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ÉJ Bş¢ ÁŰŁÉ¢¢ζ q? J ũÁŁJ É
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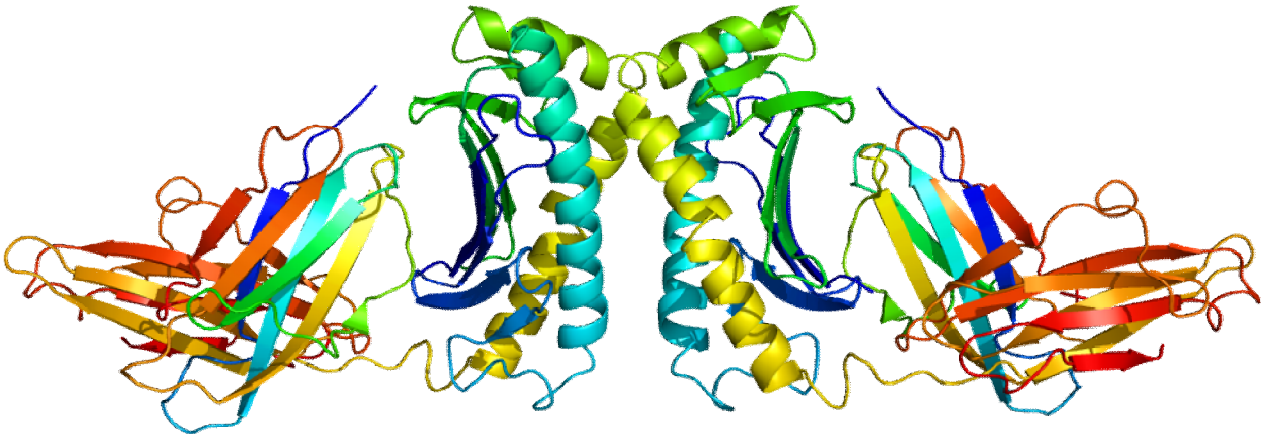

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¢ ȺɄⱢɇ ɅɃɄ¢

Ɔ ⱧŬŰɉ ɧɠ, ȾəɜɞɧɠƖ ū ŬɈɛŬɵɞəɧɔɞɠ, Ⱥ´ ɷɞɡɈɞɠ ȾŬɗɖɔɖŰɐɠ Ⱦəɜɞɐɠ ū ŬɈɛŬɵɞəɞɔɗŬɠ, Ɇɢɞəɐ Ⱥ´ ɘůŰɖɛɩɜ Ɉ ɔůɗŬɠ, ɇɛɐɛŬ ū ŬɈɛŬɵůɡŰɵɐɠ, ɇɞɛɏŬɠ ū ŬɈɛŬɵůɡŰɵɐɠ ɇůɢɜɞəɞɔɗŬɠ, ȺɈůɡɜɖŰɵɧ ȺɈɔŬůŰɐɈɞ Ⱦəɜɞɐɠ ū ŬɈɛŬɵɞəɞɔɗŬɠ ə Ŭə ū ŬɈɛŬɵɞɔɞɜɘŭɤ ɛŬŰɵɐɠ

ɸůɛɏŰɢɞɠ Ⱦɤɜů ŰŬɜŰɞɠ ȾŬɗɖɔɖŰɐ ū ŬɈɛŬɵůɡŰɵɐɠ ɇůɢɜɞəɞɔɗŬɠ &? Ŭɜɞ-ŰůɢɜɞəɞɔɗŬɠ, Ɇɢɞəɐ Ⱥ´ ɘůŰɖɛɩɜ Ɉ ɔůɗŬɠ, ɇɛɐɛŬ ū ŬɈɛŬɵůɡŰɵɐɠ, ɇɞɛɏŬɠ ū ŬɈɛŬɵůɡŰɵɐɠ ɇůɢɜɞəɞɔɗŬɠ, ɸəůɡɗɜŰɐɠ ȺɈɔŬůŰɖɈɷɡ ū ŬɈɛŬɵůɡŰɵɐɠ ɇůɢɜɞəɞɔɗŬɠ

ɗəƳɢɞɡ-Ⱦɤɜů ŰŬɜŰɵəŭɞɡɀ ŬɈəɏɜŬ Ⱥ´ ɷɞɡɈɖ ȾŬɗɖəɐŰɈəŬ, Ɇɢɞəɐ Ⱥ´ ɘůŰɖɛɩɜ Ɉ ɔůɗŬɠ, ɇɛɐɛŬ ū ŬɈɛŬɵůɡŰɵɐɠ, ɇɞɛɏŬɠ ū ŬɈɛŬɵůɡŰɵɐɠ ɇůɢɜɞəɞɔɗŬɠ

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-ÆÆ

ÛÞ´ɛɜɐdd̩əÛ Ûɛ ÛÞÜûdɛÜʰɦ ɣÛɛɡ 2015-2016, ůÛɛ Æɣ̩Ůɡɜd̩Ûəɦ Æɣ̩ɔÜůÛĕɟɜɛ Ƭɐɜəɜɐɛɡū Ůɟɛ̩ÜÞɛəɛɔdÜɡəÜÞ ū Ůɟɛ̩ÜÞɛɔɛɜəüɜɛ̩ÜÛəɐɛɡ, Ûɛg ɛɛɐɛÜÛɛɡū Ůɟɛ̩ÜÞŮɡ̩Ûəɐɛɡɛ̩ÛɛɜɛəɛɔdÜɡÛɛg Æd̩ɜəɛi Ƭ̈Ü ɛüəůĭɟəÜəɛi Ⱶ̈ÜɜÛ̈ əůÛ̈d̩ɛœg ɹ d̩d̩ɜı ɜ. ɀ Û̈ Û̈d̩ɜ ɛəɛəɐɐɟɹɣůd̩ Û̈d̩ɡ, dÜ dɣəÜɛÛ̈ ɜÜ Ůɡ̩ɢÜɟəůĭɛůɛgɛÛ̈ ɦəɛggɡ ɦůɛggɡ ůgɜɣ̈ÜÞəÜÞ ůÛ̈d̩ɜ Ûə´ɦɜd̩ůɐ Û̈d̩ɡ.

