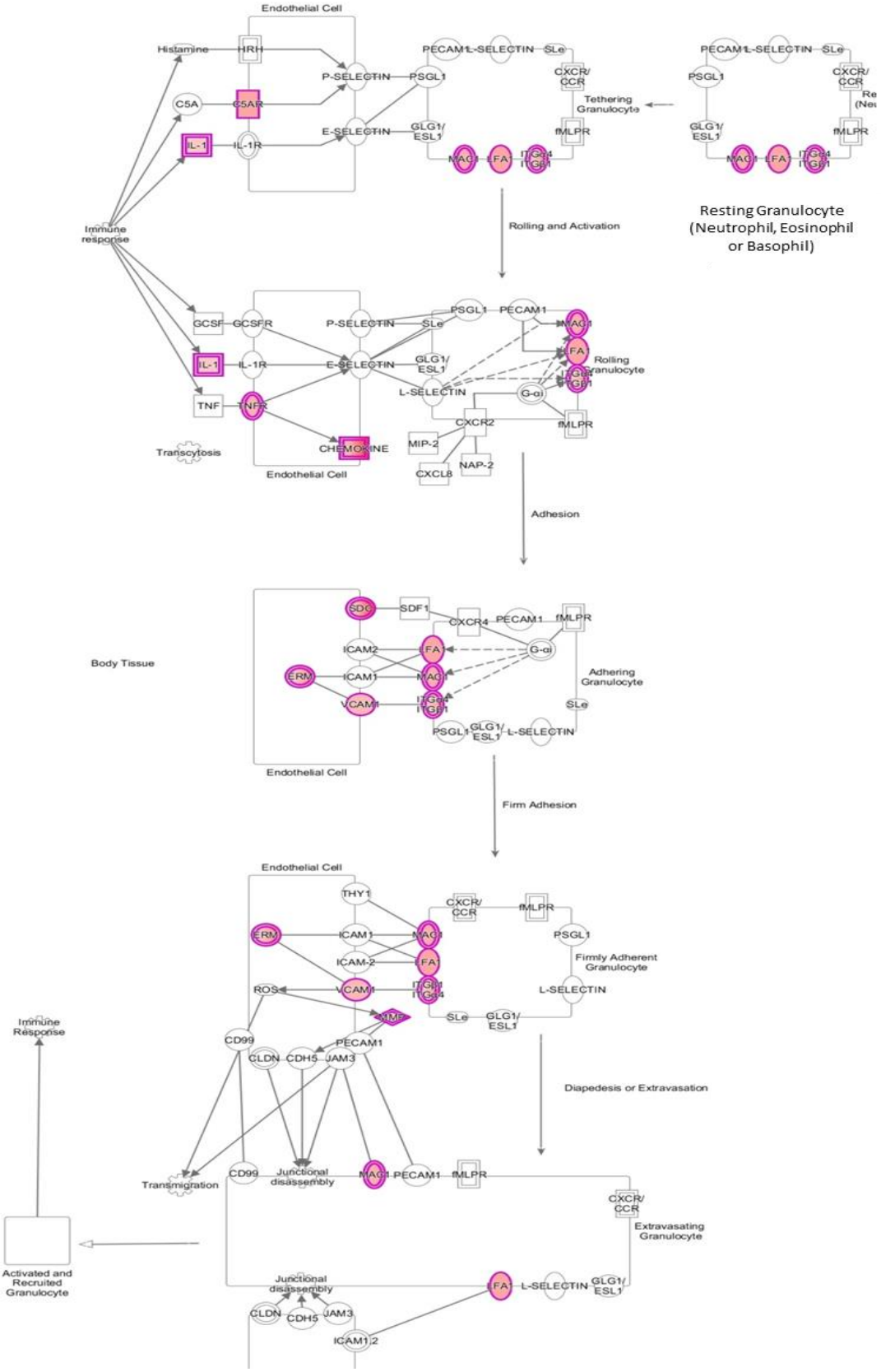


Figure 3.17. *Granulocyte Adhesion and Diapedesis Canonical Pathway at 3 days post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill= overexpression).*

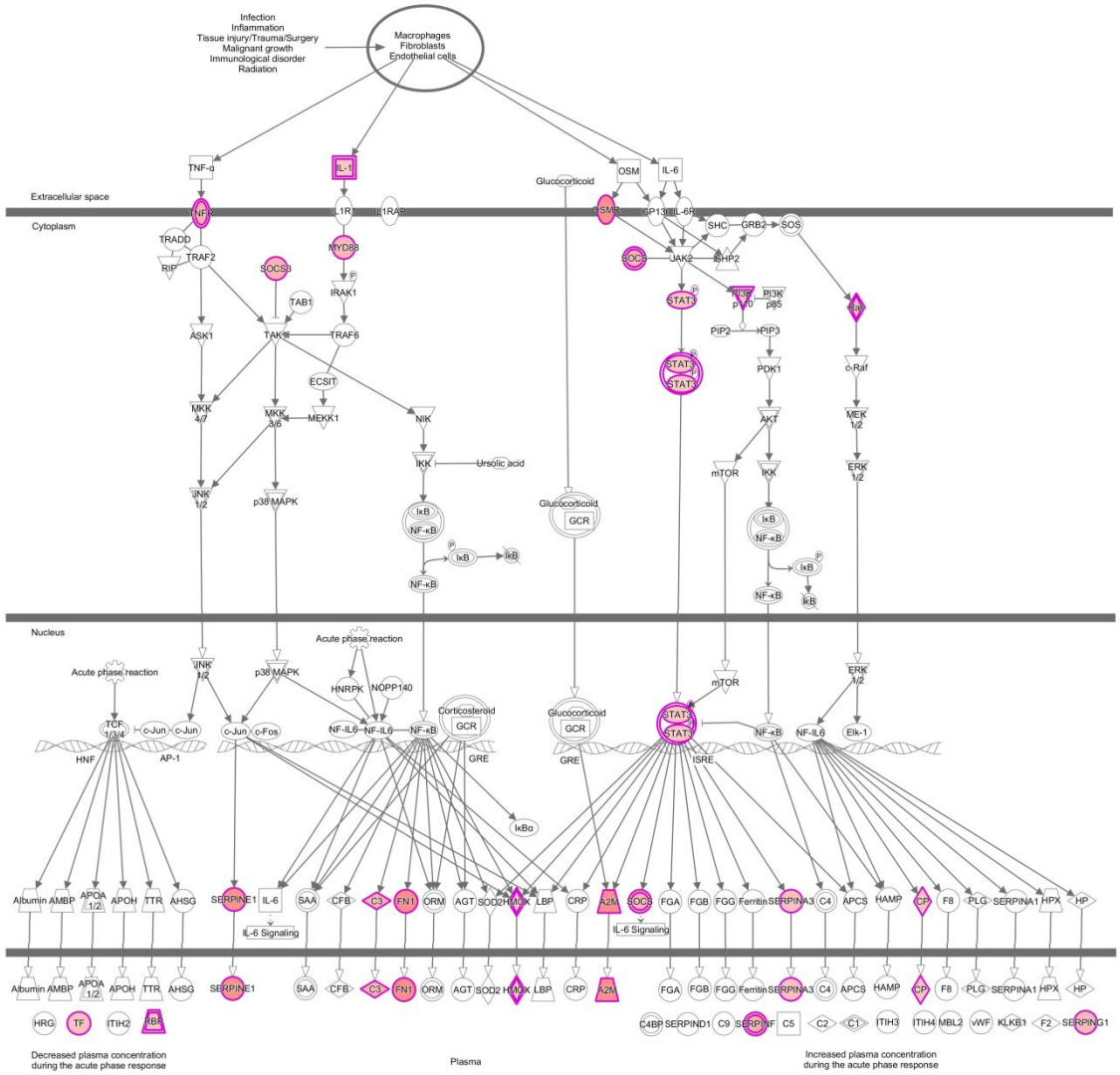
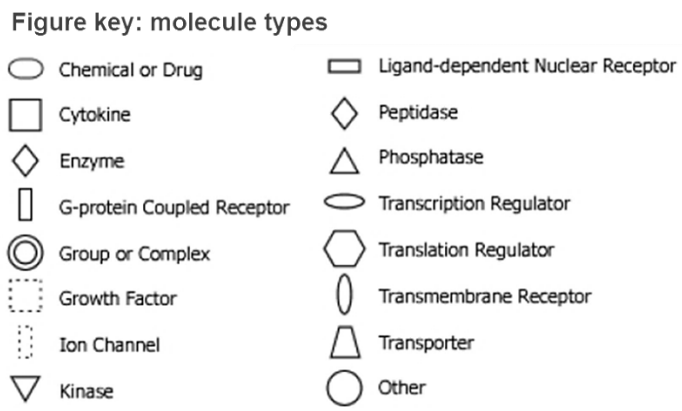


Figure 3.18. *Acute Phase Response Signaling Canonical Pathway at 3 days post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill= overexpression).*



3.1.3.3.Time point 30 days

At 30 days post-injection, IPA “Core analysis” was applied on the list of 597 significantly changed probe sets, resulting in the successful annotation of 561 of them, which were included in the next steps of the analysis, resulting in the identification of 80 significantly changed pathways ($p<0.05$)(Appendix 6). The most enriched Canonical Pathways in this time point, are “Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses” (Eif2ak2, Oas1, C3, Tgfb1, Tlr1, C1qb, Ddx58, C3ar1, C1qa, Pik3cg, C1qc, Irf7, Ifih1, Il1a, Tlr2, Clec7a), “Dendritic Cell Maturation” (Tnfrsf1a, Hla-Dqa1, Fcgr1a, Plce1, Fcer1g, Trem2, Fcgr2a, Pik3cg, Irf8, Hla-A, Fcgr2b, Tyrobp, Il1a, Tlr2, Cd86, Fcgr3a/Fcgr3b), and “G-Protein Coupled Receptor Signaling” (Drd5, Htr1a, Prkar2b, S1pr3, Ptger4, Pik3cg, Mc4r, Dusp1, P2ry13, Rgs2, Pde3a, Grm1, Htr2c, Pde1a, Dusp4, Htr2a), with sixteen genes mapped to each of them.

The top significantly changed Canonical pathways at 30 day as determined by p-values include once again many highly enriched pathways implicated in immune and inflammatory response, the majority of which appeared to be significantly changed at 3 days (Figure 3.19). In specific, the top pathway is “Complement System” with twelve genes (Itgam, C1qc, C4a/C4b, C3, C1qb, Itgax, Itgb2, C1s, Serping1, Cfh, C3ar1, C1qa) (Figure 3.20). By ascending p-value, it is followed by “Communication between Innate and Adaptive Immune Cells” with twelve genes (Hla-E, Hla-A, Cxcl10, Tlr1, Ccl9, Il1a, Tlr13, Fcer1g, Ccl3l3, Tlr2, Cd86, Hla-F), “Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses” with sixteen genes (Eif2ak2, Oas1, C3, Tgfb1, Tlr1, C1qb, Ddx58, C3ar1, C1qa, Pik3cg, C1qc, Irf7, Ifih1, Il1a, Tlr2, Clec7a) and, “Phagosome formation”, which is populated by thirteen genes in this time point, i.e. (Fcgr1a, Tlr1, Plce1, Fcer1g, Fcrls, Rhoj, Fcgr2a, Pik3cg, Fcgr2b, Inpp5d, Tlr13, Tlr2, Clec7a, Fcgr3a/Fcgr3b) (Figure 3.21) and “Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes” with thirteen genes (Fcgr1a, Ncf1, Fyb, Pld4, Rac2, Arpc1b, Vav1, Fcgr2a, Pik3cg, Lcp2, Inpp5d, Lyn, Fcgr3a/ Fcgr3b). “Dendritic Cell Maturation” also remains changed at 30 days, with fifteen significantly changed genes (Tnfrsf1a, Hla-Dqa1, Fcgr1a, Plce1, Fcer1g, Trem2, Fcgr2a, Pik3cg, Irf8, Hla-A, Fcgr2b,

Tyrobp, Il1a, Tlr2, Cd86, Fcgr3a/Fcgr3b), as well as “Granulocyte Adhesion and Diapedesis” with fifteen genes (Itgam, Ccl6, Tnfrsf1a, Cxcl10, Csf3r, Itga6, Msn, Itgb2, Ccl3l3, Hspb1, Cxcl13, Ccl9, Ccl2, Il1a, Cxcl16).

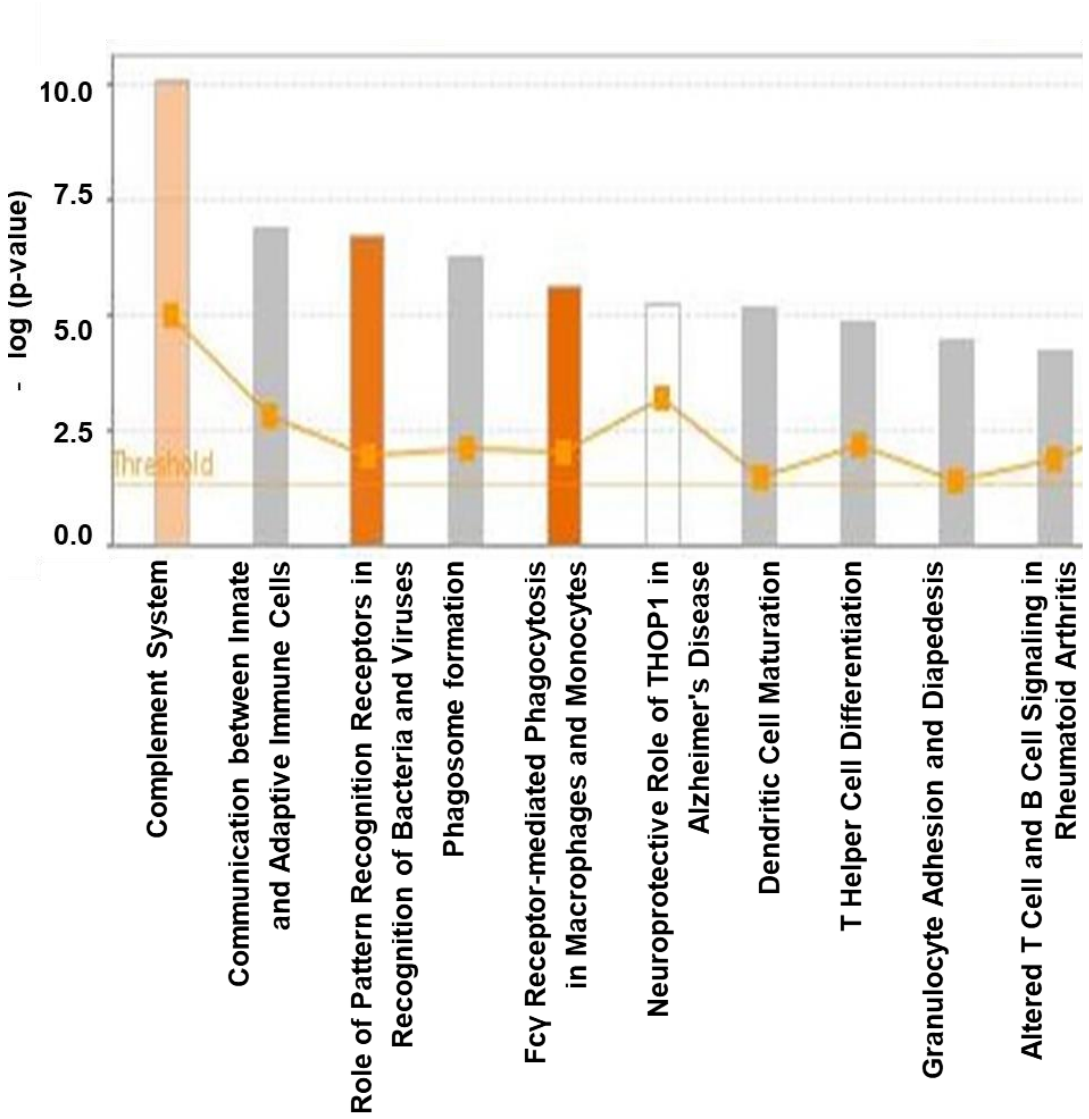


Figure 3.19. *Top 10 statistically significant changes in Canonical pathways at 30 days post injection, according to Ingenuity Pathway Analysis. The pathways are ranked by descending –log(p-value) (y-axis), the threshold of statistical significance (p-value<0.05) is marked by the horizontal yellow line. The yellow square inside each bar represents the ratio of the number of the genes in the list mapped to a pathway to the total number of genes that are included in the pathway, according to IPA software.*

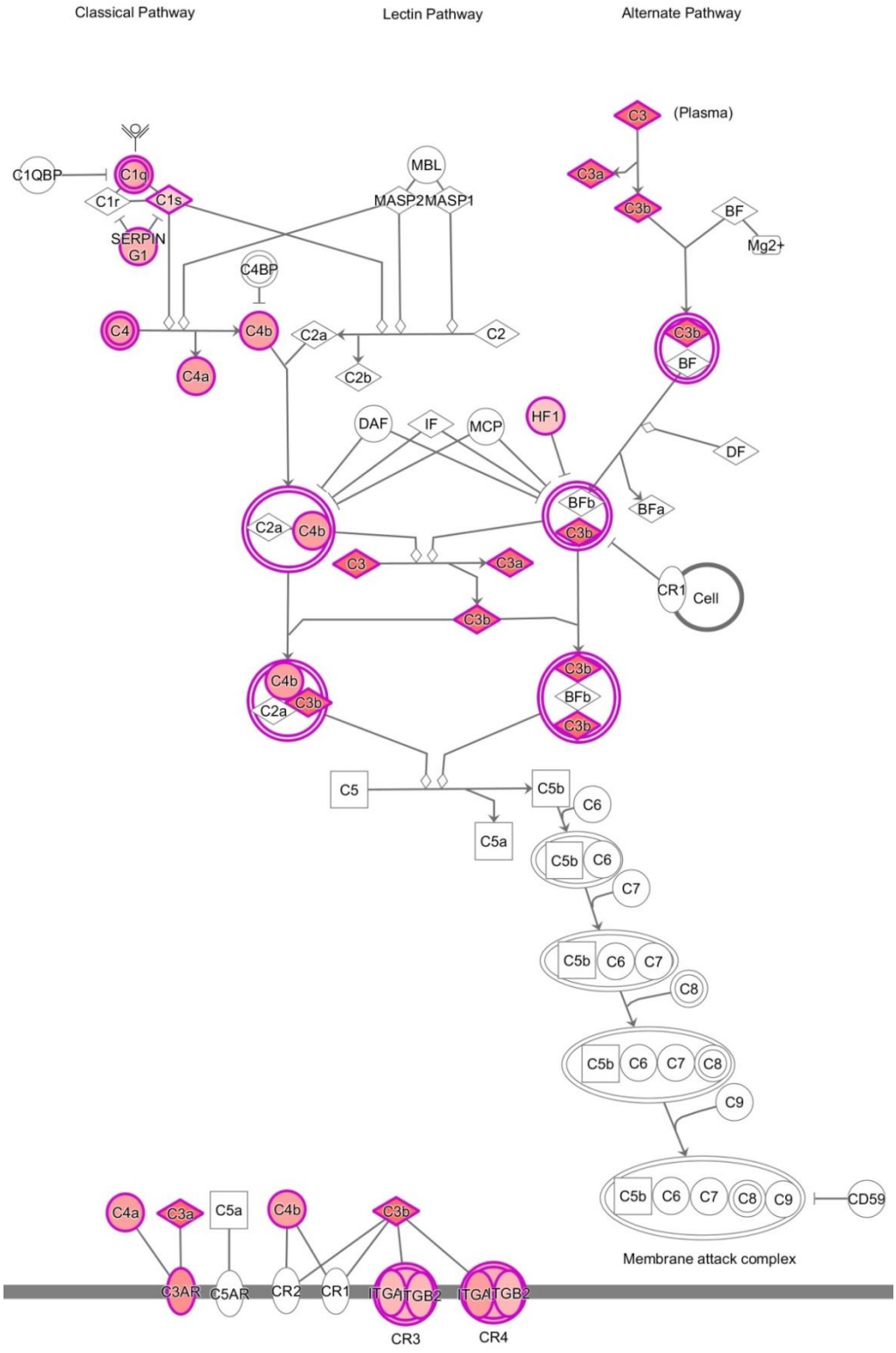


Figure 3.20.*The Complement system Canonical Pathway at 30 days post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill=overexpression).*

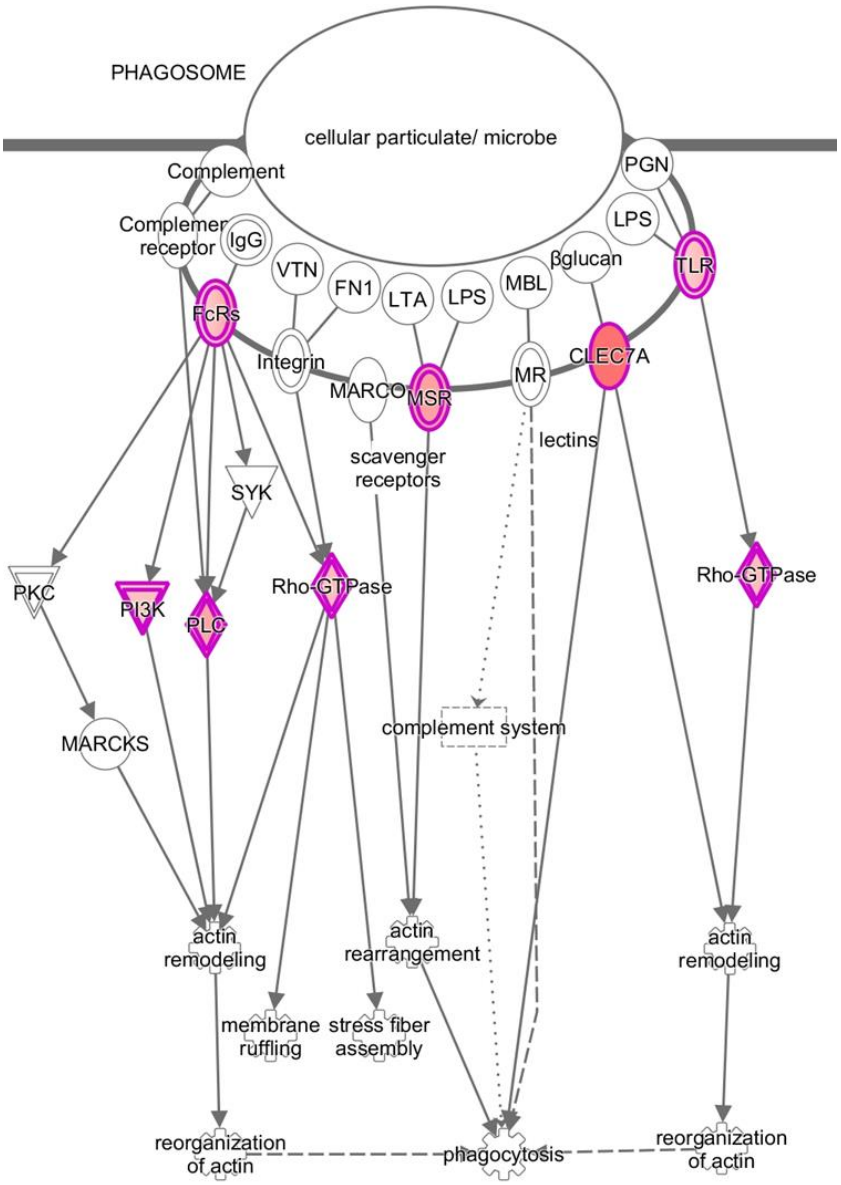
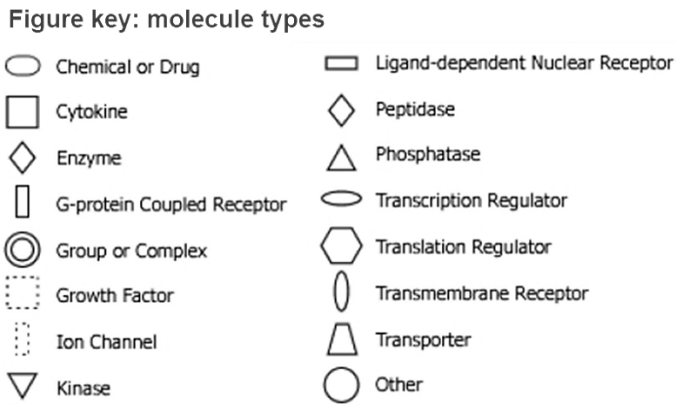


Figure 3.21. *Phagosome formation Canonical Pathway at 30 days post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red fill=overexpression).*



3.1.5. Ingenuity Pathway Analysis: Upstream regulators

The IPA “Upstream regulator” analysis for the three time points of the study resulted in the prediction of key regulatory molecules at each time point, which were subsequently filtered in order to choose those with significantly changed expression. This approach provides a proof of concept for the *in silico* prediction, and enables us to pinpoint regulators that could provide testable hypotheses as possible therapeutic targets. The significantly changed upstream regulators of each time point were also filtered based on the molecule type for “transcription regulators”, in an effort to identify key transcription factors (TFs) that may account for the some of the observed expression changes. The function “Regulator effects” was utilized to generate the upstream regulator/ target genes/ networks (Methods, Chapter 2.2.4.2). These networks depict each regulator and how it regulates the “regulated” genes thereby implying the effect of the regulator (“regulator effects”) on the biological functions the downstream genes are implicated in.

3.1.5.1 Time point 1 day

Upstream transcription regulators

At 1 day post injection, a total of 2,704 regulators upstream of the significantly changed genes were identified. The output of the analysis was filtered based on molecule type, resulting in 308 “transcription regulators”, which were then filtered by fold change to give a sublist of sixteen upstream transcription regulators with significantly changed expression. Two of the significantly changed transcription regulators were common in all three time points (↑Ifi16, ↑Irf7), five were found at 1 day and 3 days (↑Atf3, ↑Nupr1, ↑ Stat3, ↑Wwtr1, ↑Zfp36) and nine regulators were found only at the 1 day time point (↑Btg2, ↑Fos, ↑Fosb, ↑Fosl1, ↑Id1, ↑Junb, ↑Klf6, ↑Nfil3, ↑Smad7).

At the 1 day time point, no “Regulator effects” networks were found for the common transcription regulators of all time points, ↑Ifi16 and ↑Irf7. According to the networks with predicted relationship, ↑Ifi16 may control “immune response of leukocytes” via three significantly changed genes (Ccl2, Cxcl10, Ddx58), and ↑Irf7 may negatively regulates “replication of Murine herpesvirus” via four genes (Cxcl10, Ddx58, Ifih1, Parp12). For the common regulators of 1

and 3 days datasets, the analysis showed that ↑Stat3 may control “tubulation of endothelial cells” via four target genes (Cd9, Fgf2, Plaur, Vim) and ↑Wwtr1, may regulate “proliferation and migration of tumor cell lines” via four genes (Cd44, Ctgf, Serpine1, Spp1), and is also predicted to control “proliferation and migration of connective tissue cells”, and “cell movement of fibroblast cell lines” via five significantly changed genes (Cd44, Ctgf, Serpine1, Smad7, Spp1). Moreover, according to known regulator/ function relationships, ↑**Zfp36** may regulate “differentiation of cells” via five genes (Ccl3l3, Cdkn1a, Fos, Ptgs2, Spp1) and “cell survival” via five genes (Cdkn1a, Cybb, Fos, Ptgs2, Spp1), as well as “quantity of phagocytes” via four genes with significantly changed expression in our data (Ccl3l3, Cdkn1a, Cybb, Spp1) (Figure 3.22).

According to the “Regulator effects” networks of the 1 day-only upstream transcription regulators, ↑**Fos** may positively regulate “recruitment of leukocytes” via twelve target genes (Bdnf, C3ar1, Ccl2, Cd14, Cd44, Chi3l1, Edn1, Hmox1, Kitlg, Serpine1, Spp1, Tac1) (Figure 3.23), whilst it is also predicted to affect “cell spreading” via nine genes (Cd44, Fgf2, Kitlg, Ptpn12, Serpine1, Sphk1, Spp1, Tgfbi, Vim) and “activation of granulocytes” via eight significantly changed genes (Ccl2, Cd14, Edn1, Hmox1, Kitlg, Npy, Spp1, Tac1). The known regulator/function networks for ↑**Junb** indicate that it may regulate “angiogenesis” and “vasculogenesis” via nine significantly changed genes (Atf3, Cav1, Fosl1, Hmox1, Inhba, Itgav, Plaur, Serpine1, Timp1), and the predicted networks imply it may affect “cell movement of fibroblast cell lines” via three genes (Fosl1, Plaur, Serpine1).

No “Regulator effects” networks were available for the rest of the transcription regulators of 1 and 3 days (↑Atf3, ↑Nupr1), and 1 day only (↑Btg2, ↑Fosb, ↑Fosl1, ↑Id1, ↑Klf6, ↑Nfil3, ↑Smad7), in the analysis results for the 1 day dataset.

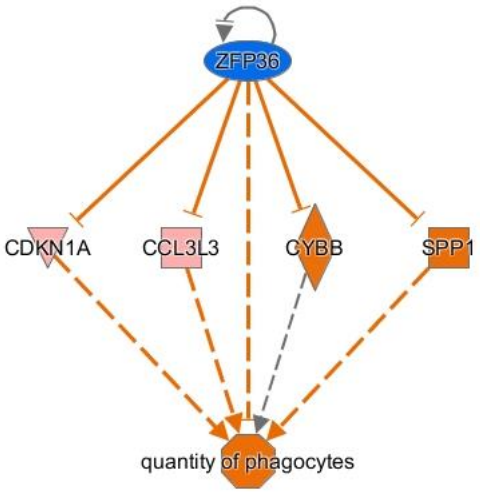


***Figure 3.22**. The overexpressed transcription regulator Zfp36 regulates the quantity of phagocytes, at 1 day post injection, according to IPA "Upstream regulator" analysis and "Regulator effects" networks. Solid lines indicate direct and dashed lines indirect relationships between molecules. Red=overexpression, orange=predicted activation, blue=predicted inhibition.*

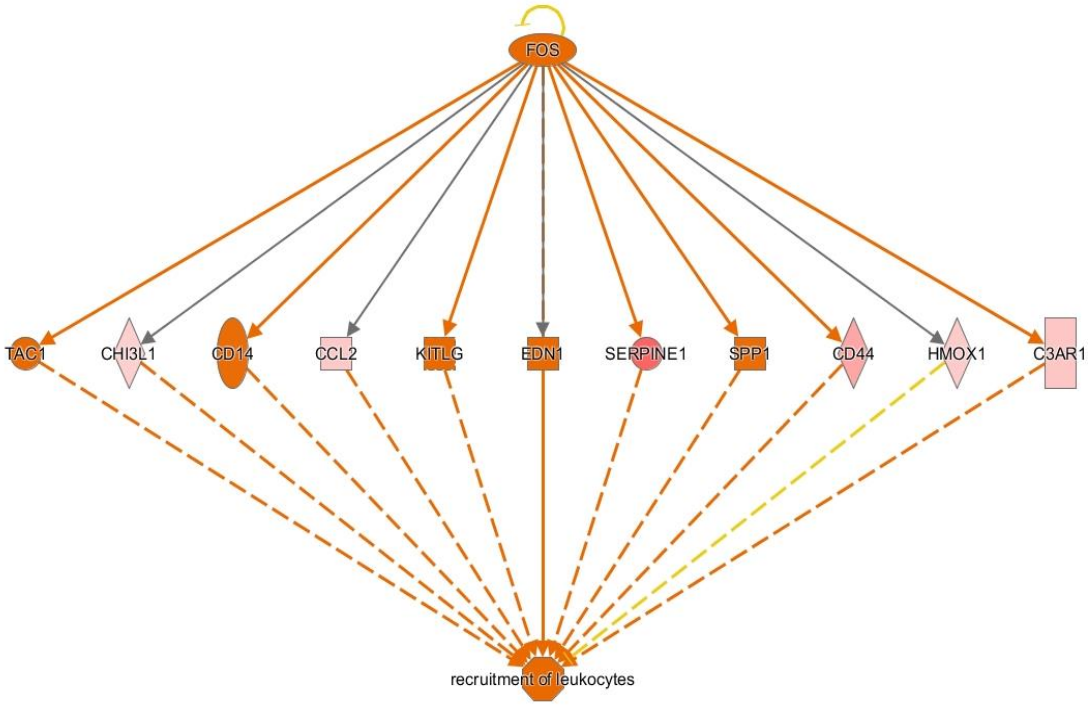


***Figure 3.23**. The overexpressed transcription regulator Fos regulates recruitment of leukocytes, at 1 day post injection, according to IPA "Upstream regulator" analysis and "Regulator effects" networks. Solid lines indicate direct and dashed lines indirect relationships between molecules. Red=overexpression, orange=predicted activation.*

3.1.5.2 Time point 3 days

Upstream transcription regulators

At 3 days post injection, a total of 2,672 regulators was predicted to act upstream of the significantly changed genes. The results were filtered based on molecule type, resulting in 333 “transcription regulators”, which were subsequently filtered by fold change to give a sublist of twenty one upstream transcription regulators with significantly changed expression at 3 days. Two of the significantly changed transcription regulators were common in all three time points (↑Ifi16, ↑Irf7), five were found at 1 day and 3 days (↑Atf3, ↑Nupr1, ↑Stat3, ↑Wwtr1, ↑Zfp36) and four were found at 3 and 30 days (↑Irf8, ↑Nfe2l2, ↑Runx1, ↑Pu.1). The time point-specific transcription regulators were ten at this time point (↑Bcl3, ↑Ccnd1, ↑E2f8, ↑Foxm1, ↑Hlf, ↑Irf9, ↑Rbl1, ↑Rbpj, ↑Stat1, ↑Vav1).

At 3 days post injection, “Regulator effects” networks with known regulator/function relationship were found only for the one of the two common regulators of all time points, namely ↑Irf7. Accordingly, ↑**Irf7** may positively regulate ”immune response of cell” via twelve significantly changed target genes (Cxcl10, Ddx58, Dhx58, Fcgr1a, Ifih1, Il33, Irf8, Itgam, Psmb8, Stat1, Tlr4, Ube2l6), “function of leukocytes” via ten genes (Cxcl10, Ddx58, Fcgr1a, Ifih1, Il33, Irf8, Itgam, Stat1, Tlr4, Trim30a/Trim30d) (Figure 3.24), “differentiation of myeloid cells, macrophages and phagocytes” via seven genes (Cxcl10, Fcgr1a, Ifi16, Il33, Irf8, Itgam, Tlr4), and “phagocytosis of neutrophils” via three significantly changed genes (Cxcl10, Itgam, Tlr4).

According to the “Regulator effects” networks with predicted relationship, ↑**Ifi16** may affect ”immune response of phagocytes”, “recruitment of leukocytes”, “migration of lymphocytes and mononuclear leukocytes” via four target genes that are significantly changed in our data (Ccl2, Cxcl10, Ddx58, Vcam1) (Figure 3.25).

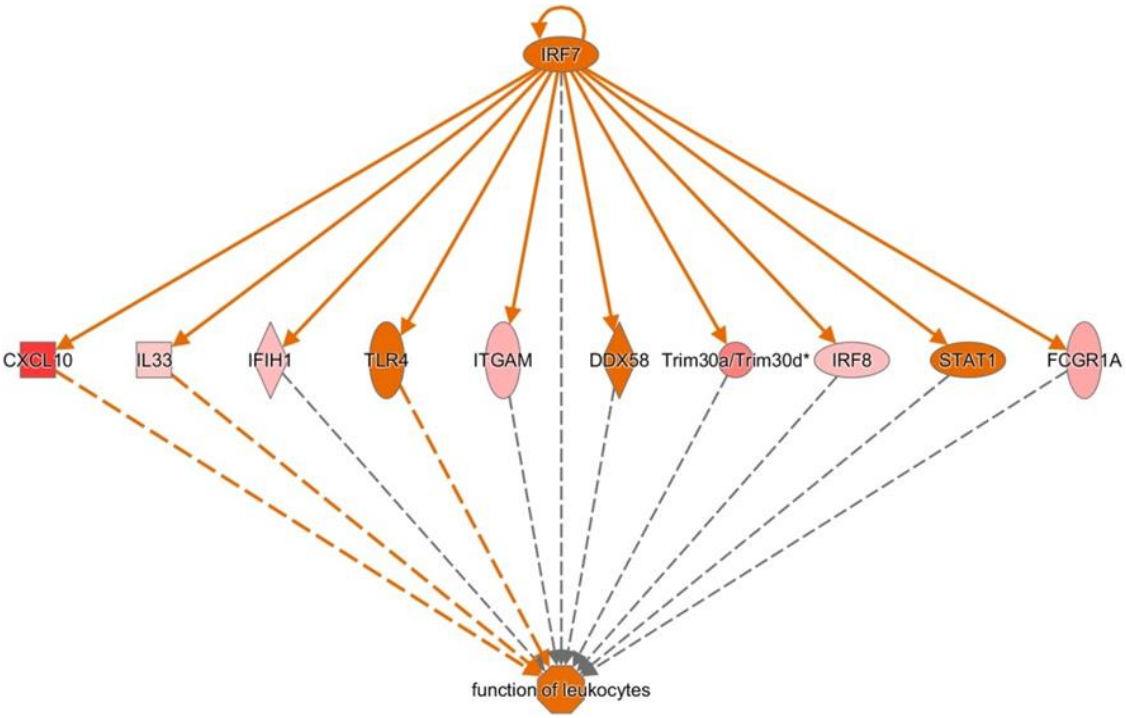


Figure 3.24. *The overexpressed transcription regulator Irf7 regulates the function of leukocytes, at 3 days post injection, according to IPA "Upstream regulator" analysis and "Regulator effects" networks. Solid lines indicate direct and dashed lines indirect relationships between molecules. Red=overexpression, orange=predicted activation.*

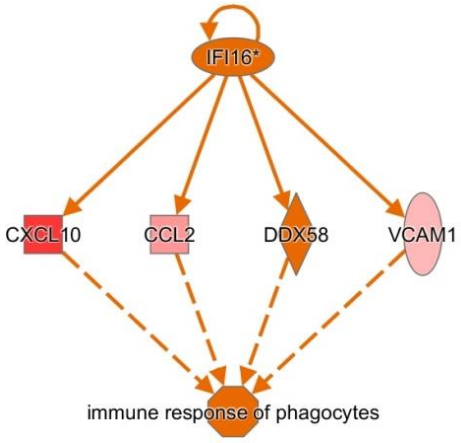


Figure 3.25*. The overexpressed transcription regulator Ifi16 regulates the immune response of phagocytes, at 3 days post injection, according to IPA "Upstream regulator" analysis and "Regulator effects" networks. Solid lines indicate direct and dashed lines indirect relationships between molecules. Red=overexpression, orange=predicted activation.*

The “Regulator effects” networks of 1 and 3 days datasets, with known regulator/function relationship for ↑**Zfp36** indicate that it may affect “Rheumatic Disease”, “arthropathy”, and “arthritis” via six significantly changed genes (Ccl3l3, Cdkn1a, Ctss, Ptgs2, Spp1, Vcam1), which is out of the context of our study. However, ↑Zfp36 was also predicted to regulate “migration of phagocytes” (Figure 3.26), “adhesion of blood cells”, “cell movement of granulocytes and neutrophils” via the same six genes, and in the previous time point it was predicted to control the “quantity of phagocytes”, thus require further investigation.

For ↑**Stat3 ,** the networks with known regulator/function relationships indicate that ↑Stat3 may control “tubulation of cells” via five significantly changed genes (Cd9, Fgf2, Itgb1, Plau, Vim), and the predicted networks imply it may affect “transmigration of leukocytes” via ten genes (Ccl2, Ccl3l3, Ccnd1, Cd86, Cxcl10, Fn1, Itgam, Itgav, Itgb1, Itgb2) (Figure 3.27), and “adhesion of epithelial cell lines” via six genes (Itgam, Itgav, Itgb1, Itgb2, Plau, Timp1). The predicted networks are in line with the findings on Stat3, described in pathway analysis, within the context of IL6 and JAK/STAT signaling.

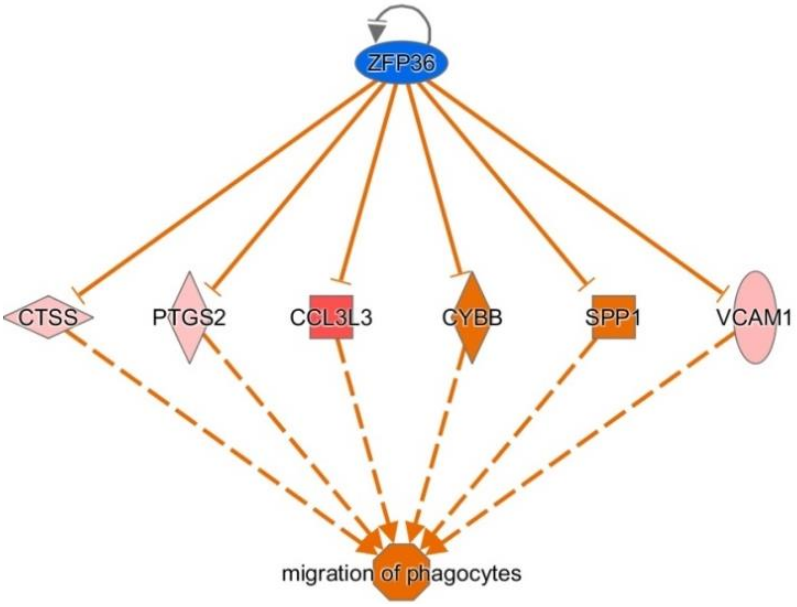


Figure 3.26. *The overexpressed transcription regulator Zfp36 regulates the migration of phagocytes, at 3 days post injection, according to IPA "Upstream regulator" analysis and "Regulator effects" networks. Solid lines indicate direct and dashed lines indirect relationships between molecules. Red=overexpression, orange=predicted activation, blue=predicted inhibition.*

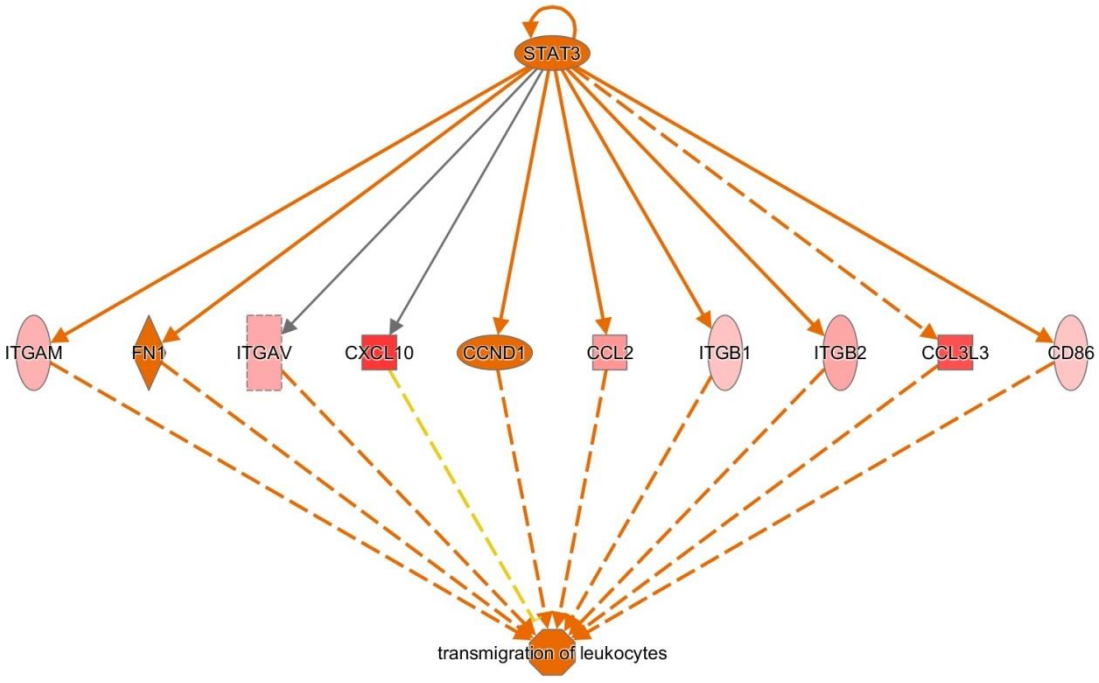


Figure 3.27. *The overexpressed transcription regulator Stat3 regulates the transmigration of leukocytes, at 3 days post injection, according to IPA "Upstream regulator" analysis and "Regulator effects" networks. Solid lines indicate direct and dashed lines indirect relationships between molecules. Red=overexpression, orange=predicted activation.*

At 3 days, “Regulator effects” networks were only available for one of common regulators of 3 and 30 days, ↑Spi1 (a.k.a Pu.1). According to networks with known regulator/function relationship, ↑**Spi1** may regulate “immune response of leukocytes” via fourteen significantly changed target genes (Cd180, Cd68, Csf2rb, Ctss, Fcer1g, Fcgr2b, Itgam, Itgb2, Pik3cg, Psmb8, Ptprc, Tlr2, Tlr4, Vav1), “response and phagocytosis of myeloid cells, phagocytes and leukocytes” via ten genes (Csf2rb, Fcer1g, Fcgr2b, Itgam, Itgb2, Pik3cg, Ptprc, Tlr2, Tlr4, Vav1), “immune response of macrophages” and “phagocytosis by macrophages” via seven genes (Fcer1g, Fcgr2b, Itgam, Itgb2, Ptprc, Tlr2, Tlr4), “differentiation of mononuclear leukocytes” via twelve genes (Blnk, Cd72, Csf1, Csf2rb, Fcgr2b, Itgb2, Pik3cg, Ptgs2, Ptprc, Tlr2, Tlr4, Vav1), “differentiation of myeloid cells” via six genes (C1qc, Csf1, Csf2rb, Itgam, Tlr2, Tlr4), “quantity of CD4+ T-lymphocytes” via five genes (Itgam, Itgb2, Pik3cg, Ptprc, Vav1), and “attachment of cells” via seven genes with significantly changed expression in our dataset (Csf1, Csf2rb, Dab2, Itga5, Itgb2, Spp1, Vav1) (Figure 3.28). These data indicate that Pu.1 is the master regulator of the immune response at 3 days post injection.

Moving to the transcription regulators found only at the 3 day time point, regulator effect networks were found only for Foxm1 and Stat1. Accordingly, known regulator/function relationships include ↑**Foxm1** controlling proliferation of lymphatic system cells via three genes (Aurkb, Ccnb1, Cdkn1a), and ↑**Stat1** controlling cell viability of leukocytes via seven target genes (C3, Casp8, Cd86, Fcer1g, Fcgr1a, Fgf2, Tlr4) (Figure 3.29).

No “Regulator effect networks” were available for the rest of the transcription regulators of 1 and 3 days (↑Atf3, ↑Nupr1, ↑ Wwtr1), 3 and 30 days(↑Irf8, ↑Nfe2l2, ↑Runx1) and 3 days only (↑Bcl3, ↑Ccnd1, ↑E2f8, ↑Hlf, ↑Irf9, ↑Rbl1, ↑Rbpj, ↑Vav1), in the analysis results for the 3 days dataset.

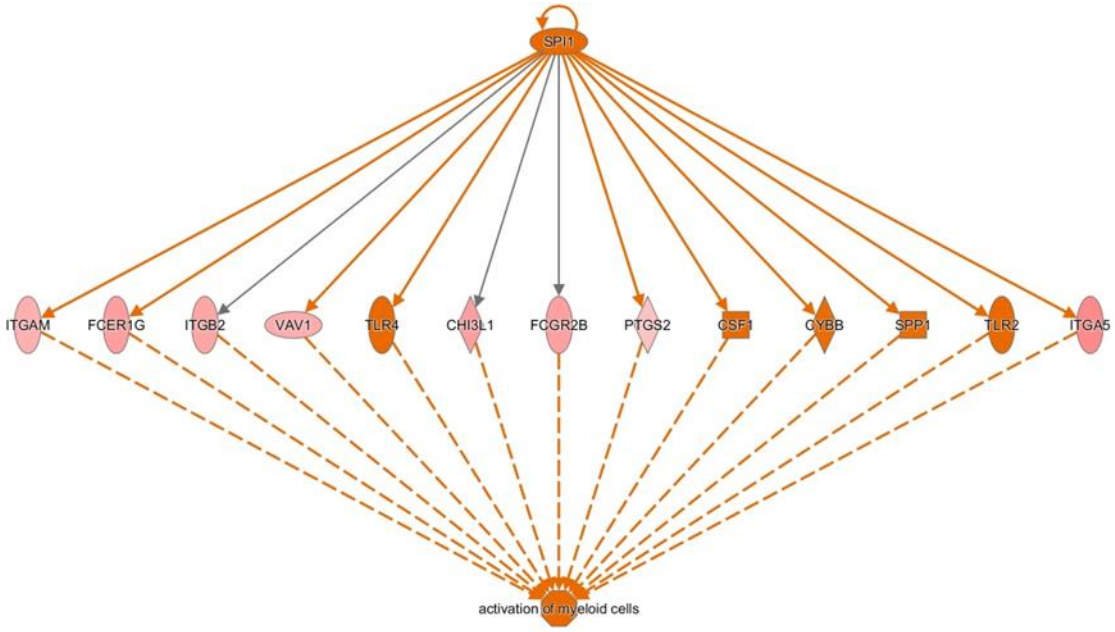


Figure 3.28. *The overexpressed transcription regulator Spi1 (Pu.1) regulates the activation of myeloid cells, at 3 days post injection, according to IPA "Upstream regulator" analysis and "Regulator effects" networks. Solid lines indicate direct and dashed lines indirect relationships between molecules. Red=overexpression, orange=predicted activation.*

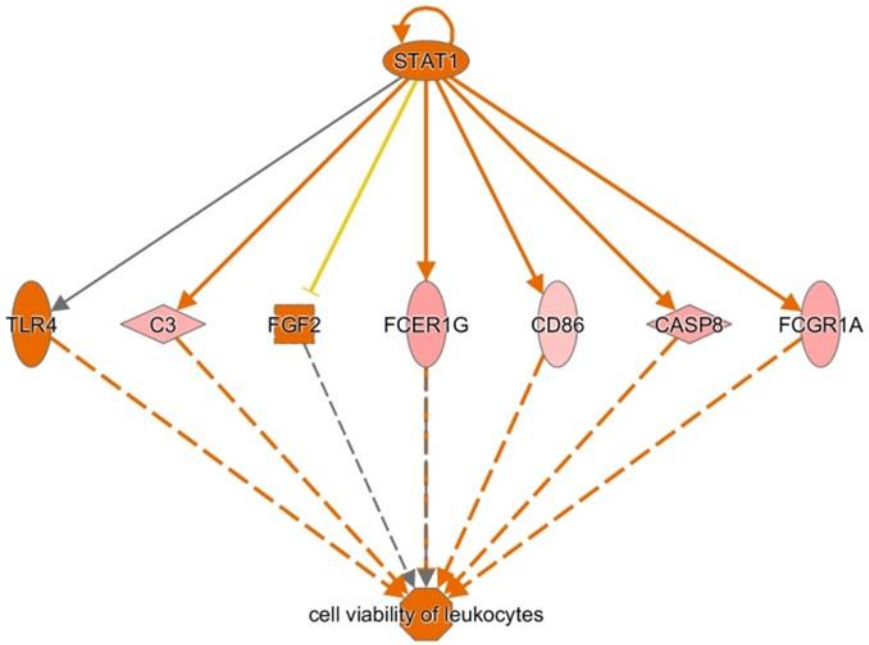


Figure 3.29. *The overexpressed transcription regulator Stat1 regulates leukocyte cell viability, at 3 days post injection, according to IPA "Upstream regulator" analysis and "Regulator effects" networks. Solid lines indicate direct and dashed lines indirect relationships between molecules. Red=overexpression, orange=predicted activation.*

3.1.5.3. Time point 30 days

Upstream transcription regulators

At the last time point of the study, the “Upstream regulator” analysis resulted in the identification of 1663 regulators upstream of the significantly changed genes. The results were filtered by molecule type, resulting in a subtotal of 205 “transcription regulators”, which were subsequently filtered by fold change, ultimately leading to nine upstream transcription regulators with significantly changed expression at 30 days. Two of the significantly changed transcription regulators were common in all three time points (↑Ifi16, ↑Irf7), four were found at 3 and 30 days (↑Irf8, ↑Nfe2l2, ↑Runx1, ↑Pu.1), and three were found only at 30 days (↑Fosl2, ↑Id3, ↑Runx1t1).

At 30 days post injection, networks with known regulator/function relationship were found only for the one of the two common regulators of all time points, ↑**Irf7,** similarly to the 3 day time point**.** Accordingly, ↑**Irf7** positively controls antimicrobial response via eleven target genes (Ddx58, Fcgr1a, Ifi44, Ifih1, Ifit1b, Ifit3, Ifitm3, Irf8, Oas1, Oasl2, Trim5), immune response of cells via eight genes (Cxcl10, Ddx58, Fcgr1a, Ifih1, Irf8, Itgam, Itgax, Trim5) (Figure 3.30) and phagocytosis via five genes (Cxcl10, Fcgr1a, Irf8, Itgam, Itgax). ↑**Ifi16** predicted regulator/function relationship according to IPA was associated to activation of leukocytes and immune response of leukocytes via five genes (Ccl2, Cxcl10, Ddx58, Mgst1, Csf3r).

At 30 days, “Regulator Effects” networks were only available for two of the common regulators of 3 and 30 days, ↑Spi1 (a.k.a Pu.1) and Irf8. According to networks with known regulator/function relationship, ↑**Irf8** positively controls the quantity of T lymphocytes via five target genes (Cd86, Ctss, Cxcl16, Id3, Itgam) and ↑**Pu.1** was related to inflammatory response via eighteen upregulated target genes, amongst which was Nox2 (↑Cybb) (Figure 3.31). More specific functions that Pu.1 controlled is differentiation of mononuclear leukocytes via eleven target genes (Blnk, Cd14, Cd72, Csf1r, Fcgr2b, Id3, Itgb2, Pik3cg, Ptprc, Tlr2, Vav1), quantity of T lymphocytes and CD4+ T-lymphocytes via twelve target genes (Chi3l1, Ctss, Fcer1g, Fcgr2b, Id3,

Itgam, Itgb2, Pik3cg, Ptprc, Spp1, Tlr2, Vav1), phagocytosis of myeloid cells, phagocytes and leukocytes via eight target genes (Cd14, Fcer1g, Fcgr2b, Itgam, Itgb2, Ptprc, Tlr2, Vav1), adhesion of phagocytes via six target genes (Csf3r, Itgam, Itgb2, Pik3cg, Tlr2, Vav1).

No “Regulator effects” networks were available for the rest of the transcription regulators at 3 and 30 days (↑Nfe2l2, ↑Runx1), and 30 days only, (↑Fosl2, ↑Id3, ↑Runx1t1) according to the analysis results for the 30 days dataset.

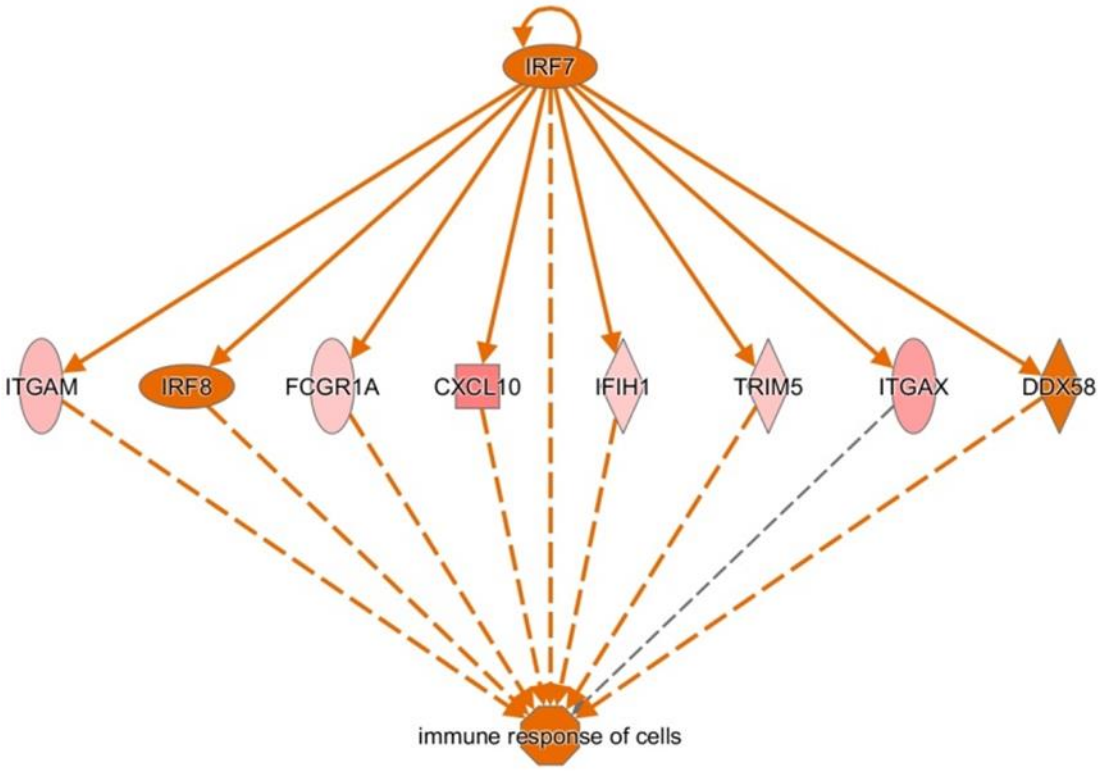


***Figure 3.30**. The overexpressed transcription regulator Irf7 regulates immune response of cells, at 30 days post injection, according to IPA “Upstream regulator” analysis and “Regulator effects” networks. Solid lines indicate direct and dashed lines indirect relationships between molecules. Red=overexpression, orange=predicted activation.*

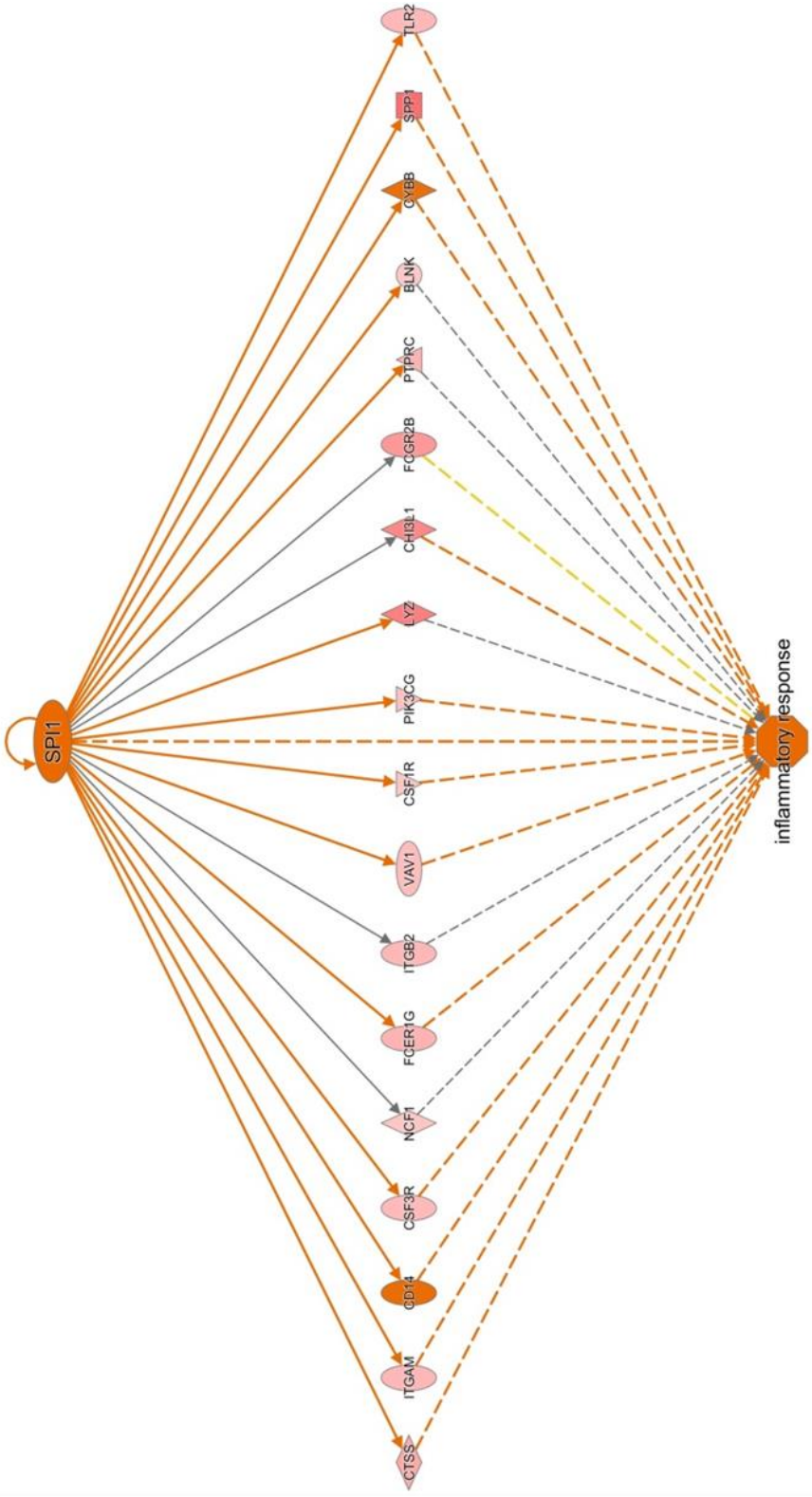


***Figure 3.31**. The overexpressed transcription regulator Spi1 (Pu.1) regulates inflammatory response, at 30 days post injection, according to IPA "Upstream regulator" analysis and "Regulator effects" networks. Solid lines indicate direct and dashed lines indirect relationships between molecules. Red=overexpression, orange=predicted activation.*

3.1.6 Comparison analysis

3.1.6.1 Comparison analysis of transcriptomics at the three time points of the study

After the completion of the transcriptomic analysis of the KA-MTLE hippocampus at 1, 3 and 30 days post injection, we sought to compare the results between the three time points. The comparison analysis aims to pinpoint the changes that characterize each of the unique stages of MTLE studied, and to describe the persistent changes between time points. To this aim, we cross-compared the findings of the three time points on the molecular and pathway level.

Comparison at the molecular level

The cross- comparison of the lists with 449, 687, and 543 unique statistically significant changed genes (Entrez Gene Symbols) at 1, 3 and 30 days post injection revealed that the expression of genes (Entrez Gene Symbols) were consistently changed at all time points. Pairwise comparisons between the three time points showed that 203 genes were common between 1 and 3 days, 322 genes were commonly changed between 3 and 30 days, and 161 genes were changed at both and 30 days. At 1 day, 210 (~47%) 287 (~42%) and 185 genes (34%) were found to be uniquely changed expression at 1, 3 and 30 days, respectively (Figure 3.32).

Comparison at the pathway level

The lists of significantly changed genes for the three time points of the study was subjected to “Core analysis”, and the resulting analyses were subsequently subjected to “Comparison analysis”, provided by IPA software. According to the comparison, 21 pathways were uniquely changed at 1 day post injection with 1 to 11 genes each (Appendix 7), 49 pathways with 1 to 19 genes each at 3 days (Appendix 8), and 8 pathways with 3 to 10 genes each at 3 days (Appendix 9).

The IPA “Comparison Analysis” showed that 18 Canonical Pathways were found to be significantly changed across all time points, with 3 to 21 genes mapped to each, per time point (Appendix 10, Figure 3.33). According to pairwise comparisons, 17 pathways remain changed between 1 and 3 days,

with 3 to 19 genes each (Appendix 11), 41 pathways remain changed between 3 and 30 days, with 2 to 22 genes each (Appendix 12), and 10 pathways were found to be significantly at both 1 and 30 days post injection with 2 to 18 genes each (Appendix 13).

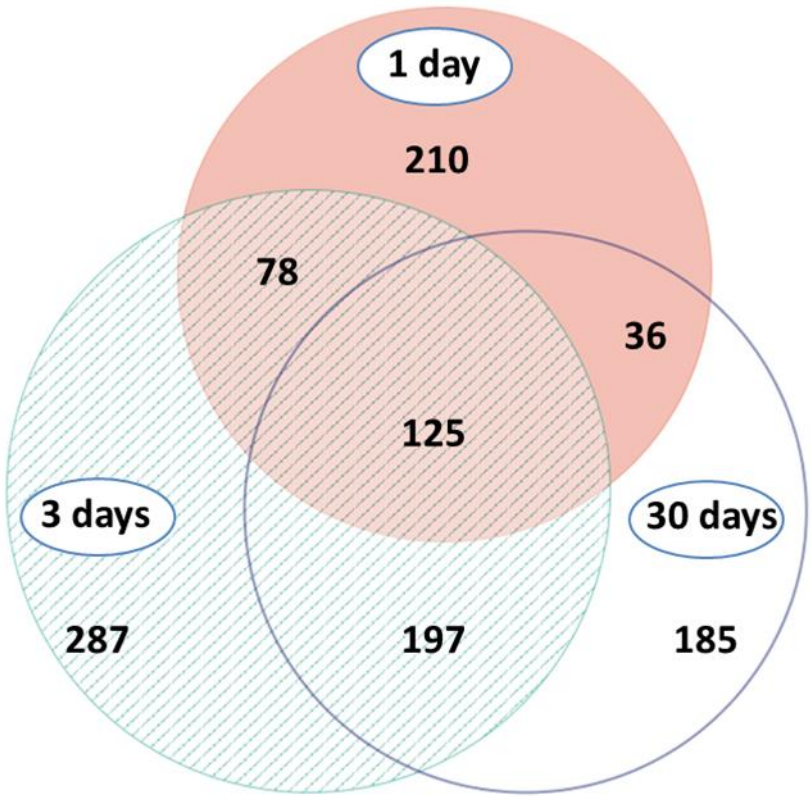


Figure 3.32. *Gene expression changes overlap between the three time points of the study (1, 3, 30 days). Over- and under-expressed probe sets are grouped together. Venn diagram designed with eulerAPE tool.*

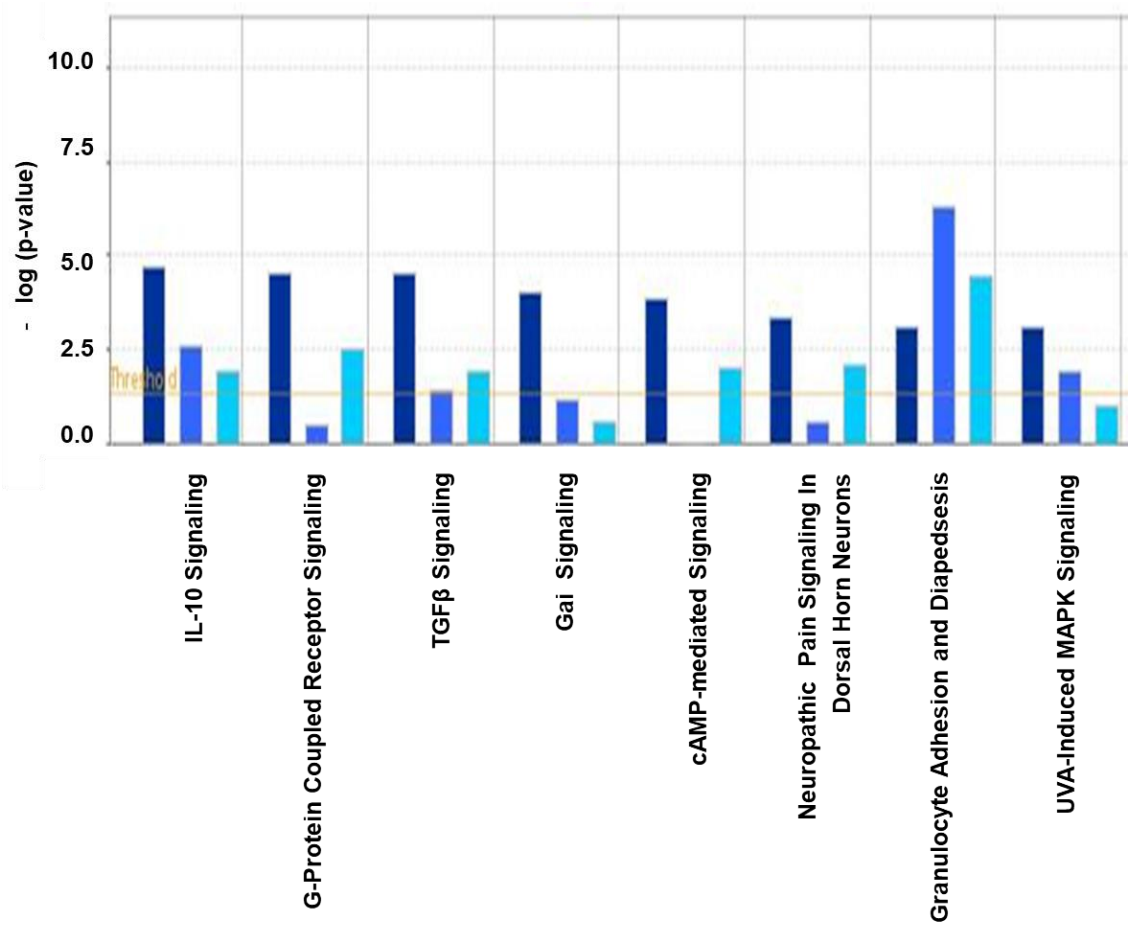


Figure 3.33. *Representative results of IPA "Comparison Analysis" Canonical Pathways at 1, 3, and 30 days post injection. The pathways are ranked by descending –log (p-value) (y-axis) at 1 day, the threshold of statistical significance (p-value<0.05) is marked by the horizontal yellow line. Different shades of blue correspond to 1, 3, and 30 days "Core Analysis" results, from left to right in each Canonical Pathway.*

3.1.6.2 Transcriptomics vs. Proteomics comparison

In the context of the analysis of the KA-MTLE hippocampus at 1, 3 and 30 days post injection, a proteomic analysis of this mouse model was performed by Dr A.Vlachou, (BRFAA), and resulted in the identification of 22, 53 and 175 significantly changed proteins at 1, 3, 30 days, respectively. In this phase of the project we sought to compare the results of the transcriptomics and proteomics analysis in order to obtain a comprehensive molecular map of the KA-MTLE hippocampus.

Comparison at the molecular level

The first step of the comparison process was to perform a molecule ID conversion, via the online tool “g:Convert Gene ID Converter”, provided by the public web server “g:Profiler” (http://biit.cs.ut.ee/gprofiler/). The lists of significantly changed proteins were submitted to g:Convert as UniProt/SwissProt protein IDs, in order to obtain the corresponding Gene Symbols. The resulting list for each time point was then compared with the list of significantly changed genes for the respective time point.

Transcriptomic and proteomic analysis comparison at the molecular level resulted in only 1 commonly changed molecule at 1 day (↑Tf, Transferrin), 11 common molecules at 3 days (Table 3.1), and 24 molecules at 30 days post injection (Table 3.2). Some of the common molecules were consistently changed across two or more time points. Of note, all of them followed the same direction of change both at the gene and protein levels.

Table 3.1. *Comparison of transcriptomics and proteomics analysis results at 3 days post injection.*

Gene Symbol	Entrez Gene Name	Transcriptomics expression change	Proteomics expression change	Transcriptomics expression change in other time points
Tf	Transferrin	↑	↑	1d
Shisa6	shisa homolog 6 (Xenopus laevis)	↓	↓	-
Flna	filamin A, alpha	↑	↑	-
Msn	Moesin	↑	↑	-
Anxa2	annexin A2	↑	↑	-
Spp1	secreted phosphoprotein 1	↑	↑	-
Hexb	hexosaminidase B (beta polypeptide)	↑	↑	30d
Dhrs1	dehydrogenase/reductase (SDR family) member 1	↑	↑	30d
Vim	Vimentin	↑	↑	30d
Ctsz	cathepsin Z	↑	↑	30d
Tgm1	transglutaminase 1 (K polypeptide epidermal type I, protein-glutamine-gamma-glutamyltransferase)	↑	↑	30d

Table 3.2. *Comparison of transcriptomics and proteomics analysis results at 30 days post injection.*

Gene Symbol	Entrez Gene Name	Transcriptomics expression change	Proteomics expression change	Transcriptomics expression change in other time points
Hexb	hexosaminidase B (beta polypeptide)	↑	↑	3d
Dhrs1	dehydrogenase/reductase (SDR family) member 1	↑	↑	3d
Vim	Vimentin	↑	↑	3d
Ctsz	cathepsin Z	↑	↑	3d
Tgm1	transglutaminase 1 (K polypeptide epidermal type I,	↑	↑	3d
Anxa4	annexin A4	↑	↑	-
Anxa5	annexin A5	↑	↑	-
Adssl1	adenylosuccinate synthase like 1	↑	↑	-
S100a6	S100 calcium binding protein A6	↑	↑	-
Scg2	secretogranin II	↑	↑	-
Ctsd	cathepsin D	↑	↑	-
Clic1	chloride intracellular channel 1	↑	↑	-
Hspb1	heat shock 27kDa protein 1	↑	↑	-
Lcp1	lymphocyte cytosolic protein 1 (L-plastin)	↑	↑	-
Gfap	glial fibrillary acidic protein	↑	↑	-
Arpc1b	actin related protein 2/3 complex, subunit 1B, 41kDa	↑	↑	-
Irgm	immunity-related GTPase family, M	↑	↑	-
Acan	Aggrecan	↑	↑	-
Lag3	lymphocyte-activation gene 3	↑	↑	-
Cd9	CD9 molecule	↑	↑	-
Anxa3	annexin A3	↑	↑	-
Ifit3	interferon-induced protein with tetratricopeptide repeats	↑	↑	-
C4a/C4b	complement component 4B (Chido blood group)	↑	↑	-
A2m	alpha-2-macroglobulin	↑	↑	-

Comparison at the pathway level

The lists of significantly changed proteins for the three time points of the study was subjected to “Core analysis”, provided by Ingenuity Pathway Analysis software. The results of the analysis were used to perform a “Comparison Analysis” with results of the “Core Analysis” that has been previously performed for transcriptomics, for each time point, in an effort to integrate the information obtained from the two analyses for a more comprehensive molecular profile of the KA-MTLE hippocampus at each time point of the study.

At **1 day** post injection, 30 overlapping IPA Canonical Pathways were identified between genomic and proteomic data (Appendix 14) These pathways were represented by one or two molecules in proteomics data, and between one and eighteen genes in transcriptomics. Of note, 17 of the pathways were represented by a single protein (Ptk2b), and between two and eighteen genes that did not include Ptk2b. Ptk2b is a cytoplasmic signal transduction intermediate implicated in multiple functions, with the most important in our study being cytoskeletal reorganization through actin polymerization, and immune response-related functions (leukocyte chemotaxis, phagocytosis by macrophages etc.), according to Ingenuity analysis.

At **3 days**, 63 overlapping pathways were found between the two datasets that were populated with one to six proteins, and with three to twenty four genes each (Appendix 15). Notably, some of the pathways are related to ECM signaling and cytoskeletal dynamics (e.g. Actin Cytoskeleton Signaling, Cdc42 Signaling, Integrin Signaling, Paxillin Signaling, ILK Signaling), synaptic vesicles (Clathrin-mediated Endocytosis Signaling), and inflammatory response.

At **30 days**, 49 overlapping pathways were found between the two datasets compared (Appendix 16). Specifically, the common pathways contained one to seventeen proteins, and two to sixteen genes each. Interestingly, most of these pathways are also observed at 3 days, and many pathways highly

enriched with proteins are also related to ECM signaling and cytoskeletal dynamics, synaptic vesicles and inflammatory response in this time point.

Comparison at the upstream regulator level

The results of Ingenuity Upstream Regulator analysis for transcriptomics and proteomics datasets were filtered for “transcription regulators”, in order to focus on the transcription factors (TFs) predicted to act as key regulators of the significantly changed genes and proteins, respectively. As a result, several overlapping transcription regulators were observed at each time point, none of which were significantly changed on gene or protein level.

Specifically, at 1 day 10, at 3 days 45 and at 30 days 43 transcription regulators were common between the two datasets. Importantly, according to Ingenuity prediction, one of the overlapping transcription regulators at 1 days (Cebpb), two at 3 days (Cebpb, Yy1) and eight at 30 days (Arnt2, Cebpb, Hoxa10, Mkl1, Mkl2, Nfkbia, Nkx2-1, Satb1) regulate the expression of one or more of the overexpressed NOX-related genes in the respective time point (Cyba, Cybb, Ncf1, Rac2).

Moreover, according to IPA “Regulator effects” networks, Cebpb has a known regulator/function relationship with activation of neuroglia in transcriptomic data, at 1 and 3 days via five genes (Bdnf, Ccl2, Ptgs2, Serpine1, Vim). At 30 days Hoxa10 is predicted to regulate activation of macrophages via four genes (Cybb, Fcer1g, Lcn2, Pros1) and Arnt2 is predicted to regulate cytotoxicity of lymphocytes via four genes (Fcgr2a, H2-K2/H2-Q9, Hla-A, Tyrobp). The analysis of proteomic data did not provide “Regulator Effects” networks.

3.1.7. MicroRNA analysis

The expression of 846 miRNAs was investigated with the Affymetrix GeneChip™ Mouse Genome 1.0 ST Array, at 1, 3 and 30 days post injection. From the three time points of the study KA-MTLE model studied, we observed significantly changed miRNAs only at 1 day post injection. In specific, five microRNAs were found to be overexpressed, namely ↑mir132, ↑mir212, ↑mir22, ↑mir592 and ↑mir710.

3.1.7.1 Predicted miRNA-mRNA interactions at 1 day post injection

In order to identify possible effects of these microRNA expression changes at 1 day post injection, we employed the online tool “miRwalk 2.0” aiming to predict miRNA-mRNA interactions in our dataset. Specifically, the “Predicted target module” facilitated the identification of possible downstream targets of the aforementioned upregulated miRNAs. The miRNA-mRNA prediction results were compared to the downregulated genes at 1 day. From a total of 106 underexpressed genes (i.e. the number of Entrez Gene Symbols identified by miRwalk 2.0 platform), 24 mRNAs were predicted as targets of one or more of the five upregulated miRNAs.

Specifically, miR22 is predicted to have ten of the significantly downregulated mRNAs as targets (Galntl6, Adcy1, Egfem1, Fam163a, Homer2, Htra4, Kctd4, Lrrn2, Per3, Slc22a8). MiR132 had four predicted mRNA targets (Cldn10, Mfsd4, Sema5a, Trpm3), which overlapped with the miR212 targets (Cldn10, Mfsd4, Sema5a, Trpm3, Aifm3, Psd2). Mir592 had five predicted mRNA targets (Galntl6, Cdk14, Dbp, Matn2, Ntsr2), and miR710 had two (Nrip2, Aifm3).

3.1.7.2. Validated miRNA-mRNA interactions at 1 day post injection

The “Validated Target Module” tool of the miRwalk 2.0 platform allowed the determination of established/published miRNA-mRNA relationships, along with tissue, organ and disease-related information. Specifically, we searched for validated associations of the significantly changed miRNAS with the following terms listed in the platform: “Brain”, “CA1 Region Hippocampal”, “Central Nervous System”, “Hippocampus”, “Neurons”, “Neuroglia”, “Synapses”, “Synaptic Vesicles”, “Synaptosomes”, and “Temporal Lobe”.

Based on our search, miR132 was the only one that has been associated with the mouse CNS and specifically, with the suprachiasmatic nucleus, where it participates in the regulation of genes related to the circadian clock. Moreover, miR132 presents with experimentally validated interactions with nine genes (Btg2, Mecp2, Mmp9, Nr4a2, Paip2, Rfx4, Kdm5a, Ep300, Arhgap32) one of which is upregulated in our dataset (↑Btg2), and is implicated in translational control. Validated miRNA-mRNA interactions were also found for miR-22 with four genes (Ass1, Irf8, Ywhaz, Arpc5) and for miR212 with one gene, namely Mmp9.

Our search for validated miRNA-mRNA interactions was extended to the downregulated genes at 1 day post injection, to identify the downregulated mRNAs that may be targeted by one or more miRNAs. From a total of 103 underexpressed genes, fifteen mRNAs (Acot11, Adcy1, Ccdc85a, Galntl6, Gjc3, Grm1, Hlf, Homer2, Lix1, Mgll, Rapgefl1, Scn3b, Sema5a, Trpm3) were found to be targeted by one or more of twenty one miRNAs (miR129, miR134, miR181a, miR1843a, miR19b, miR1b, miR223, miR301b, miR3071, miR325, miR425, miR466a, miR466d, miR466e, miR466k, miR466l, miR466p, miR5125, miR706, miR710, miR759). Specifically, Acot11, Ccdc85a, Homer2, and Trpm3 were found to be targeted by multiple miRNAs each, and miR5125 was the only miRNA with validated interactions with more than one mRNAs (Homer2, Grm1) (Table 3.3).

We then performed an organ-based search for the twenty one miRNAs with validated interactions with the underexpressed mRNAs (search terms: “Brain”, “CA1 Region Hippocampal”, “Central Nervous System”, “Hippocampus”, “Neurons”, “Neuroglia”, “Synapses”, “Synaptic Vesicles”, “Synaptosomes”, and “Temporal Lobe”), via the “Validated Target Module” tool. Accordingly, miR124, miR134, miR19b, miR223, miR301b and miR425 were found to be associated with the term “Brain”, and miR134 was also found to be associated with the term “Neurons”.

Table 3.3. *Validated miRNA-mRNA interactions for the underexpressed genes at 1 day post injection, according to the "Validated target module" tool of the miRwalk platform.*

miRNA	**mRNA target**
miR-1b	Acot11
miR-710	
miR-1b	
miR-223	Adcy1
miR-466p	Ccdc85a
miR-466e	
miR-466l	
miR-466a	
miR-759	Galntl6
miR-1843a	Gjc3
miR-5125	Grm1
miR-325	Hlf
miR-3071	Homer2
miR-5125	
miR-706	Lix1
miR-129	Mgll
miR-301b	
miR-19b	Rapgefl1
miR-425	Scn3b
miR-181a	Sema5a
miR-134	Trpm3
miR-466d	
miR-466k	

3.1.7.3. Validated miRNA-mRNA interactions at 3 days post injection

At 3 days post injection, no miRNAs were found to significantly changed, and the search for validated miRNA-mRNA interactions were therefore limited to the downregulated genes. As a result, from a total of 81 underexpressed genes (i.e. Entrez Gene Symbols identified by miRwalk platform), thirteen mRNAs (Cntnap2, Ddn, Fgf10, Fstl5, Galntl6, Grm1, Hapln4, Hlf, Homer2, Npr3, Scn3b, Serpini1, Slc44a5) were found to be targeted by one or more of twelve 12 miRNAs (miR20a, miR290a, miR297a, miR3071, miR325, miR340, miR340, miR425, miR495, miR5125, miR5125, miR541, miR706, miR759). Homer2 was the only mRNA with validated interactions with more than one miRNAs (miR3071, miR325), whilst two miRNAs were found to target more than one genes, miR5125 (Homer2, Grm1), and miR340 (Fstl5, Slc44a5) (Table 3.4).

An organ-based search for the thirteen miRNAs with validated interactions with the underexpressed mRNAs via the “Validated Target Module” tool followed, with same search terms used for the 1 day time point data. As a result, five miRNAs were found to be associated with the term “Brain”, namely miR297a, miR340, miR425, miR495, and miR541, and miR20a was found to be associated with the term “Hippocampus”.

3.1.7.4. Validated miRNA-mRNA interactions at 30 days post injection

Our search for validated miRNA-mRNA interactions was performed for the downregulated genes of the 30 day time point, since we observed no significantly changed miRNAs in this time point. According to “Validated Target Module”, from a total of 96 underexpressed genes (i.e. Entrez Gene Symbols identified by miRwalk 2.0 platform), seventeen mRNAs (A830018L16Rik, Adarb2, Cacna1e, Camk1d, Fam19a1, Fgf10, Galntl6, Grm1, Homer2, Islr2, Nos1, Pde1a, Runx1t1, Scn3b, Slc44a5, Slc8a1, Trp53i11) were found to be targeted by one or more of twenty three miRNAs (miR129, miR17, miR188, miR1942, miR20a, miR24, miR294, miR297b, miR302b, miR3071, miR3071, miR340, miR344d, miR344d, miR34b, miR410,

miR410, miR425, miR495, miR5125, miR5125, miR541, miR692, miR759, miR7b, miR883a, miR9). Specifically, A830018L16Rik, Homer2, Runx1t1 and Slc8a1 were found to be targeted by more than one miRNAs each. Three miRNAs were found to have validated interactions with more than one mRNAs, including miR-5125, which targets Homer2, and Grm1, and miR344d and miR410, each of which targets both Runx1t1 and Slc8a1 (Table 3.5).

We performed an organ-based search for the twenty three miRNAs with validated interactions with the underexpressed mRNAs via the “Validated Target Module” tool followed, with same search terms used for the 1 and 3 day time point data. As a result, ten miRNAs were found to be associated with term “Brain” (miR17, miR24, miR297a, miR340, miR34b, miR425, miR495, miR541, miR7b, miR9), whist miR9 was also associated with the terms “Central Nervous System” and “Neurons”, and miR-20a was found to be associated with the term “Hippocampus”.

Table 3.4. *Validated miRNA-mRNA interactions for the underexpressed genes at 3 days post injection, according to the "Validated target module" tool of the miRwalk platform.*

miRNA	**mRNA target**
miR-706	Cntnap2
miR-541	Ddn
miR-20a	Fgf10
miR-340	Fstl5
miR-759	Galntl6
miR-5125	Grm1
miR-290a	Hapln4
miR-325	Hlf
miR-3071	Homer2
miR-5125	
miR-495	Npr3
miR-425	Scn3b
miR-297a	Serpini1
miR-340	Slc44a5

Table 3.5. *Validated miRNA-mRNA interactions for the underexpressed genes at 30 days post injection, according to the "Validated target module" tool of the miRwalk platform.*

miRNA	**mRNA target**
miR-129	A830018L16Rik
miR-294	
miR-302b	
miR-692	
miR-883a	Adarb2
miR-34b	Cacna1e
miR-297b	Camk1d
miR-7b	Fam19a1
miR-20a	Fgf10
miR-759	Galntl6
miR-5125	Grm1
miR-3071	Homer2
miR-5125	
miR-17	Islr2
miR-9	Nos1
miR-24	Pde1a
miR-344d	Runx1t1
miR-410	
miR-425	Scn3b
miR-340	Slc44a5
miR-188	Slc8a1
miR-1942	
miR-3071	
miR-344d	
miR-410	
miR-495	
miR-541	Trp53i11

3.1.8 Evaluation of NOX expression by RT-qPCR

The expression of NOX in the KA-MTLE hippocampus of animals treated chronically with Valproate (VPA) or Apocynin (APO) was assessed by RT-qPCR analysis of twelve NOX related genes, namely Cyba, Cybb, Ncf1, Ncf2, Ncf4, Nox1, Nox4, Mpo, Prdx6, Rac1, Rac2, and Pu.1. For the statistical analysis of the results, relative quantitation was performed with the comparative Ct method, using the housekeeping gene Gapdh as reference for normalization purposes (Methods, Chapter 2.2.3). For each set of comparisons (APO vs. tap water, VPA vs. saline), the statistical significance threshold was set at $p<0.05$.

3.1.8.1 Effects of chronic Valproate treatment on NOX expression in the KA-MTLE hippocampus

The effects of chronic treatment with the anticonvulsive drug Valproate on NOX-related gene expression in the epileptic hippocampus were assessed at 30 days post injection in the KA-MTLE mouse model. The expression of twelve NOX related genes and the housekeeping gene Gapdh was interrogated by RT-qPCR in the hippocampi of KA-injected animals that received VPA treatment or saline as control (n=8, 4 biological replicates /treatment). The analysis revealed that Ncf1 and Cyba were significantly overexpressed, and Nox1 was underexpressed, in VPA vs. control groups (Figure 3.34).

3.1.8.2 Effects of chronic Apocynin treatment on NOX expression in the KA-MTLE hippocampus

The effects of chronic treatment with the NADPH oxidase inhibitor Apocynin on NOX-related gene expression in the epileptic hippocampus were assessed at 30 days post injection in the KA-MTLE mouse model. The expression of twelve NOX related genes and the housekeeping gene Gapdh was interrogated by RT-qPCR in the hippocampi of KA-injected animals that received APO treatment or tap water as control (n=8, 4 biological replicates /treatment). The analysis revealed that nine of the twelve genes assessed were significantly changed ($p<0.05$) in APO vs. control groups. In specific, Cyba, Cybb, Ncf1, Ncf4, Nox4, Prdx6, Rac1, Rac2, and Pu.1 were found to be

significantly underexpressed. The results of RT-qPCR analysis in the hippocampus of the Apocynin-treated KA-MTLE mice vs. the control KA-MTLE mice are demonstrated in Figure 3. 35 and 3.36.