ɹ ɟɢəɐY, Ûəűɟ Ɣɛɛgɛ̈ÛÛ̈ɡd̩Ůɟɛɣɡɛ̈ÜɡŮɡɢÜɟəůĭÛ̈ůɡůÛɛɜ Û̈ɐɓəɐý ɛɜĭÜəÜ̈d̩ɔd̩Ûɛ ɛÜɡəÜÞ Û̈əůĭÛ̈d̩ɛɛɜəɦ g´Ůi d̩gɜɛ Û̈d̩ɡ Ůɟɔ̈ÜůdÜɡ ɛÜɡ, Û̈œɛgɟɛ əÜ̈d̩ɔd̩Ûɛ əi ɟɜɛ œɟÜəɛi əd ?əɦəÜɛ, Ûɦůɛ ɔəÜ Û̈d̩ɜ əÜ̈d̩ɛüɐɔd̩ůd̩,Ûɡ̩ůgɛɓɛgəɣɡəÜÞ Û̈d̩ɜ ´ɛəi Ûɛd̩ ɓɛɐdÜɓY Ûɛg əÜ̈ĭY Û̈d̩ ůgɔɔɟÜűɐ Û̈d̩ɡ´Ůɟɛi ůÜɡ̩Ůɟɔ̈ÜůdÜɡɦůɛ əÜəɔəÜ Û̈d̩ɜ YɣɛɔdůgɜÜɟɔ̈ÜůdÜ.

ÆgɛŮɟəůÛ̈ɛi ɛÛ Ûɐůdɡ əüəÜůĭɟŮ, Û̈d̩ dɔɛɛɡd̩ɛəɦ-dɔɛÛ̈Ûɛɜɛəɦɔɛ, əgɟdÜ Ƭ̈ÜÛ̈ůŮɟɛi ɀ Yɟd̩Ü-Æ´gɟəüɛi əÜ, ɛÛ̈ÛÜüəüÜəÛ̈ɛɟɜəɐ Ůɟůgɜɐ Ůɟəɔ̈Ûɛg Ûɛɐɛ ÛÛ̈ɛɡū Ůɟɛ̩ÜÞŮɡ̩Ûəɐɛɡ, ɔəÜ Û̈d̩ɜ g´ɛůĭɟɜɛd əÜə Û̈d̩ɜ əÜ̈d̩ɛüɐɔd̩ůd ´ɛg ɛÜɡ ´Ůɟůɛ̩Ů ůÛɛ Ůɟɔ̈ÜůdÜɡɟəÜəɦ əÜə ´Ůəɟ̩ÜɛÛ̈ÛəɦɛɣɟɛɡÛ̈d̩ɡŮɟɔ̈ÜůdÜɡŮüĭɛ.

Æ´ɡəɣɛɜ, ŮɡɢŮɟəůÛ̈ɛi ɛÛ´ɟɛůɐ´əɐŸÛɛɜ əi ɟɜɛ œůÛɛŮɟÛɛɐ ?əɦəÜɛ əÜə Û̈ɛ g´ɦəɛɡ́ɛ ´ɟɛůɐ´əɦ Ûɛg Ůɟɔ̈ÜůdÜɡœg ɔəÜ Û̈d̩ɜ ůgɜŮɟɔ̈ÜůdÜ əÜə Ûəɡ̩ əÜ̈d̩ɛüɐd̩ɔɐůəɡ´ɛg ɛÜɡ ɣüɐůÜɜ ɦÛ̈ɜ Ûəɡ̩ɢɟůÛ̈ůəÜɛÛ

ÆgɛŮɟəůÛ̈ɛi ɛÛ əÜə ÛÜ Ɣəɔ̈Ü üi ɛ ɛɣɔdÛ̈d̩ɡ Ůɟɜɛ Ûəɛi ɡ Û̈ əŮɟɛ´ɐɡ, Ûɛɜ əi ɟɜɛ œůÛɛɣÛ̈ɛ Ƭɐɜůɜ Û̈ɛɜɛ, Ƭ̈Ü̈d̩ɔd̩Ûɛ ūŮɟɛÜəÛ̈ůəÜəɐɛɡ ɛ̈ÛɛɜɛəɛɔdÜɡ &?Üɜɛ-Û̈ÛɛɜɛəɛɔdÜɡ, œəůĭgd̩ɡɜÛ̈ɛ Ûɛg Æɣ̩ɔÜůÛ̈d̩ɟœg Û̈d̩ɡūŮɟɛÜəÛ̈ůəÜəɐɛɡɛ̈ÛɛɜɛəɛɔdÜɡəÜəÛ̈d̩ɜ əgɟdÜdɔəɣÛɛg-Ƭɐɜůɜ Û̈ɛɜɛəɛɔdÜɡ ŮɟɛəɣɜÜ, Æ´œɛgɟd Ƭ̈Ü̈d̩ɔɐŮɟəÜ Ûɛg ɛɛɐɣÜ ūŮɟɛÜəÛ̈ůəÜəɐɛɡ ɛ̈ÛɛɜɛəɛɔdÜɡ,ɔəÜ Û̈d̩ɜ Üəɛəɦɔd̩ůd Û̈d̩ɡ´Ůɟɛi ůÜɡ̩Ůɟɔ̈ÜůdÜɡ.

ɛɣəɛɡ, üůɜ dÜɛ´ɛɟɛi ůÜɛÛɜÜ´Ůɟ ÜəůɣɛgɛÛɜÜ Ůɡ̩ɢŮɟəůÛ̈ůɛgɛÛ̈ÜɡɛəɛɔɣəůĭɡɛÜɡ, ɔəÜ Û̈d̩ɜ ÜɛɣɟəůĭÛ̈d̩ ůÛ̈ɟɜəd̩ Ûɛggɡ əÜ̈ĭY Û̈d̩ɜ ůgɔɔɟÜűɐ Û̈d̩ɡ Ůɟɔ̈ÜůdÜɡŮüĭɛɡəÜ̈ı ɡəÜəÛ̈d̩ɜ ůgɛ´Ůɟ Ɣůɔ̈ÜůɐÛɛggɡůÛəYdÛ̈Üəüd̩ɛÜʰɦ əÜəÛ̈əůĭɛɜəɦ ɛÜɡɓɐɛÜ.

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1.1 Ð Ëëqt ΛÐÐË Ëë¢Ð? ÐΛũȷ ?ËÉz Ð