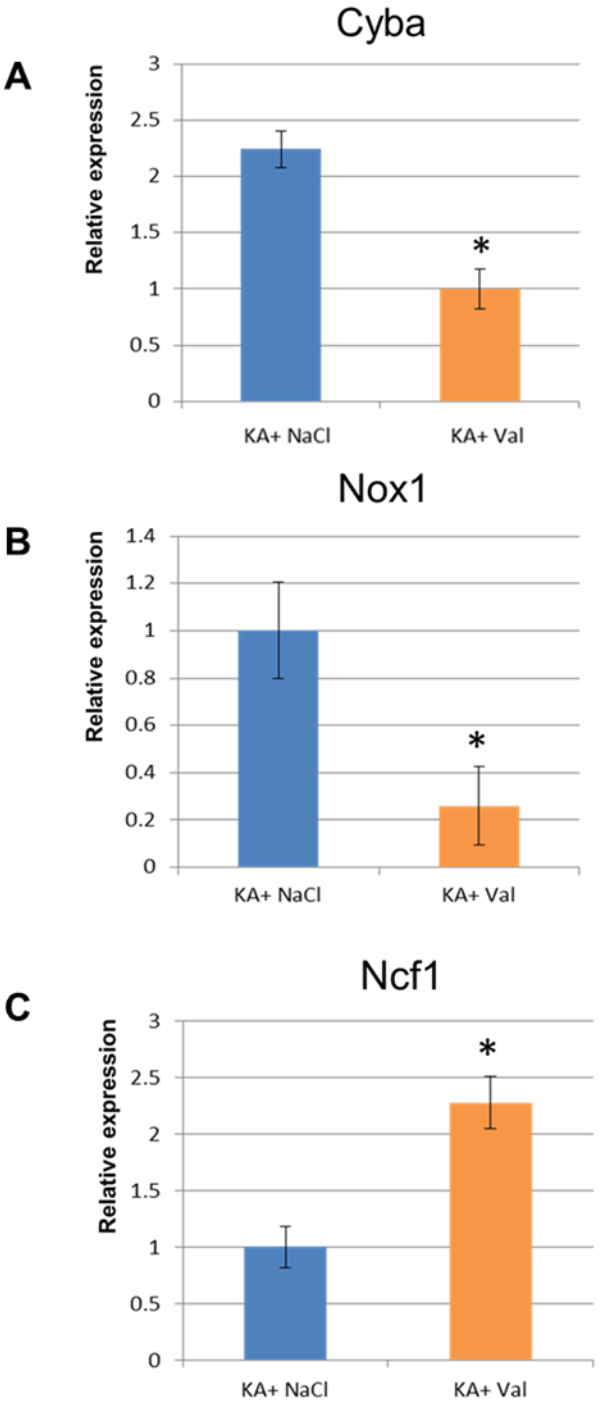


Figure 3.34. *NOX gene expression changes in the hippocampus of Valproate-treated KA-MTLE mice. RT-qPCR results for A. Cyba, B. Nox1, Ncf1 and C Pu.1. *p<0.05.*

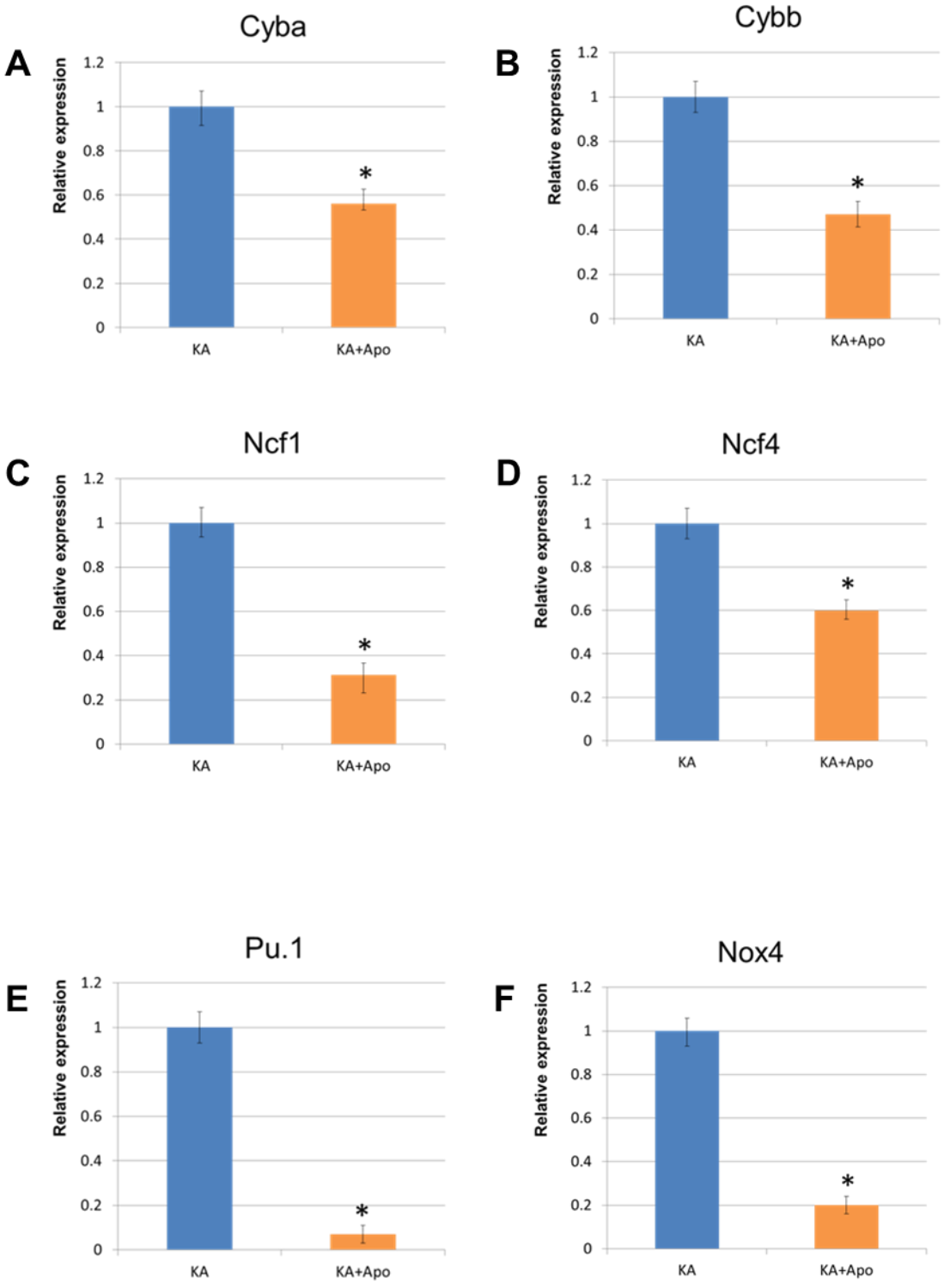


Figure 3.35. *NOX gene expression changes in the hippocampus of Apocynin-treated KA-MTLE mice. RT-qPCR results for A. Cyba, B. Cybb, C. Ncf1, D.Ncf4, E Pu.1 and F.Nox4. *p<0.05.*

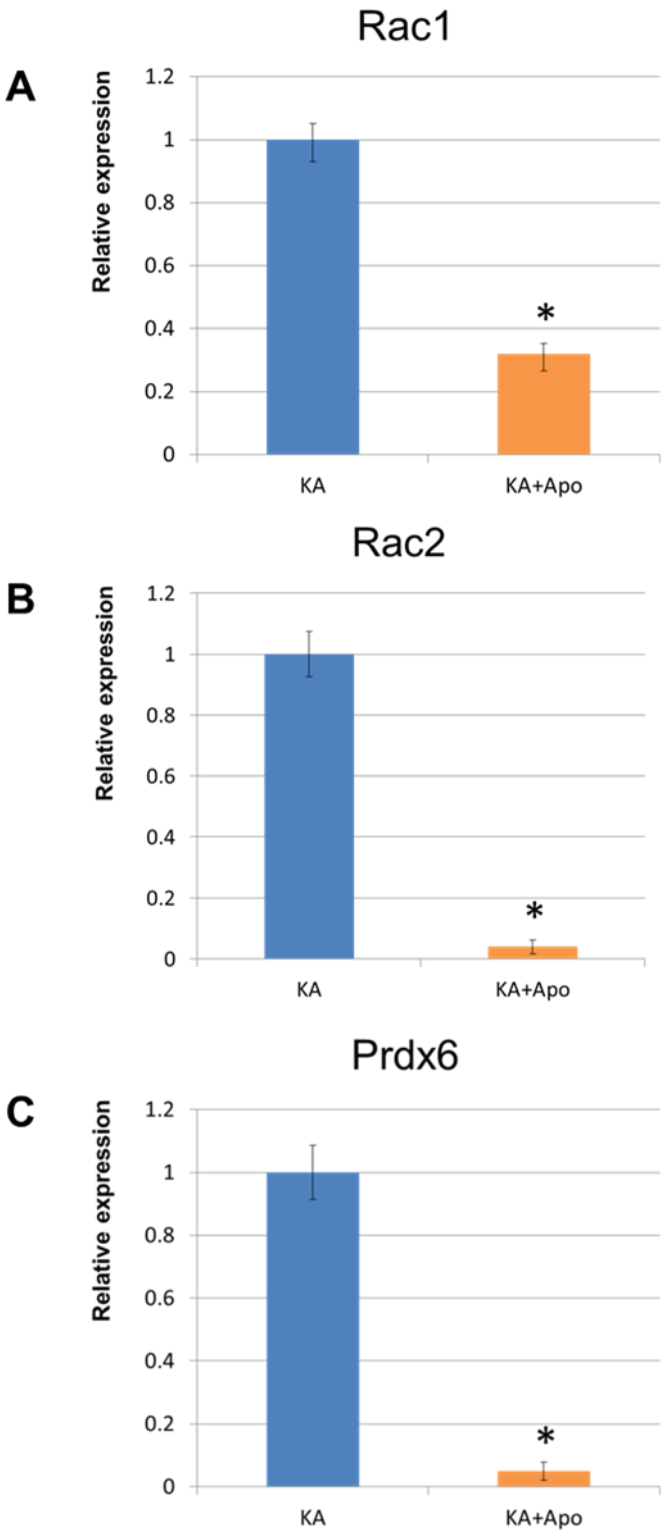


Figure 3.36. *NOX gene expression changes in the hippocampus of Apocynin-treated KA-MTLE mice. RT-qPCR results for A.Rac1, B.Rac2, C.Prdx6. *p<0.05.*

3.2. NOX4 KO KA-MTLE MOUSE MODEL

3.2.1. Statistically significant changes in global gene expression of the NOX4-KO KA-MTLE mouse hippocampus

Extensive statistical and bioinformatical analyses were performed the evaluation of transcriptomic data derived from microarray experiments on KA-MTLE NOX4 KO mice samples, in order to determine the specific gene expression changes induced by the deletion of NOX4 to the hippocampus. ANOVA analysis with a range of FDR-adjusted p-value and fold change thresholds (FDR-adjusted p-value <0.05,<0.01; fold change >2, >1.75, >1.5) was used to compare NOX4 KO and WT animals, at 30 days post KA injection. The analysis showed no significant changes in gene expression between the two sample groups.

With respect to these results, a number of additional steps were taken to interrogate the interference of possible outlier samples. Although all samples met the designated Quality Controls criteria of the microarray experiment, a closer inspection of the experimental results indicate the presence of an atypical outlier sample in the analysis (Figure 3.s 37). As demonstrated in Figure 3.37A, although pm_ mean[1](grey line) is higher than mm_mean[2] (green line) for all samples as expected, sample 6_NOX4KO_2 has overall much higher raw intensity than the rest of the samples assessed in the experiment. Moreover, in Figure 3.37B, which depicts normalized global expression levels across all arrays, Relative Log Expression signal[3] for sample 6_NOX4KO_2 exhibits different distribution in comparison to the rest of the arrays. Furthermore, according to Principal Component Analysis (Figure 3.38), the dataset generated by sample 6_NOX4KO_2 is poorly correlated

[1] Pm_ mean: the raw intensity for all perfect match probes on the array (prior to normalization, RMA background correction etc). The target is specifically hybridized to the perfect match probes.

[2] Mm_mean: the raw intensity of all mismatch probes on the array. The target should not hybridize to mismatch probes, they are used to detect non-specific hybridization and give local background, to compare the pm probes with.

[3] Relative Log Expression signal: plots the distribution of the log probe set signal values on each array vs. the median log probe set signal value across all selected arrays.

with the rest of the NOX4 KO samples interrogated in this experiment, rendering the data generated from this sample group highly heterogeneous and thus diminishing the expression difference between NOX KO and WT samples beyond statistical significance. In order to test this hypothesis, we repeated the analysis excluding sample 6_NOX4KO_2. As demonstrated in comparison Figure 3.39, after the exclusion of possible outlier 6_NOX4KO_2 (Figure 3.39B) the raw intensity levels of all the samples of the experiment vary much less. However, the exclusion of this sample had no effect on the observed differences in gene expression between KA-MTLE NOX4 KO and KA-MTLE WT hippocampi). ANOVA analysis was performed with a range of thresholds (FDR-adjusted p-value <0.05,<0.01; fold change >2, >1.75, >1.5), but no statistically significant changes in gene expression between the two sample groups were found.

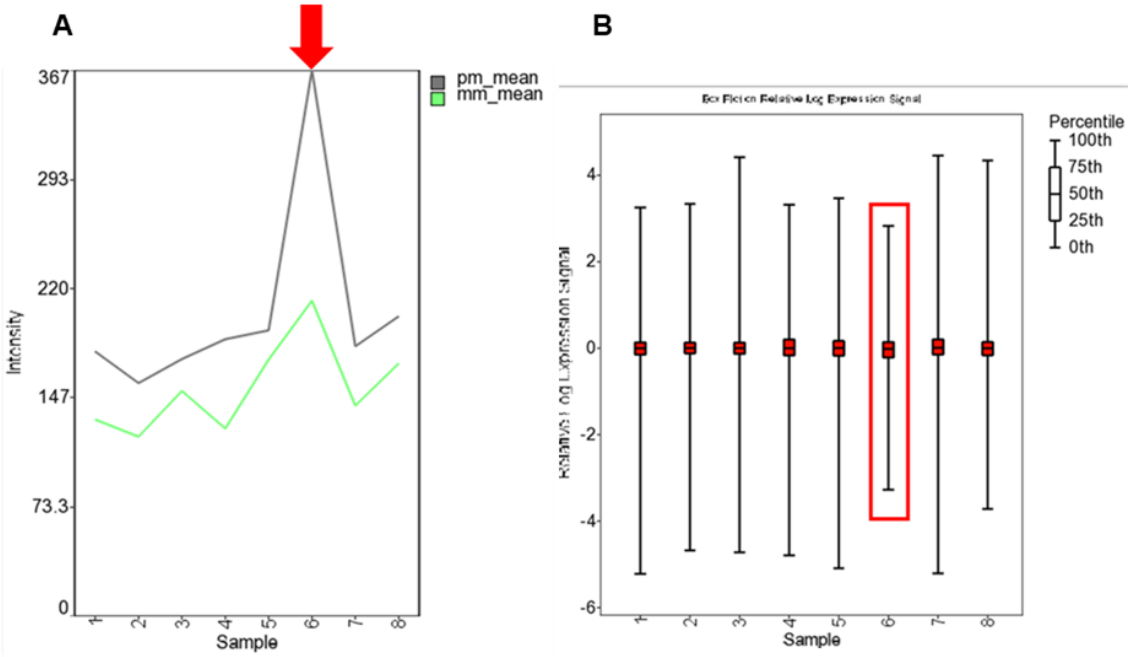


Figure 3.37. *Quality controls for microarray analysis of KA-MTLE WT and NOX4 KO samples.* ***A.*** *Quality evaluation of specific vs. non-specific hybridization across all arrays. The x-axis and the y-axis represent samples and raw intensity of the probes in the array, prior to normalization and RMA background correction.* ***B.*** *Quality evaluation of the normalized global expression levels across all arrays (red box: 25th-75th percentile).The possible outlier sample 6_NOX4KO_2 is indicated by the red arrow in A, and the red rectangle in B.*

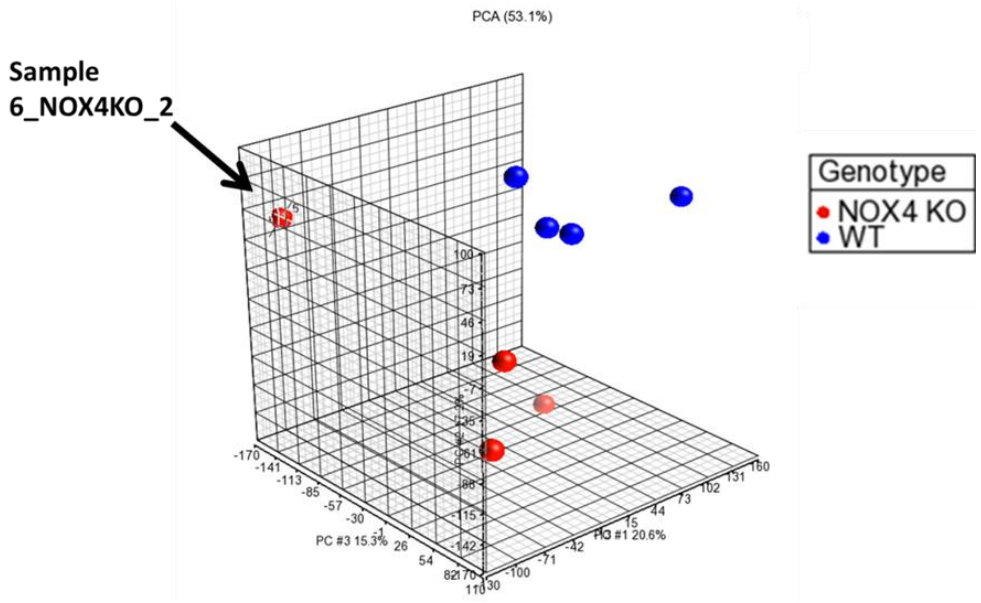


Figure 3.38. *Principal component analysis to determine the correlation of the datasets in 3D space (red: KA-MTLE WT, blue: KA-MTLE NOX4 KO). The possible outlier sample 6_NOX4KO_2 is indicated by the arrow.*

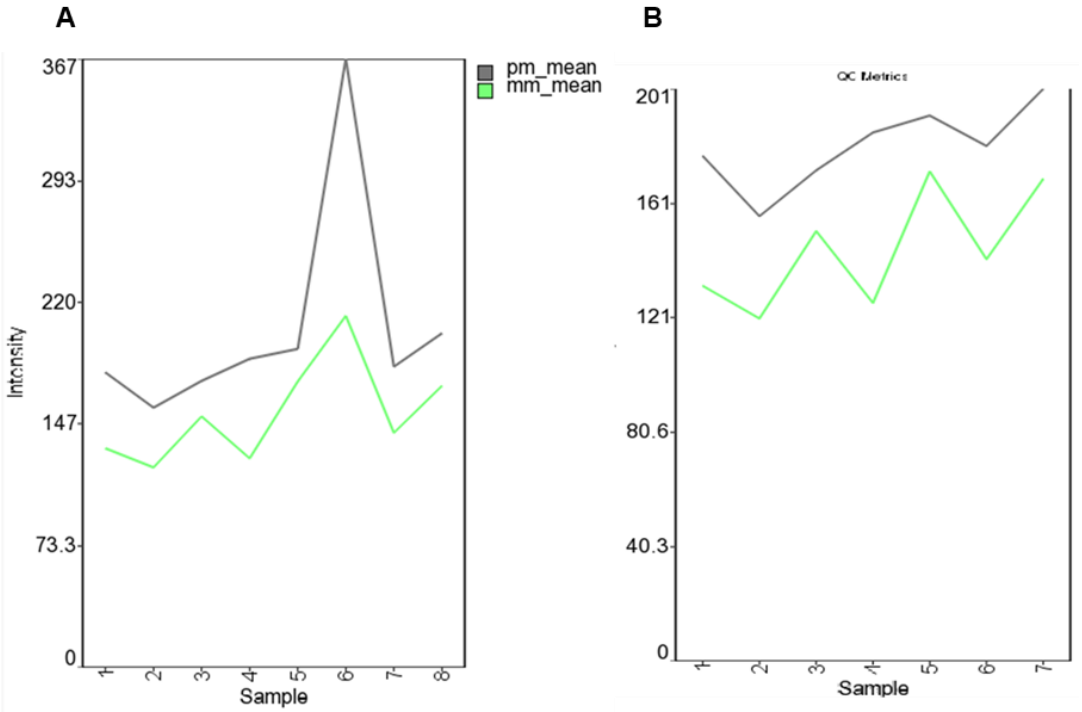


Figure 3.39. *Quality controls for microarray analysis of KA-MTLE WT and NOX4 KO samples. Quality evaluation of specific vs. non-specific hybridization across all arrays. The x-axis and the y-axis represent samples and raw intensity of the probes in the array, prior to normalization and RMA background correction.* ***A.*** *All samples of the experiment included.* ***B.*** *Exclusion of possible outlier sample 6_NOX4KO_2.*

3.3. HUMAN MTLE

3.3.1 Statistically significant changes in global gene expression of the human MTLE hippocampus

The microarray analysis of the transcriptome of the epileptic hippocampi obtained from MTLE patients was followed by extensive bioinformatical and statistical analysis, in order to determine the specific gene expression changes between patient subgroups.

Specifically, ANOVA analysis was applied for the comparison of subgroups with distinct histopathological features, i.e. hippocampal sclerosis (HS vs. non HS), febrile seizures (FS vs. non FS), focal cortical dysplasia (FCD vs. non FCD), and granule cell dispersion (GCD vs. No GCD). To facilitate the determination of the appropriate fold change threshold according to the sample size of each subgroup comparison, power analysis was performed. Accordingly, a range of different statistical thresholds were applied for each of the analyses in order to have a better appreciation of the data, as described in detail below.

3.3.1.1 Hippocampal Sclerosis (HS vs. non HS)

To determine the effects of Hippocampal Sclerosis to the transcriptome of the human epileptic hippocampus, we classified the samples according to the presence of HS, as determined by histopathological examination and MRI (Methods, Chapter 2.2.2). We grouped samples with ILAE Type 1 and Type 2 HS together, since only two samples with Type 2 HS were available and are inadequate for statistical analysis Moreover, as shown in Figure 3.40, no clear distinction can be made between the datasets produced by Type and Type 2 samples. ANOVA analysis was performed for the comparison of human MTLE samples with HS (n=10/ Type 1 HS, n=2/Type 2 HS) vs. No HS (n=5), and power analysis was applied for the determination of fold change (Figure 3.41). Accordingly, we tested FDR adjusted p-values <0.01, and 0.05; with fold change >2, >1.75, and >1.5, but no statistically significant changes in gene expression were observed between HS and NO HS subgroups. We next applied unadjusted p-value thresholds <0.01 and <0.05, with fold change >2, >1.5, and >1.3. At unadjusted p-value <0.05 and fold change >1.3, we

identified 222 significantly changed transcripts, with 122 (61%) of them being overexpressed and 100 (39%) underexpressed. The fold changes of individual probe sets ranged from 2.18 (F5, coagulation factor V (proaccelerin, labile factor) to -2.00 (NPAS4, neuronal PAS domain protein 4) (Appendix 17).

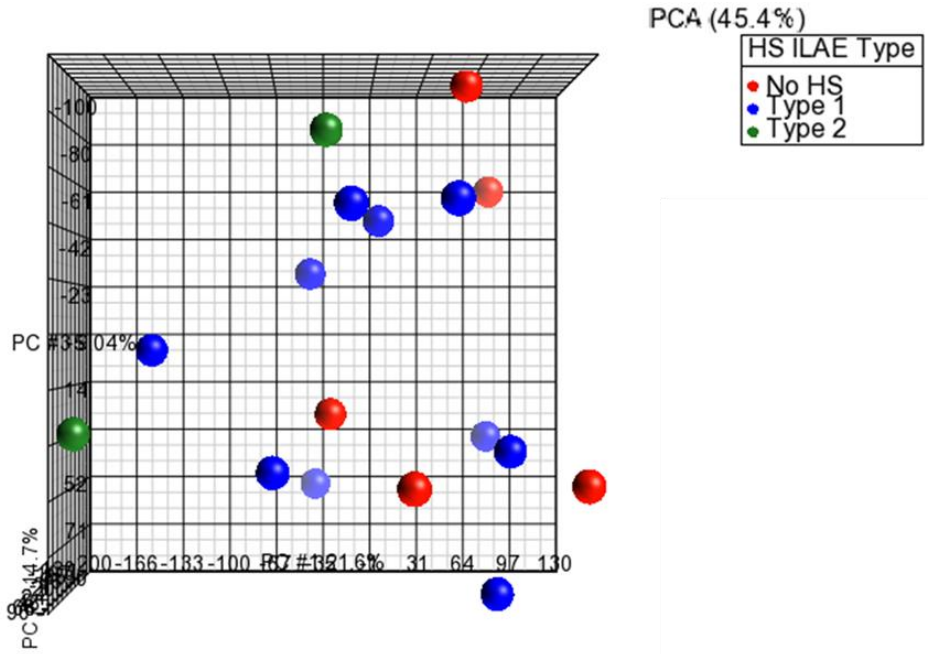


Figure 3.40. *Principal Component Analysis to determine the correlation of the datasets in 3D space (red: human MTLE without HS, blue: human MTLE with ILAE Type 1 HS, green: human MTLE with ILAE Type 2 HS). All HS (Type 1, Type 2) and No HS samples were used for the comparison between the two groups.*

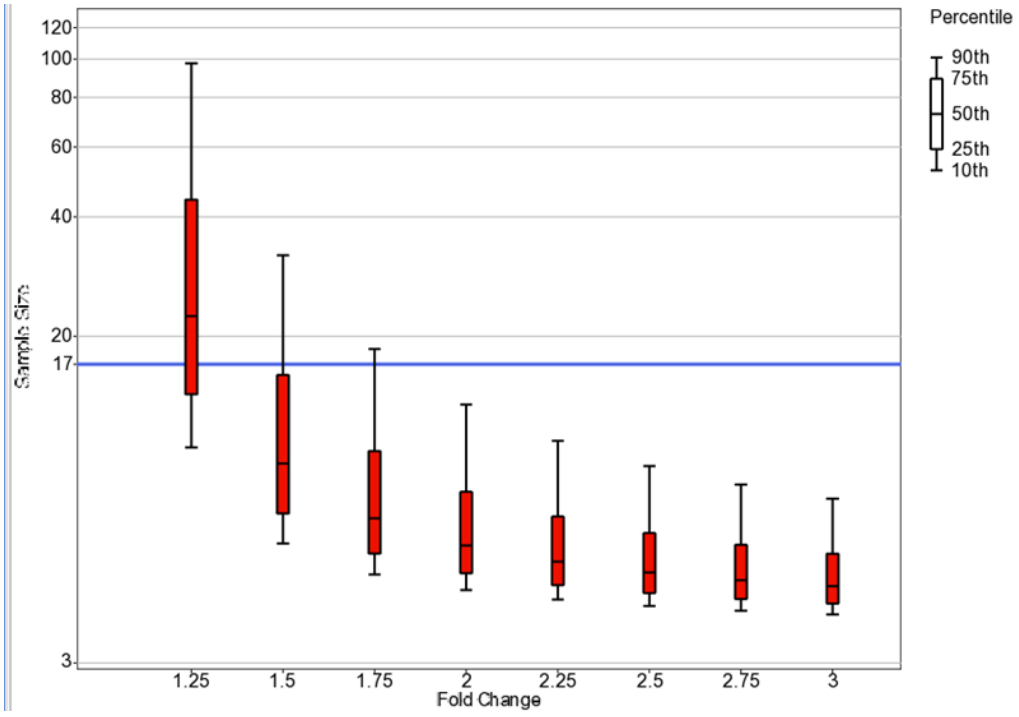


Figure 3.41 *.Power analysis for the determination of the appropriate fold change threshold, for the comparison of human MTLE samples with and without Hippocampal Sclerosis (HS vs. non HS.)*

3.3.1.2. Febrile Seizures subgroup (FS vs. non FS)

To determine the effects of Febrile Seizures to the transcriptome of the human epileptic hippocampus, we classified the samples according to the occurrence of FS (Methods, Chapter 2.2.2). Outlier samples were excluded from the analysis, and PCA showed a clear distinction between FS and No FS subgroups (Figure 3.42). ANOVA analysis was performed for the comparison of human MTLE samples with FS (n=7) vs. No FS (n=6), and power analysis was applied for the determination of fold change (Figure 3.43). Accordingly, we tested FDR adjusted p-value <0.01, with fold change >2, >1.75, and >1.5, but no statistically significant changes in gene expression were observed between FS and NO FS subgroups. We next applied a more lenient FDR adjusted p-value threshold (<0.05) with the most appropriate fold change threshold indicated by power analysis (>2), that resulted in the identification of 32 significantly changed transcripts between FS and NO FS subgroups (Appendix 18). Specifically, all of the probe sets were overexpressed, with the fold changes of individual probe sets ranging from 5.86 (SERPINA3 // serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, a) to 2.02 (SFRP2, secreted frizzled-related protein 2).

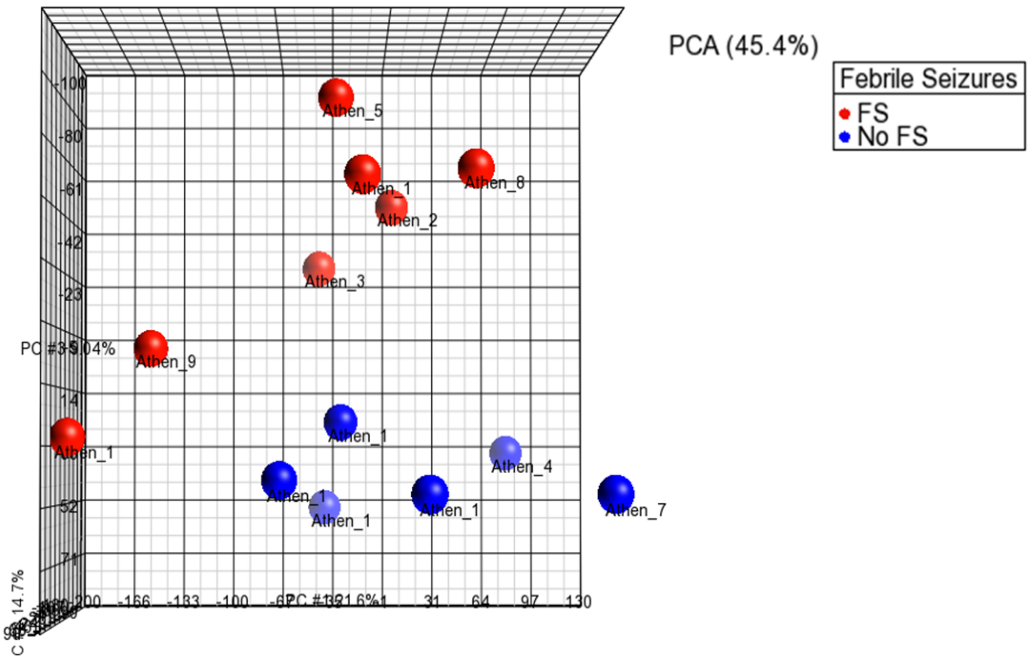


Figure 3.42. *Principal Component Analysis to determine the correlation of the datasets in 3D space (red: human MTLE with FS, blue: human MTLE without FS). Outlier samples were excluded from the analysis, and all FS and no FS samples were used for the comparison of the two groups*

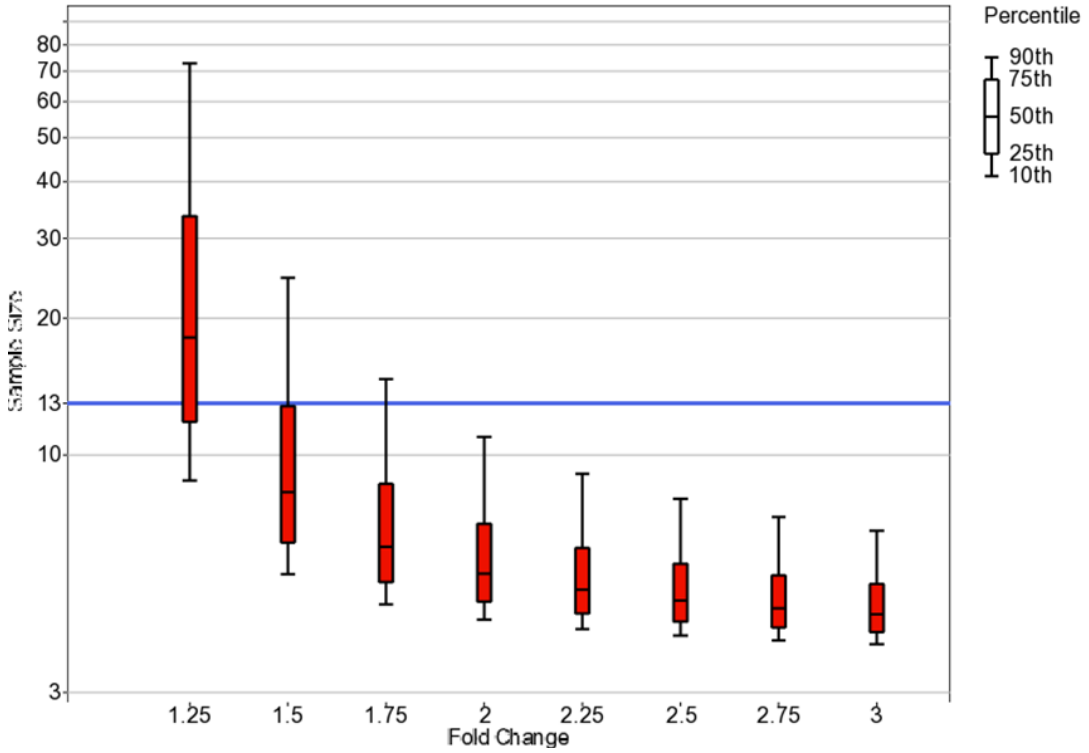


Figure 3.43. *Power analysis for the determination of the appropriate fold change threshold, for the comparison of human MTLE samples with and without Febrile Seizures (FS vs. non FS).*

3.3.1.3 Focal Cortical Dysplasia (FCD vs. non FCD)

To determine the effects of Focal Cortical Dysplasia to the transcriptome of the human epileptic hippocampus, we classified the samples according to the presence of FCD (Methods, Chapter 2.2.2). Outlier samples were excluded from the analysis, and PCA showed a clear distinction between FCD and No FCD subgroups (Figure 3.44). ANOVA analysis was performed for the comparison of human MTLE samples with FCD (n=3) vs. No FCD (n=8), and power analysis was applied for the determination of fold change (Figure 3.45). Accordingly, we tested FDR adjusted p-value <0.01, with fold change >2.25, >2 and >1.75, but no statistically significant changes in gene expression were observed between FCD and No FCD subgroups. We next applied an FDR adjusted p-value threshold of <0.05, with fold change >2.25, that resulting in the identification of 14 significantly changed transcripts. Specifically, all of the 14 probe sets were overexpressed, with the fold changes of individual probe sets ranging from 9.45 (SERPINA3, serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, a) to 2.35 (CPAMD8, C3 and PZP-like, alpha-2-macroglobulin domain containing 8) (Appendix 19).

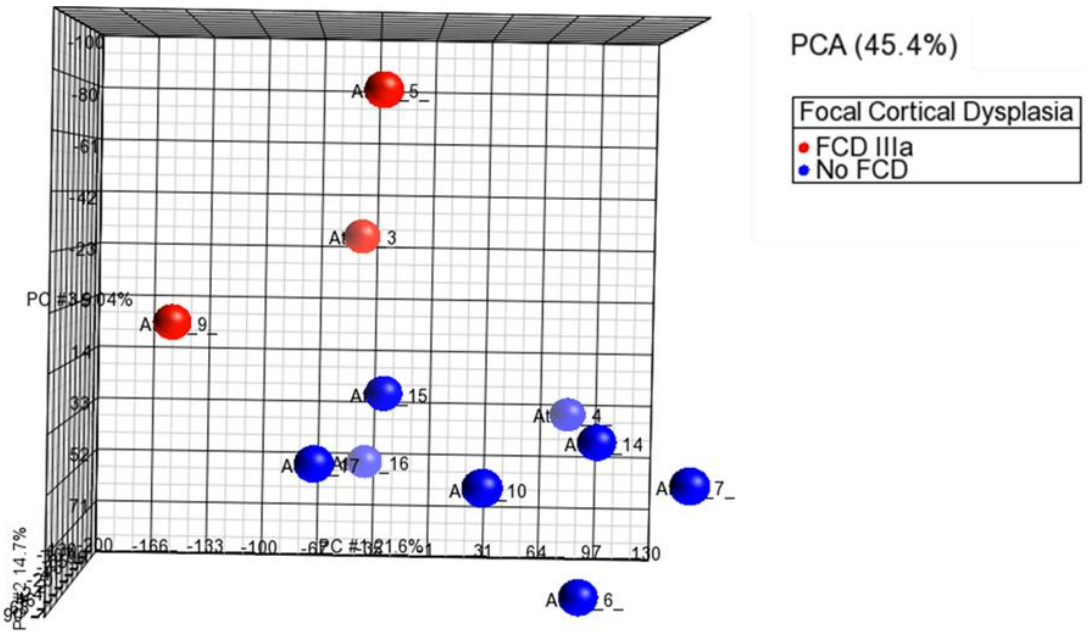


Figure 3.44. *Principal Component Analysis to determine the correlation of the datasets in 3D space (red: human MTLE with FCD IIIa type, blue: human MTLE without FCD). All FCD samples and a subset of 8 selected no FCD samples were used for the comparison.*

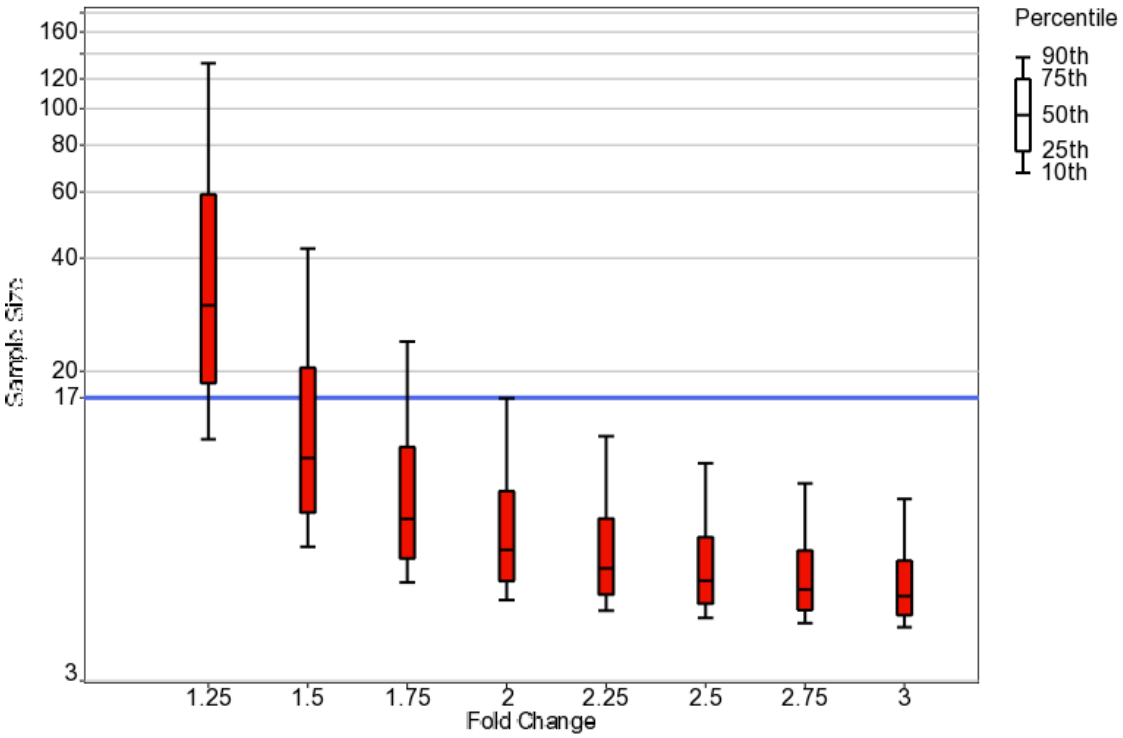


Figure 3.45. *Power analysis for the determination of the appropriate fold change threshold, for the comparison of human MTLE samples with and without Focal Cortical Dysplasia (FCD vs. No FCD).*

3.3.1.4 Granule Cell Dispersion (GCD vs. No GCD)

To determine the effects of Granule Cell Dispersion to the transcriptome of the human epileptic hippocampus, we classified the samples according to the presence of GCD (Methods, Chapter 2.2.2). Single-sample groups (i.e., slight GCD, slight GCL, no assignment) were excluded from the analysis, and groups of 4 selected samples/condition were compared, with the PCA showing a clear distinction between GCD and No GCD subgroups (Figure 3.46). ANOVA analysis was performed for the comparison of human MTLE samples with GCD (n=4) vs. No GCD (n=4), and power analysis was applied for the determination of fold change (Figure 3.47). Accordingly, we tested FDR adjusted p-value <0.01, with fold change >2.5, >2.25 and >12, but no statistically significant changes in gene expression were observed between GCD and No GCD subgroups. We next applied an FDR adjusted p-value threshold of <0.05, with fold change >2.5, >2.25 and >2, and AEBP1 (AE Binding Protein 1, fold change: 2.65) was the only significantly changed transcript observed in every fold change threshold tested.

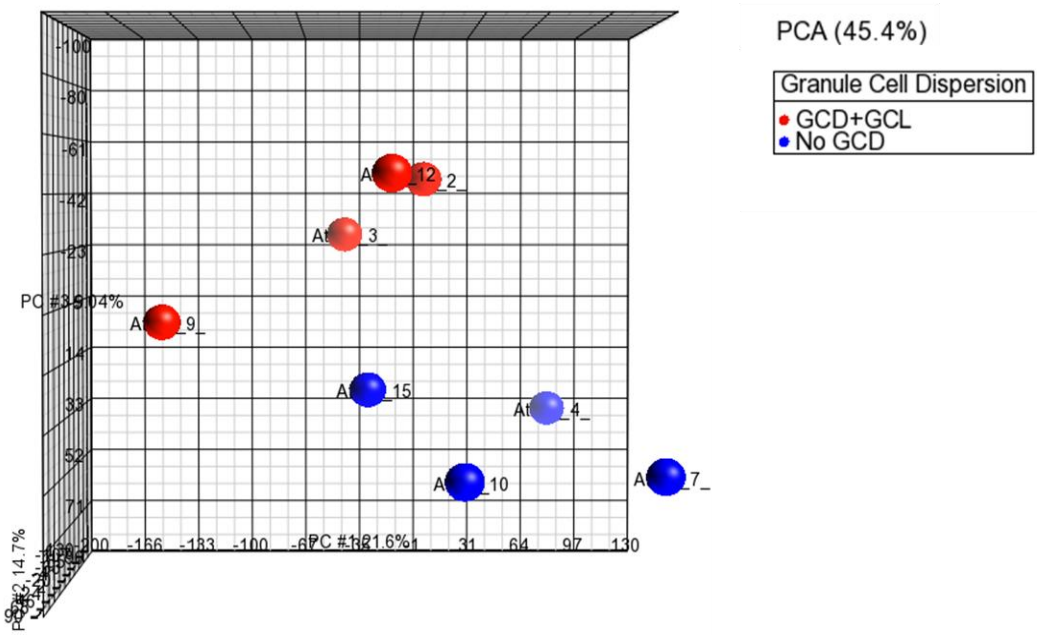


Figure 3.46. *Principal component analysis to determine the correlation of the datasets in 3D space (red: human MTLE with GCD and GCL, blue: human MTLE without GCD. Single-sample groups (i.e., slight GCD, slight GCL, no assignment) were excluded from the analysis; groups of selected 4 samples/condition were compared*.

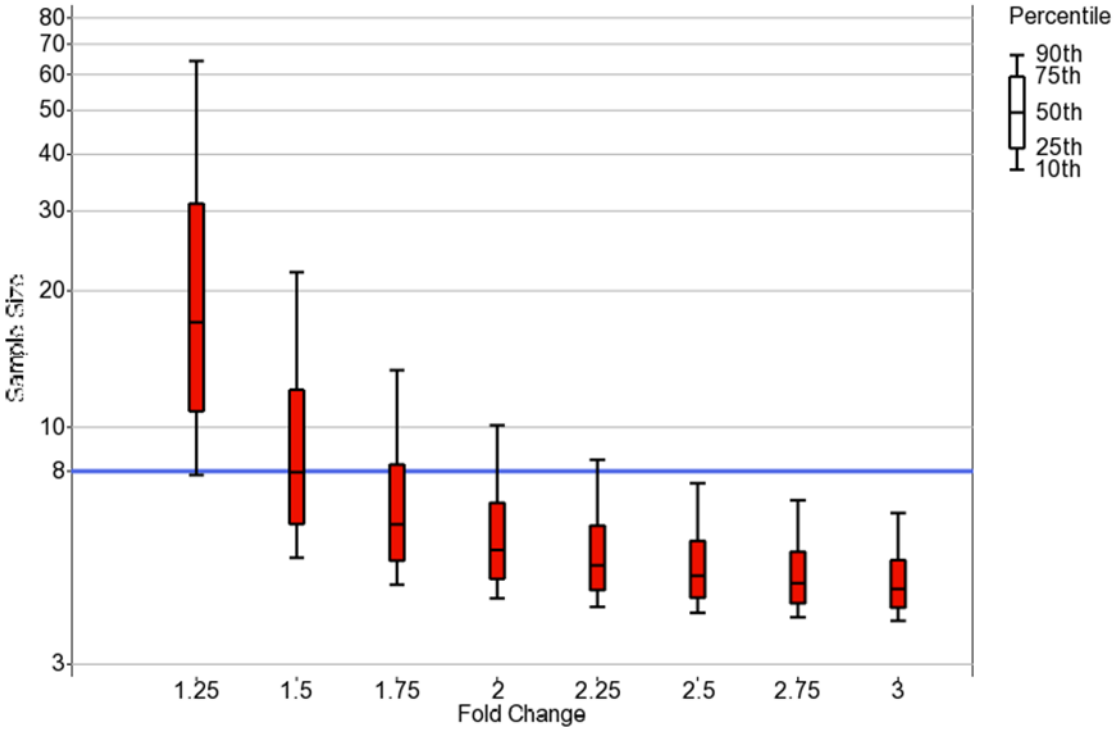


Figure 3.47. *Power analysis for the determination of the appropriate fold change threshold, for the comparison of human MTLE samples with and without Granule Cell Dispersion (GCD vs. No GCD).*

3.3.2 Ingenuity Pathway Analysis (HS vs. no HS)

The list of significantly changed genes obtained from the comparison of HS vs. No HS human MTLE sample groups (p-value<0.05, fold change>1.3) was subjected to “Core Analysis” via IPA software, as previously described in the section Methods (Chapter 2.2.4.2). IPA software mapped a total of 210 unique genes (Entrez Gene Symbols) in IPA knowledge database, which were used for the next steps of the analysis (“Analysis ready” molecules).

3.3.2.1 Ingenuity Pathway Analysis: Significantly changed functions

According to functional categorization results of IPA “Core Analysis”, the top significantly changed “Physiological system development and function” category is “Nervous system development and function”, which also is the most populated one, with 44 genes (ADCY8, AKAP5, APLN, ASCL1, CACNA2D1, CDHR1, CNGA3, CYP26B1, DAO, DLGAP3, DOC2A, GLRA1, ID1, ITGB8, JPH3, KCNH3, KCNK9, KCNN1, KIF3C, LRAT, MAP2K1, mir-181, mir-21, NPAS4, NPY5R, NRN1, PAX6, PHACTR4, PIP5K1C, PPP3R1, PRKG1, QPCT, RFX4,RGR, RGS9, RTN4RL1, S100A8, SCG5, SFRP2, SLC30A3, SLC7A11, SLC8A2, SYT5, SYTL4).

The top 5 enriched subcategories in “Nervous system development and function” include “neurotransmission” with 13 genes (AKAP5, DLGAP3, DOC2A, GLRA1, JPH3, KCNK9, KCNN1, mir-181, NPY5R, PIP5K1C, PPP3R1, SLC7A11, SYT5), “Memory” with 11 genes (ADCY8, JPH3, KCNH3, MAP2K1, NPAS4, PAX6, PPP3R1, QPCT, SLC30A3, SLC7A11, SLC8A2), “Synaptic transmission” with 10 genes (AKAP5, DLGAP3, DOC2A, GLRA1, KCNN1, NPY5R, PIP5K1C, PPP3R1, SLC7A11, SYT5), “Long-term potentiation” with 9 genes (ADCY8, AKAP5, DAO, DOC2A, JPH3, KCNH3, MAP2K1, PPP3R1, SLC8A2), and “Excitatory postsynaptic potential” which is populated by 8 genes (AKAP5, DLGAP3, DOC2A, JPH3, mir-181, NPAS4, NRN1, PIP5K1C).

The top significantly changed “Molecular and Cellular Function” category is “Cell-To-Cell Signaling and Interaction” with 31 genes (ADCY8, AKAP5,

APLN, CACNA2D1, CD99, CNGA3, DAO, DLGAP3, DOC2A, F5, GLRA1, JPH3, KCNH3, KCNK9, KCNN1, MAP2K1, mir-181, mir-21, NPAS4, NPY5R, NRN1, PIP5K1C, PPP3R1, PRKG1, PTPN20, SLC7A11, SLC8A2, ST6GALNAC2, SYT5, TJP2, TOLLIP). The most enriched significantly changed "Molecular and Cellular Function" category is "Molecular Transport", with 38 genes (AHCYL1, AKAP5, AP1S1, APLN, ATP6V1G2, CACNA2D1, CNGA3, CYBRD1, CYP26B1, DIO2, FBLN5, GLRA1, KCNH3, KCNK1, KCNN1, KCNV1, LRAT, MAP2K1, MYOM1, NDFIP2, NPY5R, PAX6, PON3, PRDX6, PRKG1, S100A8, SCG5, SLC12A4, SLC30A3, SLC38A1, SLC45A4, SLC7A11, SLC8A2, SLCO4C1, SYTL4, TJP2, TTN, UGP2).

Importantly, 12 significantly changed genes were specifically categorized under the "Diseases and Disorders" category "Neurological Disease", in the subcategory "Seizures" (AKAP5, AP1S1, CACNA2D1, CAMKK1, EGR4, GLRA1, KCNH3, KCNK1, KCNV1, LAMP5, NPY5R, SCG5).

3.3.2.2 Ingenuity Pathway Analysis: Significantly changed Canonical Pathways

IPA "Core Analysis" resulted in the identification of 35 Canonical Pathways that were significantly changed ($p<0.05$) between HS and No HS sample groups (Table 3.6). A total of 43 out of 210 genes analyzed were mapped to known molecular pathways, and the top twenty pathways are demonstrated in Figure 3.48. According to the analysis results, the significantly changed pathway populated by the greatest number of genes is "Protein Kinase A Signaling" with ten genes (↓PPP3R1, ↓AKAP5, ↓PDE2A, ↑CNGA3, ↑PLCE1, ↓MAP2K1, ↑TTN, ↑ADCY8, ↑ADD3, ↑PLCD3 (Figure 3.49), followed by "Gap Junction Signaling" with seven genes (↓PPP3R1, ↓MAP2K1, ↑PRKG1, ↑TJP2, ↑PLCE1, ↑ADCY8, ↑PLCD3) (Figure 3.50) which was found to be the top significantly changed Canonical Pathway, as determined by p-value.

The pathways that follow with 6 genes include "Phospholipase C Signaling" (↓PPP3R1, ↓MAP2K1, ↑PLCE1, ↑ADCY8, ↑PLCD3, ↑AHNAK) (Figure 3.51), "cAMP-mediated signaling" (↓PPP3R1, ↓PDE2A, ↓AKAP5, ↓MAP2K1, ↑ADCY8, ↑CNGA3) (Figure 3.52), "Superpathway of Inositol Phosphate Compounds" (↓PPP1R1C, ↓PPFIA4, ↑PLCE1, ↑PIP5K1C, ↑PTPN20,

↑PLCD3), “Dopamine-DARPP32 Feedback in cAMP Signaling” (↓PPP3R1, ↓CAMKK1, ↑PRKG1, ↑PLCE1, ↑ADCY8, ↑PLCD3) (Figure 3.53). “Synaptic Long Term Potentiation” follows with 5 genes (↓PPP3R1, ↓MAP2K1, ↑PLCE1, ↑ADCY8, ↑PLCD3) (Figure 3.54), and amongst the top twenty significantly changed Canonical Pathways, we also report “Synaptic Long Term Depression” (↑PLCD3, ↑PRKG1, ↑PLCE1, ↓MAP2K1), “Gαs Signaling” (↓MAP2K1, ↑CNGA3, ↑ADCY8, ↑ADD3) (Figure 3.55), “P2Y Purigenic Receptor Signaling Pathway” (↓MAP2K1,↑ADCY8, ↑PLCD3, ↑PLCE1) and “Phagosome Maturation” with 4 genes (↓ATP6V1H, ↓ATP6V1G2, ↑PRDX6, ↑CTSH).

Table 3.6. *Significantly changed IPA Canonical Pathways in HS vs. No HS human MTLE samples (p<0.05).The pathways are ranked by descending number of genes mapped to each of them.*

#	IPA Canonical Pathway	No of genes	Gene Symbols
1	Protein Kinase A Signaling	10	PPP3R1,CNGA3,PLCE1,PDE2A, MAP2K1,TTN,ADCY8,ADD3,AKAP5,PLCD3
2	Gap Junction Signaling	7	PPP3R1,PRKG1,TJP2,PLCE1,MAP2K1,ADCY8,PLCD3
3	Role of NFAT in Cardiac Hypertrophy	7	SLC8A2,PPP3R1,PLCE1,MAP2K1,ADCY8,AKAP5,PLCD3
4	Cellular Effects of Sildenafil (Viagra)	6	KCNN1,PRKG1,PLCE1,PDE2A,ADCY8,PLCD3
5	Dopamine-DARPP32 Feedback in cAMP Signaling	6	PPP3R1,PRKG1,PLCE1,CAMKK1,ADCY8,PLCD3
6	cAMP-mediated signaling	6	PPP3R1,CNGA3,PDE2A,MAP2K1,ADCY8,AKAP5
7	Superpathway of Inositol Phosphate Compounds	6	PPP1R1C,PLCE1,PIP5K1C,PTPN20,PPFIA4,PLCD3
8	Phospholipase C Signaling	6	PPP3R1,PLCE1,MAP2K1,ADCY8,PLCD3,AHNAK
9	Synaptic Long Term Potentiation	5	PPP3R1,PLCE1,MAP2K1,ADCY8,PLCD3
10	Sperm Motility	5	CNGA3,PRKG1,PLCE1,PDE2A,PLCD3
11	D-myo-inositol-5-phosphate Metabolism	5	PPP1R1C,PLCE1,PTPN20,PPFIA4,PLCD3
12	Aldosterone Signaling in Epithelial Cells	5	PLCE1,PIP5K1C,MAP2K1,DNAJC5G,PLCD3
13	Leptin Signaling in Obesity	4	PLCE1,MAP2K1,ADCY8,PLCD3
14	Gαs Signaling	4	CNGA3,MAP2K1,ADCY8,ADD3
15	PI3K Signaling in B Lymphocytes	4	PPP3R1,PLCE1,MAP2K1,PLCD3
16	P2Y Purigenic Receptor Signaling Pathway	4	PLCE1,MAP2K1,ADCY8,PLCD3
17	Cardiac β-adrenergic Signaling	4	SLC8A2,PDE2A,ADCY8,AKAP5
18	Synaptic Long Term Depression	4	PRKG1,PLCE1,MAP2K1,PLCD3
19	Phagosome Maturation	4	PRDX6,CTSH,ATP6V1H,ATP6V1G2
20	D-myo-inositol (1,4,5)-Trisphosphate Biosynthesis	3	PLCE1,PIP5K1C,PLCD3
21	Phototransduction Pathway	3	RGR,CNGA3,RGS9
22	Melatonin Signaling	3	PLCE1,MAP2K1,PLCD3
23	GPCR-Mediated Integration of Enteroendocrine Signaling Exemplified by an L Cell	3	PLCE1,ADCY8,PLCD3
24	Heparan Sulfate Biosynthesis	3	PRDX6,SULT1C4,B3GAT2
25	GPCR-Mediated Nutrient Sensing in Enteroendocrine Cells	3	PLCE1,ADCY8,PLCD3
26	α-Adrenergic Signaling	3	SLC8A2,MAP2K1,ADCY8
27	Ubiquinol-10 Biosynthesis	2	BCKDHB,CYP26B1

#	IPA Canonical Pathway	No of genes	Gene Symbols
	(Eukaryotic)		
28	Netrin Signaling	2	PPP3R1,PRKG1
29	Glycine Degradation (Creatine Biosynthesis)	1	GATM
30	Thyronamine and Iodothyronamine Metabolism	1	DIO2
31	Thyroid Hormone Metabolism I (via Deiodination)	1	DIO2
32	Branched-chain α-keto acid Dehydrogenase Complex	1	BCKDHB
33	Acetate Conversion to Acetyl-CoA	1	ACSS3
34	Serine Biosynthesis	1	PSAT1
35	α-tocopherol Degradation	1	CYP4F12

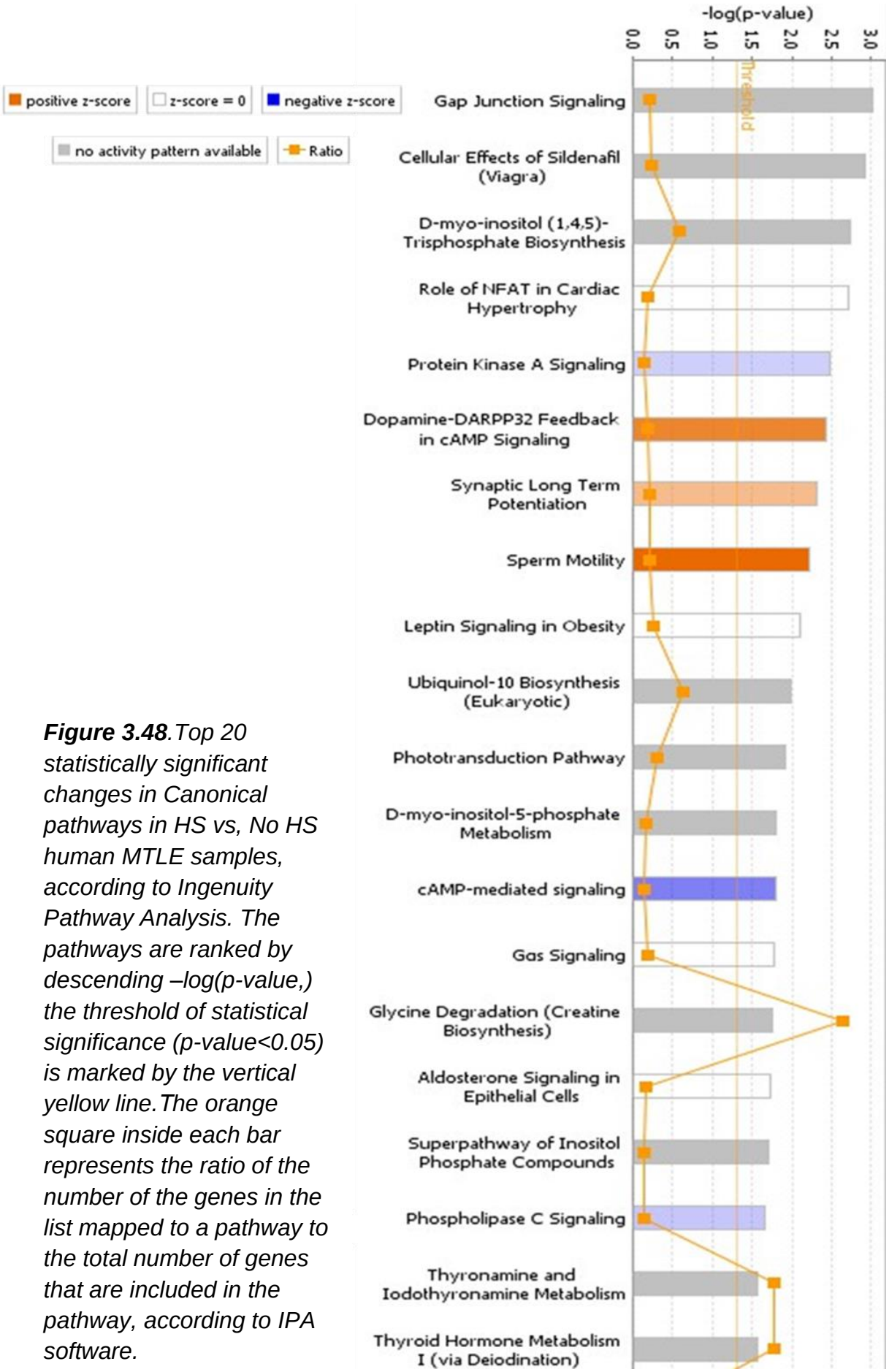


Figure 3.48*.Top 20 statistically significant changes in Canonical pathways in HS vs, No HS human MTLE samples, according to Ingenuity Pathway Analysis. The pathways are ranked by descending –log(p-value,) the threshold of statistical significance (p-value<0.05) is marked by the vertical yellow line.The orange square inside each bar represents the ratio of the number of the genes in the list mapped to a pathway to the total number of genes that are included in the pathway, according to IPA software.*

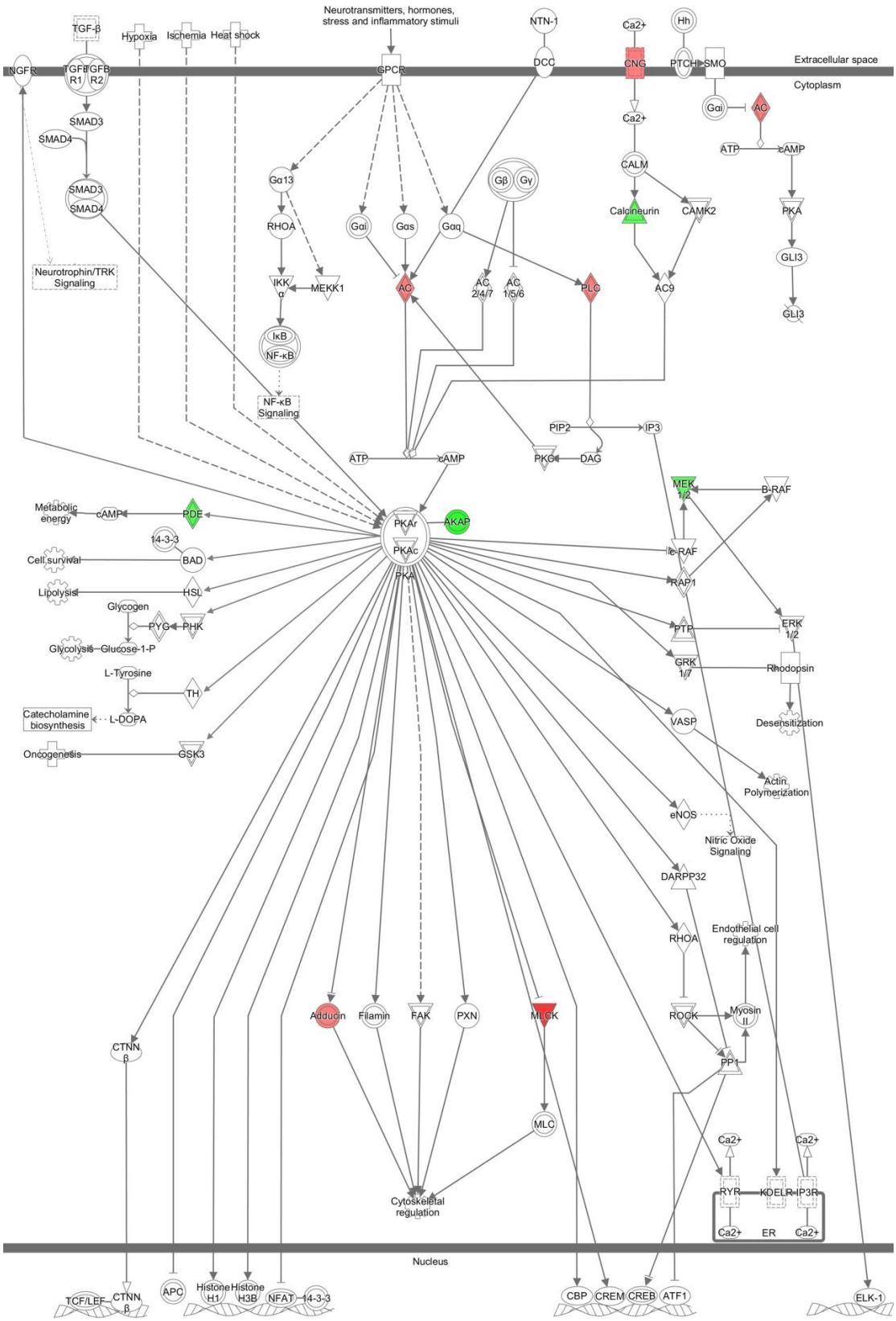


Figure 3.49. *Protein Kinase A Signaling Canonical Pathway in HS vs. No HS human MTLE samples Image generated via IPA software (bold outline=gene with significantly changed expression, red=overexpression, green=underexpression).*

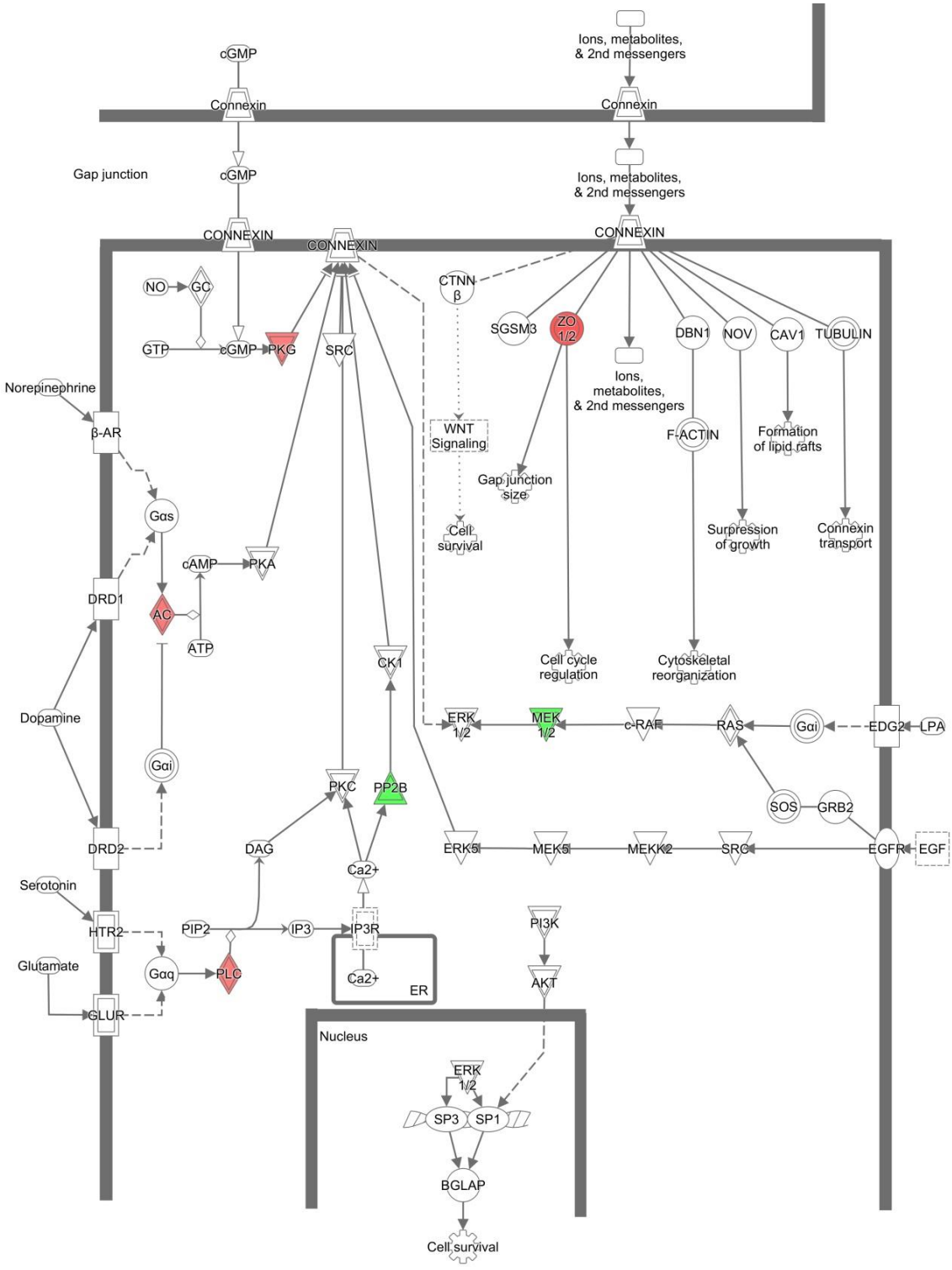


Figure 3.50. *Gap Junction Signaling Canonical Pathway in HS vs. No HS human MTLE samples Image generated via IPA software (bold outline=gene with significantly changed expression, red=overexpression, green=underexpression).*

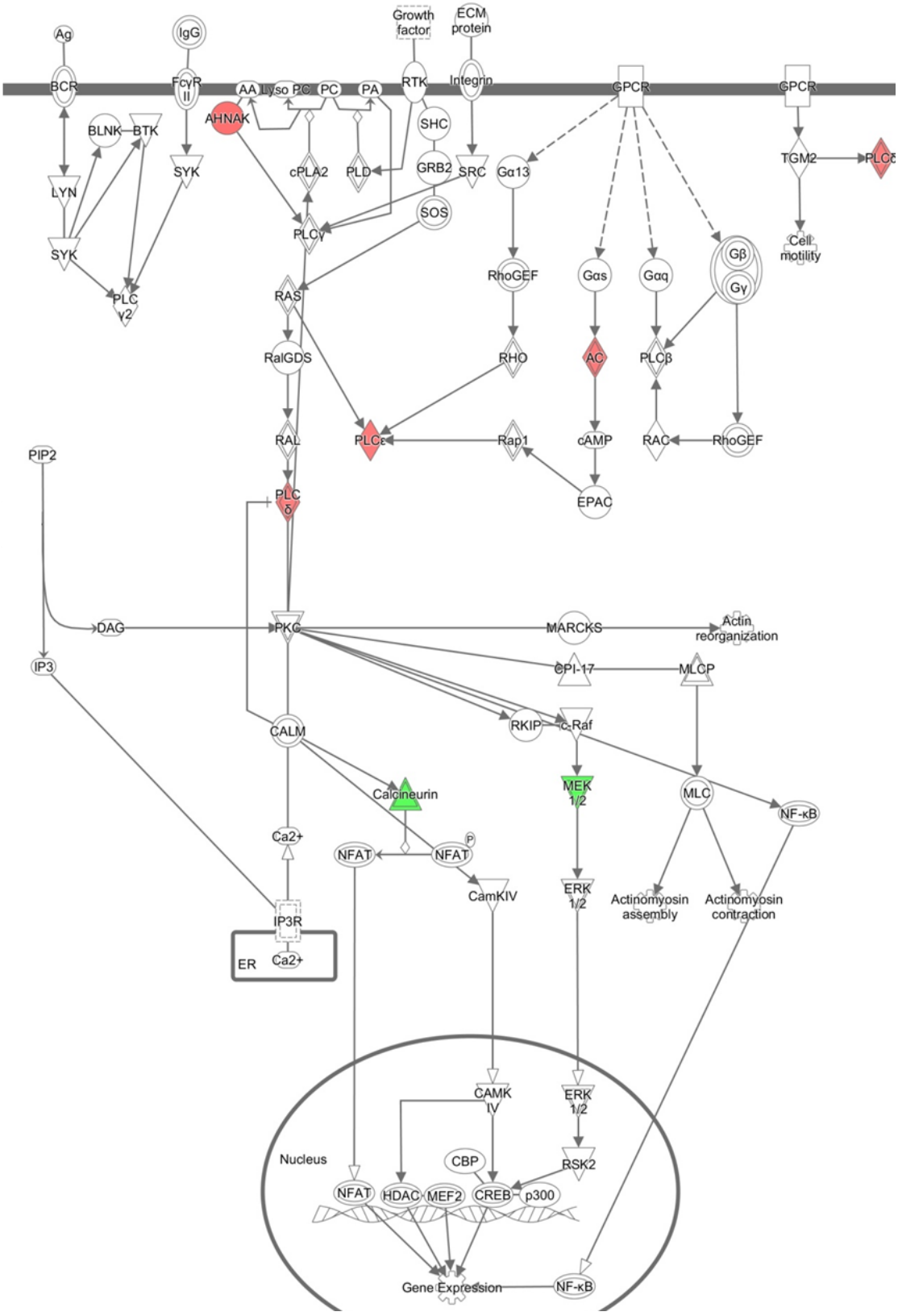


Figure 3.51. *Phospholipase C Signaling Canonical Pathway in HS vs. No HS human MTLE samples Image generated via IPA software (bold outline=gene with significantly changed expression, red=overexpression, green=underexpression).*

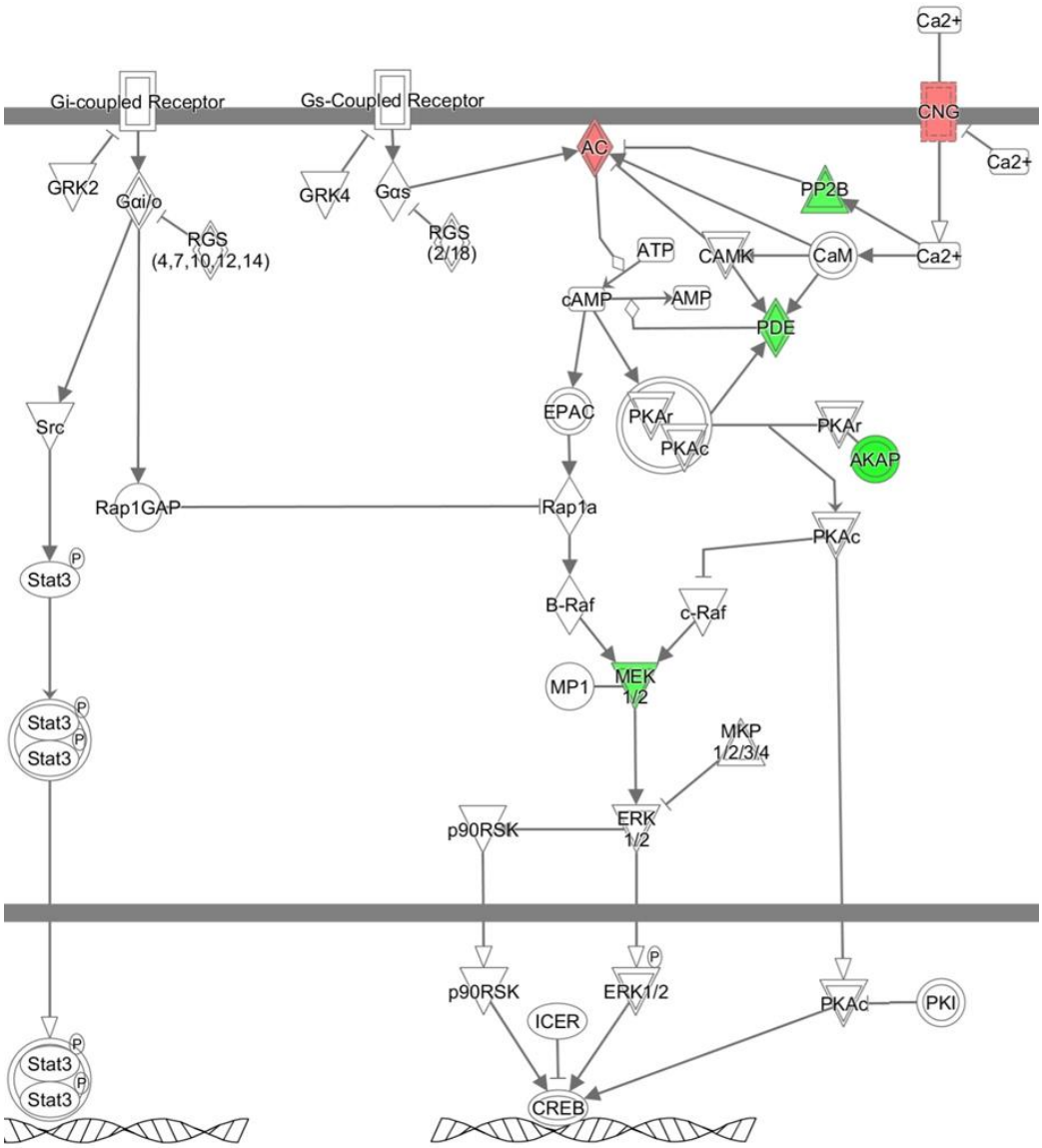
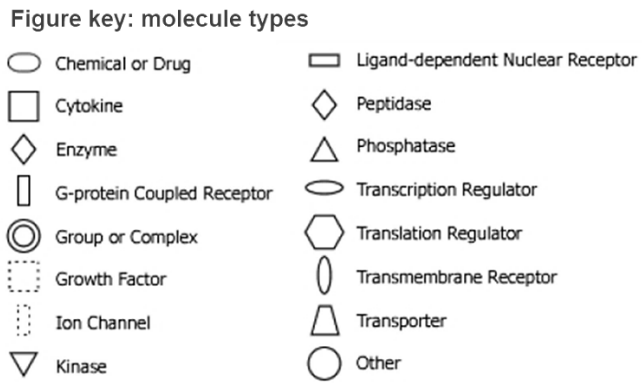


Figure 3.52. *cAMP-mediated signaling Canonical Pathway in HS vs. No HS human MTLE samples. Image generated via IPA software (bold outline=gene with significantly changed expression, red=overexpression, green=underexpression).*



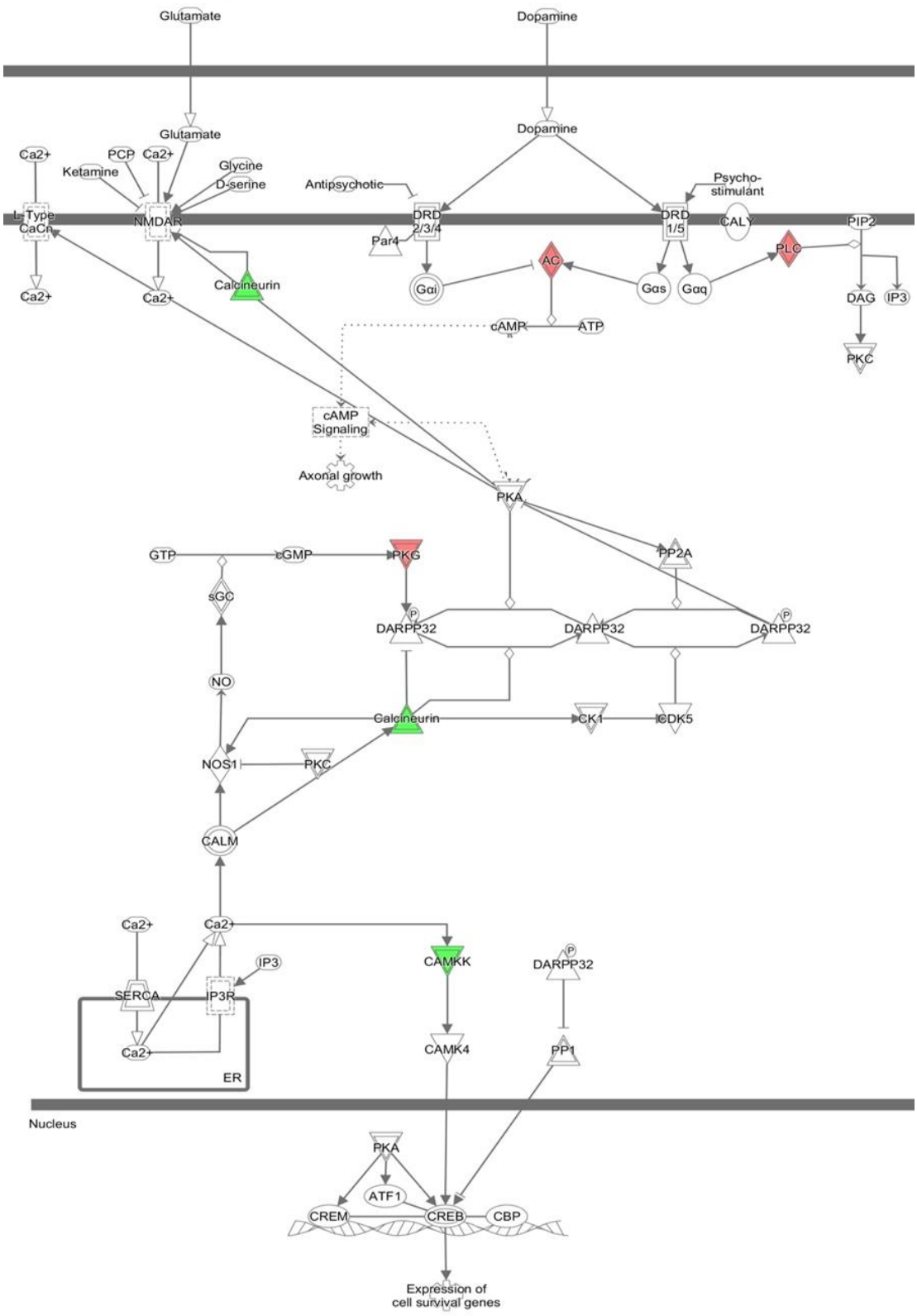


Figure 3.53. *Dopamine-DARPP32 Feedback in cAMP Signaling Canonical Pathway in HS vs. No HS human MTLE samples. Image generated via IPA software. (bold outline=gene with significantly changed expression, red=overexpression, green=underexpression)*

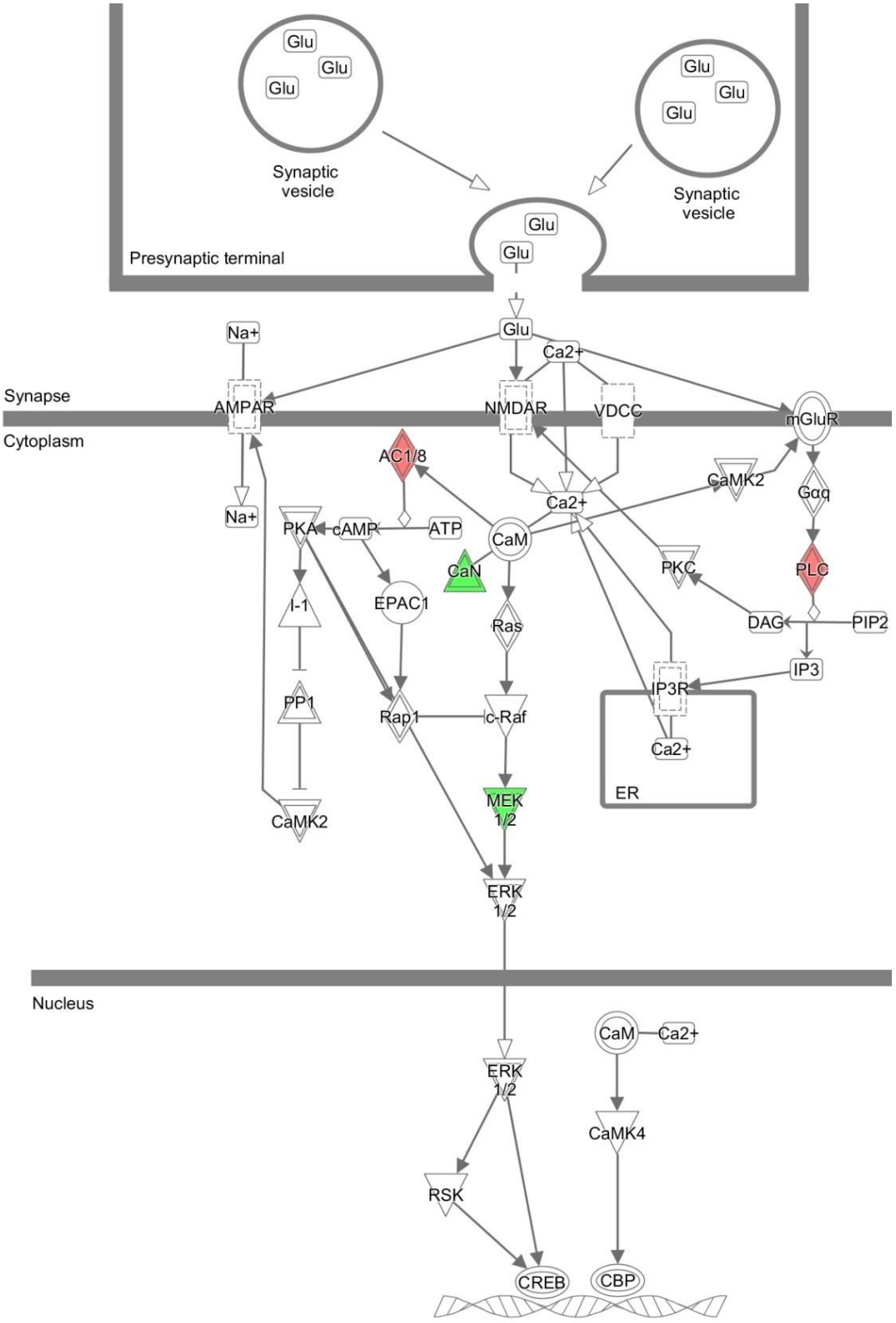


Figure 3.54. *Synaptic Long Term Potentiation Canonical Pathway in HS vs. No HS human MTLE samples. Image generated via IPA software (bold outline=gene with significantly changed expression, red=overexpression, green=underexpression).*

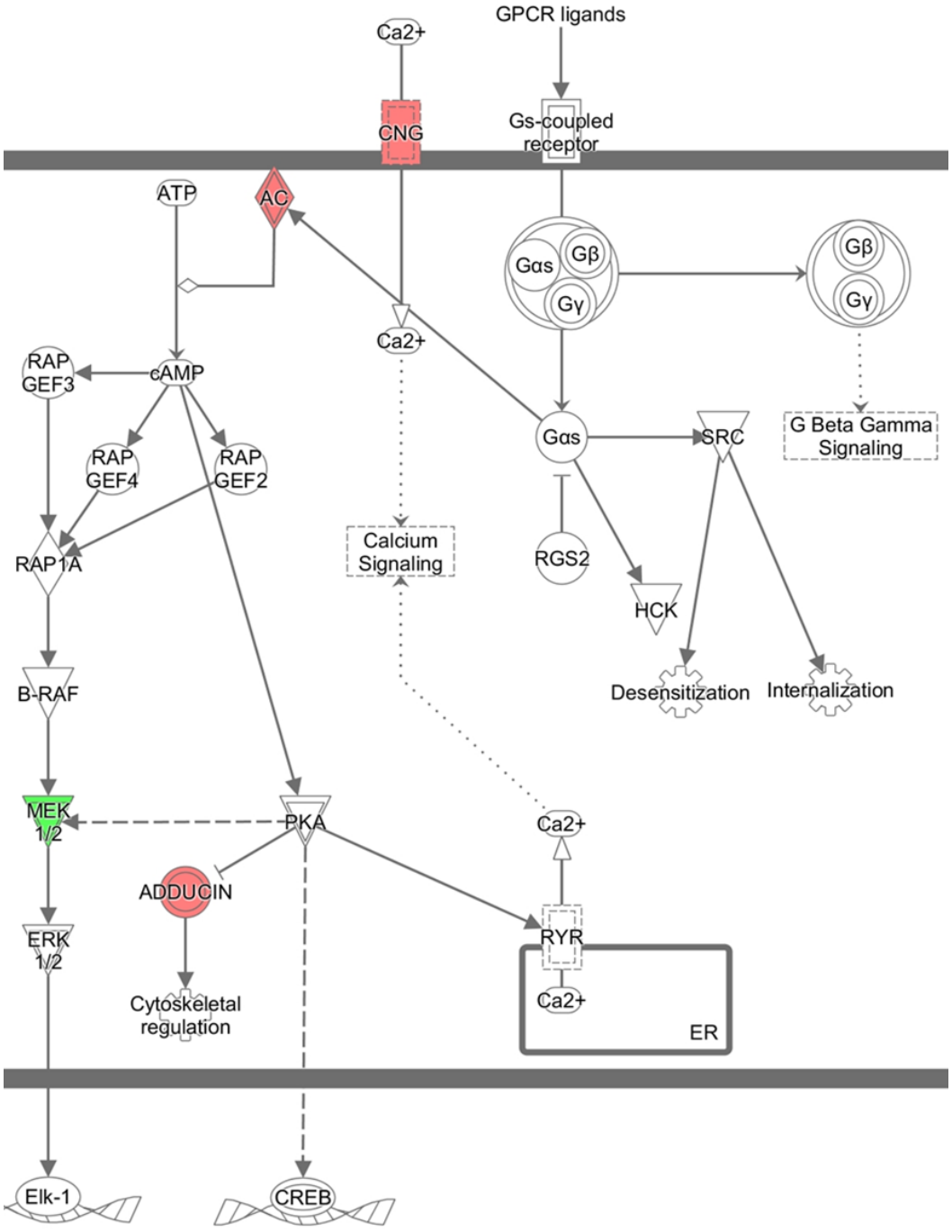


Figure 3.55. *Gα$_s$ Signaling Canonical Pathway in HS vs. No HS human MTLE samples. Image generated via IPA software. (bold outline=gene with significantly changed expression, red=overexpression, green=underexpression).*

3.3.2.3. Ingenuity Pathway Analysis: Upstream regulators

We next performed “Upstream regulator” analysis for the significantly changed genes in HS vs. No HS samples, for the prediction of key regulatory molecules. The upstream regulators were filtered based on the molecule type for “transcription regulators”, in an effort to identify key transcription factors (TFs) that may account for the some of the observed expression changes, and resulted in the identification of 29 genes (ATRX, CBX5, CNOT7, CREB1, DR1, FOXP2, GATA4, GFI1, GSX2, H2AFX, HAND2, HNF1B, HOXA9, LHX2, MAFB, MEF2C, MYC, MYOCD, NEUROG1, NKX2-5, ONECUT2, PAX2, PAX7, PRDM5, SMARCA4, STAT5A, TBX5, TFAP4, ZNF536). However, none of these predicted regulators were found to have significantly changed expression in our study.

4. DISCUSSION

4.1. KA-MTLE MOUSE MODEL

The aim of this study was to uncover the molecular changes during the establishment of KA-MTLE in mice, in order to delineate the underlying pathogenic mechanisms of MTLE and identify novel therapeutic targets. The approach utilized included global trancsriptomic profiling of the epileptic hippocampus of the KA-MTLE mouse model [58, 140] in three time points, representative of different stages of MTLE development and progression (1, 3 30 days post injection). More specifically, transcriptomic analysis with microarrays was performed at 1 day post KA injection, when the KA-induced SE has ended and no epileptiform activity is detected, at 3 days when the spontaneous seizures begin to occur, and at 30 days when the MTLE syndrome has already been established and reached the chronic stage, which is characterized by recurrent spontaneous seizures and hippocampal sclerosis. The lists of significantly changed genes obtained from microarrays (449, 729 and 542 genes at 1, 3, 30 days, see Appendices 1, 2, 3), were subjected to extensive analyses, with the aid of data-mining bioinformatics software (Ingenuity, geneXplain, miRwalk).