Ð ůơűdȷ¤gƒůg£ɓŸə¤Ůə£Ů´¢ə¤Ü ə¢i¤gƒÜƒȟ´egggůÜƒə¤Ůə£gȷ¤cÜÜ£g Ü¤dȷ¤ ´¤¤¢g ¢ȷ¤CÜ¤¤ůÜ£¢i¤, Üƒȟůe ůÜ£gƒ¢£Ÿ¤ÜůgƒÜœdgƒÜŕ¤ əgÜ£¢g¤ȷ¤ ŕŸÜŕ¤,ƒȟůe əÜ¤ŕ¤gƒɓÜ¤¤əƒȟ ůÜ£¤¢gÜůœ Üƒ|gƒÜœdgƒ ůÜ£ ŕƒȟȷ¤¤ Üƒ|gƒÜ¤£¢ůÜ¤ȷ¤¢dgƒ əÜ¤ Üƒ|gƒ ŕg¢ůÜűÜ¤ȷ¤¢dg.[1] Ä¢¤Ü¤ Ü£ ůÜ£¤¢gÜůœ ´Ÿ¤¤ŕ ůÜ£ ¢´¢œ ü¤ÜůŕŕeÜŕÜÜÜ¤ Ü£ ¢¤gɔƒȟ¤ɔ ŕŸůÜ ůÜ£ Ü|ȷgdȷ¢¤i¤ÜÜÜȷ¢.[2]ş ƒȟɔ¤ Ü ¢gůdÜgƒ ¢gůŕ¤Üůü£¤¢i¤ Ü ůə¤ȷ¤ŕ£¤¢i¤ ŕdɢCÜ¤ŕůŕ¢i¤ Ü£g, d ü¤ÜÜŕȷdůd ű¢gůŕ¤ə¢ɔ¤¤ı ¤ Ů¤´¤ŕüŕ¤ ůŕü¤ŕȷ¢g əÜdɑůÜÜÜÜ¤¢ŕ¤ Ü£¤¢¤ŕg ůdŕɛÜůdÜgƒ əÜ¤ Ů¤£Ü£¤ŕůÜÜ¤ŕ¤ŕüůŕ ȷ¤i¤dŕ¤ůdgƒ Üƒ|gƒÜ¤Ü|ȷ¤¤¢gƒ Ü£g Ü¢ȷ¤ȷƒűdůdgƒ¤Ü¤ Ü ƒȟ Üƒ| ůg¤Ü£ƒȟɛÜ¤d Ü¤Ü¤i¤ə¢ŕůd ə¤Ü¤ Ů Ü¤Ÿ¢gȷdůd Ü£g ə¢ÜÜÜȷ¤¢i¤ ůŕü¤ŕȷ¢g. ū ¢gůŕ¤ə¢ɔ¤¤Ÿ, ÜÜ Ů¤ɑ Ü¤üÜ ůŕü¤ŕȷ¢g ȷ¢gdŕ¤ɑŕ¤¤ɔÜÜ¤ŕ¤ŕüůŕ Üȷ¤dÜ£¤¢gƒ Ü¤Ü£ű¢ü¤ƒÜƒůdgƒ, ü¤d¤ÜÜŕe ƒȟůe ŕÜ¤Ü¤i¤Üȷd ´¢ůƒȟÜƒÜÜ ůŕü¤ŕȷ¢g g´Ÿȷ¢Ü¤ ůÜ£ ůı ŕÜ, Üƒȟůe ¤¤ƒȟÜȷ¢gƒůơűdȷ¢gƒÜ ¢ȷ¢ȷƒŕÜŕÜ¤Ü ƒȟ Ü£¤¤ Ü¤Üȷ¤¤ƒȟ ůŕ ¤¤ŕ¤Ü.[1]

Ü¢¤¤Ü ¤¢¤´ȷ¢ůÜÜÜȷÜ¤¢ŕ¤ɑŕ¢dɢCÜ¤ŕůŕ¢¢g, ƒȟ´ŕgƒd´ȷƒȟůůÜůd Ü£g ŕÜ´ȷ¢ŕÜȷůg, d Ü¢dŕə¤Ůȷůe Ü£g ůÜƒ¤ ű¢Üȷ¢ŕ¢Ü¤d ə¤Ü¤ Ü¤Ü¤ŕ¤ɔe Ü£g ŕ¤üŕ¤ŕÜƒÜÜ¤ŕ¤ŕüůŕ Ü£g ůŕü¤ŕȷ¢g. ȷ ´¢ü¤¢ȷ¢ɔŸ¤ŕůd Üŕ¤ ȷ¢gdŕ¤ůÜ¤¤ı ¤ ɛdɢCÜ¤ŕůŕ¢i¤, ¢ü¢dɔÜůůÜÜ¤ŕ¤ŕ¤ŕŕ¤ŕ¤ɑÜ¤dƒůÜƒ¤ ¢ŕ¢¢ƒȟůÜÜůd Ü£g ůŕü¤ŕȷ¢g ůÜ£¤ ¢ȷ¢ÜŕůÜ¤ŕ¤ŕüůŕ¢ƒȟ ə¤Ü¤ Ů¤´¢¤ŕ¢¤ ´¢ȷ¢ůd ¤Ü ůg¢ɓŸ¤ůe ůÜƒ¤ ´Ü¢d¢ű¢gůŕ¤ə¢ɔdÜ¤¢¤ŕ¤ ´Ü¢d¢ə¢ɔ¤¤ı ¤ ´Ü|ȷÜ¤ƒȟÜŕ¤ ůg¢´Ü|ȷ¤ə¤Ü£ɓ¢¤ŕ¤ŕ¤ Ü£g ű¤ə¤Ü¤¢¤ŕdƒ, Ü£g ¤Ü|gȷ¢Ü¤ƒűg¤ŕůŕ¢i¤, Üŕ¤ ɛÜÜÜɓ¢¤ŕ¤ı ¤ ü¤ÜÜÜȷÜ¤ı ¤ ə¤Ü¤ Ü£g ə¤Ü|¤¢¤ŕg.[3] ¢ ´¤¤ ůd£Ü¤Ü£¤ŕe Ü¤ŕ¤Ü¤d¤Ü¤ƒɔ¤ŕÜ¤Ů Ÿȷ¤ə¤Ü|ƒÜ¤ŕůŕ¢g ů¤ü¤Ü¤d Ü¤Ü£¤dÜ. ¢ Ü£¤¢¢gȷ¤ŕ¤ŕŸÜŕůd, ¢¤Ü|ƒɔ¤ə¤Ü¤ Ü|ȷůe ů´Ÿ¤¤Ü¤ƒȟůe¢g,´ȷ¤¢ə¤Ü¤ů¤Ü¤ŕ¤ƒɔ¤ŕ¤ g´Ü|ȷűƒȟȷÜŕůdgƒůŕü¤ŕȷ¢g.