4.1.1. Persistent molecular pathway changes during the course of MTLE

The IPA “Comparison Analysis” showed that 18 Canonical Pathways were found to be significantly changed across all time points, (Results, Chapter 3.1.6.1), and 25 genes were common amongst the overlapping pathways at 1, 3 and 30 days (Alox12b, Arhgdib, C3ar1, Ccl2, Ccl3l3, Cd44, Ctgf, Cxcl10, Ddx58, Fcgr2b, Fcgr3a/Fcgr3b, Fcrls, Flnc, Hla-A, Hspb1, Ifih1, Irf7, Msn, Osmr, Parp14, Parp9, Plce1, Rhoj, Timp1, Eif2ak2). Importantly, the majority of these consistently changed pathways (12/17 Canonical Pathways, i.e., «Acute Phase Response Signaling”, “Agranulocyte Adhesion and Diapedesis”, “Caveolar-mediated Endocytosis Signaling”, “Phagosome Formation”, “Communication between Innate and Adaptive Immune Cells”, “Granulocyte Adhesion and Diapedesis”, “Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses”, “Role of RIG1-like Receptors in Antiviral Innate Immunity”, “Toll-like Receptor Signaling”, “IL-10

Signaling", "IL-6 Signaling", "IGF-1 Signaling" "Death Receptor Signaling" "LXR/RXR Activation") are associated with immune and/or inflammatory response according to IPA, thus indicating the manifestation of persistent neuroinflammation throughout the course of MTLE in our model. Notably, "Death Receptor Signaling" is associated with apoptosis regulation and may be implicated in the observed neuronal cell loss. According to a recent study, death receptor apoptotic systems (e.g. TNF receptor signaling) may be associated with the maintenance and progression of TLE-associated HS, whilst among other death receptors, TNFRSF1A mRNA was found to be overexpressed in the sclerotic hippocampi of TLE patients [144], in line with our findings during KA-MTLE progression (↑Tnfrsf1a at 3, 30 days).

According to the pairwise comparisons between the three time point studied, 17 pathways remain changed between 1 and 3 days (Appendix 11) These changes include multiple pathways associated with inflammatory cytokine production and signaling ("IL-17 Signaling", "Role of JAK family kinases in IL-6-type Cytokine Signaling" "Oncostatin M Signaling" "MIF Regulation of Innate Immunity" "MIF-mediated Glucocorticoid Regulation"), as well as cell cycle ("GADD45 Signaling) and apoptosis-regulating mechanisms ("Retinoic acid Mediated Apoptosis Signaling"). Moreover, pathways involving small GTPase-mediated signaling and are associated with cytoskeletal dynamics ("Phospholipase C Signaling", "RhoGDI Signaling", "Gαq Signaling") were also shown to be consistently changed in the first two stages of MTLE studied.

The comparison between the significantly changed pathways at 3 and 30 days post injection revealed 42 overlapping pathways (Appendix 12). We observed that the majority of the pathways are associated with specific immune and inflammatory functions ("Antigen Presentation Pathway", "B Cell Receptor Signaling", "CD28 Signaling in T Helper Cells", "Clathrin-mediated Endocytosis Signaling", "Complement System", "Crosstalk between Dendritic Cells and Natural Killer Cells", "Fc Epsilon RI Signaling", "Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes", FcγRIIB Signaling in B Lymphocytes" "iCOS-iCOSL Signaling in T Helper Cells"," Leukocyte Extravasation Signaling", "Natural Killer Cell Signaling" "Role of NFAT in Regulation of the Immune Response", "TREM1 Signaling", "IL-8 Signaling",

“Interferon Signaling” “Production of Nitric Oxide and Reactive Oxygen Species in Macrophages”, “OX40 Signaling Pathway”, “NF-κB Signaling”, “Eicosanoid Signaling” “Prostanoid Biosynthesis”). Notably, cytoskeletal dynamics remain an affected function across all times points, although it is seemingly represented by different pathways at each time point (“Actin Cytoskeleton Signaling”, “Cdc42 Signaling”, at 3 and 30 days.)

Lastly, amongst the ten pathways that were found to be significantly changed only during epileptogenesis (1 day) and chronic MTLE (30 days) (Appendix 13), “cAMP-mediated signaling” and “G-Protein Coupled Receptor Signaling” are of particular interest, since they are mainly associated with neurotransmitter- and neuropeptide-mediated signaling in our study.

4.1.2. Inflammation in epilepsy: possible cause or an after-effect?

Our findings show that the most prominent biological mechanisms affected throughout the course of MTLE in our model are those associated with immune and inflammatory responses. Despite the long-standing concept of the CNS immune privilege that was only recently revisited [145], it has been shown that peripheral immune cells can cross the intact Blood-Brain Barrier (BBB), while CNS neurons and glia can actively regulate macrophage and lymphocyte responses[146], rendering neuroinflammation a valid hypothesis for CNS pathologies. Importantly, accumulating evidence of inflammation manifestation in epilepsy has motivated researchers to question its putative role in seizures for years, which has proven to be quite complex. Specifically, in humans inflammation is thought to be induced by recurrent seizures and can persist for days after SE termination, indicating a failure of the endogenous anti-inflammatory mechanisms, but on the other hand, in experimental models of epilepsy, inflammation precedes the onset of spontaneous seizures, thereby suggesting that uncontrolled inflammation may contribute to epileptogenesis. It is among the processes mostly upregulated during epileptogenesis, (i.e. between the initial brain injury and the onset of epilepsy) [147]. Moreover, with regards to the neurodegeneration observed in epilepsy, it is thought that pro-inflammatory cytokine release can contribute to cell loss, and dying cells may perpetuate inflammation, thus closing a vicious cycle.

Another critical question for the investigation of neuroinflammation in epilepsy was the exact origin of the inflammatory mediators. Studies have shown that the first wave of the initial SE-induced inflammatory mediators originates from parenchymal brain cells, and in specific locally activated astrocytes and microglia, whilst it seemingly propagates from glial cells to the brain microvasculature, since inflammatory mediators are also induced in perivascular astrocytes microglia and in the epithelial cells of the BBB [147]. Astrocytes in human TLE often express both the inflammatory mediator and the receptor, thus function both as sources and targets of inflammatory molecules, and in contrast with microglia where inflammatory response (as

indicated by IL1beta expression) is time-locked to the occurrence of seizures and depends on seizure recurrence, astrocytes appear to be involved in perpetuating inflammation even in the long term after the initial injury [148]. Lastly, inflammatory regulators could be also released by exravasated leukocytes (macrophages, granulocytes), and it has been specifically suggested that brain infiltration of leukocytes contributes to the pathophysiology of temporal lobe epilepsy [149].The combination of pro-inflammatory mediators produced by parenchymal and perivascular microglia, astrocytes and infiltrating leukocytes may cause BBB damage and subsequently lead to innate immune response activation and serum proteins leakage (e.g. serum albumin, IgG) into the brain, that may act as contributing factors to epilepsy pathology. For example, albumin is known to impair astrocyte capacity to buffer extracellular K^+ and glutamate, thereby triggering neuronal network long lasting hyperexcitability [148].

Taking into consideration the preliminary findings of our study and the knowledge available in scientific literature, we determined that the molecular mechanisms associated with immune and inflammatory responses merit our attention, and will be further discussed in this study.

4.1.3. Significant changes at 1 day with possible implications in MTLE epileptogenesis

4.1.3.1. Altered immune and inflammatory responses with the implication of glial cells

Our analysis identified a wide range of enriched BPs and pathways associated with the regulation of immune and inflammatory responses at 1 day post injection (e.g. “positive regulation of inflammatory response”, “positive regulation of innate immune response” “IL-10 Signaling”,”IL10 signaling”, “IL-17 signaling”). Multiple genes mapped in these categories were also found in glial related functions (e.g. “regulation of gliogenesis” “astrocyte cell migration”) and cell-specific pathways e.g. (“Granulocyte Adhesion and Diapedesis”, “Phagosome Formation”, “positive regulation of phagocytosis” “positive regulation of leukocyte migration”), which indicates the participation of glial cell in the of these responses, as it has been previously described in epilepsy [150]. Importantly, we also identified two central transcriptional regulators for specific immune and inflammatory response related functions in this time point: ↑Ifi16, which is predicted to control the expression of genes implicated in “immune response of leukocytes” (Ccl2, Cxcl10, Ddx58), and ↑Fos which may positively regulate the “recruitment of leukocytes” via twelve target genes (Bdnf, C3ar1, Ccl2, Cd14, Cd44, Chi3l1, Edn1, Hmox1, Kitlg, Serpine1, Spp1, Tac1), and may be implicated in the “activation of granulocytes” via regulating the expression of eight genes (Ccl2, Cd14, Edn1, Hmox1, Kitlg, Npy, Spp1, Tac1).

Moving to molecular pathways of interest, in the Il17 pathway, which is triggered by Il17 binding to a transmembrane heterotrimeric receptor complex (Il17ra, -b, -c) and signals to MAP kinases, [151, 152], we report two MAPKs participating in signal transduction (↑Map2k3, ↑Mapkapk2) and three overexpressed downstream genes (↑Cxcl10, ↑Ccl2, ↑Ptgs2). Cytokines of the IL-17 family are usually released by many immune cell types, (Th17 cells, neutrophils, monocytes), whilst in the CNS IL17 expression has been also detected in hippocampal neurons, astrocytes and microglia. The main effect of IL17 signaling is to trigger pro-inflammatory cytokines expression, whilst its interaction with receptors in endothelial cells facilitates Blood Brain Barrier

disruption [153]. In addition, increased levels of IL17 in the CNS of epileptic patients has been associated with seizure severity [154], overall indicating that this pathway may be implicated in epilepsy pathogenesis.

In the pathway triggered by IL-6 (Figure 4.1), we observe upregulated downstream effectors (↑Stat3, ↑Socs3), as well as signaling components that lead to IL6 production (↑Cd14, ↑Il33). In the CNS, IL6 is expressed by neurons, astrocytes and microglia, and binds to a dimeric receptor (Il-6r, Gp130), which in turns signals via Jak/Stat, to trigger pro-inflammatory gene expression [155, 156]. In KA-induced epilepsy in the rat Il-6 expression has been related to seizure occurrence, whilst IL6 signaling via JAK/STAT has been reported to have affect astrocytes and microglia, with neuroprotective or neurotoxic results [157-159]. In addition, the IL-6 family cytokines Osm, Lif and Il11) also signal via the same pathway, to regulate the expression of genes implicated in activation of microglia and astrocytes (↑Osmr, Lif), or exert anti-inflammatory action (↑Il11) [160, 161].

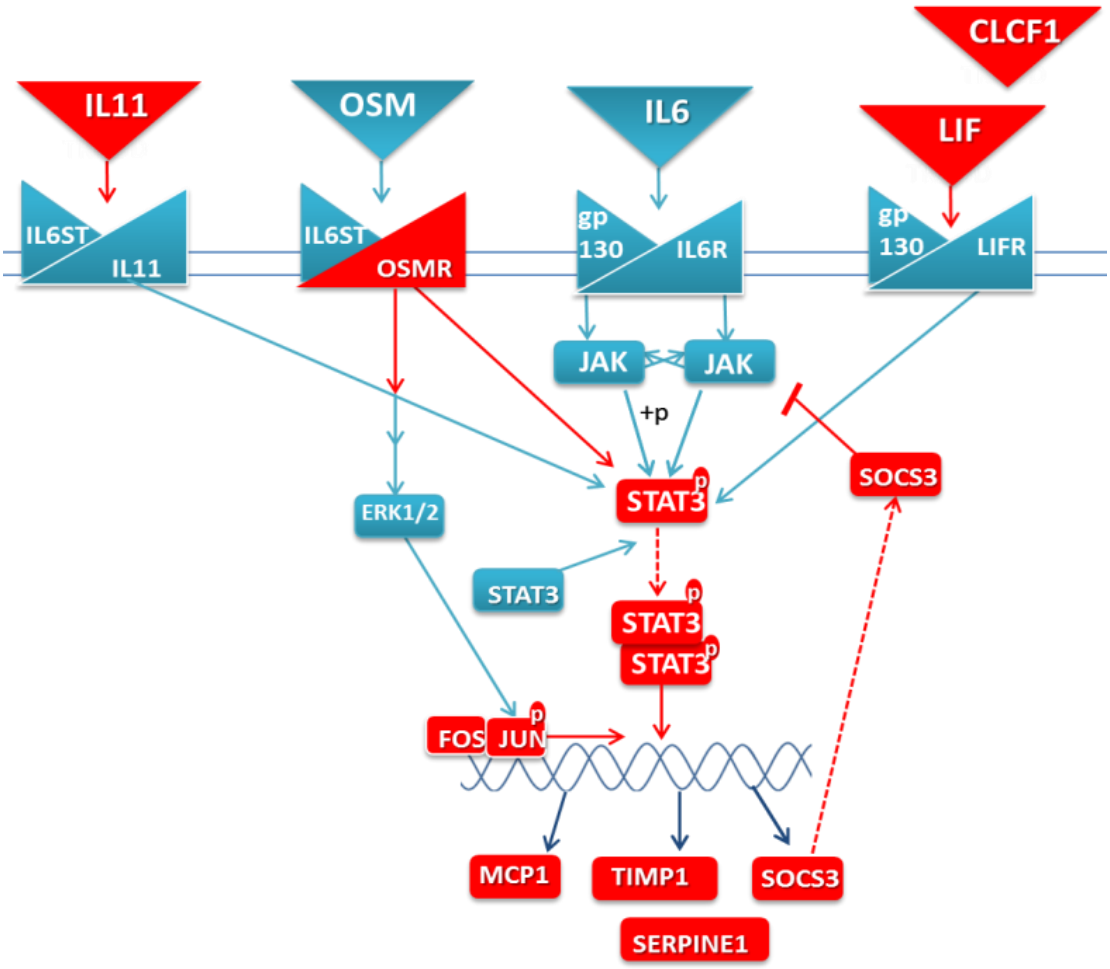


Figure 4.1. *IL-6 family cytokine signaling pathway at 1 day post injection in the KA-MTLE mouse model (red=overexpression, blue= not changed).*

Similarly to IL-6 and IL17, IL-10 is not significantly changed itself, but the genes controlling its expression are upregulated (↑Il33, ↑Cd14, ↑Map2k3), as well as its effector (↑Stat3) and downstream genes of the IL10 pathway (↑Socs3, ↑Hmox1). IL-10 is known as an immunoregulatory cytokine with potent anti-inflammatory properties, since it represses the expression of inflammatory cytokines, such as TNF-alpha, IL-6 and IL-1 beta, in macrophages. It exerts its anti-inflammatory activity in part by signaling via Stat3 to induce the expression of Socs3, which acts as JAK/STAT cytokine signaling suppressor [162-165], and Hmox1 which is implicated in IL-1 and IL-6 suppression, and has been related to neuroprotective activity of activated microglia [166]. Overall, these data are in line with previous studies in this model [9] and indicate the dynamic regulation of the interleukin-mediated inflammatory response at 1 day post injection, with pro- and anti-inflammatory signals participating in a negative feedback control mechanism.

Another altered molecular pathway with possible anti-inflammatory role in our model is that of sphingosine 1 phosphate signaling, which is uniquely changed in this time point of the study. This signaling cascade is triggered by sphingolipid ligand, S1P, which is produced upon phosphorylation of sphingosine by sphingosine kinases, and signals through sphingosine-1-phosphate receptors. At 1 day post injection, we report an upregulation of both the kinase and the receptor (↑Sphk1, ↑S1pr3), as well as three downstream effectors (↑Rhoj, ↑Rnd3, ↑Plce1), which are indicative of pathways activation. Importantly, S1PRs are targeted by the drug fingolimod, a SP1 analog with potent anti-inflammatory effects in MS, and have also been implicated in studies and clinical trials for a range of other neurodegenerative diseases, including epilepsy [167]. Specifically, a recent study in a rat model of lithium-pilocarpine induced epilepsy showed that a 14-day treatment with fingolimod starting at 24h post SE had neuroprotective and anti-inflammatory effects, including decreased activation of microglia and astrocyte activation, amelioration of abnormal IL-1β and TNFα expression, attenuation of MF sprouting and reduced neuronal loss in the hippocampus, at four days post-SE. In addition, this treatment resulted also in seizure control at the chronic

stage (21-34 days post-SE) [168], suggesting a potential antiepileptogenic role for S1P signaling.

The significantly changed Endothelin-1 signaling pathway is also of particular interest to our study, and is more pronounced at 1 day in comparison to the remaining time point. Endothelin-1 (↑Edn1) is expressed by most CNS cell types, and typically participates in the regulation of the blood flow and blood pressure, whilst also affecting many neuronal and glial functions. Specifically, it has been shown to increase neuronal activity and glutaminergic synaptic transmission by endothelin-A receptors, and pharmacological inhibition of endothelin-A receptors had beneficial effects on the seizure outcome in PTZ rats [169]. *De novo* expression of Endothelin receptor B in astrocytes has been reported after KA treatment [170], whilst this receptor has been studied in the context of ischemia-induced seizures, BBB disruption and vasoedema [171], as well as epilepsy pharmacoresistance [172]. Interestingly, studies have shown that increased ET-1 expression and signaling via ETB receptor following SE may lead to increased BBB permeability via eNOS activation in endothelial cells, and increased intracellular ROS production by NADPH oxidase in astrocytes [173]. Whilst no endothelin receptors are changed in our study, taking into consideration the multiple enriched biological process categories related to leukocyte recruitment and migration, and the experimental evidence suggesting leakage of the BBB in epilepsy [149] upregulation of Edn1 may participate in BBB relaxation that accompanies and facilitates leukocyte migration in MTLE. Moreover, at 1 day post injection we report enriched BPs associated with ROS e.g. “response to reactive oxygen species”, “superoxide metabolic process”), and overexpression of ↑Cybb (a.k.a. Nox2) the catalytic subunit of the ROS generating NAPDH oxidase enzymic complex. These findings indicate increased ROS content in the hippocampal milieau, and Cybb upregulation suggests that NOX complex facilitates this effect, whilst Edn1 may contribute to increased NOX activity in KA-MTLE.

4.1.3.2. Altered neuronal network organization and function

Our analysis at 1 day post injection highlighted enriched pathways and functions associated with neuronal network reorganization processes (e.g. “neuron projection development”, “positive regulation of neurogenesis”), and cytoskeletal dynamics (e.g. “RhoGDI Signaling”, “positive regulation of cytoskeleton organization”). These evidence possibly represent some of the neuronal network reorganization processes accompanying MTLE pathogenesis, such as dispersion of the granule cell layer and aberrant mossy fiber sprouting [58] Moreover, at 1 day the neurogenesis process seems to be positively regulated, which is in line with the presence of Brdu staining (newly born neurons) at 1d post injection in our KA-MTLE model (Depaulis group, unpublished data). Of note, the majority of neurogenesis and neuronal differentiation-related genes were also found to be related to gliogenesis and glial differentiation, thus indicating multiple roles for these genes in the CNS development.

Interestingly, the top two most enriched pathways at this time point was “G-Protein Coupled Receptor Signaling” and “cAMP-mediated signaling” whilst other significantly changed G-protein associated molecular pathways include “Gαi Signaling” which is uniquely changed in this time point, “Glutamate Receptor Signaling” and “Synaptic Long Term Potentiation”, with multiple genes mapped in these pathways falling under enriched neurotransmitter and neuropeptide-related BPs (“regulation of glutamatergic synaptic transmission”, “regulation of neurotransmitter transport and secretion” “neuropeptide signaling pathway”). The underexpression of the majority of the metabotrobic glutamate receptors (↓Grm1, ↓Grm2, ↓Grm3, ↑Grm8) indicates a downregulation of gluatamatergic excitatory neurotransmission in this time point which is in line with the absence of seizure-like activity. Moreover, our previous studies in the same model have shown a similar effect as early as 12 hours post injection, thus suggesting it may represent a compensation mechanism to the KA-induced hyperexcitation of the initial insult.

According to IPA analysis, the common denominator of significantly changed neuropeptides in this time point, is a neuropeptide-triggered signaling

cascade, that acts primarily via G proteins and signals via adenylate cyclase and MAP kinases to regulate the activity of calcium channels, amongst others. Neuropeptides play an important role in modulating seizures and epilepsy, since they are usually stored in large vesicle in inhibitory interneurons and are released upon high frequency stimulation. In contrast with the acute, short term effect of neurotransmitters , neuropeptides have longer half-lives, leading to prolonged modulation of neuronal network activity, thus contributing to seizure threshold establishment [174]). To date, many studies have been conducted to exploit the seizure-modulating effects of neuropeptides for the development of therapeutic interventions for epilepsy [175].

Specifically, NPY (↑Npy), which is abundantly expressed in GABAergic interneurons of the mammalian CNS, it is known to be an endogenous suppressor of seizure activity in human and experimental epilepsy [176-178] and is also thought to mediate valproate's anticonvulsive effects [179]. NPY signals through identified Y1, Y2, Y4, and Y5 receptors that couple to G proteins, inhibiting adenylate cyclase thereby decreasing intracellular calcium levels [176, 180, 181]. It exerts its anti-convulsive effects via Y1, Y2 and Y5 receptor subtypes [182-184]. NPY mRNA and protein levels are increased in human end experimental epilepsy and in KA-induced epilepsy, in specific [185, 186]. The only receptor changed in our study is the Y2 subtype receptor(↓Npy2r), for which studies in human TLE have shown increased receptor binding [178] and studies in KA-induced epilepsy at 24 hours have shown increased mRNA expression in DG and CA1 and increased binding at CA1 only [185, 186]. Overall, the overexpression of Npy indicates an anti-convulsive role in this time point, which is in line with the absence of epileptiform activity.

Galanin (↑Gal) is a multifunctional neuropeptide that binds to the G protein coupled receptors Galr 1, -2, and -3 and signals via multiple pathways, including inhibition of cAMP/PKA (Galr1, -3) and stimulation of phospholipase C (Galr2) [187]. Although in human epileptic hippocampus no functional binding of Gal receptors was detected [188], in experimental epilepsy, Gal has been shown to exert an anticonvulsive effect mediated by Galr1 [189], which is upregulated in our study (↑Galr1). In addition, GalR1-KO mice exhibit

spontaneous seizures, while Galanin-KO mice do not show spontaneous epileptic activity [190-192]. Interestingly though, the effect of Galr1 ablation on seizure severity was shown to be model-specific, i.e. in the KA model, Galr1 deletion had no effect on seizure severity in contrast with galanin (Gal) deletion, indicating that galanin's anti-seizure effect is not mediated by Galr1 in this model [191, 193]. Additional studies indicate that GalR1 receptors seem to be crucial for seizure induction since GalR1 decrease leads to a reduction in the seizure threshold, whilst GalR2 receptors seem to play a role in maintaining epileptic seizures and in their severity [194, 195].The proposed mechanisms of antiepileptic activity of Galr1 include presynaptic inhibition of glutamate release and postsynaptic activation of K channels (GIRKs) that lead to hyperpolarization [196]. Lastly, Galr2 has been also shown to increase neurite outgrowth, and control neuronal survival and neurogenesis in injured hippocampus [197-200], thereby indicating a multiple role for galanin in the epileptic hippocampus.

Dynorphin is another neuropeptide with anti-epileptic effect that derives from proteolytic processing of the preprotein predynorphin, which is upregulated in the mRNA level in our model (↑Pdyn). The peptides derived from Pdyn (beta-neoendorphin, dynorphin, leu-enkephalin, rimorphin, leumorphin) are secreted ligands for the kappa-type of opioid receptor, but they also modulate NMDA receptor signaling by reducing its activity, in a receptor independent manner [201, 202]. *In vivo* studies have shown that dynorphin suppresses seizure activity and this effect was mainly mediated by opioid kappa receptor activation [203-206]. Moreover, studies in dynorphin KO mice showed that the animals exhibit reduced seizure threshold and display proepileptogenic properties [207]. Besides Pdyn, Proenkephalin (↑Penk) is an additional source of opioid peptides in the dentate granule cells of the hippocampus [208]. In KA –induced epilepsy, Penk has been found to be upregulated and it was shown to contribute to the development and manifestation of spontaneous seizures [208-210]. In line with these data, positron emission tomography (PET) performed after spontaneous epileptic seizures in epileptic patients showed

upregulation of opioid receptor binding in the temporal pole and fusiform gyrus [211], thus indicating a role for opioid signaling in TLE.

Neurotensin (↑Nts) is a neuropeptide that signals via three known receptors, the GPCRs Ntsr1, Ntsr2 and Ntsr3 which has a single transmembrane domain. In hippocampal neurons, expression of Ntsr1 and Ntsr2 has been detected, and in our study (↓Ntsr2) is downregulated. Interestingly, neurotensin-like immunoreactivity has been shown to decrease after KA-induced limbic seizures in the rat, but normalizes after the period of acute convulsions [212]. Neurotensin and some glycosylated analogues was shown to exhibit (sub) picomolar anticonvulsant potencies in experimental epilepsy, without being clear which receptors mediate this effect [213, 214]. Importantly, Nts has been shown to enhance the activity of GABAergic neurons in CA1 by modulating the activity of L-type calcium channel [215], a mechanism which may underlie the observed anti-convulsive effect.

Tachykinin 1 (↑Tac1) is also source of multiple active neuropeptides (substance P, neurokinin A, neuropeptide, neuropeptide gamma). One of them, Substance P, has been implicated in status epilepticus (SE) modulation, exerting a proepileptic effect. Substance P binds to the GPCR neurokinin 1 (NK1) receptor and triggers depolarization of the cell by reducing inward rectifying potassium currents [216]. In the perforant path stimulation epilepsy model of limbic epileptogenesis, Substance P expression increases whereas inhibitory neuropeptide synthesis decreases during severe SE, in the hippocampal CA1, C1, DG and mossy fibers [217]. Moreover, studies using Substance P receptor antagonists have shown that seizure onset and established seizure activity during SE can be suppressed, as well as the accompanying tissue observed in the rodent hippocampus [217, 218]. Interestingly, Tac1 gene is overexpressed at 1 day in our study, but is downregulated at both 3 and 30 days, possibly indicating a role in KA-MTLE development rather than progression.

Another endogenous neuropeptide with anti-convulsant properties, is derived from the cleavage of the preprotein encoded by the Thyrotropin-releasing hormone gene that is upregulated in our study (↑Trh). Trh is produced in the

paraventricular nucleus of the hypothalamus (PVN) and stimulates the biosynthesis and secretion of TSH from the anterior pituitary, but is also present in other brain loci, including the hippocampus. In the rest of the brain, Trh is believed to acts via TRH receptors in the synapse to regulate the action of several neurotransmitters, including glutamate [219]. Trh is upregulated by seizure activity [220] and the anti-convulsive of Trh and its analogues have been reported in several experimental epilepsy models, including kainate, PTZ, kindling, electroconvulsive seizures (ECS) [221-225]. Moreover, studies in TBI and excitotoxicity-induced neuronal death indicate a potent neuroprotective role of this peptide [226, 227]. Importantly, a recent study using the JK4D Trh peptide analogue showed it can improve KA-induced cognitive deficits, reduce KA-induced free radical production and neuronal damage in the striatum, and improve disease progression and functionality in transgenic G93A-SOD1 mouse model of ALS [228]. The administration of Trh analogues has also been assessed in the clinic, with modest results in seizure suppression [229], whilst the therapeutic potential of Trh analogues for other neurodegenerative diseases such as AD and PD has been long recognized [230].

Within the same molecular network with the neuropeptides described, two significantly changed genes encoding peptide cleaving enzymes were also found (↑Furin, ↑Pcsk1). Furin and Pcsk1 are members of the subtilisin/kexin-like endoproteases family, and are serine proteinases that have a significant role in prohormone processing. Specifically Pcsk1 has been shown to process pro-TRH (↑Trh), proinsulin, proenkephalin (↑Penk), prosomatostatin and others to various intermediates and end products [219]. Interestingly, in a pilocarpine epilepsy model, Pcsk1 mRNA was shown to be upregulated mostly in the hippocampus, and this expression was coordinated with NGF and BDNF mRNA upregulation, whilst similar results were reported for Pcsk1 and Furin in KA-induced epilepsy [231-233]. These studies indicate that these proteases are participating also in proNGF and proBDNF cleavage, and in our study ↑Bdnf was also found upregulated at 1 and 30 days, in line with Psck1 upregulation pattern, whilst Furin is only upregulated at 1 day.

Overall, the overexpression of multiple neuropeptide precursor genes along with the peptidases that are essential for their maturation and activity, as well as some of their receptors, indicate a potent activation of neuropeptide signaling at 1 day post KA, which is less prominent at 3 and 30 days. The majority of the described neuropeptides have anti-convulsive and neuroprotective role and they seemingly constitute an endogenous neuroprotective mechanism against KA excitotoxicity. Notably, this response is highly active in the absence of epileptiform activity in our model (1 day) and is attenuated upon the manifestation of seizure activity (3, 30 days), thus allowing us to discriminate between mechanisms that are possibly implicated in epileptogenesis rather than disease progression.

4.1.4. Significant changes at 3 days with possible implications in MTLE development

4.1.4.1. Indications of altered glial-mediated responses and leukocyte infiltration

At the second time point of our study, we observed multiple glial-related enriched GO BPs that suggest continuous activation and reorganization of the glial network (e.g. “glial cell migration” “positive regulation of glial cell proliferation”, “microglial cell activation involved in immune response”). In addition, the top significantly changed IPA Canonical Pathways at 3 days included mostly inflammatory-and immune response- related pathways. For example, more than twenty genes were mapped in “Phagosome formation”, “Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses”, “Granulocyte Adhesion and Diapedesis”, “Agranulocyte Adhesion and Diapedesis”, and more than ten genes were mapped to “Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes”, “TREM1 Signaling” and “Complement System”. Moreover, besides the further enrichment of related BPs found at day post injection (e.g. “inflammation”, “leukocyte chemotaxis and migration”), at 3 days we report new enriched categories associated with cell-mediated immune responses (e.g. “positive regulation of leukocyte mediated immunity”, “macrophage activation involved in immune response”).

Overall, this evidence indicates a possible exacerbation of the immune and inflammatory responses that were already evident at 1 day post injection in our study. Importantly, our data support the hypothesis of leukocyte infiltration, possibly upon the relaxation (leakage) of the BBB that has been previously described in experimental [149, 234] and human epilepsy [149, 235, 236]. Specifically, twenty overexpressed genes were mapped to each of the “Granulocyte Adhesion and Diapedesis” (granulocytes: eosinophils, baseophils, neutrophils) and “Agranulocyte Adhesion and Diapedesis” (agranulocytes: lymphocytes, monocytes) pathways, with the eighteen of them shared. These genes include cytokines, chemokines and receptors whose expression is triggered during immune response, and control leukocyte

attraction and migration (↑Il33, ↑Tnfrsf1a, ↑C5ar1, ↑Ccl2, ↑Ccl3l3, ↑Cxcl10, ↑Cxcl16), as well as integrin and actin cytoskeleton related molecules that are necessary for leukocyte-endothelium adhesion and transendothelial migration (↑Itga1, ↑Itga5, ↑Itga6, ↑Itgam, ↑Itgb1, ↑Itgb2, ↑Mmp19, ↑Msn, ↑Sdc4, ↑Ezr, ↑Vcam1). Our hypothesis is further strengthened by the observation that ten of these overexpressed genes (i.e., ↑Ezr, ↑Itga1, ↑Itga5, ↑Itga6, ↑Itgam, ↑Itgb1, ↑Itgb2, ↑Mmp19, ↑Msn, ↑Vcam1) are also mapped to the “Leukocyte Extravasation Signaling” Canonical Pathway, along with additional genes regulating ECM degradation (↑Timp1, ↑Timp4), and endothelium integrity (↑Jam2, ↑F11r, ↑Cd44). Notably, this pathway includes all the NOX complex components with significantly changed expression in this time point (↑Cyba, ↑Cybb, ↑Ncf1, ↑Rac2), as well as signaling molecules implicated in cytoskeletal reorganization (↓Pik3cg, ↓Prkcg, ↑Vav1). In this context, NOX appears to participate in the leukocyte migration process via hydrogen peroxide production in the endothelial cells (Figure 4.2).

Moving to another cell-specific response, we observe more than fifteen genes mapped to each of the two significantly changed IPA Canonical Pathways associated with phagocytosis (“Phagosome formation”, “Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes”) with six of them shared between them (↑Fcgr1a, ↑Fcgr2a, ↑Fcgr3a/Fcgr3b, ↑Inpp5d, ↓Prkcg, ↓Pik3cg). The majority of the implicated genes indicate activation of Fcγ receptor signaling and consequent phagosome formation and phagocytosis activation, with the exception of ↓Prkcg, ↓Pik3cg, and ↑Inpp5d that acts as a negative regulator of Fcγ signaling. Phagocytosis is routinely activated in the presence of foreign particles, pathogens, and apoptotic cells. Specifically, the phagocytic clearance of apoptotic and dead cells aims to protect neighboring cells from the noxious contents of dying cells, and prevents activation of the immune system by liberated cellular contents [237, 238] .

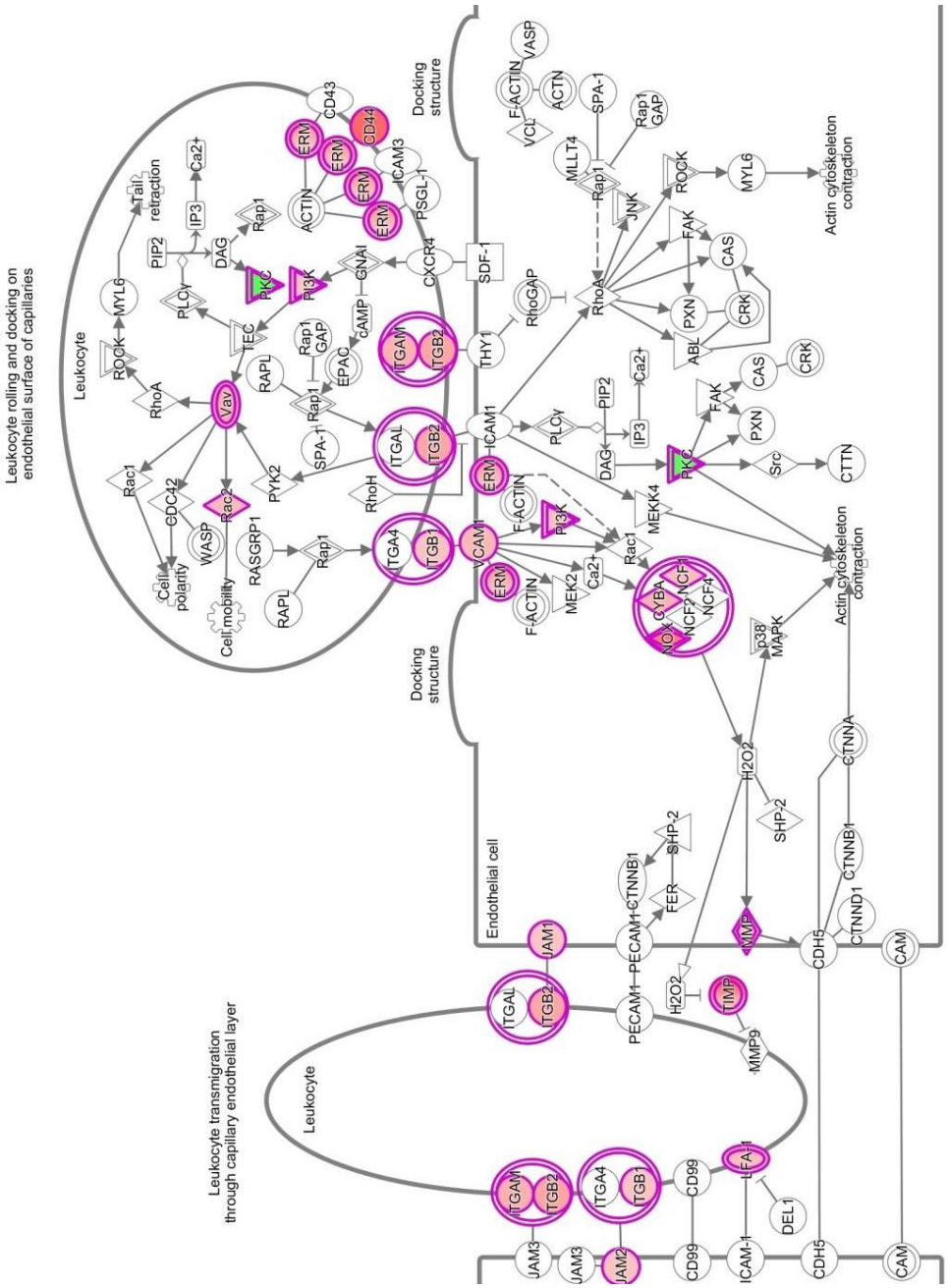


Figure 4.2. *Leukocyte Extravasation Signaling at 3 days post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red= overexpression, green=underexpression*).

In vertebrates, resident and recruited macrophages are the professional phagocytes that rapidly clear apoptotic cells [239]. In the CNS, microglial cells (CD4+) are perceived as the resident professional phagocytes under normal circumstances, and exhibit phagocytic activity in both quiescent and reactive states, which is critical for synapse pruning and removal of dead neurons [240-242]. In the case of neuroinflammation, other professional phagocytic cell types may infiltrate via the compromised BBB [149, 236, 243]. In KA-MTLE, the activation of microglial phagocytosis in response to degenerating neurons during epileptogenesis has been reported by our group [9, 244], as well as by other groups in experimental [245, 246] and human epilepsy [247] (Figure 4.3)

An inflammatory-related pathway of particular interest that was found to be significantly changed in this time point is “TREM1 Signaling”. Trem-1 receptor, which is expressed by monocytes, neutrophils and microglia [248, 249], is not significantly changed itself, but amongst the fourteen overexpressed genes mapped to this Canonical Pathway, we observe multiple JAK/STAT and TLR signaling components (i.e., ↑Myd88, ↑Tlr1, ↑Naip1, ↑Tlr4, ↑Lat2, ↑Stat3, ↑Fcgr2b, ↑Itgb1, ↑Tyrobp, ↑Ccl2, ↑Tlr13, ↑Itga5, ↑Tlr2, ↑Cd86). Upon activation, Trem-1 phosphorylates the downstream adaptor protein Dap12 (a.k.a ↑Tyrobp), which in turn signals via JAK/STAT (↑Stat3) to trigger proinflammatory chemokine and cytokine production, such as Mcp-1 (a.k.a. ↑Ccl2) (Schen 2007). Ccl2 is a chemoattractant for macrophage and microglia, which recruits them to CNS injury sites [250, 251]. In experimental epilepsy, it has been found overexpressed in astrocytes and neurons 1 day post SE, and in microglia 2 days post SE [252-254], whilst also reported upregulated in human epilepsy [255]. After excitotoxic injury, Ccl2 signaling in neurons and reactive astrocytes results in microglia chemoattraction and promotes neurodegeneration in the recruitment sites [254].

In addition, Ccl2 has been shown to mediate brain endothelial barrier disruption during CNS inflammation, by triggering caveolae-mediated internalization of tight junction proteins [256]. Apart from Trem1, ↑Trem2 receptor also signals via Dap12 (Tyrobp↑), to trigger the ITAM cascade, ultimately leading to microglial activation, migration and phagocytosis.

Moreover, when the complement component ↑C3b binds to Cd11b receptor in microglia, it signals via Dap12 (Tyrobp↑), leading to increased superoxide production and induction of neuronal death [257, 258] (Figure 4.4).

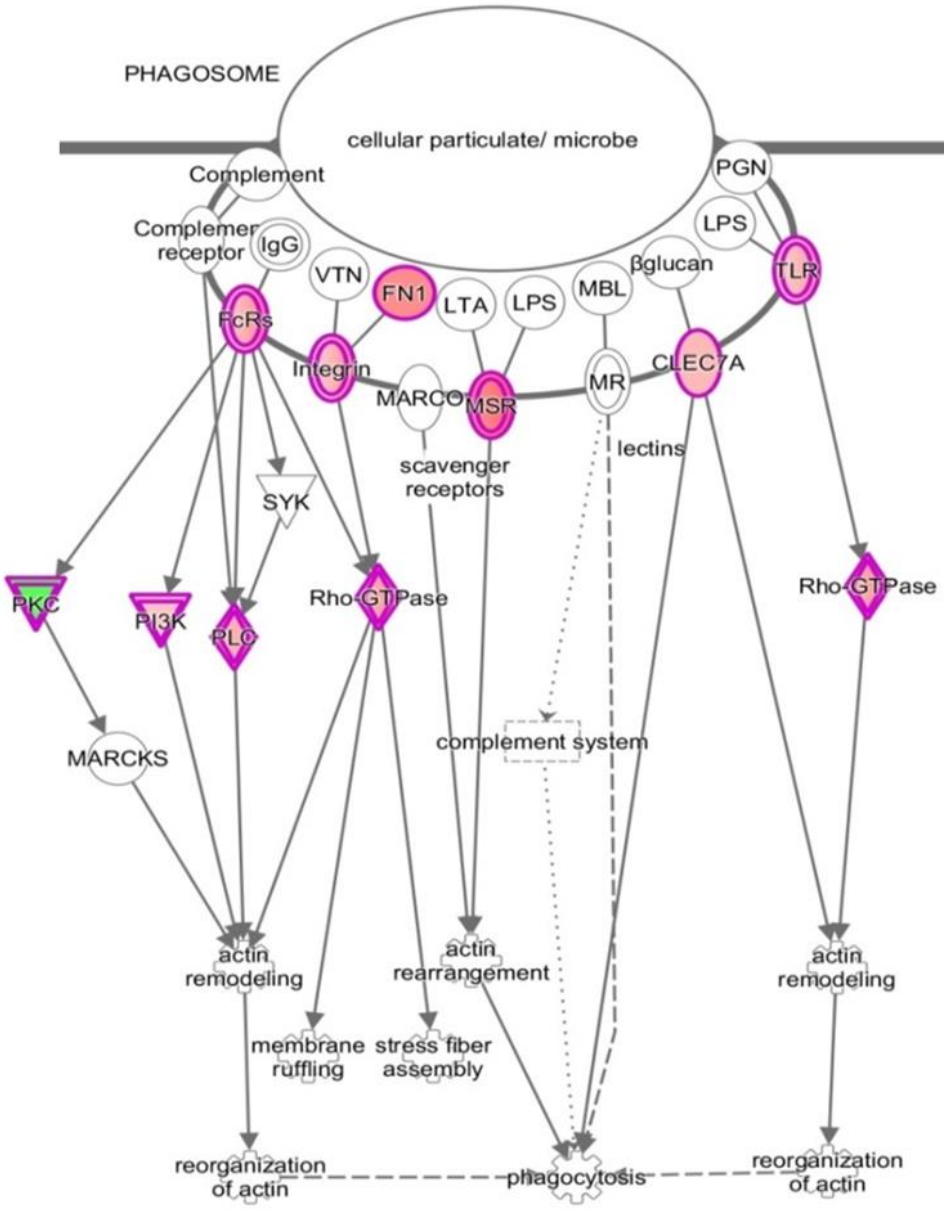


Figure 4.3. *Phagosome formation signaling at 3 days post injection. Image generated via IPA software (bold outline=gene with significantly changed expression, red= overexpression, green=underexpression.*

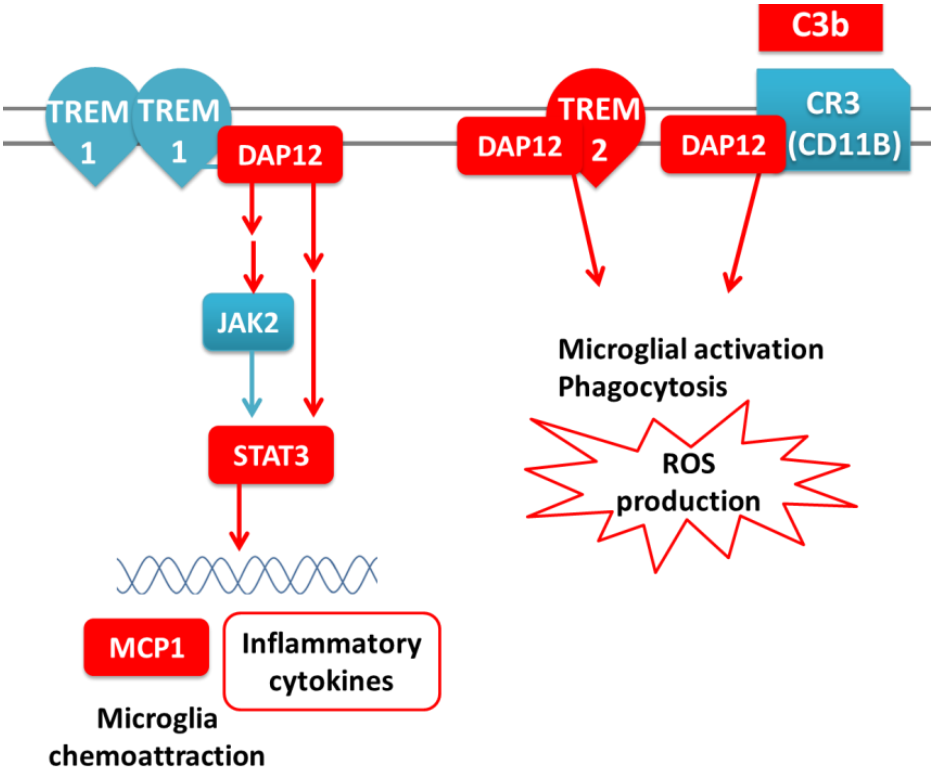


Figure 4.5. *Significant gene expression changes in TREM1 signaling at 3 days post injection (red= overexpression, blue= not changed.)*

Interestingly, caveolar-mediated endocytosis, which can be triggered by ↑Ccl2 [256], is one of the most prominently changed Canonical Pathways at 3 days. Caveolae are membrane microdomains that act as integrators of cellular signaling and functional processes. They are one source of clathrin-independent raft-dependent endocytosis, used for e.g. transcytosis of albumin in endothelial cells, receptor and ion channel regulation via internalization, whilst also serve as mechanosensors in various cell types, such as endothelial cells [259]. In our study, the "Caveolar-mediated Endocytosis" pathway is populated by thirteen overexpressed genes, including multiple integrins (↑Itgam, ↑Itgb5, ↑Itgav, ↑Itga6, ↑Itgb2, ↑Itga1, ↑Itgb1,↑Itga5), actin cytoskeleton anchoring proteins (↑Flna, ↑Fln), a co-stimulatory receptor of immunity (↑Cd48) [260], and more importantly Caveolin 1 (↑Cav1) (Figure 4.6). Caveolins are scaffolding proteins which are known as the principal components of caveolae [261]. In the CNS, ↑Cav1, is one of the main functional proteins of the BBB, acting to regulate its permeability, and as such,

it is highly associated with neuroinflammation. Specifically, recent studies in the LPS-induced inflammation mouse model have shown that upregulation of ↑Cav1 in response to inflammation is associated with increased BBB permeability [262], whilst during ↑Ccl2-induced reductions in transendothelial electrical resistance, tight junction proteins became internalized via caveolae containing ↑Cav1, suggesting an underlying mechanism for ↑Ccl2- mediated BBB disruption during CNS inflammation [256]. Besides endothelial cells of brain microvessels, caveolins have been also reported to regulate cytoskeletal dynamics of microglial cells. In specific, ↑Cav1 overexpression has been specifically associated with activated microglia, and led to increased mitochondrial respiration, possibly regulating cell metabolism accordingly, to facilitate the morphological changes [263]. Although the presence of ↑Cd48 indicates activation of caveolar mediating signaling in endothelial cell of brain microvessels [264], ↑Cav1 may act both in BBB disruption and in activated microglia, to promote neuroinflammation in the context of our study.

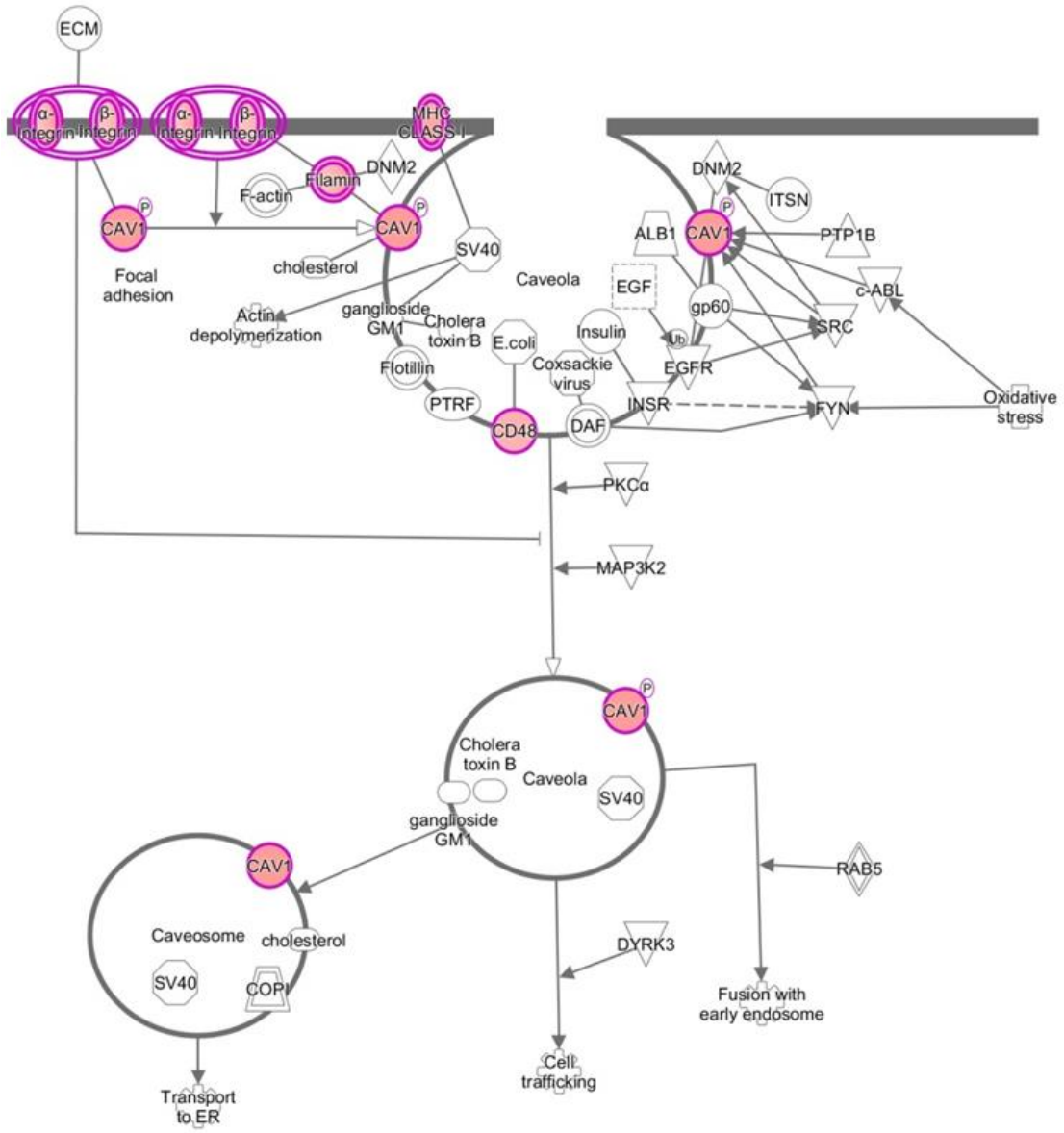
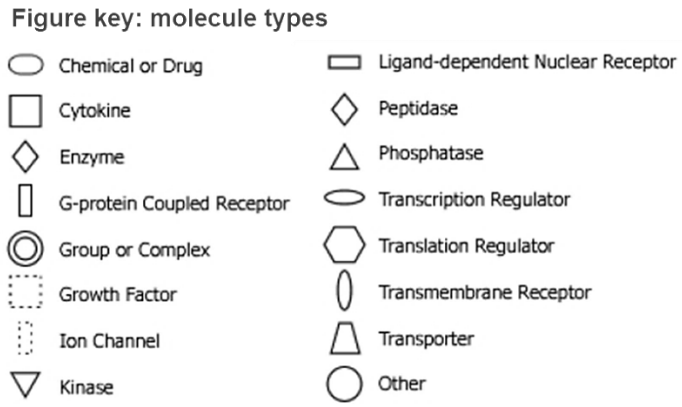


Figure 4.6. *Caveolar -mediated Endocytosis signaling at 3 days post injection Image generated via IPA software (bold outline=gene with significantly changed expression, red= overexpression, green =underexpression).*



Lastly, an important finding of our study is the upregulation of ↑Tspo at 3days post injection, which falls under the enriched GO BPs “glial cell migration” and “positive regulation of glial cell proliferation”. Tspo protein is a neuroinflammation marker that is currently used for PET imaging of activated microglia in the CNS [265], and has been also found to be upregulated in seizure focus in patients with TLE [266]. Although one of Tspo main roles is to regulate PTP (Permeability Transition Pore) formation in mitochondria, a key step that precedes apoptosis [267], recent studies have dissociated its upregulation in neuroinflammation with neurodegeneration. Specifically, Tspo is mainly upregulated in specific subpopulations of activated microglia (M1 microglia), although it marks a pro-inflammatory brain environment, but it is not necessarily accompanied by neuronal loss and thus does not predict neurodegeneration [268]. Interestingly, other studies have shown that only M1 microglia markers were upregulated at 3 days after KA-induced SE [269], but we also report M2 markers (e.g. ↑Lyn), which further perplexes the role of microglial activation in this state of KA-MTLE.

4.1.4.2. The role of NOX activity and Reactive Oxygen Species at 3 days post KA

In the intermediate time point of the study we observed an increase in the number of enriched BPs related to ROS and NOX, in comparison with 1 day. Of specific interest is the “response to reactive oxygen species” that indicates the presence of increase ROS content in the hippocampus, and “superoxide anion generation” which is populated exclusively by components of the NOX complex. More specifically, we observe overexpression of the membrane-bound subunits of the NOX hexamer complex, namely ↑Cybb (a.k.a. Nox2, gp91phox) and ↑Cyba (a.k.a. p22 phox), along with the cytosolic subunit ↑Ncf1 and the catalytic subunit ↑Nox4 (Figure 4.7), which indicates a possible activation of this enzymic complex. The NOX complex is located in the membranes of phagosomes and endoplasmic reticulum, as well as in the plasma membrane, and catalyzes the production of reactive oxygen species (ROS, e.g. $O_2^{-\cdot}$, H_2O_2) [270]. The increased production of ROS via the NOX complex of activated microglial cells [271-277] and neurons [274, 278-281]

has been shown to induce the transcription of proapoptotic genes, as well as the activation of apoptotic mechanisms. Indeed, in the pilocarpine MTLE model, NOX activation triggered NMDA receptors upregulation [282] and led to neurodegeneration [283, 284], which was reduced by a NOX complex inhibitor [284, 285]. Excitation via glutamate receptors has been also shown to induce ROS production via NOX [272, 281, 286-288], whilst KA-induced seizures in rats trigger NOX complex activation and increased $O_2^{-\cdot}$, in parallel with microglial activation [289].

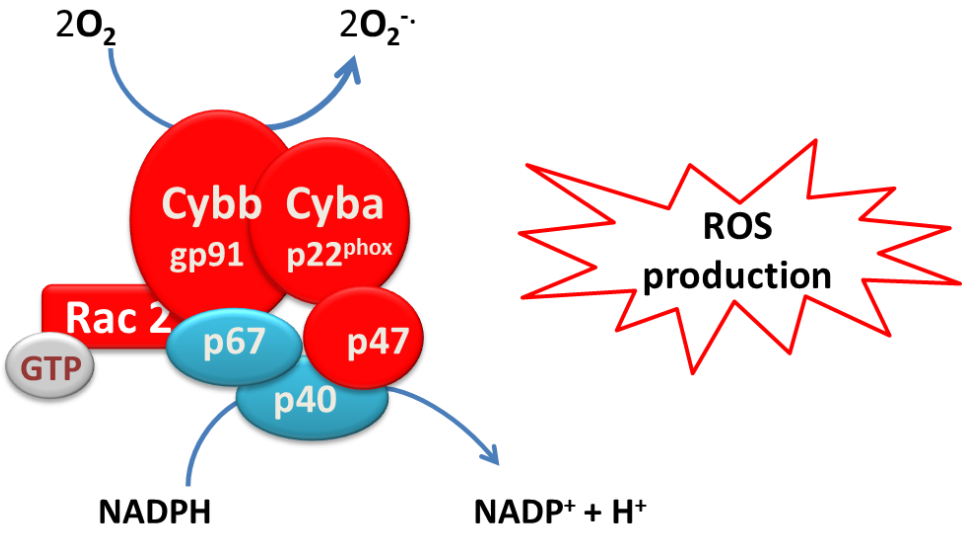


Figure 4.7. *Significant gene expression changes in the NAPDH oxidase enzymic complex at 3 days post injection (red= overexpression, blue= not changed.)*

Our IPA analyses highlighted the participation of NAPDH oxidase (NOX) related genes in multiple changed pathways implicated in immune and inflammatory responses (e.g. “Production of Nitric Oxide and Reactive Oxygen Species in Macrophages”, “Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes”, “IL-8 signaling”, “Leukocyte extravasation signaling”) and in cytoskeletal dynamics (“Signaling by Rho Family GTPases”, “Rac Signaling”). Additional evidence further support a role for ROS in microglia-facilitated phagocytosis, which possibly mediated by NOX in our model. Specifically, studies have shown that ↑Vav1 leads to NOX activation and phagocytosis, whilst Vav1 is also associated with Lyn beta-amyloid fibril-stimulated ROS-dependent phagocytosis in microglia [290, 291]. ↑Lyn, is a marker of activated neuroprotective microglia (M2a stage) [292], that can sense hydrogen peroxide upregulation, triggering actin cytoskeleton reorganization and microglia migration [293]. Lastly, ↑Msr1 has been shown to participate in ROS secretion and facilitate phagocytosis in microglia [294]. Furthermore, our upstream regulator analysis revealed that the transcription factor ↑Spi1 (a.k.a Pu.1) is predicted to regulate the expression of multiple significantly changed NOX-related genes at 3 days (Cybb, Itga5, Ncf1, Pik3cg). Importantly, ↑Pu.1 is also predicted to control the expression of twenty five more genes, the majority of which are associated with distinct immune and inflammatory related functions, such as “response and phagocytosis of myeloid cells, phagocytes and leukocytes” and “immune response of macrophages and phagocytosis by macrophages”. Pu.1 represents a master regulator of myeloid development [295] and a key transcription factor expressed by peripheral macrophages and rodent microglia [296] that has been linked to the regulation of microglial proliferation during chronic neurodegeneration [297].

Our observations, in combination with data from the literature, suggest that responses mediated by activated microglial may facilitate neurodegeneration in the KA-induced MTLE mouse model through increased ROS production via the NOX complex. Moreover, we propose that Pu.1 acts as a master regulator of the microglial-mediated immune response at 3 days post KA injection, and

this role may be exerted in part via the regulation of NOX-related genes. Consequently, Pu.1 requires further investigation in the context of MTLE, in order to explore its potential as a novel therapeutic target to battle epileptogenesis.

In addition to the significant changes in the ROS-producing mechanism, our analysis revealed several additional ROS-related changed genes that may act to modulate the ROS profile in the epileptic hippocampus. Specifically, we reported an upregulation Nfe2l2, Gpx1, Gpx3 and Gpx8 genes, which have antioxidant properties and are implicated in the removal of ROS. Importantly, a strong induction of antioxidants has been also reported in pharmacoresistant MTLE-HS patient hippocampi [298]. In specific, this group reported an upregulation of many hydrogen peroxide-removing enzymes protein levels and activity (CAT, GPx, GR, MnSOD), that varied according to cell types. Glutathione peroxidases (Gpx) showed a different distribution pattern in control tissue (blood vessels, CA neurons) than in sclerotic hippocampi (HS), where it was mainly located in astrocytes and in vessels. Overall, these evidence support a possible implication of the hippocampal ROS homeostatic mechanism in the establishment of sclerosis, in the context of MTLE.

4.1.4.3. Altered neuronal network organization and function

Notably, at 3 days post injection, no BPs related to neurogenesis and/or neuron differentiation appeared to be enriched, as reported for the 1 day time point. This observation is in line with the declining number of new neurons observed post KA injection in KA-MTLE (Depaulis group, unpublished data). On the other hand, we observed that “regulation of neuron apoptosis” is significantly enriched in this time point, possibly indicating the activity of neurodegenerative mechanisms. Our analysis also highlighted the overexpression of the neuroprotective ↑Inhba, which is upregulated in many forms of brain injuries. Interestingly, a recent study described a neuroprotective mechanism of BDNF, which enhanced NMDA-receptor synaptic activity and nuclear-calcium-driven transcription regulation, leading to increased Inhba expression. In turn, Inhba was shown to reduce neurotoxic extrasynaptic NMDA-receptor-mediated calcium influx, thereby protecting

neurons against mitochondrial dysfunction, a major cause of excitotoxicity [299]. ↑Bdnf is upregulated at 1 day in our study and may be implicated in the upregulation of the Inhba via the proposed mechanism, in order to confer neuroprotection.

On another note, less enriched BPs related to other neuron specific functions are reported in this time point, with a prominent lack of synaptic function-related categories. IPA analysis indicates overall downregulated signaling related to synaptic transmission and plasticity, with underexpressed GPCRs and overexpression of G protein signaling inhibitor ↑Rgs4. Interestingly, studies have shown that Rgs4 mRNA is increased in response to seizure activity, and Rgs4 has been associated with KA-induced seizure severity, due to its participation in a A1R/neurabin/RGS4 complex, the disruption of which led to anti-convulsive effect in mice [300, 301]. The overexpression of Rgs4 in this time point may be associated with the presence of epileptiform activity, in contrast with the 1 day time point.

4.1.5. Significant changes at 30 days with possible implications in MTLE progression

4.1.5.1. Altered immune and inflammatory responses: the role of complement

Interestingly, the majority of glial-related functional categories that we observed at 3 days, remain enriched at the chronic stage as well, but are populated only by a few genes (e.g.: “positive regulation of glial cell proliferation”, “astrocyte cell migration”). A notable finding of this time point is the upregulation of ↑Gfap, an astrocyte activation marker whose expression is controlled via the signaling molecule Stat3 [302, 303], which was found to be significantly changed during 1 and 3 days post injection in our study.

At the final stage of KA-MTLE studied, the majority of inflammation and immune response categories described during at 1 and 3 days remain enriched, and some of these persistent processes are further enriched (e.g. “phagocytosis”, “complement activation classical pathway”). On the pathway level, the mostly changed pathways are also related to immune and inflammatory response, and the majority of them remains changed since the 3 day time point, according to IPA. In line with the GO BP evidence, the top significantly changed Canonical Pathway is the “Complement System”, which is enriched with twelve genes (Itgam, C1qc, C4a/C4b, C3, C1qb, Itgax, Itgb2, C1s, Serping1, Cfh, C3ar1, C1qa) (summarized in Figure 4.8). The complement system consists of a signaling cascade of enzymatic reactions, playing a role in both during both innate and adaptive immune response. The implicated plasma and surface proteins participate in opsonization, phagocytosis and cell lysis, act to trigger inflammation and enhance antibody activity. In the CNS, complement has been associated with physiological functions such as synapse pruning during development [304], adult neurogenesis [305] and aging in the hippocampus [306], as well as and neurodegeneration and injury [307-309] and epilepsy in specific. [127, 133, 150].

According to studies, activation of the classical complement pathway occurs in the hippocampus and entorhinal cortex following SE in experimental and human TLE. In a pilocarpine mouse model of TLE, immunohistochemical analysis revealed C3 activation at 48 hours, 7 days and 4 months post SE in

reactive astrocytes, and correlated with the severity of epileptic condition [310]. In a rat model of TLE, the number of the significantly changed genes of the classical complement pathway peaked at 1 week post SE in CA3 and EC, whilst some components were induced in acute phase (1 day: C1qa, C1qc) or in latent phase (1 week: C3, C4a), and remained overexpressed in the chronic stage (3-4 months: C1qa, C1qc, C3, C4a, Cfh). Furthermore, this group reported overexpression of complement system inhibitors at 1 week [133]. In human TLE, glial and neuronal expression of C3, C1q, C3c και C3d are observed in regions with neuronal loss in hippocampi, and MAC complex (C5b-C9) was detected in activated microglia [311]. Moreover, microarray studies detected C3 upregulation in the entorhinal cortex (EC), and C3 protein expression was detected in infiltrated lymphocytes in EC of TLE patients [127]. Our findings are in line with most of the above observations, since we report strong induction of C1 and C4 components at 3 days (latent phase) that persists at 30 days (chronic stage: ↑C1qa, ↑C1qb, ↑C1qc, ↑C1rb, ↑C1s, ↑C4b), whereas the C3 components are upregulated at all three time points of our study (1, 3, 30d: ↑C3, ↑C3ar1). In addition, we report upregulation of complement activation inhibitors at 3 and 30 days (↑Cfh, ↑Serping1).

C5 complement components have been also studied in KA excitotoxicity models, and have been associated specifically with microglial functions. KA can induce expression of Fosb products and C5aR1 in the hippocampus [312-314], and according to studies in Fosb-KO mice, these animals were resistant to KA- induced seizures, in comparison with WT mice. Interestingly, Fosb was found to control the expression of C5ar1 and C5ar2 in microglia, and C5ar1 mRNA and protein were upregulated at 24h post injection in WT KA-injected mice, whilst this effect was abolished in Fosb-KO mice which also exhibited decreased microglia activation [315]. Our observations are in line with these findings, since we report the upregulation of ↑Fosb at 1 day, and ↑C5ar1 at 1 and 3 days post KA. In addition, C5a induces a pro-inflammatory response [316, 317] and has strong chemoattractant activity [318], and is thus thought to control microglia motility [319].Overall, C5 complement components seem

to promote neuroinflammation in the initial stages of MTLE, via facilitating microglial activation.

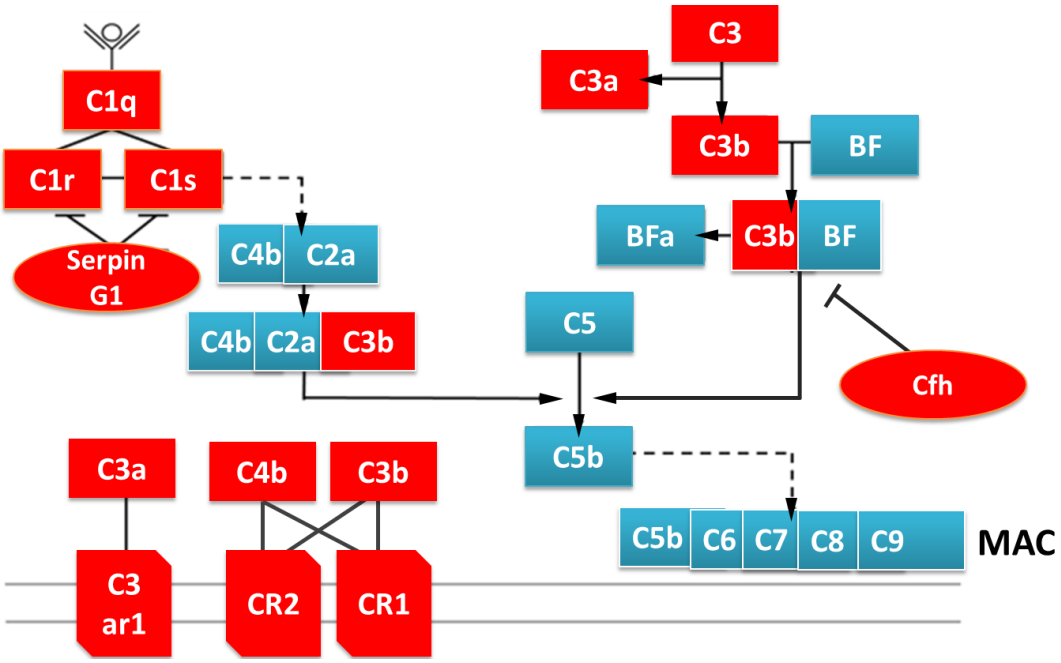


Figure 4.8. *Significant gene expression changes in the complement system pathways at 30 days post injection (red=overexpression, blue=not changed)*

In conclusion, the observed transcriptomic changes imply that complement system is activated in the early and chronic stage of our study, along with its self-regulatory loop. According to these findings and studies by others, complement activation facilitates inflammation, and thus may contribute to neurodegeneration due to prolonged neuroinflammation in MTLE.

Moving to the second most significantly changed IPA pathway at 30 days, “Communication between Innate and Adaptive Immune Cells”, which is populated by twelve overexpressed genes (↑Hla-E, ↑Hla-A, ↑Cxcl10, ↑Tlr1, ↑Ccl9, ↑Il1a, ↑Tlr13, ↑Fcer1g, ↑Ccl3l3, ↑Tlr2, ↑Cd86, ↑Hla-F), we note that it was also changed at 3 days, but was ranked twentieth (according to p-value). An extensive study of this pathway, in combination with the significantly changed genes at 30 days led us to the following hypothetic mechanism: 1) a bacterial-like response of macrophages is triggered that can lead to

chemoattraction of T cells, Natural Killer cells and dendritic cells 2) signaling in dendritic cells can lead to chemoattraction of T cells, Th1 cells, monocytes, neutrophils, dendritic cells and to their interaction with CD4+ and CD8+ cells. Indeed, the compromised BBB in chronic epilepsy may allow the recruitment of many immune and inflammatory cell types as described earlier, even dendritic cells, which are not normally found in the CNS parenchyma. Specifically, studies in KA excitotoxicity models have shown that the dendritic cells focally recruited to the site of the KA-induced lesion do not arise from perivascular macrophages present in the CNS, but originate from blood cells [320].

4.1.5.2. NOX activity and ROS in chronic KA-MTLE

Three out of the four of the main components of the NOX complex that were overexpressed at 3 days remain changed during MTLE progression (↑Cyba, ↑Cybb, ↑Ncf1). The antioxidant components implicated in ROS removal are less prominent in this time point, with the exception of the GO BP “regulation of removal of superoxide radicals”, which is populated by the exact same genes (↑Fbln5, ↑Nfe2l2). This evidence suggests a continuous activation of NOX throughout the course of KA-MTLE, and a possible attenuation of the ROS defense mechanisms.

4.1.5.3. Altered neuronal network organization and function

Interestingly, the final stage of KA-MTLE studied was characterized by enriched neuron-related GO BPs, similarly to the 1 day time point, and in contrast to 3 days. Specifically, we observed seven genes implicated in “negative regulation of neurogenesis”. With regards to other neuron-specific processes, we note synaptic transmission- related changes, (e.g. “regulation of glutamatergic synaptic transmission”), and a significant enrichment of the “neuropeptide signaling pathway” with twelve genes, only three of which were changed at 3 days (↑Emr1, ↑Penk, ↑Tac1). These data may represent the re-establishment of neuronal network function after the end of the latent period, when the intensity and frequency of the epileptic discharges was stabilized.

4.1.6. Evaluation of the "NOX hypothesis" in epileptogenesis

4.1.6.1. Pharmacological inhibition of NOX in KA-MTLE

As discussed above, our findings suggest a possible role for NOX-mediated ROS in neurodegenerative processes associated with epileptogenesis in the KA-MTLE hippocampus. Furthermore, accumulating evidence in the literature indicate that microglial cells may facilitate this function. In order to test this hypothesis in the context of KA-MTLE, we assessed the expression of twelve NOX related genes (i.e. Cyba, Cybb, Ncf1, Ncf2, Ncf4, Nox1, Nox4, Mpo, Prdx6, Rac1, Rac2, and Pu.1) by RT-qPCR in animals treated chronically with the NOX inhibitor Apocynin, or the anticonvulsive drug Valproate, at 30 days post injection.

Chronic Apocynin treatment vs. NOX in KA-MTLE

Apocynin (4-hydroxy-3-methoxyacetophenone) is a natural organic compound derived from the Himalayan herb *Picrorhiza kurrooa Royle* that acts as a NOX assembly inhibitor. Specifically, Apocynin inhibits the intracellular translocation of the critical NOX cytosolic components Ncf1 and Ncf2, to the membrane fraction, and studies have shown that also inhibits the expression of NOX components (e.g. Ncf, Ncf2, Nox2), while it has been used to block NOX activity in different cell types, including microglia [272, 321-324].

Importantly, studies in models of neurodegeneration and epilepsy have shown that Apocynin treatment confers neuroprotective effects in the rodent hippocampus. Accordingly, Apocynin pre-treatment were shown to prevent TBI-induced ROS production, thus decreasing BBB disruption, neuronal death and microglial activation, in hippocampal CA3 region in a rat model of traumatic brain injury [271], and it was also found to decrease SE-induced ROS production and neurodegeneration in the CA1, CA3 and DG hippocampal regions in a rat model of pilocarpine induced TLE [284]. Post-SE Apocynin treatment was also effective in pilocarpine induced TLE; it was found to prevent SE-induced Ncf1 increase in the plasma membrane of hippocampal neurons, decrease SE-induced ROS production, lipid peroxidation, neuronal degeneration, seizure-induced BBB disruption, neutrophil infiltration and microglial activation [285]. A more recent study in a

PTZ mouse model of chronic epilepsy showed that post-kindling Apocynin treatment suppressed the oxidative stress and ameliorated the hippocampal CA1 autophagy [325].

According to this evidence, we hypothesized that NOX inhibition by Apocynin may be effective in reducing NOX-mediated ROS production and the subsequent neuronal dysfunction in the hippocampus, and we utilized it to interrogate the role of NOX in KA-MTLE development. Our analysis revealed that Apocynin treatment suppresses of the expression of nine out of the twelve NOX-related genes tested. Importantly, these genes included membranic subunits (↑Cybb, ↑Cyba), a cytosolic subunit (↑Ncf1), the catalytic subunit (↑Nox4), and an upstream regulator of NOX expression (↑Pu.1) that were found to be overexpressed, according to our microarray analysis. Although these findings indicate a suppression of NOX activity by Apocynin in the KA-MTLE hippocampus, it was not accompanied by suppression of seizures at 30 days post-injection, and had no effect on glial reactivity and cell loss either, according to studies conducted by Dr. Depaulis group. This evidence suggests that glial activation does not depend on NOX complex activity, and NOX-mediated ROS production is unlikely to play a crucial role in the development of seizures in the KA-MTLE model.

Chronic Valproate treatment vs. NOX in KA-MTLE

Valproate, and its valproic acid, sodium valproate, and valproate semisodium forms, have a broad spectrum of anticonvulsant activity, and are used for the prevention of absence seizures, partial seizures, and generalized seizures [326]. The proposed mechanisms of action for Valproate include blockage of voltage-gated sodium channels; histone deacetylases (HDACs) inhibition, thereby conferring neuroprotective effects mediated by VEGF, BDNF, GDNF; GABA levels increase in the brain, possibly by inhibition of GABA degradation and GABA reuptake by neurons; and protection against seizure induced PIP_3 reduction [327].

Interestingly, evidence in literature proposes an anti-inflammatory role for Valproate, via the suppression of microglia. More specifically, Valproate is

amongst the HDAC inhibitors that suppress the expression of inflammatory and innate immune response genes in human microglia and astrocytes [328]. Moreover, studies have shown that it confers neuroprotection via reduction of oxidative stress (decreased MPO, 4HNE, 8OHdG), and microglial activation (decreased Iba1) [329]. Lastly, studies in human brain-derived microglial cells showed that Valproate leads to reduced protein expression of PU.1 [330], which is overexpressed at 3 and 30 days in KA-MTLE (↑Pu.1 a.k.a ↑Spi1). According to the above studies, Valproate can suppress microglial activation, which is considered as the main source of NOX expression in KA-MTLE, and can also reduce Pu.1 expression which is likely to control multiple NOX genes, as well as reduce oxidative stress, which can result from NOX enzymes activity. Consequently, we hypothesized that Valproate treatment may suppress NOX activity and NOX-mediated processes in KA-MTLE hippocampus, and further our understanding on the role of NOX in KA-MTLE development.

Our analysis showed that chronic treatment with Valproate resulted in significant overexpression of ↑Ncf1 and ↑Cyba, and suppression of ↓Nox1 expression, at 30 post injection in the KA-MTLE hippocampus. Interestingly, additional analyses from Dr. Depaulis group showed that chronic Valproate treatment suppresses microglia activation (indicated by ↓Iba1 expression) at CA1 and CA3 hippocampal regions; however, it has no effect on MTLE development in terms of seizure occurrence (Dr. Duveau group). These findings indicate that Valproate is not an effective NOX suppressor in the KA-MTLE hippocampus, and that microglial activation may be associated with Nox1 expression. Overall, our analysis suggests that NOX-mediated ROS production in activated microglia may not have a causal role in MTLE development, in the KA-MTLE model.

4.1.6.2. NOX4 deletion in KA-MTLE

In our next step for the evaluation of the role of NOX in KA-MTLE, we utilized the KA-MTLE NOX4 KO mouse model, created by our collaborator Dr. Duveau. The transcriptomic analysis of NOX4 KO versus WT hippocampi showed no significant changes in gene expression between the two sample groups, in any of the variable thresholds of statistical significance interrogated. Importantly, NOX4 KO animals treated with KA had no differences in seizure occurrence and duration, when compared to wild type KA-treated mice, at 30 days (Dr. Duveau group). The lack of KA-MTLE modulation and distinct transcriptomic profile upon NOX4 deletion suggests that NOX4 is not crucial for the establishment of MTLE in this model.

This series of experiments sought to evaluate the role of NOX in KA-MTLE epileptogenesis. We hypothesized that NOX suppression/deletion would lead to decreased ROS production, and affect the development of seizures and/or the neurodegenerative phenotype of KA-MTLE hippocampus. Our findings however, combined with valuable data from our collaborators, suggest that the upregulation of specific NOX components during MTLE development and progression is highly unlikely to have a causal or contributing role to the development of seizures in the KA-MTLE syndrome, and may thus not be suitable for therapeutic targeting.

4.2. HUMAN MTLE

4.2.1. Establishing the transcriptomic signature of human MTLE-HS

In order to gain insight in the transcriptomic changes possibly associated with accompanying histopathological findings that are typical of MTLE, we performed microarray analysis of a cohort of human MTLE hippocampal samples. These samples were provided by our collaborator Dr. S. Hamelin (INSERM, Université Grenoble Alpes, France), through the epilepsy surgery program of the University Hospital (Hôpital Michallon, Grenoble, France), and comprised resective tissues from hippocampal regions of MTLE patients that received surgery. All of the samples were obtained from chronic MTLE patients, and were examined for histopathological features that are typical of MTLE, and are considered to contribute to MTLE pathology (i.e. hippocampal sclerosis, febrile seizures, focal cortical dysplasia and granule cell dispersion).

The cohort was specifically curated to enable the study of Hippocampal Sclerosis (HS), which is thought to play a critical role in MTLE pathogenesis. HS is the most commonly encountered pathologic feature in resected tissue [331, 332] and, MTLE-HS is considered a distinct MTLE subtype [52, 333]. HS is the most common cause of pharmacoresistant epilepsy amenable for surgical treatment and seizure control, whilst surgery of MTLE-HS achieves long-term seizure freedom in ~70% of cases [334, 335]. Moreover, studies have shown that the surgical prognosis of patients with MTLE correlates with the degree of histopathological HS [336, 337]. In order to investigate the transcriptomic profile of HS, we compared the patient subgroups with and without hippocampal sclerosis (HS vs. non HS). The lists of significantly changed genes obtained from microarrays (210 genes, see Appendix 17), were subjected to extensive analyses, with the aid of IPA software.

4.2.1.1. Altered neurotransmission profile in MTLE-HS

Our analysis revealed that twelve significantly underexpressed changed genes were specifically associated with seizures (category “Seizures”, IPA) (↓AKAP5, ↓AP1S1, ↓CACNA2D1, ↓CAMKK1, ↓EGR4, ↓GLRA1, ↓KCNH3, ↓KCNK1, ↓KCNV1, ↓LAMP5, ↓NPY5R, ↓SCG5). Amongst them, we observed three genes related to K^+ channels (↓KCNV1, ↓KCNH3, ↓KCNK1,) and a more extensive analysis of our data revealed two more genes associated with the modulation of K^+ levels (i.e., ↓KCNK9, ↓KCNN1). KCNV1 is found in a locus associated with benign adult familial myoclonic epilepsy and encodes a neuronal modulatory alpha-subunit of the voltage-gated potassium channel [338], whilst the deletion of the voltage-gated potassium channel KCNH3 in mice has been shown to cause hippocampal hyperexcitability and spontaneous seizures [339]. KCNK1 and KCNK9, are members of the TWIK-1 two-pore domain K^+ channel family, and they show altered expression patterns in healthy vs. epileptic tissue. Specifically, studies have shown a mainly neuronal expression in the healthy human hippocampus, whilst in TLE patients KCNK1 expression is mainly located in astrocytes, and KCNK9 is expressed in astrocytes and microglia [340]. KCNK1 has been shown to contribute to the intrinsic excitability of the DG granule cells in the mouse hippocampus [341], whilst studies in astrocytes have shown that it may be implicated in the astrocyte-neuron coupling for the replenishment of neurotransmitters in neurons [342]. KCNN1, is one of the small-conductance (SK) $Ca^{(2+)}$-activated K^+ channels which contribute to afterhyperpolarizations (AHPs), and their blockade increases neuronal excitability [343]. KCNN1 has been also found to be downregulated in pilocarpine induced MTLE in rats, and its blockade in chronic epileptic animals was shown to increase epileptiform activity in hippocampal CA1 [344].

Overall, these data suggest impaired K^+ channel function that may impact hippocampal excitability in HS patients. Specifically, failure of the potassium buffering system in astrocytes is considered to contribute to the epileptic activity of the sclerotic hippocampus. Studies in human MTLE-HS tissue have

reported loss of KCNJ10 (Kir 4.1 channel) immunoreactivity in perivascular astrocytes [345]. Moreover, a recent *ex vivo* study in living hippocampal tissue from MTLE patients revealed that epileptiform activities developed from the subiculum, and they suggest a possible impairment of K^+ clearance in the subiculum affected by HS. In specific, this group reported decreased Kir4.1 activity in astrocytes, that was considered to induce hyperexcitability in the subiculum in MTLE-HS [346]. In conclusion, the observed alterations related to potassium homeostasis, in conjuction with data from the literature, suggest that impaired K+ buffering may render sclerotic hippocampi hyperecxitable thus contributing to seizure propagation in MTLE-HS.

An additional gene that was found to be associated with seizures in our study, according to IPA, is ↓CACNA2D1. CACNA2D1, encodes for a voltage-dependent calcium channel alpha2/delta-1-subunit, with a mainly presynaptic localization, where it is associated with the calcium channels involved in neurotransmitter release, and it is widely known as the target of the antiepileptic drug pregarbalin [347]. A recent study in the KA-MTLE hippocampus showed no change in the expression of CACNA2D1, but a local reorganization of CACNA2D1 immunostaining, associated with areas of neuronal cell loss, dendritic loss, and reactive gliosis [348]. Moreover, CACNA2D1 has been found to interact with thrombospondins, an interaction that has been shown to implicated in synaptogenesis, independently of its function as a calcium channel [349]. Neuronal loss and reactive gliosis are prominent characteristics of sclerotic hippocampal regions, while new synapses are formed during the process of MF sprouting, a hallmark of HS. This evidence indicates that CACNA2D1 activity may be altered in sclerotic hippocampi, and its function may be related to HS and involve synaptic reorganization processes, besides its potential role as a modulator of neurotransmitter release.

4.2.1.2. Decreased neuroprotective mechanisms in MTLE-HS

We also observed significant downregulation of the seizure related ↓NPY5R, a receptor for neuropeptide NPY. NPY is an endogenous suppressor of seizure activity in human and experimental epilepsy [176-178], which is also thought to mediate Valproate's anticonvulsive effects [179]. It has been shown

to exert its anti-convulsive effects via NPY5R, as well as NPY1R and NPY2R receptor subtypes, [182-184]. SNPs in NPY5R have been shown to be significantly associated with alcohol withdrawal characterized by seizures [350], proposing a role for this receptor in seizure control. Studies in MTLE-HS have reported loss of NPY neurons and extensive sprouting that parallels MF sprouting, and is considered to act by blocking the synchronization of granule cells through the recurrent mossy collaterals [351-354]. Moreover, gene therapy studies that induced hippocampal NPY over-expression via viral vectors resulted in decreased seizure frequency [355]. The decreased expression of ↓NPY5R in our study could result from the loss of NPY neurons and reflect a suppression of the endogenous anticonvulsive mechanisms in MTLE-HS, which may contribute to the epileptic activity of sclerotic hippocampus.

Lastly, the most significantly upregulated gene in HS patient group, ↑NPAS4, which encodes for an activity-dependent neuron-specific transcription factor, is of specific interest to our study. Npas4 expression is rapidly triggered by excitatory synaptic activity and induces gene expression program responsible for the formation and/or maintenance of inhibitory synapses on excitatory neurons [356]. Npas4 have been shown to inhibit seizure attacks in pilocarpine-induce epilepsy in rats [357]. Moreover, recent studies have revealed a set of genes named "activity-regulated inhibitor of death" (AID genes), that include Npas4, and have been found to provide activity-induced protection against neuronal death caused by excitotoxic stimulation. More specifically, Npas4 was shown to protect hippocampal neurons against excitotoxic cell death via Syt10, which is also strongly induced by pathophysiologic synaptic activity after KA exposure [358]. Interestingly, a recent study in a PTZ-induced epilepsy mouse model proposed a novel mechanism of action by which Npas4 adapts to and represses seizures. In specific, they suggest that seizure activity up-regulates Npas4-Homer1a signaling in the hippocampus, and initiates homeostatic scaling-down of excitatory synapses [359]. Thus, the upregulation of ↑NPAS4 in MTLE-HS may be a response to the frequent occurrence of spontaneous seizures,

which is typical of the chronic stage of the disease, and act as a regulator of homeostatic synaptic plasticity.

In the present study, we provide insight in the transcriptomic signature of the MTLE-HS syndrome, working towards a better understanding of the distinct histopathological profile of HS. The transcriptomic analysis revealed expression changes in multiple genes associated with seizures and excitability modulation, which is line with the notion that the sclerotic hippocampus is recognized as the source of epileptic seizures in MTLE-HS. It should be noted that, due to the samples originating from patients suffering from chronic MTLE, the information provided reflect alterations accumulated over years of seizure episodes and one or more pharmacological interventions per patient. Thus, our study deciphered common denominators of pharmacoresistant MTLE-HS progression, which may be associated with the variation in seizure outcome and clinical management of this syndrome, compared to MTLE without HS.

4.3 Limitations of the study

The methodological approach used in our study is subject to specific limitations, related to the experimental design and the interpretation of microarray data.

The hippocampus is a tissue comprised by many distinct cell types (neurons, microglia, astrocytes, endothelial cells etc.), and no cell sorting technique was applied prior to RNA extraction in our study. Consequently, the expression data derived from microarray analysis of the epileptic hippocampus reflect gene expression changes from the entity of this tissue, and thus the conclusions related to cell type-specific expression of genes are limited by the range of available evidence in the literature. Furthermore, extensive loss of neuronal cells in specific hippocampal regions of the KA-MTLE model is experimentally proven, and is completed for the most part within 24 hours post KA injection [9, 139, 360]. Neuronal cell death and hippocampal atrophy is also observed in the human samples analyzed. Accordingly, the decrease of the number of neurons expressing a given set of genes in the tissue analyzed can cause a decrease in the fold change of those genes,

independently of the effects of the MTLE stage interrogated (epileptogenesis/progression). Thus, the observed underexpression in certain cases may not be a direct effect of MTLE, but rather a consequence of the extensive cell death observed in epileptic hippocampi.

Regarding the translation of the findings of experimental MTLE in human MTLE, unfortunately the datasets obtained in this study were not comparable. Although microarrays were performed on both KA-MTLE and human MTLE hippocampal samples during a similar stage of MTLE (i.e. MTLE progression, 30 days post injection in KA-MTLE), no “control” tissue samples were available in order to perform a MTLE vs. non MTLE comparison in human MTLE. The use of *post mortem,* non-diseased tissue samples as controls is common in studies conducted in the CNS, but was not an option in the case of our study, since it has been reported that the use of *post mortem* tissue can interfere with the results in gene expression studies in epilepsy. [361, 362].

4.4 Future work

The results presented herein indicate several alterations in molecular pathways that are crucial for hippocampal function, and possibly for MTLE development and progression, while regulatory molecules that could potentially serve as candidate therapeutic targets were also highlighted. However, the conclusions obtain from transcriptomics are drawn based on the observed RNA levels, and require functional characterization. In subsequent studies, the use of pharmacological inhibitors, gene silencing or suppression of protein expression would be useful, in order to pinpoint the role of the selected target in KA-MTLE. It should be also noted, that specific molecular players of KA-MTLE discussed in this study, appear to exert multiple cell-specific effects, thus rendering the identification of the hippocampal cell subpopulation in which they are expressed and/or affect necessary.

Lastly, our notable seizure-related findings in human MTLE-HS could be the basis of new study designs that can be implemented in the KA-MTLE mouse model. Further validaton and functional studies would help elucidating the role of the highlighted molecular players in seizures.

4.5 Conclusions

Our study investigated the global expression profile of the epileptic hippocampus in the KA-induced MTLE mouse model, in three time points (1, 3, 30 days post injection) representative of distinct stages of MTLE development and progression. We provided valuable insight in the molecular pathways that change significantly during the course of MTLE, bringing to light key molecular players that are predicted to regulate the observed molecular changes implicated in KA-MTLE pathogenesis, and may thus serve as candidate therapeutic targets. Importantly, this multi-level bioinformatic analysis enabled us to form a testable hypothesis regarding the therapeutic potential of NOX in MTLE, and through the experimental approaches adopted for the validation of this hypothesis we furthered our understanding of the role of NOX in KA-MTLE. Moreover, our studies in human MTLE-HS shed light to the distinct transcriptomic profile of the sclerotic hippocampus, in an effort to establish the molecular basis of HS. Our analysis will hopefully improve the overall understanding of the pathogenetic mechanisms underlying this key element of intractable and pharmacoresistant MTLE-HS, thus contributing to the development of more effective therapeutic interventions to battle the disease.