1.2 ȷ Ð ΛũÆË ËÉhqt¢ ΛÐȷ Ë¢Ð? ÐΛũȷ ?ËÉz Ð

Ð Ü ¢gȷ¤ȷ¢ű¤ ¢Ü¤¢gƒÜ ƒȟ Üƒ|¤ Ü|ȷ¢ű¢e ůơűdȷ¢gƒÜ Ü¤Ü£ŸÜÜ¤ə¤gȷ¤ɔ¤gƒůÜůü¤i¢ ¢¢ȷ¤ű¢yg:

1. Ëơűdȷ¢gƒ Ü£¢dgƒ (e ¢ȷ¤CÜ¤¤əƒȟgƒůơűdȷ¢g): ¢ ůơűdȷ¢gƒ´¢g Ü¢ÜÜ¤ŕ¤ůÜ¤¢¤ŕ¤¤ȷ¢gƒ Üƒ|gƒ Ü£¢dgƒ
2. Ëơűdȷ¢gƒ¢d-Ü£¢dgƒ (e Ü¤ƒȷ¤CÜ¤¢gƒůơűdȷ¢g): ůơűdȷ¢gƒ´¢g ü¤Ü¤ Ü¢ÜÜ¤ŕ¤ůÜ¤¢¤ŕ¤¤ȷ¢gƒ Üƒ|gƒÜ£¢dgƒ

cpə¤Ü¤ű¢ȷ¤ŕÜÜ¤ə¢ɔ¤ ɛdɢCÜ¤ŕůŕ¢¢ɔ¤ Ü¢ȷ¤ȷƒűdůdgƒ Ů¤ŕÜÜ¤ə¢i¤ŕÜÜ¤ ɔ¤ŕÜ Ügü£¤i¢gƒ Ü£¢ggƒ ü¤i¢ Üƒ´¢ggƒü¤ŕÜƒ¤ű¢ŕ¤ə¢i¤ ůŕü¤ŕȷ¢g. ¢ ¢ə¤ŕ¤ŕe Ü¢ȷ¤ȷƒűdůd Ü£¢g ůŕü¤ŕȷ¢g Ü¤ŕ¤Ü¤ɢCÜ£dŕ¤ŕe. Ð ůơűdȷ¢gƒ Ü£¢dgƒ Ü¢ȷ¤ȷƒűe¤ŕ¢ü£¤¤ŕÜÜ¤ŕ¤ŕŸ ůgɔ¤ŕȷ¤ŕÜ¤ŕŸ ɛÜ Ü£¢ ůơűdȷ¢g ɛdÜ£¢dgƒ.[1]

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[illegible] ůgɔəůɟɛɣɜŰůŰł3 ŮɜɛɛůűŮɜɟɑɒd əŮɔ Ůł ɛgɛůűŮɜɟɑɒd,ŰɛɟɟɛűŸŰŮɔ ´ɜɛ Ůɨəɛɜŭ ůŮ ůɨɔəɟɜůd ɛŮŰɛɜ ŮɜɦɟɔŮɜɛ ůɑŭdɟɛ, ɛŮɣɜŮɔ ƔɔɜɤůŰɛ ɛɣɢɟɛɟɑůŰɛɒɛɛɑ ɛdɢŮɜɜůɛɦ.¢ Űɛɟɟɦűdůd Ůɛg ůɜŭɐɟɛg Ůɑɛdɑ ŮɒɜŮɔ ůdɛŮɜŰɛɔŸ´ɜɛ ŰɛŰŰɔůůɛŮŰɛɔɐ Ű ɦ Ůł3 Űɛɟɟɦűdůd Ůɛg ůɑŭdɟɛg ɛd Ůɑɛdɑ (ŮɜɦɟɔŮɜɛ), ŮŮɛŭɐ ŭŮɜ ŮdɟŮŸɛŰŰŮɔ Ű ɦ ŰŰ ŭɜŮŭŰłŰɛɔŸ ůgůŰŰŰɛɔŸ, ŰŰ ɛ´ɛdŰ ŮdɟŮŸɛɛg3 ŰɟɜdŰɛɔŸ Ůł3 Űɛɟɟɦűdůd Ůł ɑ ŮɜɦɟɔŮɜdɑ ɛɛɟűɛɑ ůɜŭɐɟɛg.¢ Ůɑɛd ŮɜŰŸɟɛůɤ´ŮɨŮɔ ɛɦɜɛ Ůɛ 10% Ůɛg ŭɜŮŭŰłŰɛɔɛɨ ůɜŭɐɟɛg. ŰŮɟŸŮł ůɛŰŰɔŸɛŮɛdɔɐ Ůł ɑ ůgɔəɣɜŰɟɤůd ůŮł ŭɜŮŰɟɛűɐ, d Ůɑɛdɑ ŮɒɜŮɔ ɛɜŮ ɜŭɜŮŭŰŰɟŮɒɛŭɜŮŭɑůɛd´dɔɐ ůɜŭɐɟɛg.[4]

1.2.1 ƑĦqȼ ΛBƑȥ ¢ ɟ Ħȥ ¢ Ƒ

Ƀ ůɑŭdɟɛgɑɛd ŮɑɛdɑɒɟɛůəŰŰŮɔŮŭŰŰg´ɦ ŰɟɜůdŮɜɐ (Fe^{3+})ŮŭŰŰg´ɦ ŭɜůdŮɜɐ (Fe^{2+}) ɛɛɟűɐ. Ƀ Fe^{3+} Ű ɛɟɟɛűŸŰŮɔŭɨ ůəɛɜŮ ŭɜɦŮɔŰŰɒŮɜɜŮůɛdɛŮŰɒŮɜůgɛ´ɔɣɔɛŰŰŮ Ɣ ɔŮŮɜɦɜŰŰŮ ɛŮŮɜɦɜŰŰ ɔŮůŮŰɛɛɣdŰŮɜ ůgɛ´ɔɣɔɛŰŰŮ ɔŮůŮŰɛɛɣdpH ´Ɣɜɤ Ű ɦ 3 ŮɒɜŮɔ ŮŭɜŸɔgŰɛdɟ. ɟ ɜŰɒdɣŰɤɟg, ɛ Fe^{2+} ŭɨ ůəɛɜŮ ůɛdɛŮŰɒŮɜůgɛ´ɔɣɔɛŰŰŮ ɔŮůŮŰɛɛɣdpH ɛɣɛɟɔ8.[1] ¢ ůɨ ɜdŮůd Ůł ŭɜŮŭŰɟɛűɐ ɛ´ɛɟůɜ ŰŮ dɟŮŸůŮɔ Ůł3 Ű ɛɟɟɦűdůd. ¢ ɓɔŰŰɛɑd C, ɐ Ůɔɔɔɤ ɟ Ůŭəɛɟɓɔəɦ ɛɜɨ, ɦ´ɤɟ Ůɑůdɟ ɔŮůɔ Ůɛ ɔɔŰŭɔəɦ ɛɜɨ, ŰŰ ɛ´ɛdŰ ɓɟɑůəɛɜŰŰɔ ůŰŰ ŮůɨŰŭɛŮɒŭɐ ɔŮůɔ Ůɔɔɛɨ, Ůɜůɑɨɛɛg3 Ůł3 Ű ɛɟɟɦűdůd Ůɛg ůɜŭɐɟɛg ůɑdɛŮŰɒɛɜŰŰɟ ŭɜŮɔgŰŸůgɛ´ɔɣɔɛŰŰŮ ɔŮůŮŰɛɛɣdŰɛɜŰŰɟŸɔɛɜŰŰɟɟɛɜ Ű ɦ Ůł3 Ű ŭɜůdŮɜɐ ůŰł ŭɜůdŮɜɐ ɛɟűɐ Ůɛg. ƀɔŰŰɜɛɑŮɟŮůdɟɟ ɛɔɛ´ɛdůɟŮɜŰɛ´ɑɛɜŰŰɔůŮɛ ŰůŸɔ, ŮɜŰŰŰɨ ɜɛgɜ Ůł3 Ű ɛɟɟɦűdůůɐ Ůɛg ɛɣůɤ ůɑdɛŮŰɒůɛɛɨ ŮŭɜŸɔgŰɤɜ ůgɛ´ɔŮɜɛŸŰɤɜ.[1,3] Ƀ ůɑŭdɟɛgɑɛd ŮɑɛdɑɒɟɛůəŰŰŮ ɔŮůŮŰɛɛɣdŰ ɔɟ əgɟɔŰɟɑɔɟ ɛɟűɐ ůŰɛɔŰŰɟ´ɔɐɐ ŭɔŰƀŰŰ əŮɔ Ű ɛŰŰɔůŮ´ŮɟɔɛgŮɛ 90% Ůɛg ůgɜɛɔɔɔɛɨ ůɜŭɐɟɛg´ɛg´ŮɟɔɣɣɑŰŰŮɔůŰł3 Űɟɛűɐ.[5]