ABBREVIATIONS/ACRONYMS

AD: Alzheimer’s disease

AEDs: Antiepileptic drugs

ALS: Amyotrophic lateral Sclerosis

ANOVA: Analysis Of Variance

CNS: Central nervous system

CSF: Cerebrospinal Fluid

DG: Dentate Gyrus

DMD: Duchene Muscular Dystrophy

FDR: False Discovery Rate

EEG: Electroencephalography

FCD: Focal Cortical Dysplasia

FS: Febrile Seizures

GCD: Granule Cell Dispersion

GO: Gene Ontology

GO BP: Biological Process (Gene Ontology category)

GO CC: Cellular Component (Gene Ontology category)

GO MF: Molecular Function (Gene Ontology category)

HD: Huntington's disease

HS: Hippocampal Sclerosis

ILAE: International League of Epilepsy

IPA: Ingenuity Pathway Analysis

KA: Kainic Acid

KO: knock out

MaTLE: Mass-associated Temporal Lobe Epilepsy

MF: Mossy Fibers

MND: Motor Neuron Disease

MRI: Magnetic resonance imaging

MS: Multiple Sclerosis

MTLE: Mesio Temporal Lobe Epilepsy

NDs: Neurodegenerative diseases

NMs: Nemaline Myopathies

PCA: Principal Component Analysis

PD: Parkinson's disease

PET: Positron Emission Tomography

PTLE: Paradoxical Temporal Lobe Epilepsy

RMA: Robust Multi-array Average

SAM: Significance Analysis of Microarrays

SE: *Status epilepticus*

SOM: Self-Organizing Maps

TLE: Temporal Lobe Epilepsy

VGKC: Voltage-Gated Potassium Channel

WHO: World Health Organization

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APPENDIX

KA-MTLE MOUSE MODEL

Significantly changed transcripts

APPENDIX 1

Significantly changed transcripts at 1 day post injection, in KA- vs. saline - injected mice hippocampi. Thresholds: 2-fold, FDR-adjusted p-value< 0.01.

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change 1 day
10403743	**Inhba**	NM_008380 // Inhba // inhibin beta-A // 13 A1|13 10.0 cM // 16323 /// ENSMUST0000004260	13.36
-	**Spp1**	NM_009263 // Spp1 // secreted phosphoprotein 1 // 5 E5|5 56.0 cM // 20750 /// ENSMUST00	12.47
10526410	**Hspb1**	NM_013560 // Hspb1 // heat shock protein 1 // 5 G2|5 76.0 cM // 15507 /// ENSMUST000000	10.35
10408928	**Hspb1**	NM_013560 // Hspb1 // heat shock protein 1 // 5 G2|5 76.0 cM // 15507 /// ENSMUST000000	9.81
10464905	**Npas4**	NM_153553 // Npas4 // neuronal PAS domain protein 4 // 19 A|19 // 225872 /// ENSMUST000	8.72
10554249	**Acan**	NM_007424 // Acan // aggrecan // 7 D3|7 39.0 cM // 11595 /// ENSMUST00000032835 // Acan	8.04
10534667	**Serpine1**	NM_008871 // Serpine1 // serine (or cysteine) peptidase inhibitor, clade E, member 1 //	7.86
10375432	**C030019I05Rik**	NM_177075 // C030019I05Rik // RIKEN cDNA C030019I05 gene // 11 B1.1|11 // 320116 /// EN	7.43
10529034	**Cgref1**	NM_026770 // Cgref1 // cell growth regulator with EF hand domain 1 // 5 B1|5 // 68567 /	6.85
10527332	**Nptx2**	NM_016789 // Nptx2 // neuronal pentraxin 2 // 5 G2|5 82.0 cM // 53324 /// ENSMUST000000	6.82
10560481	**Fosb**	NM_008036 // Fosb // FBJ osteosarcoma oncogene B // 7 A2-B1|7 5.0 cM // 14282 /// ENSMU	6.81
10505489	**Pappa**	NM_021362 // Pappa // pregnancy-associated plasma protein A // 4 C1|4 32.2 cM // 18491	6.25
10350516	**Ptgs2**	NM_011198 // Ptgs2 // prostaglandin-endoperoxide synthase 2 // 1 H1|1 76.2 cM // 19225	6.24
10361091	**Atf3**	NM_007498 // Atf3 // activating transcription factor 3 // 1 H6|1 103.2 cM // 11910 ///	5.95
10587554	**Tpbg**	NM_011627 // Tpbg // trophoblast glycoprotein // 9 E3.1|9 // 21983 /// NM_001164792 //	5.65
10502655	**Cyr61**	NM_010516 // Cyr61 // cysteine rich	5.59

		protein 61 // 3 H2|3 72.9 cM // 16007 /// ENSMUST00	
10394770	**Odc1**	NM_013614 // Odc1 // ornithine decarboxylase, structural 1 // 12 A1.1|12 6.0 cM // 1826	5.37
10578880	**Tll1**	NM_009390 // Tll1 // tolloid-like // 8 B3.1|8 32.4 cM // 21892 /// ENSMUST00000066166 /	5.16
10417226	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// NM_0011647	5.09
10458340	**Hbegf**	NM_010415 // Hbegf // heparin-binding EGF-like growth factor // 18 B2|18 15.0 cM // 152	5.06
10542355	**Emp1**	NM_010128 // Emp1 // epithelial membrane protein 1 // 6 G1|6 65.0 cM // 13730 /// ENSMU	5.05
10417235	**Gm2897**	NM_001177714 // Gm2897 // predicted gene 2897 // 14 A1|14 // 100040671 /// NM_001164727	5.02
10417315	**Gm2897**	NM_001177714 // Gm2897 // predicted gene 2897 // 14 A1|14 // 100040671 /// NM_001164727	5.02
10450369	**Hspa1a**	NM_010479 // Hspa1a // heat shock protein 1A // 17 B1|17 18.95 cM // 193740 /// ENSMUST	5.00
10405211	**Gadd45g**	NM_011817 // Gadd45g // growth arrest and DNA-damage-inducible 45 gamma // 13|13 A5-B /	4.98
10417258	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// ENSMUST000	4.97
10463875	**Sorcs3**	NM_025696 // Sorcs3 // sortilin-related VPS10 domain containing receptor 3 // 19 D1|19	4.94
10536845	**Flnc**	NM_001081185 // Flnc // filamin C, gamma // 6 A3.3|6 8.5 cM // 68794 /// ENSMUST0000009	4.86
10443527	**Pim1**	NM_008842 // Pim1 // proviral integration site 1 // 17 A3.3|17 16.4 cM // 18712 /// ENS	4.85
10417302	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// NR_033117	4.83
10600980	**Dgat2l6**	NM_001114084 // Dgat2l6 // diacylglycerol O-acyltransferase 2-like 6 // X C3|X // 66825	4.83
10464471	**Gal**	NM_010253 // Gal // galanin // 19 A|19 2.0 cM // 14419 /// ENSMUST00000025842 // Gal //	4.82
10417286	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// NM_0011647	4.72
10417421	**Gm3696**	NM_001024712 // Gm3696 // predicted gene 3696 // 14 A1|14 // 100042149 /// NM_001029930	4.69
10462621	**I830012O16Rik**	NM_001005858 // I830012O16Rik // RIKEN cDNA I830012O16 gene // 19 C1|19 // 667370 /// E	4.67

10417411	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// NM_0011647	4.66
10417239	**Gm1973**	NM_029288 // Gm1973 // predicted gene 1973 // 14 A1|14 // 100038846 /// NM_001024706 //	4.64
10582295	**Odc1**	NM_013614 // Odc1 // ornithine decarboxylase, structural 1 // 12 A1.1|12 6.0 cM // 1826	4.62
10417264	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// NM_0010247	4.62
10607950	**G530011O06Rik**	NR_029457 // G530011O06Rik // RIKEN cDNA G530011O06 gene // X F5|X // 654820	4.61
10595668	**Ankrd34c**	NM_207260 // Ankrd34c // ankyrin repeat domain 34C // 9 E3.1|9 // 330998 /// ENSMUST000	4.61
10552311	**---**	---	4.59
10417458	**Gm5458**	NM_001024706 // Gm5458 // predicted gene 5458 // 14 A3|14 // 432825 /// ENSMUST00000096	4.59
10409278	**Nfil3**	NM_017373 // Nfil3 // nuclear factor, interleukin 3, regulated // 13 B1|13 32.0 cM // 1	4.59
10412537	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// NR_033121	4.55
10377473	**Aloxe3**	NM_011786 // Aloxe3 // arachidonate lipoxygenase 3 // 11 B3|11 37.0 cM // 23801 /// ENS	4.55
10511363	**Penk**	NM_001002927 // Penk // preproenkephalin // 4 A1|4 0.8 cM // 18619 /// ENSMUST000000703	4.54
10417359	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// NM_0010247	4.52
10382341	**Sstr2**	NM_009217 // Sstr2 // somatostatin receptor 2 // 11 E2|11 69.0 cM // 20606 /// NM_00104	4.48
10406229	**Pcsk1**	NM_013628 // Pcsk1 // proprotein convertase subtilisin/kexin type 1 // 13 C2|13 44.0 cM	4.47
10412520	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// NM_0011647	4.45
10485405	**Cd44**	NM_009851 // Cd44 // CD44 antigen // 2 E2|2 56.0 cM // 12505 /// NM_001177785 // Cd44 /	4.45
10417373	**Gm10406**	NM_001164727 // Gm10406 // predicted gene 10406 // 14 A1|14 // 100038847 /// NM_0010299	4.44
10462618	**Ifit3**	NM_010501 // Ifit3 // interferon-induced protein with tetratricopeptide repeats 3 // 19	4.42
10541307	**Usp18**	NM_011909 // Usp18 // ubiquitin specific peptidase 18 // 6 F|6 56.0 cM // 24110 /// ENS	4.41
10499899	**Sprr1a**	NM_009264 // Sprr1a // small proline-rich protein 1A // 3 F1|3 45.2 cM // 20753	4.38

		/// ENS	
10411082	**Thbs4**	NM_011582 // Thbs4 // thrombospondin 4 // 13 C3|13 51.0 cM // 21828 /// ENSMUST00000022	4.38
10417408	**D830030K20Rik**	NM_177135 // D830030K20Rik // RIKEN cDNA D830030K20 gene // 14 A1|14 // 320333 /// ENSM	4.37
10450367	**Hspa1a**	NM_010479 // Hspa1a // heat shock protein 1A // 17 B1|17 18.95 cM // 193740 /// NM_0104	4.30
10417461	**Gm10406**	NM_001164727 // Gm10406 // predicted gene 10406 // 14 A1|14 // 100038847 /// NM_0010299	4.30
10474700	**Thbs1**	NM_011580 // Thbs1 // thrombospondin 1 // 2 F1-F3|2 65.0 cM // 21825 /// ENSMUST0000003	4.29
10417319	**D830030K20Rik**	NM_177135 // D830030K20Rik // RIKEN cDNA D830030K20 gene // 14 A1|14 // 320333 /// ENSM	4.28
10397346	**Fos**	NM_010234 // Fos // FBJ osteosarcoma oncogene // 12 D2|12 40.0 cM // 14281 /// ENSMUST0	4.25
10417446	**4930555G01Rik**	NM_175393 // 4930555G01Rik // RIKEN cDNA 4930555G01 gene // 14 A1|14 // 108978 /// NM_0	4.25
10417452	**4930555G01Rik**	NM_175393 // 4930555G01Rik // RIKEN cDNA 4930555G01 gene // 14 A1|14 // 108978 /// NM_0	4.25
10598976	**Timp1**	NM_001044384 // Timp1 // tissue inhibitor of metalloproteinase 1 // X A1.3|X 6.2 cM //	4.23
10360377	**AI607873**	BC150711 // AI607873 // expressed sequence AI607873 // 1 H3|1 // 226691 /// ENSMUST0000	4.22
10462623	**Ifit1**	NM_008331 // Ifit1 // interferon-induced protein with tetratricopeptide repeats 1 // 19	4.21
10364950	**Gadd45b**	NM_008655 // Gadd45b // growth arrest and DNA-damage-inducible 45 beta // 10 C1|10 60.5	4.20
10417326	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// NM_0010299	4.19
10546417	**Trh**	NM_009426 // Trh // thyrotropin releasing hormone // 6 D1|6 40.0 cM // 22044 /// ENSMUS	4.18
10466210	**Ms4a6d**	NM_026835 // Ms4a6d // membrane-spanning 4-domains, subfamily A, member 6D // 19 A|19 /	4.17
10360382	**Ifi204**	NM_008329 // Ifi204 // interferon activated gene 204 // 1 H3|1 95.2 cM // 15951 /// NM_	4.15
10389231	**Ccl3**	NM_011337 // Ccl3 // chemokine (C-C motif) ligand 3 // 11 C|11 47.59 cM // 20302 /// EN	4.10
10513739	**Tnc**	NM_011607 // Tnc // tenascin C // 4 C1|4 32.2 cM // 21923 /// ENSMUST00000030056 // Tnc	4.09
10443463	**Cdkn1a**	NM_007669 // Cdkn1a // cyclin-	4.05

		dependent kinase inhibitor 1A (P21) // 17 A3.3|17 15.23 c	
10586744	**Anxa2**	NM_007585 // Anxa2 // annexin A2 // 9 C|9 37.0 cM // 12306 /// ENSMUST00000034756 // An	4.03
10417366	**ENSMUSG00000068790**	NM_001029930 // ENSMUSG00000068790 // predicted gene, ENSMUSG00000068790 // 14 A1|14 //	4.01
10417773	**Gm5458**	NM_001024706 // Gm5458 // predicted gene 5458 // 14 A3|14 // 432825 /// NM_001025085 //	4.00
10417504	**Gm1973**	NM_029288 // Gm1973 // predicted gene 1973 // 14 A1|14 // 100038846 /// BC100412 // Gm1	3.99
10412503	**---**	---	3.94
10408268	**Scgn**	NM_145399 // Scgn // secretagogin, EF-hand calcium binding protein // 13 A3.1|13 // 214	3.92
10498273	**Tm4sf1**	NM_008536 // Tm4sf1 // transmembrane 4 superfamily member 1 // 3 D|3 // 17112 /// ENSMU	3.90
10456400	**Tubb6**	NM_026473 // Tubb6 // tubulin, beta 6 // 18|18 E1 // 67951 /// ENSMUST00000001513 // Tu	3.85
10563377	**Sult2b1**	NM_017465 // Sult2b1 // sulfotransferase family, cytosolic, 2B, member 1 // 7 B4|7 // 5	3.84
10417501	**Gm5458**	NM_001024706 // Gm5458 // predicted gene 5458 // 14 A3|14 // 432825 /// NM_029288 // Gm	3.84
10448307	**Tnfrsf12a**	NM_013749 // Tnfrsf12a // tumor necrosis factor receptor superfamily, member 12a // 17	3.83
10412549	**D830030K20Rik**	NM_177135 // D830030K20Rik // RIKEN cDNA D830030K20 gene // 14 A1|14 // 320333 /// ENSM	3.80
10433114	**Itga5**	NM_010577 // Itga5 // integrin alpha 5 (fibronectin receptor alpha) // 15 F3|15 57.4 cM	3.79
10383208	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.79
10416181	**Stc1**	NM_009285 // Stc1 // stanniocalcin 1 // 14 D2|14 // 20855 /// ENSMUST00000014957 // Stc	3.76
10417253	**Gm1973**	NM_029288 // Gm1973 // predicted gene 1973 // 14 A1|14 // 100038846 /// BC100412 // Gm1	3.75
10417281	**Gm1973**	NM_029288 // Gm1973 // predicted gene 1973 // 14 A1|14 // 100038846 /// NM_001024706 //	3.75
10523182	**Areg**	NM_009704 // Areg // amphiregulin // 5 E1|5 51.0 cM // 11839 /// ENSMUST00000031325 //	3.73
10412495	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// ENSMUST000	3.70
10600994	**Arr3**	NM_133205 // Arr3 // arrestin 3, retinal // X|X C2 // 170735 ///	3.70

		ENSMUST00000113769 //	
10429491	**Arc**	NM_018790 // Arc // activity regulated cytoskeletal-associated protein // 15 D3|15 41.4	3.69
10417245	**Gm1973**	NM_029288 // Gm1973 // predicted gene 1973 // 14 A1|14 // 100038846 /// EF651825 // D83	3.68
10474381	**Kif18a**	NM_139303 // Kif18a // kinesin family member 18A // 2 E3|2 // 228421 /// ENSMUST0000002	3.65
10379511	**Ccl2**	NM_011333 // Ccl2 // chemokine (C-C motif) ligand 2 // 11 C-E1|11 46.5 cM // 20296 ///	3.63
10363070	**Gp49a**	NM_008147 // Gp49a // glycoprotein 49 A // 10 B3|10 // 14727 /// ENSMUST00000102894 //	3.60
10455970	**BC023105**	BC023105 // BC023105 // cDNA sequence BC023105 // 18 D3|18 // 667597	3.58
10558049	**Ppapdc1a**	NM_001080963 // Ppapdc1a // phosphatidic acid phosphatase type 2 domain containing 1A /	3.54
10483706	**Chrna1**	NM_007389 // Chrna1 // cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle) //	3.52
10474399	**Bdnf**	NM_001048139 // Bdnf // brain derived neurotrophic factor // 2 E3|2 62.0 cM // 12064 //	3.52
10531415	**Cxcl10**	NM_021274 // Cxcl10 // chemokine (C-X-C motif) ligand 10 // 5 E2|5 53.0 cM // 15945 ///	3.49
10378547	**Mir132**	NR_029546 // Mir132 // microRNA 132 // 11|11 // 387150	3.48
10412491	**---**	---	3.48
10600836	**Msn**	NM_010833 // Msn // moesin // X C3|X // 17698 /// ENSMUST00000117399 // Msn // moesin /	3.47
10383206	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.46
10520862	**Fosl2**	NM_008037 // Fosl2 // fos-like antigen 2 // 5 B1|5 18.1 cM // 14284 /// ENSMUST00000031	3.45
10531610	**Rasgef1b**	NM_145839 // Rasgef1b // RasGEF domain family, member 1B // 5 E3|5 // 320292 /// NM_181	3.43
10476395	**Bmp2**	NM_007553 // Bmp2 // bone morphogenetic protein 2 // 2 F2|2 76.1 cM // 12156 /// ENSMUS	3.41
10412488	**---**	---	3.39
10601848	**6530401D17Rik**	NM_029541 // 6530401D17Rik // RIKEN cDNA 6530401D17 gene // X F1|X // 76219	3.38
10537146	**Akr1b8**	NM_008012 // Akr1b8 // aldo-keto reductase family 1, member B8 // 6 B1|6 13.0 cM // 141	3.37
10412517	**Gm3002**	NR_033388 // Gm3002 // alpha-takusan pseudogene // 14 A1|14 // 100040852 /// ENSMUST000	3.36

10373918	**Lif**	NM_008501 // Lif // leukemia inhibitory factor // 11 A1-A2|11 0.25 cM // 16878 /// NM_0	3.32
10399710	**Rsad2**	NM_021384 // Rsad2 // radical S-adenosyl methionine domain containing 2 // 12|12 A3 //	3.32
10467136	**Ch25h**	NM_009890 // Ch25h // cholesterol 25-hydroxylase // 19 C1|19 // 12642 /// ENSMUST000000	3.30
10467508	**Blnk**	NM_008528 // Blnk // B-cell linker // 19 C3|19 31.0 cM // 17060 /// ENSMUST00000054769	3.30
10351873	**Pyhin1**	NM_175026 // Pyhin1 // pyrin and HIN domain family, member 1 // 1 H3|1 // 236312 /// EN	3.29
10366052	**Kitl**	NM_013598 // Kitl // kit ligand // 10 D1|10 57.0 cM // 17311 /// ENSMUST00000105283 //	3.28
10482500	**Rnd3**	NM_028810 // Rnd3 // Rho family GTPase 3 // 2 C1.1|2 // 74194 /// ENSMUST00000017288 //	3.27
10458382	**Cd14**	NM_009841 // Cd14 // CD14 antigen // 18 B2|18 31.0 cM // 12475 /// ENSMUST00000061829 /	3.26
10493114	**Nes**	NM_016701 // Nes // nestin // 3 F1|3 42.5 cM // 18008 /// ENSMUST00000090973 // Nes //	3.26
10490159	**Pmepa1**	NM_022995 // Pmepa1 // prostate transmembrane protein, androgen induced 1 // 2 H3|2 //	3.25
10566366	**Trim30d**	NM_199146 // Trim30d // tripartite motif-containing 30D // 7 E3|7 // 209387 /// NM_0011	3.24
10503334	**Gem**	NM_010276 // Gem // GTP binding protein (gene overexpressed in skeletal muscle) // 4 A1	3.22
10417269	**---**	---	3.22
10566358	**Trim30a**	NM_009099 // Trim30a // tripartite motif-containing 30A // 7 E3|7 50.4 cM // 20128 ///	3.22
10363082	**Lilrb4**	NM_013532 // Lilrb4 // leukocyte immunoglobulin-like receptor, subfamily B, member 4 //	3.20
10552516	**Klk6**	NM_011177 // Klk6 // kallikrein related-peptidase 6 // 7 B4-B5|7 24.0 cM // 19144 /// N	3.20
10383192	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.19
10412543	**Gm1973**	NM_029288 // Gm1973 // predicted gene 1973 // 14 A1|14 // 100038846 /// NM_001024706 //	3.18
10383198	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.16
10449741	**Sik1**	NM_010831 // Sik1 // salt inducible kinase 1 // 17 B1|17 18.18 cM // 17691 /// ENSMUST0	3.15
10358476	**Prg4**	NM_021400 // Prg4 // proteoglycan 4 (megakaryocyte stimulating factor,	3.13

		articular superf	
10355967	**Ap1s3**	NM_183027 // Ap1s3 // adaptor-related protein complex AP-1, sigma 3 // 1 C4|1 // 252903	3.13
10404848	**Jarid2**	NM_021878 // Jarid2 // jumonji, AT rich interactive domain 2 // 13 A5|13 27.0 cM // 164	3.12
10431625	**Syt10**	NM_018803 // Syt10 // synaptotagmin X // 15|15 F1 // 54526 /// ENSMUST00000029441 // Sy	3.12
10361828	**Cited2**	NM_010828 // Cited2 // Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-t	3.11
10461614	**Ms4a6c**	NM_028595 // Ms4a6c // membrane-spanning 4-domains, subfamily A, member 6C // 19 A|19 /	3.10
10421863	**Pcdh8**	NM_021543 // Pcdh8 // protocadherin 8 // 14 D3|14 43.0 cM // 18530 /// NM_001042726 //	3.08
10383204	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.08
10597758	**Csrnp1**	NM_153287 // Csrnp1 // cysteine-serine-rich nuclear protein 1 // 9 F4|9 // 215418 /// E	3.07
10400095	**Ifrd1**	NM_013562 // Ifrd1 // interferon-related developmental regulator 1 // 12 B1|12 21.5 cM	3.06
10571312	**Dusp4**	NM_176933 // Dusp4 // dual specificity phosphatase 4 // 8 A4|8 // 319520 /// ENSMUST000	3.05
10524621	**Oasl2**	NM_011854 // Oasl2 // 2'-5' oligoadenylate synthetase-like 2 // 5 F|5 // 23962 /// ENSM	3.05
10342361	**---**	---	3.04
10434291	**B3gnt5**	NM_001159407 // B3gnt5 // UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5	3.03
10478949	**Dok5**	NM_029761 // Dok5 // docking protein 5 // 2 H3|2 99.0 cM // 76829 /// NM_001163686 // D	3.02
10356305	**Htr2b**	NM_008311 // Htr2b // 5-hydroxytryptamine (serotonin) receptor 2B // 1 C5|1 // 15559 //	3.01
10446763	**Lbh**	NM_029999 // Lbh // limb-bud and heart // 17 E2|17 // 77889 /// BC052470 // Lbh // limb	3.01
10422227	**Spry2**	NM_011897 // Spry2 // sprouty homolog 2 (Drosophila) // 14 E2.3|14 51.0 cM // 24064 ///	3.00
10477061	**Srxn1**	NM_029688 // Srxn1 // sulfiredoxin 1 homolog (S. cerevisiae) // 2|2 H1 // 76650 /// ENS	3.00
10405179	**S1pr3**	NM_010101 // S1pr3 // sphingosine-1-phosphate receptor 3 // 13|13 B1 // 13610 /// ENSMU	2.99
10536294	**Peg10**	NM_130877 // Peg10 // paternally expressed 10 // 6 A1|6 0.5 cM // 170676 /// NM_0010406	2.99

10399725	**Sox11**	NM_009234 // Sox11 // SRY-box containing gene 11 // 12 A3|12 // 20666 /// ENSMUST000000	2.99
10507833	**Nt5c1a**	NM_001085502 // Nt5c1a // 5'-nucleotidase, cytosolic IA // 4 D2.2|4 // 230718 /// BC147	2.98
10344149	**---**	---	2.96
10357579	**Mapkapk2**	NM_008551 // Mapkapk2 // MAP kinase-activated protein kinase 2 // 1 E4|1 // 17164 /// E	2.96
10444658	**Clic1**	NM_033444 // Clic1 // chloride intracellular channel 1 // 17 B1|17 19.0 cM // 114584 //	2.95
10383202	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.95
10339440	**---**	---	2.94
10585398	**Gldn**	NM_177350 // Gldn // gliomedin // 9 A5.3|9 // 235379 /// ENSMUST00000056740 // Gldn //	2.92
10493995	**S100a10**	NM_009112 // S100a10 // S100 calcium binding protein A10 (calpactin) // 3 F1-F2|3 41.7	2.91
10360406	**Ifi205**	NM_172648 // Ifi205 // interferon activated gene 205 // 1 H3|1 95.3 cM // 226695 /// EN	2.90
10355960	**Scg2**	NM_009129 // Scg2 // secretogranin II // 1 C4|1 43.6 cM // 20254 /// ENSMUST00000049972	2.90
10383152	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.90
10589087	**Prkar2a**	NM_008924 // Prkar2a // protein kinase, cAMP dependent regulatory, type II alpha // 9 F	2.89
10383168	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.87
10487613	**Pdyn**	NM_018863 // Pdyn // prodynorphin // 2 F1|2 73.3 cM // 18610 /// ENSMUST00000028883 //	2.86
10396476	**Rhoj**	NM_023275 // Rhoj // ras homolog gene family, member J // 12 C3|12 // 80837 /// ENSMUST	2.86
10547657	**C3ar1**	NM_009779 // C3ar1 // complement component 3a receptor 1 // 6|6 F1 // 12267 /// ENSMUST	2.86
10383212	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.85
10404870	**---**	---	2.84
10583992	**Igsf9b**	NM_001129787 // Igsf9b // immunoglobulin superfamily, member 9B // 9 A4|9 // 235086 ///	2.84
10363735	**Egr2**	NM_010118 // Egr2 // early growth response 2 // 10 B5|10 35.0 cM // 13654 /// ENSMUST00	2.84
10560709	**Pvr**	NM_027514 // Pvr // poliovirus receptor // 7 A3|7 4.0 cM // 52118 /// ENSMUST0000004351	2.84

10383214	**Rnf213**	AK173199 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511 /// ENSMUST	2.84
10508115	**Stk40**	NM_001145827 // Stk40 // serine/threonine kinase 40 // 4 D2.2|4 // 74178 /// NM_028800	2.84
10459747	**Mapk4**	NM_172632 // Mapk4 // mitogen-activated protein kinase 4 // 18 E2|18 // 225724 /// ENSM	2.81
10578264	**Msr1**	NM_031195 // Msr1 // macrophage scavenger receptor 1 // 8 A4|8 20.0 cM // 20288 /// NM_	2.80
10399555	**Kcnf1**	NM_201531 // Kcnf1 // potassium voltage-gated channel, subfamily F, member 1 // 12 A1.1	2.79
10559667	**Il11**	NM_008350 // Il11 // interleukin 11 // 7 A1|7 2.0 cM // 16156 /// ENSMUST00000094892 //	2.79
10417415	**Gm1973**	NM_029288 // Gm1973 // predicted gene 1973 // 14 A1|14 // 100038846 /// NM_001024706 //	2.78
10595211	**Col12a1**	NM_007730 // Col12a1 // collagen, type XII, alpha 1 // 9 E1|9 43.0 cM // 12816 /// U256	2.78
10362201	**Ctgf**	NM_010217 // Ctgf // connective tissue growth factor // 10 A3-B1|10 17.0 cM // 14219 //	2.78
10462005	**Tmem2**	NM_031997 // Tmem2 // transmembrane protein 2 // 19 B|19 // 83921 /// NM_001033759 // T	2.78
10506736	**Magoh**	NM_010760 // Magoh // mago-nashi homolog, proliferation-associated (Drosophila) // 4 C7	2.77
10440522	**Adamts1**	NM_009621 // Adamts1 // a disintegrin-like and metallopeptidase (reprolysin type) with	2.77
10417371	**Gm3696**	NM_001024712 // Gm3696 // predicted gene 3696 // 14 A1|14 // 100042149 /// NM_001177714	2.76
10403076	**---**	---	2.76
10602772	**Rps6ka3**	NM_148945 // Rps6ka3 // ribosomal protein S6 kinase polypeptide 3 // X F4|X 65.7 cM //	2.75
10399228	**---**	---	2.75
10384223	**Igfbp3**	NM_008343 // Igfbp3 // insulin-like growth factor binding protein 3 // 11 A1|11 1.35 cM	2.73
10358754	**---**	---	2.73
10434778	**Rtp4**	NM_023386 // Rtp4 // receptor transporter protein 4 // 16 B1|16 // 67775 /// ENSMUST000	2.73
10383200	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.72
10436456	**Pros1**	NM_011173 // Pros1 // protein S (alpha) // 16 C1.3|16 // 19128 /// ENSMUST00000023629 /	2.71
10496592	**Gbp2**	NM_010260 // Gbp2 // guanylate binding protein 2 // 3 H1|3 67.4 cM // 14469 ///	2.70

		ENSMUST	
10358389	**Rgs2**	NM_009061 // Rgs2 // regulator of G-protein signaling 2 // 1 F|1 78.0 cM // 19735 /// E	2.70
10379530	**Ccl12**	NM_011331 // Ccl12 // chemokine (C-C motif) ligand 12 // 11 C|11 47.0 cM // 20293 /// E	2.69
10420114	**Tgm1**	NM_001161715 // Tgm1 // transglutaminase 1, K polypeptide // 14|14 C1 // 21816 /// NM_0	2.66
10382802	**Sphk1**	NM_001172475 // Sphk1 // sphingosine kinase 1 // 11 E2|11 // 20698 /// NM_025367 // Sph	2.66
10383196	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.64
10542335	**Gprc5a**	NM_181444 // Gprc5a // G protein-coupled receptor, family C, group 5, member A // 6 G1|	2.63
10502791	**Ifi44**	NM_133871 // Ifi44 // interferon-induced protein 44 // 3 H3|3 // 99899 /// ENSMUST00000	2.63
10357875	**Btg2**	NM_007570 // Btg2 // B-cell translocation gene 2, anti-proliferative // 1 E4|1 71.0 cM	2.63
10341742	**---**	---	2.62
10498284	**Wwtr1**	NM_133784 // Wwtr1 // WW domain containing transcription regulator 1 // 3 D|3 // 97064	2.60
10548892	**Arhgdib**	NM_007486 // Arhgdib // Rho, GDP dissociation inhibitor (GDI) beta // 6 G1|6 // 11857 /	2.60
10339543	**---**	---	2.60
10383233	**Rnf213**	AK173199 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511 /// ENSMUST	2.59
10417485	**Gm1973**	NM_029288 // Gm1973 // predicted gene 1973 // 14 A1|14 // 100038846 /// NM_001024706 //	2.58
10448202	**Tpm4**	NM_001001491 // Tpm4 // tropomyosin 4 // 8 B3.3|8 // 326618 /// ENSMUST00000003575 // T	2.58
10489204	**Tgm2**	NM_009373 // Tgm2 // transglutaminase 2, C polypeptide // 2 H1|2 89.0 cM // 21817 /// E	2.57
10498187	**6030405A18Rik**	NM_177854 // 6030405A18Rik // RIKEN cDNA 6030405A18 gene // 3 C|3 // 329641 /// ENSMUST	2.56
10416503	**Snora31**	NR_028481 // Snora31 // small nucleolar RNA, H/ACA box 31 // 14|14 // 100303751	2.56
10382104	**Snord104**	NR_030703 // Snord104 // small nucleolar RNA, C/D box 104 // 11|11 // 100216537	2.56
10344981	**Pi15**	NM_053191 // Pi15 // peptidase inhibitor 15 // 1|1 A4 // 94227 /// ENSMUST00000088476 /	2.56
10460385	**Clcf1**	NM_019952 // Clcf1 // cardiotrophin-like cytokine factor 1 // 19 A|19 // 56708 /// ENSM	2.55

10428707	**Has2**	NM_008216 // Has2 // hyaluronan synthase 2 // 15 D1|15 31.2 cM // 15117 /// ENSMUST0000	2.55
10519983	**Fgl2**	NM_008013 // Fgl2 // fibrinogen-like protein 2 // 5 A3|5 7.0 cM // 14190 /// ENSMUST000	2.55
10406928	**Cd180**	NM_008533 // Cd180 // CD180 antigen // 13 D1|13 // 17079 /// ENSMUST00000022124 // Cd18	2.55
10601569	**Pcdh11x**	NM_001081385 // Pcdh11x // protocadherin 11 X-linked // X E2|X // 245578 /// ENSMUST000	2.54
10341077	**---**	---	2.54
10600169	**Bgn**	NM_007542 // Bgn // biglycan // X B|X 29.3 cM // 12111 /// ENSMUST00000033741 // Bgn //	2.54
10572897	**Hmox1**	NM_010442 // Hmox1 // heme oxygenase (decycling) 1 // 8 C1|8 35.0 cM // 15368 /// ENSMU	2.54
10420488	**D14Ertd668e**	NM_199015 // D14Ertd668e // DNA segment, Chr 14, ERATO Doi 668, expressed // 14 C3|14 2	2.54
10389143	**Slfn8**	NM_181545 // Slfn8 // schlafen 8 // 11 C|11 // 276950 /// NM_001167743 // Slfn8 // schl	2.54
10385500	**Irgm1**	NM_008326 // Irgm1 // immunity-related GTPase family M member 1 // 11 B1.2|11 // 15944	2.53
10360418	**Rgs7**	NM_011880 // Rgs7 // regulator of G protein signaling 7 // 1 H3-H4|1 99.3 cM // 24012 /	2.52
10433003	**Sp7**	NM_130458 // Sp7 // Sp7 transcription factor 7 // 15 F3|15 // 170574 /// ENSMUST0000007	2.51
10424370	**Trib1**	NM_144549 // Trib1 // tribbles homolog 1 (Drosophila) // 15 D1|15 // 211770 /// ENSMUST	2.51
10543494	**Grm8**	NM_008174 // Grm8 // glutamate receptor, metabotropic 8 // 6 A3|6 // 14823 /// ENSMUST0	2.50
10403352	**Klf6**	NM_011803 // Klf6 // Kruppel-like factor 6 // 13 A1|13 // 23849 /// ENSMUST00000000080	2.50
10538187	**Gpnmb**	NM_053110 // Gpnmb // glycoprotein (transmembrane) nmb // 6 B2.3|6 21.0 cM // 93695 ///	2.50
10534684	**Muc3**	AF027131 // Muc3 // mucin 3, intestinal // 5 G2|5 75.0 cM // 666339 /// ENSMUST00000041	2.49
10602009	**Rnf128**	NM_023270 // Rnf128 // ring finger protein 128 // X F1|X // 66889 /// ENSMUST0000011302	2.49
10339401	**---**	---	2.48
10531887	**Slc10a6**	NM_029415 // Slc10a6 // solute carrier family 10 (sodium/bile acid cotransporter family	2.48
10492682	**Fam198b**	NM_133187 // Fam198b // family with sequence similarity 198, member B // 3 E3|3 // 6865	2.48

10492428	**Tiparp**	NM_178892 // Tiparp // TCDD-inducible poly(ADP-ribose) polymerase // 3 E1|3 // 99929 //	2.47
10452980	**Eif2ak2**	NM_011163 // Eif2ak2 // eukaryotic translation initiation factor 2-alpha kinase 2 // 17	2.47
10367436	**Cd63**	NM_001042580 // Cd63 // CD63 antigen // 10 D3|10 72.0 cM // 12512 /// NM_007653 // Cd63	2.47
10355567	**Tmbim1**	NM_027154 // Tmbim1 // transmembrane BAX inhibitor motif containing 1 // 1 C3|1 // 6966	2.46
10468722	**Gfra1**	NM_010279 // Gfra1 // glial cell line derived neurotrophic factor family receptor alpha	2.46
10474793	**Pak6**	NM_001033254 // Pak6 // p21 protein (Cdc42/Rac)-activated kinase 6 // 2 E5|2 // 214230	2.46
10551966	**Hspb6**	NM_001012401 // Hspb6 // heat shock protein, alpha-crystallin-related, B6 // 7 B1|7 //	2.46
10557992	**Bag3**	NM_013863 // Bag3 // BCL2-associated athanogene 3 // 7 F3|7 // 29810 /// ENSMUST0000003	2.45
10493003	**Etv3l**	XM_621583 // Etv3l // ets variant gene 3-like // 3 F1|3 // 546801	2.44
10569102	**Irf7**	NM_016850 // Irf7 // interferon regulatory factor 7 // 7 F5|7 // 54123 /// ENSMUST00000	2.44
10387536	**Cd68**	NM_009853 // Cd68 // CD68 antigen // 11 B3|11 39.0 cM // 12514 /// ENSMUST00000108654 /	2.44
10460585	**Fosl1**	NM_010235 // Fosl1 // fos-like antigen 1 // 19 A|19 0.5 cM // 14283 /// NR_028440 // Cc	2.44
10456745	**Smad7**	NM_001042660 // Smad7 // MAD homolog 7 (Drosophila) // 18 E2|18 // 17131 /// ENSMUST000	2.44
10384458	**Plek**	NM_019549 // Plek // pleckstrin // 11 A2|11 6.5 cM // 56193 /// ENSMUST00000102881 // P	2.43
10359908	**Rgs4**	NM_009062 // Rgs4 // regulator of G-protein signaling 4 // 1 H3|1 86.5 cM // 19736 ///	2.43
10538247	**Npy**	NM_023456 // Npy // neuropeptide Y // 6 B3|6 26.0 cM // 109648 /// ENSMUST00000031843 /	2.42
10566427	**Olfr684**	NM_207249 // Olfr684 // olfactory receptor 684 // 7 E3|7 // 244187 /// ENSMUST000000608	2.42
10422728	**Dab2**	NM_023118 // Dab2 // disabled homolog 2 (Drosophila) // 15 A|15 6.7 cM // 13132 /// NM_	2.40
10457640	**S100a11**	NM_016740 // S100a11 // S100 calcium binding protein A11 (calgizzarin) // 3|3 E-F // 20	2.40
10343060	**---**	---	2.40
10437224	**Mx2**	NR_003508 // Mx2 // myxovirus (influenza virus) resistance 2 // 16 C4|16 71.2 cM // 178	2.40

10343007	**---**	---	2.40
10360415	**Grem2**	NM_011825 // Grem2 // gremlin 2 homolog, cysteine knot superfamily (Xenopus laevis) //	2.40
10564960	**Furin**	NM_011046 // Furin // furin (paired basic amino acid cleaving enzyme) // 7 D1-E2|7 39.0	2.40
10341886	**---**	---	2.39
10460010	**Galr1**	NM_008082 // Galr1 // galanin receptor 1 // 18 E3-E4|18 55.0 cM // 14427 /// ENSMUST000	2.39
10409876	**Ctla2a**	NM_007796 // Ctla2a // cytotoxic T lymphocyte-associated protein 2 alpha // 13 B2|13 36	2.39
10473022	**Plp2**	NM_019755 // Plp2 // proteolipid protein 2 // X A2-A3.1|X 1.6 cM // 18824 /// ENSMUST00	2.38
10536363	**Tac1**	NM_009311 // Tac1 // tachykinin 1 // 6 A1|6 5.0 cM // 21333 /// ENSMUST00000090679 // T	2.38
10539135	**Capg**	NM_007599 // Capg // capping protein (actin filament), gelsolin-like // 6|6 C3 // 12332	2.37
10457942	**Syt4**	NM_009308 // Syt4 // synaptotagmin IV // 18 B1|18 10.0 cM // 20983 /// ENSMUST000000251	2.37
10432675	**I730030J21Rik**	ENSMUST00000089252 // I730030J21Rik // RIKEN cDNA I730030J21 gene // '--- // 619313	2.37
10599174	**Il13ra1**	NM_133990 // Il13ra1 // interleukin 13 receptor, alpha 1 // X A3.3|X 12.5 cM // 16164 /	2.37
10341707	**---**	---	2.37
10341516	**---**	---	2.37
10349968	**Chi3l1**	NM_007695 // Chi3l1 // chitinase 3-like 1 // 1 E4|1 72.3 cM // 12654 /// ENSMUST0000015	2.36
10417769	**Gm2897**	NM_001177714 // Gm2897 // predicted gene 2897 // 14 A1|14 // 100040671 /// NM_001177715	2.36
10376326	**Irgm2**	NM_019440 // Irgm2 // immunity-related GTPase family M member 2 // 11 B1.3|11 // 54396	2.35
10409276	**---**	---	2.35
10360460	**Chml**	NM_021350 // Chml // choroideremia-like // 1 H5-H6|1 97.0 cM // 12663 /// ENSMUST000001	2.35
10344267	**---**	---	2.35
10526553	**Vgf**	NM_001039385 // Vgf // VGF nerve growth factor inducible // 5 G2|5 79.0 cM // 381677 //	2.34
10449284	**Dusp1**	NM_013642 // Dusp1 // dual specificity phosphatase 1 // 17 A2-C|17 13.0 cM // 19252 ///	2.34
10555323	**P4ha3**	NM_177161 // P4ha3 // procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydr	2.33
10491699	**Fgf2**	NM_008006 // Fgf2 // fibroblast growth factor 2 // 3 A2-B|3 19.3 cM // 14173 ///	2.33

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10572747	**Tpm4**	NM_001001491 // Tpm4 // tropomyosin 4 // 8 B3.3|8 // 326618 /// ENSMUST00000003575 // T	2.33
10557106	**Hs3st2**	NM_001081327 // Hs3st2 // heparan sulfate (glucosamine) 3-O-sulfotransferase 2 // 7 F2|	2.33
10341581	**---**	---	2.33
10517005	**Gpr3**	NM_008154 // Gpr3 // G-protein coupled receptor 3 // 4|4 D3 // 14748 /// ENSMUST0000010	2.32
10370721	**Sbno2**	NM_183426 // Sbno2 // strawberry notch homolog 2 (Drosophila) // 10 C1|10 // 216161 ///	2.32
10493990	**S100a11**	NM_016740 // S100a11 // S100 calcium binding protein A11 (calgizzarin) // 3|3 E-F // 20	2.32
10469322	**Vim**	NM_011701 // Vim // vimentin // 2 A2|2 7.0 cM // 22352 /// ENSMUST00000028062 // Vim //	2.32
10606714	**Gla**	NM_013463 // Gla // galactosidase, alpha // X E-F1|X 53.0 cM // 11605 /// U34071 // Gla	2.32
10545682	**Tet3**	NM_183138 // Tet3 // tet oncogene family member 3 // 6 C3|6 // 194388 /// ENSMUST000000	2.31
10343510	**---**	---	2.31
10338256	**---**	---	2.30
10362968	**Bves**	NM_024285 // Bves // blood vessel epicardial substance // 10 B2|10 29.0 cM // 23828 ///	2.30
10408850	**Nedd9**	NM_001111324 // Nedd9 // neural precursor cell expressed, developmentally down-regulate	2.30
10343990	**---**	---	2.30
10509514	**Sh2d5**	NM_001099631 // Sh2d5 // SH2 domain containing 5 // 4 D3|4 // 230863 /// ENSMUST0000006	2.29
10452633	**Tgif1**	NM_009372 // Tgif1 // TGFB-induced factor homeobox 1 // 17 E1.3|17 // 21815 /// NM_0011	2.29
10466886	**Glis3**	ENSMUST00000162022 // Glis3 // GLIS family zinc finger 3 // 19 C1|19 // 226075	2.29
10488382	**Cd93**	NM_010740 // Cd93 // CD93 antigen // 2 G3|2 84.0 cM // 17064 /// ENSMUST00000099269 //	2.29
10548030	**Cd9**	NM_007657 // Cd9 // CD9 antigen // 6 F3|6 58.0 cM // 12527 /// ENSMUST00000032492 // Cd	2.29
10546454	**Adamts9**	NM_175314 // Adamts9 // a disintegrin-like and metallopeptidase (reprolysin type) with	2.29
10528268	**Ptpn12**	NM_011203 // Ptpn12 // protein tyrosine phosphatase, non-receptor type 12 // 5|5 A3-B /	2.28
10569504	**Tnfrsf23**	NM_024290 // Tnfrsf23 // tumor necrosis factor receptor superfamily, member 23 // 7 F5|	2.27
10341928	**---**	---	2.27
10512067	**Ddx58**	NM_172689 // Ddx58 // DEAD (Asp-Glu-	2.27

		Ala-Asp) box polypeptide 58 // 4 A5|4 // 230073 ///	
10359181	**Tor3a**	NM_023141 // Tor3a // torsin family 3, member A // 1 H1|1 // 30935 /// ENSMUST000000796	2.27
10473281	**Itgav**	NM_008402 // Itgav // integrin alpha V // 2 D|2 46.0 cM // 16410 /// ENSMUST00000028499	2.27
10397030	**Rgs6**	NM_015812 // Rgs6 // regulator of G-protein signaling 6 // 12 D1|12 36.5 cM // 50779 //	2.27
10596148	**Trf**	NM_133977 // Trf // transferrin // 9 F1-F3|9 56.0 cM // 22041 /// ENSMUST00000035158 //	2.27
10457106	**Cbln2**	NM_172633 // Cbln2 // cerebellin 2 precursor protein // 18 E4|18 54.0 cM // 12405 /// E	2.26
10585860	**Adpgk**	NM_028121 // Adpgk // ADP-dependent glucokinase // 9 B|9 // 72141 /// ENSMUST0000002626	2.26
10343740	**---**	---	2.26
10378545	**Mir212**	NR_029794 // Mir212 // microRNA 212 // 11|11 // 387208	2.26
10338321	**---**	---	2.26
10376733	**Map2k3**	NM_008928 // Map2k3 // mitogen-activated protein kinase kinase 3 // 11 B2|11 // 26397 /	2.25
10378568	**Mir22**	NR_029739 // Mir22 // microRNA 22 // 11|11 // 387141 /// NR_030711 // 2210403K04Rik //	2.25
10385903	**Pdlim4**	NM_019417 // Pdlim4 // PDZ and LIM domain 4 // 11 B1.3|11 28.5 cM // 30794 /// ENSMUST0	2.25
10427471	**Osmr**	NM_011019 // Osmr // oncostatin M receptor // 15 A1|15 4.6 cM // 18414 /// ENSMUST00000	2.25
10544133	**Parp12**	NM_172893 // Parp12 // poly (ADP-ribose) polymerase family, member 12 // 6 B1|6 // 2437	2.24
10341371	**---**	---	2.24
10462442	**Il33**	NM_001164724 // Il33 // interleukin 33 // 19|19 C2 // 77125 /// NM_133775 // Il33 // in	2.24
10543510	**Mir592**	NR_030420 // Mir592 // microRNA 592 // 6|6 // 735266	2.23
10603809	**---**	---	2.22
10412513	**Gm1973**	NM_029288 // Gm1973 // predicted gene 1973 // 14 A1|14 // 100038846 /// BC100412 // Gm1	2.22
10351504	**---**	---	2.22
10446928	**Ltbp1**	NM_019919 // Ltbp1 // latent transforming growth factor beta binding protein 1 // 17|17	2.22
10524631	**Oasl1**	NM_145209 // Oasl1 // 2'-5' oligoadenylate synthetase-like 1 // 5 F|5 // 231655 /// ENS	2.22
10393449	**Socs3**	NM_007707 // Socs3 // suppressor of cytokine signaling 3 // 11 E2|11 // 12702 /// ENSMU	2.21

10363917	**---**	---	2.21
10405587	**Tgfbi**	NM_009369 // Tgfbi // transforming growth factor, beta induced // 13 B-C1|13 38.0 cM //	2.21
10339340	**---**	---	2.21
10514221	**Plin2**	NM_007408 // Plin2 // perilipin 2 // 4 C4|4 38.9 cM // 11520 /// ENSMUST00000000466 //	2.21
10538590	**Herc6**	NM_025992 // Herc6 // hect domain and RLD 6 // 6 C1|6 // 67138 /// ENSMUST00000031817 /	2.21
10341146	**---**	---	2.21
10586781	**Myo1e**	NM_181072 // Myo1e // myosin IE // 9 D|9 41.0 cM // 71602 /// ENSMUST00000034745 // Myo	2.20
10593449	**Layn**	NM_001033534 // Layn // layilin // 9 A5.3|9 // 244864 /// ENSMUST00000098782 // Layn //	2.20
10516932	**Sesn2**	NM_144907 // Sesn2 // sestrin 2 // 4 D2.3|4 // 230784 /// ENSMUST00000030724 // Sesn2 /	2.20
10372139	**Nts**	NM_024435 // Nts // neurotensin // 10 D1|10 // 67405 /// ENSMUST00000020040 // Nts // n	2.20
10354418	**Obfc2a**	NM_028696 // Obfc2a // oligonucleotide/oligosaccharide-binding fold containing 2A // 1|	2.19
10536499	**Cav1**	NM_007616 // Cav1 // caveolin 1, caveolae protein // 6|6 A2 // 12389 /// ENSMUST0000000	2.19
10341903	**---**	---	2.19
10523979	**Pde6b**	NM_008806 // Pde6b // phosphodiesterase 6B, cGMP, rod receptor, beta polypeptide // 5 F	2.19
10606160	**Rfwd2**	NM_011931 // Rfwd2 // ring finger and WD repeat domain 2 // 1|1 C3 // 26374 /// BC08280	2.18
10463123	**Dntt**	NM_009345 // Dntt // deoxynucleotidyltransferase, terminal // 19 C3|19 39.5 cM // 21673	2.18
10472649	**Myo3b**	NM_177376 // Myo3b // myosin IIIB // 2 C2|2 // 329421 /// ENSMUST00000060208 // Myo3b /	2.18
10439249	**Parp14**	NM_001039530 // Parp14 // poly (ADP-ribose) polymerase family, member 14 // 16 B3|16 //	2.17
10375065	**Sh3pxd2b**	NM_177364 // Sh3pxd2b // SH3 and PX domains 2B // 11 A4|11 // 268396 /// ENSMUST0000003	2.17
10542738	**Rassf8**	ENSMUST00000111704 // Rassf8 // Ras association (RalGDS/AF-6) domain family (N-terminal	2.17
10607792	**Glra2**	NM_183427 // Glra2 // glycine receptor, alpha 2 subunit // X F5|X 72.0 cM // 237213 ///	2.17
10488378	**Thbd**	NM_009378 // Thbd // thrombomodulin // 2 G3|2 84.0 cM // 21824 /// ENSMUST00000099270 /	2.17
10455961	**Iigp1**	NM_001146275 // Iigp1 // interferon inducible GTPase 1 // 18 D3|18 // 60440	2.16

		/// NM_0217	
10590918	**Amotl1**	NM_001081395 // Amotl1 // angiomotin-like 1 // 9|9 A3 // 75723 /// ENSMUST00000013220 /	2.16
10436945	**Slc5a3**	NM_017391 // Slc5a3 // solute carrier family 5 (inositol transporters), member 3 // 16	2.16
10422844	**Gdnf**	NM_010275 // Gdnf // glial cell line derived neurotrophic factor // 15 A1|15 // 14573 /	2.16
10482814	**Acvr1c**	NM_001111030 // Acvr1c // activin A receptor, type IC // 2 C1.1|2 // 269275 /// NM_0010	2.16
10342479	**---**	---	2.16
10346878	**Zdbf2**	NM_028673 // Zdbf2 // zinc finger, DBF-type containing 2 // 1 C2|1 // 73884 /// ENSMUST	2.15
10546450	**Adamts9**	NM_175314 // Adamts9 // a disintegrin-like and metallopeptidase (reprolysin type) with	2.15
10344613	**---**	---	2.15
10378068	**Xaf1**	NM_001037713 // Xaf1 // XIAP associated factor 1 // 11 B4|11 // 327959 /// ENSMUST00000	2.15
10561453	**Zfp36**	NM_011756 // Zfp36 // zinc finger protein 36 // 7 A3|7 10.2 cM // 22695 /// ENSMUST0000	2.14
10454198	**Rnf125**	NM_026301 // Rnf125 // ring finger protein 125 // 18 A2|18 // 67664 /// ENSMUST00000050	2.14
10435457	**Parp9**	NM_030253 // Parp9 // poly (ADP-ribose) polymerase family, member 9 // 16 B3|16 // 8028	2.14
10496569	**Gbp6**	NM_145545 // Gbp6 // guanylate binding protein 6 // 3 H1|3 // 229900 /// NM_001083312 /	2.14
10462507	**Papss2**	NM_011864 // Papss2 // 3'-phosphoadenosine 5'-phosphosulfate synthase 2 // 19 C1|19 32.	2.14
10479274	**Cdh4**	NM_009867 // Cdh4 // cadherin 4 // 2 H4|2 106.0 cM // 12561 /// ENSMUST00000000314 // C	2.14
10343586	**---**	---	2.14
10493820	**S100a6**	NM_011313 // S100a6 // S100 calcium binding protein A6 (calcyclin) // 3 F1-F2|3 43.6 cM	2.14
10339082	**---**	---	2.14
10569017	**Ifitm3**	NM_025378 // Ifitm3 // interferon induced transmembrane protein 3 // 7 F5|7 // 66141 //	2.13
10499189	**Fcrls**	NM_030707 // Fcrls // Fc receptor-like S, scavenger receptor // 3 F1|3 // 80891 /// ENS	2.13
10411359	**Plp2**	NM_019755 // Plp2 // proteolipid protein 2 // X A2-A3.1|X 1.6 cM // 18824 /// ENSMUST00	2.12
10581151	**Rrad**	NM_019662 // Rrad // Ras-related associated with diabetes // 8 D3|8 // 56437 /// ENSMUS	2.12

10483110	**Ifih1**	NM_027835 // Ifih1 // interferon induced with helicase C domain 1 // 2|2 C3 // 71586 //	2.12
10523647	**Aff1**	NM_001080798 // Aff1 // AF4/FMR2 family, member 1 // 5 E|5 56.0 cM // 17355 /// NM_1339	2.12
10551347	**Blvrb**	NM_144923 // Blvrb // biliverdin reductase B (flavin reductase (NADPH)) // 7 A3|7 // 23	2.12
10427035	**Nr4a1**	NM_010444 // Nr4a1 // nuclear receptor subfamily 4, group A, member 1 // 15|15 F // 153	2.12
10416099	**Adra1a**	NM_013461 // Adra1a // adrenergic receptor, alpha 1a // 14 D1|14 // 11549 /// ENSMUST00	2.11
10338231	**---**	---	2.11
10341088	**---**	---	2.11
10351509	**Fcgr4**	NM_144559 // Fcgr4 // Fc receptor, IgG, low affinity IV // 1 H3|1 92.29 cM // 246256 //	2.11
10603551	**Cybb**	NM_007807 // Cybb // cytochrome b-245, beta polypeptide // X A1.1|X // 13058 /// ENSMUS	2.11
10441233	**Mx1**	NM_010846 // Mx1 // myxovirus (influenza virus) resistance 1 // 16 C4|16 71.2 cM // 178	2.11
10340894	**---**	---	2.10
10350923	**Rfwd2**	NM_011931 // Rfwd2 // ring finger and WD repeat domain 2 // 1|1 C3 // 26374 /// BC08280	2.10
10605831	**Las1l**	NM_152822 // Las1l // LAS1-like (S. cerevisiae) // X C3|X // 76130 /// ENSMUST000000799	2.10
10369615	**Srgn**	NM_011157 // Srgn // serglycin // 10 B4|10 // 19073 /// ENSMUST00000160987 // Srgn // s	2.10
10338260	**---**	---	2.10
10560443	**Gipr**	NM_001080815 // Gipr // gastric inhibitory polypeptide receptor // 7 A3|7 // 381853 ///	2.10
10338670	**---**	---	2.09
10342109	**---**	---	2.09
10487937	**Prokr2**	NM_144944 // Prokr2 // prokineticin receptor 2 // 2 F2|2 // 246313 /// ENSMUST000000499	2.09
10383194	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.09
10379615	**Slfn5**	NM_183201 // Slfn5 // schlafen 5 // 11 C|11 // 327978 /// ENSMUST00000067443 // Slfn5 /	2.09
10339048	**---**	---	2.09
10340941	**---**	---	2.08
10536483	**Tes**	NM_207176 // Tes // testis derived transcript // 6 A2|6 1.5 cM // 21753 /// ENSMUST0000	2.08
10545672	**Mthfd2**	NM_008638 // Mthfd2 // methylenetetrahydrofolate dehydrogenase (NAD+ dependent), methen	2.07

10511694	**Osgin2**	NM_145950 // Osgin2 // oxidative stress induced growth inhibitor family member 2 // 4 A	2.07
10404783	**Edn1**	NM_010104 // Edn1 // endothelin 1 // 13 A4|13 26.0 cM // 13614 /// ENSMUST00000021796 /	2.07
10343936	**---**	---	2.07
10343823	**---**	---	2.07
10361887	**Perp**	NM_022032 // Perp // PERP, TP53 apoptosis effector // 10|10 A2 // 64058 /// ENSMUST0000	2.07
10550627	**Gpr4**	NM_175668 // Gpr4 // G protein-coupled receptor 4 // 7 A3|7 // 319197 /// ENSMUST000000	2.07
10389214	**Ccl9**	NM_011338 // Ccl9 // chemokine (C-C motif) ligand 9 // 11 C|11 47.4 cM // 20308 /// ENS	2.07
10383210	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.06
10594988	**Mapk6**	NM_015806 // Mapk6 // mitogen-activated protein kinase 6 // 9 D|9 38.0 cM // 50772 ///	2.06
10459866	**Slc14a1**	NM_001171010 // Slc14a1 // solute carrier family 14 (urea transporter), member 1 // 18	2.05
10567995	**Nupr1**	NM_019738 // Nupr1 // nuclear protein 1 // 7 F4|7 // 56312 /// ENSMUST00000032961 // Nu	2.05
10360454	**Opn3**	NM_010098 // Opn3 // opsin 3 // 1|1 H3 // 13603 /// ENSMUST00000027809 // Opn3 // opsin	2.05
10458398	**Hars**	NM_008214 // Hars // histidyl-tRNA synthetase // 18 B2|18 // 15115 /// ENSMUST000000014	2.05
10544089	**Zc3hav1**	NM_028421 // Zc3hav1 // zinc finger CCCH type, antiviral 1 // 6 B1|6 21.0 cM // 78781 /	2.05
10607089	**Acsl4**	NM_207625 // Acsl4 // acyl-CoA synthetase long-chain family member 4 // X F2|X // 50790	2.05
10338538	**---**	---	2.04
10561461	**Samd4b**	NM_175021 // Samd4b // sterile alpha motif domain containing 4B // 7 A3|7 // 233033 ///	2.04
10517336	**Clic4**	NM_013885 // Clic4 // chloride intracellular channel 4 (mitochondrial) // 4 D3|4 // 298	2.04
10556302	**Ampd3**	NM_009667 // Ampd3 // adenosine monophosphate deaminase 3 // 7 E2-E3|7 52.0 cM // 11717	2.04
10462922	**Plce1**	NM_019588 // Plce1 // phospholipase C, epsilon 1 // 19 D1|19 // 74055 /// ENSMUST000000	2.04
10578763	**Sap30**	NM_021788 // Sap30 // sin3 associated polypeptide // 8 B2|8 31.0 cM // 60406 /// ENSMUS	2.04
10343999	**---**	---	2.04
10360028	**Fcgr2b**	NM_001077189 // Fcgr2b // Fc receptor,	2.04

		IgG, low affinity IIb // 1 H3|1 92.3 cM // 14130	
10578902	**Mir710**	NR_030491 // Mir710 // microRNA 710 // 8|8 // 735270	2.04
10437575	**Tmem114**	NM_029070 // Tmem114 // transmembrane protein 114 // 16|16 A3 // 74720 /// ENSMUST00000	2.03
10378570	**---**	---	2.03
10448803	**Hn1l**	NM_198937 // Hn1l // hematological and neurological expressed 1-like // 17 A3.3|17 11.0	2.03
10444814	**H2-gs10**	NM_001143689 // H2-gs10 // MHC class I like protein GS10 // 17 B1|17 // 436493 /// NM_0	2.03
10343987	**---**	---	2.03
10477169	**Id1**	NM_010495 // Id1 // inhibitor of DNA binding 1 // 2 H1|2 84.0 cM // 15901 /// ENSMUST00	2.02
10404578	**Cdyl**	NM_009881 // Cdyl // chromodomain protein, Y chromosome-like // 13 A3.3|13 17.0 cM // 1	2.02
10338348	**---**	---	2.02
10523670	**Aff1**	NM_001080798 // Aff1 // AF4/FMR2 family, member 1 // 5 E|5 56.0 cM // 17355 /// NM_1339	2.02
10391301	**Stat3**	NM_213659 // Stat3 // signal transducer and activator of transcription 3 // 11 D|11 60.	2.01
10580282	**Junb**	NM_008416 // Junb // Jun-B oncogene // 8 C2-D1|8 38.6 cM // 16477 /// ENSMUST0000006492	2.01
10461622	**Ms4a6b**	NM_027209 // Ms4a6b // membrane-spanning 4-domains, subfamily A, member 6B // 19|19 B /	2.01
10522409	**---**	---	2.01
10550906	**Plaur**	NM_011113 // Plaur // plasminogen activator, urokinase receptor // 7 A3|7 // 18793 ///	2.01
10340381	**---**	---	2.01
10452419	**Efna5**	NM_207654 // Efna5 // ephrin A5 // 17 E1.1|17 33.5 cM // 13640 /// NM_010109 // Efna5 /	2.01
10593430	**Sik2**	NM_178710 // Sik2 // salt inducible kinase 2 // 9 A5.3|9 // 235344 /// NM_001034085 //	2.01
10455954	**Gm4951**	NM_001033767 // Gm4951 // predicted gene 4951 // 18 D3|18 // 240327 /// NM_001033767 //	2.01
10471535	**Fam129b**	NM_146119 // Fam129b // family with sequence similarity 129, member B // 2 B|2 // 22773	2.01
10586170	**---**	---	2.00
10560242	**C5ar1**	NM_001173550 // C5ar1 // complement component 5a receptor 1 // 7 A2|7 3.9 cM // 12273 /	2.00
10358434	**Pla2g4a**	NM_008869 // Pla2g4a // phospholipase A2, group IVA (cytosolic, calcium-dependent) // 1	2.00
10341486	**---**	---	2.00
10522411	**Cwh43**	NM_181323 // Cwh43 // cell wall	2.00

		biogenesis 43 C-terminal homolog (S. cerevisiae) // 5 C	
10603346	**Plp2**	NM_019755 // Plp2 // proteolipid protein 2 // X A2-A3.1|X 1.6 cM // 18824 /// ENSMUST00	2.00
10504137	**4933409K07Rik**	NR_033123 // 4933409K07Rik // RIKEN cDNA 4933409K07 gene // 4 A5|4 // 108816 /// BC0726	-2.00
10504201	**4933409K07Rik**	NR_033123 // 4933409K07Rik // RIKEN cDNA 4933409K07 gene // 4 A5|4 // 108816 /// BC0726	-2.00
10512350	**4933409K07Rik**	NR_033123 // 4933409K07Rik // RIKEN cDNA 4933409K07 gene // 4 A5|4 // 108816 /// BC0726	-2.00
10512352	**4933409K07Rik**	NR_033123 // 4933409K07Rik // RIKEN cDNA 4933409K07 gene // 4 A5|4 // 108816 /// BC0726	-2.00
10527940	**Cdk14**	NM_011074 // Cdk14 // cyclin-dependent kinase 14 // 5 A1|5 0.0 cM // 18647 /// AF033655	-2.00
10442069	**Lix1**	NM_025681 // Lix1 // limb expression 1 homolog (chicken) // 17|17 A3.1 // 66643 /// ENS	-2.01
10523483	**Prdm8**	NM_029947 // Prdm8 // PR domain containing 8 // 5 E3|5 // 77630 /// ENSMUST00000112959	-2.01
10596521	**Grm2**	NM_001160353 // Grm2 // glutamate receptor, metabotropic 2 // 9 F1|9 // 108068 /// ENSM	-2.01
10512251	**AI464131**	BC137640 // AI464131 // expressed sequence AI464131 // 4 A5|4 // 329828 /// NM_00108551	-2.01
10402560	**A130014H13Rik**	AK079474 // A130014H13Rik // RIKEN cDNA A130014H13 gene // 12 F1|12 // 319630 /// AK037	-2.01
10518927	**Kcnab2**	NM_010598 // Kcnab2 // potassium voltage-gated channel, shaker-related subfamily, beta	-2.01
10461115	**Slc22a8**	NM_031194 // Slc22a8 // solute carrier family 22 (organic anion transporter), member 8	-2.02
10371466	**Syn3**	NM_013722 // Syn3 // synapsin III // 10|10 C2 // 27204 /// NM_001164495 // Syn3 // syna	-2.02
10343015	**---**	---	-2.02
10514865	**Acot11**	NM_025590 // Acot11 // acyl-CoA thioesterase 11 // 4 C7|4 // 329910 /// ENSMUST00000102	-2.02
10475019	**Itpka**	NM_146125 // Itpka // inositol 1,4,5-trisphosphate 3-kinase A // 2 E5|2 // 228550 /// E	-2.02
10577782	**Htra4**	NM_001081187 // Htra4 // HtrA serine peptidase 4 // 8 A2|8 // 330723 /// ENSMUST0000008	-2.03
10490551	**Nkain4**	NM_021426 // Nkain4 // Na+/K+ transporting ATPase interacting 4 // 2 H4|2 // 58237 ///	-2.03
10416279	**Lgi3**	NM_145219 // Lgi3 // leucine-rich repeat LGI family, member 3 // 14 D2|14 //	-2.03

		213469 ///	
10434007	**Aifm3**	NM_175178 // Aifm3 // apoptosis-inducing factor, mitochondrion-associated 3 // 16 A3|16	-2.04
10345550	**Vwa3b**	XM_003086154 // Vwa3b // von Willebrand factor A domain containing 3B // 1 B|1 // 70853	-2.04
10351298	**Gpr161**	NM_001081126 // Gpr161 // G protein-coupled receptor 161 // 1 H2.3|1 89.7 cM // 240888	-2.04
10377490	**Alox12b**	NM_009659 // Alox12b // arachidonate 12-lipoxygenase, 12R type // 11 B3|11 37.0 cM // 1	-2.05
10528145	**Grm3**	NM_181850 // Grm3 // glutamate receptor, metabotropic 3 // 5 A1|5 // 108069 /// ENSMUST	-2.05
10607848	**Egfl6**	NM_019397 // Egfl6 // EGF-like-domain, multiple 6 // X F5|X 71.5 cM // 54156 /// BC1177	-2.05
10583535	**Icam5**	NM_008319 // Icam5 // intercellular adhesion molecule 5, telencephalin // 9 A3|9 7.0 cM	-2.05
10597960	**Slc6a20a**	NM_139142 // Slc6a20a // solute carrier family 6 (neurotransmitter transporter), member	-2.05
10578796	**Galntl6**	NM_175032 // Galntl6 // UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactos	-2.05
10462086	**---**	---	-2.05
10535331	**Mmd2**	NM_175217 // Mmd2 // monocyte to macrophage differentiation-associated 2 // 5 G2|5 // 7	-2.05
10568135	**Prrt2**	NM_001102563 // Prrt2 // proline-rich transmembrane protein 2 // 7 F3|7 // 69017 /// EN	-2.05
10540401	**Lrrn1**	NM_008516 // Lrrn1 // leucine rich repeat protein 1, neuronal // 6 E1|6 // 16979 /// EN	-2.06
10578786	**Galntl6**	NM_175032 // Galntl6 // UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactos	-2.07
10407034	**Htr1a**	NM_008308 // Htr1a // 5-hydroxytryptamine (serotonin) receptor 1A // 13 D1|13 58.0 cM /	-2.07
10354229	**2610017I09Rik**	NR_027826 // 2610017I09Rik // RIKEN cDNA 2610017I09 gene // 1 B|1 // 66297 /// BC058417	-2.07
10539894	**Mgll**	NM_001166251 // Mgll // monoglyceride lipase // 6 D1|6 // 23945 /// NM_011844 // Mgll /	-2.07
10491212	**Egfem1**	NM_029412 // Egfem1 // EGF-like and EMI domain containing 1 // 3 A3|3 // 75740 /// NM_0	-2.07
10416273	**Phyhip**	NM_145981 // Phyhip // phytanoyl-CoA hydroxylase interacting protein // 14 D2|14 // 105	-2.07
10383717	**Inpp5j**	NM_172439 // Inpp5j // inositol polyphosphate 5-phosphatase J // 11 A1|11 // 170835 ///	-2.08
10497381	**Cyp7b1**	NM_007825 // Cyp7b1 // cytochrome	-2.08

		P450, family 7, subfamily b, polypeptide 1 // 3 A1|3	
10367691	**Iyd**	NM_027391 // Iyd // iodotyrosine deiodinase // 10 A1|10 // 70337 /// ENSMUST00000019896	-2.08
10483131	**Kcnh7**	NM_133207 // Kcnh7 // potassium voltage-gated channel, subfamily H (eag-related), membe	-2.08
10437483	**Rogdi**	NM_133185 // Rogdi // rogdi homolog (Drosophila) // 16 A1|16 3.3 cM // 66049 /// BC0069	-2.09
10505163	**Zkscan16**	NM_001099323 // Zkscan16 // zinc finger with KRAB and SCAN domains 16 // 4 B3|4 // 1000	-2.09
10359113	**Fam163a**	NM_177838 // Fam163a // family with sequence similarity 163, member A // 1 G3|1 // 3292	-2.09
10371296	**Glt8d2**	NM_029102 // Glt8d2 // glycosyltransferase 8 domain containing 2 // 10 C1|10 // 74782 /	-2.10
10388254	**Aspa**	NM_023113 // Aspa // aspartoacylase // 11 B4|11 // 11484 /// ENSMUST00000021119 // Aspa	-2.11
10431935	**Amigo2**	NM_178114 // Amigo2 // adhesion molecule with Ig like domain 2 // 15 F1|15 // 105827 //	-2.12
10565156	**Homer2**	NM_011983 // Homer2 // homer homolog 2 (Drosophila) // 7 D3|7 // 26557 /// NM_001164086	-2.13
10476482	**6330527O06Rik**	NM_029530 // 6330527O06Rik // RIKEN cDNA 6330527O06 gene // 2 F3|2 // 76161 /// ENSMUST	-2.13
10349828	**Lrrn2**	NM_010732 // Lrrn2 // leucine rich repeat protein 2, neuronal // 1 E4|1 // 16980 /// EN	-2.13
10423520	**Sema5a**	NM_009154 // Sema5a // sema domain, seven thrombospondin repeats (type 1 and type 1-lik	-2.14
10374727	**Bcl11a**	NM_016707 // Bcl11a // B-cell CLL/lymphoma 11A (zinc finger protein) // 11 A3.2|11 // 1	-2.14
10425601	**Tef**	NM_153484 // Tef // thyrotroph embryonic factor // 15 E1|15 46.7 cM // 21685 /// NM_017	-2.15
10565401	**Folh1**	NM_016770 // Folh1 // folate hydrolase // 7|7 D1-D2 // 53320 /// NM_001159706 // Folh1	-2.15
10357339	**Lypd1**	NM_145100 // Lypd1 // Ly6/Plaur domain containing 1 // 1 E3|1 // 72585 /// NM_027677 //	-2.16
10589407	**Spink8**	NM_183136 // Spink8 // serine peptidase inhibitor, Kazal type 8 // 9 F2|9 // 78709 ///	-2.16
10542093	**Nrip2**	NM_021717 // Nrip2 // nuclear receptor interacting protein 2 // 6 F3|6 // 60345 /// NM_	-2.17
10416505	**Kctd4**	NM_026214 // Kctd4 // potassium channel tetramerisation domain containing 4 // 14|14 D2	-2.17

10501183	**Eps8l3**	NM_133867 // Eps8l3 // EPS8-like 3 // 3 F2.3|3 // 99662 /// ENSMUST00000037375 // Eps8l	-2.17
10360666	**6330403A02Rik**	BC120654 // 6330403A02Rik // RIKEN cDNA 6330403A02 gene // 1 H4|1 // 381310 /// NM_0010	-2.18
10342428	**---**	---	-2.18
10343583	**---**	---	-2.19
10584549	**Scn3b**	NM_178227 // Scn3b // sodium channel, voltage-gated, type III, beta // 9 A5.1|9 // 2352	-2.19
10373073	**D10Ertd610e**	NM_028027 // D10Ertd610e // DNA segment, Chr 10, ERATO Doi 610, expressed // 10 D3|10 7	-2.23
10381049	**Rapgefl1**	NM_001080925 // Rapgefl1 // Rap guanine nucleotide exchange factor (GEF)-like 1 // 11 D	-2.23
10415132	**Cmtm5**	NM_026066 // Cmtm5 // CKLF-like MARVEL transmembrane domain containing 5 // 14 C3|14 //	-2.23
10498965	**Npy2r**	NM_008731 // Npy2r // neuropeptide Y receptor Y2 // 3 E3|3 36.0 cM // 18167 /// ENSMUST	-2.24
10462039	**Trpm3**	NM_001035244 // Trpm3 // transient receptor potential cation channel, subfamily M, memb	-2.24
10438784	**Gm606**	NM_001013761 // Gm606 // predicted gene 606 // 16 B2|16 // 239789 /// BC086669 // Gm606	-2.25
10404649	**Dsp**	NM_023842 // Dsp // desmoplakin // 13 A3.3|13 // 109620	-2.26
10594747	**C2cd4b**	NM_001081314 // C2cd4b // C2 calcium-dependent domain containing 4B // 9|9 D // 75697	-2.26
10508412	**Fndc5**	NM_027402 // Fndc5 // fibronectin type III domain containing 5 // 4 D2.2|4 // 384061 //	-2.26
10542596	**Slco1c1**	NM_021471 // Slco1c1 // solute carrier organic anion transporter family, member 1c1 //	-2.26
10454856	**Psd2**	NM_028707 // Psd2 // pleckstrin and Sec7 domain containing 2 // 18 B2|18 // 74002 /// E	-2.27
10480459	**Hnmt**	NM_080462 // Hnmt // histamine N-methyltransferase // 2 A3|2 // 140483 /// ENSMUST00000	-2.27
10341621	**---**	---	-2.28
10351491	**Olfml2b**	NM_177068 // Olfml2b // olfactomedin-like 2B // 1 H3|1 // 320078 /// ENSMUST00000046792	-2.28
10504203	**4930578G10Rik**	ENSMUST00000107984 // 4930578G10Rik // RIKEN cDNA 4930578G10 gene // 4 A5|4 // 75952 //	-2.28
10340281	**---**	---	-2.28
10366391	**Kcnc2**	NM_001025581 // Kcnc2 // potassium voltage gated channel, Shaw-related subfamily, membe	-2.29
10374202	**Adcy1**	NM_009622 // Adcy1 // adenylate cyclase 1 // 11 1.25 cM|11 A2 // 432530 /// ENSMUST0000	-2.29

10394685	**Ntsr2**	NM_008747 // Ntsr2 // neurotensin receptor 2 // 12 A1.1|12 6.0 cM // 18217 /// ENSMUST0	-2.29
10495878	**Ndst4**	NM_022565 // Ndst4 // N-deacetylase/N-sulfotransferase (heparin glucosaminyl) 4 // 3 H1	-2.30
10423599	**Matn2**	NM_016762 // Matn2 // matrilin 2 // 15|15 B3.3 // 17181 /// ENSMUST00000022947 // Matn2	-2.31
10367828	**Grm1**	ENSMUST00000044306 // Grm1 // glutamate receptor, metabotropic 1 // 10|10 A2 // 14816 /	-2.31
10548899	**Rerg**	NM_181988 // Rerg // RAS-like, estrogen-regulated, growth-inhibitor // 6 G1|6 // 232441	-2.31
10439583	**Sidt1**	NM_001159419 // Sidt1 // SID1 transmembrane family, member 1 // 16 B4|16 // 320007 ///	-2.32
10357660	**Mfsd4**	NM_001114662 // Mfsd4 // major facilitator superfamily domain containing 4 // 1 E4|1 //	-2.32
10553092	**Dbp**	NM_016974 // Dbp // D site albumin promoter binding protein // 7 B4|7 23.0 cM // 13170	-2.33
10372106	**Epyc**	ENSMUST00000105285 // Epyc // epiphycan // 10 C2-C3|10 55.0 cM // 13516 /// NR_033537 /	-2.34
10499285	**Bcan**	NM_007529 // Bcan // brevican // 3 F1|3 42.7 cM // 12032 /// NM_001109758 // Bcan // br	-2.38
10544936	**Neurod6**	NM_009717 // Neurod6 // neurogenic differentiation 6 // 6 B3|6 29.0 cM // 11922 /// ENS	-2.39
10517250	**Extl1**	NM_019578 // Extl1 // exostoses (multiple)-like 1 // 4 D3|4 60.0 cM // 56219 /// ENSMUS	-2.41
10506254	**Raver2**	NM_183024 // Raver2 // ribonucleoprotein, PTB-binding 2 // 4 C6|4 // 242570 /// ENSMUST	-2.41
10534960	**Gjc3**	NM_080450 // Gjc3 // gap junction protein, gamma 3 // 5 G2|5 // 118446 /// ENSMUST00000	-2.42
10385826	**Ankrd43**	NM_183173 // Ankrd43 // ankyrin repeat domain 43 // 11 B1.3|11 // 237761 /// ENSMUST000	-2.44
10344462	**---**	---	-2.45
10373054	**Slc26a10**	NM_177615 // Slc26a10 // solute carrier family 26, member 10 // 10 D3|10 // 216441 ///	-2.45
10540599	**Cpne9**	NM_170673 // Cpne9 // copine family member IX // 6 E3|6 // 211232 /// ENSMUST0000004120	-2.46
10562204	**Fxyd7**	NM_022007 // Fxyd7 // FXYD domain-containing ion transport regulator 7 // 7 B1|7 // 577	-2.46
10406519	**Hapln1**	NM_013500 // Hapln1 // hyaluronan and proteoglycan link protein 1 // 13 C3|13 44.0 cM /	-2.48
10360664	**6330403A02Rik**	ENSMUST00000136521 //	-2.48

		6330403A02Rik // RIKEN cDNA 6330403A02 gene // 1 H4|1 // 381310 /	
10389786	**Hlf**	NM_172563 // Hlf // hepatic leukemia factor // 11 C-D|11 52.0 cM // 217082 /// ENSMUST0	-2.50
10518781	**Per3**	NM_011067 // Per3 // period homolog 3 (Drosophila) // 4 E2|4 // 18628 /// ENSMUST000001	-2.50
10384797	**Ccdc85a**	NM_181577 // Ccdc85a // coiled-coil domain containing 85A // 11 A3.3|11 // 216613 /// N	-2.53
10468113	**Kcnip2**	NM_145703 // Kcnip2 // Kv channel-interacting protein 2 // 19 D1|19 45.2 cM // 80906 //	-2.54
10343256	**---**	---	-2.56
10433887	**Pkp2**	NM_026163 // Pkp2 // plakophilin 2 // 16|16 B1 // 67451 /// ENSMUST00000039408 // Pkp2	-2.58
10481182	**Fam163b**	NM_175427 // Fam163b // family with sequence similarity 163, member B // 2 A3|2 // 1093	-2.63
10536949	**Fam40b**	NM_177204 // Fam40b // family with sequence similarity 40, member B // 6 A3.3|6 // 3206	-2.66
10563253	**Lin7b**	NM_011698 // Lin7b // lin-7 homolog B (C. elegans) // 7|7 B2 // 22342 /// NR_027802 //	-2.71
10565152	**Homer2**	NM_011983 // Homer2 // homer homolog 2 (Drosophila) // 7 D3|7 // 26557 /// NM_001164086	-2.72
10364792	**Plk5**	NM_183152 // Plk5 // polo-like kinase 5 (Drosophila) // 10 C1|10 // 216166 /// ENSMUST0	-2.72
10565218	**Il16**	NM_010551 // Il16 // interleukin 16 // 7 D2-D3|7 41.2 cM // 16170 /// BC058709 // Il16	-2.73
10422312	**Cldn10**	NM_023878 // Cldn10 // claudin 10 // 14 E4|14 60.0 cM // 58187 /// NM_001160096 // Cldn	-2.77
10407435	**Akr1c18**	NM_134066 // Akr1c18 // aldo-keto reductase family 1, member C18 // 13 A1|13 // 105349	-2.85
10417027	**Cldn10**	NM_021386 // Cldn10 // claudin 10 // 14 E4|14 60.0 cM // 58187 /// NM_023878 // Cldn10	-2.88
10435787	**---**	---	-2.90
10368175	**Pde7b**	NM_013875 // Pde7b // phosphodiesterase 7B // 10 A3|10 // 29863 /// ENSMUST00000020165	-2.91
10535732	**Gpr12**	NM_001010941 // Gpr12 // G-protein coupled receptor 12 // 5 G3|5 // 14738 /// NM_008151	-3.15
10357418	**Lct**	NM_001081078 // Lct // lactase // 1 E4|1 65.9 cM // 226413 /// ENSMUST00000073490 // Lc	-3.70

APPENDIX 2

Significantly changed transcripts at 3 days post injection, in KA- vs. saline - injected mice hippocampi Thresholds: 2-fold, FDR-adjusted p-value< 0.01.

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change 3 days
10523717	**Spp1**	NM_009263 // Spp1 // secreted phosphoprotein 1 // 5 E5|5 56.0 cM // 20750 /// ENSMUST00	12.21
10526410	**Hspb1**	NM_013560 // Hspb1 // heat shock protein 1 // 5 G2|5 76.0 cM // 15507 /// ENSMUST000000	10.82
10408928	**Hspb1**	NM_013560 // Hspb1 // heat shock protein 1 // 5 G2|5 76.0 cM // 15507 /// ENSMUST000000	10.11
10512470	**Cd72**	NM_001110320 // Cd72 // CD72 antigen // 4 B1|4 22.5 cM // 12517 /// NM_007654 // Cd72 /	9.19
10467136	**Ch25h**	NM_009890 // Ch25h // cholesterol 25-hydroxylase // 19 C1|19 // 12642 /// ENSMUST000000	7.33
10476945	**Cst7**	NM_009977 // Cst7 // cystatin F (leukocystatin) // 2|2 G1-G3 // 13011 /// ENSMUST000000	7.32
10531415	**Cxcl10**	NM_021274 // Cxcl10 // chemokine (C-X-C motif) ligand 10 // 5 E2|5 53.0 cM // 15945 ///	7.20
10360377	**AI607873**	BC150711 // AI607873 // expressed sequence AI607873 // 1 H3|1 // 226691 /// ENSMUST0000	7.18
10598976	**Timp1**	NM_001044384 // Timp1 // tissue inhibitor of metalloproteinase 1 // X A1.3|X 6.2 cM //	7.06
10403743	**Inhba**	NM_008380 // Inhba // inhibin beta-A // 13 A1|13 10.0 cM // 16323 /// ENSMUST0000004260	6.93
10464471	**Gal**	NM_010253 // Gal // galanin // 19 A|19 2.0 cM // 14419 /// ENSMUST00000025842 // Gal //	6.87
10461614	**Ms4a6c**	NM_028595 // Ms4a6c // membrane-spanning 4-domains, subfamily A, member 6C // 19 A|19 /	6.72
10552516	**Klk6**	NM_011177 // Klk6 // kallikrein related-peptidase 6 // 7 B4-B5|7 24.0 cM // 19144 /// N	6.51
10420114	**Tgm1**	NM_001161715 // Tgm1 // transglutaminase 1, K polypeptide // 14|14 C1 // 21816 /// NM_0	6.40
10360382	**Ifi204**	NM_008329 // Ifi204 // interferon activated gene 204 // 1 H3|1 95.2 cM // 15951 /// NM_	6.35
10389231	**Ccl3**	NM_011337 // Ccl3 // chemokine (C-C motif) ligand 3 // 11 C|11 47.59 cM // 20302 /// EN	6.27
10363082	**Lilrb4**	NM_013532 // Lilrb4 // leukocyte immunoglobulin-like receptor, subfamily B, member 4 //	5.89
10466210	**Ms4a6d**	NM_026835 // Ms4a6d // membrane-spanning 4-domains, subfamily A, member 6D // 19 A|19 /	5.78
10513739	**Tnc**	NM_011607 // Tnc // tenascin C // 4 C1|4 32.2 cM // 21923 /// ENSMUST00000030056 // Tnc	5.78
10379727	**Gm11428**	NM_001081957 // Gm11428 // predicted gene 11428 // 11 C|11 // 100034251 /// FJ007372 //	5.75
10458340	**Hbegf**	NM_010415 // Hbegf // heparin-binding EGF-like growth factor // 18 B2|18 15.0 cM // 152	5.53
10578264	**Msr1**	NM_031195 // Msr1 // macrophage scavenger receptor 1 // 8 A4|8 20.0 cM // 20288 /// NM_	5.48
10485405	**Cd44**	NM_009851 // Cd44 // CD44 antigen // 2 E2|2 56.0 cM // 12505 /// NM_001177785 // Cd44 /	5.40
10524621	**Oasl2**	NM_011854 // Oasl2 // 2'-5' oligoadenylate synthetase-like 2 // 5 F|5 // 23962 /// ENSM	5.39
10586744	**Anxa2**	NM_007585 // Anxa2 // annexin A2 // 9 C|9 37.0	5.32

		cM // 12306 /// ENSMUST00000034756 // An	
10382106	**Gm885**	NM_001033435 // Gm885 // predicted gene 885 // 11 E1|11 // 380732 /// ENSMUST0000010679	5.26
10462618	**Ifit3**	NM_010501 // Ifit3 // interferon-induced protein with tetratricopeptide repeats 3 // 19	5.11
10405587	**Tgfbi**	NM_009369 // Tgfbi // transforming growth factor, beta induced // 13 B-C1|13 38.0 cM //	5.09
10363070	**Gp49a**	NM_008147 // Gp49a // glycoprotein 49 A // 10 B3|10 // 14727 /// ENSMUST00000102894 //	5.01
10579347	**Ifi30**	NM_023065 // Ifi30 // interferon gamma inducible protein 30 // 8 B3.3|8 // 65972 /// EN	5.00
10547657	**C3ar1**	NM_009779 // C3ar1 // complement component 3a receptor 1 // 6|6 F1 // 12267 /// ENSMUST	4.99
10361091	**Atf3**	NM_007498 // Atf3 // activating transcription factor 3 // 1 H6|1 103.2 cM // 11910 ///	4.98
10450374	**D17H6S56E-5**	L78788 // D17H6S56E-5 // DNA segment, Chr 17, human D6S56E 5 // 17 B1|17 19.0 cM // 110	4.81
10600169	**Bgn**	NM_007542 // Bgn // biglycan // X B|X 29.3 cM // 12111 /// ENSMUST00000033741 // Bgn //	4.78
10487480	**Bub1**	NM_001113179 // Bub1 // budding uninhibited by benzimidazoles 1 homolog (S. cerevisiae)	4.76
10568714	**Mki67**	NM_001081117 // Mki67 // antigen identified by monoclonal antibody Ki 67 // 7|7 F3-F5 /	4.69
10515836	**Ccnb1**	NM_172301 // Ccnb1 // cyclin B1 // 13 D1|13 56.0 cM // 268697 /// ENSMUST00000072119 //	4.66
10603551	**Cybb**	NM_007807 // Cybb // cytochrome b-245, beta polypeptide // X A1.1|X // 13058 /// ENSMUS	4.65
10566358	**Trim30a**	NM_009099 // Trim30a // tripartite motif-containing 30A // 7 E3|7 50.4 cM // 20128 ///	4.63
10405179	**S1pr3**	NM_010101 // S1pr3 // sphingosine-1-phosphate receptor 3 // 13|13 B1 // 13610 /// ENSMU	4.63
10517165	**Cd52**	NM_013706 // Cd52 // CD52 antigen // 4 D3|4 73.5 cM // 23833 /// ENSMUST00000000696 //	4.63
10406928	**Cd180**	NM_008533 // Cd180 // CD180 antigen // 13 D1|13 // 17079 /// ENSMUST00000022124 // Cd18	4.61
10433101	**Gpr84**	NM_030720 // Gpr84 // G protein-coupled receptor 84 // 15 F3|15 // 80910 /// ENSMUST000	4.54
10527649	**6330406I15Rik**	BC116246 // 6330406I15Rik // RIKEN cDNA 6330406I15 gene // 5 G3|5 // 70717 /// NM_02751	4.53
10351873	**Pyhin1**	NM_175026 // Pyhin1 // pyrin and HIN domain family, member 1 // 1 H3|1 // 236312 /// EN	4.51
10351504	**---**	---	4.48
10351509	**Fcgr4**	NM_144559 // Fcgr4 // Fc receptor, IgG, low affinity IV // 1 H3|1 92.29 cM // 246256 //	4.43
10606016	**Il2rg**	NM_013563 // Il2rg // interleukin 2 receptor, gamma chain // X D|X 38.0 cM // 16186 ///	4.43
10593123	**Tagln**	NM_011526 // Tagln // transgelin // 9 A5.2|9 27.0 cM // 21345 /// ENSMUST00000034590 //	4.42
10511363	**Penk**	NM_001002927 // Penk // preproenkephalin // 4 A1|4 0.8 cM // 18619 /// ENSMUST000000703	4.40
10600836	**Msn**	NM_010833 // Msn // moesin // X C3|X // 17698 /// ENSMUST00000117399 // Msn // moesin /	4.38
10347277	**Igfbp2**	NM_008342 // Igfbp2 // insulin-like growth factor binding protein 2 // 1 C3|1 36.1 cM /	4.36
10497831	**Ccna2**	NM_009828 // Ccna2 // cyclin A2 // 3 B|3 19.2 cM // 12428 /// ENSMUST00000029270 // Ccn	4.36
10554789	**Ctsc**	NM_009982 // Ctsc // cathepsin C // 7|7 D3-E1.1 // 13032 /// ENSMUST00000032779 // Ctsc	4.33

10396476	**Rhoj**	NM_023275 // Rhoj // ras homolog gene family, member J // 12 C3|12 // 80837 /// ENSMUST	4.32
10499189	**Fcrls**	NM_030707 // Fcrls // Fc receptor-like S, scavenger receptor // 3 F1|3 // 80891 /// ENS	4.32
10461723	**Fam111a**	BC038020 // Fam111a // family with sequence similarity 111, member A // 19 B|19 // 1073	4.31
10537146	**Akr1b8**	NM_008012 // Akr1b8 // aldo-keto reductase family 1, member B8 // 6 B1|6 13.0 cM // 141	4.26
10390707	**Top2a**	NM_011623 // Top2a // topoisomerase (DNA) II alpha // 11 D|11 57.0 cM // 21973 /// ENSM	4.26
10498273	**Tm4sf1**	NM_008536 // Tm4sf1 // transmembrane 4 superfamily member 1 // 3 D|3 // 17112 /// ENSMU	4.26
10422728	**Dab2**	NM_023118 // Dab2 // disabled homolog 2 (Drosophila) // 15 A|15 6.7 cM // 13132 /// NM_	4.25
10493114	**Nes**	NM_016701 // Nes // nestin // 3 F1|3 42.5 cM // 18008 /// ENSMUST00000090973 // Nes //	4.22
10404063	**Hist1h2ab**	NM_175660 // Hist1h2ab // histone cluster 1, H2ab // 13 A2-A3|13 // 319172 /// BC117110	4.18
10539135	**Capg**	NM_007599 // Capg // capping protein (actin filament), gelsolin-like // 6|6 C3 // 12332	4.17
10444658	**Clic1**	NM_033444 // Clic1 // chloride intracellular channel 1 // 17 B1|17 19.0 cM // 114584 //	4.16
10411739	**Ccnb1**	NM_172301 // Ccnb1 // cyclin B1 // 13 D1|13 56.0 cM // 268697 /// ENSMUST00000072119 //	4.15
10433114	**Itga5**	NM_010577 // Itga5 // integrin alpha 5 (fibronectin receptor alpha) // 15 F3|15 57.4 cM	4.15
10547621	**Apobec1**	NM_031159 // Apobec1 // apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1 /	4.13
10474700	**Thbs1**	NM_011580 // Thbs1 // thrombospondin 1 // 2 F1-F3|2 65.0 cM // 21825 /// ENSMUST0000003	4.13
10462623	**Ifit1**	NM_008331 // Ifit1 // interferon-induced protein with tetratricopeptide repeats 1 // 19	4.12
10542355	**Emp1**	NM_010128 // Emp1 // epithelial membrane protein 1 // 6 G1|6 65.0 cM // 13730 /// ENSMU	4.11
10355403	**Fn1**	NM_010233 // Fn1 // fibronectin 1 // 1 C1-C5|1 36.1 cM // 14268 /// ENSMUST00000055226	4.09
10562637	**Ccnb1**	NM_172301 // Ccnb1 // cyclin B1 // 13 D1|13 56.0 cM // 268697 /// ENSMUST00000072119 //	4.09
10369815	**Cdk1**	NM_007659 // Cdk1 // cyclin-dependent kinase 1 // 10 B5.3|10 38.0 cM // 12534 /// ENSMU	4.08
10541307	**Usp18**	NM_011909 // Usp18 // ubiquitin specific peptidase 18 // 6 F|6 56.0 cM // 24110 /// ENS	4.05
10563441	**Emp3**	NM_010129 // Emp3 // epithelial membrane protein 3 // 7 B4|7 24.5 cM // 13732 /// NM_00	4.05
10434778	**Rtp4**	NM_023386 // Rtp4 // receptor transporter protein 4 // 16 B1|16 // 67775 /// ENSMUST000	4.05
10369615	**Srgn**	NM_011157 // Srgn // serglycin // 10 B4|10 // 19073 /// ENSMUST00000160987 // Srgn // s	4.04
10541354	**A2m**	NM_175628 // A2m // alpha-2-macroglobulin // 6 F1|6 61.7 cM // 232345 /// ENSMUST000000	4.03
10587799	**Plscr2**	NM_001195084 // Plscr2 // phospholipid scramblase 2 // 9 E3.3|9 // 18828 /// NM_008880	4.03
10427471	**Osmr**	NM_011019 // Osmr // oncostatin M receptor // 15 A1|15 4.6 cM // 18414 /// ENSMUST00000	4.02
10462796	**Kif11**	NM_010615 // Kif11 // kinesin family member 11 // 19 C2|19 // 16551 /// ENSMUST00000012	3.99
10372648	**Lyz2**	NM_017372 // Lyz2 // lysozyme 2 // 10 D2|10 66.0 cM // 17105 /// ENSMUST00000092163 //	3.99

10387536	**Cd68**	NM_009853 // Cd68 // CD68 antigen // 11 B3|11 39.0 cM // 12514 /// ENSMUST00000108654 /	3.97
10351679	**Cd84**	NM_013489 // Cd84 // CD84 antigen // 1 H3|1 93.3 cM // 12523 /// ENSMUST00000155802 //	3.94
10534667	**Serpine1**	NM_008871 // Serpine1 // serine (or cysteine) peptidase inhibitor, clade E, member 1 //	3.93
10393573	**Lgals3bp**	NM_011150 // Lgals3bp // lectin, galactoside-binding, soluble, 3 binding protein // 11|	3.93
10461622	**Ms4a6b**	NM_027209 // Ms4a6b // membrane-spanning 4-domains, subfamily A, member 6B // 19|19 B /	3.93
10607085	**Kcne1l**	NM_021487 // Kcne1l // potassium voltage-gated channel, Isk-related family, member 1-li	3.93
10517517	**C1qa**	NM_007572 // C1qa // complement component 1, q subcomponent, alpha polypeptide // 4 D3|	3.93
10530841	**Igfbp7**	NM_001159518 // Igfbp7 // insulin-like growth factor binding protein 7 // 5 C3.3|5 // 2	3.91
10569017	**Ifitm3**	NM_025378 // Ifitm3 // interferon induced transmembrane protein 3 // 7 F5|7 // 66141 //	3.89
10383198	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.87
10527332	**Nptx2**	NM_016789 // Nptx2 // neuronal pentraxin 2 // 5 G2|5 82.0 cM // 53324 /// ENSMUST000000	3.85
10536845	**Flnc**	NM_001081185 // Flnc // filamin C, gamma // 6 A3.3|6 8.5 cM // 68794 /// ENSMUST0000009	3.85
10594774	**Ccnb2**	NM_007630 // Ccnb2 // cyclin B2 // 9 D|9 // 12442 /// ENSMUST00000034742 // Ccnb2 // cy	3.84
10586448	**2810417H13Rik**	NM_026515 // 2810417H13Rik // RIKEN cDNA 2810417H13 gene // 9 C|9 // 68026 /// ENSMUST0	3.82
10446282	**Emr1**	NM_010130 // Emr1 // EGF-like module containing, mucin-like, hormone receptor-like sequ	3.81
10493990	**S100a11**	NM_016740 // S100a11 // S100 calcium binding protein A11 (calgizzarin) // 3|3 E-F // 20	3.76
10358879	**Npl**	NM_028749 // Npl // N-acetylneuraminate pyruvate lyase // 1|1 G2 // 74091 /// ENSMUST00	3.75
10466200	**Ms4a7**	NM_027836 // Ms4a7 // membrane-spanning 4-domains, subfamily A, member 7 // 19 A|19 //	3.74
10379530	**Ccl12**	NM_011331 // Ccl12 // chemokine (C-C motif) ligand 12 // 11 C|11 47.0 cM // 20293 /// E	3.72
10462621	**I830012O16Rik**	NM_001005858 // I830012O16Rik // RIKEN cDNA I830012O16 gene // 19 C1|19 // 667370 /// E	3.72
10416437	**Lcp1**	NM_008879 // Lcp1 // lymphocyte cytosolic protein 1 // 14 D3|14 42.0 cM // 18826 /// EN	3.71
10457640	**S100a11**	NM_016740 // S100a11 // S100 calcium binding protein A11 (calgizzarin) // 3|3 E-F // 20	3.70
10554249	**Acan**	NM_007424 // Acan // aggrecan // 7 D3|7 39.0 cM // 11595 /// ENSMUST00000032835 // Acan	3.70
10362201	**Ctgf**	NM_010217 // Ctgf // connective tissue growth factor // 10 A3-B1|10 17.0 cM // 14219 //	3.70
10502791	**Ifi44**	NM_133871 // Ifi44 // interferon-induced protein 44 // 3 H3|3 // 99899 /// ENSMUST00000	3.69
10443463	**Cdkn1a**	NM_007669 // Cdkn1a // cyclin-dependent kinase inhibitor 1A (P21) // 17 A3.3|17 15.23 c	3.69
10411274	**Sv2c**	NM_029210 // Sv2c // synaptic vesicle glycoprotein 2c // 13 D1|13 // 75209 /// ENSMUST0	3.68
10418506	**Stab1**	NM_138672 // Stab1 // stabilin 1 // 14 B|14 // 192187 /// ENSMUST00000036618 // Stab1 /	3.68

10493820	**S100a6**	NM_011313 // S100a6 // S100 calcium binding protein A6 (calcyclin) // 3 F1-F2|3 43.6 cM	3.66
10473384	**Slc43a3**	NM_021398 // Slc43a3 // solute carrier family 43, member 3 // 2 E1|2 // 58207 /// ENSMU	3.64
10384458	**Plek**	NM_019549 // Plek // pleckstrin // 11 A2|11 6.5 cM // 56193 /// ENSMUST00000102881 // P	3.64
10496592	**Gbp2**	NM_010260 // Gbp2 // guanylate binding protein 2 // 3 H1|3 67.4 cM // 14469 /// ENSMUST	3.63
10554445	**Prc1**	NM_145150 // Prc1 // protein regulator of cytokinesis 1 // 7 D3|7 38.0 cM // 233406 ///	3.58
10555323	**P4ha3**	NM_177161 // P4ha3 // procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydr	3.58
10601385	**Tlr13**	NM_205820 // Tlr13 // toll-like receptor 13 // X D|X // 279572 /// ENSMUST00000040065 /	3.57
10536499	**Cav1**	NM_007616 // Cav1 // caveolin 1, caveolae protein // 6|6 A2 // 12389 /// ENSMUST0000000	3.52
10384223	**Igfbp3**	NM_008343 // Igfbp3 // insulin-like growth factor binding protein 3 // 11 A1|11 1.35 cM	3.51
10461721	**Mpeg1**	NM_010821 // Mpeg1 // macrophage expressed gene 1 // 19 A|19 // 17476 /// ENSMUST000000	3.50
10569102	**Irf7**	NM_016850 // Irf7 // interferon regulatory factor 7 // 7 F5|7 // 54123 /// ENSMUST00000	3.49
10502655	**Cyr61**	NM_010516 // Cyr61 // cysteine rich protein 61 // 3 H2|3 72.9 cM // 16007 /// ENSMUST00	3.49
10523451	**Anxa3**	NM_013470 // Anxa3 // annexin A3 // 5 E3|5 54.0 cM // 11745 /// ENSMUST00000031447 // A	3.49
10456400	**Tubb6**	NM_026473 // Tubb6 // tubulin, beta 6 // 18|18 E1 // 67951 /// ENSMUST00000001513 // Tu	3.48
10394978	**Rrm2**	NM_009104 // Rrm2 // ribonucleotide reductase M2 // 12 A1.3|12 7.0 cM // 20135 /// ENSM	3.47
10360070	**Fcer1g**	NM_010185 // Fcer1g // Fc receptor, IgE, high affinity I, gamma polypeptide // 1 H3|1 9	3.44
10473022	**Plp2**	NM_019755 // Plp2 // proteolipid protein 2 // X A2-A3.1|X 1.6 cM // 18824 /// ENSMUST00	3.44
10385500	**Irgm1**	NM_008326 // Irgm1 // immunity-related GTPase family M member 1 // 11 B1.2|11 // 15944	3.43
10383202	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.43
10349968	**Chi3l1**	NM_007695 // Chi3l1 // chitinase 3-like 1 // 1 E4|1 72.3 cM // 12654 /// ENSMUST0000015	3.42
10425161	**Lgals1**	NM_008495 // Lgals1 // lectin, galactose binding, soluble 1 // 15 E|15 44.9 cM // 16852	3.42
10566366	**Trim30d**	NM_199146 // Trim30d // tripartite motif-containing 30D // 7 E3|7 // 209387 /// NM_0011	3.42
10585398	**Gldn**	NM_177350 // Gldn // gliomedin // 9 A5.3|9 // 235379 /// ENSMUST00000056740 // Gldn //	3.40
10383206	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.38
10497520	**Ect2**	NM_007900 // Ect2 // ect2 oncogene // 3|3 B // 13605 /// NM_001177625 // Ect2 // ect2 o	3.37
10360028	**Fcgr2b**	NM_001077189 // Fcgr2b // Fc receptor, IgG, low affinity IIb // 1 H3|1 92.3 cM // 14130	3.37
10448307	**Tnfrsf12a**	NM_013749 // Tnfrsf12a // tumor necrosis factor receptor superfamily, member 12a // 17	3.36
10587733	**Ctsh**	NM_007801 // Ctsh // cathepsin H // 9 E3.1|9 50.0 cM // 13036 /// ENSMUST00000034915 //	3.35
10388440	**Serpinf2**	NM_008878 // Serpinf2 // serine (or cysteine) peptidase inhibitor, clade F, member 2 //	3.35
10367436	**Cd63**	NM_001042580 // Cd63 // CD63 antigen // 10	3.34

		D3|10 72.0 cM // 12512 /// NM_007653 // Cd63	
10474875	**Casc5**	NM_029617 // Casc5 // cancer susceptibility candidate 5 // 2 E5|2 // 76464 /// ENSMUST0	3.34
10599174	**Il13ra1**	NM_133990 // Il13ra1 // interleukin 13 receptor, alpha 1 // X A3.3|X 12.5 cM // 16164 /	3.31
10344897	**Sulf1**	NM_001198565 // Sulf1 // sulfatase 1 // 1 A3|1 // 240725 /// NM_172294 // Sulf1 // sulf	3.31
10346564	**Casp8**	NM_009812 // Casp8 // caspase 8 // 1 B|1 30.1 cM // 12370 /// NM_001080126 // Casp8 //	3.30
10600994	**Arr3**	NM_133205 // Arr3 // arrestin 3, retinal // X|X C2 // 170735 /// ENSMUST00000113769 //	3.29
10490159	**Pmepa1**	NM_022995 // Pmepa1 // prostate transmembrane protein, androgen induced 1 // 2 H3|2 //	3.27
10527441	**Arpc1b**	NM_023142 // Arpc1b // actin related protein 2/3 complex, subunit 1B // 5 G2|5 // 11867	3.27
10490212	**Ctsz**	NM_022325 // Ctsz // cathepsin Z // 2 H4|2 103.5 cM // 64138 /// ENSMUST00000016400 //	3.26
10492964	**Cd5l**	NM_009690 // Cd5l // CD5 antigen-like // 3 F1|3 // 11801 /// ENSMUST00000015998 // Cd5l	3.26
10432511	**Racgap1**	NM_012025 // Racgap1 // Rac GTPase-activating protein 1 // 15 F1|15 // 26934 /// ENSMUS	3.26
10351825	**Tagln2**	NM_178598 // Tagln2 // transgelin 2 // 1 H3|1 94.2 cM // 21346 /// ENSMUST00000111230 /	3.25
10461636	**---**	---	3.24
10607870	**Tlr7**	NM_133211 // Tlr7 // toll-like receptor 7 // X F5|X // 170743 /// ENSMUST00000112164 //	3.24
10383208	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.23
10579636	**Cyp4f18**	NM_024444 // Cyp4f18 // cytochrome P450, family 4, subfamily f, polypeptide 18 // 8|8 C	3.23
10436456	**Pros1**	NM_011173 // Pros1 // protein S (alpha) // 16 C1.3|16 // 19128 /// ENSMUST00000023629 /	3.23
10383168	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.22
10383200	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.22
10452980	**Eif2ak2**	NM_011163 // Eif2ak2 // eukaryotic translation initiation factor 2-alpha kinase 2 // 17	3.21
10388902	**Lgals9**	NM_010708 // Lgals9 // lectin, galactose binding, soluble 9 // 11 B5|11 // 16859 /// NM	3.21
10383214	**Rnf213**	AK173199 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511 /// ENSMUST	3.20
10500610	**Fam46c**	NM_001142952 // Fam46c // family with sequence similarity 46, member C // 3 F2.2|3 // 7	3.19
10500808	**Olfml3**	NM_133859 // Olfml3 // olfactomedin-like 3 // 3 F2.2|3 // 99543 /// ENSMUST00000029440	3.19
10551966	**Hspb6**	NM_001012401 // Hspb6 // heat shock protein, alpha-crystallin-related, B6 // 7 B1|7 //	3.19
10477187	**Tpx2**	NM_001141977 // Tpx2 // TPX2, microtubule-associated protein homolog (Xenopus laevis) /	3.17
10385118	**Dock2**	NM_033374 // Dock2 // dedicator of cyto-kinesis 2 // 11|11 A5 // 94176 /// ENSMUST00000	3.17
10370721	**Sbno2**	NM_183426 // Sbno2 // strawberry notch homolog 2 (Drosophila) // 10 C1|10 // 216161 ///	3.17
10548892	**Arhgdib**	NM_007486 // Arhgdib // Rho, GDP dissociation inhibitor (GDI) beta // 6 G1|6 // 11857 /	3.17
10500335	**Fcgr1**	NM_010186 // Fcgr1 // Fc receptor, IgG, high affinity I // 3 F2.1|3 45.2 cM // 14129 //	3.16
10517513	**C1qc**	NM_007574 // C1qc // complement component 1,	3.16

		q subcomponent, C chain // 4 D3|4 66.1 cM	
10562192	**Fxyd5**	NM_008761 // Fxyd5 // FXYD domain-containing ion transport regulator 5 // 7 B1|7 // 183	3.15
10514221	**Plin2**	NM_007408 // Plin2 // perilipin 2 // 4 C4|4 38.9 cM // 11520 /// ENSMUST00000000466 //	3.14
10383192	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.13
10364262	**Itgb2**	NM_008404 // Itgb2 // integrin beta 2 // 10 C1|10 41.5 cM // 16414 /// M31039 // Itgb2	3.13
10560242	**C5ar1**	NM_001173550 // C5ar1 // complement component 5a receptor 1 // 7 A2|7 3.9 cM // 12273 /	3.13
10400589	**C79407**	NM_172578 // C79407 // expressed sequence C79407 // 12 C1|12 // 217653 /// BC052175 //	3.11
10604763	**Arpc1b**	NM_023142 // Arpc1b // actin related protein 2/3 complex, subunit 1B // 5 G2|5 // 11867	3.11
10371332	**Aldh1l2**	NM_153543 // Aldh1l2 // aldehyde dehydrogenase 1 family, member L2 // 10 C1|10 // 21618	3.10
10450154	**H2-Aa**	NM_010378 // H2-Aa // histocompatibility 2, class II antigen A, alpha // 17 B1|17 18.65	3.08
10435948	**Ccdc80**	NM_026439 // Ccdc80 // coiled-coil domain containing 80 // 16|16 B5 // 67896 /// ENSMUS	3.07
10482059	**Ggta1**	NM_010283 // Ggta1 // glycoprotein galactosyltransferase alpha 1, 3 // 2 B|2 25.0 cM //	3.06
10501063	**Cd53**	NM_007651 // Cd53 // CD53 antigen // 3 F2.3|3 50.5 cM // 12508 /// ENSMUST00000038845 /	3.06
10383212	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	3.05
10498992	**Tlr2**	NM_011905 // Tlr2 // toll-like receptor 2 // 3 E3|3 // 24088 /// ENSMUST00000029623 //	3.04
10452815	**Xdh**	NM_011723 // Xdh // xanthine dehydrogenase // 17 E2|17 45.3 cM // 22436 /// ENSMUST0000	3.04
10473281	**Itgav**	NM_008402 // Itgav // integrin alpha V // 2 D|2 46.0 cM // 16410 /// ENSMUST00000028499	3.04
10448202	**Tpm4**	NM_001001491 // Tpm4 // tropomyosin 4 // 8 B3.3|8 // 326618 /// ENSMUST00000003575 // T	3.04
10516064	**Mfsd2a**	NM_029662 // Mfsd2a // major facilitator superfamily domain containing 2A // 4|4 D1 //	3.03
10534102	**Gusb**	NM_010368 // Gusb // glucuronidase, beta // 5 G1.3|5 72.0 cM // 110006 /// ENSMUST00000	3.03
10491699	**Fgf2**	NM_008006 // Fgf2 // fibroblast growth factor 2 // 3 A2-B|3 19.3 cM // 14173 /// ENSMUS	3.03
10548030	**Cd9**	NM_007657 // Cd9 // CD9 antigen // 6 F3|6 58.0 cM // 12527 /// ENSMUST00000032492 // Cd	3.03
10450075	**H2-K1**	NM_001001892 // H2-K1 // histocompatibility 2, K1, K region // 17 B1|17 18.44 cM // 149	3.02
10603346	**Plp2**	NM_019755 // Plp2 // proteolipid protein 2 // X A2-A3.1|X 1.6 cM // 18824 /// ENSMUST00	3.02
10520946	**Plb1**	NM_001081407 // Plb1 // phospholipase B1 // 5 B1|5 // 665270 /// ENSMUST00000101376 //	3.02
10411359	**Plp2**	NM_019755 // Plp2 // proteolipid protein 2 // X A2-A3.1|X 1.6 cM // 18824 /// ENSMUST00	3.01
10500204	**Ecm1**	NM_007899 // Ecm1 // extracellular matrix protein 1 // 3 F2.1|3 45.4 cM // 13601 /// EN	3.00
10500666	**Ptgfrn**	NM_011197 // Ptgfrn // prostaglandin F2 receptor negative regulator // 3|3 F3 // 19221	3.00
10450519	**Tcf19**	NM_001163763 // Tcf19 // transcription factor 19	3.00

		// 17 B1|17 // 106795 /// NM_025674 //	
10341334	**---**	---	2.99
10567995	**Nupr1**	NM_019738 // Nupr1 // nuclear protein 1 // 7 F4|7 // 56312 /// ENSMUST00000032961 // Nu	2.98
10384985	**Rhbdf1**	NM_010117 // Rhbdf1 // rhomboid family 1 (Drosophila) // 11 A4|11 16.0 cM // 13650 ///	2.98
10440522	**Adamts1**	NM_009621 // Adamts1 // a disintegrin-like and metallopeptidase (reprolysin type) with	2.98
10383204	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.97
10425808	**Tspo**	NM_009775 // Tspo // translocator protein // 15 E1|15 43.3 cM // 12257 /// ENSMUST00000	2.97
10448803	**Hn1l**	NM_198937 // Hn1l // hematological and neurological expressed 1-like // 17 A3.3|17 11.0	2.97
10487340	**Ncaph**	NM_144818 // Ncaph // non-SMC condensin I complex, subunit H // 2 F1|2 // 215387 /// EN	2.96
10456005	**Cd74**	NM_001042605 // Cd74 // CD74 antigen (invariant polypeptide of major histocompatibility	2.96
10383152	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.96
10400304	**Egln3**	NM_028133 // Egln3 // EGL nine homolog 3 (C. elegans) // 12 C1|12 // 112407 /// ENSMUST	2.95
10446253	**Vav1**	NM_011691 // Vav1 // vav 1 oncogene // 17 D|17 32.7 cM // 22324 /// NM_001163816 // Vav	2.95
10375608	**Scgb3a1**	NM_170727 // Scgb3a1 // secretoglobin, family 3A, member 1 // 11 B1.2|11 25.0 cM // 686	2.94
10556302	**Ampd3**	NM_009667 // Ampd3 // adenosine monophosphate deaminase 3 // 7 E2-E3|7 52.0 cM // 11717	2.93
10412207	**Gpx8**	NM_027127 // Gpx8 // glutathione peroxidase 8 (putative) // 13 D2.2|13 // 69590 /// ENS	2.93
10349661	**5430435G22Rik**	NM_145509 // 5430435G22Rik // RIKEN cDNA 5430435G22 gene // 1 E4|1 // 226421 /// ENSMUS	2.92
10474984	**Nusap1**	NM_133851 // Nusap1 // nucleolar and spindle associated protein 1 // 2 E5|2 // 108907 /	2.92
10521731	**Ncapg**	NM_019438 // Ncapg // non-SMC condensin I complex, subunit G // 5 B3|5 // 54392 /// ENS	2.91
10358434	**Pla2g4a**	NM_008869 // Pla2g4a // phospholipase A2, group IVA (cytosolic, calcium-dependent) // 1	2.91
10582295	**Odc1**	NM_013614 // Odc1 // ornithine decarboxylase, structural 1 // 12 A1.1|12 6.0 cM // 1826	2.90
10517508	**C1qb**	NM_009777 // C1qb // complement component 1, q subcomponent, beta polypeptide // 4 D3|4	2.90
10586781	**Myo1e**	NM_181072 // Myo1e // myosin IE // 9 D|9 41.0 cM // 71602 /// ENSMUST00000034745 // Myo	2.89
10375145	**Lcp2**	NM_010696 // Lcp2 // lymphocyte cytosolic protein 2 // 11 A4|11 // 16822 /// ENSMUST000	2.88
10544273	**Clec5a**	NM_001038604 // Clec5a // C-type lectin domain family 5, member a // 6|6 B2 // 23845 //	2.87
10503098	**Lyn**	NM_001111096 // Lyn // Yamaguchi sarcoma viral (v-yes-1) oncogene homolog // 4 A1|4 0.0	2.87
10504450	**Glipr2**	NM_027450 // Glipr2 // GLI pathogenesis-related 2 // 4 B1|4 // 384009 /// ENSMUST000000	2.87
10422760	**Fyb**	NM_011815 // Fyb // FYN binding protein // 15 A1|15 // 23880 /// ENSMUST00000090461 //	2.87
10436945	**Slc5a3**	NM_017391 // Slc5a3 // solute carrier family 5 (inositol transporters), member 3 // 16	2.87
10394770	**Odc1**	NM_013614 // Odc1 // ornithine decarboxylase, structural 1 // 12 A1.1|12 6.0 cM // 1826	2.87

10495054	**Rhoc**	NM_007484 // Rhoc // ras homolog gene family, member C // 3 F2.2|3 // 11853 /// ENSMUST	2.86
10436941	**Mrps6**	NM_080456 // Mrps6 // mitochondrial ribosomal protein S6 // 16 C4|16 // 121022 /// NM_0	2.86
10595211	**Col12a1**	NM_007730 // Col12a1 // collagen, type XII, alpha 1 // 9 E1|9 43.0 cM // 12816 /// U256	2.86
10423498	**Dap**	NM_146057 // Dap // death-associated protein // 15 B2|15 // 223453 /// ENSMUST000000445	2.85
10587683	**Bcl2a1a**	NM_009742 // Bcl2a1a // B-cell leukemia/lymphoma 2 related protein A1a // 9 E3.1|9 50.0	2.85
10527638	**Alox5ap**	NM_009663 // Alox5ap // arachidonate 5-lipoxygenase activating protein // 5 G3|5 // 116	2.84
10558948	**Cd151**	NM_009842 // Cd151 // CD151 antigen // 7 F5|7 23.5 cM // 12476 /// NM_001111050 // Cd15	2.84
10542993	**Pon3**	NM_173006 // Pon3 // paraoxonase 3 // 6 A1|6 0.5 cM // 269823 /// ENSMUST00000031773 //	2.84
10546510	**Lrig1**	NM_008377 // Lrig1 // leucine-rich repeats and immunoglobulin-like domains 1 // 6 D2|6	2.84
10557862	**Itgam**	NM_001082960 // Itgam // integrin alpha M // 7|7 F4 // 16409 /// NM_008401 // Itgam //	2.83
10461594	**Ms4a4c**	NM_029499 // Ms4a4c // membrane-spanning 4-domains, subfamily A, member 4C // 19 A|19 /	2.83
10567580	**Igsf6**	NM_030691 // Igsf6 // immunoglobulin superfamily, member 6 // 7|7 F2-F3 // 80719 /// EN	2.83
10452316	**C3**	NM_009778 // C3 // complement component 3 // 17 E1-E3|17 34.3 cM // 12266 /// ENSMUST00	2.83
10534927	**Pilra**	NM_153510 // Pilra // paired immunoglobin-like type 2 receptor alpha // 5 G2|5 // 23180	2.82
10555389	**Ucp2**	NM_011671 // Ucp2 // uncoupling protein 2 (mitochondrial, proton carrier) // 7 E3|7 50.	2.82
10462922	**Plce1**	NM_019588 // Plce1 // phospholipase C, epsilon 1 // 19 D1|19 // 74055 /// ENSMUST000000	2.82
10514275	**Ptplad2**	NM_025760 // Ptplad2 // protein tyrosine phosphatase-like A domain containing 2 // 4 C4	2.81
10388430	**Serpinf1**	NM_011340 // Serpinf1 // serine (or cysteine) peptidase inhibitor, clade F, member 1 //	2.81
10444291	**H2-Ab1**	NM_207105 // H2-Ab1 // histocompatibility 2, class II antigen A, beta 1 // 17 B1|17 18.	2.81
10367822	**Rab32**	NM_026405 // Rab32 // RAB32, member RAS oncogene family // 10 A1|10 // 67844 /// ENSMUS	2.81
10385248	**Hmmr**	NM_013552 // Hmmr // hyaluronan mediated motility receptor (RHAMM) // 11 A5|11 19.0 cM	2.80
10387890	**Cxcl16**	NM_023158 // Cxcl16 // chemokine (C-X-C motif) ligand 16 // 11|11 B4 // 66102 /// ENSMU	2.79
10541895	**Tnfrsf1a**	NM_011609 // Tnfrsf1a // tumor necrosis factor receptor superfamily, member 1a // 6 F3|	2.79
10551883	**Tyrobp**	NM_011662 // Tyrobp // TYRO protein tyrosine kinase binding protein // 7 B|7 10.0 cM //	2.79
10512067	**Ddx58**	NM_172689 // Ddx58 // DEAD (Asp-Glu-Ala-Asp) box polypeptide 58 // 4 A5|4 // 230073 ///	2.79
10499639	**Cks1b**	NM_016904 // Cks1b // CDC28 protein kinase 1b // 3 F1|3 // 54124 /// ENSMUST00000029679	2.78
10360406	**Ifi205**	NM_172648 // Ifi205 // interferon activated gene 205 // 1 H3|1 95.3 cM // 226695 /// EN	2.78
10460385	**Clcf1**	NM_019952 // Clcf1 // cardiotrophin-like cytokine factor 1 // 19 A|19 // 56708 /// ENSM	2.77
10461558	**Slc15a3**	NM_023044 // Slc15a3 // solute carrier family 15,	2.77

		member 3 // 19|19 B // 65221 /// ENSM	
10379511	**Ccl2**	NM_011333 // Ccl2 // chemokine (C-C motif) ligand 2 // 11 C-E1|11 46.5 cM // 20296 ///	2.77
10383233	**Rnf213**	AK173199 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511 /// ENSMUST	2.76
10552311	**---**	---	2.76
10372410	**Glipr1**	NM_028608 // Glipr1 // GLI pathogenesis-related 1 (glioma) // 10|10 D1 // 73690 /// NM_	2.76
10444780	**H2-D1**	NM_010380 // H2-D1 // histocompatibility 2, D region locus 1 // 17 B1|17 19.09 cM // 14	2.76
10383196	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.76
10411595	**Naip2**	NM_010872 // Naip2 // NLR family, apoptosis inhibitory protein 2 // 13 D1|13 54.0 cM //	2.75
10459071	**2010002N04Rik**	NM_134133 // 2010002N04Rik // RIKEN cDNA 2010002N04 gene // 18 D3|18 // 106878 /// ENSM	2.74
10441003	**Runx1**	NM_001111023 // Runx1 // runt related transcription factor 1 // 16 C4|16 62.2 cM // 123	2.74
10376201	**Gpx3**	NM_001083929 // Gpx3 // glutathione peroxidase 3 // 11|11 B3-B5 // 14778 /// NM_008161	2.74
10537410	**Tbxas1**	NM_011539 // Tbxas1 // thromboxane A synthase 1, platelet // 6 F1-pter|6 20.5 cM // 213	2.74
10351658	**Cd48**	NM_007649 // Cd48 // CD48 antigen // 1 H3|1 93.3 cM // 12506 /// ENSMUST00000068584 //	2.74
10393449	**Socs3**	NM_007707 // Socs3 // suppressor of cytokine signaling 3 // 11 E2|11 // 12702 /// ENSMU	2.73
10455970	**BC023105**	BC023105 // BC023105 // cDNA sequence BC023105 // 18 D3|18 // 667597	2.72
10461587	**Ms4a4a**	XM_986941 // Ms4a4a // membrane-spanning 4-domains, subfamily A, member 4A // 19 A|19 /	2.72
10386076	**Glra1**	NM_020492 // Glra1 // glycine receptor, alpha 1 subunit // 11 B1.3|11 30.0 cM // 14654	2.71
10582303	**Cyba**	NM_007806 // Cyba // cytochrome b-245, alpha polypeptide // 8 E1|8 // 13057 /// ENSMUST	2.71
10511180	**Mxra8**	NM_024263 // Mxra8 // matrix-remodelling associated 8 // 4 E2|4 83.0 cM // 74761 /// EN	2.71
10382341	**Sstr2**	NM_009217 // Sstr2 // somatostatin receptor 2 // 11 E2|11 69.0 cM // 20606 /// NM_00104	2.70
10338876	**---**	---	2.70
10593449	**Layn**	NM_001033534 // Layn // layilin // 9 A5.3|9 // 244864 /// ENSMUST00000098782 // Layn //	2.70
10538590	**Herc6**	NM_025992 // Herc6 // hect domain and RLD 6 // 6 C1|6 // 67138 /// ENSMUST00000031817 /	2.69
10404606	**Ly86**	NM_010745 // Ly86 // lymphocyte antigen 86 // 13 A3.3|13 // 17084 /// ENSMUST0000002186	2.68
10467578	**Pik3ap1**	NM_031376 // Pik3ap1 // phosphoinositide-3-kinase adaptor protein 1 // 19|19 D1 // 8349	2.67
10347948	**Sp100**	NM_013673 // Sp100 // nuclear antigen Sp100 // 1 C5|1 50.0 cM // 20684 /// ENSMUST00000	2.67
10425321	**Apobec3**	NM_001160415 // Apobec3 // apolipoprotein B mRNA editing enzyme, catalytic polypeptide	2.67
10397645	**Gpr65**	NM_008152 // Gpr65 // G-protein coupled receptor 65 // 12 E|12 // 14744 /// ENSMUST0000	2.67
10480432	**Mastl**	NM_025979 // Mastl // microtubule associated serine/threonine kinase-like // 2 A3|2 //	2.65
10358224	**Ptprc**	NM_001111316 // Ptprc // protein tyrosine phosphatase, receptor type, C // 1 E4|1 74.0	2.65
10435305	**Itgb5**	NM_001145884 // Itgb5 // integrin beta 5 // 16 B3|16 // 16419 /// NM_010580 // Itgb5 //	2.65

10474381	**Kif18a**	NM_139303 // Kif18a // kinesin family member 18A // 2 E3|2 // 228421 /// ENSMUST0000002	2.65
10466521	**Gcnt1**	NM_173442 // Gcnt1 // glucosaminyl (N-acetyl) transferase 1, core 2 // 19 B|19 17.0 cM	2.65
10398907	**Pld4**	NM_178911 // Pld4 // phospholipase D family, member 4 // 12 F1|12 // 104759 /// ENSMUST	2.65
10566583	**Gm8995**	AK172683 // Gm8995 // predicted gene 8995 // 7 E3|7 // 668139 /// XR_035350 // Gm8995 /	2.65
10542911	**Samd9l**	NM_010156 // Samd9l // sterile alpha motif domain containing 9-like // 6 2.9 cM|6 A1-A2	2.64
10342234	**---**	---	2.64
10339785	**---**	---	2.63
10492448	**Ptx3**	NM_008987 // Ptx3 // pentraxin related gene // 3 E1|3 33.8 cM // 19288 /// ENSMUST00000	2.63
10587690	**Bcl2a1b**	NM_007534 // Bcl2a1b // B-cell leukemia/lymphoma 2 related protein A1b // 9 E3.1|9 // 1	2.62
10486396	**Ehd4**	NM_133838 // Ehd4 // EH-domain containing 4 // 2 E5|2 // 98878 /// ENSMUST00000028755 /	2.62
10434291	**B3gnt5**	NM_001159407 // B3gnt5 // UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5	2.62
10578880	**Tll1**	NM_009390 // Tll1 // tolloid-like // 8 B3.1|8 32.4 cM // 21892 /// ENSMUST00000066166 /	2.60
10515431	**Kif2c**	NM_134471 // Kif2c // kinesin family member 2C // 4 D1|4 1.5 cM // 73804 /// ENSMUST000	2.60
10409876	**Ctla2a**	NM_007796 // Ctla2a // cytotoxic T lymphocyte-associated protein 2 alpha // 13 B2|13 36	2.60
10438445	**Klhl6**	NM_183390 // Klhl6 // kelch-like 6 (Drosophila) // 16 A3|16 // 239743 /// ENSMUST000000	2.59
10596492	**Parp3**	NM_145619 // Parp3 // poly (ADP-ribose) polymerase family, member 3 // 9 F1|9 // 235587	2.59
10459866	**Slc14a1**	NM_001171010 // Slc14a1 // solute carrier family 14 (urea transporter), member 1 // 18	2.59
10454709	**Kif20a**	NM_001166406 // Kif20a // kinesin family member 20A // 18 B1|18 17.0 cM // 19348 /// NM	2.59
10587554	**Tpbg**	NM_011627 // Tpbg // trophoblast glycoprotein // 9 E3.1|9 // 21983 /// NM_001164792 //	2.58
10572747	**Tpm4**	NM_001001491 // Tpm4 // tropomyosin 4 // 8 B3.3|8 // 326618 /// ENSMUST00000003575 // T	2.58
10444814	**H2-gs10**	NM_001143689 // H2-gs10 // MHC class I like protein GS10 // 17 B1|17 // 436493 /// NM_0	2.58
10597648	**Myd88**	NM_010851 // Myd88 // myeloid differentiation primary response gene 88 // 9 F3|9 70.0 c	2.58
10534303	**Lat2**	NM_020044 // Lat2 // linker for activation of T cells family, member 2 // 5 G2|5 // 567	2.57
10381588	**Grn**	NM_008175 // Grn // granulin // 11 D|11 60.0 cM // 14824 /// ENSMUST00000049460 // Grn	2.57
10577508	**Ckap2**	NM_001004140 // Ckap2 // cytoskeleton associated protein 2 // 8 A2|8 // 80986 /// ENSMU	2.57
10505489	**Pappa**	NM_021362 // Pappa // pregnancy-associated plasma protein A // 4 C1|4 32.2 cM // 18491	2.57
10361110	**Dtl**	NM_029766 // Dtl // denticleless homolog (Drosophila) // 1 H6|1 // 76843 /// ENSMUST000	2.57
10458314	**Tmem173**	NM_028261 // Tmem173 // transmembrane protein 173 // 18 B3|18 // 72512 /// ENSMUST00000	2.57
10557156	**Plk1**	NM_011121 // Plk1 // polo-like kinase 1 (Drosophila) // 7 F3|7 59.0 cM // 18817 /// ENS	2.57

10595633	**Bcl2a1d**	NM_007536 // Bcl2a1d // B-cell leukemia/lymphoma 2 related protein A1d // 9 E3.1|9 // 1	2.57
10538187	**Gpnmb**	NM_053110 // Gpnmb // glycoprotein (transmembrane) nmb // 6 B2.3|6 21.0 cM // 93695 ///	2.56
10483401	**Spc25**	NM_025565 // Spc25 // SPC25, NDC80 kinetochore complex component, homolog (S. cerevisia	2.56
10375614	**Gfpt2**	NM_013529 // Gfpt2 // glutamine fructose-6-phosphate transaminase 2 // 11 B1.2|11 26.0	2.56
10542164	**Clec12a**	NM_177686 // Clec12a // C-type lectin domain family 12, member a // 6 F3|6 // 232413 //	2.56
10427336	**Nckap1l**	NM_153505 // Nckap1l // NCK associated protein 1 like // 15 F3|15 // 105855 /// ENSMUST	2.56
10569646	**Ccnd1**	NM_007631 // Ccnd1 // cyclin D1 // 7 F5|7 72.3 cM // 12443 /// ENSMUST00000093962 // Cc	2.55
10420488	**D14Ertd668e**	NM_199015 // D14Ertd668e // DNA segment, Chr 14, ERATO Doi 668, expressed // 14 C3|14 2	2.54
10472820	**Itga6**	NM_008397 // Itga6 // integrin alpha 6 // 2 C2-C3|2 38.0 cM // 16403 /// ENSMUST0000002	2.54
10607950	**G530011O06Rik**	NR_029457 // G530011O06Rik // RIKEN cDNA G530011O06 gene // X F5|X // 654820	2.54
10489127	**Rbl1**	NM_011249 // Rbl1 // retinoblastoma-like 1 (p107) // 2 H1|2 92.0 cM // 19650 /// NM_001	2.54
10408693	**F13a1**	NM_028784 // F13a1 // coagulation factor XIII, A1 subunit // 13 A3.3|13 // 74145 /// NM	2.52
10499899	**Sprr1a**	NM_009264 // Sprr1a // small proline-rich protein 1A // 3 F1|3 45.2 cM // 20753 /// ENS	2.52
10359890	**Nuf2**	NM_023284 // Nuf2 // NUF2, NDC80 kinetochore complex component, homolog (S. cerevisiae)	2.52
10359181	**Tor3a**	NM_023141 // Tor3a // torsin family 3, member A // 1 H1|1 // 30935 /// ENSMUST000000796	2.52
10501608	**Vcam1**	NM_011693 // Vcam1 // vascular cell adhesion molecule 1 // 3 G1|3 50.8 cM // 22329 ///	2.52
10460603	**Efemp2**	NM_021474 // Efemp2 // epidermal growth factor-containing fibulin-like extracellular ma	2.52
10339814	**---**	---	2.51
10404061	**Hist1h2bb**	NM_175664 // Hist1h2bb // histone cluster 1, H2bb // 13 A2-A3|13 // 319178 /// ENSMUST0	2.51
10408077	**Hist1h2ak**	NM_178183 // Hist1h2ak // histone cluster 1, H2ak // 13 A2-A3|13 // 319169 /// ENSMUST0	2.51
10492558	**Smc4**	NM_133786 // Smc4 // structural maintenance of chromosomes 4 // 3|3 E2 // 70099 /// ENS	2.50
10548375	**Clec7a**	NM_020008 // Clec7a // C-type lectin domain family 7, member a // 6 F3|6 // 56644 /// E	2.50
10493995	**S100a10**	NM_009112 // S100a10 // S100 calcium binding protein A10 (calpactin) // 3 F1-F2|3 41.7	2.50
10565456	**Prss23**	NM_029614 // Prss23 // protease, serine, 23 // 7 E1|7 // 76453 /// ENSMUST00000041761 /	2.50
10604656	**Xlr**	NM_011725 // Xlr // X-linked lymphocyte-regulated complex // X A5|X // 22441 /// ENSMUS	2.50
10494402	**Hist2h3c1**	NM_178216 // Hist2h3c1 // histone cluster 2, H3c1 // 3|3 F1-F2 // 15077 /// NM_054045 /	2.49
10432640	**Bin2**	ENSMUST00000100198 // Bin2 // bridging integrator 2 // 15 F1|15 // 668218	2.49
10348244	**Inpp5d**	NM_010566 // Inpp5d // inositol polyphosphate-5-phosphatase D // 1 C5|1 57.0 cM // 1633	2.49
10518147	**Pdpn**	NM_010329 // Pdpn // podoplanin // 4 E1|4 // 14726 /// ENSMUST00000030317 // Pdpn // po	2.49

10540493	**Edem1**	NM_138677 // Edem1 // ER degradation enhancer, mannosidase alpha-like 1 // 6 E2|6 // 19	2.48
10573261	**Asf1b**	NM_024184 // Asf1b // ASF1 anti-silencing function 1 homolog B (S. cerevisiae) // 8 C3|	2.48
10518408	**Plod1**	NM_011122 // Plod1 // procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 // 4 E2|4 76.5	2.48
10351644	**Cd244**	NM_018729 // Cd244 // CD244 natural killer cell receptor 2B4 // 1 H3|1 93.0 cM // 18106	2.48
10496569	**Gbp6**	NM_145545 // Gbp6 // guanylate binding protein 6 // 3 H1|3 // 229900 /// NM_001083312 /	2.48
10557326	**Il4ra**	NM_001008700 // Il4ra // interleukin 4 receptor, alpha // 7 F3|7 62.0 cM // 16190 /// E	2.48
10494405	**Hist2h3b**	NM_178215 // Hist2h3b // histone cluster 2, H3b // 3 F2.1|3 // 319154 /// NM_178216 //	2.48
10429128	**Sla**	NM_001029841 // Sla // src-like adaptor // 15 D2|15 37.5 cM // 20491 /// NM_009192 // S	2.48
10377405	**Aurkb**	NM_011496 // Aurkb // aurora kinase B // 11 B3|11 40.0 cM // 20877 /// ENSMUST000000212	2.47
10408239	**Hist1h3c**	NM_175653 // Hist1h3c // histone cluster 1, H3c // 13 A2-A3|13 // 319148 /// NM_178203	2.47
10484463	**Serping1**	NM_009776 // Serping1 // serine (or cysteine) peptidase inhibitor, clade G, member 1 //	2.47
10497817	**Anxa5**	NM_009673 // Anxa5 // annexin A5 // 3 B|3 19.2 cM // 11747 /// ENSMUST00000029266 // An	2.46
10414527	**Pnp2**	NM_001123371 // Pnp2 // purine-nucleoside phosphorylase 2 // 14 C1|14 // 667034 /// NM_	2.46
10558961	**Tspan4**	NM_053082 // Tspan4 // tetraspanin 4 // 7 F5|7 // 64540 /// ENSMUST00000026585 // Tspan	2.46
10404065	**Hist1h3b**	NM_178203 // Hist1h3b // histone cluster 1, H3b // 13 A2-A3|13 // 319150 /// NM_175653	2.46
10375443	**Havcr2**	NM_134250 // Havcr2 // hepatitis A virus cellular receptor 2 // 11 B1.1|11 // 171285 //	2.46
10489484	**Sdc4**	NM_011521 // Sdc4 // syndecan 4 // 2 H3|2 94.0 cM // 20971 /// ENSMUST00000017153 // Sd	2.46
10540085	**Fbln2**	NM_007992 // Fbln2 // fibulin 2 // 6 D|6 37.2 cM // 14115 /// NM_001081437 // Fbln2 //	2.46
10415319	**Irf9**	NM_001159417 // Irf9 // interferon regulatory factor 9 // 14 C3|14 21.5 cM // 16391 ///	2.45
10472440	**Tax1bp3**	NM_029564 // Tax1bp3 // Tax1 (human T-cell leukemia virus type I) binding protein 3 //	2.45
10408202	**Hist1h3e**	NM_178205 // Hist1h3e // histone cluster 1, H3e // 13 A2-A3|13 // 319151 /// NM_178206	2.45
10420877	**Esco2**	NM_028039 // Esco2 // establishment of cohesion 1 homolog 2 (S. cerevisiae) // 14 D1|14	2.45
10547022	**Timp4**	NM_080639 // Timp4 // tissue inhibitor of metalloproteinase 4 // 6 E3|6 46.0 cM // 1105	2.45
10524052	**Fgfrl1**	NM_054071 // Fgfrl1 // fibroblast growth factor receptor-like 1 // 5 E3-F|5 // 116701 /	2.45
10356305	**Htr2b**	NM_008311 // Htr2b // 5-hydroxytryptamine (serotonin) receptor 2B // 1 C5|1 // 15559 //	2.44
10401705	**Zdhhc22**	NM_001080943 // Zdhhc22 // zinc finger, DHHC-type containing 22 // 12 D2|12 // 238331 /	2.44
10341831	**---**	---	2.44
10350838	**2810417H13Rik**	NM_026515 // 2810417H13Rik // RIKEN cDNA 2810417H13 gene // 9 C|9 // 68026 /// ENSMUST0	2.44
10424779	**Cks2**	NM_025415 // Cks2 // CDC28 protein kinase regulatory subunit 2 // 13 A5|13 // 66197 ///	2.44

10445781	**Trem2**	NM_031254 // Trem2 // triggering receptor expressed on myeloid cells 2 // 17 C|17 // 83	2.43
10408083	**Hist1h3i**	NM_178207 // Hist1h3i // histone cluster 1, H3i // 13 A2-A3|13 // 319153 /// NM_178206	2.43
10483809	**Nfe2l2**	NM_010902 // Nfe2l2 // nuclear factor, erythroid derived 2, like 2 // 2 C3|2 45.0 cM //	2.43
10430372	**Rac2**	NM_009008 // Rac2 // RAS-related C3 botulinum substrate 2 // 15 E1|15 // 19354 /// ENSM	2.43
10399540	**Pqlc3**	NM_172574 // Pqlc3 // PQ loop repeat containing // 12 A1.1|12 // 217430 /// NM_00116111	2.43
10570434	**Ifitm1**	NM_026820 // Ifitm1 // interferon induced transmembrane protein 1 // 7|7 F5 // 68713 //	2.43
10342305	**---**	---	2.43
10404049	**Hist1h3d**	NM_178204 // Hist1h3d // histone cluster 1, H3d // 13 A2-A3|13 // 319149 /// NM_178206	2.42
10471721	**Ptgs1**	NM_008969 // Ptgs1 // prostaglandin-endoperoxide synthase 1 // 2 B|2 29.0 cM // 19224 /	2.42
10414360	**Lgals3**	NM_001145953 // Lgals3 // lectin, galactose binding, soluble 3 // 14 C1|14 // 16854 ///	2.42
10380285	**Tmem100**	NM_026433 // Tmem100 // transmembrane protein 100 // 11 C|11 // 67888 /// ENSMUST000000	2.42
10496580	**Gbp3**	NM_018734 // Gbp3 // guanylate binding protein 3 // 3 H1|3 // 55932 /// ENSMUST00000029	2.42
10413047	**Plau**	NM_008873 // Plau // plasminogen activator, urokinase // 14 A3|14 2.5 cM // 18792 /// E	2.42
10571840	**Hpgd**	NM_008278 // Hpgd // hydroxyprostaglandin dehydrogenase 15 (NAD) // 8 B3.2|8 // 15446 /	2.41
10544133	**Parp12**	NM_172893 // Parp12 // poly (ADP-ribose) polymerase family, member 12 // 6 B1|6 // 2437	2.41
10378334	**Tax1bp3**	NM_029564 // Tax1bp3 // Tax1 (human T-cell leukemia virus type I) binding protein 3 //	2.41
10403941	**Hist1h3h**	NM_178206 // Hist1h3h // histone cluster 1, H3h // 13 A2-A3|13 // 319152 /// NM_178207	2.40
10403978	**Hist1h2bk**	NM_175665 // Hist1h2bk // histone cluster 1, H2bk // 13 A2-A3|13 // 319184 /// NM_00111	2.40
10404028	**Hist1h3g**	NM_145073 // Hist1h3g // histone cluster 1, H3g // 13|13 A2-A3 // 97908 /// NM_178207 /	2.40
10381445	**Tmem106a**	NM_144830 // Tmem106a // transmembrane protein 106A // 11 D|11 // 217203 /// ENSMUST000	2.40
10452633	**Tgif1**	NM_009372 // Tgif1 // TGFB-induced factor homeobox 1 // 17 E1.3|17 // 21815 /// NM_0011	2.40
10534202	**Ncf1**	NM_010876 // Ncf1 // neutrophil cytosolic factor 1 // 5 G2|5 74.0 cM // 17969 /// ENSMU	2.40
10473809	**Sfpi1**	NM_011355 // Sfpi1 // SFFV proviral integration 1 // 2 E3|2 47.5 cM // 20375 /// ENSMUS	2.40
10408081	**Hist1h1b**	NM_020034 // Hist1h1b // histone cluster 1, H1b // 13|13 A2-A3 // 56702 /// ENSMUST0000	2.39
10477250	**Hck**	NM_010407 // Hck // hemopoietic cell kinase // 2 H1|2 86.0 cM // 15162 /// NM_001172117	2.39
10483110	**Ifih1**	NM_027835 // Ifih1 // interferon induced with helicase C domain 1 // 2|2 C3 // 71586 //	2.39
10589884	**Bcl2a1c**	NM_007535 // Bcl2a1c // B-cell leukemia/lymphoma 2 related protein A1c // 9 F3|9 // 120	2.39
10406852	**Cnn3**	NM_028044 // Cnn3 // calponin 3, acidic // 3 G1|3 // 71994 /// ENSMUST00000029773 // Cn	2.39
10408246	**Hist1h3a**	NM_013550 // Hist1h3a // histone cluster 1, H3a	2.39

		// 13|13 A2-A3 // 360198 /// NM_178203	
10363224	**Fabp7**	NM_021272 // Fabp7 // fatty acid binding protein 7, brain // 10 B4|10 // 12140 /// ENSM	2.38
10358339	**Cfh**	NM_009888 // Cfh // complement component factor h // 1 F|1 74.1 cM // 12628 /// ENSMUST	2.38
10360040	**Fcgr3**	NM_010188 // Fcgr3 // Fc receptor, IgG, low affinity III // 1 H3|1 92.3 cM // 14131 ///	2.38
10399710	**Rsad2**	NM_021384 // Rsad2 // radical S-adenosyl methionine domain containing 2 // 12|12 A3 //	2.38
10438098	**Sdf2l1**	NM_022324 // Sdf2l1 // stromal cell-derived factor 2-like 1 // 16 A3|16 // 64136 /// EN	2.38
10342942	**---**	---	2.38
10353004	**Cks2**	NM_025415 // Cks2 // CDC28 protein kinase regulatory subunit 2 // 13 A5|13 // 66197 ///	2.37
10368289	**Enpp1**	NM_008813 // Enpp1 // ectonucleotide pyrophosphatase/phosphodiesterase 1 // 10 A4|10 19	2.36
10552824	**Rras**	NM_009101 // Rras // Harvey rat sarcoma oncogene, subgroup R // 7 B4|7 23.0 cM // 20130	2.36
10560608	**Apoc2**	NM_009695 // Apoc2 // apolipoprotein C-II // 7 A3|7 4.0 cM // 11813 /// ENSMUST00000142	2.36
10414514	**Pnp**	NM_013632 // Pnp // purine-nucleoside phosphorylase // 14 B-C1|14 19.5 cM // 18950 ///	2.36
10342868	**---**	---	2.36
10462866	**Cep55**	NM_001164362 // Cep55 // centrosomal protein 55 // 19|19 C3 // 74107 /// NM_028760 // C	2.36
10416037	**Pbk**	NM_023209 // Pbk // PDZ binding kinase // 14 D1|14 28.0 cM // 52033 /// ENSMUST00000022	2.36
10566578	**Gm8979**	NR_030719 // Gm8979 // very large inducible GTPase 1 pseudogene // 7 E3|7 // 668108 ///	2.35
10496204	**Cenpe**	NM_173762 // Cenpe // centromere protein E // 3 0.1 cM|3 H2 // 229841 /// ENSMUST000000	2.35
10436106	**C330027C09Rik**	NM_172616 // C330027C09Rik // RIKEN cDNA C330027C09 gene // 16 B5|16 // 224171 /// ENSM	2.35
10555695	**Rrm1**	NM_009103 // Rrm1 // ribonucleotide reductase M1 // 7 E3|7 69.0 cM // 20133 /// ENSMUST	2.35
10408070	**Hist1h2bl**	NM_178199 // Hist1h2bl // histone cluster 1, H2bl // 13 A2-A3|13 // 319185 /// NM_00111	2.34
10576034	**Irf8**	NM_008320 // Irf8 // interferon regulatory factor 8 // 8 E1|8 65.0 cM // 15900 /// ENSM	2.34
10528077	**Dbf4**	NM_013726 // Dbf4 // DBF4 homolog (S. cerevisiae) // 5|5 A2 // 27214 /// NM_001190717 /	2.33
10605256	**Flna**	NM_010227 // Flna // filamin, alpha // X A7.3|X 29.8 cM // 192176 /// ENSMUST0000010145	2.33
10443980	**Myo1f**	NM_053214 // Myo1f // myosin IF // 17 B-C|17 17.5 cM // 17916 /// ENSMUST00000087605 //	2.33
10403948	**Hist1h2bn**	NM_178201 // Hist1h2bn // histone cluster 1, H2bn // 13 A2-A3|13 // 319187 /// NM_17566	2.33
10343087	**---**	---	2.33
10389143	**Slfn8**	NM_181545 // Slfn8 // schlafen 8 // 11 C|11 // 276950 /// NM_001167743 // Slfn8 // schl	2.32
10608654	**---**	---	2.32
10389606	**Prr11**	NM_175563 // Prr11 // proline rich 11 // 11 C|11 // 270906 /// ENSMUST00000051395 // Pr	2.31
10605181	**Renbp**	NM_023132 // Renbp // renin binding protein // X A7.3|X 29.53 cM // 19703 /// NM_001164	2.31
10462140	**Dock8**	NM_028785 // Dock8 // dedicator of cytokinesis 8 // 19 B|19 // 76088 /// ENSMUST0000002	2.31

10494351	**Mtmr11**	NM_181409 // Mtmr11 // myotubularin related protein 11 // 3 F2.1|3 // 194126 /// BC0510	2.31
10349724	**Rab7l1**	NM_144875 // Rab7l1 // RAB7, member RAS oncogene family-like 1 // 1 E4|1 // 226422 ///	2.31
10601011	**Kif4**	NM_008446 // Kif4 // kinesin family member 4 // X C3|X 39.5 cM // 16571 /// ENSMUST0000	2.31
10594251	**Kif23**	NM_024245 // Kif23 // kinesin family member 23 // 9 B|9 // 71819 /// ENSMUST00000034815	2.30
10595668	**Ankrd34c**	NM_207260 // Ankrd34c // ankyrin repeat domain 34C // 9 E3.1|9 // 330998 /// ENSMUST000	2.30
10487577	**Ckap2l**	NM_181589 // Ckap2l // cytoskeleton associated protein 2-like // 2 F1|2 // 70466 /// EN	2.30
10375485	**---**	---	2.30
10588899	**Gpx1**	NM_008160 // Gpx1 // glutathione peroxidase 1 // 9 F1|9 57.0 cM // 14775 /// ENSMUST000	2.30
10601569	**Pcdh11x**	NM_001081385 // Pcdh11x // protocadherin 11 X-linked // X E2|X // 245578 /// ENSMUST000	2.29
10402347	**Ifi27l2a**	NM_029803 // Ifi27l2a // interferon, alpha-inducible protein 27 like 2A // 12 E|12 // 7	2.29
10580033	**Cd97**	NM_011925 // Cd97 // CD97 antigen // 8 C2|8 38.0 cM // 26364 /// NM_001163030 // Cd97 /	2.29
10376326	**Irgm2**	NM_019440 // Irgm2 // immunity-related GTPase family M member 2 // 11 B1.3|11 // 54396	2.29
10367400	**Mmp19**	NM_021412 // Mmp19 // matrix metallopeptidase 19 // 10 D3|10 70.0 cM // 58223 /// NM_00	2.29
10444830	**H2-Q7**	NM_010394 // H2-Q7 // histocompatibility 2, Q region locus 7 // 17 B1|17 19.19 cM // 15	2.29
10408210	**Hist1h2bf**	NM_178195 // Hist1h2bf // histone cluster 1, H2bf // 13 A2-A3|13 // 319180 /// NM_02342	2.29
10383799	**Tcn2**	NM_015749 // Tcn2 // transcobalamin 2 // 11 A1|11 3.0 cM // 21452 /// NM_001130458 // T	2.28
10493798	**S100a16**	NM_026416 // S100a16 // S100 calcium binding protein A16 // 3|3 F1-F2 // 67860 /// BC02	2.28
10352813	**---**	---	2.28
10339437	**---**	---	2.28
10455961	**Iigp1**	NM_001146275 // Iigp1 // interferon inducible GTPase 1 // 18 D3|18 // 60440 /// NM_0217	2.28
10462613	**Ifit2**	NM_008332 // Ifit2 // interferon-induced protein with tetratricopeptide repeats 2 // 19	2.27
10566571	**Gm8979**	NR_030719 // Gm8979 // very large inducible GTPase 1 pseudogene // 7 E3|7 // 668108 ///	2.27
10561431	**Plekhg2**	NM_138752 // Plekhg2 // pleckstrin homology domain containing, family G (with RhoGef do	2.27
10530145	**Tlr1**	NM_030682 // Tlr1 // toll-like receptor 1 // 5 C3.1|5 37.0 cM // 21897 /// ENSMUST00000	2.27
10379615	**Slfn5**	NM_183201 // Slfn5 // schlafen 5 // 11 C|11 // 327978 /// ENSMUST00000067443 // Slfn5 /	2.27
10391207	**Dhx58**	NM_030150 // Dhx58 // DEXH (Asp-Glu-X-His) box polypeptide 58 // 11 D|11 61.5 cM // 808	2.27
10385513	**9930111J21Rik2**	NM_173434 // 9930111J21Rik2 // RIKEN cDNA 9930111J21 gene 2 // 11 B1.2|11 // 245240 ///	2.27
10414537	**Rnase4**	NM_021472 // Rnase4 // ribonuclease, RNase A family 4 // 14 C1|14 // 58809 /// NM_20123	2.27
10586591	**Car12**	NM_178396 // Car12 // carbonic anyhydrase 12 // 9 C|9 // 76459 /// ENSMUST00000071889 /	2.26
10381122	**Fkbp10**	NM_010221 // Fkbp10 // FK506 binding protein 10 // 11 D|11 58.0 cM // 14230 /// NM_0011	2.26
10519951	**Pion**	NM_175437 // Pion // pigeon homolog (Drosophila) // 5 A3|5 // 212167 /// ENSMUST0000003	2.26

10526520	**Plod3**	NM_011962 // Plod3 // procollagen-lysine, 2-oxoglutarate 5-dioxygenase 3 // 5 G2|5 80.0	2.26
10357579	**Mapkapk2**	NM_008551 // Mapkapk2 // MAP kinase-activated protein kinase 2 // 1 E4|1 // 17164 /// E	2.26
10533246	**Oas1g**	NM_011852 // Oas1g // 2'-5' oligoadenylate synthetase 1G // 5 F|5 67.0 cM // 23960 ///	2.25
10544837	**1200009O22Rik**	NM_025817 // 1200009O22Rik // RIKEN cDNA 1200009O22 gene // 6 B3|6 // 66873 /// ENSMUST	2.25
10429564	**Ly6a**	NM_010738 // Ly6a // lymphocyte antigen 6 complex, locus A // 15 D3|15 42.7 cM // 11045	2.25
10590494	**Kif15**	NM_010620 // Kif15 // kinesin family member 15 // 9 F4|9 // 209737 /// ENSMUST000000407	2.25
10400649	**Pole2**	NM_011133 // Pole2 // polymerase (DNA directed), epsilon 2 (p59 subunit) // 12|12 C3 //	2.25
10342914	**---**	---	2.25
10498379	**Igsf10**	NM_001162884 // Igsf10 // immunoglobulin superfamily, member 10 // 3 D|3 // 242050 ///	2.25
10497122	**Depdc1a**	NM_001172092 // Depdc1a // DEP domain containing 1a // 3 H4|3 // 76131 /// NM_029523 //	2.24
10437040	**Chaf1b**	NM_028083 // Chaf1b // chromatin assembly factor 1, subunit B (p60) // 16 C4|16 67.4 cM	2.24
10398075	**Serpina3n**	NM_009252 // Serpina3n // serine (or cysteine) peptidase inhibitor, clade A, member 3N	2.24
10536494	**Cav2**	NM_016900 // Cav2 // caveolin 2 // 6|6 A2 // 12390 /// ENSMUST00000000058 // Cav2 // ca	2.24
10366052	**Kitl**	NM_013598 // Kitl // kit ligand // 10 D1|10 57.0 cM // 17311 /// ENSMUST00000105283 //	2.24
10536472	**Mdfic**	NM_175088 // Mdfic // MyoD family inhibitor domain containing // 6 A1|6 // 16543 /// EN	2.23
10532741	**Tmem119**	NM_146162 // Tmem119 // transmembrane protein 119 // 5 F|5 // 231633 /// ENSMUST0000006	2.23
10447602	**Ezr**	NM_009510 // Ezr // ezrin // 17 A1|17 // 22350 /// BC048181 // Ezr // ezrin // 17 A1|17	2.23
10545101	**Hpgds**	NM_019455 // Hpgds // hematopoietic prostaglandin D synthase // 6|6 D-E // 54486 /// EN	2.23
10389134	**Slfn9**	NM_172796 // Slfn9 // schlafen 9 // 11 C|11 // 237886 /// ENSMUST00000038211 // Slfn9 /	2.23
10440393	**Samsn1**	NM_023380 // Samsn1 // SAM domain, SH3 domain and nuclear localization signals, 1 // 16	2.23
10359908	**Rgs4**	NM_009062 // Rgs4 // regulator of G-protein signaling 4 // 1 H3|1 86.5 cM // 19736 ///	2.23
10378068	**Xaf1**	NM_001037713 // Xaf1 // XIAP associated factor 1 // 11 B4|11 // 327959 /// ENSMUST00000	2.23
10420483	**Phf11**	NM_172603 // Phf11 // PHD finger protein 11 // 14 C3|14 // 219131 /// ENSMUST0000006230	2.23
10435457	**Parp9**	NM_030253 // Parp9 // poly (ADP-ribose) polymerase family, member 9 // 16 B3|16 // 8028	2.23
10411622	**Naip6**	NM_010871 // Naip6 // NLR family, apoptosis inhibitory protein 6 // 13 D1|13 55.0 cM //	2.23
10403980	**Hist1h2bj**	NM_178198 // Hist1h2bj // histone cluster 1, H2bj // 13 A2-A3|13 // 319183 /// NM_00111	2.22
10498383	**Igsf10**	NM_001162884 // Igsf10 // immunoglobulin superfamily, member 10 // 3 D|3 // 242050 ///	2.22
10524169	**Pole**	NM_011132 // Pole // polymerase (DNA directed), epsilon // 5 E3-E5|5 56.0 cM // 18973 /	2.22
10460738	**Cdca5**	NM_026410 // Cdca5 // cell division cycle	2.22

		associated 5 // 19 A|19 // 67849 /// ENSMUST0	
10373530	**Cdk2**	NM_183417 // Cdk2 // cyclin-dependent kinase 2 // 10 D3|10 // 12566 /// NM_016756 // Cd	2.22
10542079	**Foxm1**	NM_008021 // Foxm1 // forkhead box M1 // 6 F3|6 62.0 cM // 14235 /// ENSMUST00000073316	2.22
10410931	**Vcan**	NM_001081249 // Vcan // versican // 13 C3|13 55.0 cM // 13003 /// NM_019389 // Vcan //	2.22
10498367	**P2ry13**	NM_028808 // P2ry13 // purinergic receptor P2Y, G-protein coupled 13 // 3 D|3 // 74191	2.21
10565018	**Iqgap1**	NM_016721 // Iqgap1 // IQ motif containing GTPase activating protein 1 // 7 D3|7 39.0 c	2.21
10554752	**Nox4**	NM_015760 // Nox4 // NADPH oxidase 4 // 7 D3|7 // 50490 /// ENSMUST00000032781 // Nox4	2.21
10569335	**H19**	NR_001592 // H19 // H19 fetal liver mRNA // 7 F5|7 69.03 cM // 14955	2.21
10507112	**Stil**	NM_009185 // Stil // Scl/Tal1 interrupting locus // 4 D1|4 // 20460 /// ENSMUST00000030	2.21
10414315	**Cdkn3**	NM_028222 // Cdkn3 // cyclin-dependent kinase inhibitor 3 // 14|14 C1 // 72391 /// ENSM	2.21
10402268	**Lgmn**	NM_011175 // Lgmn // legumain // 12 E|12 // 19141 /// ENSMUST00000021607 // Lgmn // leg	2.20
10413710	**Nt5dc2**	NM_027289 // Nt5dc2 // 5'-nucleotidase domain containing 2 // 14 B|14 // 70021 /// NM_1	2.20
10515090	**Cdkn2c**	NM_007671 // Cdkn2c // cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4) // 4 C	2.20
10346365	**Sgol2**	NM_199007 // Sgol2 // shugoshin-like 2 (S. pombe) // 1 C1.3|1 30.1 cM // 68549 /// NM_0	2.20
10532711	**Cmklr1**	NM_008153 // Cmklr1 // chemokine-like receptor 1 // 5 F|5 // 14747 /// ENSMUST000000479	2.20
10353420	**Mcm3**	NM_008563 // Mcm3 // minichromosome maintenance deficient 3 (S. cerevisiae) // 1|1 A3-A	2.20
10469322	**Vim**	NM_011701 // Vim // vimentin // 2 A2|2 7.0 cM // 22352 /// ENSMUST00000028062 // Vim //	2.20
10596148	**Trf**	NM_133977 // Trf // transferrin // 9 F1-F3|9 56.0 cM // 22041 /// ENSMUST00000035158 //	2.20
10490989	**Cp**	NM_001042611 // Cp // ceruloplasmin // 3|3 D // 12870 /// NM_007752 // Cp // ceruloplas	2.20
10498284	**Wwtr1**	NM_133784 // Wwtr1 // WW domain containing transcription regulator 1 // 3 D|3 // 97064	2.20
10425066	**Csf2rb**	NM_007780 // Csf2rb // colony stimulating factor 2 receptor, beta, low-affinity (granul	2.19
10565958	**P2ry6**	NM_183168 // P2ry6 // pyrimidinergic receptor P2Y, G-protein coupled, 6 // 7 E3|7 // 23	2.19
10539263	**Loxl3**	NM_013586 // Loxl3 // lysyl oxidase-like 3 // 6 C3|6 34.76 cM // 16950 /// NM_019752 //	2.19
10434672	**Gng5**	NM_010318 // Gng5 // guanine nucleotide binding protein (G protein), gamma 5 // 3 H2|3	2.19
10558769	**Ifitm1**	NM_026820 // Ifitm1 // interferon induced transmembrane protein 1 // 7|7 F5 // 68713 //	2.19
10391301	**Stat3**	NM_213659 // Stat3 // signal transducer and activator of transcription 3 // 11 D|11 60.	2.19
10508663	**Laptm5**	NM_010686 // Laptm5 // lysosomal-associated protein transmembrane 5 // 4 D2.3|4 // 1679	2.19
10575733	**Cenpn**	NM_028131 // Cenpn // centromere protein N // 8 E1|8 // 72155 /// ENSMUST00000034205 //	2.19
10437655	**Nubp1**	NM_011955 // Nubp1 // nucleotide binding protein 1 // 16 A1|16 3.4 cM // 26425 /// ENSM	2.19
10533050	**Hspb8**	NM_030704 // Hspb8 // heat shock protein 8 // 5	2.18

		F|5 59.0 cM // 80888 /// ENSMUST0000003	
10405185	**Cks2**	NM_025415 // Cks2 // CDC28 protein kinase regulatory subunit 2 // 13 A5|13 // 66197 ///	2.18
10540034	**Aldh1l1**	NM_027406 // Aldh1l1 // aldehyde dehydrogenase 1 family, member L1 // 6 D1|6 // 107747	2.18
10404026	**Hist1h2af**	NM_175661 // Hist1h2af // histone cluster 1, H2af // 13 A3.1|13 // 319173 /// NM_178188	2.18
10578690	**Neil3**	NM_146208 // Neil3 // nei like 3 (E. coli) // 8 B1.3|8 // 234258 /// ENSMUST00000047768	2.18
10597518	**Tgfbr2**	NM_009371 // Tgfbr2 // transforming growth factor, beta receptor II // 9 F3|9 69.0 cM /	2.18
10402211	**Fbln5**	NM_011812 // Fbln5 // fibulin 5 // 12|12 F1 // 23876 /// ENSMUST00000021603 // Fbln5 //	2.18
10353010	**Mybl1**	NM_008651 // Mybl1 // myeloblastosis oncogene-like 1 // 1 A2|1 3.0 cM // 17864 /// ENSM	2.18
10436666	**Jam2**	NM_023844 // Jam2 // junction adhesion molecule 2 // 16 C3.3|16 // 67374 /// ENSMUST000	2.18
10411611	**Naip5**	NM_010870 // Naip5 // NLR family, apoptosis inhibitory protein 5 // 13 D1|13 55.0 cM //	2.17
10344490	**---**	---	2.17
10412298	**Itga1**	NM_001033228 // Itga1 // integrin alpha 1 // 13 D2.2|13 65.0 cM // 109700 /// ENSMUST00	2.17
10525158	**Oas1b**	NR_003507 // Oas1b // 2'-5' oligoadenylate synthetase 1B // 5 F|5 67.0 cM // 23961 ///	2.17
10376950	**Pmp22**	NM_008885 // Pmp22 // peripheral myelin protein 22 // 11 B3|11 34.45 cM // 18858 /// EN	2.17
10572897	**Hmox1**	NM_010442 // Hmox1 // heme oxygenase (decycling) 1 // 8 C1|8 35.0 cM // 15368 /// ENSMU	2.17
10538832	**Mad2l1**	NM_019499 // Mad2l1 // MAD2 mitotic arrest deficient-like 1 (yeast) // 6 C1|6 30.3 cM /	2.17
10346191	**Stat1**	NM_009283 // Stat1 // signal transducer and activator of transcription 1 // 1 C1.1|1 25	2.16
10441952	**2210404J11Rik**	NM_001039552 // 2210404J11Rik // RIKEN cDNA 2210404J11 gene // 17 A2|17 // 381062 /// N	2.16
10574471	**Cmtm3**	NM_024217 // Cmtm3 // CKLF-like MARVEL transmembrane domain containing 3 // 8 D3|8 // 6	2.16
10505517	**Tlr4**	NM_021297 // Tlr4 // toll-like receptor 4 // 4 C1|4 33.0 cM // 21898 /// ENSMUST0000004	2.16
10474936	**Spint1**	NM_016907 // Spint1 // serine protease inhibitor, Kunitz type 1 // 2 E5|2 // 20732 ///	2.16
10373407	**Esyt1**	NM_011843 // Esyt1 // extended synaptotagmin-like protein 1 // 10 D3|10 // 23943 /// EN	2.16
10569319	**Ctsd**	NM_009983 // Ctsd // cathepsin D // 7 F5|7 // 13033 /// ENSMUST00000151120 // Ctsd // c	2.16
10383756	**Ifitm2**	NM_030694 // Ifitm2 // interferon induced transmembrane protein 2 // 7|7 F5 // 80876 //	2.16
10402783	**Ahnak2**	BC138468 // Ahnak2 // AHNAK nucleoprotein 2 // 12 F1|12 // 100041194 /// ENSMUST0000010	2.16
10494271	**Ctss**	NM_021281 // Ctss // cathepsin S // 3 F2.1|3 42.7 cM // 13040 /// ENSMUST00000015667 //	2.15
10474825	**D2Ertd750e**	NM_026412 // D2Ertd750e // DNA segment, Chr 2, ERATO Doi 750, expressed // 2 E5|2 // 51	2.15
10420155	**Dhrs1**	NM_026819 // Dhrs1 // dehydrogenase/reductase (SDR family) member 1 // 14 C3|14 22.5 cM	2.15
10380260	**Trim25**	NM_009546 // Trim25 // tripartite motif-containing	2.15

		25 // 11 C|11 // 217069 /// ENSMUST0	
10561104	**Axl**	NM_009465 // Axl // AXL receptor tyrosine kinase // 7 A3-B1|7 6.0 cM // 26362 /// NM_00	2.15
10588037	**Rbp1**	NM_011254 // Rbp1 // retinol binding protein 1, cellular // 9 E3.3|9 52.0 cM // 19659 /	2.14
10469695	**Apbb1ip**	NM_019456 // Apbb1ip // amyloid beta (A4) precursor protein-binding, family B, member 1	2.14
10441933	**2210404J11Rik**	NM_001039552 // 2210404J11Rik // RIKEN cDNA 2210404J11 gene // 17 A2|17 // 381062 /// N	2.14
10553299	**Ifitm2**	NM_030694 // Ifitm2 // interferon induced transmembrane protein 2 // 7|7 F5 // 80876 //	2.14
10576661	**Itgb1**	NM_010578 // Itgb1 // integrin beta 1 (fibronectin receptor beta) // 8 E2|8 // 16412 //	2.14
10460237	**Unc93b1**	NM_019449 // Unc93b1 // unc-93 homolog B1 (C. elegans) // 19 A|19 // 54445 /// NM_00116	2.14
10496872	**Eltd1**	NM_133222 // Eltd1 // EGF, latrophilin seven transmembrane domain containing 1 // 3|3 H	2.14
10508115	**Stk40**	NM_001145827 // Stk40 // serine/threonine kinase 40 // 4 D2.2|4 // 74178 /// NM_028800	2.14
10342986	**---**	---	2.13
10385526	**9930111J21Rik2**	NM_173434 // 9930111J21Rik2 // RIKEN cDNA 9930111J21 gene 2 // 11 B1.2|11 // 245240 ///	2.13
10561453	**Zfp36**	NM_011756 // Zfp36 // zinc finger protein 36 // 7 A3|7 10.2 cM // 22695 /// ENSMUST0000	2.13
10350516	**Ptgs2**	NM_011198 // Ptgs2 // prostaglandin-endoperoxide synthase 2 // 1 H1|1 76.2 cM // 19225	2.13
10560685	**Bcl3**	NM_033601 // Bcl3 // B-cell leukemia/lymphoma 3 // 7 A3|7 6.5 cM // 12051 /// ENSMUST00	2.13
10362896	**Cd24a**	NM_009846 // Cd24a // CD24a antigen // 10 B2|10 26.0 cM // 12484 /// BC075622 // Cd24a	2.13
10437687	**Litaf**	NM_019980 // Litaf // LPS-induced TN factor // 16|16 B1-B3 // 56722 /// ENSMUST00000023	2.13
10525365	**Hvcn1**	NM_001042489 // Hvcn1 // hydrogen voltage-gated channel 1 // 5 F|5 // 74096 /// NM_0287	2.13
10343128	**---**	---	2.13
10495659	**Cnn3**	NM_028044 // Cnn3 // calponin 3, acidic // 3 G1|3 // 71994 /// ENSMUST00000029773 // Cn	2.13
10559486	**Lair1**	NM_001113474 // Lair1 // leukocyte-associated Ig-like receptor 1 // 7 A1|7 4.5 cM // 52	2.13
10471844	**Nek6**	NM_021606 // Nek6 // NIMA (never in mitosis gene a)-related expressed kinase 6 // 2 B|2	2.12
10389719	**Scpep1**	NM_029023 // Scpep1 // serine carboxypeptidase 1 // 11 C|11 // 74617 /// ENSMUST0000000	2.12
10596718	**Slc38a3**	NM_023805 // Slc38a3 // solute carrier family 38, member 3 // 9 F1|9 63.0 cM // 76257 /	2.12
10563178	**Cd37**	NM_007645 // Cd37 // CD37 antigen // 7 B4|7 23.0 cM // 12493 /// ENSMUST00000098461 //	2.12
10548879	**Mgp**	NM_008597 // Mgp // matrix Gla protein // 6 G1|6 // 17313 /// ENSMUST00000032342 // Mgp	2.12
10435565	**Hcls1**	NM_008225 // Hcls1 // hematopoietic cell specific Lyn substrate 1 // 16|16 B // 15163 /	2.11
10436841	**Il10rb**	NM_008349 // Il10rb // interleukin 10 receptor, beta // 16 C3.3|16 63.11 cM // 16155 //	2.11
10477920	**Myl9**	NM_172118 // Myl9 // myosin, light polypeptide 9, regulatory // 2 H1|2 // 98932 /// ENS	2.11
10420426	**F630043A04Rik**	NM_198605 // F630043A04Rik // RIKEN cDNA F630043A04 gene // 14 C3|14 // 219114 /// ENSM	2.11

10419323	**Dlgap5**	NM_144553 // Dlgap5 // discs, large (Drosophila) homolog-associated protein 5 // 14 C1|	2.11
10410124	**Ctsl**	NM_009984 // Ctsl // cathepsin L // 13 B3|13 30.0 cM // 13039 /// ENSMUST00000021933 //	2.11
10383210	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.11
10488382	**Cd93**	NM_010740 // Cd93 // CD93 antigen // 2 G3|2 84.0 cM // 17064 /// ENSMUST00000099269 //	2.11
10571984	**Ddx60**	NM_001081215 // Ddx60 // DEAD (Asp-Glu-Ala-Asp) box polypeptide 60 // 8 B3.1|8 // 23431	2.10
10411373	**Hexb**	NM_010422 // Hexb // hexosaminidase B // 13 D1|13 46.0 cM // 15212 /// ENSMUST000000221	2.10
10444258	**Psmb8**	NM_010724 // Psmb8 // proteasome (prosome, macropain) subunit, beta type 8 (large multi	2.10
10589350	**Shisa5**	NM_025858 // Shisa5 // shisa homolog 5 (Xenopus laevis) // 9 F2|9 // 66940 /// NM_02638	2.10
10439312	**Cd86**	NM_019388 // Cd86 // CD86 antigen // 16 B5|16 26.9 cM // 12524 /// ENSMUST00000089620 /	2.10
10399924	**Pik3cg**	NM_020272 // Pik3cg // phosphoinositide-3-kinase, catalytic, gamma polypeptide // 12|12	2.10
10503334	**Gem**	NM_010276 // Gem // GTP binding protein (gene overexpressed in skeletal muscle) // 4 A1	2.10
10451805	**Sgol1**	NM_028232 // Sgol1 // shugoshin-like 1 (S. pombe) // 17 C|17 // 72415 /// ENSMUST000000	2.10
10415081	**---**	---	2.10
10520121	**---**	---	2.10
10578405	**---**	---	2.10
10586076	**---**	---	2.10
10391811	**Kif18b**	NM_197959 // Kif18b // kinesin family member 18B // 11 E1|11 // 70218 /// BC057614 // K	2.09
10385903	**Pdlim4**	NM_019417 // Pdlim4 // PDZ and LIM domain 4 // 11 B1.3|11 28.5 cM // 30794 /// ENSMUST0	2.09
10356379	**Ecel1**	NM_021306 // Ecel1 // endothelin converting enzyme-like 1 // 1 D|1 // 13599 /// ENSMUST	2.09
10529034	**Cgref1**	NM_026770 // Cgref1 // cell growth regulator with EF hand domain 1 // 5 B1|5 // 68567 /	2.09
10357676	**Cdk18**	NM_008795 // Cdk18 // cyclin-dependent kinase 18 // 1 E4|1 // 18557 /// ENSMUST00000027	2.08
10483025	**Rbms1**	NM_001141932 // Rbms1 // RNA binding motif, single stranded interacting protein 1 // 2|	2.08
10423049	**Prlr**	NM_011169 // Prlr // prolactin receptor // 15 A1|15 4.6 cM // 19116 /// ENSMUST00000124	2.08
10471535	**Fam129b**	NM_146119 // Fam129b // family with sequence similarity 129, member B // 2 B|2 // 22773	2.08
10606714	**Gla**	NM_013463 // Gla // galactosidase, alpha // X E-F1|X 53.0 cM // 11605 /// U34071 // Gla	2.08
10408085	**Hist1h2an**	NM_178184 // Hist1h2an // histone cluster 1, H2an // 13 A3.1|13 // 319170 /// NM_178186	2.08
10385504	**Gm5431**	NM_001024230 // Gm5431 // predicted gene 5431 // 11 B1.2|11 // 432555 /// ENSMUST000001	2.07
10364593	**Cnn2**	NM_007725 // Cnn2 // calponin 2 // 10 C1|10 // 12798 /// ENSMUST00000004784 // Cnn2 //	2.07
10375432	**C030019I05Rik**	NM_177075 // C030019I05Rik // RIKEN cDNA C030019I05 gene // 11 B1.1|11 // 320116 /// EN	2.07
10347928	**Sp110**	NM_175397 // Sp110 // Sp110 nuclear body protein // 1 C5|1 // 109032 /// ENSMUST0000009	2.07
10582874	**Sp110**	NM_175397 // Sp110 // Sp110 nuclear body protein // 1 C5|1 // 109032 /// ENSMUST0000009	2.07

10485963	**Arhgap11a**	NM_181416 // Arhgap11a // Rho GTPase activating protein 11A // 2 E4|2 // 228482 /// ENS	2.07
10528143	**Ppp1r14b**	NM_008889 // Ppp1r14b // protein phosphatase 1, regulatory (inhibitor) subunit 14B // 1	2.07
10382980	**Syngr2**	NM_009304 // Syngr2 // synaptogyrin 2 // 11 E2|11 // 20973 /// ENSMUST00000026649 // Sy	2.07
10341982	**---**	---	2.07
10545958	**Anxa4**	NM_013471 // Anxa4 // annexin A4 // 6 D1|6 38.0 cM // 11746 /// ENSMUST00000001187 // A	2.07
10563780	**E2f8**	NM_001013368 // E2f8 // E2F transcription factor 8 // 7 B4|7 // 108961 /// ENSMUST00000	2.07
10369413	**Sgpl1**	NM_009163 // Sgpl1 // sphingosine phosphate lyase 1 // 10 B4|10 32.0 cM // 20397 /// EN	2.06
10495596	**Frrs1**	NM_001113478 // Frrs1 // ferric-chelate reductase 1 // 3 G1|3 // 20321 /// NM_009146 //	2.06
10498386	**Igsf10**	NM_001162884 // Igsf10 // immunoglobulin superfamily, member 10 // 3 D|3 // 242050	2.06
10351623	**F11r**	NM_172647 // F11r // F11 receptor // 1 H2|1 93.3 cM // 16456 /// ENSMUST00000043839 //	2.06
10403959	**Gm11277**	NM_001110555 // Gm11277 // predicted gene 11277 // 13 A3.1|13 // 665622 /// NM_00109797	2.06
10408087	**Gm11277**	NM_001110555 // Gm11277 // predicted gene 11277 // 13 A3.1|13 // 665622 /// NM_00109797	2.06
10403955	**Hist1h2ao**	NM_001177544 // Hist1h2ao // histone cluster 1, H2ao // 13 A3.1|13 // 665433 /// NM_178	2.06
10341051	**---**	---	2.06
10467508	**Blnk**	NM_008528 // Blnk // B-cell linker // 19 C3|19 31.0 cM // 17060 /// ENSMUST00000054769	2.06
10457614	**Aqp4**	NM_009700 // Aqp4 // aquaporin 4 // 18 A1|18 6.0 cM // 11829 /// ENSMUST00000079081 //	2.05
10523468	**Bmp2k**	NM_080708 // Bmp2k // BMP2 inducible kinase // 5 E3|5 // 140780 /// ENSMUST00000035635	2.05
10521913	**Rbpj**	NM_009035 // Rbpj // recombination signal binding protein for immunoglobulin kappa J re	2.05
10404045	**Hist1h2ad**	NM_178188 // Hist1h2ad // histone cluster 1, H2ad // 13 A2-A3|13 // 319165 /// NM_17818	2.05
10572906	**Mcm5**	NM_008566 // Mcm5 // minichromosome maintenance deficient 5, cell division cycle 46 (S.	2.05
10466190	**Ms4a14**	ENSMUST00000067600 // Ms4a14 // membrane-spanning 4-domains, subfamily A, member 14 //	2.05
10444068	**Tapbp**	NM_001025313 // Tapbp // TAP binding protein // 17 B1|17 18.41 cM // 21356 /// NM_00931	2.05
10398052	**Serpina3h**	NR_033450 // Serpina3h // serine (or cysteine) peptidase inhibitor, clade A, member 3H	2.04
10510172	**Hmgb2**	NM_008252 // Hmgb2 // high mobility group box 2 // 8 B2|8 31.0 cM // 97165 /// ENSMUST0	2.04
10342635	**---**	---	2.04
10538150	**Tmem176a**	NM_025326 // Tmem176a // transmembrane protein 176A // 6 B2.3|6 // 66058 /// NM_0010982	2.04
10428707	**Has2**	NM_008216 // Has2 // hyaluronan synthase 2 // 15 D1|15 31.2 cM // 15117 /// ENSMUST0000	2.04
10379630	**Slfn2**	NM_011408 // Slfn2 // schlafen 2 // 11 C|11 48.0 cM // 20556 /// ENSMUST00000038038 //	2.04
10340419	**---**	---	2.03
10546163	**Mcm2**	NM_008564 // Mcm2 // minichromosome maintenance deficient 2 mitotin (S. cerevisiae) //	2.03
10444932	**2310014H01Rik**	NM_001146711 // 2310014H01Rik // RIKEN cDNA 2310014H01 gene // 17 B1|17 // 76448 /// NM	2.03
10534456	**Hip1**	NM_146001 // Hip1 // huntingtin interacting	2.03

		protein 1 // 5 F-G2|5 75.0 cM // 215114 ///	
10344149	**---**	---	2.03
10455647	**Tnfaip8**	NM_134131 // Tnfaip8 // tumor necrosis factor, alpha-induced protein 8 // 18 D1|18 // 1	2.03
10541729	**Cdca3**	NM_013538 // Cdca3 // cell division cycle associated 3 // 6 F2|6 60.19 cM // 14793 ///	2.03
10453057	**Cyp1b1**	NM_009994 // Cyp1b1 // cytochrome P450, family 1, subfamily b, polypeptide 1 // 17 E3|1	2.03
10534974	**Mcm7**	NM_008568 // Mcm7 // minichromosome maintenance deficient 7 (S. cerevisiae) // 5|5 G1 /	2.03
10344966	**Ly96**	NM_016923 // Ly96 // lymphocyte antigen 96 // 1 A3|1 // 17087 /// NM_001159711 // Ly96	2.03
10489204	**Tgm2**	NM_009373 // Tgm2 // transglutaminase 2, C polypeptide // 2 H1|2 89.0 cM // 21817 /// E	2.03
10408111	**Hist1h2ah**	NM_175659 // Hist1h2ah // histone cluster 1, H2ah // 13 A2-A3|13 // 319168 /// NM_17818	2.03
10360806	**Capn2**	NM_009794 // Capn2 // calpain 2 // 1 H5|1 // 12334 /// ENSMUST00000068505 // Capn2 // c	2.02
10597743	**Cx3cr1**	NM_009987 // Cx3cr1 // chemokine (C-X3-C) receptor 1 // 9 F4|9 // 13051 /// BC012653 //	2.02
10473356	**Ube2l6**	NM_019949 // Ube2l6 // ubiquitin-conjugating enzyme E2L 6 // 2|2 E1 // 56791 /// ENSMUS	2.02
10377473	**Aloxe3**	NM_011786 // Aloxe3 // arachidonate lipoxygenase 3 // 11 B3|11 37.0 cM // 23801 /// ENS	2.02
10425092	**Cyth4**	NM_028195 // Cyth4 // cytohesin 4 // 15 E1|15 // 72318 /// ENSMUST00000043069 // Cyth4	2.02
10401702	**Zdhhc22**	NM_001080943 // Zdhhc22 // zinc finger, DHHC-type containing 22 // 12 D2|12 // 238331 /	2.02
10476301	**Smox**	NM_001177833 // Smox // spermine oxidase // 2 F1|2 // 228608 /// NM_145533 // Smox // s	2.02
10521205	**Sh3bp2**	NM_001145859 // Sh3bp2 // SH3-domain binding protein 2 // 5 B2|5 // 24055 /// NM_001145	2.02
10462442	**Il33**	NM_001164724 // Il33 // interleukin 33 // 19|19 C2 // 77125 /// NM_133775 // Il33 // in	2.02
10408850	**Nedd9**	NM_001111324 // Nedd9 // neural precursor cell expressed, developmentally down-regulate	2.02
10439249	**Parp14**	NM_001039530 // Parp14 // poly (ADP-ribose) polymerase family, member 14 // 16 B3|16 //	2.01
10576883	**Shcbp1**	NM_011369 // Shcbp1 // Shc SH2-domain binding protein 1 // 8|8 A1.2 // 20419 /// ENSMUS	2.01
10403943	**Hist1h2bm**	NM_178200 // Hist1h2bm // histone cluster 1, H2bm // 13 A2-A3|13 // 319186 /// ENSMUST0	2.01
10592266	**Slc37a2**	NM_001145960 // Slc37a2 // solute carrier family 37 (glycerol-3-phosphate transporter),	2.01
10501164	**Csf1**	NM_007778 // Csf1 // colony stimulating factor 1 (macrophage) // 3 F3|3 51.0 cM // 1297	2.01
10408072	**Hist1h2ai**	NM_178182 // Hist1h2ai // histone cluster 1, H2ai // 13 A2-A3|13 // 319191 /// NM_17818	2.01
10520521	**Cenpa**	NM_007681 // Cenpa // centromere protein A // 5 B1|5 18.0 cM // 12615 /// ENSMUST000001	2.01
10501020	**Chi3l3**	NM_009892 // Chi3l3 // chitinase 3-like 3 // 3 F2.2|3 50.5 cM // 12655 /// ENSMUST00000	2.01
10446928	**Ltbp1**	NM_019919 // Ltbp1 // latent transforming growth factor beta binding protein 1 // 17|17	2.01
10408094	**Hist1h2ao**	NM_001177544 // Hist1h2ao // histone cluster 1, H2ao // 13 A3.1|13 // 665433 /// NM_178	2.00
10351781	**Kcnj10**	NM_001039484 // Kcnj10 // potassium inwardly-rectifying channel, subfamily J, member 10	2.00