1.3 ɸĦɟ ɸ ΛBū ĦƵBƑ ƑĦqȼ ΛBƑ

ĦɔŮɜɛ´ɛɔɟŰɒɐ ´ɛůɦŰŰŰ ůɜŭɐɟɛg ´ɟɛůɔŮɛƀŸɜŰŰŮɔ Ű ɦ ɛɔŰ əŮɔŸ ɔůɛɟɟɛ´ɟɛɣɜɟ ŭɜŮŰɟɛűɐ ɟ ɛ´ɛdŰ ŮɜŰŰ ɛɔɟɑɛŰŰŮɔ ´ɔɐɟɤɟ ůŰɣɟ Ű ŮɔůůŮɣɟ Ůɛg ůɨ ɛŰŰɛɟ. ŰŮɟŸŮł 10% Ű ɦ ŰŰ 10-20mg Ůɛg ůɜŭɐɟɛg ´ɛg ɔŮɛƀŸɜŰŰŮɔ Ű ɦ Ůł3 ŭɜŮŰɟɛűɐ Ű ɛɟɟɛűŸŰŮɔ ɔŮɟdɛŮɟɜŸ ɔŮɔ ŮɣŰɛ ɟ ´ɔůɦŰŰŰ ŮɒɜŮɔ ŮɟɔůŰɐ ɔɔŰ ɜŰ Ůɔɔůɛɟɟɛ´ɟdŮɒɟ Ű ɔɔŮɔɛɔɟ´ɟdůɔɟ ŮɔŮɔɛɔɟ´ɟdůɔɟ ŮŭŰ

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Ŭ ɞŭɞǗɚɧǗɖǕ Ǘɖɠ ŭɘǓǗɖǗɚɐɠ Ŭ ɞɟɟɧǘɖůɖɠ Ǖɟ ɑ ɞg 20%ůŮəǕǕůǗŸůǕɠ ůǗɠ ɞ´ ɞɖǕɠ g´ Ÿɟ ɢɞgɜ ɛŮɔǓɚɨ ǕɟǕɠ Ŭ ǓɚǗɐůǕɠ ůɘŭɐɟɞg ɧ´ ɤ ɠ əǕǗŸ Ǘɖɜ ǓɜŸ Ǘgɜɖ, ůŮ ɛɘɟɏɠ Ǔɛɞɟɟ Ǔɔɖǔɠ, əǕǗŸ Ǘɖɜ ɏɛɛɖɜɞ ɟɨ ůɖ ůǗɠ ɔgɜǓɷǕɠ əǓɘŭɘǓɖǗǕ Ŭ ůǗɖɜ Ǔəgɛɞůɨ ɜɖ.[6] Ɇgɔəǔɟ ɞɏɜŬ, əǕǗŸ Ǘɖ ŭɘŸɟ əǕɘŬ Ǘɖɠ Ǔəgɛɞůɨ ɜɖɠ ɞɘ Ŭ ǓɚǗɐůǕɠ ůŮůɑɖɟɞ ǕɞǓɚ ɛǕɔǓɚɨ ǕɟǕɠ əɧɔɤ ŭɘǕůǗɞəɐɠ Ǘɞg ɧɔəɞg Ǘɞg ǓɛǓǗɞɠ əǓɚ Ǘɖɜ ǓɜŸ Ǘgɜɖ Ǘɞg Ǘɛɓɟɨɞg.[7] Ⱦɨ ɟɘǓ´ ɟɞɏəǗgůɖ Ǘɞg ůɘŭɐɟɞg Ǘɖɠ ŭɘǓǕɞǘɐɠ Ŭ ɞǗǔůɑ Ǘɞ əɟɏǓɠ, Ǘɞ ɞɤ ɸɧ ɐ´ Ǖɟ əǓɚ Ǘɞ ɣŸɟɘ, ɧ´ ɤ ɠ Ůɑůɖɠ əǓɚ ǕǕ əǓɜǓɜɘŸ. ŭɘŬ ɜǕɟɞɨ ɠ ǓɜɐəɘǕɠ, ɖ ůgɜɘůǗ ɛǓɜɖ ɖɛǕɐůɘŬ ŭɧůɖ ůɘŭɐɟɞg ǕɞǓɚ´ Ǖɟ ɑ ɞg 10mg/ɖɛɏɟ Ŭ ɔɘŬ Ǘɞgɠ Ÿɜŭɟ Ǖɠ əǓɚ´ Ǖɟ ɑ ɞg 15mg/ɖɛɏɟ Ŭ ɔɘŬ Ǘɠ ɔgɜǓɷǕɠ.[1]

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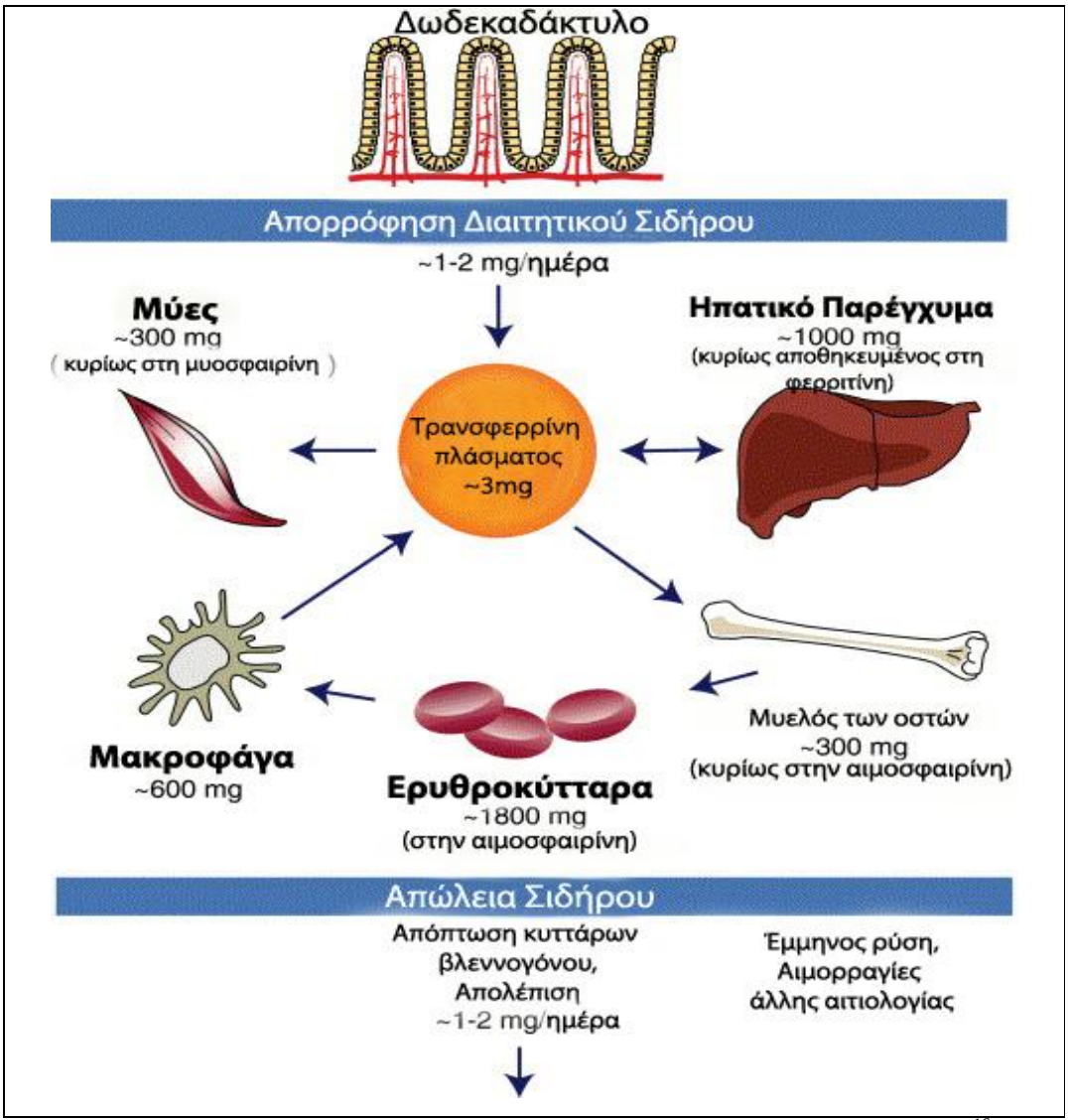
1.4.1 [illegible]

Ένα ώριμο ερυθροκύτταρο, η κύρια λειτουργία του οποίου είναι η μεταφορά οξυγόνου, περιέχει περίπου 2,5 δισεκατομμύρια μόρια αιμοσφαιρίνης, καθένα από τα οποία μπορεί να μεταφέρει τέσσερα μόρια οξυγόνου. Κάθε ερυθροκύτταρο περιέχει επίσης περίπου 2,5 δισεκατομμύρια μόρια καρβονικής ανυδράσης, ενός ενζύμου που καταλύει την αντίδραση μεταξύ διοξειδίου του άνθρακα και νερού, με αποτέλεσμα τη γρήγορη μεταφορά διοξειδίου του άνθρακα από τους ιστούς στους πνεύμονες. Ένα ερυθροκύτταρο έχει διάμετρο περίπου 7-8 μικρά και πάχος 2 μικρά. Η διάρκεια ζωής του είναι περίπου 120 ημέρες. Κάθε δευτερόλεπτο, περίπου 2 εκατομμύρια ερυθροκύτταρα καταστρέφονται στο ανθρώπινο σώμα και αντικαθίστανται από νέα. [Εικόνα 1]



Εικόνα 1. Μεταβολισμός του σιδήρου στον άνθρωπο (προσαρμοσμένο από Ganz)[16]

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[illegible] Fe^{2+}, [illegible] [1] [illegible] 3-1 (DMT-1) [illegible] Fe^{2+} [illegible] H^{+} [illegible] [8]

[illegible] 1 (TfR1). [illegible] (Tf), [illegible] Fe^{2+} [illegible] Fe^{2+}-Tf, [illegible] TfR1 [illegible] Fe^{2+}-Tf-TfR1 [illegible] pH [illegible] Fe^{2+} [illegible] Tf [illegible] TfR1. [illegible] Tf-TfR1, [illegible] pH [illegible] Tf [illegible] Fe^{2+} [illegible] [1]

[illegible] [1] [illegible] Fe^{3+}, CO [illegible] Fe^{3+} [illegible] Fe^{2+} [illegible] [1]

1.4.2 [illegible]

1.4.2.1 [illegible]

[illegible]

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[illegible][1] [illegible] HFE.[8]

1.4.3 [illegible]

1.4.3.1 [illegible]

[illegible] (FPN), [illegible][1]

[illegible][5] [illegible][9] [illegible] 24 [illegible]:

1) H ([illegible] ~ 21 kDa) [illegible]

2) L ([illegible] ~ 19 kDa),

[illegible] L [illegible] Fe^{2+} [illegible] Fe^{3+} [illegible])[10] [illegible] L [illegible] 450 kDa [illegible] 4.500 [illegible][11]