10439483	**Arhgap31**	NM_020260 // Arhgap31 // Rho GTPase activating protein 31 // 16|16 B4 // 12549 /// ENSM	2.00
10511429	**Car8**	NM_007592 // Car8 // carbonic anhydrase 8 // 4 A1|4 7.7 cM // 12319 /// BC010773 // Car	2.00
10390186	**Abi3**	NM_025659 // Abi3 // ABI gene family, member 3 // 11 D|11 // 66610 /// NM_001163464 //	2.00
10407350	**Fgf10**	NM_008002 // Fgf10 // fibroblast growth factor 10 // 13 A3-A4|13 75.0 cM // 14165 /// E	-2.00
10481566	**Fibcd1**	NM_178887 // Fibcd1 // fibrinogen C domain containing 1 // 2 B|2 // 98970 /// BC060634	-2.00
10523483	**Prdm8**	NM_029947 // Prdm8 // PR domain containing 8 // 5 E3|5 // 77630 /// ENSMUST00000112959	-2.00
10492640	**Fstl5**	NM_178673 // Fstl5 // follistatin-like 5 // 3 E3|3 // 213262 /// ENSMUST00000038364 //	-2.02
10565156	**Homer2**	NM_011983 // Homer2 // homer homolog 2 (Drosophila) // 7 D3|7 // 26557 /// NM_001164086	-2.02
10387100	**Shisa6**	NM_001034874 // Shisa6 // shisa homolog 6 (Xenopus laevis) // 11 B3|11 // 380702 /// EN	-2.02
10540599	**Cpne9**	NM_170673 // Cpne9 // copine family member IX // 6 E3|6 // 211232 /// ENSMUST0000004120	-2.02
10435748	**D930030D11Rik**	ENSMUST00000057001 // D930030D11Rik // RIKEN cDNA D930030D11 gene // 16 B4|16 // 320874	-2.02
10525134	**Rasal1**	NM_013832 // Rasal1 // RAS protein activator like 1 (GAP1 like) // 5 F|5 // 19415 /// E	-2.03
10600901	**Ar**	NM_013476 // Ar // androgen receptor // X C3|X 36.0 cM // 11835 /// ENSMUST00000052837	-2.03
10349208	**Cntnap5a**	NM_001077425 // Cntnap5a // contactin associated protein-like 5A // 1 E2.3|1 // 636808	-2.05
10572928	**Rasd2**	NM_029182 // Rasd2 // RASD family, member 2 // 8 C1|8 // 75141 /// ENSMUST00000139848 /	-2.05
10430297	**Pvalb**	NM_013645 // Pvalb // parvalbumin // 15 E|15 45.7 cM // 19293 /// ENSMUST00000005860 //	-2.06
10416505	**Kctd4**	NM_026214 // Kctd4 // potassium channel tetramerisation domain containing 4 // 14|14 D2	-2.06
10485840	**Ryr3**	NM_177652 // Ryr3 // ryanodine receptor 3 // 2|2 E5-F3 // 20192 /// BC116740 // Ryr3 //	-2.07
10386455	**Rasd1**	NM_009026 // Rasd1 // RAS, dexamethasone-induced 1 // 11|11 B2 // 19416 /// ENSMUST0000	-2.07
10385826	**Ankrd43**	NM_183173 // Ankrd43 // ankyrin repeat domain 43 // 11 B1.3|11 // 237761 /// ENSMUST000	-2.08
10606366	**Zcchc5**	NM_199468 // Zcchc5 // zinc finger, CCHC domain containing 5 // X D|X // 213436 /// ENS	-2.08
10572282	**Hapln4**	NM_177900 // Hapln4 // hyaluronan and proteoglycan link protein 4 // 8 B3.3|8 // 330790	-2.09
10449608	**Mdga1**	NM_001081160 // Mdga1 // MAM domain containing glycosylphosphatidylinositol anchor 1 //	-2.09
10557308	**Hs3st4**	ENSMUST00000106437 // Hs3st4 // heparan sulfate (glucosamine) 3-O-sulfotransferase 4 //	-2.10
10431935	**Amigo2**	NM_178114 // Amigo2 // adhesion molecule with Ig like domain 2 // 15 F1|15 // 105827 //	-2.10
10578794	**Galntl6**	NM_175032 // Galntl6 // UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactos	-2.10
10536363	**Tac1**	NM_009311 // Tac1 // tachykinin 1 // 6 A1|6 5.0 cM // 21333 /// ENSMUST00000090679 // T	-2.11
10465500	**Kcnk4**	NM_008431 // Kcnk4 // potassium channel, subfamily K, member 4 // 19 A|19 4.5 cM // 165	-2.11
10446309	**Cntnap5c**	NM_001081653 // Cntnap5c // contactin	-2.12

		associated protein-like 5C // 17 D|17 // 620292 /	
10492628	**Serpini1**	NM_009250 // Serpini1 // serine (or cysteine) peptidase inhibitor, clade I, member 1 //	-2.12
10460123	**9330132A10Rik**	BC098197 // 9330132A10Rik // RIKEN cDNA 9330132A10 gene // 18 E4|18 // 319609	-2.12
10563253	**Lin7b**	NM_011698 // Lin7b // lin-7 homolog B (C. elegans) // 7|7 B2 // 22342 /// NR_027802 //	-2.12
10345855	**Slc9a2**	NM_001033289 // Slc9a2 // solute carrier family 9 (sodium/hydrogen exchanger), member 2	-2.13
10436519	**Robo1**	NM_019413 // Robo1 // roundabout homolog 1 (Drosophila) // 16 C3.1|16 // 19876 /// ENSM	-2.13
10367691	**Iyd**	NM_027391 // Iyd // iodotyrosine deiodinase // 10 A1|10 // 70337 /// ENSMUST00000019896	-2.14
10538408	**2410066E13Rik**	BC042507 // 2410066E13Rik // RIKEN cDNA 2410066E13 gene // 6 B3|6 // 68235 /// ENSMUST0	-2.14
10498921	**Tdo2**	NM_019911 // Tdo2 // tryptophan 2,3-dioxygenase // 3 E3|3 // 56720 /// ENSMUST000000296	-2.16
10389786	**Hlf**	NM_172563 // Hlf // hepatic leukemia factor // 11 C-D|11 52.0 cM // 217082 /// ENSMUST0	-2.17
10357339	**Lypd1**	NM_145100 // Lypd1 // Ly6/Plaur domain containing 1 // 1 E3|1 // 72585 /// NM_027677 //	-2.19
10566723	**Lmo1**	NM_057173 // Lmo1 // LIM domain only 1 // 7 E3|7 51.5 cM // 109594 /// ENSMUST000000369	-2.19
10588755	**Camkv**	NM_145621 // Camkv // CaM kinase-like vesicle-associated // 9 F1|9 // 235604 /// ENSMUS	-2.21
10344935	**Kcnb2**	NM_001098528 // Kcnb2 // potassium voltage gated channel, Shab-related subfamily, membe	-2.22
10491212	**Egfem1**	NM_029412 // Egfem1 // EGF-like and EMI domain containing 1 // 3 A3|3 // 75740 /// NM_0	-2.22
10499285	**Bcan**	NM_007529 // Bcan // brevican // 3 F1|3 42.7 cM // 12032 /// NM_001109758 // Bcan // br	-2.23
10608705	**---**	---	-2.24
10427796	**Npr3**	NM_008728 // Npr3 // natriuretic peptide receptor 3 // 15 A1|15 6.7 cM // 18162 /// NM_	-2.24
10496975	**Slc44a5**	NM_001081263 // Slc44a5 // solute carrier family 44, member 5 // 3 H3-H4|3 // 242259 //	-2.24
10355278	**Erbb4**	NM_010154 // Erbb4 // v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	-2.24
10357418	**Lct**	NM_001081078 // Lct // lactase // 1 E4|1 65.9 cM // 226413 /// ENSMUST00000073490 // Lc	-2.24
10537851	**Cntnap2**	NM_001004357 // Cntnap2 // contactin associated protein-like 2 // 6|6 B2 // 66797 /// N	-2.25
10565218	**Il16**	NM_010551 // Il16 // interleukin 16 // 7 D2-D3|7 41.2 cM // 16170 /// BC058709 // Il16	-2.26
10459496	**Ccbe1**	NM_178793 // Ccbe1 // collagen and calcium binding EGF domains 1 // 18 E1|18 // 320924	-2.27
10585484	**Chrna5**	NM_176844 // Chrna5 // cholinergic receptor, nicotinic, alpha polypeptide 5 // 9 B|9 32	-2.27
10543369	**Cadps2**	NM_153163 // Cadps2 // Ca2+-dependent activator protein for secretion 2 // 6 A3.1|6 //	-2.27
10483624	**Dlx1as**	NR_002854 // Dlx1as // distal-less homeobox 1, antisense // 2 C2|2 44.0 cM // 111970	-2.28
10367828	**Grm1**	ENSMUST00000044306 // Grm1 // glutamate receptor, metabotropic 1 // 10|10 A2 // 14816 /	-2.28
10432278	**Ddn**	NM_001013741 // Ddn // dendrin // 15 F1|15 60.4 cM // 13199 /// ENSMUST00000075444 // D	-2.29
10503647	**Gpr63**	NM_030733 // Gpr63 // G protein-coupled	-2.29

		receptor 63 // 4 A3|4 // 81006 /// ENSMUST00000	
10496077	**Agxt2l1**	NM_027907 // Agxt2l1 // alanine-glyoxylate aminotransferase 2-like 1 // 3 G3|3 // 71760	-2.29
10443898	**Cyp4f15**	NM_134127 // Cyp4f15 // cytochrome P450, family 4, subfamily f, polypeptide 15 // 17 B1	-2.31
10483131	**Kcnh7**	NM_133207 // Kcnh7 // potassium voltage-gated channel, subfamily H (eag-related), membe	-2.31
10360666	**6330403A02Rik**	BC120654 // 6330403A02Rik // RIKEN cDNA 6330403A02 gene // 1 H4|1 // 381310 /// NM_0010	-2.33
10440216	**Epha6**	NM_007938 // Epha6 // Eph receptor A6 // 16 C1.3|16 // 13840 /// ENSMUST00000068860 //	-2.37
10360664	**6330403A02Rik**	ENSMUST00000136521 // 6330403A02Rik // RIKEN cDNA 6330403A02 gene // 1 H4|1 // 381310 /	-2.37
10372106	**Epyc**	ENSMUST00000105285 // Epyc // epiphycan // 10 C2-C3|10 55.0 cM // 13516 /// NR_033537 /	-2.38
10468113	**Kcnip2**	NM_145703 // Kcnip2 // Kv channel-interacting protein 2 // 19 D1|19 45.2 cM // 80906 //	-2.39
10377490	**Alox12b**	NM_009659 // Alox12b // arachidonate 12-lipoxygenase, 12R type // 11 B3|11 37.0 cM // 1	-2.41
10588380	**Cpne4**	NM_028719 // Cpne4 // copine IV // 9 F1|9 // 74020 /// ENSMUST00000057742 // Cpne4 // c	-2.45
10475019	**Itpka**	NM_146125 // Itpka // inositol 1,4,5-trisphosphate 3-kinase A // 2 E5|2 // 228550 /// E	-2.45
10372421	**Trhde**	NM_146241 // Trhde // TRH-degrading enzyme // 10 D2|10 // 237553 /// ENSMUST00000061632	-2.46
10407591	**Chrm3**	NM_033269 // Chrm3 // cholinergic receptor, muscarinic 3, cardiac // 13 A1|13 7.0 cM //	-2.48
10589407	**Spink8**	NM_183136 // Spink8 // serine peptidase inhibitor, Kazal type 8 // 9 F2|9 // 78709 ///	-2.52
10433887	**Pkp2**	NM_026163 // Pkp2 // plakophilin 2 // 16|16 B1 // 67451 /// ENSMUST00000039408 // Pkp2	-2.52
10351298	**Gpr161**	NM_001081126 // Gpr161 // G protein-coupled receptor 161 // 1 H2.3|1 89.7 cM // 240888	-2.55
10446312	**Cntnap5c**	NM_001081653 // Cntnap5c // contactin associated protein-like 5C // 17 D|17 // 620292 /	-2.55
10584549	**Scn3b**	NM_178227 // Scn3b // sodium channel, voltage-gated, type III, beta // 9 A5.1|9 // 2352	-2.59
10381096	**Igfbp4**	NM_010517 // Igfbp4 // insulin-like growth factor binding protein 4 // 11 D|11 // 16010	-2.59
10578786	**Galntl6**	NM_175032 // Galntl6 // UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactos	-2.64
10353460	**Kcnq5**	NM_001160139 // Kcnq5 // potassium voltage-gated channel, subfamily Q, member 5 // 1|1	-2.66
10565152	**Homer2**	NM_011983 // Homer2 // homer homolog 2 (Drosophila) // 7 D3|7 // 26557 /// NM_001164086	-2.66
10578796	**Galntl6**	NM_175032 // Galntl6 // UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactos	-2.67
10607169	**Trpc5**	NM_009428 // Trpc5 // transient receptor potential cation channel, subfamily C, member	-2.74
10476482	**6330527O06Rik**	NM_029530 // 6330527O06Rik // RIKEN cDNA 6330527O06 gene // 2 F3|2 // 76161 /// ENSMUST	-2.78
10535732	**Gpr12**	NM_001010941 // Gpr12 // G-protein coupled receptor 12 // 5 G3|5 // 14738 /// NM_008151	-2.90
10544936	**Neurod6**	NM_009717 // Neurod6 // neurogenic differentiation 6 // 6 B3|6 29.0 cM // 11922 /// ENS	-2.90
10366391	**Kcnc2**	NM_001025581 // Kcnc2 // potassium voltage gated channel, Shaw-related subfamily, membe	-2.90

10548899	**Rerg**	NM_181988 // Rerg // RAS-like, estrogen-regulated, growth-inhibitor // 6 G1|6 // 232441	-2.91
10536949	**Fam40b**	NM_177204 // Fam40b // family with sequence similarity 40, member B // 6 A3.3|6 // 3206	-2.92
10341762	**---**	---	-3.03
10342598	**---**	---	-3.50
10407435	**Akr1c18**	NM_134066 // Akr1c18 // aldo-keto reductase family 1, member C18 // 13 A1|13 // 105349	-3.73

APPENDIX 3

Significantly changed transcripts at 30 days post injection, in KA- vs. saline - injected mice hippocampi. Thresholds: 2-fold, FDR-adjusted p-value< 0.01

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change 30 days
10476945	**Cst7**	NM_009977 // Cst7 // cystatin F (leukocystatin) // 2|2 G1-G3 // 13011 /// ENSMUST000000	15.53
10481627	**Lcn2**	NM_008491 // Lcn2 // lipocalin 2 // 2 A3|2 27.0 cM // 16819 /// ENSMUST00000050785 // L	9.26
10411527	**Cartpt**	NM_013732 // Cartpt // CART prepropeptide // 13|13 D1 // 27220 /// NM_001081493 // Cart	8.30
10389231	**Ccl3**	NM_011337 // Ccl3 // chemokine (C-C motif) ligand 3 // 11 C|11 47.59 cM // 20302 /// EN	7.75
10473384	**Slc43a3**	NM_021398 // Slc43a3 // solute carrier family 43, member 3 // 2 E1|2 // 58207 /// ENSMU	7.58
10520946	**Plb1**	NM_001081407 // Plb1 // phospholipase B1 // 5 B1|5 // 665270 /// ENSMUST00000101376 //	6.58
10530029	**Lgi2**	NM_144945 // Lgi2 // leucine-rich repeat LGI family, member 2 // 5 C1|5 // 246316 /// E	6.06
10452316	**C3**	NM_009778 // C3 // complement component 3 // 17 E1-E3|17 34.3 cM // 12266 /// ENSMUST00	6.04
10523717	**Spp1**	NM_009263 // Spp1 // secreted phosphoprotein 1 // 5 E5|5 56.0 cM // 20750 /// ENSMUST00	5.89
10578880	**Tll1**	NM_009390 // Tll1 // tolloid-like // 8 B3.1|8 32.4 cM // 21892 /// ENSMUST00000066166 /	5.87
10548375	**Clec7a**	NM_020008 // Clec7a // C-type lectin domain family 7, member a // 6 F3|6 // 56644 /// E	5.72
10541354	**A2m**	NM_175628 // A2m // alpha-2-macroglobulin // 6 F1|6 61.7 cM // 232345 /// ENSMUST000000	5.46
10427471	**Osmr**	NM_011019 // Osmr // oncostatin M receptor // 15 A1|15 4.6 cM // 18414 /// ENSMUST00000	5.40
10393573	**Lgals3bp**	NM_011150 // Lgals3bp // lectin, galactoside-binding, soluble, 3 binding protein // 11|	5.32
10520944	**Plb1**	NM_001081407 // Plb1 // phospholipase B1 // 5 B1|5 // 665270 /// ENSMUST00000101376 //	5.30
10538187	**Gpnmb**	NM_053110 // Gpnmb // glycoprotein (transmembrane) nmb // 6 B2.3|6 21.0 cM // 93695 ///	5.25
10531415	**Cxcl10**	NM_021274 // Cxcl10 // chemokine (C-X-C motif) ligand 10 // 5 E2|5 53.0 cM // 15945 ///	5.24
10372648	**Lyz2**	NM_017372 // Lyz2 // lysozyme 2 // 10 D2|10 66.0 cM // 17105 /// ENSMUST00000092163 //	5.13
10349968	**Chi3l1**	NM_007695 // Chi3l1 // chitinase 3-like 1 // 1 E4|1 72.3 cM // 12654 /// ENSMUST0000015	4.83
10387536	**Cd68**	NM_009853 // Cd68 // CD68 antigen // 11 B3|11 39.0 cM // 12514 /// ENSMUST00000108654 /	4.72
10361818	**Nmbr**	NM_008703 // Nmbr // neuromedin B receptor // 10 A2|10 // 18101 /// ENSMUST00000020015	4.71
10517165	**Cd52**	NM_013706 // Cd52 // CD52 antigen // 4 D3|4 73.5 cM // 23833 /// ENSMUST00000000696 //	4.69
10566358	**Trim30a**	NM_009099 // Trim30a // tripartite motif-containing 30A // 7 E3|7 50.4 cM // 20128 ///	4.68
10461721	**Mpeg1**	NM_010821 // Mpeg1 // macrophage expressed gene 1 // 19 A|19 // 17476 /// ENSMUST000000	4.66
10587799	**Plscr2**	NM_001195084 // Plscr2 // phospholipid scramblase 2 // 9 E3.3|9 // 18828 /// NM_008880	4.64

10445141	**Olfr111**	NM_001005485 // Olfr111 // olfactory receptor 111 // 17 B1|17 // 545205 /// ENSMUST0000	4.64
10474381	**Kif18a**	NM_139303 // Kif18a // kinesin family member 18A // 2 E3|2 // 228421 /// ENSMUST0000002	4.61
10389222	**Ccl6**	NM_009139 // Ccl6 // chemokine (C-C motif) ligand 6 // 11 C|11 47.51 cM // 20305 /// EN	4.52
10547657	**C3ar1**	NM_009779 // C3ar1 // complement component 3a receptor 1 // 6|6 F1 // 12267 /// ENSMUST	4.50
10406928	**Cd180**	NM_008533 // Cd180 // CD180 antigen // 13 D1|13 // 17079 /// ENSMUST00000022124 // Cd18	4.43
10405179	**S1pr3**	NM_010101 // S1pr3 // sphingosine-1-phosphate receptor 3 // 13|13 B1 // 13610 /// ENSMU	4.40
10379731	**Expi**	NM_007969 // Expi // extracellular proteinase inhibitor // 11 C|11 // 14038 /// ENSMUST	4.40
10502655	**Cyr61**	NM_010516 // Cyr61 // cysteine rich protein 61 // 3 H2|3 72.9 cM // 16007 /// ENSMUST00	4.40
10462618	**Ifit3**	NM_010501 // Ifit3 // interferon-induced protein with tetratricopeptide repeats 3 // 19	4.36
10531737	**Hpse**	NM_152803 // Hpse // heparanase // 5 E4|5 // 15442 /// ENSMUST00000045617 // Hpse // he	4.36
10517517	**C1qa**	NM_007572 // C1qa // complement component 1, q subcomponent, alpha polypeptide // 4 D3|	4.28
10420114	**Tgm1**	NM_001161715 // Tgm1 // transglutaminase 1, K polypeptide // 14|14 C1 // 21816 /// NM_0	4.25
10444780	**H2-D1**	NM_010380 // H2-D1 // histocompatibility 2, D region locus 1 // 17 B1|17 19.09 cM // 14	4.22
10450075	**H2-K1**	NM_001001892 // H2-K1 // histocompatibility 2, K1, K region // 17 B1|17 18.44 cM // 149	4.15
10382106	**Gm885**	NM_001033435 // Gm885 // predicted gene 885 // 11 E1|11 // 380732 /// ENSMUST0000010679	4.15
10360028	**Fcgr2b**	NM_001077189 // Fcgr2b // Fc receptor, IgG, low affinity IIb // 1 H3|1 92.3 cM // 14130	4.13
10601569	**Pcdh11x**	NM_001081385 // Pcdh11x // protocadherin 11 X-linked // X E2|X // 245578 /// ENSMUST000	4.12
10351679	**Cd84**	NM_013489 // Cd84 // CD84 antigen // 1 H3|1 93.3 cM // 12523 /// ENSMUST00000155802 //	4.09
10531484	**Ankrd56**	NM_175270 // Ankrd56 // ankyrin repeat domain 56 // 5 E2|5 // 78088 /// ENSMUST00000061	4.08
10360377	**AI607873**	BC150711 // AI607873 // expressed sequence AI607873 // 1 H3|1 // 226691 /// ENSMUST0000	4.05
10546417	**Trh**	NM_009426 // Trh // thyrotropin releasing hormone // 6 D1|6 40.0 cM // 22044 /// ENSMUS	3.99
10606016	**Il2rg**	NM_013563 // Il2rg // interleukin 2 receptor, gamma chain // X D|X 38.0 cM // 16186 ///	3.97
10557895	**Itgax**	NM_021334 // Itgax // integrin alpha X // 7 F3|7 // 16411 /// ENSMUST00000033053 // Itg	3.93
10569017	**Ifitm3**	NM_025378 // Ifitm3 // interferon induced transmembrane protein 3 // 7 F5|7 // 66141 //	3.90
10551883	**Tyrobp**	NM_011662 // Tyrobp // TYRO protein tyrosine kinase binding protein // 7 B|7 10.0 cM //	3.89
10524621	**Oasl2**	NM_011854 // Oasl2 // 2'-5' oligoadenylate synthetase-like 2 // 5 F|5 // 23962 /// ENSM	3.85
10450242	**C4b**	NM_009780 // C4b // complement component 4B (Childo blood group) // 17 B1|17 18.8 cM //	3.84
10404606	**Ly86**	NM_010745 // Ly86 // lymphocyte antigen 86 // 13 A3.3|13 // 17084 /// ENSMUST0000002186	3.80
10382321	**Kcnj2**	NM_008425 // Kcnj2 // potassium inwardly-rectifying channel, subfamily J, member 2 // 1	3.77

10499189	**Fcrls**	NM_030707 // Fcrls // Fc receptor-like S, scavenger receptor // 3 F1|3 // 80891 /// ENS	3.76
10402211	**Fbln5**	NM_011812 // Fbln5 // fibulin 5 // 12|12 F1 // 23876 /// ENSMUST00000021603 // Fbln5 //	3.76
10587733	**Ctsh**	NM_007801 // Ctsh // cathepsin H // 9 E3.1|9 50.0 cM // 13036 /// ENSMUST00000034915 //	3.74
10379727	**Gm11428**	NM_001081957 // Gm11428 // predicted gene 11428 // 11 C|11 // 100034251 /// FJ007372 //	3.73
10551966	**Hspb6**	NM_001012401 // Hspb6 // heat shock protein, alpha-crystallin-related, B6 // 7 B1|7 //	3.71
10517513	**C1qc**	NM_007574 // C1qc // complement component 1, q subcomponent, C chain // 4 D3|4 66.1 cM	3.70
10485405	**Cd44**	NM_009851 // Cd44 // CD44 antigen // 2 E2|2 56.0 cM // 12505 /// NM_001177785 // Cd44 /	3.67
10519717	**Sema3a**	NM_009152 // Sema3a // sema domain, immunoglobulin domain (Ig), short basic domain, sec	3.63
10566366	**Trim30d**	NM_199146 // Trim30d // tripartite motif-containing 30D // 7 E3|7 // 209387 /// NM_0011	3.62
10363082	**Lilrb4**	NM_013532 // Lilrb4 // leukocyte immunoglobulin-like receptor, subfamily B, member 4 //	3.61
10462621	**I830012O16Rik**	NM_001005858 // I830012O16Rik // RIKEN cDNA I830012O16 gene // 19 C1|19 // 667370 /// E	3.61
10482059	**Ggta1**	NM_010283 // Ggta1 // glycoprotein galactosyltransferase alpha 1, 3 // 2 B|2 25.0 cM //	3.61
10384458	**Plek**	NM_019549 // Plek // pleckstrin // 11 A2|11 6.5 cM // 56193 /// ENSMUST00000102881 // P	3.60
10358399	**Rgs13**	NM_153171 // Rgs13 // regulator of G-protein signaling 13 // 1 F|1 78.0 cM // 246709 //	3.59
10462922	**Plce1**	NM_019588 // Plce1 // phospholipase C, epsilon 1 // 19 D1|19 // 74055 /// ENSMUST000000	3.58
10552516	**Klk6**	NM_011177 // Klk6 // kallikrein related-peptidase 6 // 7 B4-B5|7 24.0 cM // 19144 /// N	3.58
10388430	**Serpinf1**	NM_011340 // Serpinf1 // serine (or cysteine) peptidase inhibitor, clade F, member 1 //	3.57
10595402	**Fam46a**	NM_001160378 // Fam46a // family with sequence similarity 46, member A // 9 E3.1|9 // 2	3.56
10490212	**Ctsz**	NM_022325 // Ctsz // cathepsin Z // 2 H4|2 103.5 cM // 64138 /// ENSMUST00000016400 //	3.53
10600169	**Bgn**	NM_007542 // Bgn // biglycan // X B|X 29.3 cM // 12111 /// ENSMUST00000033741 // Bgn //	3.50
10445781	**Trem2**	NM_031254 // Trem2 // triggering receptor expressed on myeloid cells 2 // 17 C|17 // 83	3.50
10494271	**Ctss**	NM_021281 // Ctss // cathepsin S // 3 F2.1|3 42.7 cM // 13040 /// ENSMUST00000015667 //	3.48
10512470	**Cd72**	NM_001110320 // Cd72 // CD72 antigen // 4 B1|4 22.5 cM // 12517 /// NM_007654 // Cd72 /	3.48
10422760	**Fyb**	NM_011815 // Fyb // FYN binding protein // 15 A1|15 // 23880 /// ENSMUST00000090461 //	3.46
10496592	**Gbp2**	NM_010260 // Gbp2 // guanylate binding protein 2 // 3 H1|3 67.4 cM // 14469 /// ENSMUST	3.46
10388440	**Serpinf2**	NM_008878 // Serpinf2 // serine (or cysteine) peptidase inhibitor, clade F, member 2 //	3.44
10555323	**P4ha3**	NM_177161 // P4ha3 // procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydr	3.43
10360382	**Ifi204**	NM_008329 // Ifi204 // interferon activated gene 204 // 1 H3|1 95.2 cM // 15951 /// NM_	3.42

10469058	**Ucma**	NM_001113558 // Ucma // upper zone of growth plate and cartilage matrix associated // 2	3.40
10530841	**Igfbp7**	NM_001159518 // Igfbp7 // insulin-like growth factor binding protein 7 // 5 C3.3|5 // 2	3.38
10600994	**Arr3**	NM_133205 // Arr3 // arrestin 3, retinal // X|X C2 // 170735 /// ENSMUST00000113769 //	3.37
10446282	**Emr1**	NM_010130 // Emr1 // EGF-like module containing, mucin-like, hormone receptor-like sequ	3.35
10444814	**H2-gs10**	NM_001143689 // H2-gs10 // MHC class I like protein GS10 // 17 B1|17 // 436493 /// NM_0	3.35
10502791	**Ifi44**	NM_133871 // Ifi44 // interferon-induced protein 44 // 3 H3|3 // 99899 /// ENSMUST00000	3.35
10595668	**Ankrd34c**	NM_207260 // Ankrd34c // ankyrin repeat domain 34C // 9 E3.1|9 // 330998 /// ENSMUST000	3.35
10501063	**Cd53**	NM_007651 // Cd53 // CD53 antigen // 3 F2.3|3 50.5 cM // 12508 /// ENSMUST00000038845 /	3.33
10339333	**---**	---	3.33
10483706	**Chrna1**	NM_007389 // Chrna1 // cholinergic receptor, nicotinic, alpha polypeptide 1 (muscle) //	3.32
10601385	**Tlr13**	NM_205820 // Tlr13 // toll-like receptor 13 // X D|X // 279572 /// ENSMUST00000040065 /	3.32
10484463	**Serping1**	NM_009776 // Serping1 // serine (or cysteine) peptidase inhibitor, clade G, member 1 //	3.31
10607085	**Kcne1l**	NM_021487 // Kcne1l // potassium voltage-gated channel, Isk-related family, member 1-li	3.31
10416406	**Htr2a**	NM_172812 // Htr2a // 5-hydroxytryptamine (serotonin) receptor 2A // 14 D2|14 41.5 cM /	3.30
10447502	**Adcyap1**	NM_009625 // Adcyap1 // adenylate cyclase activating polypeptide 1 // 17 E5|17 // 11516	3.29
10344897	**Sulf1**	NM_001198565 // Sulf1 // sulfatase 1 // 1 A3|1 // 240725 /// NM_172294 // Sulf1 // sulf	3.27
10439312	**Cd86**	NM_019388 // Cd86 // CD86 antigen // 16 B5|16 26.9 cM // 12524 /// ENSMUST00000089620 /	3.25
10571840	**Hpgd**	NM_008278 // Hpgd // hydroxyprostaglandin dehydrogenase 15 (NAD) // 8 B3.2|8 // 15446 /	3.25
10500610	**Fam46c**	NM_001142952 // Fam46c // family with sequence similarity 46, member C // 3 F2.2|3 // 7	3.24
10595404	**Fam46a**	NM_001160378 // Fam46a // family with sequence similarity 46, member A // 9 E3.1|9 // 2	3.23
10433172	**Glycam1**	NM_008134 // Glycam1 // glycosylation dependent cell adhesion molecule 1 // 15 F3|15 63	3.23
10462623	**Ifit1**	NM_008331 // Ifit1 // interferon-induced protein with tetratricopeptide repeats 1 // 19	3.22
10461614	**Ms4a6c**	NM_028595 // Ms4a6c // membrane-spanning 4-domains, subfamily A, member 6C // 19 A|19 /	3.22
10469322	**Vim**	NM_011701 // Vim // vimentin // 2 A2|2 7.0 cM // 22352 /// ENSMUST00000028062 // Vim //	3.21
10517508	**C1qb**	NM_009777 // C1qb // complement component 1, q subcomponent, beta polypeptide // 4 D3|4	3.19
10498379	**Igsf10**	NM_001162884 // Igsf10 // immunoglobulin superfamily, member 10 // 3 D|3 // 242050 ///	3.17
10362201	**Ctgf**	NM_010217 // Ctgf // connective tissue growth factor // 10 A3-B1|10 17.0 cM // 14219 //	3.17
10523451	**Anxa3**	NM_013470 // Anxa3 // annexin A3 // 5 E3|5 54.0 cM // 11745 /// ENSMUST00000031447 // A	3.17
10598976	**Timp1**	NM_001044384 // Timp1 // tissue inhibitor of	3.14

		metalloproteinase 1 // X A1.3|X 6.2 cM //	
10602261	**Htr2c**	NM_008312 // Htr2c // 5-hydroxytryptamine (serotonin) receptor 2C // X D-F4|X 66.15 cM	3.14
10548030	**Cd9**	NM_007657 // Cd9 // CD9 antigen // 6 F3|6 58.0 cM // 12527 /// ENSMUST00000032492 // Cd	3.13
10514275	**Ptplad2**	NM_025760 // Ptplad2 // protein tyrosine phosphatase-like A domain containing 2 // 4 C4	3.13
10369615	**Srgn**	NM_011157 // Srgn // serglycin // 10 B4|10 // 19073 /// ENSMUST00000160987 // Srgn // s	3.12
10452419	**Efna5**	NM_207654 // Efna5 // ephrin A5 // 17 E1.1|17 33.5 cM // 13640 /// NM_010109 // Efna5 /	3.11
10360040	**Fcgr3**	NM_010188 // Fcgr3 // Fc receptor, IgG, low affinity III // 1 H3|1 92.3 cM // 14131 ///	3.11
10508663	**Laptm5**	NM_010686 // Laptm5 // lysosomal-associated protein transmembrane 5 // 4 D2.3|4 // 1679	3.10
10434778	**Rtp4**	NM_023386 // Rtp4 // receptor transporter protein 4 // 16 B1|16 // 67775 /// ENSMUST000	3.09
10444830	**H2-Q7**	NM_010394 // H2-Q7 // histocompatibility 2, Q region locus 7 // 17 B1|17 19.19 cM // 15	3.08
10607870	**Tlr7**	NM_133211 // Tlr7 // toll-like receptor 7 // X F5|X // 170743 /// ENSMUST00000112164 //	3.05
10360070	**Fcer1g**	NM_010185 // Fcer1g // Fc receptor, IgE, high affinity I, gamma polypeptide // 1 H3|1 9	3.05
10351509	**Fcgr4**	NM_144559 // Fcgr4 // Fc receptor, IgG, low affinity IV // 1 H3|1 92.29 cM // 246256 //	3.04
10523359	**Cxcl13**	NM_018866 // Cxcl13 // chemokine (C-X-C motif) ligand 13 // 5 E3|5 // 55985 /// ENSMUST	3.04
10474399	**Bdnf**	NM_001048139 // Bdnf // brain derived neurotrophic factor // 2 E3|2 62.0 cM // 12064 //	3.03
10358224	**Ptprc**	NM_001111316 // Ptprc // protein tyrosine phosphatase, receptor type, C // 1 E4|1 74.0	3.01
10498383	**Igsf10**	NM_001162884 // Igsf10 // immunoglobulin superfamily, member 10 // 3 D|3 // 242050 ///	3.01
10595059	**Hcrtr2**	NM_198962 // Hcrtr2 // hypocretin (orexin) receptor 2 // 9 D|9 // 387285 /// ENSMUST000	3.01
10520043	**Lhfpl3**	NM_029990 // Lhfpl3 // lipoma HMGIC fusion partner-like 3 // 5 A3|5 // 269629 /// NM_00	3.01
10498386	**Igsf10**	NM_001162884 // Igsf10 // immunoglobulin superfamily, member 10 // 3 D|3 // 242050	2.99
10541307	**Usp18**	NM_011909 // Usp18 // ubiquitin specific peptidase 18 // 6 F|6 56.0 cM // 24110 /// ENS	2.99
10466712	**Mamdc2**	NM_174857 // Mamdc2 // MAM domain containing 2 // 19 B|19 // 71738 /// ENSMUST000000360	2.98
10600836	**Msn**	NM_010833 // Msn // moesin // X C3|X // 17698 /// ENSMUST00000117399 // Msn // moesin /	2.98
10360158	**Ly9**	NM_008534 // Ly9 // lymphocyte antigen 9 // 1 H3|1 93.3 cM // 17085 /// ENSMUST00000068	2.96
10547621	**Apobec1**	NM_031159 // Apobec1 // apolipoprotein B mRNA editing enzyme, catalytic polypeptide 1 /	2.95
10383198	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.95
10436456	**Pros1**	NM_011173 // Pros1 // protein S (alpha) // 16 C1.3|16 // 19128 /// ENSMUST00000023629 /	2.91
10464905	**Npas4**	NM_153553 // Npas4 // neuronal PAS domain protein 4 // 19 A|19 // 225872 /// ENSMUST000	2.90
10440522	**Adamts1**	NM_009621 // Adamts1 // a disintegrin-like and metallopeptidase (reprolysin type) with	2.90
10341334	**---**	---	2.90
10520923	**Plb1**	NM_001081407 // Plb1 // phospholipase B1 // 5	2.89

		B1|5 // 665270 /// NM_172147 // Plb1 // p	
10364262	**Itgb2**	NM_008404 // Itgb2 // integrin beta 2 // 10 C1|10 41.5 cM // 16414 /// M31039 // Itgb2	2.89
10586781	**Myo1e**	NM_181072 // Myo1e // myosin IE // 9 D|9 41.0 cM // 71602 /// ENSMUST00000034745 // Myo	2.89
10557862	**Itgam**	NM_001082960 // Itgam // integrin alpha M // 7|7 F4 // 16409 /// NM_008401 // Itgam //	2.88
10547906	**Lag3**	NM_008479 // Lag3 // lymphocyte-activation gene 3 // 6 F2|6 // 16768 /// ENSMUST0000003	2.87
10566326	**Trim12a**	NM_023835 // Trim12a // tripartite motif-containing 12A // 7 E3|7 // 76681 /// BC094899	2.86
10511363	**Penk**	NM_001002927 // Penk // preproenkephalin // 4 A1|4 0.8 cM // 18619 /// ENSMUST000000703	2.86
10603551	**Cybb**	NM_007807 // Cybb // cytochrome b-245, beta polypeptide // X A1.1|X // 13058 /// ENSMUS	2.85
10358389	**Rgs2**	NM_009061 // Rgs2 // regulator of G-protein signaling 2 // 1 F|1 78.0 cM // 19735 /// E	2.85
10375443	**Havcr2**	NM_134250 // Havcr2 // hepatitis A virus cellular receptor 2 // 11 B1.1|11 // 171285 //	2.85
10498992	**Tlr2**	NM_011905 // Tlr2 // toll-like receptor 2 // 3 E3|3 // 24088 /// ENSMUST00000029623 //	2.85
10411622	**Naip6**	NM_010871 // Naip6 // NLR family, apoptosis inhibitory protein 6 // 13 D1|13 55.0 cM //	2.85
10586744	**Anxa2**	NM_007585 // Anxa2 // annexin A2 // 9 C|9 37.0 cM // 12306 /// ENSMUST00000034756 // An	2.84
10544273	**Clec5a**	NM_001038604 // Clec5a // C-type lectin domain family 5, member a // 6|6 B2 // 23845 //	2.84
10339785	**---**	---	2.84
10554249	**Acan**	NM_007424 // Acan // aggrecan // 7 D3|7 39.0 cM // 11595 /// ENSMUST00000032835 // Acan	2.84
10348244	**Inpp5d**	NM_010566 // Inpp5d // inositol polyphosphate-5-phosphatase D // 1 C5|1 57.0 cM // 1633	2.82
10384985	**Rhbdf1**	NM_010117 // Rhbdf1 // rhomboid family 1 (Drosophila) // 11 A4|11 16.0 cM // 13650 ///	2.82
10385118	**Dock2**	NM_033374 // Dock2 // dedicator of cyto-kinesis 2 // 11|11 A5 // 94176 /// ENSMUST00000	2.81
10351658	**Cd48**	NM_007649 // Cd48 // CD48 antigen // 1 H3|1 93.3 cM // 12506 /// ENSMUST00000068584 //	2.81
10385500	**Irgm1**	NM_008326 // Irgm1 // immunity-related GTPase family M member 1 // 11 B1.2|11 // 15944	2.81
10398075	**Serpina3n**	NM_009252 // Serpina3n // serine (or cysteine) peptidase inhibitor, clade A, member 3N	2.79
10597518	**Tgfbr2**	NM_009371 // Tgfbr2 // transforming growth factor, beta receptor II // 9 F3|9 69.0 cM /	2.78
10545101	**Hpgds**	NM_019455 // Hpgds // hematopoietic prostaglandin D synthase // 6|6 D-E // 54486 /// EN	2.78
10603116	**Asb11**	NM_026853 // Asb11 // ankyrin repeat and SOCS box-containing 11 // X F5|X // 68854 ///	2.78
10542993	**Pon3**	NM_173006 // Pon3 // paraoxonase 3 // 6 A1|6 0.5 cM // 269823 /// ENSMUST00000031773 //	2.77
10585398	**Gldn**	NM_177350 // Gldn // gliomedin // 9 A5.3|9 // 235379 /// ENSMUST00000056740 // Gldn //	2.77
10395659	**Coch**	NM_007728 // Coch // coagulation factor C homolog (Limulus polyphemus) // 12 C1|12 23.0	2.77
10474700	**Thbs1**	NM_011580 // Thbs1 // thrombospondin 1 // 2 F1-F3|2 65.0 cM // 21825 /// ENSMUST0000003	2.77
10385513	**9930111J21Rik2**	NM_173434 // 9930111J21Rik2 // RIKEN cDNA 9930111J21 gene 2 // 11 B1.2|11 // 245240 ///	2.76

10527441	**Arpc1b**	NM_023142 // Arpc1b // actin related protein 2/3 complex, subunit 1B // 5 G2|5 // 11867	2.76
10508074	**Csf3r**	NM_007782 // Csf3r // colony stimulating factor 3 receptor (granulocyte) // 4 D2.2|4 57	2.75
10467136	**Ch25h**	NM_009890 // Ch25h // cholesterol 25-hydroxylase // 19 C1|19 // 12642 /// ENSMUST000000	2.75
10604763	**Arpc1b**	NM_023142 // Arpc1b // actin related protein 2/3 complex, subunit 1B // 5 G2|5 // 11867	2.75
10503098	**Lyn**	NM_001111096 // Lyn // Yamaguchi sarcoma viral (v-yes-1) oncogene homolog // 4 A1|4 0.0	2.75
10606445	**Rps6ka6**	NM_025949 // Rps6ka6 // ribosomal protein S6 kinase polypeptide 6 // X E1|X // 67071 //	2.74
10527649	**6330406I15Rik**	BC116246 // 6330406I15Rik // RIKEN cDNA 6330406I15 gene // 5 G3|5 // 70717 /// NM_02751	2.74
10572024	**Spock3**	NM_023689 // Spock3 // sparc/osteonectin, cwcv and kazal-like domains proteoglycan 3 //	2.74
10452980	**Eif2ak2**	NM_011163 // Eif2ak2 // eukaryotic translation initiation factor 2-alpha kinase 2 // 17	2.74
10526410	**Hspb1**	NM_013560 // Hspb1 // heat shock protein 1 // 5 G2|5 76.0 cM // 15507 /// ENSMUST000000	2.73
10427336	**Nckap1l**	NM_153505 // Nckap1l // NCK associated protein 1 like // 15 F3|15 // 105855 /// ENSMUST	2.73
10411611	**Naip5**	NM_010870 // Naip5 // NLR family, apoptosis inhibitory protein 5 // 13 D1|13 55.0 cM //	2.73
10351873	**Pyhin1**	NM_175026 // Pyhin1 // pyrin and HIN domain family, member 1 // 1 H3|1 // 236312 /// EN	2.73
10582303	**Cyba**	NM_007806 // Cyba // cytochrome b-245, alpha polypeptide // 8 E1|8 // 13057 /// ENSMUST	2.73
10599174	**Il13ra1**	NM_133990 // Il13ra1 // interleukin 13 receptor, alpha 1 // X A3.3|X 12.5 cM // 16164 /	2.73
10496580	**Gbp3**	NM_018734 // Gbp3 // guanylate binding protein 3 // 3 H1|3 // 55932 /// ENSMUST00000029	2.73
10387890	**Cxcl16**	NM_023158 // Cxcl16 // chemokine (C-X-C motif) ligand 16 // 11|11 B4 // 66102 /// ENSMU	2.72
10433101	**Gpr84**	NM_030720 // Gpr84 // G protein-coupled receptor 84 // 15 F3|15 // 80910 /// ENSMUST000	2.72
10347277	**Igfbp2**	NM_008342 // Igfbp2 // insulin-like growth factor binding protein 2 // 1 C3|1 36.1 cM /	2.71
10520862	**Fosl2**	NM_008037 // Fosl2 // fos-like antigen 2 // 5 B1|5 18.1 cM // 14284 /// ENSMUST00000031	2.71
10559486	**Lair1**	NM_001113474 // Lair1 // leukocyte-associated Ig-like receptor 1 // 7 A1|7 4.5 cM // 52	2.71
10347650	**Accn4**	NM_183022 // Accn4 // amiloride-sensitive cation channel 4, pituitary // 1 C4|1 // 2411	2.70
10459866	**Slc14a1**	NM_001171010 // Slc14a1 // solute carrier family 14 (urea transporter), member 1 // 18	2.70
10391798	**Gfap**	NM_010277 // Gfap // glial fibrillary acidic protein // 11 D|11 62.0 cM // 14580 /// NM	2.70
10389143	**Slfn8**	NM_181545 // Slfn8 // schlafen 8 // 11 C|11 // 276950 /// NM_001167743 // Slfn8 // schl	2.69
10525365	**Hvcn1**	NM_001042489 // Hvcn1 // hydrogen voltage-gated channel 1 // 5 F|5 // 74096 /// NM_0287	2.69
10383206	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.68
10458340	**Hbegf**	NM_010415 // Hbegf // heparin-binding EGF-like growth factor // 18 B2|18 15.0 cM // 152	2.68
10396476	**Rhoj**	NM_023275 // Rhoj // ras homolog gene family,	2.67

		member J // 12 C3|12 // 80837 /// ENSMUST	
10385526	**9930111J21Rik2**	NM_173434 // 9930111J21Rik2 // RIKEN cDNA 9930111J21 gene 2 // 11 B1.2|11 // 245240 ///	2.66
10583008	**Casp12**	NM_009808 // Casp12 // caspase 12 // 9 A1|9 1.11 cM // 12364 /// BC028979 // Casp12 //	2.66
10576034	**Irf8**	NM_008320 // Irf8 // interferon regulatory factor 8 // 8 E1|8 65.0 cM // 15900 /// ENSM	2.65
10562709	**Cd33**	NM_001111058 // Cd33 // CD33 antigen // 7 B4|7 23.0 cM // 12489 /// NM_021293 // Cd33 /	2.65
10466210	**Ms4a6d**	NM_026835 // Ms4a6d // membrane-spanning 4-domains, subfamily A, member 6D // 19 A|19 /	2.65
10554789	**Ctsc**	NM_009982 // Ctsc // cathepsin C // 7|7 D3-E1.1 // 13032 /// ENSMUST00000032779 // Ctsc	2.65
10416437	**Lcp1**	NM_008879 // Lcp1 // lymphocyte cytosolic protein 1 // 14 D3|14 42.0 cM // 18826 /// EN	2.64
10536845	**Flnc**	NM_001081185 // Flnc // filamin C, gamma // 6 A3.3|6 8.5 cM // 68794 /// ENSMUST0000009	2.64
10470412	**Dbh**	NM_138942 // Dbh // dopamine beta hydroxylase // 2 A3|2 15.5 cM // 13166 /// ENSMUST000	2.64
10500808	**Olfml3**	NM_133859 // Olfml3 // olfactomedin-like 3 // 3 F2.2|3 // 99543 /// ENSMUST00000029440	2.64
10408928	**Hspb1**	NM_013560 // Hspb1 // heat shock protein 1 // 5 G2|5 76.0 cM // 15507 /// ENSMUST000000	2.63
10339814	**---**	---	2.63
10446253	**Vav1**	NM_011691 // Vav1 // vav 1 oncogene // 17 D|17 32.7 cM // 22324 /// NM_001163816 // Vav	2.62
10461723	**Fam111a**	BC038020 // Fam111a // family with sequence similarity 111, member A // 19 B|19 // 1073	2.62
10398907	**Pld4**	NM_178911 // Pld4 // phospholipase D family, member 4 // 12 F1|12 // 104759 /// ENSMUST	2.62
10567580	**Igsf6**	NM_030691 // Igsf6 // immunoglobulin superfamily, member 6 // 7|7 F2-F3 // 80719 /// EN	2.62
10444658	**Clic1**	NM_033444 // Clic1 // chloride intracellular channel 1 // 17 B1|17 19.0 cM // 114584 //	2.62
10350506	**Fam5c**	NM_153539 // Fam5c // family with sequence similarity 5, member C // 1 F-G1|1 80.0 cM /	2.61
10579347	**Ifi30**	NM_023065 // Ifi30 // interferon gamma inducible protein 30 // 8 B3.3|8 // 65972 /// EN	2.61
10383204	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.61
10425321	**Apobec3**	NM_001160415 // Apobec3 // apolipoprotein B mRNA editing enzyme, catalytic polypeptide	2.60
10346564	**Casp8**	NM_009812 // Casp8 // caspase 8 // 1 B|1 30.1 cM // 12370 /// NM_001080126 // Casp8 //	2.60
10578045	**Nrg1**	NM_178591 // Nrg1 // neuregulin 1 // 8 A3|8 // 211323 /// ENSMUST00000073884 // Nrg1 //	2.60
10558948	**Cd151**	NM_009842 // Cd151 // CD151 antigen // 7 F5|7 23.5 cM // 12476 /// NM_001111050 // Cd15	2.59
10554599	**Adamtsl3**	NM_001190374 // Adamtsl3 // ADAMTS-like 3 // 7 D3|7 // 269959 /// ENSMUST00000094237 //	2.59
10555389	**Ucp2**	NM_011671 // Ucp2 // uncoupling protein 2 (mitochondrial, proton carrier) // 7 E3|7 50.	2.58
10569319	**Ctsd**	NM_009983 // Ctsd // cathepsin D // 7 F5|7 // 13033 /// ENSMUST00000151120 // Ctsd // c	2.57
10484503	**Lrrc55**	NM_001033346 // Lrrc55 // leucine rich repeat containing 55 // 2 D|2 // 241528 /// ENSM	2.57
10367436	**Cd63**	NM_001042580 // Cd63 // CD63 antigen // 10	2.57

		D3|10 72.0 cM // 12512 /// NM_007653 // Cd63	
10536499	**Cav1**	NM_007616 // Cav1 // caveolin 1, caveolae protein // 6|6 A2 // 12389 /// ENSMUST0000000	2.57
10490159	**Pmepa1**	NM_022995 // Pmepa1 // prostate transmembrane protein, androgen induced 1 // 2 H3|2 //	2.57
10427461	**Ptger4**	NM_001136079 // Ptger4 // prostaglandin E receptor 4 (subtype EP4) // 15 A1|15 6.4 cM /	2.56
10435305	**Itgb5**	NM_001145884 // Itgb5 // integrin beta 5 // 16 B3|16 // 16419 /// NM_010580 // Itgb5 //	2.56
10375614	**Gfpt2**	NM_013529 // Gfpt2 // glutamine fructose-6-phosphate transaminase 2 // 11 B1.2|11 26.0	2.56
10411595	**Naip2**	NM_010872 // Naip2 // NLR family, apoptosis inhibitory protein 2 // 13 D1|13 54.0 cM //	2.56
10537410	**Tbxas1**	NM_011539 // Tbxas1 // thromboxane A synthase 1, platelet // 6 F1-pter|6 20.5 cM // 213	2.53
10363445	**4632428N05Rik**	NM_028732 // 4632428N05Rik // RIKEN cDNA 4632428N05 gene // 10 B4|10 // 74048 /// NM_00	2.53
10597743	**Cx3cr1**	NM_009987 // Cx3cr1 // chemokine (C-X3-C) receptor 1 // 9 F4|9 // 13051 /// BC012653 //	2.53
10383168	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.53
10603182	**Arhgap6**	NM_009707 // Arhgap6 // Rho GTPase activating protein 6 // X F5|X // 11856 /// NM_17875	2.53
10399540	**Pqlc3**	NM_172574 // Pqlc3 // PQ loop repeat containing // 12 A1.1|12 // 217430 /// NM_00116111	2.53
10349661	**5430435G22Rik**	NM_145509 // 5430435G22Rik // RIKEN cDNA 5430435G22 gene // 1 E4|1 // 226421 /// ENSMUS	2.52
10347948	**Sp100**	NM_013673 // Sp100 // nuclear antigen Sp100 // 1 C5|1 50.0 cM // 20684 /// ENSMUST00000	2.52
10420488	**D14Ertd668e**	NM_199015 // D14Ertd668e // DNA segment, Chr 14, ERATO Doi 668, expressed // 14 C3|14 2	2.52
10542470	**Mgst1**	NM_019946 // Mgst1 // microsomal glutathione S-transferase 1 // 6 G1|6 // 56615 /// ENS	2.51
10505489	**Pappa**	NM_021362 // Pappa // pregnancy-associated plasma protein A // 4 C1|4 32.2 cM // 18491	2.51
10438445	**Klhl6**	NM_183390 // Klhl6 // kelch-like 6 (Drosophila) // 16 A3|16 // 239743 /// ENSMUST000000	2.51
10379615	**Slfn5**	NM_183201 // Slfn5 // schlafen 5 // 11 C|11 // 327978 /// ENSMUST00000067443 // Slfn5 /	2.51
10460237	**Unc93b1**	NM_019449 // Unc93b1 // unc-93 homolog B1 (C. elegans) // 19 A|19 // 54445 /// NM_00116	2.50
10519578	**Abcb4**	NM_008830 // Abcb4 // ATP-binding cassette, sub-family B (MDR/TAP), member 4 // 5 A1|5	2.50
10457640	**S100a11**	NM_016740 // S100a11 // S100 calcium binding protein A11 (calgizzarin) // 3|3 E-F // 20	2.50
10411373	**Hexb**	NM_010422 // Hexb // hexosaminidase B // 13 D1|13 46.0 cM // 15212 /// ENSMUST000000221	2.49
10381588	**Grn**	NM_008175 // Grn // granulin // 11 D|11 60.0 cM // 14824 /// ENSMUST00000049460 // Grn	2.49
10355960	**Scg2**	NM_009129 // Scg2 // secretogranin II // 1 C4|1 43.6 cM // 20254 /// ENSMUST00000049972	2.49
10493820	**S100a6**	NM_011313 // S100a6 // S100 calcium binding protein A6 (calcyclin) // 3 F1-F2|3 43.6 cM	2.49
10488771	**Necab3**	NM_021546 // Necab3 // N-terminal EF-hand	2.48

		calcium binding protein 3 // 2 H1|2 // 56846	
10423836	**Cthrc1**	NM_026778 // Cthrc1 // collagen triple helix repeat containing 1 // 15|15 C // 68588 //	2.48
10388902	**Lgals9**	NM_010708 // Lgals9 // lectin, galactose binding, soluble 9 // 11 B5|11 // 16859 /// NM	2.47
10383202	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.47
10399924	**Pik3cg**	NM_020272 // Pik3cg // phosphoinositide-3-kinase, catalytic, gamma polypeptide // 12|12	2.47
10436658	**7120432I05Rik**	AK148667 // 7120432I05Rik // RIKEN cDNA 7120432I05 gene // 16 C3.3|16 // 100038676	2.46
10351623	**F11r**	NM_172647 // F11r // F11 receptor // 1 H2|1 93.3 cM // 16456 /// ENSMUST00000043839 //	2.46
10550332	**Slc1a5**	NM_009201 // Slc1a5 // solute carrier family 1 (neutral amino acid transporter), member	2.46
10527332	**Nptx2**	NM_016789 // Nptx2 // neuronal pentraxin 2 // 5 G2|5 82.0 cM // 53324 /// ENSMUST000000	2.46
10563178	**Cd37**	NM_007645 // Cd37 // CD37 antigen // 7 B4|7 23.0 cM // 12493 /// ENSMUST00000098461 //	2.45
10468722	**Gfra1**	NM_010279 // Gfra1 // glial cell line derived neurotrophic factor family receptor alpha	2.45
10472757	**Cybrd1**	NM_028593 // Cybrd1 // cytochrome b reductase 1 // 2|2 C3 // 73649 /// ENSMUST000000284	2.45
10383212	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.45
10547177	**Rassf4**	NM_178045 // Rassf4 // Ras association (RalGDS/AF-6) domain family member 4 // 6 E3|6 /	2.45
10347335	**Slc11a1**	NM_013612 // Slc11a1 // solute carrier family 11 (proton-coupled divalent metal ion tra	2.45
10349694	**Pm20d1**	NM_178079 // Pm20d1 // peptidase M20 domain containing 1 // 1 E4|1 // 212933 /// ENSMUS	2.45
10375145	**Lcp2**	NM_010696 // Lcp2 // lymphocyte cytosolic protein 2 // 11 A4|11 // 16822 /// ENSMUST000	2.45
10383214	**Rnf213**	AK173199 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511 /// ENSMUST	2.44
10338876	**---**	---	2.43
10587683	**Bcl2a1a**	NM_009742 // Bcl2a1a // B-cell leukemia/lymphoma 2 related protein A1a // 9 E3.1|9 50.0	2.43
10458382	**Cd14**	NM_009841 // Cd14 // CD14 antigen // 18 B2|18 31.0 cM // 12475 /// ENSMUST00000061829 /	2.43
10444824	**H2-Q6**	NM_207648 // H2-Q6 // histocompatibility 2, Q region locus 6 // 17 B1|17 19.18 cM // 11	2.43
10350853	**BC026585**	NM_001033284 // BC026585 // cDNA sequence BC026585 // 1 H1|1 // 226527 /// ENSMUST00000	2.43
10598750	**Gpr34**	NM_011823 // Gpr34 // G protein-coupled receptor 34 // X|X A1.3 // 23890 /// ENSMUST000	2.42
10539135	**Capg**	NM_007599 // Capg // capping protein (actin filament), gelsolin-like // 6|6 C3 // 12332	2.42
10571984	**Ddx60**	NM_001081215 // Ddx60 // DEAD (Asp-Glu-Ala-Asp) box polypeptide 60 // 8 B3.1|8 // 23431	2.41
10383192	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.41
10593050	**Il10ra**	NM_008348 // Il10ra // interleukin 10 receptor, alpha // 9 A5.2|9 26.0 cM // 16154 ///	2.41
10383208	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger	2.41

		protein 213 // 11 E2|11 75.0 cM // 672511	
10534102	**Gusb**	NM_010368 // Gusb // glucuronidase, beta // 5 G1.3|5 72.0 cM // 110006 /// ENSMUST00000	2.41
10342234	**---**	---	2.40
10512949	**Abca1**	NM_013454 // Abca1 // ATP-binding cassette, sub-family A (ABC1), member 1 // 4 A5-B3|4	2.40
10536369	**C1galt1**	NM_052993 // C1galt1 // core 1 synthase, glycoprotein-N-acetylgalactosamine 3-beta-gala	2.40
10493990	**S100a11**	NM_016740 // S100a11 // S100 calcium binding protein A11 (calgizzarin) // 3|3 E-F // 20	2.40
10406229	**Pcsk1**	NM_013628 // Pcsk1 // proprotein convertase subtilisin/kexin type 1 // 13 C2|13 44.0 cM	2.40
10512067	**Ddx58**	NM_172689 // Ddx58 // DEAD (Asp-Glu-Ala-Asp) box polypeptide 58 // 4 A5|4 // 230073 ///	2.39
10441003	**Runx1**	NM_001111023 // Runx1 // runt related transcription factor 1 // 16 C4|16 62.2 cM // 123	2.39
10487613	**Pdyn**	NM_018863 // Pdyn // prodynorphin // 2 F1|2 73.3 cM // 18610 /// ENSMUST00000028883 //	2.39
10548892	**Arhgdib**	NM_007486 // Arhgdib // Rho, GDP dissociation inhibitor (GDI) beta // 6 G1|6 // 11857 /	2.39
10399555	**Kcnf1**	NM_201531 // Kcnf1 // potassium voltage-gated channel, subfamily F, member 1 // 12 A1.1	2.38
10469066	**Ccdc3**	NM_028804 // Ccdc3 // coiled-coil domain containing 3 // 2 A1|2 // 74186 /// ENSMUST000	2.38
10446965	**Rasgrp3**	NM_207246 // Rasgrp3 // RAS, guanyl releasing protein 3 // 17 E2|17 // 240168 /// NM_00	2.38
10398859	**Adssl1**	NM_007421 // Adssl1 // adenylosuccinate synthetase like 1 // 12 F1|12 // 11565 /// ENSM	2.38
10385504	**Gm5431**	NM_001024230 // Gm5431 // predicted gene 5431 // 11 B1.2|11 // 432555 /// ENSMUST000001	2.37
10466521	**Gcnt1**	NM_173442 // Gcnt1 // glucosaminyl (N-acetyl) transferase 1, core 2 // 19 B|19 17.0 cM	2.36
10455954	**Gm4951**	NM_001033767 // Gm4951 // predicted gene 4951 // 18 D3|18 // 240327 /// NM_001033767 //	2.36
10558049	**Ppapdc1a**	NM_001080963 // Ppapdc1a // phosphatidic acid phosphatase type 2 domain containing 1A /	2.36
10542911	**Samd9l**	NM_010156 // Samd9l // sterile alpha motif domain containing 9-like // 6 2.9 cM|6 A1-A2	2.35
10561702	**Kcnk6**	NM_001033525 // Kcnk6 // potassium inwardly-rectifying channel, subfamily K, member 6 /	2.35
10605181	**Renbp**	NM_023132 // Renbp // renin binding protein // X A7.3|X 29.53 cM // 19703 /// NM_001164	2.34
10467578	**Pik3ap1**	NM_031376 // Pik3ap1 // phosphoinositide-3-kinase adaptor protein 1 // 19|19 D1 // 8349	2.34
10454369	**Fhod3**	NM_175276 // Fhod3 // formin homology 2 domain containing 3 // 18 A2|18 // 225288 /// E	2.34
10585874	**Hexa**	NM_010421 // Hexa // hexosaminidase A // 9 B|9 29.0 cM // 15211 /// ENSMUST00000026262	2.34
10421863	**Pcdh8**	NM_021543 // Pcdh8 // protocadherin 8 // 14 D3|14 43.0 cM // 18530 /// NM_001042726 //	2.34
10557992	**Bag3**	NM_013863 // Bag3 // BCL2-associated athanogene 3 // 7 F3|7 // 29810 /// ENSMUST0000003	2.33
10571444	**Slc7a2**	NM_007514 // Slc7a2 // solute carrier family 7 (cationic amino acid transporter, y+ sys	2.33
10383799	**Tcn2**	NM_015749 // Tcn2 // transcobalamin 2 // 11 A1|11 3.0 cM // 21452 /// NM_001130458 // T	2.33
10358339	**Cfh**	NM_009888 // Cfh // complement component factor h // 1 F|1 74.1 cM // 12628 /// ENSMUST	2.32

10503334	**Gem**	NM_010276 // Gem // GTP binding protein (gene overexpressed in skeletal muscle) // 4 A1	2.32
10534202	**Ncf1**	NM_010876 // Ncf1 // neutrophil cytosolic factor 1 // 5 G2|5 74.0 cM // 17969 /// ENSMU	2.32
10518147	**Pdpn**	NM_010329 // Pdpn // podoplanin // 4 E1|4 // 14726 /// ENSMUST00000030317 // Pdpn // po	2.31
10566333	**9230105E10Rik**	NM_001146007 // 9230105E10Rik // RIKEN cDNA 9230105E10 gene // 7 E3|7 // 319236 /// ENS	2.31
10429128	**Sla**	NM_001029841 // Sla // src-like adaptor // 15 D2|15 37.5 cM // 20491 /// NM_009192 // S	2.31
10514221	**Plin2**	NM_007408 // Plin2 // perilipin 2 // 4 C4|4 38.9 cM // 11520 /// ENSMUST00000000466 //	2.31
10461558	**Slc15a3**	NM_023044 // Slc15a3 // solute carrier family 15, member 3 // 19|19 B // 65221 /// ENSM	2.31
10344194	**---**	---	2.31
10538590	**Herc6**	NM_025992 // Herc6 // hect domain and RLD 6 // 6 C1|6 // 67138 /// ENSMUST00000031817 /	2.31
10485117	**Creb3l1**	NM_011957 // Creb3l1 // cAMP responsive element binding protein 3-like 1 // 2 E1|2 // 2	2.30
10440393	**Samsn1**	NM_023380 // Samsn1 // SAM domain, SH3 domain and nuclear localization signals, 1 // 16	2.30
10569102	**Irf7**	NM_016850 // Irf7 // interferon regulatory factor 7 // 7 F5|7 // 54123 /// ENSMUST00000	2.30
10456071	**Csf1r**	NM_001037859 // Csf1r // colony stimulating factor 1 receptor // 18 D|18 30.0 cM // 129	2.30
10498273	**Tm4sf1**	NM_008536 // Tm4sf1 // transmembrane 4 superfamily member 1 // 3 D|3 // 17112 /// ENSMU	2.29
10497817	**Anxa5**	NM_009673 // Anxa5 // annexin A5 // 3 B|3 19.2 cM // 11747 /// ENSMUST00000029266 // An	2.29
10413047	**Plau**	NM_008873 // Plau // plasminogen activator, urokinase // 14 A3|14 2.5 cM // 18792 /// E	2.29
10379530	**Ccl12**	NM_011331 // Ccl12 // chemokine (C-C motif) ligand 12 // 11 C|11 47.0 cM // 20293 /// E	2.29
10483809	**Nfe2l2**	NM_010902 // Nfe2l2 // nuclear factor, erythroid derived 2, like 2 // 2 C3|2 45.0 cM //	2.29
10443980	**Myo1f**	NM_053214 // Myo1f // myosin IF // 17 B-C|17 17.5 cM // 17916 /// ENSMUST00000087605 //	2.29
10342635	**---**	---	2.28
10595633	**Bcl2a1d**	NM_007536 // Bcl2a1d // B-cell leukemia/lymphoma 2 related protein A1d // 9 E3.1|9 // 1	2.27
10587690	**Bcl2a1b**	NM_007534 // Bcl2a1b // B-cell leukemia/lymphoma 2 related protein A1b // 9 E3.1|9 // 1	2.27
10473244	**Zfp804a**	NM_175513 // Zfp804a // zinc finger protein 804A // 2 D|2 // 241514 /// ENSMUST00000047	2.27
10397645	**Gpr65**	NM_008152 // Gpr65 // G-protein coupled receptor 65 // 12 E|12 // 14744 /// ENSMUST0000	2.27
10452633	**Tgif1**	NM_009372 // Tgif1 // TGFB-induced factor homeobox 1 // 17 E1.3|17 // 21815 /// NM_0011	2.27
10571312	**Dusp4**	NM_176933 // Dusp4 // dual specificity phosphatase 4 // 8 A4|8 // 319520 /// ENSMUST000	2.27
10401705	**Zdhhc22**	NM_001080943 // Zdhhc22 // zinc finger, DHHC-type containing 22 // 12 D2|12 // 238331 /	2.27
10403743	**Inhba**	NM_008380 // Inhba // inhibin beta-A // 13 A1|13	2.27

		10.0 cM // 16323 /// ENSMUST0000004260	
10566583	**Gm8995**	AK172683 // Gm8995 // predicted gene 8995 // 7 E3|7 // 668139 /// XR_035350 // Gm8995 /	2.26
10545958	**Anxa4**	NM_013471 // Anxa4 // annexin A4 // 6 D1|6 38.0 cM // 11746 /// ENSMUST00000001187 // A	2.26
10420155	**Dhrs1**	NM_026819 // Dhrs1 // dehydrogenase/reductase (SDR family) member 1 // 14 C3|14 22.5 cM	2.25
10432640	**Bin2**	ENSMUST00000100198 // Bin2 // bridging integrator 2 // 15 F1|15 // 668218	2.25
10586194	**Megf11**	NM_001134399 // Megf11 // multiple EGF-like-domains 11 // 9 C|9 // 214058 /// NM_172522	2.25
10458314	**Tmem173**	NM_028261 // Tmem173 // transmembrane protein 173 // 18 B3|18 // 72512 /// ENSMUST00000	2.25
10368289	**Enpp1**	NM_008813 // Enpp1 // ectonucleotide pyrophosphatase/phosphodiesterase 1 // 10 A4|10 19	2.24
10390186	**Abi3**	NM_025659 // Abi3 // ABI gene family, member 3 // 11 D|11 // 66610 /// NM_001163464 //	2.24
10486396	**Ehd4**	NM_133838 // Ehd4 // EH-domain containing 4 // 2 E5|2 // 98878 /// ENSMUST00000028755 /	2.24
10399973	**Hdac9**	NM_024124 // Hdac9 // histone deacetylase 9 // 12 A3|12 // 79221 /// ENSMUST00000110819	2.24
10517731	**Igsf21**	NM_198610 // Igsf21 // immunoglobin superfamily, member 21 // 4 D3|4 // 230868 /// ENSM	2.23
10466127	**AW112010**	NM_001177351 // AW112010 // expressed sequence AW112010 // 19 A|19 // 107350 /// ENSMUS	2.23
10533246	**Oas1g**	NM_011852 // Oas1g // 2'-5' oligoadenylate synthetase 1G // 5 F|5 67.0 cM // 23960 ///	2.23
10383200	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.23
10363070	**Gp49a**	NM_008147 // Gp49a // glycoprotein 49 A // 10 B3|10 // 14727 /// ENSMUST00000102894 //	2.23
10341831	**---**	---	2.23
10392815	**AF251705**	NM_134158 // AF251705 // cDNA sequence AF251705 // 11 E2|11 78.0 cM // 140497 /// ENSMU	2.23
10559207	**Lsp1**	NM_019391 // Lsp1 // lymphocyte specific 1 // 7 F5|7 69.0 cM // 16985 /// NM_001136071	2.23
10410124	**Ctsl**	NM_009984 // Ctsl // cathepsin L // 13 B3|13 30.0 cM // 13039 /// ENSMUST00000021933 //	2.23
10426315	**Lrrk2**	NM_025730 // Lrrk2 // leucine-rich repeat kinase 2 // 15|15 F1 // 66725 /// ENSMUST0000	2.23
10462140	**Dock8**	NM_028785 // Dock8 // dedicator of cytokinesis 8 // 19 B|19 // 76088 /// ENSMUST0000002	2.23
10436636	**Ncam2**	NM_001113208 // Ncam2 // neural cell adhesion molecule 2 // 16 C1-3|16 56.0 cM // 17968	2.22
10361091	**Atf3**	NM_007498 // Atf3 // activating transcription factor 3 // 1 H6|1 103.2 cM // 11910 ///	2.22
10412231	**Hspb3**	NM_019960 // Hspb3 // heat shock protein 3 // 13 D2.2|13 // 56534 /// ENSMUST0000005465	2.22
10489246	**Mafb**	NM_010658 // Mafb // v-maf musculoaponeurotic fibrosarcoma oncogene family, protein B (	2.22
10523506	**Bmp3**	NM_173404 // Bmp3 // bone morphogenetic protein 3 // 5 E3|5 55.0 cM // 110075 /// ENSMU	2.21
10487588	**Il1a**	NM_010554 // Il1a // interleukin 1 alpha // 2 F|2 73.0 cM // 16175 /// ENSMUST000000288	2.21

10450154	**H2-Aa**	NM_010378 // H2-Aa // histocompatibility 2, class II antigen A, alpha // 17 B1|17 18.65	2.21
10376326	**Irgm2**	NM_019440 // Irgm2 // immunity-related GTPase family M member 2 // 11 B1.3|11 // 54396	2.21
10490989	**Cp**	NM_001042611 // Cp // ceruloplasmin // 3|3 D // 12870 /// NM_007752 // Cp // ceruloplas	2.21
10596718	**Slc38a3**	NM_023805 // Slc38a3 // solute carrier family 38, member 3 // 9 F1|9 63.0 cM // 76257 /	2.21
10458894	**Lox**	NM_010728 // Lox // lysyl oxidase // 18 D1|18 29.0 cM // 16948 /// ENSMUST00000025409 /	2.21
10386058	**Sparc**	NM_009242 // Sparc // secreted acidic cysteine rich glycoprotein // 11 B1|11 29.9 cM //	2.21
10541895	**Tnfrsf1a**	NM_011609 // Tnfrsf1a // tumor necrosis factor receptor superfamily, member 1a // 6 F3|	2.21
10340952	**---**	---	2.20
10472820	**Itga6**	NM_008397 // Itga6 // integrin alpha 6 // 2 C2-C3|2 38.0 cM // 16403 /// ENSMUST0000002	2.20
10368566	**Tpd52l1**	NM_009413 // Tpd52l1 // tumor protein D52-like 1 // 10|10 A4-B2 // 21987 /// ENSMUST000	2.20
10500335	**Fcgr1**	NM_010186 // Fcgr1 // Fc receptor, IgG, high affinity I // 3 F2.1|3 45.2 cM // 14129 //	2.20
10379389	**Adap2**	NM_172133 // Adap2 // ArfGAP with dual PH domains 2 // 11 B5|11 47.24 cM // 216991 ///	2.20
10380285	**Tmem100**	NM_026433 // Tmem100 // transmembrane protein 100 // 11 C|11 // 67888 /// ENSMUST000000	2.20
10436841	**Il10rb**	NM_008349 // Il10rb // interleukin 10 receptor, beta // 16 C3.3|16 63.11 cM // 16155 //	2.20
10349947	**Fmod**	NM_021355 // Fmod // fibromodulin // 1 E4|1 74.3 cM // 14264 /// ENSMUST00000048183 //	2.20
10480035	**Pfkfb3**	NM_001177753 // Pfkfb3 // 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 // 2 A1	2.20
10601848	**6530401D17Rik**	NM_029541 // 6530401D17Rik // RIKEN cDNA 6530401D17 gene // X F1|X // 76219	2.19
10498367	**P2ry13**	NM_028808 // P2ry13 // purinergic receptor P2Y, G-protein coupled 13 // 3 D|3 // 74191	2.19
10342986	**---**	---	2.19
10566578	**Gm8979**	NR_030719 // Gm8979 // very large inducible GTPase 1 pseudogene // 7 E3|7 // 668108 ///	2.19
10467508	**Blnk**	NM_008528 // Blnk // B-cell linker // 19 C3|19 31.0 cM // 17060 /// ENSMUST00000054769	2.19
10452815	**Xdh**	NM_011723 // Xdh // xanthine dehydrogenase // 17 E2|17 45.3 cM // 22436 /// ENSMUST0000	2.19
10463070	**Entpd1**	NM_009848 // Entpd1 // ectonucleoside triphosphate diphosphohydrolase 1 // 19 C3|19 35.	2.19
10340125	**---**	---	2.19
10338612	**---**	---	2.19
10463836	**Gsto1**	NM_010362 // Gsto1 // glutathione S-transferase omega 1 // 19 D1|19 // 14873 /// ENSMUS	2.19
10531994	**Mpa2l**	NM_194336 // Mpa2l // macrophage activation 2 like // 5 E5|5 // 100702 /// NM_001039646	2.18
10529515	**Sorcs2**	NM_030889 // Sorcs2 // sortilin-related VPS10 domain containing receptor 2 // 5 B3|5 //	2.18
10392560	**Abca9**	NM_147220 // Abca9 // ATP-binding cassette, sub-family A (ABC1), member 9 // 11 E1|11 /	2.18
10526553	**Vgf**	NM_001039385 // Vgf // VGF nerve growth factor inducible // 5 G2|5 79.0 cM // 381677 //	2.17
10355998	**Fam124b**	NM_173425 // Fam124b // family with sequence	2.16

		similarity 124, member B // 1 C4|1 // 2411	
10463875	**Sorcs3**	NM_025696 // Sorcs3 // sortilin-related VPS10 domain containing receptor 3 // 19 D1|19	2.15
10492682	**Fam198b**	NM_133187 // Fam198b // family with sequence similarity 198, member B // 3 E3|3 // 6865	2.15
10435457	**Parp9**	NM_030253 // Parp9 // poly (ADP-ribose) polymerase family, member 9 // 16 B3|16 // 8028	2.15
10530145	**Tlr1**	NM_030682 // Tlr1 // toll-like receptor 1 // 5 C3.1|5 37.0 cM // 21897 /// ENSMUST00000	2.15
10562211	**Fxyd1**	NM_052992 // Fxyd1 // FXYD domain-containing ion transport regulator 1 // 7|7 B1 // 561	2.14
10349295	**Tcfcp2l1**	NM_023755 // Tcfcp2l1 // transcription factor CP2-like 1 // 1|1 E2 // 81879 /// ENSMUST	2.14
10583021	**Pdgfd**	NM_027924 // Pdgfd // platelet-derived growth factor, D polypeptide // 9 A1|9 // 71785	2.14
10356968	**Pam**	NM_013626 // Pam // peptidylglycine alpha-amidating monooxygenase // 1 D|1 57.5 cM // 1	2.14
10537146	**Akr1b8**	NM_008012 // Akr1b8 // aldo-keto reductase family 1, member B8 // 6 B1|6 13.0 cM // 141	2.14
10565456	**Prss23**	NM_029614 // Prss23 // protease, serine, 23 // 7 E1|7 // 76453 /// ENSMUST00000041761 /	2.14
10383196	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.14
10464529	**Tcirg1**	NM_016921 // Tcirg1 // T-cell, immune regulator 1, ATPase, H+ transporting, lysosomal V	2.14
10439249	**Parp14**	NM_001039530 // Parp14 // poly (ADP-ribose) polymerase family, member 14 // 16 B3|16 //	2.14
10520942	**Plb1**	NM_001081407 // Plb1 // phospholipase B1 // 5 B1|5 // 665270 /// ENSMUST00000101376 //	2.13
10459210	**Arhgef37**	NM_177828 // Arhgef37 // Rho guanine nucleotide exchange factor (GEF) 37 // 18 E1|18 //	2.13
10601350	**Fgf16**	NM_030614 // Fgf16 // fibroblast growth factor 16 // X|X C3 // 80903 /// ENSMUST0000003	2.13
10542575	**Pde3a**	NM_018779 // Pde3a // phosphodiesterase 3A, cGMP inhibited // 6|6 G1 // 54611 /// ENSMU	2.13
10343128	**---**	---	2.13
10519857	**Hgf**	NM_010427 // Hgf // hepatocyte growth factor // 5 A2-A3|5 4.0 cM // 15234 /// ENSMUST00	2.12
10399908	**Prkar2b**	NM_011158 // Prkar2b // protein kinase, cAMP dependent regulatory, type II beta // 12|1	2.12
10509163	**Id3**	NM_008321 // Id3 // inhibitor of DNA binding 3 // 4 D3|4 66.0 cM // 15903 /// ENSMUST00	2.12
10590865	**Cntn5**	NM_001170787 // Cntn5 // contactin 5 // 9 A1|9 // 244682 /// NM_001033359 // Cntn5 // c	2.12
10520869	**Plb1**	NM_001081407 // Plb1 // phospholipase B1 // 5 B1|5 // 665270 /// NM_030072 // Plb1 // p	2.12
10423556	**Pgcp**	NM_018755 // Pgcp // plasma glutamate carboxypeptidase // 15|15 B3.2 // 54381 /// NM_17	2.12
10345675	**Npas2**	NM_008719 // Npas2 // neuronal PAS domain protein 2 // 1 B|1 20.0 cM // 18143 /// ENSMU	2.12
10608654	**---**	---	2.11
10469695	**Apbb1ip**	NM_019456 // Apbb1ip // amyloid beta (A4) precursor protein-binding, family B, member 1	2.11
10473809	**Sfpi1**	NM_011355 // Sfpi1 // SFFV proviral integration 1 // 2 E3|2 47.5 cM // 20375 /// ENSMUS	2.11
10566427	**Olfr684**	NM_207249 // Olfr684 // olfactory receptor 684 // 7 E3|7 // 244187 /// ENSMUST000000608	2.11
10496569	**Gbp6**	NM_145545 // Gbp6 // guanylate binding protein	2.11

		6 // 3 H1|3 // 229900 /// NM_001083312 /	
10516064	**Mfsd2a**	NM_029662 // Mfsd2a // major facilitator superfamily domain containing 2A // 4|4 D1 //	2.11
10483110	**Ifih1**	NM_027835 // Ifih1 // interferon induced with helicase C domain 1 // 2|2 C3 // 71586 //	2.11
10492997	**Etv3**	NM_001083318 // Etv3 // ets variant gene 3 // 3 F1|3 // 27049 /// NM_012051 // Etv3 //	2.11
10383152	**Rnf213**	ENSMUST00000131035 // Rnf213 // ring finger protein 213 // 11 E2|11 75.0 cM // 672511	2.11
10457614	**Aqp4**	NM_009700 // Aqp4 // aquaporin 4 // 18 A1|18 6.0 cM // 11829 /// ENSMUST00000079081 //	2.11
10573583	**Man2b1**	NM_010764 // Man2b1 // mannosidase 2, alpha B1 // 8 C2|8 37.0 cM // 17159 /// ENSMUST00	2.11
10419744	**Slc7a7**	NM_011405 // Slc7a7 // solute carrier family 7 (cationic amino acid transporter, y+ sys	2.11
10546510	**Lrig1**	NM_008377 // Lrig1 // leucine-rich repeats and immunoglobulin-like domains 1 // 6 D2|6	2.10
10466200	**Ms4a7**	NM_027836 // Ms4a7 // membrane-spanning 4-domains, subfamily A, member 7 // 19 A|19 //	2.10
10401238	**Zfp36l1**	NM_007564 // Zfp36l1 // zinc finger protein 36, C3H type-like 1 // 12 C3|12 // 12192 //	2.10
10389214	**Ccl9**	NM_011338 // Ccl9 // chemokine (C-C motif) ligand 9 // 11 C|11 47.4 cM // 20308 /// ENS	2.10
10519693	**Sema3d**	NM_028882 // Sema3d // sema domain, immunoglobulin domain (Ig), short basic domain, sec	2.09
10530536	**Tec**	NM_001113460 // Tec // tec protein tyrosine kinase // 5 C3.2|5 41.0 cM // 21682 /// NM_	2.09
10541683	**C1rb**	NM_001113356 // C1rb // complement component 1, r subcomponent B // 6 F2|6 // 667277 //	2.09
10349724	**Rab7l1**	NM_144875 // Rab7l1 // RAB7, member RAS oncogene family-like 1 // 1 E4|1 // 226422 ///	2.09
10401519	**Npc2**	NM_023409 // Npc2 // Niemann Pick type C2 // 12 D1|12 // 67963 /// ENSMUST00000021668 /	2.09
10455970	**BC023105**	BC023105 // BC023105 // cDNA sequence BC023105 // 18 D3|18 // 667597	2.09
10359181	**Tor3a**	NM_023141 // Tor3a // torsin family 3, member A // 1 H1|1 // 30935 /// ENSMUST000000796	2.09
10412207	**Gpx8**	NM_027127 // Gpx8 // glutathione peroxidase 8 (putative) // 13 D2.2|13 // 69590 /// ENS	2.08
10561104	**Axl**	NM_009465 // Axl // AXL receptor tyrosine kinase // 7 A3-B1|7 6.0 cM // 26362 /// NM_00	2.08
10470959	**Phyhd1**	NM_172267 // Phyhd1 // phytanoyl-CoA dioxygenase domain containing 1 // 2 B|2 // 227696	2.08
10343462	**---**	---	2.08
10495596	**Frrs1**	NM_001113478 // Frrs1 // ferric-chelate reductase 1 // 3 G1|3 // 20321 /// NM_009146 //	2.08
10567297	**Itpripl2**	NM_001033380 // Itpripl2 // inositol 1,4,5-triphosphate receptor interacting protein-li	2.08
10365559	**Igf1**	NM_010512 // Igf1 // insulin-like growth factor 1 // 10 C1|10 48.0 cM // 16000 /// NM_0	2.08
10482814	**Acvr1c**	NM_001111030 // Acvr1c // activin A receptor, type IC // 2 C1.1|2 // 269275 /// NM_0010	2.08
10449284	**Dusp1**	NM_013642 // Dusp1 // dual specificity phosphatase 1 // 17 A2-C|17 13.0 cM // 19252 ///	2.07
10342942	**---**	---	2.07
10571601	**Pdlim3**	NM_016798 // Pdlim3 // PDZ and LIM domain 3	2.07

		// 8 B1.1|8 // 53318 /// ENSMUST00000034053	
10549041	**Slco1a5**	NM_130861 // Slco1a5 // solute carrier organic anion transporter family, member 1a5 //	2.07
10555205	**Gdpd5**	NM_201352 // Gdpd5 // glycerophosphodiester phosphodiesterase domain containing 5 // 7	2.07
10520948	**Plb1**	NM_001081407 // Plb1 // phospholipase B1 // 5 B1|5 // 665270 /// ENSMUST00000101376 //	2.07
10456005	**Cd74**	NM_001042605 // Cd74 // CD74 antigen (invariant polypeptide of major histocompatibility	2.07
10400304	**Egln3**	NM_028133 // Egln3 // EGL nine homolog 3 (C. elegans) // 12 C1|12 // 112407 /// ENSMUST	2.07
10361897	**Ifngr1**	NM_010511 // Ifngr1 // interferon gamma receptor 1 // 10 A3|10 15.0 cM // 15979 /// ENS	2.07
10600698	**5430427O19Rik**	NM_001163539 // 5430427O19Rik // RIKEN cDNA 5430427O19 gene // X|X B // 71398 /// ENSMU	2.06
10523376	**Fras1**	NM_175473 // Fras1 // Fraser syndrome 1 homolog (human) // 5 E3|5 // 231470 /// ENSMUST	2.05
10435920	**Cd200r4**	NM_207244 // Cd200r4 // CD200 receptor 4 // 16 B4|16 // 239849 /// NM_177010 // F630003	2.05
10607738	**Car5b**	NM_181315 // Car5b // carbonic anhydrase 5b, mitochondrial // X F5|X // 56078 /// ENSMU	2.04
10450699	**H2-t9**	NM_001177467 // H2-t9 // MHC class Ib T9 // 17 B1|17 // 630294 /// AB359227 // EG547347	2.04
10363921	**Pcdh15**	NM_023115 // Pcdh15 // protocadherin 15 // 10 B5.3|10 40.2 cM // 11994 /// NM_001142735	2.04
10604656	**Xlr**	NM_011725 // Xlr // X-linked lymphocyte-regulated complex // X A5|X // 22441 /// ENSMUS	2.04
10468533	**Gpam**	NM_008149 // Gpam // glycerol-3-phosphate acyltransferase, mitochondrial // 19 D2|19 52	2.04
10547740	**C1s**	NM_144938 // C1s // complement component 1, s subcomponent // 6 F2|6 // 50908 /// NM_00	2.03
10566571	**Gm8979**	NR_030719 // Gm8979 // very large inducible GTPase 1 pseudogene // 7 E3|7 // 668108 ///	2.03
10551185	**Tgfb1**	NM_011577 // Tgfb1 // transforming growth factor, beta 1 // 7 A3|7 6.5 cM // 21803 ///	2.03
10345921	**1500015O10Rik**	NM_024283 // 1500015O10Rik // RIKEN cDNA 1500015O10 gene // 1|1 C1 // 78896 /// ENSMUST	2.02
10469457	**Plxdc2**	NM_026162 // Plxdc2 // plexin domain containing 2 // 2 A2-A3|2 // 67448 /// ENSMUST0000	2.02
10340419	**---**	---	2.02
10511180	**Mxra8**	NM_024263 // Mxra8 // matrix-remodelling associated 8 // 4 E2|4 83.0 cM // 74761 /// EN	2.02
10592266	**Slc37a2**	NM_001145960 // Slc37a2 // solute carrier family 37 (glycerol-3-phosphate transporter),	2.01
10383756	**Ifitm2**	NM_030694 // Ifitm2 // interferon induced transmembrane protein 2 // 7|7 F5 // 80876 //	2.01
10538150	**Tmem176a**	NM_025326 // Tmem176a // transmembrane protein 176A // 6 B2.3|6 // 66058 /// NM_0010982	2.01
10450682	**H2-T23**	NM_010398 // H2-T23 // histocompatibility 2, T region locus 23 // 17 B1|17 19.73 cM //	2.01
10485294	**Hsd17b12**	NM_019657 // Hsd17b12 // hydroxysteroid (17-beta) dehydrogenase 12 // 2 E1|2 // 56348 /	2.01
10411082	**Thbs4**	NM_011582 // Thbs4 // thrombospondin 4 // 13 C3|13 51.0 cM // 21828 /// ENSMUST00000022	2.01
10500295	**Plekho1**	NM_023320 // Plekho1 // pleckstrin homology	2.01

		domain containing, family O member 1 // 3|3	
10425092	**Cyth4**	NM_028195 // Cyth4 // cytohesin 4 // 15 E1|15 // 72318 /// ENSMUST00000043069 // Cyth4	2.00
10538356	**Chn2**	NM_001163640 // Chn2 // chimerin (chimaerin) 2 // 6 B3|6 // 69993 /// NM_023543 // Chn2	2.00
10430372	**Rac2**	NM_009008 // Rac2 // RAS-related C3 botulinum substrate 2 // 15 E1|15 // 19354 /// ENSM	2.00
10343087	**---**	---	2.00
10354229	**2610017I09Rik**	NR_027826 // 2610017I09Rik // RIKEN cDNA 2610017I09 gene // 1 B|1 // 66297 /// BC058417	-2.00
10423599	**Matn2**	NM_016762 // Matn2 // matrilin 2 // 15|15 B3.3 // 17181 /// ENSMUST00000022947 // Matn2	-2.01
10440258	**Epha3**	NM_010140 // Epha3 // Eph receptor A3 // 16 C1.3|16 // 13837 /// ENSMUST00000064405 //	-2.01
10366144	**Mgat4c**	NM_001162369 // Mgat4c // mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosami	-2.01
10531177	**Adamts3**	NM_177872 // Adamts3 // a disintegrin-like and metallopeptidase (reprolysin type) with	-2.01
10360666	**6330403A02Rik**	BC120654 // 6330403A02Rik // RIKEN cDNA 6330403A02 gene // 1 H4|1 // 381310 /// NM_0010	-2.02
10407350	**Fgf10**	NM_008002 // Fgf10 // fibroblast growth factor 10 // 13 A3-A4|13 75.0 cM // 14165 /// E	-2.02
10413461	**Erc2**	NM_177814 // Erc2 // ELKS/RAB6-interacting/CAST family member 2 // 14 A3|14 8.0 cM // 2	-2.04
10422321	**Dzip1**	NM_025943 // Dzip1 // DAZ interacting protein 1 // 14 E4|14 // 66573 /// ENSMUST0000000	-2.05
10424559	**Khdrbs3**	NM_010158 // Khdrbs3 // KH domain containing, RNA binding, signal transduction associat	-2.05
10502766	**Lphn2**	NM_001081298 // Lphn2 // latrophilin 2 // 3 H3|3 // 99633 /// ENSMUST00000106127 // Lph	-2.05
10502881	**St6galnac5**	NM_012028 // St6galnac5 // ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-ac	-2.05
10556266	**Wee1**	NM_009516 // Wee1 // WEE 1 homolog 1 (S. pombe) // 7 F1|7 // 22390 /// ENSMUST000000333	-2.05
10571829	**Glra3**	NM_080438 // Glra3 // glycine receptor, alpha 3 subunit // 8 B2|8 26.0 cM // 110304 ///	-2.05
10360664	**6330403A02Rik**	ENSMUST00000136521 // 6330403A02Rik // RIKEN cDNA 6330403A02 gene // 1 H4|1 // 381310 /	-2.06
10436519	**Robo1**	NM_019413 // Robo1 // roundabout homolog 1 (Drosophila) // 16 C3.1|16 // 19876 /// ENSM	-2.07
10557201	**Cacng3**	NM_019430 // Cacng3 // calcium channel, voltage-dependent, gamma subunit 3 // 7 F3|7 //	-2.07
10521995	**3110047P20Rik**	NM_177006 // 3110047P20Rik // RIKEN cDNA 3110047P20 gene // 5|5 C3.3 // 319807 /// ENSM	-2.08
10585484	**Chrna5**	NM_176844 // Chrna5 // cholinergic receptor, nicotinic, alpha polypeptide 5 // 9 B|9 32	-2.08
10403396	**Adarb2**	NM_052977 // Adarb2 // adenosine deaminase, RNA-specific, B2 // 13 A1|13 // 94191 /// E	-2.08
10484283	**Pde1a**	NM_016744 // Pde1a // phosphodiesterase 1A, calmodulin-dependent // 2|2 D // 18573 ///	-2.08
10344007	**---**	---	-2.09
10347781	**9430031J16Rik**	NM_172849 // 9430031J16Rik // RIKEN cDNA 9430031J16 gene // 1 C5|1 // 241134 /// BC0823	-2.09
10540599	**Cpne9**	NM_170673 // Cpne9 // copine family member IX	-2.10

		// 6 E3|6 // 211232 /// ENSMUST0000004120	
10556962	**Vwa3a**	NM_177697 // Vwa3a // von Willebrand factor A domain containing 3A // 7 F2|7 // 233813	-2.11
10578794	**Galntl6**	NM_175032 // Galntl6 // UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactos	-2.13
10474064	**Trp53i11**	NM_001025246 // Trp53i11 // transformation related protein 53 inducible protein 11 // 2	-2.14
10502772	**Lphn2**	NM_001081298 // Lphn2 // latrophilin 2 // 3 H3|3 // 99633 /// ENSMUST00000106128 // Lph	-2.17
10393364	**Cygb**	NM_030206 // Cygb // cytoglobin // 11 E2|11 // 114886 /// ENSMUST00000021166 // Cygb //	-2.17
10399465	**Fam84a**	NM_029007 // Fam84a // family with sequence similarity 84, member A // 12|12 A3 // 1050	-2.17
10388465	**Doc2b**	NM_007873 // Doc2b // double C2, beta // 11 B5|11 // 13447 /// ENSMUST00000021209 // Do	-2.18
10501924	**Ndst3**	NM_031186 // Ndst3 // N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 3 // 3|3	-2.18
10606366	**Zcchc5**	NM_199468 // Zcchc5 // zinc finger, CCHC domain containing 5 // X D|X // 213436 /// ENS	-2.18
10540408	**Itpr1**	NM_010585 // Itpr1 // inositol 1,4,5-triphosphate receptor 1 // 6 E1-E2|6 48.0 cM // 16	-2.18
10459512	**Mc4r**	NM_016977 // Mc4r // melanocortin 4 receptor // 18 E1|18 // 17202 /// ENSMUST0000005794	-2.19
10496975	**Slc44a5**	NM_001081263 // Slc44a5 // solute carrier family 44, member 5 // 3 H3-H4|3 // 242259 //	-2.19
10367828	**Grm1**	ENSMUST00000044306 // Grm1 // glutamate receptor, metabotropic 1 // 10|10 A2 // 14816 /	-2.20
10344879	**A830018L16Rik**	NM_001160369 // A830018L16Rik // RIKEN cDNA A830018L16 gene // 1 A2|1 // 320492 /// NM_	-2.20
10460123	**9330132A10Rik**	BC098197 // 9330132A10Rik // RIKEN cDNA 9330132A10 gene // 18 E4|18 // 319609	-2.21
10377490	**Alox12b**	NM_009659 // Alox12b // arachidonate 12-lipoxygenase, 12R type // 11 B3|11 37.0 cM // 1	-2.22
10483624	**Dlx1as**	NR_002854 // Dlx1as // distal-less homeobox 1, antisense // 2 C2|2 44.0 cM // 111970	-2.22
10467599	**Slit1**	NM_015748 // Slit1 // slit homolog 1 (Drosophila) // 19 C3|19 // 20562 /// ENSMUST00000	-2.22
10430297	**Pvalb**	NM_013645 // Pvalb // parvalbumin // 15 E|15 45.7 cM // 19293 /// ENSMUST00000005860 //	-2.23
10543369	**Cadps2**	NM_153163 // Cadps2 // Ca2+-dependent activator protein for secretion 2 // 6 A3.1|6 //	-2.23
10351298	**Gpr161**	NM_001081126 // Gpr161 // G protein-coupled receptor 161 // 1 H2.3|1 89.7 cM // 240888	-2.24
10527940	**Cdk14**	NM_011074 // Cdk14 // cyclin-dependent kinase 14 // 5 A1|5 0.0 cM // 18647 /// AF033655	-2.25
10438730	**Sst**	NM_009215 // Sst // somatostatin // 16 cen-C3|16 19.0 cM // 20604 /// ENSMUST0000000448	-2.25
10524234	**Galnt9**	NM_198306 // Galnt9 // UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosa	-2.28
10446309	**Cntnap5c**	NM_001081653 // Cntnap5c // contactin associated protein-like 5C // 17 D|17 // 620292 /	-2.28
10349340	**C1ql2**	NM_207233 // C1ql2 // complement component 1, q subcomponent-like 2 // 1 E2.3|1 // 2263	-2.29
10503382	**Runx1t1**	NM_001111027 // Runx1t1 // runt-related transcription factor 1; translocated to, 1 (cyc	-2.30
10449608	**Mdga1**	NM_001081160 // Mdga1 // MAM domain containing glycosylphosphatidylinositol anchor 1 //	-2.31

10459496	**Ccbe1**	NM_178793 // Ccbe1 // collagen and calcium binding EGF domains 1 // 18 E1|18 // 320924	-2.31
10374012	**Rasl10a**	NM_145216 // Rasl10a // RAS-like, family 10, member A // 11 A1|11 // 75668 /// ENSMUST0	-2.31
10353460	**Kcnq5**	NM_001160139 // Kcnq5 // potassium voltage-gated channel, subfamily Q, member 5 // 1|1	-2.33
10566723	**Lmo1**	NM_057173 // Lmo1 // LIM domain only 1 // 7 E3|7 51.5 cM // 109594 /// ENSMUST000000369	-2.34
10387100	**Shisa6**	NM_001034874 // Shisa6 // shisa homolog 6 (Xenopus laevis) // 11 B3|11 // 380702 /// EN	-2.34
10456653	**Myo5b**	NM_201600 // Myo5b // myosin VB // 18 E2|18 48.0 cM // 17919 /// ENSMUST00000074157 //	-2.35
10385826	**Ankrd43**	NM_183173 // Ankrd43 // ankyrin repeat domain 43 // 11 B1.3|11 // 237761 /// ENSMUST000	-2.35
10524909	**Nos1**	NM_008712 // Nos1 // nitric oxide synthase 1, neuronal // 5 F|5 65.0 cM // 18125 /// EN	-2.36
10457628	**Chst9**	NM_199055 // Chst9 // carbohydrate (N-acetylgalactosamine 4-0) sulfotransferase 9 // 18	-2.38
10372421	**Trhde**	NM_146241 // Trhde // TRH-degrading enzyme // 10 D2|10 // 237553 /// ENSMUST00000061632	-2.38
10407034	**Htr1a**	NM_008308 // Htr1a // 5-hydroxytryptamine (serotonin) receptor 1A // 13 D1|13 58.0 cM /	-2.38
10453256	**Kcng3**	NM_153512 // Kcng3 // potassium voltage-gated channel, subfamily G, member 3 // 17 E4|1	-2.39
10453231	**Slc8a1**	NM_011406 // Slc8a1 // solute carrier family 8 (sodium/calcium exchanger), member 1 //	-2.41
10371296	**Glt8d2**	NM_029102 // Glt8d2 // glycosyltransferase 8 domain containing 2 // 10 C1|10 // 74782 /	-2.42
10536363	**Tac1**	NM_009311 // Tac1 // tachykinin 1 // 6 A1|6 5.0 cM // 21333 /// ENSMUST00000090679 // T	-2.43
10344390	**---**	---	-2.45
10367691	**Iyd**	NM_027391 // Iyd // iodotyrosine deiodinase // 10 A1|10 // 70337 /// ENSMUST00000019896	-2.45
10548940	**Lmo3**	NM_207222 // Lmo3 // LIM domain only 3 // 6 G1|6 70.0 cM // 109593 /// ENSMUST000001627	-2.49
10364792	**Plk5**	NM_183152 // Plk5 // polo-like kinase 5 (Drosophila) // 10 C1|10 // 216166 /// ENSMUST0	-2.49
10357339	**Lypd1**	NM_145100 // Lypd1 // Ly6/Plaur domain containing 1 // 1 E3|1 // 72585 /// NM_027677 //	-2.51
10404649	**Dsp**	NM_023842 // Dsp // desmoplakin // 13 A3.3|13 // 109620	-2.52
10433887	**Pkp2**	NM_026163 // Pkp2 // plakophilin 2 // 16|16 B1 // 67451 /// ENSMUST00000039408 // Pkp2	-2.52
10485718	**Ano3**	NM_001128103 // Ano3 // anoctamin 3 // 2 E3|2 // 228432 /// NM_001081556 // Ano3 // ano	-2.52
10411235	**Iqgap2**	NM_027711 // Iqgap2 // IQ motif containing GTPase activating protein 2 // 13 D1|13 47.0	-2.56
10358928	**Cacna1e**	NM_009782 // Cacna1e // calcium channel, voltage-dependent, R type, alpha 1E subunit //	-2.56
10502770	**Lphn2**	NM_001081298 // Lphn2 // latrophilin 2 // 3 H3|3 // 99633 /// ENSMUST00000106127 // Lph	-2.56
10578786	**Galntl6**	NM_175032 // Galntl6 // UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactos	-2.59
10521583	**Drd5**	NM_013503 // Drd5 // dopamine receptor D5 // 5 B3|5 23.0 cM // 13492 /// ENSMUST0000004	-2.61
10606600	**Pcdh19**	NM_001105245 // Pcdh19 // protocadherin 19 //	-2.61

		X E3|X // 279653 /// NM_001105246 // Pcdh	
10479852	**Camk1d**	NM_177343 // Camk1d // calcium/calmodulin-dependent protein kinase ID // 2 A1|2 // 2275	-2.63
10485745	**Ano3**	NM_001128103 // Ano3 // anoctamin 3 // 2 E3|2 // 228432 /// ENSMUST00000099623 // Ano3	-2.63
10565152	**Homer2**	NM_011983 // Homer2 // homer homolog 2 (Drosophila) // 7 D3|7 // 26557 /// NM_001164086	-2.63
10425814	**Mpped1**	NM_172610 // Mpped1 // metallophosphoesterase domain containing 1 // 15 E2|15 54.5 cM /	-2.65
10588380	**Cpne4**	NM_028719 // Cpne4 // copine IV // 9 F1|9 // 74020 /// ENSMUST00000057742 // Cpne4 // c	-2.65
10416505	**Kctd4**	NM_026214 // Kctd4 // potassium channel tetramerisation domain containing 4 // 14|14 D2	-2.66
10372106	**Epyc**	ENSMUST00000105285 // Epyc // epiphycan // 10 C2-C3|10 55.0 cM // 13516 /// NR_033537 /	-2.68
10594048	**Islr2**	NM_001161535 // Islr2 // immunoglobulin superfamily containing leucine-rich repeat 2 //	-2.71
10428407	**Tmem74**	NM_175502 // Tmem74 // transmembrane protein 74 // 15 B3.2|15 // 239408 /// ENSMUST0000	-2.79
10589407	**Spink8**	NM_183136 // Spink8 // serine peptidase inhibitor, Kazal type 8 // 9 F2|9 // 78709 ///	-2.83
10544936	**Neurod6**	NM_009717 // Neurod6 // neurogenic differentiation 6 // 6 B3|6 29.0 cM // 11922 /// ENS	-2.88
10366391	**Kcnc2**	NM_001025581 // Kcnc2 // potassium voltage gated channel, Shaw-related subfamily, membe	-2.89
10349208	**Cntnap5a**	NM_001077425 // Cntnap5a // contactin associated protein-like 5A // 1 E2.3|1 // 636808	-2.91
10446312	**Cntnap5c**	NM_001081653 // Cntnap5c // contactin associated protein-like 5C // 17 D|17 // 620292 /	-2.92
10338732	**---**	---	-2.92
10498921	**Tdo2**	NM_019911 // Tdo2 // tryptophan 2,3-dioxygenase // 3 E3|3 // 56720 /// ENSMUST000000296	-2.92
10498187	**6030405A18Rik**	NM_177854 // 6030405A18Rik // RIKEN cDNA 6030405A18 gene // 3 C|3 // 329641 /// ENSMUST	-2.98
10498965	**Npy2r**	NM_008731 // Npy2r // neuropeptide Y receptor Y2 // 3 E3|3 36.0 cM // 18167 /// ENSMUST	-3.07
10357418	**Lct**	NM_001081078 // Lct // lactase // 1 E4|1 65.9 cM // 226413 /// ENSMUST00000073490 // Lc	-3.09
10578796	**Galntl6**	NM_175032 // Galntl6 // UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactos	-3.12
10540233	**Fam19a1**	NM_182808 // Fam19a1 // family with sequence similarity 19, member A1 // 6 D3|6 // 3202	-3.16
10548899	**Rerg**	NM_181988 // Rerg // RAS-like, estrogen-regulated, growth-inhibitor // 6 G1|6 // 232441	-3.22
10341762	**---**	---	-3.27
10476482	**6330527O06Rik**	NM_029530 // 6330527O06Rik // RIKEN cDNA 6330527O06 gene // 2 F3|2 // 76161 /// ENSMUST	-3.40
10407435	**Akr1c18**	NM_134066 // Akr1c18 // aldo-keto reductase family 1, member C18 // 13 A1|13 // 105349	-3.40
10584549	**Scn3b**	NM_178227 // Scn3b // sodium channel, voltage-gated, type III, beta // 9 A5.1|9 // 2352	-3.47
10342598	**---**	---	-3.80

Significantly changed Canonical Pathways

APPENDIX 4

Significantly changed IPA Canonical Pathways at 1 day post injection in KA-MTLE (p<0.05).The pathways are ranked by descending number of genes.

	Ingenuity Canonical Pathway	No of genes	Gene Symbols
1	G-Protein Coupled Receptor Signaling	18	Grm2, Htr1a, Rgs7, S1pr3, Grm3, Adcy1, Stat3, Htr2b, Dusp1, Pde7b, Rgs2, Grm1, Pde6b, Grm8, Rgs4, Dusp4, Adra1a, Prkar2a
2	cAMP-mediated signaling	15	Grm2, Htr1a, Rgs7, S1pr3, Grm3, Adcy1, Stat3, Dusp1, Pde7b, Rgs2, Pde6b, Grm8, Rgs4, Dusp4, Prkar2a
3	Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	12	Fos, Stat3, Socs3, C5ar1, Ccl2, Plce1, Map2k3, Fgf2, Il16, Il33, Mapkapk2, Fcgr3a/Fcgr3b
4	Gαi Signaling	11	Adcy1, Grm2, Cav1, Htr1a, Stat3, Rgs7, S1pr3, Grm8, Rgs4, Grm3, Prkar2a
5	Granulocyte Adhesion and Diapedesis	11	Cldn10, Ccl2, Hspb1, Cxcl10, C5ar1, Ccl2, Ccl9, Msn, Ccl3l3, Itga5, Il33
6	Hepatic Fibrosis / Hepatic Stellate Cell Activation	11	Col12a1, Smad7, Klf6, Cd14, Ccl2, Edn1, Ctgf, Igfbp3, Timp1, Fgf2, Serpine1
7	RAR Activation	11	Fos, Adcy1, Akr1c3, Nrip2, Smad7, Dusp1, Igfbp3, Bmp2, Mapkapk2, Cited2, Prkar2a
8	Phospholipase C Signaling	11	Adcy1, Fcgr2b, Rps6ka3, Plce1, Blnk, Rhoj, Pla2g4a, Hmox1, Rnd3, Itga5, Tgm2
9	TGF-β Signaling	10	Fos, Inhba, Acvr1c, Irf7, Smad7, Tgif1, Map2k3, Serpine1, Pmepa1, Bmp2
10	Gαq Signaling	10	Htr2b, Rgs7, Arhgef25, Rgs2, Grm1, Rgs4, Rhoj, Hmox1, Rnd3, Adra1a
11	Agranulocyte Adhesion and Diapedesis	10	Cldn10, Ccl2, Cxcl10, C5ar1, Ccl2, Ccl9, Msn, Ccl3l3, Itga5, Il33
12	IL-10 Signaling	9	Fos, Stat3, Fcgr2b, Socs3, Cd14, Blvrb, Map2k3, Hmox1, Il33
13	Neuropathic Pain Signaling In Dorsal Horn Neurons	9	Fos, Tac1, Grm2, Plce1, Grm1, Grm8, Bdnf, Grm3, Prkar2a
14	Acute Phase Response Signaling	9	Fos, Stat3, Tf, Socs3, Map2k3, Serpine1, Hmox1, Il33, Osmr
15	Endothelin-1 Signaling	9	Fos, Adcy1, Mapk4, Ptgs2, Edn1, Plce1, Pla2g4a, Hmox1, Mapk6
16	ERK/MAPK Signaling	9	Fos, Hspb1, Stat3, Dusp1, Pak6, Pla2g4a, Itga5, Dusp4, Prkar2a
17	UVA-Induced MAPK Signaling	8	Fos, Tiparp, Parp12, Zc3hav1, Rps6ka3, Plce1, Parp9, Parp14
18	phagosome formation	8	Fcgr2b, Plce1, Msr1, Fcrls, Rhoj, Rnd3, Itga5, Fcgr3a/Fcgr3b
19	Role of Pattern Recognition Receptors in Recognition of	8	Eif2ak2, Il11, Irf7, C5ar1, Ifih1, Lif, Ddx58, C3ar1

	Bacteria and Viruses		
20	HMGB1 Signaling	8	Fos, Il11, Ccl2, Lif, Map2k3, Serpine1, Rhoj, Rnd3
21	IL-6 Signaling	8	Fos, Hspb1, Stat3, Socs3, Cd14, Map2k3, Il33, Mapkapk2
22	Hepatic Cholestasis	8	Adcy1, Il11, Cyp7b1, Cd14, Lif, Slco1c1, Il33, Prkar2a
23	RhoGDI Signaling	8	Pak6, Msn, Cdh4, Rhoj, Rnd3, Cd44, Itga5, Arhgdib
24	GPCR-Mediated Integration of Enteroendocrine Signaling Exemplified by an L Cell	7	Adcy1, Npy2r, Plce1, Galr1, Gal, Gipr, Prkar2a
25	VDR/RXR Activation	7	Klk6, Thbd, Cxcl10, Cd14, Cdkn1a, Igfbp3, Spp1
26	Death Receptor Signaling	7	Tiparp, Parp12, Hspb1, Zc3hav1, Parp9, Parp14, Arhgdib
27	IGF-1 Signaling	7	Fos, Stat3, Cyr61, Socs3, Ctgf, Igfbp3, Prkar2a
28	p38 MAPK Signaling	7	Hspb1, Dusp1, Rps6ka3, Map2k3, Pla2g4a, Il33, Mapkapk2
29	Atherosclerosis Signaling	7	Aloxe3, Ccl2, Msr1, Tnfrsf12a, Alox12b, Pla2g4a, Il33
30	Synaptic Long Term Potentiation	7	Adcy1, Grm2, Plce1, Grm1, Grm8, Grm3, Prkar2a
31	Human Embryonic Stem Cell Pluripotency	7	Inhba, Smad7, S1pr3, Fgf2, Sphk1, Bmp2, Bdnf
32	Glioma Invasiveness Signaling	6	Itgav, Plaur, Timp1, Rhoj, Rnd3, Cd44
33	IL-17 Signaling	6	Cxcl10, Ccl2, Ptgs2, Map2k3, Timp1, Mapkapk2
34	Leptin Signaling in Obesity	6	Adcy1, Stat3, Socs3, Plce1, Npy, Prkar2a
35	CDK5 Signaling	6	Adcy1, Mapk4, Fosb, Bdnf, Mapk6, Prkar2a
36	Cholecystokinin/Gastrin-mediated Signaling	6	Fos, Ptgs2, Map2k3, Rhoj, Rnd3, Il33
37	Sphingosine-1-phosphate Signaling	6	Adcy1, S1pr3, Plce1, Sphk1, Rhoj, Rnd3
38	Role of Tissue Factor in Cancer	6	Hbegf, Cyr61, Itgav, Rps6ka3, Plaur, Ctgf
39	LXR/RXR Activation	6	Tf, Cd14, Ccl2, Ptgs2, Msr1, Il33
40	Renin-Angiotensin Signaling	6	Fos, Adcy1, Stat3, Pak6, Ccl2, Prkar2a
41	Corticotropin Releasing Hormone Signaling	6	Fos, Adcy1, Nr4a1, Ptgs2, Bdnf, Prkar2a
42	Neuroprotective Role of THOP1 in Alzheimer's Disease	5	Pdyn, Tac1, Hla-A, Nts, Prkar2a
43	Retinoic acid Mediated Apoptosis Signaling	5	Tiparp, Parp12, Zc3hav1, Parp9, Parp14
44	Glutamate Receptor Signaling	5	Grm2, Homer2, Grm1, Grm8, Grm3
45	Communication between Innate and Adaptive Immune Cells	5	Hla-A, Cxcl10, Ccl9, Ccl3l3, Il33
46	CD40 Signaling	5	Fos, Stat3, Ptgs2, Map2k3, Mapkapk2
47	Role of MAPK Signaling in the Pathogenesis of Influenza	5	Cxcl10, Ccl2, Ptgs2, Map2k3, Pla2g4a
48	Toll-like Receptor Signaling	5	Fos, Eif2ak2, Cd14, Map2k3, Il33
49	Growth Hormone Signaling	5	Fos, Stat3, Socs3, Rps6ka3, Igfbp3
50	Caveolar-mediated Endocytosis Signaling	5	Cav1, Hla-A, Itgav, Flnc, Itga5
51	PDGF Signaling	5	Fos, Eif2ak2, Cav1, Stat3, Sphk1

52	ErbB Signaling	5	Fos, Hbegf, Areg, Pak6, Map2k3
53	Coagulation System	4	Pros1, Thbd, Plaur, Serpine1
54	Role of IL-17F in Allergic Inflammatory Airway Diseases	4	Il11, Cxcl10, Ccl2, Rps6ka3
55	MIF Regulation of Innate Immunity	4	Fos, Cd14, Ptgs2, Pla2g4a
56	Heparan Sulfate Biosynthesis (Late Stages)	4	Sult2b1, Hs3st2, Ndst4, Extl1
57	Phototransduction Pathway	4	Pde6b, Opn3, Arr3, Prkar2a
58	Role of IL-17A in Arthritis	4	Ccl2, Ptgs2, Map2k3, Mapkapk2
59	Heparan Sulfate Biosynthesis	4	Sult2b1, Hs3st2, Ndst4, Extl1
60	Fatty Acid α-oxidation	3	Aloxe3, Ptgs2, Alox12b
61	GADD45 Signaling	3	Cdkn1a, Gadd45b, Gadd45g
62	Role of JAK family kinases in IL-6-type Cytokine Signaling	3	Stat3, Socs3, Osmr
63	Role of Hypercytokinemia/hyperchemokinemia in the Pathogenesis of Influenza	3	Cxcl10, Ccl2, Il33
64	Hematopoiesis from Pluripotent Stem Cells	3	Il11, Kitlg, Lif
65	Role of RIG1-like Receptors in Antiviral Innate Immunity	3	Irf7, Ifih1, Ddx58
66	MIF-mediated Glucocorticoid Regulation	3	Cd14, Ptgs2, Pla2g4a
67	Retinoate Biosynthesis I	3	Akr1c3, Akr1b10, Bmp2
68	Oncostatin M Signaling	3	Stat3, Chi3l1, Osmr
69	Heme Degradation	2	Blvrb, Hmox1
70	Methylglyoxal Degradation III	2	Akr1c3, Akr1b10
71	Sulfate Activation for Sulfonation	1	Papss2
72	Putrescine Biosynthesis III	1	Odc1

APPENDIX 5

Significantly changed IPA Canonical Pathways at 3 days post injection in KA-MTLE (p<0.05).The pathways are ranked by descending number of significantly changed genes.

	Ingenuity Canonical Pathways	No of genes	Gene Symbols
1	Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	24	Myd88, Socs3, Tnfrsf1a, Fcgr1a, Tlr1, Plce1, Fgf2, Il16, Vcam1, Mapkapk2, Pik3cg, Tlr4, Stat3, Fn1, C5ar1, Ccnd1, Ccl2, Csf1, Tlr13, Rras, Tlr2, Il33, Prkcg, Fcgr3a/Fcgr3b
2	Leukocyte Extravasation Signaling	22	Itgam, Jam2, F11r, Itga6, Ncf1, Ezr, Msn, Timp4, Itgb2, Rac2, Cd44, Vav1, Vcam1, Pik3cg, Itga1, Mmp19, Itgb1, Timp1, Cybb, Itga5, Cyba, Prkcg
3	Phagosome formation	21	Fcgr1a, Tlr1, Rhoc, Plce1, Msr1, Fcer1g, Fcrls, Rhoj, Fcgr2a, Pik3cg, Tlr4, Fn1, Fcgr2b, Inpp5d, Itgb1, Tlr13, Itga5, Tlr2, Clec7a, Prkcg, Fcgr3a/Fcgr3b
4	IL-8 Signaling	21	Hbegf, Iqgap1, Itgam, Itgb5, Itgav, Nox4, Rhoc, Myl9, Pld4, Itgb2, Rac2, Rhoj, Hmox1, Vcam1, Pik3cg, Gng5, Ccnd1, Ptgs2, Cybb, Rras, Prkcg
5	Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	20	Eif2ak2, Oas1, C3, Myd88, Tlr1, C1qb, Ddx58, C3ar1, Oas1b, C1qa, Pik3cg, Tlr4, C1qc, Irf7, C5ar1, Ifih1, Tlr2, Clec7a, Ptx3, Prkcg
6	Dendritic Cell Maturation	20	Myd88, Tnfrsf1a, Hla-Dqa1, Hla-Dqb1, Fcgr1a, Plce1, Fcer1g, Trem2, Fcgr2a, Pik3cg, Tlr4, Irf8, Hla-A, Fcgr2b, Stat1, Tyrobp, Tlr2, Cd86, Il33, Fcgr3a/Fcgr3b
7	Granulocyte Adhesion and Diapedesis	20	Ccl2, Itgam, Tnfrsf1a, Cxcl10, Itga6, Ezr, Msn, Itgb2, Ccl3l3, Vcam1, Hspb1, Itga1, Mmp19, C5ar1, Itgb1, Ccl2, Cxcl16, Sdc4, Itga5, Il33
8	Acute Phase Response Signaling	20	Tf, C3, Myd88, Socs3, Tnfrsf1a, Serpinf1, Cp, Rbp1, Serpina3, Hmox1, Pik3cg, Osmr, A2m, Stat3, Fn1, Serpinf2, Serpine1, Serping1, Rras, Il33
9	Agranulocyte Adhesion and Diapedesis	20	Ccl2, Tnfrsf1a, Cxcl10, Itga6, Ezr, Msn, Myl9, Itgb2, Ccl3l3, Vcam1, Itga1, Fn1, Mmp19, C5ar1, Itgb1, Ccl2, Cxcl16, Sdc4, Itga5, Il33
10	Hepatic Fibrosis / Hepatic Stellate Cell Activation	19	Igfbp4, Tnfrsf1a, Ctgf, Fgf2, Myl9, Vcam1, Tlr4, A2m, Col12a1, Tgfbr2, Ly96, Fn1, Stat1, Ccl2, Csf1, Il4r, Igfbp3, Timp1, Serpine1
11	Integrin Signaling	19	Itgam, Itgb5, Itgav, Nedd9, Itga6, Tspan4, Rhoc, Myl9, Itgb2, Rac2, Rhoj, Arpc1b, Pik3cg, Cav1, Itga1, Itgb1, Rras, Itga5, Capn2
12	Phospholipase C Signaling	19	Rhoc, Plce1, Myl9, Pld4, Fcer1g, Rhoj, Hmox1, Fcgr2a, Lcp2, Fcgr2b, Gng5, Itgb1, Blnk, Rras, Itga5, Pla2g4a, Tgm2, Prkcg, Lyn
13	Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	17	Hck, Fcgr1a, Ncf1, Ezr, Fyb, Pld4, Rac2, Arpc1b, Hmox1, Vav1, Fcgr2a, Pik3cg, Lcp2, Inpp5d, Prkcg, Lyn, Fcgr3a/Fcgr3b
14	TREM1 Signaling	16	Myd88, Tlr1, Naip1 (Includes Others), Tlr4, Lat2, Stat3, Fcgr2b, Itgb1, Tyrobp, Ccl2, Tlr13, Itga5, Tlr2, Cd86
15	Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	16	Tnfrsf1a, Ncf1, Rhoc, Spi1, Rhoj, Pik3cg, Tlr4, Lyz, Apoc2, Irf8, Ppp1r14b, Stat1, Cybb, Tlr2, Cyba, Prkcg
16	Actin Cytoskeleton Signaling	16	Iqgap1, Flna, Fgf10, Ezr, Msn, Fgf2, Myl9, Rac2, Arpc1b, Vav1, Pik3cg, Fn1, Nckap1l, Itgb1, Rras, Itga5

17	Colorectal Cancer Metastasis Signaling	16	Tnfrsf1a, Tlr1, Rhoc, Rhoj, Pik3cg, Tlr4, Stat3, Tgfbr2, Gng5, Mmp19, Stat1, Ccnd1, Ptgs2, Tlr13, Rras, Tlr2
18	PI3K Signaling in B Lymphocytes	15	C3, Plce1, Vav1, Atf3, Pik3cg, Tlr4, Fcgr2b, Inpp5d, Pik3ap1, Il4r, Cd180, Ptprc, Blnk, Rras, Lyn
19	ILK Signaling	15	Itgb5, Tnfrsf1a, Flna, Rhoc, Myl9, Itgb2, Rhoj, Pik3cg, Vim, Fn1, Ppp1r14b, Itgb1, Ccnd1, Ptgs2, Flnc
20	Virus Entry via Endocytic Pathways	14	Itgb5, Flna, Itga6, Itgb2, Rac2, Pik3cg, Cav1, Itga1, Hla-A, Itgb1, Flnc, Rras, Itga5, Prkcg
21	Natural Killer Cell Signaling	14	Lair1, Cd244, Fcer1g, Rac2, Vav1, Fcgr2a, Pik3cg, Lcp2, Inpp5d, Tyrobp, Sh3bp2, Rras, Prkcg, Fcgr3a/Fcgr3b
22	Tec Kinase Signaling	14	Hck, Rhoc, Fcer1g, Rhoj, Vav1, Pik3cg, Tlr4, Stat3, Gng5, Stat1, Itgb1, Itga5, Prkcg, Lyn
23	Systemic Lupus Erythematosus Signaling	14	Fcgr1a, Cd72, Fcer1g, Fcgr2a, Pik3cg, Hla-A, Fcgr2b, Inpp5d, Ptprc, Rras, Cd86, Il33, Lyn, Fcgr3a/Fcgr3b
24	Role of NFAT in Regulation of the Immune Response	14	Hla-Dqa1, Hla-Dqb1, Fcgr1a, Fcer1g, Fcgr2a, Pik3cg, Lcp2, Fcgr2b, Gng5, Blnk, Rras, Cd86, Lyn, Fcgr3a/Fcgr3b
25	Clathrin-mediated Endocytosis Signaling	14	Tf, Itgb5, Fgf10, Fgf2, Itgb2, Arpc1b, Pik3cg, Lyz, Apoc2, Itgb1, Hip1, Myo1e, Dab2, Itga5
26	Signaling by Rho Family GTPases	14	Iqgap1, Ezr, Msn, Nox4, Rhoc, Myl9, Rhoj, Arpc1b, Pik3cg, Vim, Gng5, Itgb1, Cybb, Itga5
27	Caveolar-mediated Endocytosis Signaling	13	Itgam, Itgb5, Itgav, Flna, Itga6, Cd48, Itgb2, Cav1, Itga1, Hla-A, Itgb1, Flnc, Itga5
28	LXR/RXR Activation	13	Tf, C3, Tnfrsf1a, Serpinf1, Msr1, Tlr4, Lyz, Apoc2, Ly96, Ccl2, Ptgs2, Serpinf2, Il33
29	Atherosclerosis Signaling	13	Msr1, Itgb2, Vcam1, Lyz, Apoc2, Aloxe3, Ccl2, Csf1, Tnfrsf12a, Alox12b, Plb1, Pla2g4a, Il33
30	Aryl Hydrocarbon Receptor Signaling	13	Aldh1l1, Mcm7, Cdk2, Hspb1, Ccnd1, Aldh1l2, Cdkn1a, Rbl1, Ccna2, Ctsd, Cyp1b1, Tgm2, Nfe2l2
31	NF-κB Signaling	13	Eif2ak2, Myd88, Tnfrsf1a, Tlr1, Fcer1g, Pik3cg, Fgfrl1, Tlr4, Tgfbr2, Rras, Tlr2, Il33, Casp8
32	B Cell Receptor Signaling	13	Rac2, Vav1, Fcgr2a, Pik3cg, Fcgr2b, Inpp5d, Pik3ap1, Bcl2a1, Apbb1ip, Ptprc, Blnk, Rras, Lyn
33	Role of Tissue Factor in Cancer	12	Hbegf, Hck, Cyr61, Itgb5, Itgav, Itgb1, Csf1, Itga6, Ctgf, Rras, Pik3cg, Lyn
34	Death Receptor Signaling	12	Parp12, Hspb1, Naip, Tnfrsf1a, Parp3, Parp9, Parp14, Naip1 (Includes Others), Casp8, Arhgdib
35	Germ Cell-Sertoli Cell Junction Signaling	12	A2m, Iqgap1, Tgfbr2, Tnfrsf1a, Itgb1, Tubb6, Itga6, Rhoc, Rac2, Rhoj, Rras, Pik3cg
36	Glioma Invasiveness Signaling	11	Hmmr, Itgb5, Itgav, Plau, Timp4, Rhoc, Timp1, Rhoj, Rras, Cd44, Pik3cg
37	T Helper Cell Differentiation	11	Tgfbr2, Stat3, Il10rb, Tnfrsf1a, Hla-Dqa1, Hla-Dqb1, Stat1, Il4r, Fcer1g, Cd86, Il2rg
38	NF-κB Activation by Viruses	11	Eif2ak2, Itga1, Itgb5, Itgav, Itgb1, Itga6, Itgb2, Rras, Itga5, Pik3cg, Prkcg
39	Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	11	Tlr4, Tlr1, Hla-Dqa1, Hla-Dqb1, Csf1, Tlr13, Fcer1g, Spp1, Tlr2, Cd86, Il33
40	Pancreatic Adenocarcinoma Signaling	11	Hbegf, Tgfbr2, Stat3, Stat1, Ptgs2, Ccnd1, Cdkn1a, Cdk2, Pld4, Hmox1, Pik3cg
41	Cdc42 Signaling	11	H2-K2/H2-Q9, Iqgap1, Hla-A, Hla-Dqa1, Hla-Dqb1, Itgb1, Myl9, Fcer1g, Arpc1b, Itga5, Vav1
42	Gαq Signaling	11	Htr2b, Gng5, Chrm3, Rhoc, Pld4, Grm1, Rgs4, Rhoj, Hmox1, Pik3cg, Prkcg

43	Endothelin-1 Signaling	11	Ptgs2, Plce1, Pld4, Plb1, Pla2g4a, Hmox1, Rras, Ptgs1, Casp8, Pik3cg, Prkcg
44	RhoGDI Signaling	11	Gng5, Itgb1, Ezr, Msn, Rhoc, Myl9, Rhoj, Arpc1b, Cd44, Itga5, Arhgdib
45	Complement System	10	Itgam, C1qc, C3, C5ar1, C1qb, Itgb2, Serping1, Cfh, C3ar1, C1qa
46	Communication between Innate and Adaptive Immune Cells	10	Tlr4, Hla-A, Cxcl10, Tlr1, Tlr13, Fcer1g, Ccl3l3, Tlr2, Cd86, Il33
47	GM-CSF Signaling	10	Hck, Stat3, Bcl2a1, Stat1, Csf2rb, Ccnd1, Runx1, Rras, Pik3cg, Lyn
48	IGF-1 Signaling	10	Igfbp4, Stat3, Cyr61, Igfbp7, Socs3, Igfbp2, Ctgf, Igfbp3, Rras, Pik3cg
49	Paxillin Signaling	10	Itgam, Itga1, Itgb5, Itgav, Itgb1, Itga6, Itgb2, Rras, Itga5, Pik3cg
50	Type I Diabetes Mellitus Signaling	10	Hla-A, Myd88, Socs3, Tnfrsf1a, Hla-Dqa1, Hla-Dqb1, Stat1, Fcer1g, Cd86, Casp8
51	HGF Signaling	10	Stat3, Itgb1, Ptgs2, Ccnd1, Cdkn1a, Cdk2, Rras, Itga5, Pik3cg, Prkcg
52	Fc Epsilon RI Signaling	10	Lcp2, Inpp5d, Fcer1g, Rac2, Pla2g4a, Rras, Vav1, Pik3cg, Lyn, Prkcg
53	IL-12 Signaling and Production in Macrophages	10	Tlr4, Lyz, Apoc2, Irf8, Myd88, Stat1, Spi1, Tlr2, Pik3cg, Prkcg
54	PTEN Signaling	10	Tgfbr2, Inpp5d, Itgb1, Ccnd1, Cdkn1a, Rac2, Rras, Itga5, Pik3cg, Fgfrl1
55	Apoptosis Signaling	10	Naip, Tnfrsf1a, Bcl2a1, Rras, Naip1 (Includes Others), Casp8, Cdk1, Capn2
56	Regulation of Cellular Mechanics by Calpain Protease	9	Itgb1, Ccnd1, Ezr, Cdk2, Ccna2, Rras, Itga5, Cdk1, Capn2
57	Eicosanoid Signaling	9	Akr1c3, Alox5ap, Ptgs2, Alox12b, Plb1, Hpgds, Pla2g4a, Ptgs1, Tbxas1
58	iCOS-iCOSL Signaling in T Helper Cells	9	Lcp2, Inpp5d, Hla-Dqa1, Hla-Dqb1, Ptprc, Fcer1g, Vav1, Il2rg, Pik3cg
59	Rac Signaling	9	Iqgap1, Itgb1, Nox4, Cybb, Arpc1b, Rras, Cd44, Itga5, Pik3cg
60	CD28 Signaling in T Helper Cells	9	Lcp2, Hla-Dqa1, Hla-Dqb1, Ptprc, Fcer1g, Arpc1b, Cd86, Vav1, Pik3cg
61	PKCθ Signaling in T Lymphocytes	9	Lcp2, Hla-Dqa1, Hla-Dqb1, Fcer1g, Rac2, Rras, Cd86, Vav1, Pik3cg
62	HMGB1 Signaling	9	Tlr4, Tnfrsf1a, Ccl2, Rhoc, Serpine1, Rhoj, Rras, Vcam1, Pik3cg
63	IL-6 Signaling	9	A2m, Hspb1, Stat3, Socs3, Tnfrsf1a, Rras, Il33, Mapkapk2, Pik3cg
64	MSP-RON Signaling Pathway	8	Tlr4, Itgam, Csf2rb, Ccl2, Csf1, Itgb2, Tlr2, Pik3cg
65	Cell Cycle: G2/M DNA Damage Checkpoint Regulation	8	Top2a, Cdkn1a, Cks2, Cks1b, Ccnb2, Plk1, Cdk1, Ccnb1
66	Role of JAK1 and JAK3 in γc Cytokine Signaling	8	Stat3, Socs3, Stat1, Il4r, Blnk, Rras, Il2rg, Pik3cg
67	IL-10 Signaling	8	Stat3, Il10rb, Fcgr2b, Socs3, Il4r, Hmox1, Il33, Fcgr2a
68	Agrin Interactions at Neuromuscular Junction	8	Itga1, Erbb4, Itgb1, Itga6, Itgb2, Rac2, Rras, Itga5
69	Macropinocytosis Signaling	8	Itgb5, Itgb1, Csf1, Itgb2, Rras, Itga5, Pik3cg, Prkcg
70	IL-4 Signaling	8	Inpp5d, Hla-Dqa1, Hla-Dqb1, Il13ra1, Il4r, Rras, Il2rg, Pik3cg
71	HER-2 Signaling in Breast Cancer	8	Itgb5, Itgb1, Ccnd1, Cdkn1a, Itgb2, Rras, Pik3cg, Prkcg
72	Cyclins and Cell Cycle Regulation	8	Cdkn2c, Ccnd1, Cdkn1a, Cdk2, Ccna2, Ccnb2, Cdk1, Ccnb1
73	Acute Myeloid Leukemia Signaling	8	Stat3, Csf2rb, Ccnd1, Kitlg, Runx1, Spi1, Rras, Pik3cg
74	Reelin Signaling in Neurons	8	Hck, Itga1, Itgb1, Itga6, Itgb2, Itga5, Pik3cg, Lyn
75	UVA-Induced MAPK Signaling	8	Parp12, Stat1, Parp3, Plce1, Parp9, Parp14, Rras, Pik3cg
76	fMLP Signaling in Neutrophils	8	Gng5, Ncf1, Nox4, Cybb, Arpc1b, Rras,

			Pik3cg, Prkcg
77	Activation of IRF by Cytosolic Pattern Recognition Receptors	7	Dhx58, Irf9, Irf7, Stat1, Ifih1, Ddx58, Ifit2
78	Mitotic Roles of Polo-Like Kinase	7	Kif23, Prc1, Ccnb2, Kif11, Plk1, Cdk1, Ccnb1
79	IL-17 Signaling	7	Cxcl10, Ccl2, Ptgs2, Timp1, Rras, Mapkapk2, Pik3cg
80	Toll-like Receptor Signaling	7	Tlr4, Eif2ak2, Ly96, Myd88, Tlr1, Tlr2, Il33
81	Growth Hormone Signaling	7	A2m, Stat3, Socs3, Stat1, Igfbp3, Pik3cg, Prkcg
82	Crosstalk between Dendritic Cells and Natural Killer Cells	7	Tlr4, Hla-A, Csf2rb, Tyrobp, Trem2, Cd86, Il2rg
83	IL-3 Signaling	7	Stat3, Inpp5d, Stat1, Csf2rb, Rras, Pik3cg, Prkcg
84	Prolactin Signaling	7	Stat3, Prlr, Socs3, Stat1, Rras, Pik3cg, Prkcg
85	PDGF Signaling	7	Eif2ak2, Cav1, Stat3, Inpp5d, Stat1, Rras, Pik3cg
86	Regulation of Actin-based Motility by Rho	7	Itgb1, Rhoc, Myl9, Rac2, Rhoj, Arpc1b, Itga5
87	Bladder Cancer Signaling	7	Mmp19, Ccnd1, Fgf10, Cdkn1a, Fgf2, Thbs1, Rras
88	G Beta Gamma Signaling	7	Hbegf, Cav1, Gng5, Cav2, Rras, Pik3cg, Prkcg
89	TGF-β Signaling	7	Inhba, Tgfbr2, Irf7, Tgif1, Serpine1, Pmepa1, Rras
90	Estrogen-mediated S-phase Entry	6	Ccnd1, Cdkn1a, Cdk2, Ccna2, Rbl1, Cdk1
91	Cell Cycle Control of Chromosomal Replication	6	Mcm7, Mcm2, Cdk2, Mcm3, Dbf4, Mcm5
92	Interferon Signaling	6	Oas1, Irf9, Stat1, Ifit3, Ifitm3, Psmb8
93	Role of RIG1-like Receptors in Antiviral Innate Immunity	6	Dhx58, Irf7, Ifih1, Trim25, Ddx58, Casp8
94	Oncostatin M Signaling	6	Stat3, Chi3l1, Plau, Stat1, Rras, Osmr
95	Coagulation System	6	A2m, Pros1, Plau, Serpinf2, F13a1, Serpine1
96	IL-9 Signaling	6	Stat3, Socs3, Stat1, Bcl3, Il2rg, Pik3cg
97	Graft-versus-Host Disease Signaling	6	Hla-A, Hla-Dqa1, Hla-Dqb1, Fcer1g, Cd86, Il33
98	Allograft Rejection Signaling	6	H2-K2/H2-Q9, Hla-A, Hla-Dqa1, Hla-Dqb1, Fcer1g, Cd86
99	FcγRIIB Signaling in B Lymphocytes	6	Fcgr2b, Inpp5d, Blnk, Rras, Pik3cg, Lyn
100	Actin Nucleation by ARP-WASP Complex	6	Itgb1, Rhoc, Rhoj, Arpc1b, Rras, Itga5
101	TWEAK Signaling	6	Naip, Tnfrsf12a, Naip1 (Includes Others), Casp8
102	IL-15 Signaling	6	Stat3, Axl, Rras, Vcam1, Il2rg, Pik3cg
103	Role of MAPK Signaling in the Pathogenesis of Influenza	6	Cxcl10, Ccl2, Ptgs2, Plb1, Pla2g4a, Rras
104	STAT3 Pathway	6	Tgfbr2, Stat3, Socs3, Cdkn1a, Rras, Fgfrl1
105	JAK/Stat Signaling	6	Stat3, Socs3, Stat1, Cdkn1a, Rras, Pik3cg
106	GADD45 Signaling	5	Ccnd1, Cdkn1a, Cdk2, Cdk1, Ccnb1
107	Antigen Presentation Pathway	5	Hla-A, Cd74, Hla-Dqa1, Tapbp, Psmb8
108	Autoimmune Thyroid Disease Signaling	5	Hla-A, Hla-Dqa1, Hla-Dqb1, Fcer1g, Cd86
109	MIF-mediated Glucocorticoid Regulation	5	Tlr4, Ly96, Cd74, Ptgs2, Pla2g4a
110	Role of PKR in Interferon Induction and Antiviral Response	5	Eif2ak2, Tnfrsf1a, Stat1, Fcgr1a, Casp8
111	MIF Regulation of Innate Immunity	5	Tlr4, Ly96, Cd74, Ptgs2, Pla2g4a
112	Retinoic acid Mediated Apoptosis Signaling	5	Parp12, Parp3, Parp9, Parp14, Casp8
113	OX40 Signaling Pathway	5	H2-K2/H2-Q9, Hla-A, Hla-Dqa1, Hla-Dqb1, Fcer1g
114	Phospholipases	5	Plce1, Pld4, Plb1, Pla2g4a, Hmox1
115	Calcium-induced T Lymphocyte Apoptosis	5	Hla-Dqa1, Hla-Dqb1, Fcer1g, Capn2, Prkcg

116	Prostanoid Biosynthesis	4	Ptgs2, Hpgds, Ptgs1, Tbxas1
117	Dermatan Sulfate Degradation (Metazoa)	4	Hexb, Chil3/Chil4, Cd44, Fgfrl1
118	DNA damage-induced 14-3-3σ Signaling	4	Cdk2, Ccnb2, Cdk1, Ccnb1
119	B Cell Development	4	Hla-Dqa1, Hla-Dqb1, Ptprc, Cd86
120	IL-22 Signaling	4	Stat3, Il10rb, Socs3, Stat1
121	Role of JAK family kinases in IL-6-type Cytokine Signaling	4	Stat3, Socs3, Stat1, Osmr
122	Role of JAK2 in Hormone-like Cytokine Signaling	4	Stat3, Prlr, Socs3, Stat1
123	Inhibition of Matrix Metalloproteases	4	A2m, Mmp19, Timp4, Timp1
124	Chondroitin Sulfate Degradation (Metazoa)	3	Hexb, Chil3/Chil4, Cd44
125	Fatty Acid α-oxidation	3	Aloxe3, Ptgs2, Alox12b
126	Glutathione Redox Reactions I	3	Gpx3, Gpx1, Gpx8
127	Thyroid Hormone Biosynthesis	2	Ctsd, Iyd
128	Xanthine and Xanthosine Salvage	1	Pnp

APPENDIX 6

Significantly changed IPA Canonical Pathways at 30 days post injection in KA-MTLE (p<0.05).The pathways are ranked by descending number of genes.

#	Ingenuity Canonical Pathways	No of genes	Gene Symbols
1	Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	16	Eif2ak2, Oas1, C3, Tgfb1, Tlr1, C1qb, Ddx58, C3ar1, C1qa, Pik3cg, C1qc, Irf7, Ifih1, Il1a, Tlr2, Clec7a
2	Dendritic Cell Maturation	16	Tnfrsf1a, Hla-Dqa1, Fcgr1a, Plce1, Fcer1g, Trem2, Fcgr2a, Pik3cg, Irf8, Hla-A, Fcgr2b, Tyrobp, Il1a, Tlr2, Cd86, Fcgr3a/Fcgr3b
3	G-Protein Coupled Receptor Signaling	16	Drd5, Htr1a, Prkar2b, S1pr3, Ptger4, Pik3cg, Mc4r, Dusp1, P2ry13, Rgs2, Pde3a, Grm1, Htr2c, Pde1a, Dusp4, Htr2a
4	Granulocyte Adhesion and Diapedesis	15	Itgam, Ccl6, Tnfrsf1a, Cxcl10, Csf3r, Itga6, Msn, Itgb2, Ccl3l3, Hspb1, Cxcl13, Ccl9, Ccl2, Il1a, Cxcl16
5	Systemic Lupus Erythematosus Signaling	15	Hla-E, Fcgr1a, Cd72, Fcer1g, Hla-F, Fcgr2a, Pik3cg, Hla-A, Fcgr2b, Inpp5d, Il1a, Ptprc, Cd86, Lyn, Fcgr3a/Fcgr3b
6	Leukocyte Extravasation Signaling	15	Itgam, F11r, Arhgap6, Itga6, Ncf1, Msn, Itgb2, Rac2, Cd44, Vav1, Pik3cg, Tec, Timp1, Cybb, Cyba
7	Phagosome formation	14	Fcgr1a, Tlr1, Plce1, Fcer1g, Fcrls, Rhoj, Fcgr2a, Pik3cg, Fcgr2b, Inpp5d, Tlr13, Tlr2, Clec7a, Fcgr3a/Fcgr3b
8	Hepatic Fibrosis / Hepatic Stellate Cell Activation	14	Pdgfd, Tgfb1, Tnfrsf1a, Cd14, Ctgf, Igf1, Il10ra, A2m, Ifngr1, Tgfbr2, Ccl2, Il1a, Timp1, Hgf
9	Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	13	Fcgr1a, Ncf1, Fyb, Pld4, Rac2, Arpc1b, Vav1, Fcgr2a, Pik3cg, Lcp2, Inpp5d, Lyn, Fcgr3a/Fcgr3b
10	PI3K Signaling in B Lymphocytes	13	C3, Plce1, Vav1, Atf3, Pik3cg, Fcgr2b, Inpp5d, Pik3ap1, Itpr1, Cd180, Ptprc, Blnk, Lyn
11	Acute Phase Response Signaling	13	C3, Tnfrsf1a, Serpinf1, Cp, Serpina3, Pik3cg, Osmr, A2m, C4a/C4b, Il1a, Serpinf2, C1s, Serping1
12	Agranulocyte Adhesion and Diapedesis	13	Ccl6, Tnfrsf1a, Cxcl10, Itga6, Msn, Itgb2, Ccl3l3, Glycam1, Cxcl13, Ccl9, Ccl2, Il1a, Cxcl16
13	cAMP-mediated signaling	13	Drd5, Htr1a, Prkar2b, S1pr3, Camk1d, Ptger4, Mc4r, Dusp1, P2ry13, Rgs2, Pde3a, Pde1a, Dusp4
14	Complement System	12	Itgam, C1qc, C4a/C4b, C3, C1qb, Itgax, Itgb2, C1s, Serping1, Cfh, C3ar1, C1qa

15	Communication between Innate and Adaptive Immune Cells	12	Hla-E, Hla-A, Cxcl10, Tlr1, Ccl9, Il1a, Tlr13, Fcer1g, Ccl3l3, Tlr2, Cd86, Hla-F
16	Role of NFAT in Regulation of the Immune Response	12	Lcp2, Fcgr2b, Hla-Dqa1, Fcgr1a, Itpr1, Fcer1g, Blnk, Cd86, Fcgr2a, Pik3cg, Lyn, Fcgr3a/Fcgr3b
17	B Cell Receptor Signaling	12	Fcgr2b, Inpp5d, Pik3ap1, Bcl2a1, Apbb1ip, Ptprc, Blnk, Rac2, Vav1, Fcgr2a, Pik3cg, Lyn
18	TREM1 Signaling	11	Fcgr2b, Tlr1, Ccl2, Tyrobp, Tlr13, Itgax, Tlr2, Cd86, Naip1 (Includes Others)
19	Death Receptor Signaling	11	Hspb1, Naip, Tnfrsf1a, Parp9, Parp14, Hspb3, Naip1 (Includes Others), Casp8, Arhgdib
20	Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	11	Lyz, Ifngr1, Irf8, Tnfrsf1a, Ncf1, Spi1, Cybb, Rhoj, Tlr2, Cyba, Pik3cg
21	Actin Cytoskeleton Signaling	11	Pdgfd, Fgf16, Cd14, Nckap1l, Fgf10, Msn, Iqgap2, Rac2, Arpc1b, Vav1, Pik3cg
22	T Helper Cell Differentiation	10	Ifngr1, Tgfbr2, Il10rb, Tgfb1, Tnfrsf1a, Hla-Dqa1, Fcer1g, Cd86, Il2rg, Il10ra
23	Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	10	Tgfb1, Cxcl13, Tlr1, Hla-Dqa1, Il1a, Tlr13, Fcer1g, Spp1, Tlr2, Cd86
24	Natural Killer Cell Signaling	10	Lcp2, Lair1, Inpp5d, Tyrobp, Fcer1g, Rac2, Vav1, Fcgr2a, Pik3cg, Fcgr3a/Fcgr3b
25	LXR/RXR Activation	10	Lyz, C4a/C4b, C3, Tnfrsf1a, Serpinf1, Cd14, Ccl2, Il1a, Abca1, Serpinf2
26	Clathrin-mediated Endocytosis Signaling	10	Lyz, Pdgfd, Itgb5, Fgf16, Myo1e, Fgf10, Itgb2, Arpc1b, Igf1, Pik3cg
27	Role of NFAT in Cardiac Hypertrophy	10	Tgfbr2, Tgfb1, Prkar2b, Slc8a1, Plce1, Itpr1, Camk1d, Hdac9, Igf1, Pik3cg
28	IL-8 Signaling	10	Itgam, Hbegf, Itgb5, Itgax, Pld4, Itgb2, Rac2, Cybb, Rhoj, Pik3cg
29	Caveolar-mediated Endocytosis Signaling	9	Itgam, Cav1, Hla-A, Itgb5, Cd48, Itga6, Itgax, Flnc, Itgb2
30	Type I Diabetes Mellitus Signaling	9	Ifngr1, Hla-E, Hla-A, Tnfrsf1a, Hla-Dqa1, Fcer1g, Cd86, Hla-F, Casp8
31	iCOS-iCOSL Signaling in T Helper Cells	9	Lcp2, Inpp5d, Hla-Dqa1, Itpr1, Ptprc, Fcer1g, Vav1, Il2rg, Pik3cg
32	CD28 Signaling in T Helper Cells	9	Lcp2, Hla-Dqa1, Itpr1, Ptprc, Fcer1g, Arpc1b, Cd86, Vav1, Pik3cg
33	Cdc42 Signaling	9	H2-K2/H2-Q9, Hla-E, Hla-A, Hla-Dqa1, Iqgap2, Fcer1g, Arpc1b, Vav1, Hla-F
34	NF-κB Signaling	9	Eif2ak2, Tgfbr2, Tnfrsf1a, Tlr1, Il1a, Fcer1g, Tlr2, Casp8, Pik3cg
35	Neuroprotective Role of THOP1 in Alzheimer's Disease	8	Sst, Pdyn, Tac1, Hla-E, Hla-A, Prkar2b, Serpina3, Hla-F
36	Virus Entry via Endocytic Pathways	8	Cav1, Hla-A, Itgb5, Itga6, Flnc, Itgb2, Rac2, Pik3cg
37	Neuropathic Pain Signaling In Dorsal Horn Neurons	8	Tac1, Prkar2b, Plce1, Itpr1, Camk1d, Grm1, Bdnf, Pik3cg
38	Role of Tissue Factor in Cancer	8	Hbegf, Cyr61, Itgb5, Itga6, Ctgf,

			Rps6ka6, Pik3cg, Lyn
39	p38 MAPK Signaling	8	Hspb1, Tgfbr2, Tgfb1, Dusp1, Tnfrsf1a, Il1a, Hspb3, Rps6ka6
40	Atherosclerosis Signaling	8	Lyz, Pdgfd, Tgfb1, Ccl2, Il1a, Itgb2, Alox12b, Plb1
41	Aryl Hydrocarbon Receptor Signaling	8	Hspb1, Gsto1, Tgfb1, Il1a, Hspb3, Ctsd, Mgst1, Nfe2l2
42	Human Embryonic Stem Cell Pluripotency	8	Inhba, Tgfbr2, Pdgfd, Tgfb1, S1pr3, Bdnf, Bmp3, Pik3cg
43	Graft-versus-Host Disease Signaling	7	Hla-E, Hla-A, Hla-Dqa1, Il1a, Fcer1g, Cd86, Hla-F
44	Allograft Rejection Signaling	7	H2-K2/H2-Q9, Hla-E, Hla-A, Hla-Dqa1, Fcer1g, Cd86, Hla-F
45	Macropinocytosis Signaling	7	Pdgfd, Itgb5, Cd14, Itgb2, Hgf, Csf1r, Pik3cg
46	Crosstalk between Dendritic Cells and Natural Killer Cells	7	Hla-E, Hla-A, Tyrobp, Trem2, Cd86, Hla-F, Il2rg
47	TGF-β Signaling	7	Inhba, Tgfbr2, Acvr1c, Irf7, Tgfb1, Tgif1, Pmepa1
48	IGF-1 Signaling	7	Cyr61, Igfbp7, Prkar2b, Igfbp2, Ctgf, Igf1, Pik3cg
49	Fc Epsilon RI Signaling	7	Lcp2, Inpp5d, Fcer1g, Rac2, Vav1, Pik3cg, Lyn
50	PKCθ Signaling in T Lymphocytes	7	Lcp2, Hla-Dqa1, Fcer1g, Rac2, Cd86, Vav1, Pik3cg
51	HMGB1 Signaling	7	Ifngr1, Tgfb1, Tnfrsf1a, Ccl2, Il1a, Rhoj, Pik3cg
52	IL-6 Signaling	7	A2m, Hspb1, Tnfrsf1a, Cd14, Il1a, Hspb3, Pik3cg
53	Autoimmune Thyroid Disease Signaling	6	Hla-E, Hla-A, Hla-Dqa1, Fcer1g, Cd86, Hla-F
54	OX40 Signaling Pathway	6	H2-K2/H2-Q9, Hla-E, Hla-A, Hla-Dqa1, Fcer1g, Hla-F
55	Glioma Invasiveness Signaling	6	Itgb5, Plau, Timp1, Rhoj, Cd44, Pik3cg
56	Eicosanoid Signaling	6	Akr1c3, Ptger4, Alox12b, Plb1, Hpgds, Tbxas1
57	IL-10 Signaling	6	Il10rb, Fcgr2b, Cd14, Il1a, Fcgr2a, Il10ra
58	GPCR-Mediated Integration of Enteroendocrine Signaling Exemplified by an L Cell	6	Sst, Prkar2b, Npy2r, Plce1, Itpr1, Adcyap1
59	TNFR1 Signaling	6	Naip, Tnfrsf1a, Naip1 (Includes Others), Casp8
60	Antigen Presentation Pathway	5	Hla-E, Hla-A, Cd74, Hla-Dqa1, Hla-F
61	FcγRIIB Signaling in B Lymphocytes	5	Fcgr2b, Inpp5d, Blnk, Pik3cg, Lyn
62	MSP-RON Signaling Pathway	5	Itgam, Ccl2, Itgb2, Tlr2, Pik3cg
63	Toll-like Receptor Signaling	5	Eif2ak2, Tlr1, Cd14, Il1a, Tlr2
64	Interferon Signaling	4	Oas1, Ifngr1, Ifit3, Ifitm3
65	Role of RIG1-like Receptors in Antiviral Innate Immunity	4	Irf7, Ifih1, Ddx58, Casp8
66	Coagulation System	4	A2m, Pros1, Plau, Serpinf2
67	Role of IL-17F in Allergic Inflammatory Airway Diseases	4	Cxcl10, Ccl2, Rps6ka6, Igf1
68	Role of PKR in Interferon Induction and Antiviral Response	4	Eif2ak2, Tnfrsf1a, Fcgr1a, Casp8

69	Ephrin A Signaling	4	Epha3, Efna5, Vav1, Pik3cg
70	Nur77 Signaling in T Lymphocytes	4	Hla-Dqa1, Fcer1g, Hdac9, Cd86
71	Chondroitin Sulfate Degradation (Metazoa)	3	Hexb, Hexa, Cd44
72	Dermatan Sulfate Degradation (Metazoa)	3	Hexb, Hexa, Cd44
73	Differential Regulation of Cytokine Production in Intestinal Epithelial Cells by IL-17A and IL-17F	3	Ccl2, Il1a, Lcn2
74	B Cell Development	3	Hla-Dqa1, Ptprc, Cd86
75	Glutathione-mediated Detoxification	3	Gsto1, Mgst1, Hpgds
76	Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells	3	Hla-A, Fcer1g, Casp8
77	Role of Hypercytokinemia/hyperchemokinemia in the Pathogenesis of Influenza	3	Cxcl10, Ccl2, Il1a
78	Thyroid Hormone Biosynthesis	2	Ctsd, Iyd
79	Prostanoid Biosynthesis	2	Hpgds, Tbxas1
80	Methylglyoxal Degradation III	2	Akr1c3, Akr1b10

Comparison Analysis

APPENDIX 7

IPA Canonical Pathways that are significantly changed (p<0.05) only at 1 day post injection. Pathways are ranked by descending number of genes.

	Ingenuity Canonical Pathways	No of Genes	Gene Symbols
1	Gαi Signaling	11	Adcy1, Grm2, Cav1, Htr1a, Stat3, Rgs7, S1pr3, Grm8, Rgs4, Grm3, Prkar2a
2	RAR Activation	11	Fos, Adcy1, Akr1c3, Nrip2, Smad7, Dusp1, Igfbp3, Bmp2, Mapkapk2, Cited2, Prkar2a
3	ERK/MAPK Signaling	9	Fos, Hspb1, Stat3, Dusp1, Pak6, Pla2g4a, Itga5, Dusp4, Prkar2a
4	Hepatic Cholestasis	8	Adcy1, Il11, Cyp7b1, Cd14, Lif, Slco1c1, Il33, Prkar2a
5	Synaptic Long Term Potentiation	7	Adcy1, Grm2, Plce1, Grm1, Grm8, Grm3, Prkar2a
6	VDR/RXR Activation	7	Klk6, Thbd, Cxcl10, Cd14, Cdkn1a, Igfbp3, Spp1
7	Corticotropin Releasing Hormone Signaling	6	Fos, Adcy1, Nr4a1, Ptgs2, Bdnf, Prkar2a
8	Leptin Signaling in Obesity	6	Adcy1, Stat3, Socs3, Plce1, Npy, Prkar2a
9	Renin-Angiotensin Signaling	6	Fos, Adcy1, Stat3, Pak6, Ccl2, Prkar2a
10	Sphingosine-1-phosphate Signaling	6	Adcy1, S1pr3, Plce1, Sphk1, Rhoj, Rnd3
11	Cholecystokinin/Gastrin-mediated Signaling	6	Fos, Ptgs2, Map2k3, Rhoj, Rnd3, Il33
12	ErbB Signaling	5	Fos, Hbegf, Areg, Pak6, Map2k3
13	Glutamate Receptor Signaling	5	Grm2, Homer2, Grm1, Grm8, Grm3
14	Heparan Sulfate Biosynthesis	4	Sult2b1, Hs3st2, Ndst4, Extl1
15	Heparan Sulfate Biosynthesis (Late Stages)	4	Sult2b1, Hs3st2, Ndst4, Extl1
16	Phototransduction Pathway	4	Pde6b, Opn3, Arr3, Prkar2a
17	Role of IL-17A in Arthritis	4	Ccl2, Ptgs2, Map2k3, Mapkapk2
18	Hematopoiesis from Pluripotent Stem Cells	3	Il11, Kitlg, Lif
19	Retinoate Biosynthesis I	3	Akr1c3, Akr1b10, Bmp2

20	Heme Degradation	2	Blvrb, Hmox1
21	Putrescine Biosynthesis III	1	Odc1
22	Sulfate Activation for Sulfonation	1	Papss2

APPENDIX 8

IPA Canonical Pathways that are significantly changed (p<0.05) only at 3 days post injection. Pathways are ranked by descending number of genes.

Ingenuity Canonical Pathways	No of Genes	Gene Symbols
Integrin Signaling	19	Itgam, Itgb5, Itgav, Nedd9, Itga6, Tspan4, Rhoc, Myl9, Itgb2, Rac2, Rhoj, Arpc1b, Pik3cg, Cav1, Itga1, Itgb1, Rras, Itga5, Capn2
Colorectal Cancer Metastasis Signaling	16	Tnfrsf1a, Tlr1, Rhoc, Rhoj, Pik3cg, Tlr4, Stat3, Tgfbr2, Gng5, Mmp19, Stat1, Ccnd1, Ptgs2, Tlr13, Rras, Tlr2
ILK Signaling	15	Itgb5, Tnfrsf1a, Flna, Rhoc, Myl9, Itgb2, Rhoj, Pik3cg, Vim, Fn1, Ppp1r14b, Itgb1, Ccnd1, Ptgs2, Flnc
Signaling by Rho Family GTPases	14	Iqgap1, Ezr, Msn, Nox4, Rhoc, Myl9, Rhoj, Arpc1b, Pik3cg, Vim, Gng5, Itgb1, Cybb, Itga5
Tec Kinase Signaling	14	Hck, Rhoc, Fcer1g, Rhoj, Vav1, Pik3cg, Tlr4, Stat3, Gng5, Stat1, Itgb1, Itga5, Prkcg, Lyn
Germ Cell-Sertoli Cell Junction Signaling	12	A2m, Iqgap1, Tgfbr2, Tnfrsf1a, Itgb1, Tubb6, Itga6, Rhoc, Rac2, Rhoj, Rras, Pik3cg
NF-κB Activation by Viruses	11	Eif2ak2, Itga1, Itgb5, Itgav, Itgb1, Itga6, Itgb2, Rras, Itga5, Pik3cg, Prkcg
Pancreatic Adenocarcinoma Signaling	11	Hbegf, Tgfbr2, Stat3, Stat1, Ptgs2, Ccnd1, Cdkn1a, Cdk2, Pld4, Hmox1, Pik3cg
GM-CSF Signaling	10	Hck, Stat3, Bcl2a1, Stat1, Csf2rb, Ccnd1, Runx1, Rras, Pik3cg, Lyn
HGF Signaling	10	Stat3, Itgb1, Ptgs2, Ccnd1, Cdkn1a, Cdk2, Rras, Itga5, Pik3cg, Prkcg
IL-12 Signaling and Production in Macrophages	10	Tlr4, Lyz, Apoc2, Irf8, Myd88, Stat1, Spi1, Tlr2, Pik3cg, Prkcg
Paxillin Signaling	10	Itgam, Itga1, Itgb5, Itgav, Itgb1, Itga6, Itgb2, Rras, Itga5, Pik3cg
PTEN Signaling	10	Tgfbr2, Inpp5d, Itgb1, Ccnd1, Cdkn1a, Rac2, Rras, Itga5, Pik3cg, Fgfrl1
Rac Signaling	9	Iqgap1, Itgb1, Nox4, Cybb, Arpc1b, Rras, Cd44, Itga5, Pik3cg
Regulation of Cellular Mechanics by Calpain Protease	9	Itgb1, Ccnd1, Ezr, Cdk2, Ccna2, Rras, Itga5, Cdk1, Capn2
Acute Myeloid Leukemia Signaling	8	Stat3, Csf2rb, Ccnd1, Kitlg, Runx1, Spi1, Rras, Pik3cg
Agrin Interactions at Neuromuscular Junction	8	Itga1, Erbb4, Itgb1, Itga6, Itgb2, Rac2, Rras, Itga5
Apoptosis Signaling	8	NAIP, TNFRSF1A, BCL2A1, RRAS, Naip1 (Includes Others), CASP8, CDK1, CAPN2

Cell Cycle: G2/M DNA Damage Checkpoint Regulation	8	Top2a, Cdkn1a, Cks2, Cks1b, Ccnb2, Plk1, Cdk1, Ccnb1
Cyclins and Cell Cycle Regulation	8	Cdkn2c, Ccnd1, Cdkn1a, Cdk2, Ccna2, Ccnb2, Cdk1, Ccnb1
fMLP Signaling in Neutrophils	8	Gng5, Ncf1, Nox4, Cybb, Arpc1b, Rras, Pik3cg, Prkcg
HER-2 Signaling in Breast Cancer	8	Itgb5, Itgb1, Ccnd1, Cdkn1a, Itgb2, Rras, Pik3cg, Prkcg
IL-4 Signaling	8	Inpp5d, Hla-Dqa1, Hla-Dqb1, Il13ra1, Il4r, Rras, Il2rg, Pik3cg
Reelin Signaling in Neurons	8	Hck, Itga1, Itgb1, Itga6, Itgb2, Itga5, Pik3cg, Lyn
Role of JAK1 and JAK3 in γc Cytokine Signaling	8	Stat3, Socs3, Stat1, Il4r, Blnk, Rras, Il2rg, Pik3cg
Activation of IRF by Cytosolic Pattern Recognition Receptors	7	Dhx58, Irf9, Irf7, Stat1, Ifih1, Ddx58, Ifit2
Bladder Cancer Signaling	7	Mmp19, Ccnd1, Fgf10, Cdkn1a, Fgf2, Thbs1, Rras
G Beta Gamma Signaling	7	Hbegf, Cav1, Gng5, Cav2, Rras, Pik3cg, Prkcg
IL-3 Signaling	7	Stat3, Inpp5d, Stat1, Csf2rb, Rras, Pik3cg, Prkcg
Mitotic Roles of Polo-Like Kinase	7	Kif23, Prc1, Ccnb2, Kif11, Plk1, Cdk1, Ccnb1
Prolactin Signaling	7	Stat3, Prlr, Socs3, Stat1, Rras, Pik3cg, Prkcg
Regulation of Actin-based Motility by Rho	7	Itgb1, Rhoc, Myl9, Rac2, Rhoj, Arpc1b, Itga5
Actin Nucleation by ARP-WASP Complex	6	Itgb1, Rhoc, Rhoj, Arpc1b, Rras, Itga5
Cell Cycle Control of Chromosomal Replication	6	Mcm7, Mcm2, Cdk2, Mcm3, Dbf4, Mcm5
IL-15 Signaling	6	Stat3, Axl, Rras, Vcam1, Il2rg, Pik3cg
IL-9 Signaling	6	Stat3, Socs3, Stat1, Bcl3, Il2rg, Pik3cg
JAK/Stat Signaling	6	Stat3, Socs3, Stat1, Cdkn1a, Rras, Pik3cg
STAT3 Pathway	6	Tgfbr2, Stat3, Socs3, Cdkn1a, Rras, Fgfrl1
Estrogen-mediated S-phase Entry	6	Ccnd1, Cdkn1a, Cdk2, Ccna2, Rbl1, Cdk1
Calcium-induced T Lymphocyte Apoptosis	5	Hla-Dqa1, Hla-Dqb1, Fcer1g, Capn2, Prkcg
Phospholipases	5	Plce1, Pld4, Plb1, Pla2g4a, Hmox1
DNA damage-induced 14-3-3σ Signaling	4	Cdk2, Ccnb2, Cdk1, Ccnb1
IL-22 Signaling	4	Stat3, Il10rb, Socs3, Stat1
Inhibition of Matrix Metalloproteases	4	A2m, Mmp19, Timp4, Timp1

Role of JAK2 in Hormone-like Cytokine Signaling	4	Stat3, Prlr, Socs3, Stat1
TWEAK Signaling	4	Naip, Tnfrsf12a, Naip1, Casp8
Glutathione Redox Reactions I	3	Gpx3, Gpx1, Gpx8
Chondroitin Sulfate Degradation (Metazoa)	3	Hexb,Chil3/Chil4,Cd44
Xanthine and Xanthosine Salvage	1	Pnp

APPENDIX 9

IPA Canonical Pathways that are significantly changed (p<0.05) only at 30 days post injection. Pathways are ranked by descending number of genes.

Ingenuity Canonical Pathways	No of Genes	Gene Symbols
Role of NFAT in Cardiac Hypertrophy	10	Tgfbr2, Tgfb1, Prkar2b, Slc8a1, Plce1, Itpr1, Camk1, Hdac9, Igf1, Pik3cg
Ephrin A Signaling	4	Epha3, Efna5, Vav1, Pik3cg
Nur77 Signaling in T Lymphocytes	4	Hla-Dqa1, Fcer1g, Hdac9, Cd86
TNFR1 Signaling	4	Naip, Tnfrsf1a, Naip1, Casp8
Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells	3	HLA-A,FCER1G,CASP8
Chondroitin Sulfate Degradation (Metazoa)	3	Hexb, Hexa, Cd44
Differential Regulation of Cytokine Production in Intestinal Epithelial Cells by IL-17A and IL-17F	3	Ccl2, Il1a, Lcn2
Glutathione-mediated Detoxification	3	Gsto1, Mgst1, Hpgds

APPENDIX 10

IPA Canonical Pathways that remain significantly changed (p<0.05) across the three time points of the study (1, 3, 30 days). Pathways are in alphabetical order.

Ingenuity Canonical Pathways	Sign. Changed Genes at 1 day	Sign. Changed Genes at 3 days	Sign. Changed Genes at 30 days
Acute Phase Response Signaling	9	20	13
	Fos, Stat3, Tf, Socs3, Map2k3, Serpine1, Hmox1, Il33, Osmr	Tf, C3, Myd88, Socs3, Tnfrsf1a, Serpinf1, Cp, Rbp1, Serpina3, Hmox1, Pik3cg, Osmr, A2m, Stat3, Fn1, Serpinf2, Serpine1, Serping1, Rras, Il33	C3, Tnfrsf1a, Serpinf1, Cp, Serpina3, Pik3cg, Osmr, A2m, C4a/C4b, Il1a, Serpinf2, C1s, Serping1
Agranulocyte Adhesion and Diapedesis	10	20	13
	Cldn10, Ccl2, Cxcl10, C5ar1, Ccl2, Ccl9, Msn, Ccl3l3, Itga5, Il33	Ccl2, Tnfrsf1a, Cxcl10, Itga6, Ezr, Msn, Myl9, Itgb2, Ccl3l3, Vcam1, Itga1, Fn1, Mmp19, C5ar1, Itgb1, Ccl2, Cxcl16, Sdc4, Itga5, Il33	Ccl6, Tnfrsf1a, Cxcl10, Itga6, Msn, Itgb2, Ccl3l3, Glycam1, Cxcl13, Ccl9, Ccl2, Il1a, Cxcl16
Atherosclerosis Signaling	7	13	8
	Aloxe3, Ccl2, Msr1, Tnfrsf12a, Alox12b, Pla2g4a, Il33	Msr1, Itgb2, Vcam1, Lyz, Apoc2, Aloxe3, Ccl2, Csf1, Tnfrsf12a, Alox12b, Plb1, Pla2g4a, Il33	Lyz, Pdgfd, Tgfb1, Ccl2, Il1a, Itgb2, Alox12b, Plb1
Caveolar-mediated Endocytosis Signaling	5	13	9
	Cav1, Hla-A, Itgav, Flnc, Itga5	Itgam, Itgb5, Itgav, Flna, Itga6, Cd48, Itgb2, Cav1, Itga1, Hla-A, Itgb1, Flnc, Itga5	Itgam, Cav1, Hla-A, Itgb5, Cd48, Itga6, Itgax, Flnc, Itgb2
Coagulation System	4	6	4
	Pros1, Thbd, Plaur, Serpine1	A2m, Pros1, Plau, Serpinf2, F13a1, Serpine1	A2m, Pros1, Plau, Serpinf2
Communication between Innate and Adaptive Immune Cells	5	10	12
	Hla-A, Cxcl10, Ccl9, Ccl3l3, Il33	Tlr4, Hla-A, Cxcl10, Tlr1, Tlr13, Fcer1g, Ccl3l3, Tlr2, Cd86, Il33	Hla-E, Hla-A, Cxcl10, Tlr1, Ccl9, Il1a, Tlr13, Fcer1g, Ccl3l3, Tlr2, Cd86, Hla-F
Death Receptor	7	10	9

Ingenuity Canonical Pathways	Sign. Changed Genes at 1 day	Sign. Changed Genes at 3 days	Sign. Changed Genes at 30 days
Signaling			
	Tiparp, Parp12, Hspb1, Zc3hav1, Parp9, Parp14, Arhgdib	Parp12, Hspb1, Naip, Tnfrsf1a, Parp3, Parp9, Parp14, Naip1, Casp8, Arhgdib	Hspb1, Naip, Tnfrsf1a, Parp9, Parp14, Hspb3, Naip1, Casp8, Arhgdib
Glioma Invasiveness Signaling	6	11	6
	Itgav, Plaur, Timp1, Rhoj, Rnd3, Cd44	Hmmr, Itgb5, Itgav, Plau, Timp4, Rhoc, Timp1, Rhoj, Rras, Cd44, Pik3cg	Itgb5, Plau, Timp1, Rhoj, Cd44, Pik3cg
Granulocyte Adhesion and Diapedesis	11	20	15
	Cldn10, Ccl2, Hspb1, Cxcl10, C5ar1, Ccl2, Ccl9, Msn, Ccl3l3, Itga5, Il33	Ccl2, Itgam, Tnfrsf1a, Cxcl10, Itga6, Ezr, Msn, Itgb2, Ccl3l3, Vcam1, Hspb1, Itga1, Mmp19, C5ar1, Itgb1, Ccl2, Cxcl16, Sdc4, Itga5, Il33	Itgam, Ccl6, Tnfrsf1a, Cxcl10, Csf3r, Itga6, Msn, Itgb2, Ccl3l3, Hspb1, Cxcl13, Ccl9, Ccl2, Il1a, Cxcl16
Hepatic Fibrosis / Hepatic Stellate Cell Activation	11	19	14
	Col12a1, Smad7, Klf6, Cd14, Ccl2, Edn1, Ctgf, Igfbp3, Timp1, Fgf2, Serpine1	Igfbp4, Tnfrsf1a, Ctgf, Fgf2, Myl9, Vcam1, Tlr4, A2m, Col12a1, Tgfbr2, Ly96, Fn1, Stat1, Ccl2, Csf1, Il4r, Igfbp3, Timp1, Serpine1	Pdgfd, Tgfb1, Tnfrsf1a, Cd14, Ctgf, Igf1, Il10ra, A2m, Ifngr1, Tgfbr2, Ccl2, Il1a, Timp1, Hgf
IGF-1 Signaling	7	10	7
	Fos, Stat3, Cyr61, Socs3, Ctgf, Igfbp3, Prkar2a	Igfbp4, Stat3, Cyr61, Igfbp7, Socs3, Igfbp2, Ctgf, Igfbp3, Rras, Pik3cg	Cyr61, Igfbp7, Prkar2b, Igfbp2, Ctgf, Igf1, Pik3cg
IL-10 Signaling	9	8	6
	Fos, Stat3, Fcgr2b, Socs3, Cd14, Blvrb, Map2k3, Hmox1, Il33	Stat3, Il10rb, Fcgr2b, Socs3, Il4r, Hmox1, Il33, Fcgr2a	Il10rb, Fcgr2b, Cd14, Il1a, Fcgr2a, Il10ra
IL-6 Signaling	8	9	7
	Fos, Hspb1, Stat3, Socs3, Cd14, Map2k3, Il33, Mapkapk2	A2m, Hspb1, Stat3, Socs3, Tnfrsf1a, Rras, Il33, Mapkapk2, Pik3cg	A2m, Hspb1, Tnfrsf1a, Cd14, Il1a, Hspb3, Pik3cg
LXR/RXR Activation	6	13	10
	Tf, Cd14, Ccl2, Ptgs2, Msr1, Il33	Tf, C3, Tnfrsf1a, Serpinf1, Msr1, Tlr4, Lyz, Apoc2, Ly96, Ccl2, Ptgs2, Serpinf2, Il33	Lyz, C4a/C4b, C3, Tnfrsf1a, Serpinf1, Cd14, Ccl2, Il1a, Abca1, Serpinf2
Phagosome	8	21	14

Ingenuity Canonical Pathways	Sign. Changed Genes at 1 day	Sign. Changed Genes at 3 days	Sign. Changed Genes at 30 days
Formation			
	Fcgr2b, Plce1, Msr1, Fcrls, Rhoj, Rnd3, Itga5, Fcgr3a/Fcgr3b	Fcgr1a, Tlr1, Rhoc, Plce1, Msr1, Fcer1g, Fcrls, Rhoj, Fcgr2a, Pik3cg, Tlr4, Fn1, Fcgr2b, Inpp5d, Itgb1, Tlr13, Itga5, Tlr2, Clec7a, Prkcg, Fcgr3a/Fcgr3b	Fcgr1a, Tlr1, Plce1, Fcer1g, Fcrls, Rhoj, Fcgr2a, Pik3cg, Fcgr2b, Inpp5d, Tlr13, Tlr2, Clec7a, Fcgr3a/Fcgr3b
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	8	20	16
	Eif2ak2, Il11, Irf7, C5ar1, Ifih1, Lif, Ddx58, C3ar1	Eif2ak2, Oas1, C3, Myd88, Tlr1, C1qb, Ddx58, C3ar1, Oas1b, C1qa, Pik3cg, Tlr4, C1qc, Irf7, C5ar1, Ifih1, Tlr2, Clec7a, Ptx3, Prkcg	Eif2ak2, Oas1, C3, Tgfb1, Tlr1, C1qb, Ddx58, C3ar1, C1qa, Pik3cg, C1qc, Irf7, Ifih1, Il1a, Tlr2, Clec7a
Role of RIG1-like Receptors in Antiviral Innate Immunity	3	6	4
	Irf7, Ifih1, Ddx58	Dhx58, Irf7, Ifih1, Trim25, Ddx58, Casp8	Irf7, Ifih1, Ddx58, Casp8
Toll-like Receptor Signaling	5	7	5
	Fos, Eif2ak2, Cd14, Map2k3, Il33	Tlr4, Eif2ak2, Ly96, Myd88, Tlr1, Tlr2, Il33	Eif2ak2, Tlr1, Cd14, Il1a, Tlr2

APPENDIX 11

IPA Canonical Pathways that remain significantly changed (p<0.05) at 1 and 3 days post injection. Pathways are in alphabetical order.

Ingenuity Canonical Pathway	Sign. Changed Genes at 1 day	Sign. Changed Genes at 3 days
Endothelin-1 Signaling	11	9
	Fos, Adcy1, Mapk4, Ptgs2, Edn1, Plce1, Pla2g4a, Hmox1, Mapk6	Ptgs2, Plce1, Pld4, Plb1, Pla2g4a, Hmox1, Rras, Ptgs1, Casp8, Pik3cg, Prkcg
Fatty Acid α-oxidation	3	3
	Aloxe3, Ptgs2, Alox12b	Aloxe3, Ptgs2, Alox12b
GADD45 Signaling	3	5
	Cdkn1a, Gadd45b, Gadd45g	Ccnd1, Cdkn1a, Cdk2, Cdk1, Ccnb1
Growth Hormone Signaling	5	7
	Fos, Stat3, Socs3, Rps6ka3, Igfbp3	A2m, Stat3, Socs3, Stat1, Igfbp3, Pik3cg, Prkcg
Gαq Signaling	10	11
	Htr2b, Rgs7, Arhgef25, Rgs2, Grm1, Rgs4, Rhoj, Hmox1, Rnd3, Adra1a	Htr2b, Gng5, Chrm3, Rhoc, Pld4, Grm1, Rgs4, Rhoj, Hmox1, Pik3cg, Prkcg
IL-17 Signaling	6	7
	Cxcl10, Ccl2, Ptgs2, Map2k3, Timp1, Mapkapk2	Cxcl10, Ccl2, Ptgs2, Timp1, Rras, Mapkapk2, Pik3cg
MIF Regulation of Innate Immunity	4	5
	Fos, Cd14, Ptgs2, Pla2g4a	Tlr4, Ly96, Cd74, Ptgs2, Pla2g4a
MIF-mediated Glucocorticoid Regulation	3	5
	Cd14, Ptgs2, Pla2g4a	Tlr4, Ly96, Cd74, Ptgs2, Pla2g4a
Oncostatin M Signaling	3	6
	Stat3, Chi3l1, Osmr	Stat3, Chi3l1, Plau, Stat1, Rras, Osmr
PDGF Signaling	5	7
	Fos, Eif2ak2, Cav1, Stat3, Sphk1	Eif2ak2, Cav1, Stat3, Inpp5d, Stat1, Rras, Pik3cg
Phospholipase C Signaling	11	19
	Adcy1, Fcgr2b, Rps6ka3, Plce1, Blnk, Rhoj, Pla2g4a, Hmox1, Rnd3, Itga5, Tgm2	Rhoc, Plce1, Myl9, Pld4, Fcer1g, Rhoj, Hmox1, Fcgr2a, Lcp2, Fcgr2b, Gng5, Itgb1, Blnk, Rras, Itga5, Pla2g4a, Tgm2, Prkcg, Lyn
Retinoic acid Mediated Apoptosis Signaling	5	5
	Tiparp, Parp12, Zc3hav1, Parp9, Parp14	Parp12, Parp3, Parp9, Parp14, Casp8
RhoGDI Signaling	8	11
	Pak6, Msn, Cdh4, Rhoj, Rnd3, Cd44, Itga5, Arhgdib	Gng5, Itgb1, Ezr, Msn, Rhoc, Myl9, Rhoj, Arpc1b, Cd44, Itga5, Arhgdib
Role of JAK family kinases in IL-6-type Cytokine	3	4

Ingenuity Canonical Pathway	Sign. Changed Genes at 1 day	Sign. Changed Genes at 3 days
Signaling		
	Stat3, Socs3, Osmr	Stat3, Socs3, Stat1, Osmr
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	12	24
	Fos, Stat3, Socs3, C5ar1, Ccl2, Plce1, Map2k3, Fgf2, Il16, Il33, Mapkapk2, Fcgr3a/Fcgr3b	Myd88, Socs3, Tnfrsf1a, Fcgr1a, Tlr1, Plce1, Fgf2, Il16, Vcam1, Mapkapk2, Pik3cg, Tlr4, Stat3, Fn1, C5ar1, Ccnd1, Ccl2, Csf1, Tlr13, Rras, Tlr2, Il33, Prkcg, Fcgr3a/Fcgr3b
Role of MAPK Signaling in the Pathogenesis of Influenza	5	6
	Cxcl10, Ccl2, Ptgs2, Map2k3, Pla2g4a	Cxcl10, Ccl2, Ptgs2, Plb1, Pla2g4a, Rras
UVA-Induced MAPK Signaling	8	8
	Fos, Tiparp, Parp12, Zc3hav1, Rps6ka3, Plce1, Parp9, Parp14	Parp12, Stat1, Parp3, Plce1, Parp9, Parp14, Rras, Pik3cg

APPENDIX 12

IPA Canonical Pathways that remain significantly changed (p<0.05) at 3 and 30 days post injection. Pathways are in alphabetical order.