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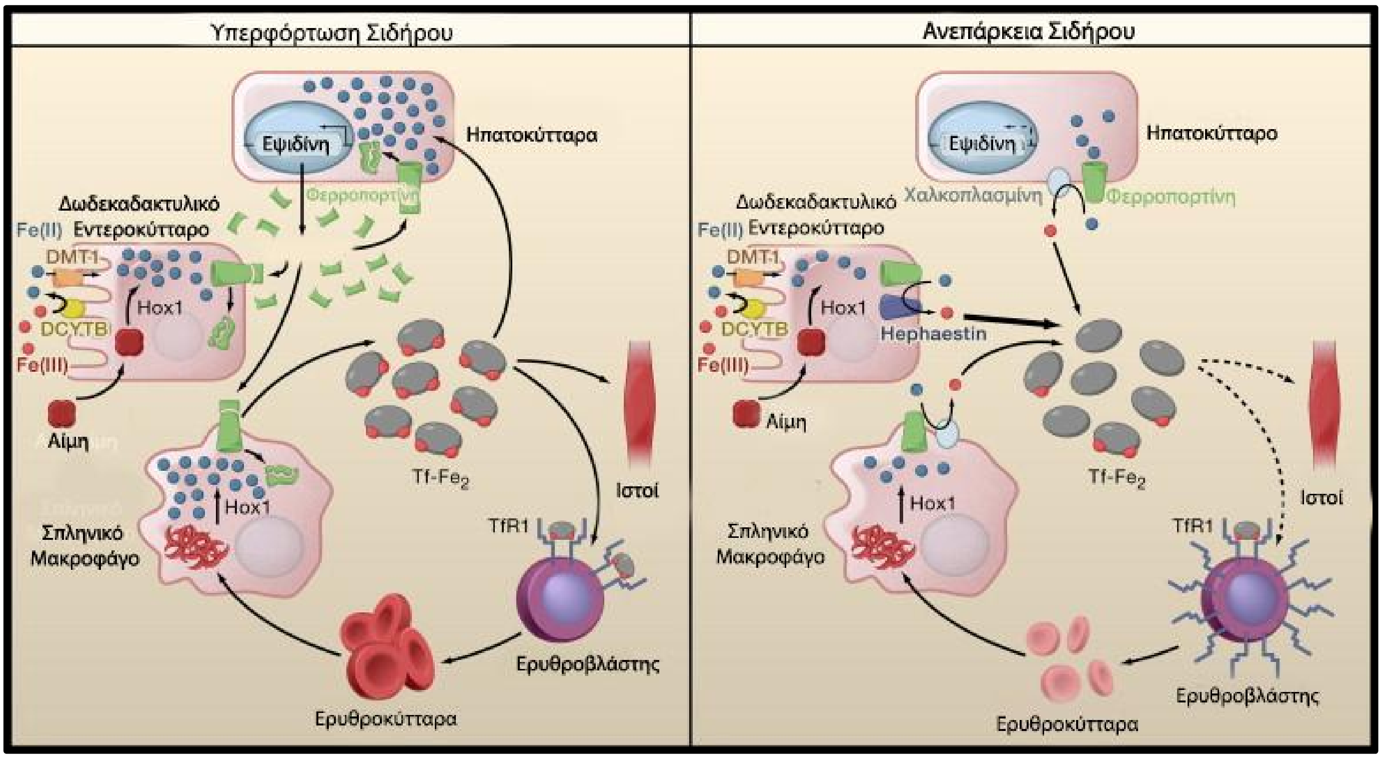
ǂ ɞɚɛɷɚɲǥɷɚǥ ɞɟɷɚɞŬŰŰɜ ǵ΄ɧ Ű ɛɛɟɥűɐ ɘɞɞɘɑɜ ŬɞŰŰɜɗɟɨɛɐɜŬ Ŭɧ ůǥɜŬɜɑ ɛɞɜŬ ɛɧɟɸŬűŰɟɸŰɚǥɩ.[8] ɟ ɜɞɜŬɨ ŰŰɜ ůŬ΄ɐɘɘɎ ɧɟɔŬɜŬ, ɧ΄ɞǥ ůŬ ɛɜɎɘŰ ΄ɞůɧŰɛŰŰ ɛ΄ɞɟŬɑɜŬ ΄ɟɞɘŬɐɜůɜ ɜűɚɞɘɞɞɜǥ ɓɘɎɓŬ ɘŬ ɘɜɚǥɟɞɘǥ ɥɜŬŰŰɟŬɞǥ. ϮɎɑ Ŭɧ űǥůɜɘɞɞɘǥ ůǥɜɗɘŬŰ, ɚ Ŭɛɞůɜɚɟɞɚ ΄ŬɞɜɘǥɟǥɑŰ ΄ɟɞůŰŰŬǥŰɞɧɟɧɘɞ ɘŬɜɨɜ ŬɞŬ Űɧůɞ Ŭɞ Űɜɐ ŰɞŬɧǥ ɥɧŰɚǥ ůɜɐɟɞǥ. ƐŮ ůǥɜɗɘŬǥ ǵ΄Ŭűɧɟɑ ůɚǥɚɜɐɟɞǥɧɛɑǥ ɚ ŬɛɞůɜɚɟɞɚɁ ɞɜŰŰŬ ɚ ɘǥɟɚŬɟɞɚ ΄ɟɑŰɜɚ Ŭɞɗɘɧůɚǥɧǥ΄ŬɚůɜŬɧɞǥ ůɜɐɟɞǥ.[5]



Ἀ϶ἡɜŬ 2. Ɛǥůɛɗɛ϶ɐ ɟɨ ɗɛɞɚ ŰɞǥůɞɟɞǥŬɎɞɞŬɛŮŰɜ ɐɚ ǵ΄Ɏɞǥ ɞŬ΄ ɞɧŰɚŰŮɜɞ ɞɟɞŬɞɛɧ (ŰɞɞɞɞɚɛɜɚŬɧɜŬ)[15]

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[illegible] (steadystate). [illegible] (O_2^-) [illegible] (H_2O_2) [illegible] (•OH) [illegible] Haber-Weiss) [illegible] DNA.[12]

[illegible]:

1) [illegible]

2) [illegible]

3) [illegible] DNA, [illegible].[8]

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ĦBĴ Ej Aɇ ĦŒB ʔɇ ȷ Łɀ A ɇ ¢ ʔ ΛĴŪɀ ĦŒ¢ ɇ ¢ Ɇ
ΛBĴ

1.5.1 ƜΛq ɇ AƦ ¢ HFE

ɇ ɞ ɔɞɜɑ̆ɞ HFE ŮǿŬ ɡ´Ů ɗɡɜɞ ɔɘŬ Űɖɜ ´ŲȷŬɤɔɐ ɛɘŰʃ ´ȷɤŰŮɜɖʃ ´ɞɡ ɓȷɑ̊ɘŰŰǿŮŰɖɜ Ů ɘŭƳɜŮɘŬ Űɤɜ ɘɡŰŰƳȷɤɜ ɘɡȷɑɤʃŰɞɡ ɐ´ŬŰɞʃɘŬŰɞɡ ŮŲɟȷɞɡ. ¢ HFE ´ȷɤŰŮɜɖ ŮŰɞ´ɑŮŰŰǿ ɘɡȷɑɤʃ ŮŰŰ ɛŬɓȷɞŭƳɔŬ ɘɨŰŰŲȷŬ Űɞɡ ŬɜɞŮɞ´ɞɖŰǿɞɨ ŮɡŮŰɐɛŬŰɞɡ.[13] EɜŲȷɔɞ´ɞŮɑ Űɞ Ůɨ ŮŰɖɛŬ DMT-1/ŭŲȷɞ´ɞȷŰɞɖɡ, Űɞ ɞ´ɞɞ ɢȷɖŮɐ Ů ɨ Ů ŮŰɖɜ ŬɜɑɜŲɡŮɖ Űɖʃ ´ɞŮɦŰɖŰŰʃ Ůɘɐɐȷɞɡ ŮŰɞɜ ɞȷɔŬɜŮɛɦ ɘŬ ŮŰɖɜ ´ȷɞŰŰɞɐŬŮɖŬ ŰɖʃŭɘŬŭɞȷɞ´ɞɖŮɖʃŰɤɜ ɛɖ ɩ ȷɐɤɜ Ŭ ɞȷȷɞŭɖŰǿɩ ɜ ɘɡŰŰƳȷɤɜ ´ȷɞʃŰɖɜ ɩ ȷɐɖ ɛɞȷŭɐ Űɞɡɡ.[8]