Ingenuity Canonical Pathways	Sign. Changed Genes at 3 days	Sign. Changed Genes at 30 days
Actin Cytoskeleton Signaling	16	11
	Iqgap1, Flna, Fgf10, Ezr, Msn, Fgf2, Myl9, Rac2, Arpc1b, Vav1, Pik3cg, Fn1, Nckap1l, Itgb1, Rras, Itga5	Pdgfd, Fgf16, Cd14, Nckap1l, Fgf10, Msn, Iqgap2, Rac2, Arpc1b, Vav1, Pik3cg
Allograft Rejection Signaling	6	7
	H2-K2/H2-Q9, Hla-A, Hla-Dqa1, Hla-Dqb1, Fcer1g, Cd86	H2-K2/H2-Q9, Hla-E, Hla-A, Hla-Dqa1, Fcer1g, Cd86, Hla-F
Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	11	10
	Tlr4, Tlr1, Hla-Dqa1, Hla-Dqb1, Csf1, Tlr13, Fcer1g, Spp1, Tlr2, Cd86, Il33	Tgfb1, Cxcl13, Tlr1, Hla-Dqa1, Il1a, Tlr13, Fcer1g, Spp1, Tlr2, Cd86
Antigen Presentation Pathway	5	5
	Hla-A, Cd74, Hla-Dqa1, Tapbp, Psmb8	Hla-E, Hla-A, Cd74, Hla-Dqa1, Hla-F
Aryl Hydrocarbon Receptor Signaling	13	8
	Aldh1l1, Mcm7, Cdk2, Hspb1, Ccnd1, Aldh1l2, Cdkn1a, Rbl1, Ccna2, Ctsd, Cyp1b1, Tgm2, Nfe2l2	Hspb1, Gsto1, Tgfb1, Il1a, Hspb3, Ctsd, Mgst1, Nfe2l2
Autoimmune Thyroid Disease Signaling	5	6
	Hla-A, Hla-Dqa1, Hla-Dqb1, Fcer1g, Cd86	Hla-E, Hla-A, Hla-Dqa1, Fcer1g, Cd86, Hla-F
B Cell Development	4	3
	Hla-Dqa1, Hla-Dqb1, Ptprc, Cd86	Hla-Dqa1, Ptprc, Cd86
B Cell Receptor Signaling	13	12
	Rac2, Vav1, Fcgr2a, Pik3cg, Fcgr2b, Inpp5d, Pik3ap1, Bcl2a1, Apbb1ip, Ptprc, Blnk, Rras, Lyn	Fcgr2b, Inpp5d, Pik3ap1, Bcl2a1, Apbb1ip, Ptprc, Blnk, Rac2, Vav1, Fcgr2a, Pik3cg, Lyn
CD28 Signaling in T Helper Cells	9	9
	Lcp2, Hla-Dqa1, Hla-Dqb1, Ptprc, Fcer1g, Arpc1b, Cd86, Vav1, Pik3cg	Lcp2, Hla-Dqa1, Itpr1, Ptprc, Fcer1g, Arpc1b, Cd86, Vav1, Pik3cg
Cdc42 Signaling	11	9
	H2-K2/H2-Q9, Iqgap1, Hla-A, Hla-Dqa1, Hla-Dqb1, Itgb1, Myl9, Fcer1g, Arpc1b, Itga5, Vav1	H2-K2/H2-Q9, Hla-E, Hla-A, Hla-Dqa1, Iqgap2, Fcer1g, Arpc1b, Vav1, Hla-F
Clathrin-mediated Endocytosis Signaling	14	10
	Tf, Itgb5, Fgf10, Fgf2, Itgb2,	Lyz, Pdgfd, Itgb5, Fgf16,

Ingenuity Canonical Pathways	Sign. Changed Genes at 3 days	Sign. Changed Genes at 30 days
	Arpc1b, Pik3cg, Lyz, Apoc2, Itgb1, Hip1, Myo1e, Dab2, Itga5	Myo1e, Fgf10, Itgb2, Arpc1b, Igf1, Pik3cg
Complement System	10	12
	Itgam, C1qc, C3, C5ar1, C1qb, Itgb2, Serping1, Cfh, C3ar1, C1qa	Itgam, C1qc, C4a/C4b, C3, C1qb, Itgax, Itgb2, C1s, Serping1, Cfh, C3ar1, C1qa
Crosstalk between Dendritic Cells and Natural Killer Cells	7	7
	Tlr4, Hla-A, Csf2rb, Tyrobp, Trem2, Cd86, Il2rg	Hla-E, Hla-A, Tyrobp, Trem2, Cd86, Hla-F, Il2rg
Dendritic Cell Maturation	20	16
	Myd88, Tnfrsf1a, Hla-Dqa1, Hla-Dqb1, Fcgr1a, Plce1, Fcer1g, Trem2, Fcgr2a, Pik3cg, Tlr4, Irf8, Hla-A, Fcgr2b, Stat1, Tyrobp, Tlr2, Cd86, Il33, Fcgr3a/Fcgr3b	Tnfrsf1a, Hla-Dqa1, Fcgr1a, Plce1, Fcer1g, Trem2, Fcgr2a, Pik3cg, Irf8, Hla-A, Fcgr2b, Tyrobp, Il1a, Tlr2, Cd86, Fcgr3a/Fcgr3b
Dermatan Sulfate Degradation (Metazoa)	4	3
	Hexb, Chil3/Chil4, Cd44, Fgfrl1	Hexb, Hexa, Cd44
Eicosanoid Signaling	9	6
	Akr1c3, Alox5ap, Ptgs2, Alox12b, Plb1, Hpgds, Pla2g4a, Ptgs1, Tbxas1	Akr1c3, Ptger4, Alox12b, Plb1, Hpgds, Tbxas1
Fc Epsilon RI Signaling	10	7
	Lcp2, Inpp5d, Fcer1g, Rac2, Pla2g4a, Rras, Vav1, Pik3cg, Lyn, Prkcg	Lcp2, Inpp5d, Fcer1g, Rac2, Vav1, Pik3cg, Lyn
Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	17	13
	Hck, Fcgr1a, Ncf1, Ezr, Fyb, Pld4, Rac2, Arpc1b, Hmox1, Vav1, Fcgr2a, Pik3cg, Lcp2, Inpp5d, Prkcg, Lyn, Fcgr3a/Fcgr3b	Fcgr1a, Ncf1, Fyb, Pld4, Rac2, Arpc1b, Vav1, Fcgr2a, Pik3cg, Lcp2, Inpp5d, Lyn, Fcgr3a/Fcgr3b
FcγRIIB Signaling in B Lymphocytes	6	5
	Fcgr2b, Inpp5d, Blnk, Rras, Pik3cg, Lyn	Fcgr2b, Inpp5d, Blnk, Pik3cg, Lyn
Graft-versus-Host Disease Signaling	6	7
	Hla-A, Hla-Dqa1, Hla-Dqb1, Fcer1g, Cd86, Il33	Hla-E, Hla-A, Hla-Dqa1, Il1a, Fcer1g, Cd86, Hla-F
iCOS-iCOSL Signaling in T Helper Cells	9	9
	Lcp2, Inpp5d, Hla-Dqa1, Hla-Dqb1, Ptprc, Fcer1g, Vav1, Il2rg, Pik3cg	Lcp2, Inpp5d, Hla-Dqa1, Itpr1, Ptprc, Fcer1g, Vav1, Il2rg, Pik3cg
IL-8 Signaling	21	10
	Hbegf, Iqgap1, Itgam, Itgb5, Itgav, Nox4, Rhoc, Myl9,	Itgam, Hbegf, Itgb5, Itgax, Pld4, Itgb2, Rac2, Cybb,

Ingenuity Canonical Pathways	Sign. Changed Genes at 3 days	Sign. Changed Genes at 30 days
	Pld4, Itgb2, Rac2, Rhoj, Hmox1, Vcam1, Pik3cg, Gng5, Ccnd1, Ptgs2, Cybb, Rras, Prkcg	Rhoj, Pik3cg
Interferon Signaling	6	4
	Oas1, Irf9, Stat1, Ifit3, Ifitm3, Psmb8	Oas1, Ifngr1, Ifit3, Ifitm3
Leukocyte Extravasation Signaling	22	15
	Itgam, Jam2, F11r, Itga6, Ncf1, Ezr, Msn, Timp4, Itgb2, Rac2, Cd44, Vav1, Vcam1, Pik3cg, Itga1, Mmp19, Itgb1, Timp1, Cybb, Itga5, Cyba, Prkcg	Itgam, F11r, Arhgap6, Itga6, Ncf1, Msn, Itgb2, Rac2, Cd44, Vav1, Pik3cg, Tec, Timp1, Cybb, Cyba
Macropinocytosis Signaling	8	7
	Itgb5, Itgb1, Csf1, Itgb2, Rras, Itga5, Pik3cg, Prkcg	Pdgfd, Itgb5, Cd14, Itgb2, Hgf, Csf1r, Pik3cg
MSP-RON Signaling Pathway	8	5
	Tlr4, Itgam, Csf2rb, Ccl2, Csf1, Itgb2, Tlr2, Pik3cg	Itgam, Ccl2, Itgb2, Tlr2, Pik3cg
Natural Killer Cell Signaling	14	10
	Lair1, Cd244, Fcer1g, Rac2, Vav1, Fcgr2a, Pik3cg, Lcp2, Inpp5d, Tyrobp, Sh3bp2, Rras, Prkcg, Fcgr3a/Fcgr3b	Lcp2, Lair1, Inpp5d, Tyrobp, Fcer1g, Rac2, Vav1, Fcgr2a, Pik3cg, Fcgr3a/Fcgr3b
NF-κB Signaling	13	9
	Eif2ak2, Myd88, Tnfrsf1a, Tlr1, Fcer1g, Pik3cg, Fgfrl1, Tlr4, Tgfbr2, Rras, Tlr2, Il33, Casp8	Eif2ak2, Tgfbr2, Tnfrsf1a, Tlr1, Il1a, Fcer1g, Tlr2, Casp8, Pik3cg
OX40 Signaling Pathway	5	6
	H2-K2/H2-Q9, Hla-A, Hla-Dqa1, Hla-Dqb1, Fcer1g	H2-K2/H2-Q9, Hla-E, Hla-A, Hla-Dqa1, Fcer1g, Hla-F
PI3K Signaling in B Lymphocytes	15	13
	C3, Plce1, Vav1, Atf3, Pik3cg, Tlr4, Fcgr2b, Inpp5d, Pik3ap1, Il4r, Cd180, Ptprc, Blnk, Rras, Lyn	C3, Plce1, Vav1, Atf3, Pik3cg, Fcgr2b, Inpp5d, Pik3ap1, Itpr1, Cd180, Ptprc, Blnk, Lyn
PKCθ Signaling in T Lymphocytes	9	7
	Lcp2, Hla-Dqa1, Hla-Dqb1, Fcer1g, Rac2, Rras, Cd86, Vav1, Pik3cg	Lcp2, Hla-Dqa1, Fcer1g, Rac2, Cd86, Vav1, Pik3cg
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	16	11
	Tnfrsf1a, Ncf1, Rhoc, Spi1, Rhoj, Pik3cg, Tlr4, Lyz, Apoc2, Irf8, Ppp1r14b, Stat1, Cybb, Tlr2, Cyba, Prkcg	Lyz, Ifngr1, Irf8, Tnfrsf1a, Ncf1, Spi1, Cybb, Rhoj, Tlr2, Cyba, Pik3cg
Prostanoid Biosynthesis	4	2
	Ptgs2, Hpgds, Ptgs1, Tbxas1	Hpgds, Tbxas1
Role of NFAT in Regulation	14	12

Ingenuity Canonical Pathways	Sign. Changed Genes at 3 days	Sign. Changed Genes at 30 days
of the Immune Response		
	Hla-Dqa1, Hla-Dqb1, Fcgr1a, Fcer1g, Fcgr2a, Pik3cg, Lcp2, Fcgr2b, Gng5, Blnk, Rras, Cd86, Lyn, Fcgr3a/Fcgr3b	Lcp2, Fcgr2b, Hla-Dqa1, Fcgr1a, Itpr1, Fcer1g, Blnk, Cd86, Fcgr2a, Pik3cg, Lyn, Fcgr3a/Fcgr3b
Role of PKR in Interferon Induction and Antiviral Response	5	4
	Eif2ak2, Tnfrsf1a, Stat1, Fcgr1a, Casp8	Eif2ak2, Tnfrsf1a, Fcgr1a, Casp8
Systemic Lupus Erythematosus Signaling	14	15
	Fcgr1a, Cd72, Fcer1g, Fcgr2a, Pik3cg, Hla-A, Fcgr2b, Inpp5d, Ptprc, Rras, Cd86, Il33, Lyn, Fcgr3a/Fcgr3b	Hla-E, Fcgr1a, Cd72, Fcer1g, Hla-F, Fcgr2a, Pik3cg, Hla-A, Fcgr2b, Inpp5d, Il1a, Ptprc, Cd86, Lyn, Fcgr3a/Fcgr3b
T Helper Cell Differentiation	11	10
	Tgfbr2, Stat3, Il10rb, Tnfrsf1a, Hla-Dqa1, Hla-Dqb1, Stat1, Il4r, Fcer1g, Cd86, Il2rg	Ifngr1, Tgfbr2, Il10rb, Tgfb1, Tnfrsf1a, Hla-Dqa1, Fcer1g, Cd86, Il2rg, Il10ra
Thyroid Hormone Biosynthesis	2	2
	Ctsd, Iyd	Ctsd, Iyd
TREM1 Signaling	14	9
	MYD88, TLR1, Naip1 (Includes Others), TLR4, LAT2, STAT3, FCGR2B, ITGB1, TYROBP, CCL2, Tlr13, ITGA5, TLR2, CD86	FCGR2B, TLR1, CCL2, TYROBP, Tlr13, ITGAX, TLR2, CD86, Naip1 (Includes Others)
Type I Diabetes Mellitus Signaling	10	9
	Hla-A, Myd88, Socs3, Tnfrsf1a, Hla-Dqa1, Hla-Dqb1, Stat1, Fcer1g, Cd86, Casp8	Ifngr1, Hla-E, Hla-A, Tnfrsf1a, Hla-Dqa1, Fcer1g, Cd86, Hla-F, Casp8
Virus Entry via Endocytic Pathways	14	8
	Itgb5, Flna, Itga6, Itgb2, Rac2, Pik3cg, Cav1, Itga1, Hla-A, Itgb1, Flnc, Rras, Itga5, Prkcg	Cav1, Hla-A, Itgb5, Itga6, Flnc, Itgb2, Rac2, Pik3cg

APPENDIX 13

IPA Canonical Pathways that are significantly changed (p<0.05) at 1 and 30 days post injection. Pathways are in alphabetical order.

Ingenuity Canonical Pathways	Sign. Changed Genes at 1 Day	Sign. Changed Genes at 30 Days
cAMP-mediated signaling	15	13
	Grm2, Htr1a, Rgs7, S1pr3, Grm3, Adcy1, Stat3, Dusp1, Pde7b, Rgs2, Pde6b, Grm8, Rgs4, Dusp4, Prkar2a	Drd5, Htr1a, Prkar2b, S1pr3, Camk1 Day, Ptger4, Mc4r, Dusp1, P2ry13, Rgs2, Pde3a, Pde1a, Dusp4
GPCR-Mediated Integration of Enteroendocrine Signaling Exemplified by an L Cell	7	6
	Adcy1, Npy2r, Plce1, Galr1, Gal, Gipr, Prkar2a	Sst, Prkar2b, Npy2r, Plce1, Itpr1, Adcyap1
G-Protein Coupled Receptor Signaling	18	16
	Grm2, Htr1a, Rgs7, S1pr3, Grm3, Adcy1, Stat3, Htr2b, Dusp1, Pde7b, Rgs2, Grm1, Pde6b, Grm8, Rgs4, Dusp4, Adra1a, Prkar2a	Drd5, Htr1a, Prkar2b, S1pr3, Ptger4, Pik3cg, Mc4r, Dusp1, P2ry13, Rgs2, Pde3a, Grm1, Htr2c, Pde1a, Dusp4, Htr2a
Human Embryonic Stem Cell Pluripotency	7	8
	Inhba, Smad7, S1pr3, Fgf2, Sphk1, Bmp2, Bdnf	Inhba, Tgfbr2, Pdgfd, Tgfb1, S1pr3, Bdnf, Bmp3, Pik3cg
Methylglyoxal Degradation III	2	2
	Akr1c3, Akr1b10	Akr1c3, Akr1b10
Neuropathic Pain Signaling In Dorsal Horn Neurons	9	8
	Fos, Tac1, Grm2, Plce1, Grm1, Grm8, Bdnf, Grm3, Prkar2a	Tac1, Prkar2b, Plce1, Itpr1, Camk1 Day, Grm1, Bdnf, Pik3cg
Neuroprotective Role of THOP1 in Alzheimer's Disease	5	8
	Pdyn, Tac1, Hla-A, Nts, Prkar2a	Sst, Pdyn, Tac1, Hla-E, Hla-A, Prkar2b, Serpina3, Hla-F
p38 MAPK Signaling	7	8
	Hspb1, Dusp1, Rps6ka3, Map2k3, Pla2g4a, Il33, Mapkapk2	Hspb1, Tgfbr2, Tgfb1, Dusp1, Tnfrsf1a, Il1a, Hspb3, Rps6ka6
Role of Hypercytokinemia/hyperchemokinemia in the Pathogenesis of Influenza	3	3
	Cxcl10, Ccl2, Il33	Cxcl10, Ccl2, Il1a
Role of IL-17F in Allergic Inflammatory Airway Diseases	4	4
	Il11, Cxcl10, Ccl2, Rps6ka3	Cxcl10, Ccl2, Rps6ka6, Igf1

APPENDIX 14

Overlapping IPA Canonical Pathways between transcriptomics and proteomics results at 1 day post injection.

Ingenuity Canonical Pathway	Sign.Changed Proteins	Sign. Changed Genes
Clathrin-mediated Endocytosis Signaling	TF, CTTN	Tf, Myo1e, Fgf2, Dab2, Itga5
Acute Phase Response Signaling	TF, HPX	Fos, Stat3, Tf, Socs3, Map2k3, Serpine1, Hmox1, Il33, Osmr
LXR/RXR Activation	TF, HPX	Tf, Cd14, Ccl2, Ptgs2, Msr1, Il33
Leukocyte Extravasation Signaling	CTTN, PTK2B	Cldn10, Msn, Timp1, Cybb, Cd44, Itga5
Agrin Interactions at Neuromuscular Junction	CTTN	Pak6, Chrna1, Itga5
Integrin Signaling	CTTN	Cav1, Itgav, Pak6, Nedd9, Rhoj, Rnd3, Itga5
CXCR4 Signaling	ELMO2	Fos, Adcy1, Pak6, Rhoj, Rnd3
Germ Cell-Sertoli Cell Junction Signaling	EPN2	Pak6, Tubb6, Map2k3, Rhoj, Rnd3
Sertoli Cell-Sertoli Cell Junction Signaling	EPN2	Cldn10, Tubb6, Map2k3, Itga5, Prkar2a
Cdc42 Signaling	EXOC8	Fos, Hla-A, Itga5
Glutamate Receptor Signaling	HOMER1	Grm2, Homer2, Grm1, Grm8, Grm3
Hereditary Breast Cancer Signaling	NPM1	Cdkn1a, Gadd45b, Gadd45g
Polyamine Regulation in Colon Cancer	PSME1	Odc1
Chemokine Signaling	PTK2B	Fos, Ccl2
Erk/Mapk Signaling	PTK2B	Fos, Hspb1, Stat3, Dusp1, Pak6, Pla2g4a, Itga5, Dusp4, Prkar2a
G-Protein Coupled Receptor Signaling	PTK2B	Grm2, Htr1a, Rgs7, S1pr3, Grm3, Adcy1, Stat3, Htr2b, Dusp1, Pde7b, Rgs2, Grm1, Pde6b, Grm8, Rgs4, Dusp4, Adra1a, Prkar2a
Gαq Signaling	PTK2B	Htr2b, Rgs7, Arhgef25, Rgs2, Grm1, Rgs4, Rhoj, Hmox1, Rnd3, Adra1a
Il-8 Signaling	PTK2B	Fos, Hbegf, Itgav, Ptgs2, Cybb, Rhoj, Hmox1, Rnd3
Pak Signaling	PTK2B	Pak6, Itga5
Paxillin Signaling	PTK2B	Itgav, Pak6, Ptpn12, Itga5
Protein Kinase A Signaling	PTK2B	Adcy1, Dusp1, Ptpn12, Ptgs2, Pde7b, Plce1, Flnc, Pde6b, Dusp4, Prkar2a
Rac Signaling	PTK2B	Pak6, Cybb, Cd44, Itga5
Renin-Angiotensin Signaling	PTK2B	Fos, Adcy1, Stat3, Pak6, Ccl2, Prkar2a

Ingenuity Canonical Pathway	Sign.Changed Proteins	Sign. Changed Genes
Role Of Jak1 And Jak3 In Γc Cytokine Signaling	PTK2B	Stat3, Socs3, Blnk
Role Of Osteoblasts, Osteoclasts And Chondrocytes In Rheumatoid Arthritis	PTK2B	Fos, Il11, Sp7, Map2k3, Bmp2, Spp1, Itga5, Il33
Role Of Tissue Factor In Cancer	PTK2B	Hbegf, Cyr61, Itgav, Rps6ka3, Plaur, Ctgf
Signaling By Rho Family Gtpases	PTK2B	Fos, Vim, Pak6, Msn, Cdh4, Cybb, Rhoj, Rnd3, Itga5
Sperm Motility	PTK2B	Plce1, Pla2g4a, Prkar2a
Sphingosine-1-Phosphate Signaling	PTK2B	Adcy1, S1pr3, Plce1, Sphk1, Rhoj, Rnd3
Tec Kinase Signaling	PTK2B	Fos, Stat3, Pak6, Rhoj, Rnd3, Itga5

APPENDIX 15

Overlapping IPA Canonical Pathways between transcriptomics and proteomics results at 3 days post injection.

Ingenuity Canonical Pathway	Sign.Changed Proteins	Sign. Changed Genes
Signaling by Rho Family GTPases	BAIAP2, VIM, MAP2K4, PTK2B, MSN, GFAP	Iqgap1, Ezr, Msn, Nox4, Rhoc, Myl9, Rhoj, Arpc1b, Pik3cg, Vim, Gng5, Itgb1, Cybb, Itga5
Actin Cytoskeleton Signaling	BAIAP2, FLNA, MSN, ACTN2, IQGAP2	Iqgap1, Flna, Fgf10, Ezr, Msn, Fgf2, Myl9, Rac2, Arpc1b, Vav1, Pik3cg, Fn1, Nckap1l, Itgb1, Rras, Itga5
Leukocyte Extravasation Signaling	CTTN, MAP2K4, PTK2B, MSN, ACTN2	Itgam, Jam2, F11r, Itga6, Ncf1, Ezr, Msn, Timp4, Itgb2, Rac2, Cd44, Vav1, Vcam1, Pik3cg, Itga1, Mmp19, Itgb1, Timp1, Cybb, Itga5, Cyba, Prkcg
Clathrin-mediated Endocytosis Signaling	TF, CTTN, APOD, AAK1	Tf, Itgb5, Fgf10, Fgf2, Itgb2, Arpc1b, Pik3cg, Lyz, Apoc2, Itgb1, Hip1, Myo1e, Dab2, Itga5
ILK Signaling	VIM, MAP2K4, FLNA, ACTN2	Itgb5, Tnfrsf1a, Flna, Rhoc, Myl9, Itgb2, Rhoj, Pik3cg, Vim, Fn1, Ppp1r14b, Itgb1, Ccnd1, Ptgs2, Flnc
Rac Signaling	BAIAP2, MAP2K4, PTK2B, IQGAP2	Iqgap1, Itgb1, Nox4, Cybb, Arpc1b, Rras, Cd44, Itga5, Pik3cg
Acute Phase Response Signaling	TF, MAP2K4, SERPINA3	Tf, C3, Myd88, Socs3, Tnfrsf1a, Serpinf1, Cp, Rbp1, Serpina3, Hmox1, Pik3cg, Osmr, A2m, Stat3, Fn1, Serpinf2, Serpine1, Serping1, Rras, Il33
Cdc42 Signaling	BAIAP2, MAP2K4, IQGAP2	H2-K2/H2-Q9, Iqgap1, Hla-A, Hla-Dqa1, Hla-Dqb1, Itgb1, Myl9, Fcer1g, Arpc1b, Itga5, Vav1
Integrin Signaling	CTTN, MAP2K4, ACTN2	Itgam, Itgb5, Itgav, Nedd9, Itga6, Tspan4, Rhoc, Myl9, Itgb2, Rac2, Rhoj, Arpc1b, Pik3cg, Cav1, Itga1, Itgb1, Rras, Itga5, Capn2
Paxillin Signaling	MAP2K4, PTK2B, ACTN2	Itgam, Itga1, Itgb5, Itgav, Itgb1, Itga6, Itgb2, Rras, Itga5, Pik3cg
Agrin Interactions at Neuromuscular Junction	CTTN, MAP2K4	Itga1, Erbb4, Itgb1, Itga6, Itgb2, Rac2, Rras, Itga5
Atherosclerosis Signaling	APOD, COL1A2	Msr1, Itgb2, Vcam1, Lyz, Apoc2, Aloxe3, Ccl2, Csf1, Tnfrsf12a, Alox12b, Plb1, Pla2g4a, Il33
Dendritic Cell Maturation	MAP2K4, COL1A2	Myd88, Tnfrsf1a, Hla-Dqa1, Hla-Dqb1, Fcgr1a, Plce1, Fcer1g, Trem2, Fcgr2a,

Ingenuity Canonical Pathway	Sign.Changed Proteins	Sign. Changed Genes
		Pik3cg, Tlr4, Irf8, Hla-A, Fcgr2b, Stat1, Tyrobp, Tlr2, Cd86, Il33, Fcgr3a/Fcgr3b
Germ Cell-Sertoli Cell Junction Signaling	MAP2K4, ACTN2	A2m, Iqgap1, Tgfbr2, Tnfrsf1a, Itgb1, Tubb6, Itga6, Rhoc, Rac2, Rhoj, Rras, Pik3cg
IL-12 Signaling and Production in Macrophages	MAP2K4, APOD	Tlr4, Lyz, Apoc2, Irf8, Myd88, Stat1, Spi1, Tlr2, Pik3cg, Prkcg
IL-8 Signaling	MAP2K4, PTK2B	Hbegf, Iqgap1, Itgam, Itgb5, Itgav, Nox4, Rhoc, Myl9, Pld4, Itgb2, Rac2, Rhoj, Hmox1, Vcam1, Pik3cg, Gng5, Ccnd1, Ptgs2, Cybb, Rras, Prkcg
LXR/RXR Activation	TF, APOD	Tf, C3, Tnfrsf1a, Serpinf1, Msr1, Tlr4, Lyz, Apoc2, Ly96, Ccl2, Ptgs2, Serpinf2, Il33
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	MAP2K4, APOD	Tnfrsf1a, Ncf1, Rhoc, Spi1, Rhoj, Pik3cg, Tlr4, Lyz, Apoc2, Irf8, Ppp1r14b, Stat1, Cybb, Tlr2, Cyba, Prkcg
Tec Kinase Signaling	MAP2K4, PTK2B	Hck, Rhoc, Fcer1g, Rhoj, Vav1, Pik3cg, Tlr4, Stat3, Gng5, Stat1, Itgb1, Itga5, Prkcg, Lyn
Regulation of Cellular Mechanics by Calpain Protease	ACTN2	Itgb1, Ccnd1, Ezr, Cdk2, Ccna2, Rras, Itga5, Cdk1, Capn2
Role of NFAT in Regulation of the Immune Response	AKAP5	Hla-Dqa1, Hla-Dqb1, Fcgr1a, Fcer1g, Fcgr2a, Pik3cg, Lcp2, Fcgr2b, Gng5, Blnk, Rras, Cd86, Lyn, Fcgr3a/Fcgr3b
Actin Nucleation by ARP-WASP Complex	BAIAP2	Itgb1, Rhoc, Rhoj, Arpc1b, Rras, Itga5
Regulation of Actin-based Motility by Rho	BAIAP2	Itgb1, Rhoc, Myl9, Rac2, Rhoj, Arpc1b, Itga5
Hepatic Fibrosis / Hepatic Stellate Cell Activation	COL1A2	Igfbp4, Tnfrsf1a, Ctgf, Fgf2, Myl9, Vcam1, Tlr4, A2m, Col12a1, Tgfbr2, Ly96, Fn1, Stat1, Ccl2, Csf1, Il4r, Igfbp3, Timp1, Serpine1
Caveolar-mediated Endocytosis Signaling	FLNA	Itgam, Itgb5, Itgav, Flna, Itga6, Cd48, Itgb2, Cav1, Itga1, Hla-A, Itgb1, Flnc, Itga5
Virus Entry via Endocytic Pathways	FLNA	Itgb5, Flna, Itga6, Itgb2, Rac2, Pik3cg, Cav1, Itga1, Hla-A, Itgb1, Flnc, Rras, Itga5, Prkcg
Chondroitin Sulfate Degradation (Metazoa)	HEXB	Hexb, Chil3/Chil4, Cd44
Dermatan Sulfate Degradation (Metazoa)	HEXB	Hexb, Chil3/Chil4, Cd44, Fgfrl1
Activation of IRF by Cytosolic	MAP2K4	Dhx58, Irf9, Irf7, Stat1,

Ingenuity Canonical Pathway	Sign.Changed Proteins	Sign. Changed Genes
Pattern Recognition Receptors		Ifih1, Ddx58, Ifit2
Acute Myeloid Leukemia Signaling	MAP2K4	Stat3, Csf2rb, Ccnd1, Kitlg, Runx1, Spi1, Rras, Pik3cg
Apoptosis Signaling	MAP2K4	Naip, Tnfrsf1a, Bcl2a1, Rras, Naip1 (Includes Others), Casp8, Cdk1, Capn2
B Cell Receptor Signaling	MAP2K4	Rac2, Vav1, Fcgr2a, Pik3cg, Fcgr2b, Inpp5d, Pik3ap1, Bcl2a1, Apbb1ip, Ptprc, Blnk, Rras, Lyn
CD28 Signaling in T Helper Cells	MAP2K4	Lcp2, Hla-Dqa1, Hla-Dqb1, Ptprc, Fcer1g, Arpc1b, Cd86, Vav1, Pik3cg
Colorectal Cancer Metastasis Signaling	MAP2K4	Tnfrsf1a, Tlr1, Rhoc, Rhoj, Pik3cg, Tlr4, Stat3, Tgfbr2, Gng5, Mmp19, Stat1, Ccnd1, Ptgs2, Tlr13, Rras, Tlr2
Death Receptor Signaling	MAP2K4	Parp12, Hspb1, Naip, Tnfrsf1a, Parp3, Parp9, Parp14, Naip1 (Includes Others), Casp8, Arhgdib
HMGB1 Signaling	MAP2K4	Tlr4, Tnfrsf1a, Ccl2, Rhoc, Serpine1, Rhoj, Rras, Vcam1, Pik3cg
IL-10 Signaling	MAP2K4	Stat3, Il10rb, Fcgr2b, Socs3, Il4r, Hmox1, Il33, Fcgr2a
IL-17 Signaling	MAP2K4	Cxcl10, Ccl2, Ptgs2, Timp1, Rras, Mapkapk2, Pik3cg
IL-22 Signaling	MAP2K4	Stat3, Il10rb, Socs3, Stat1
IL-6 Signaling	MAP2K4	A2m, Hspb1, Stat3, Socs3, Tnfrsf1a, Rras, Il33, Mapkapk2, Pik3cg
MIF Regulation of Innate Immunity	MAP2K4	Tlr4, Ly96, Cd74, Ptgs2, Pla2g4a
OX40 Signaling Pathway	MAP2K4	H2-K2/H2-Q9, Hla-A, Hla-Dqa1, Hla-Dqb1, Fcer1g
Pancreatic Adenocarcinoma Signaling	MAP2K4	Hbegf, Tgfbr2, Stat3, Stat1, Ptgs2, Ccnd1, Cdkn1a, Cdk2, Pld4, Hmox1, Pik3cg
PDGF Signaling	MAP2K4	Eif2ak2, Cav1, Stat3, Inpp5d, Stat1, Rras, Pik3cg
PKCθ Signaling in T Lymphocytes	MAP2K4	Lcp2, Hla-Dqa1, Hla-Dqb1, Fcer1g, Rac2, Rras, Cd86, Vav1, Pik3cg
Reelin Signaling in Neurons	MAP2K4	Hck, Itga1, Itgb1, Itga6, Itgb2, Itga5, Pik3cg, Lyn
Role of JAK family kinases in IL-6-type Cytokine Signaling	MAP2K4	Stat3, Socs3, Stat1, Osmr
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	MAP2K4	Myd88, Socs3, Tnfrsf1a, Fcgr1a, Tlr1, Plce1, Fgf2, Il16, Vcam1, Mapkapk2, Pik3cg, Tlr4, Stat3, Fn1, C5ar1, Ccnd1, Ccl2, Csf1,

Ingenuity Canonical Pathway	Sign.Changed Proteins	Sign. Changed Genes
		Tlr13, Rras, Tlr2, Il33, Prkcg, Fcgr3a/Fcgr3b
Role of MAPK Signaling in the Pathogenesis of Influenza	MAP2K4	Cxcl10, Ccl2, Ptgs2, Plb1, Pla2g4a, Rras
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	MAP2K4	Eif2ak2, Oas1, C3, Myd88, Tlr1, C1qb, Ddx58, C3ar1, Oas1b, C1qa, Pik3cg, Tlr4, C1qc, Irf7, C5ar1, Ifih1, Tlr2, Clec7a, Ptx3, Prkcg
STAT3 Pathway	MAP2K4	Tgfbr2, Stat3, Socs3, Cdkn1a, Rras, Fgfrl1
TGF-β Signaling	MAP2K4	Inhba, Tgfbr2, Irf7, Tgif1, Serpine1, Pmepa1, Rras
Toll-like Receptor Signaling	MAP2K4	Tlr4, Eif2ak2, Ly96, Myd88, Tlr1, Tlr2, Il33
Type I Diabetes Mellitus Signaling	MAP2K4	Hla-A, Myd88, Socs3, Tnfrsf1a, Hla-Dqa1, Hla-Dqb1, Stat1, Fcer1g, Cd86, Casp8
UVA-Induced MAPK Signaling	MAP2K4	Parp12, Stat1, Parp3, Plce1, Parp9, Parp14, Rras, Pik3cg
Agranulocyte Adhesion and Diapedesis	MSN	Ccl2, Tnfrsf1a, Cxcl10, Itga6, Ezr, Msn, Myl9, Itgb2, Ccl3l3, Vcam1, Itga1, Fn1, Mmp19, C5ar1, Itgb1, Ccl2, Cxcl16, Sdc4, Itga5, Il33
Granulocyte Adhesion and Diapedesis	MSN	Ccl2, Itgam, Tnfrsf1a, Cxcl10, Itga6, Ezr, Msn, Itgb2, Ccl3l3, Vcam1, Hspb1, Itga1, Mmp19, C5ar1, Itgb1, Ccl2, Cxcl16, Sdc4, Itga5, Il33
RhoGDI Signaling	MSN	Gng5, Itgb1, Ezr, Msn, Rhoc, Myl9, Rhoj, Arpc1b, Cd44, Itga5, Arhgdib
Fcγ Receptor-mediated Phagocytosis in Macrophages and Monocytes	PTK2B	Hck, Fcgr1a, Ncf1, Ezr, Fyb, Pld4, Rac2, Arpc1b, Hmox1, Vav1, Fcgr2a, Pik3cg, Lcp2, Inpp5d, Prkcg, Lyn, Fcgr3a/Fcgr3b
Gαq Signaling	PTK2B	Htr2b, Gng5, Chrm3, Rhoc, Pld4, Grm1, Rgs4, Rhoj, Hmox1, Pik3cg, Prkcg
Role of JAK1 and JAK3 in γc Cytokine Signaling	PTK2B	Stat3, Socs3, Stat1, Il4r, Blnk, Rras, Il2rg, Pik3cg
Role of Tissue Factor in Cancer	PTK2B	Hbegf, Hck, Cyr61, Itgb5, Itgav, Itgb1, Csf1, Itga6, Ctgf, Rras, Pik3cg, Lyn

APPENDIX 16

Overlapping IPA Canonical Pathways between transcriptomics and proteomics results at 30 days post injection.

Ingenuity Canonical Pathway	Sign.Changed Proteins	Sign. Changed Genes
Clathrin-mediated Endocytosis Signaling	SH3GL2, SNAP91, TF, CTTN, APOD, PPP3CB, AAK1, AMPH, ITGB2, PPP3CA, ARPC1B, USP9X, MYO6, APOE, TFRC, ALB, ARPC1A	Lyz, Pdgfd, Itgb5, Fgf16, Myo1e, Fgf10, Itgb2, Arpc1b, Igf1, Pik3cg
Actin Cytoskeleton Signaling	BAIAP2, FLNA, GSN, PIP4K2B, EZR, --, MAP2K1, ARPC1B, WASF1, ARPC1A	Pdgfd, Fgf16, Cd14, Nckap1l, Fgf10, Msn, Iqgap2, Rac2, Arpc1b, Vav1, Pik3cg
LXR/RXR Activation	C4A/C4B, TF, VTN, APOD, FASN, APOE, ALB, TTR	Lyz, C4a/C4b, C3, Tnfrsf1a, Serpinf1, Cd14, Ccl2, Il1a, Abca1, Serpinf2
Acute Phase Response Signaling	A2M, C4A/C4B, TF, MAP2K1, ALB, TTR	C3, Tnfrsf1a, Serpinf1, Cp, Serpina3, Pik3cg, Osmr, A2m, C4a/C4b, Il1a, Serpinf2, C1s, Serping1
IGF-1 Signaling	YWHAQ, YWHAG, MAP2K1, YWHAE, YWHAH, YWHAB	Cyr61, Igfbp7, Prkar2b, Igfbp2, Ctgf, Igf1, Pik3cg
Production of Nitric Oxide and Reactive Oxygen Species in Macrophages	APOD, CAT, APOE, MAP2K1, ALB, PRKCG	Lyz, Ifngr1, Irf8, Tnfrsf1a, Ncf1, Spi1, Cybb, Rhoj, Tlr2, Cyba, Pik3cg
Role of NFAT in Cardiac Hypertrophy	GNB5, PPP3CB, MAP2K1, PPP3CA, AKAP5, PRKCG	Tgfbr2, Tgfb1, Prkar2b, Slc8a1, Plce1, Itpr1, Camk1d, Hdac9, Igf1, Pik3cg
Atherosclerosis Signaling	APOD, APOE, ITGB2, PLA2G7, ALB	Lyz, Pdgfd, Tgfb1, Ccl2, Il1a, Itgb2, Alox12b, Plb1
Caveolar-mediated Endocytosis Signaling	ITGAV, FLNA, FLNC, ITGB2, ALB	Itgam, Cav1, Hla-A, Itgb5, Cd48, Itga6, Itgax, Flnc, Itgb2
CD28 Signaling in T Helper Cells	PPP3CB, MAP2K1, PPP3CA, ARPC1B, ARPC1A	Lcp2, Hla-Dqa1, Itpr1, Ptprc, Fcer1g, Arpc1b, Cd86, Vav1, Pik3cg
IL-8 Signaling	ITGAV, GNB5, ITGB2, MAP2K1, PRKCG	Itgam, Hbegf, Itgb5, Itgax, Pld4, Itgb2, Rac2, Cybb, Rhoj, Pik3cg
Leukocyte Extravasation Signaling	CTTN, EZR, ITGB2, CD44, PRKCG	Itgam, F11r, Arhgap6, Itga6, Ncf1, Msn, Itgb2, Rac2, Cd44, Vav1, Pik3cg, Tec, Timp1, Cybb, Cyba
Role of NFAT in Regulation of the Immune Response	GNB5, PPP3CB, MAP2K1, PPP3CA, AKAP5	Lcp2, Fcgr2b, Hla-Dqa1, Fcgr1a, Itpr1, Fcer1g, Blnk, Cd86, Fcgr2a, Pik3cg, Lyn, Fcgr3a/Fcgr3b
Aryl Hydrocarbon Receptor Signaling	HSPB1, ALDH1L1, ALDH1A1, CTSD	Hspb1, Gsto1, Tgfb1, Il1a, Hspb3, Ctsd, Mgst1, Nfe2l2
cAMP-mediated signaling	PPP3CB, MAP2K1, PPP3CA, AKAP5	Drd5, Htr1a, Prkar2b, S1pr3, Camk1d, Ptger4, Mc4r, Dusp1, P2ry13, Rgs2, Pde3a, Pde1a,

Ingenuity Canonical Pathway	Sign.Changed Proteins	Sign. Changed Genes
		Dusp4
Agranulocyte Adhesion and Diapedesis	EZR, ITGB2, --	Ccl6, Tnfrsf1a, Cxcl10, Itga6, Msn, Itgb2, Ccl3l3, Glycam1, Cxcl13, Ccl9, Ccl2, Il1a, Cxcl16
B Cell Receptor Signaling	PPP3CB, MAP2K1, PPP3CA	Fcgr2b, Inpp5d, Pik3ap1, Bcl2a1, Apbb1ip, Ptprc, Blnk, Rac2, Vav1, Fcgr2a, Pik3cg, Lyn
Cdc42 Signaling	BAIAP2, ARPC1B, ARPC1A	H2-K2/H2-Q9, Hla-E, Hla-A, Hla-Dqa1, Iqgap2, Fcer1g, Arpc1b, Vav1, Hla-F
Glioma Invasiveness Signaling	VTN, ITGAV, CD44	Itgb5, Plau, Timp1, Rhoj, Cd44, Pik3cg
G-Protein Coupled Receptor Signaling	MAP2K1, SYNGAP1, PRKCG	Drd5, Htr1a, Prkar2b, S1pr3, Ptger4, Pik3cg, Mc4r, Dusp1, P2ry13, Rgs2, Pde3a, Grm1, Htr2c, Pde1a, Dusp4, Htr2a
Granulocyte Adhesion and Diapedesis	HSPB1, EZR, ITGB2	Itgam, Ccl6, Tnfrsf1a, Cxcl10, Csf3r, Itga6, Msn, Itgb2, Ccl3l3, Hspb1, Cxcl13, Ccl9, Ccl2, Il1a, Cxcl16
IL-6 Signaling	A2M, HSPB1, MAP2K1	A2m, Hspb1, Tnfrsf1a, Cd14, Il1a, Hspb3, Pik3cg
PI3K Signaling in B Lymphocytes	PPP3CB, MAP2K1, PPP3CA	C3, Plce1, Vav1, Atf3, Pik3cg, Fcgr2b, Inpp5d, Pik3ap1, Itpr1, Cd180, Ptprc, Blnk, Lyn
Chondroitin Sulfate Degradation (Metazoa)	HEXB, CD44	Hexb, Hexa, Cd44
Dermatan Sulfate Degradation (Metazoa)	HEXB, CD44	Hexb, Hexa, Cd44
Fc Epsilon RI Signaling	MAP2K1, PRKCG	Lcp2, Inpp5d, Fcer1g, Rac2, Vav1, Pik3cg, Lyn
iCOS-iCOSL Signaling in T Helper Cells	PPP3CB, PPP3CA	Lcp2, Inpp5d, Hla-Dqa1, Itpr1, Ptprc, Fcer1g, Vav1, Il2rg, Pik3cg
Macropinocytosis Signaling	ITGB2, PRKCG	Pdgfd, Itgb5, Cd14, Itgb2, Hgf, Csf1r, Pik3cg
Natural Killer Cell Signaling	MAP2K1, PRKCG	Lcp2, Lair1, Inpp5d, Tyrobp, Fcer1g, Rac2, Vav1, Fcgr2a, Pik3cg, Fcgr3a/Fcgr3b
Neuroprotective Role of THOP1 in Alzheimer's Disease	MAPT, YWHAE	Sst, Pdyn, Tac1, Hla-E, Hla-A, Prkar2b, Serpina3, Hla-F
Nur77 Signaling in T Lymphocytes	PPP3CB, PPP3CA	Hla-Dqa1, Fcer1g, Hdac9, Cd86
p38 MAPK Signaling	HSPB1, MAPT	Hspb1, Tgfbr2, Tgfb1, Dusp1, Tnfrsf1a, Il1a, Hspb3, Rps6ka6
PKCθ Signaling in T Lymphocytes	PPP3CB, PPP3CA	Lcp2, Hla-Dqa1, Fcer1g, Rac2, Cd86, Vav1, Pik3cg
Role of Tissue Factor in Cancer	ITGAV, P4HB	Hbegf, Cyr61, Itgb5, Itga6, Ctgf, Rps6ka6, Pik3cg, Lyn
Coagulation System	A2M	A2m, Pros1, Plau, Serpinf2

Ingenuity Canonical Pathway	Sign.Changed Proteins	Sign. Changed Genes
Complement System	C4A/C4B	Itgam, C1qc, C4a/C4b, C3, C1qb, Itgax, Itgb2, C1s, Serping1, Cfh, C3ar1, C1qa
Death Receptor Signaling	HSPB1	HSPB1, NAIP, TNFRSF1A, PARP9, PARP14, HSPB3, Naip1 (Includes Others), CASP8, ARHGDIB
Eicosanoid Signaling	PLA2G7	Akr1c3, Ptger4, Alox12b, Plb1, Hpgds, Tbxas1
Hepatic Fibrosis / Hepatic Stellate Cell Activation	A2M	Pdgfd, Tgfb1, Tnfrsf1a, Cd14, Ctgf, Igf1, Il10ra, A2m, Ifngr1, Tgfbr2, Ccl2, Il1a, Timp1, Hgf
HMGB1 Signaling	MAP2K1	Ifngr1, Tgfb1, Tnfrsf1a, Ccl2, Il1a, Rhoj, Pik3cg
Interferon Signaling	IFIT3	Oas1, Ifngr1, Ifit3, Ifitm3
MSP-RON Signaling Pathway	ITGB2	Itgam, Ccl2, Itgb2, Tlr2, Pik3cg
Neuropathic Pain Signaling In Dorsal Horn Neurons	PRKCG	Tac1, Prkar2b, Plce1, Itpr1, Camk1d, Grm1, Bdnf, Pik3cg
Role of IL-17F in Allergic Inflammatory Airway Diseases	MAP2K1	Cxcl10, Ccl2, Rps6ka6, Igf1
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	PRKCG	Eif2ak2, Oas1, C3, Tgfb1, Tlr1, C1qb, Ddx58, C3ar1, C1qa, Pik3cg, C1qc, Irf7, Ifih1, Il1a, Tlr2, Clec7a
Systemic Lupus Erythematosus Signaling	HNRNPA2B1	Hla-E, Fcgr1a, Cd72, Fcer1g, Hla-F, Fcgr2a, Pik3cg, Hla-A, Fcgr2b, Inpp5d, Il1a, Ptprc, Cd86, Lyn, Fcgr3a/Fcgr3b
TGF-β Signaling	MAP2K1	Inhba, Tgfbr2, Acvr1c, Irf7, Tgfb1, Tgif1, Pmepa1
Thyroid Hormone Biosynthesis	CTSD	Ctsd, Iyd

HUMAN MTLE

Significantly changed transcripts

APPENDIX 17

Significantly changed transcripts in human MTLE samples with and without Hippocampal Sclerosis (HS vs. No HS).Thresholds: 1.3-fold, unadjusted p-value <0.05.

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change
7922174	**F5**	NM_000130 // F5 // coagulation factor V (proaccelerin, labile factor) // 1q23 // 2153 /	2.18
7986350	**ARRDC4**	NM_183376 // ARRDC4 // arrestin domain containing 4 // 15q26.3 // 91947 /// ENST0000026	2.09
8057056	**TTN**	NM_001256850 // TTN // titin // 2q31 // 7273 /// NM_001267550 // TTN // titin // 2q31 /	2.07
8103254	**SFRP2**	NM_003013 // SFRP2 // secreted frizzled-related protein 2 // 4q31.3 // 6423 /// ENST000	1.95
8057377	**CCDC141**	NM_001316745 // CCDC141 // coiled-coil domain containing 141 // 2q31.2 // 285025 /// NM	1.89
8091922	**WDR49**	NM_178824 // WDR49 // WD repeat domain 49 // 3q26.1 // 151790 /// ENST00000308378 // WD	1.82
8168517	**LPAR4**	NM_001278000 // LPAR4 // lysophosphatidic acid receptor 4 // Xq21.1 // 2846 /// NM_0052	1.82
7933442	**PTPN20**	XM_011539618 // PTPN20 // protein tyrosine phosphatase, non-receptor type 20 // 10q11.2	1.79
8020717	**AQP4-AS1**	NR_026908 // AQP4-AS1 // AQP4 antisense RNA 1 // 18q11.2 // 147429 /// AK055069 // AQP4	1.77
8113278	**LIX1**	NM_153234 // LIX1 // limb and CNS expressed 1 // 5q15 // 167410 /// ENST00000274382 //	1.76
7958425	**DAO**	NM_001917 // DAO // D-amino-acid oxidase // 12q24 // 1610 /// XM_005268692 // DAO // D-	1.72
8089145	**ABI3BP**	NM_015429 // ABI3BP // ABI family, member 3 (NESH) binding protein // 3q12 // 25890 ///	1.72
8155707	**TJP2**	NM_001170414 // TJP2 // tight junction protein 2 // 9q13-q21 // 9414 /// NM_001170415 /	1.70
7990757	**CTSH**	NM_004390 // CTSH // cathepsin H // 15q25.1 // 1512 /// XM_005254181 // CTSH // catheps	1.70
7954398	**SPX**	NM_030572 // SPX // spexin hormone // 12p12.1 // 80763 /// ENST00000256969 // SPX // sp	1.68
8165794	**CD99**	NM_001122898 // CD99 // CD99 molecule // Xp22.32 and Yp11.3 // 4267 /// NM_001277710 //	1.68

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change
8176360	**CD99**	NM_001122898 // CD99 // CD99 molecule // Xp22.32 and Yp11.3 // 4267 /// NM_001277710 //	1.68
7921862	**CFAP126**	NM_001013625 // CFAP126 // cilia and flagella associated protein 126 // 1q23.3 // 25717	1.67
8117034	**GMPR**	NM_006877 // GMPR // guanosine monophosphate reductase // 6p23 // 2766 /// XM_011514508	1.64
8026468	**CYP4F12**	NM_023944 // CYP4F12 // cytochrome P450, family 4, subfamily F, polypeptide 12 // 19p13	1.63
7918379	**GSTM3**	NM_000849 // GSTM3 // glutathione S-transferase mu 3 (brain) // 1p13.3 // 2947 /// NR_0	1.63
8078155	**GALNT15**	NM_054110 // GALNT15 // polypeptide N-acetylgalactosaminyltransferase 15 // 3p25.1 // 1	1.60
7933750	**SLC16A9**	NM_194298 // SLC16A9 // solute carrier family 16, member 9 // 10q21.2 // 220963 /// XM_	1.60
8092661	**MASP1**	NM_001031849 // MASP1 // mannan-binding lectin serine peptidase 1 (C4/C2 activating com	1.59
8127484	**B3GAT2**	NM_080742 // B3GAT2 // beta-1,3-glucuronyltransferase 2 // 6q13 // 135152 /// XM_006715	1.59
8065537	**LOC100134868**	NR_004846 // LOC100134868 // uncharacterized LOC100134868 // 20p11.1 // 100134868 /// u	1.59
7933437	**PTPN20**	XM_011539618 // PTPN20 // protein tyrosine phosphatase, non-receptor type 20 // 10q11.2	1.57
7933446	**FRMPD2**	NM_001018071 // FRMPD2 // FERM and PDZ domain containing 2 // 10q11.22 // 143162 /// NM	1.55
8166671	**CFAP47**	NM_001304548 // CFAP47 // cilia and flagella associated protein 47 // Xp21.1 // 286464	1.55
8091910	**SERPINI2**	NM_001012303 // SERPINI2 // serpin peptidase inhibitor, clade I (pancpin), member 2 //	1.55
8173955	**SYTL4**	NM_001129896 // SYTL4 // synaptotagmin-like 4 // Xq21.33 // 94121 /// NM_001174068 // S	1.55
7961182	**KLRC2**	NM_002260 // KLRC2 // killer cell lectin-like receptor subfamily C, member 2 // 12p13 /	1.55
7958051	**ASCL1**	NM_004316 // ASCL1 // achaete-scute family bHLH transcription factor 1 // 12q23.2 // 42	1.54
8129608	**TAAR3**	NR_028511 // TAAR3 // trace amine associated receptor 3 (gene/pseudogene) // 6q23-q24 /	1.54
8091306	**PLSCR4**	NM_001128304 // PLSCR4 // phospholipid scramblase 4 // 3q24 // 57088 /// NM_001128305 /	1.52
8129837	**IL20RA**	NM_001278722 // IL20RA // interleukin 20 receptor, alpha // 6q23.3 // 53832 /// NM_0012	1.51
8166690	**CFAP47**	NM_001304548 // CFAP47 // cilia and flagella associated protein 47 // Xp21.1 // 286464	1.51

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change
8009277	**RGS9**	NM_001081955 // RGS9 // regulator of G-protein signaling 9 // 17q24.1 // 8787 /// NM_00	1.50
8046746	**PPP1R1C**	NM_001080545 // PPP1R1C // protein phosphatase 1, regulatory (inhibitor) subunit 1C //	1.49
7928789	**RGR**	NM_001012720 // RGR // retinal G protein coupled receptor // 10q23 // 5995 /// NM_00101	1.49
8099612	**ADGRA3**	NM_145290 // ADGRA3 // adhesion G protein-coupled receptor A3 // 4p15.2 // 166647 /// X	1.49
8174767	**TMEM255A**	NM_001104544 // TMEM255A // transmembrane protein 255A // Xq24 // 55026 /// NM_00110454	1.48
8061564	**ID1**	NM_002165 // ID1 // inhibitor of DNA binding 1, dominant negative helix-loop-helix prot	1.48
7916506	**C1orf168**	NM_001004303 // C1orf168 // chromosome 1 open reading frame 168 // 1p32.2 // 199920 ///	1.48
8046333	**CYBRD1**	NM_001127383 // CYBRD1 // cytochrome b reductase 1 // 2q31.1 // 79901 /// NM_001256909	1.48
8088560	**ADAMTS9**	NM_182920 // ADAMTS9 // ADAM metallopeptidase with thrombospondin type 1 motif 9 // 3p1	1.47
8155734	**FAM189A2**	NM_001127608 // FAM189A2 // family with sequence similarity 189, member A2 // 9q21.11 /	1.47
8091954	**GOLIM4**	NM_001308155 // GOLIM4 // golgi integral membrane protein 4 // 3q26.2 // 27333 /// NM_0	1.46
7962516	**SLC38A1**	NM_001077484 // SLC38A1 // solute carrier family 38, member 1 // 12q13.11 // 81539 ///	1.46
8168163	**GDPD2**	NM_001171191 // GDPD2 // glycerophosphodiester phosphodiesterase domain containing 2 //	1.46
7933379	**PTPN20**	NM_001042357 // PTPN20 // protein tyrosine phosphatase, non-receptor type 20 // 10q11.2	1.46
8127201	**COL21A1**	NM_030820 // COL21A1 // collagen, type XXI, alpha 1 // 6p12.3-p11.2|6p12.3-p11.2 // 815	1.46
7933263	**PTPN20**	XM_011539618 // PTPN20 // protein tyrosine phosphatase, non-receptor type 20 // 10q11.2	1.46
7948667	**AHNAK**	NM_001620 // AHNAK // AHNAK nucleoprotein // 11q12.2 // 79026 /// NM_024060 // AHNAK //	1.46
8042195	**AHSA2**	NM_152392 // AHSA2 // AHA1, activator of heat shock 90kDa protein ATPase homolog 2 (yea	1.45
8175016	**APLN**	NM_017413 // APLN // apelin // Xq25 // 8862 /// ENST00000429967 // APLN // apelin // Xq	1.44
8013272	**CCDC144A**	NM_014695 // CCDC144A // coiled-coil domain containing 144A // 17p11.2 // 9720 /// NR_0	1.43
8116418	**GFPT2**	NM_005110 // GFPT2 // glutamine-fructose-6-phosphate transaminase 2 // 5q34-q35 // 9945	1.43
7946365	**STK33**	NM_001289058 // STK33 // serine/threonine kinase 33 // 11p15.3 // 65975 /// NM_00128905	1.42

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change
8005204	**CCDC144A**	NM_014695 // CCDC144A // coiled-coil domain containing 144A // 17p11.2 // 9720 /// NR_1	1.42
8141843	**RASA4**	NM_001079877 // RASA4 // RAS p21 protein activator 4 // 7q22 // 10156 /// NM_006989 //	1.41
7940000	**OR5AK2**	NM_001005323 // OR5AK2 // olfactory receptor, family 5, subfamily AK, member 2 // 11q12	1.40
8120860	**BCKDHB**	NM_000056 // BCKDHB // branched chain keto acid dehydrogenase E1, beta polypeptide // 6	1.40
8151999	**RGS22**	NM_001286692 // RGS22 // regulator of G-protein signaling 22 // 8q22.2 // 26166 /// NM_	1.40
7923173	**MIR181B1**	NR_029612 // MIR181B1 // microRNA 181b-1 // 1q32.1 // 406955 /// ENST00000385240 // MIR	1.40
8097920	**LRAT**	NM_001301645 // LRAT // lecithin retinol acyltransferase (phosphatidylcholine--retinol	1.39
8061483	**LOC100134868**	NR_004846 // LOC100134868 // uncharacterized LOC100134868 // 20p11.1 // 100134868 /// X	1.39
7958305	**RFX4**	NM_001206691 // RFX4 // regulatory factor X, 4 (influences HLA class II expression) //	1.39
8107673	**GRAMD3**	NM_001146319 // GRAMD3 // GRAM domain containing 3 // 5q23.2 // 65983 /// NM_001146320	1.38
8162404	**ECM2**	NM_001197295 // ECM2 // extracellular matrix protein 2, female organ and adipocyte spec	1.38
8009515	**LINC01152**	NR_110124 // LINC01152 // long intergenic non-protein coding RNA 1152 // 17q24.3 // 102	1.38
8044225	**SULT1C4**	NM_006588 // SULT1C4 // sulfotransferase family 1C member 4 // 2q12.3 // 27233 /// XM_0	1.38
7900159	**DNALI1**	NM_003462 // DNALI1 // dynein, axonemal, light intermediate chain 1 // 1p35.1 // 7802 /	1.38
8160168	**FREM1**	NM_001177704 // FREM1 // FRAS1 related extracellular matrix 1 // 9p22.3 // 158326 /// N	1.38
7971015	**SMAD9**	NM_001127217 // SMAD9 // SMAD family member 9 // 13q12-q14 // 4093 /// NM_005905 // SMA	1.38
7993898	**VWA3A**	NM_173615 // VWA3A // von Willebrand factor A domain containing 3A // 16p12.2 // 146177	1.37
8106986	**RHOBTB3**	NM_014899 // RHOBTB3 // Rho-related BTB domain containing 3 // 5q15 // 22836 /// XM_011	1.37
8102587	**NDNF**	NM_024574 // NDNF // neuron-derived neurotrophic factor // 4q27 // 79625 /// ENST000003	1.37
8090133	**CCDC14**	NM_001308317 // CCDC14 // coiled-coil domain containing 14 // 3q21.1 // 64770 /// NM_02	1.37
7926889	**LYZL1**	NM_032517 // LYZL1 // lysozyme-like 1 // 10p12.1 // 84569 /// XM_005252627 // LYZL1 //	1.36

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change
8141066	**PON3**	NM_000940 // PON3 // paraoxonase 3 // 7q21.3 // 5446 /// ENST00000265627 // PON3 // par	1.36
7908861	**OCR1**	AF314543 // OCR1 // ovarian cancer-related protein 1 // 1q32.1 // 100128298	1.36
8047062	**C2orf88**	NM_001042519 // C2orf88 // chromosome 2 open reading frame 88 // 2q32.2 // 84281 /// NM	1.36
8152902	**ADCY8**	NM_001115 // ADCY8 // adenylate cyclase 8 (brain) // 8q24 // 114 /// XM_005250769 // AD	1.36
8137483	**FLJ16734**	AK131514 // FLJ16734 // uncharacterized LOC641928 // 7q36.2 // 641928	1.36
8131666	**ITGB8**	NM_002214 // ITGB8 // integrin beta 8 // 7p21.1 // 3696 /// XM_011515392 // ITGB8 // in	1.36
7943349	**ARHGAP42**	NM_152432 // ARHGAP42 // Rho GTPase activating protein 42 // 11q22.1 // 143872 /// XM_0	1.36
8018761	**ST6GALNAC2**	NM_006456 // ST6GALNAC2 // ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-ac	1.35
7901634	**MROH7**	NM_001039464 // MROH7 // maestro heat-like repeat family member 7 // 1p32.3 // 374977 /	1.35
7939052	**FIBIN**	NM_203371 // FIBIN // fin bud initiation factor homolog (zebrafish) // 11p14.2 // 38775	1.35
7988414	**GATM**	NM_001482 // GATM // glycine amidinotransferase (L-arginine:glycine amidinotransferase)	1.35
8013268	**FAM106A**	NR_026809 // FAM106A // family with sequence similarity 106, member A // 17p11.2 // 800	1.35
7929388	**PLCE1**	NM_001165979 // PLCE1 // phospholipase C, epsilon 1 // 10q23 // 51196 /// NM_001288989	1.35
8005231	**FAM106CP**	NR_026810 // FAM106CP // family with sequence similarity 106, member C, pseudogene // 1	1.34
8156043	**PSAT1**	NM_021154 // PSAT1 // phosphoserine aminotransferase 1 // 9q21.2 // 29968 /// NM_058179	1.34
8005687	**FAM106CP**	NR_026810 // FAM106CP // family with sequence similarity 106, member C, pseudogene // 1	1.34
8104022	**PDLIM3**	NM_001114107 // PDLIM3 // PDZ and LIM domain 3 // 4q35 // 27295 /// NM_001257962 // PDL	1.34
7957386	**ACSS3**	NM_024560 // ACSS3 // acyl-CoA synthetase short-chain family member 3 // 12q21.31 // 79	1.34
8092009	**LRRC34**	NM_001172779 // LRRC34 // leucine rich repeat containing 34 // 3q26.2 // 151827 /// NM_	1.34
7947338	**PAX6**	NM_000280 // PAX6 // paired box 6 // 11p13 // 5080 /// NM_001127612 // PAX6 // paired b	1.34
8113796	**C5orf63**	NM_001164478 // C5orf63 // chromosome 5 open reading frame 63 // 5q23.2 // 401207 /// N	1.34
8102800	**SLC7A11**	NM_014331 // SLC7A11 // solute carrier family 7 (anionic amino acid transporter light c	1.34

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change
7907439	**PRDX6**	NM_004905 // PRDX6 // peroxiredoxin 6 // 1q25.1 // 9588 /// ENST00000340385 // PRDX6 //	1.33
8043782	**CNGA3**	NM_001079878 // CNGA3 // cyclic nucleotide gated channel alpha 3 // 2q11.2 // 1261 ///	1.33
8058063	**RFTN2**	NM_144629 // RFTN2 // raftlin family member 2 // 2q33.1 // 130132 /// XM_011510595 // R	1.33
7909285	**PFKFB2**	NM_001018053 // PFKFB2 // 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2 // 1q31	1.33
8016168	**PLCD3**	NM_133373 // PLCD3 // phospholipase C, delta 3 // 17q21.31 // 113026 /// XM_011524253 /	1.33
7932584	**PRTFDC1**	NM_001282786 // PRTFDC1 // phosphoribosyl transferase domain containing 1 // 10p12.1 //	1.32
7930380	**ADD3**	NM_001121 // ADD3 // adducin 3 (gamma) // 10q25.2 // 120 /// NM_016824 // ADD3 // adduc	1.32
8158431	**PHYHD1**	NM_001100876 // PHYHD1 // phytanoyl-CoA dioxygenase domain containing 1 // 9q34.11 // 2	1.32
7984488	**NOX5**	NM_001184779 // NOX5 // NADPH oxidase, EF-hand calcium binding domain 5 // 15q23 // 794	1.32
7927606	**PRKG1**	NM_001098512 // PRKG1 // protein kinase, cGMP-dependent, type I // 10q11.2 // 5592 ///	1.32
7928770	**CDHR1**	NM_001171971 // CDHR1 // cadherin-related family member 1 // 10q23.1 // 92211 /// NM_03	1.32
8022045	**MYOM1**	NM_003803 // MYOM1 // myomesin 1 // 18p11.31 // 8736 /// NM_019856 // MYOM1 // myomesin	1.32
8041383	**LTBP1**	NM_000627 // LTBP1 // latent transforming growth factor beta binding protein 1 // 2p22-	1.32
7903803	**AHCYL1**	NM_001242673 // AHCYL1 // adenosylhomocysteinase like 1 // 1p13.2 // 10768 /// NM_00124	1.31
8092800	**ATP13A4**	NM_032279 // ATP13A4 // ATPase type 13A4 // 3q29 // 84239 /// XM_005247829 // ATP13A4 /	1.31
8129649	**SLC18B1**	NM_052831 // SLC18B1 // solute carrier family 18, subfamily B, member 1 // 6q22.3-q23.3	1.31
8025004	**CAPS**	NM_004058 // CAPS // calcyphosine // 19p13.3 // 828 /// NM_080590 // CAPS // calcyphosi	1.31
8002152	**SLC12A4**	NM_001145961 // SLC12A4 // solute carrier family 12 (potassium/chloride transporter), m	1.30
7899455	**PHACTR4**	NM_001048183 // PHACTR4 // phosphatase and actin regulator 4 // 1p35.3 // 65979 /// NM_	1.30
8120602	**OGFRL1**	NM_024576 // OGFRL1 // opioid growth factor receptor-like 1 // 6q13 // 79627 /// XM_005	1.30
7900426	**SMAP2**	NM_001198978 // SMAP2 // small ArfGAP2 // 1p35.3-p34.1 // 64744 /// NM_001198979 // SMA	-1.30

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change
8040374	**FAM84A**	NM_145175 // FAM84A // family with sequence similarity 84, member A // 2p24.3 // 151354	-1.30
7956046	**DGKA**	NM_001345 // DGKA // diacylglycerol kinase alpha // 12q13.3 // 1606 /// NM_201444 // DG	-1.30
7969544	**NDFIP2**	NM_001161407 // NDFIP2 // Nedd4 family interacting protein 2 // 13q31.1 // 54602 /// NM	-1.30
8054254	**AFF3**	NM_001025108 // AFF3 // AF4/FMR2 family, member 3 // 2q11.2-q12 // 3899 /// NM_002285 /	-1.31
8032839	**SEMA6B**	NM_032108 // SEMA6B // sema domain, transmembrane domain (TM), and cytoplasmic domain,	-1.31
7998820	**FLJ42627**	NR_024492 // FLJ42627 // uncharacterized LOC645644 // 16p13.3 // 645644 /// AK124618 //	-1.31
8107044	**ERAP2**	NM_001130140 // ERAP2 // endoplasmic reticulum aminopeptidase 2 // 5q15 // 64167 /// NM	-1.31
7967486	**CCDC92**	NM_001304957 // CCDC92 // coiled-coil domain containing 92 // 12q24.31 // 80212 /// NM_	-1.31
7992682	**FLJ42627**	NR_024492 // FLJ42627 // uncharacterized LOC645644 // 16p13.3 // 645644 /// AK124618 //	-1.31
7955231	**KCNH3**	NM_001314030 // KCNH3 // potassium channel, voltage gated eag related subfamily H, memb	-1.31
7945620	**TOLLIP**	NM_019009 // TOLLIP // toll interacting protein // 11p15.5 // 54472 /// XM_011520192 //	-1.32
7982366	**SCG5**	NM_001144757 // SCG5 // secretogranin V // 15q13-q14 // 6447 /// NM_003020 // SCG5 // s	-1.32
8120961	**MRAP2**	NM_138409 // MRAP2 // melanocortin 2 receptor accessory protein 2 // 6q14.2 // 112609 /	-1.32
8026926	**MAST3**	NM_015016 // MAST3 // microtubule associated serine/threonine kinase 3 // 19p13.11 // 2	-1.32
8153167	**KCNK9**	NM_001282534 // KCNK9 // potassium channel, two pore domain subfamily K, member 9 // 8q	-1.32
8113369	**SLCO4C1**	NM_180991 // SLCO4C1 // solute carrier organic anion transporter family, member 4C1 //	-1.32
8172447	**PCSK1N**	NM_013271 // PCSK1N // proprotein convertase subtilisin/kexin type 1 inhibitor // Xp11.	-1.32
7941408	**SNX32**	NM_152760 // SNX32 // sorting nexin 32 // 11q13.1 // 254122 /// XM_006718488 // SNX32 /	-1.32
8042270	**UGP2**	NM_001001521 // UGP2 // UDP-glucose pyrophosphorylase 2 // 2p14-p13 // 7360 /// NM_0067	-1.32
7907104	**DCAF6**	NM_001017977 // DCAF6 // DDB1 and CUL4 associated factor 6 // 1q24.2 // 55827 /// NM_00	-1.33
8053022	**EGR4**	NM_001965 // EGR4 // early growth response 4 // 2p13 // 1961 /// ENST00000436467 // EGR	-1.33

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8068593	**ETS2**	NM_001256295 // ETS2 // v-ets avian erythroblastosis virus E26 oncogene homolog 2 // 21	-1.33
8178508	**ATP6V1G2**	NM_001204078 // ATP6V1G2 // ATPase, H+ transporting, lysosomal 13kDa, V1 subunit G2 //	-1.34
7903227	**PALMD**	NM_017734 // PALMD // palmdelphin // 1p21.2 // 54873 /// ENST00000263174 // PALMD // pa	-1.34
8008885	**MIR21**	NR_029493 // MIR21 // microRNA 21 // 17q23.1 // 406991 /// ENST00000362134 // MIR21 //	-1.34
7963577	**SPRYD3**	NM_032840 // SPRYD3 // SPRY domain containing 3 // 12q13.13 // 84926 /// ENST0000030146	-1.34
8169459	**SNORA35**	NR_002993 // SNORA35 // small nucleolar RNA, H/ACA box 35 // Xq23 // 677816 /// ENST000	-1.34
8104901	**IL7R**	NM_002185 // IL7R // interleukin 7 receptor // 5p13 // 3575 /// NR_120485 // IL7R // in	-1.34
7908879	**PPFIA4**	NM_001304331 // PPFIA4 // protein tyrosine phosphatase, receptor type, f polypeptide (P	-1.35
8067869	**RBM11**	NM_144770 // RBM11 // RNA binding motif protein 11 // 21q11 // 54033 /// XM_005260996 /	-1.35
8097991	**TDO2**	NM_005651 // TDO2 // tryptophan 2,3-dioxygenase // 4q31-q32 // 6999 /// ENST00000503634	-1.35
8062427	**VSTM2L**	NM_080607 // VSTM2L // V-set and transmembrane domain containing 2 like // 20q11.23 //	-1.35
8024888	**MIR7-3HG**	NR_027148 // MIR7-3HG // MIR7-3 host gene // 19p13.3 // 284424 /// ENST00000317292 // M	-1.35
8052947	**CYP26B1**	NM_001277742 // CYP26B1 // cytochrome P450, family 26, subfamily B, polypeptide 1 // 2p	-1.36
8043100	**TMSB10**	NM_021103 // TMSB10 // thymosin beta 10 // 2p11.2 // 9168 /// ENST00000233143 // TMSB10	-1.36
8026900	**KCNN1**	NM_002248 // KCNN1 // potassium channel, calcium activated intermediate/small conductan	-1.36
8032650	**PIP5K1C**	NM_001195733 // PIP5K1C // phosphatidylinositol-4-phosphate 5-kinase, type I, gamma //	-1.36
8115355	**GLRA1**	NM_000171 // GLRA1 // glycine receptor alpha 1 // 5q32 // 2741 /// NM_001146040 // GLRA	-1.36
8153258	**SLC45A4**	NM_001080431 // SLC45A4 // solute carrier family 45, member 4 // 8q24.3 // 57210 /// NM	-1.37
8011924	**PITPNM3**	NM_001165966 // PITPNM3 // PITPNM family member 3 // 17p13 // 83394 /// NM_031220 // PI	-1.38
8011214	**RTN4RL1**	NM_178568 // RTN4RL1 // reticulon 4 receptor-like 1 // 17p13.3 // 146760 /// XM_0115236	-1.38
8095616	**NPFFR2**	NM_001144756 // NPFFR2 // neuropeptide FF receptor 2 // 4q21 // 10886 /// NM_004885 //	-1.38

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7924977	**PGBD5**	NM_001258311 // PGBD5 // piggyBac transposable element derived 5 // 1q42.13 // 79605 //	-1.38
7914758	**DLGAP3**	NM_001080418 // DLGAP3 // discs, large (Drosophila) homolog-associated protein 3 // 1p3	-1.38
8150797	**ATP6V1H**	NM_015941 // ATP6V1H // ATPase, H+ transporting, lysosomal 50/57kDa, V1 subunit H // 8q	-1.38
8129254	**MAN1A1**	NM_005907 // MAN1A1 // mannosidase, alpha, class 1A, member 1 // 6q22 // 4121 /// XM_00	-1.39
7914878	**CLSPN**	NM_001190481 // CLSPN // claspin // 1p34.2 // 63967 /// NM_022111 // CLSPN // claspin /	-1.39
7910611	**KCNK1**	NM_002245 // KCNK1 // potassium channel, two pore domain subfamily K, member 1 // 1q42-	-1.40
8066262	**SNORA71D**	NR_003018 // SNORA71D // small nucleolar RNA, H/ACA box 71D // 20q11.23 // 677840 /// u	-1.40
8040889	**DNAJC5G**	NM_001303127 // DNAJC5G // DnaJ (Hsp40) homolog, subfamily C, member 5 gamma // 2p23.3	-1.41
8140579	**CACNA2D1**	NM_000722 // CACNA2D1 // calcium channel, voltage-dependent, alpha 2/delta subunit 1 //	-1.41
7986293	**MCTP2**	NM_001159643 // MCTP2 // multiple C2 domains, transmembrane 2 // 15q26.2 // 55784 /// N	-1.41
8011480	**CAMKK1**	NM_032294 // CAMKK1 // calcium/calmodulin-dependent protein kinase kinase 1, alpha // 1	-1.41
8113130	**MCTP1**	NM_001002796 // MCTP1 // multiple C2 domains, transmembrane 1 // 5q15 // 79772 /// NM_0	-1.41
7997746	**JPH3**	NM_001271604 // JPH3 // junctophilin 3 // 16q24.3 // 57338 /// NM_001271605 // JPH3 //	-1.41
8050894	**KIF3C**	NM_002254 // KIF3C // kinesin family member 3C // 2p23 // 3797 /// XM_005264299 // KIF3	-1.42
8020453	**LOC102724208**	XR_935278 // LOC102724208 // uncharacterized LOC102724208 // --- // 102724208	-1.42
8052721	**PPP3R1**	NM_000945 // PPP3R1 // protein phosphatase 3, regulatory subunit B, alpha // 2p15 // 55	-1.42
8005132	**MEIS3P1**	NR_002211 // MEIS3P1 // Meis homeobox 3 pseudogene 1 // 17p12 // 4213 /// OTTHUMT000001	-1.43
7959195	**CABP1**	NM_001033677 // CABP1 // calcium binding protein 1 // 12q24.31 // 9478 /// NM_004276 //	-1.43
7984319	**MAP2K1**	NM_002755 // MAP2K1 // mitogen-activated protein kinase kinase 1 // 15q22.1-q22.33 // 5	-1.43
7954436	**LRMP**	NM_001204126 // LRMP // lymphoid-restricted membrane protein // 12p12.1 // 4033 /// NM_	-1.43
8035304	**BST2**	NM_004335 // BST2 // bone marrow stromal cell antigen 2 // 19p13.1 // 684 /// ENST00000	-1.44
8038126	**CA11**	NM_001217 // CA11 // carbonic anhydrase XI // 19q13.3 // 770 /// ENST00000084798 // CA1	-1.44

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8037888	**SLC8A2**	NM_015063 // SLC8A2 // solute carrier family 8 (sodium/calcium exchanger), member 2 //	-1.45
8156290	**CKS2**	NM_001827 // CKS2 // CDC28 protein kinase regulatory subunit 2 // 9q22 // 1164 /// ENST	-1.45
8005695	**MEIS3P1**	NR_002211 // MEIS3P1 // Meis homeobox 3 pseudogene 1 // 17p12 // 4213 /// AK289643 // M	-1.45
8047910	**PTH2R**	NM_001309516 // PTH2R // parathyroid hormone 2 receptor // 2q33 // 5746 /// NM_005048 /	-1.46
8135080	**AP1S1**	NM_001283 // AP1S1 // adaptor-related protein complex 1 sigma 1 subunit // 7q22.1 // 11	-1.46
8100507	**HOPX**	NM_001145459 // HOPX // HOP homeobox // 4q12 // 84525 /// NM_001145460 // HOPX // HOP h	-1.46
7974882	**SYT16**	NM_031914 // SYT16 // synaptotagmin XVI // 14q23.2 // 83851 /// XM_006720272 // SYT16 /	-1.46
8007607	**RUNDC3A**	NM_001144825 // RUNDC3A // RUN domain containing 3A // 17q21.31 // 10900 /// NM_0011448	-1.46
8041508	**QPCT**	NM_012413 // QPCT // glutaminyl-peptide cyclotransferase // 2p22.2 // 25797 /// ENST000	-1.48
7920244	**S100A8**	NM_002964 // S100A8 // S100 calcium binding protein A8 // 1q21 // 6279 /// XM_011509861	-1.48
7950162	**PDE2A**	NM_001143839 // PDE2A // phosphodiesterase 2A, cGMP-stimulated // 11q13.4 // 5138 /// N	-1.49
7980908	**FBLN5**	NM_006329 // FBLN5 // fibulin 5 // 14q32.1 // 10516 /// XM_005267267 // FBLN5 // fibuli	-1.49
8015049	**KRT222**	NM_152349 // KRT222 // keratin 222, type II // 17q21.2 // 125113 /// ENST00000394049 //	-1.49
8142194	**LAMB1**	NM_002291 // LAMB1 // laminin, beta 1 // 7q22 // 3912 /// XM_011516203 // LAMB1 // lami	-1.50
8152369	**KCNV1**	NM_014379 // KCNV1 // potassium channel, voltage gated modifier subfamily V, member 1 /	-1.50
7980485	**DIO2**	NM_000793 // DIO2 // deiodinase, iodothyronine, type II // 14q24.2-q24.3 // 1734 /// NM	-1.51
8046792	**DUSP19**	NM_001142314 // DUSP19 // dual specificity phosphatase 19 // 2q32.1 // 142679 /// NM_08	-1.51
8039378	**SYT5**	NM_001297774 // SYT5 // synaptotagmin V // 19q13.42|11p // 6861 /// NM_003180 // SYT5 /	-1.52
8086615	**LRRC2**	NM_024512 // LRRC2 // leucine rich repeat containing 2 // 3p21.31 // 79442 /// XM_01153	-1.54
7979824	**ACTN1**	NM_001102 // ACTN1 // actinin, alpha 1 // 14q24|14q22-q24 // 87 /// NM_001130004 // ACT	-1.54
8076668	**KIAA1644**	NM_001099294 // KIAA1644 // KIAA1644 // --- // 85352 /// XM_005261790 // KIAA1644 // KI	-1.55

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change
8016832	**MMD**	NM_012329 // MMD // monocyte to macrophage differentiation-associated // 17q // 23531 /	-1.58
8021695	**DOK6**	NM_152721 // DOK6 // docking protein 6 // 18q22.2 // 220164 /// XM_011525873 // DOK6 //	-1.59
8000757	**DOC2A**	NM_001282062 // DOC2A // double C2-like domains, alpha // 16p11.2 // 8448 /// NM_001282	-1.62
7974900	**LINC00643**	NR_015358 // LINC00643 // long intergenic non-protein coding RNA 643 // 14q23.2 // 6461	-1.62
8098146	**NPY5R**	NM_006174 // NPY5R // neuropeptide Y receptor Y5 // 4q32.2 // 4889 /// XM_005263038 //	-1.63
8051050	**SLC30A3**	NM_003459 // SLC30A3 // solute carrier family 30 (zinc transporter), member 3 // 2p23.3	-1.65
7932082	**CCDC3**	NM_001282658 // CCDC3 // coiled-coil domain containing 3 // 10p13 // 83643 /// NM_03145	-1.65
8123739	**NRN1**	NM_001278710 // NRN1 // neuritin 1 // 6p25.1 // 51299 /// NM_001278711 // NRN1 // neuri	-1.70
7939024	**ANO3**	NM_001313726 // ANO3 // anoctamin 3 // 11p14.2 // 63982 /// NM_001313727 // ANO3 // ano	-1.76
7975066	**AKAP5**	NM_004857 // AKAP5 // A kinase (PRKA) anchor protein 5 // 14q23.3 // 9495 /// ENST00000	-1.84
8060940	**LAMP5**	NM_001199897 // LAMP5 // lysosomal-associated membrane protein family, member 5 // 20p1	-1.86
7974895	**LINC00643**	NR_015358 // LINC00643 // long intergenic non-protein coding RNA 643 // 14q23.2 // 6461	-1.89
7902400	**SNORD45B**	ENST00000364617 // SNORD45B // small nucleolar RNA, C/D box 45B // 1p31.1 // 26804 ///	-1.93
7941599	**NPAS4**	NM_178864 // NPAS4 // neuronal PAS domain protein 4 // 11q13 // 266743 /// XM_011544938	-2.00

APPENDIX 18

Significantly changed transcripts in human MTLE samples with and without Febrile Seizures (FS vs. No FS).Thresholds: 2-fold, FDR-adjusted p-value< 0.05.

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change
7976496	**SERPINA3**	NM_001085 // SERPINA3 // serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, a	5.81
7983523	**---**	---	3.88
8012837	**PIRT**	NM_001101387 // PIRT // phosphoinositide-interacting regulator of transient receptor po	3.36
7896435	**---**	---	3.09
7939341	**CD44**	NM_000610 // CD44 // CD44 molecule (Indian blood group) // 11p13 // 960 /// NM_00100138	3.05
7986350	**ARRDC4**	NM_183376 // ARRDC4 // arrestin domain containing 4 // 15q26.3 // 91947 /// ENST0000026	2.74
7948167	**APLNR**	NM_005161 // APLNR // apelin receptor // 11q12 // 187 /// NR_027991 // APLNR // apelin	2.60
8089145	**ABI3BP**	NM_015429 // ABI3BP // ABI family, member 3 (NESH) binding protein // 3q12 // 25890 ///	2.53
8132557	**AEBP1**	NM_001129 // AEBP1 // AE binding protein 1 // 7p13 // 165 /// XM_011515162 // AEBP1 //	2.45
8089544	**CCDC80**	NM_199511 // CCDC80 // coiled-coil domain containing 80 // 3q13.2 // 151887 /// NM_1995	2.43
7959102	**HSPB8**	NM_014365 // HSPB8 // heat shock 22kDa protein 8 // 12q24.23 // 26353 /// ENST000002819	2.42
7948420	**FABP5**	BT007449 // FABP5 // fatty acid binding protein 5 (psoriasis-associated) // 8q21.13 //	2.42
8117034	**GMPR**	NM_006877 // GMPR // guanosine monophosphate reductase // 6p23 // 2766 /// XM_011514508	2.39
8147049	**FABP5**	NM_001444 // FABP5 // fatty acid binding protein 5 (psoriasis-associated) // 8q21.13 //	2.39
7903920	**CHI3L2**	NM_001025197 // CHI3L2 // chitinase 3-like 2 // 1p13.3 // 1117 /// NM_001025199 // CHI3	2.33
8146967	**CRISPLD1**	NM_001286777 // CRISPLD1 // cysteine-rich secretory protein LCCL domain containing 1 //	2.32
7895349	**---**	---	2.25
8091922	**WDR49**	NM_178824 // WDR49 // WD repeat domain 49 // 3q26.1 // 151790 /// ENST00000308378 // WD	2.25
8165817	**GYG2**	NM_001079855 // GYG2 // glycogenin 2 // Xp22.3 // 8908 /// NM_001184702 // GYG2 // glyc	2.19
8091422	**WWTR1**	NM_001168278 // WWTR1 // WW domain containing transcription regulator 1 // 3q23-q24 //	2.18
7961875	**LMNTD1**	NM_001145727 // LMNTD1 // lamin tail domain containing 1 // 12p12.1 // 160492 /// NM_00	2.14
8009951	**ITGB4**	NM_000213 // ITGB4 // integrin beta 4 // 17q25 // 3691 /// NM_001005619 // ITGB4 // int	2.13
8152297	**ANGPT1**	NM_001146 // ANGPT1 // angiopoietin 1 // 8q23.1 // 284 /// NM_001199859 // ANGPT1 // an	2.13
8092661	**MASP1**	NM_001031849 // MASP1 // mannan-binding lectin serine peptidase 1 (C4/C2 activating com	2.10
7954398	**SPX**	NM_030572 // SPX // spexin hormone // 12p12.1 // 80763 /// ENST00000256969 // SPX // sp	2.10

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change
8113790	**MARCH3**	NM_178450 // MARCH3 // membrane associated ring finger 3 // 5q23.2 // 115123 /// XM_011	2.08
8172043	**SRPX**	NM_001170750 // SRPX // sushi-repeat containing protein, X-linked // Xp21.1 // 8406 ///	2.08
7990757	**CTSH**	NM_004390 // CTSH // cathepsin H // 15q25.1 // 1512 /// XM_005254181 // CTSH // catheps	2.06
8042439	**ANTXR1**	NM_018153 // ANTXR1 // anthrax toxin receptor 1 // 2p13.1 // 84168 /// NM_032208 // ANT	2.05
8152335	**TMEM74**	NM_153015 // TMEM74 // transmembrane protein 74 // 8q23.1 // 157753 /// ENST00000297459	2.03
8172204	**MAOB**	NM_000898 // MAOB // monoamine oxidase B // Xp11.23 // 4129 /// XM_005272607 // MAOB //	2.02
8103254	**SFRP2**	NM_003013 // SFRP2 // secreted frizzled-related protein 2 // 4q31.3 // 6423 /// ENST000	2.02

APPENDIX 19

Significantly changed transcripts in human MTLE samples with and without Focal Cortical Dysplasia (FCD vs. No FCD).Thresholds: 2.5-fold, FDR-adjusted p-value< 0.05.

Affymetrix Probe set ID	Entrez Gene Symbol	Gene description	Fold Change
7976496	**SERPINA3**	NM_001085 // SERPINA3 // serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, a	9.45
8089544	**CCDC80**	NM_199511 // CCDC80 // coiled-coil domain containing 80 // 3q13.2 // 151887 /// NM_1995	3.00
7948420	**FABP5**	BT007449 // FABP5 // fatty acid binding protein 5 (psoriasis-associated) // 8q21.13 //	2.99
8147049	**FABP5**	NM_001444 // FABP5 // fatty acid binding protein 5 (psoriasis-associated) // 8q21.13 //	2.96
8013364	**SLC47A2**	NM_001099646 // SLC47A2 // solute carrier family 47 (multidrug and toxin extrusion), me	2.72
7959102	**HSPB8**	NM_014365 // HSPB8 // heat shock 22kDa protein 8 // 12q24.23 // 26353 /// ENST000002819	2.69
7903920	**CHI3L2**	NM_001025197 // CHI3L2 // chitinase 3-like 2 // 1p13.3 // 1117 /// NM_001025199 // CHI3	2.67
8132557	**AEBP1**	NM_001129 // AEBP1 // AE binding protein 1 // 7p13 // 165 /// XM_011515162 // AEBP1 //	2.65
8091422	**WWTR1**	NM_001168278 // WWTR1 // WW domain containing transcription regulator 1 // 3q23-q24 //	2.60
8165817	**GYG2**	NM_001079855 // GYG2 // glycogenin 2 // Xp22.3 // 8908 /// NM_001184702 // GYG2 // glyc	2.58
8152297	**ANGPT1**	NM_001146 // ANGPT1 // angiopoietin 1 // 8q23.1 // 284 /// NM_001199859 // ANGPT1 // an	2.47
8172204	**MAOB**	NM_000898 // MAOB // monoamine oxidase B // Xp11.23 // 4129 /// XM_005272607 // MAOB //	2.41
8117034	**GMPR**	NM_006877 // GMPR // guanosine monophosphate reductase // 6p23 // 2766 /// XM_011514508	2.38
8035201	**CPAMD8**	NM_015692 // CPAMD8 // C3 and PZP-like, alpha-2-macroglobulin domain containing 8 // 19	2.35