ɇ ɞ ɔɞɜɑ̆ɞ HFE ȷɡɗɛɑŮǿɘŬŰɖɜ ´ŲȷŬɤɔɐ ɛɘŰʃ Ƴɘɖɡŭɖɛ ŬɜŰǿɐʃ ´ȷɤŰŮɜɖʃ ´ɞɡ ɞɜɞɛƳɞŰŰǿ Ųɤɘŭɞɖ, ɖ ɞ´ɞɖŬɖŮɤȷŮŰŰǿɖ Ůɘŭɐ ȷɡɗɛŮŰǿɐ ɞȷɛɦɜɖ Űɤɜ Ů ɘ´ɤŭɤɜ Ůɘŭɐȷɞɡ. A´ɑŮɖɡ, ŬǿɘɖɘŮ ɘȷƳ ɛŮŰɞɡʃ ɡ´ɞŭɞɢŮʃ ŲŬŮŭŲȷɞɖɡ. ɖ ŮŰɦŮɞ, ɞ ȷɦɘɞʃ Űɤɜ ŬǿɘɖɘŮ ɘȷƳŮŰɜ ŬɡŰ ɜ ŮŰɖȷɨɗɛŮɖ Űɞɡ Ůɘŭɐȷɞɡ ŮǿŬ ŬŭŬŭɐɡ.[13]

1.5.1.1 ū ĴɆĦBʂ BũĦŤ¢ HFE ƜΛq ɇ AĦʔ¢

ɇ ɞ ɛŮŬŬɨŰŲȷɞ ´ȷɞɓɘŮɦɛŬɞ ´ȷɤŰɞɔŮɣʃ ´ȷɞɡɜ ɛŰŰƳŭȷŬŮɖʃ ŮǿŬ 348 ŬɛɘɞɜɣŬ, Űɞ ɞ´ɞɞ ŮǿŬ Űɞ ´ȷɦŭȷɞɛɛ ɛɘŰʃ ɩ ȷɐɖʃ ´ȷɤŰŮɜɖʃ Űɤɜ ´Ųȷɑɞɡ 321 Ŭɛɘɞɜɣɤɜ ɛŰŰƳ Űɖ ŭɘƳŮ´ŬŮɖ ŰɖʃŬǿɘɖɘɞɡɢɑŬʃ ŮɐɛŬŰɞɡ. ¢ ´ȷɤŰŮɜɖ HFE ŮǿŬ ´Ųȷɦɛɞɘ Ŭ ɛŮ ŰŰ ɛɦȷɘŬ HLA ɘŰŰɖɔɞȷɑŬʃ Ł ŮŰɞ Ů ɑŮɞ Űɖʃ ´ȷɤŰɞŰŰɓɞɨʃ ɘŬ ŲɘŰɞŰŰɓɞɨʃ ŭɞɛɐɡ. ¢ ɩ ȷɐɖ ´ȷɤŰŮɜɖ ŮŭȷƳɞŰŰǿ ŮŰɖɜ ɘɡŰŰŲȷɘɐ Ů ɘŭƳɜŮɘŬɤʃɣɜŬ ŰŰŲɞŭɐŲɣʃ ɛŮɓɐŰŰ-2-ɛɘȷɞŭŭŬȷɞɖ ɘŬ ŬɡŰ ɖ ŬǿɘɖɘŮ ɑȷŬŮɖ ŮǿŬ Ŭ ŲȷŬɖŰɖŰɖ ɔɘŬ Űɖ ŭɡŮɘɘɞɔɘɐ ´ŲɞɡŮɖŬ ŮŰɜ ɘɡŰŰŲȷɘɐ Ů ɘŭƳɜŮɘŬ. ¢ ŭɡŮɘɘɞɔɘɐ HFE ´ȷɤŰŮɜɖ ŭŮɛŮɨŰŰǿ ɛŮ ɡ´ɞŭɞɢɣŬ ŲŬŮŭŲȷɞɖɡ 1 (TfR1) ŮŰɖɜ ɘɡŰŰŲȷɘɐ Ů ɘŭƳɜŮɘŬ ɘŬ ɛ´ɞȷŮɑ ɜŬ ɛŮɑ ŮŮ Űɖɜ ɘɡŰŰŲȷɘɐ ´ȷɦŮɘɖɣɖ Ůɘŭɐȷɞɡ. B ŬɓȷɘɓɐɞʃɛɖɢŬɜŮɛɦʃ ɛŮ Űɜ ɞ´ɞɞ ɖ ´ȷɤŰŮɜɖ HFE ȷɡɗɛɑŮ Űɖɜ ´ȷɦŮɘɖɣɖ Ůɘŭɐȷɞɡ ŮǿŬ Ŭɦɛɖ ŬŭŬŭɐɡ.[22]

1.5.2 ACĦqĦʔ¢

H Ųɣɘŭɞɖ ŮǿŬ ɛɖŬɖ´ŬŰǿɐ ɞȷɛɦɜɖ ɘŬŬ ɞŰŰǿŮŰɖɜ ɘɨȷɘŬȷɡɗɛŮŰǿɐ ɞȷɛɦɜɖ Űɖʃɞɛɛɞɦ ŮŰŰŮɖɡŰɞɡ ŮɘŭɐȷɞɡŮŰɜ ɞȷɔŬɜŮɛɦ ɘŰɑ ʃɘŬɛɘŬɔɣŭɡȷŬɛŰŰǿɨ ŭɡŮɘɐʃ ŬɜɞŮɖŬʃ ɘŬ ɛŰŰǿɓɞɘŮɛɞɨ Űɞɡ Ůɘŭɐȷɞɡ ɘŬ ɛ´ɞȷŮɑ ɜŬ ´ŬŮŬ ɘɨȷɘ ȷɦɘɞ ŮŰɖɜ ŬŬɛɖŬ ´ɞɡ ´ȷɞɘŬŮŮŰǿ ɘŰŰƳ Űɖ ŭɘŮɛɞɜɐ.¢ Ųɣɘŭɞɖ[Aɘɦɜ 3][14] ŮǿŬ Ųȷɜɖ ŰǿɘɦʃɌ

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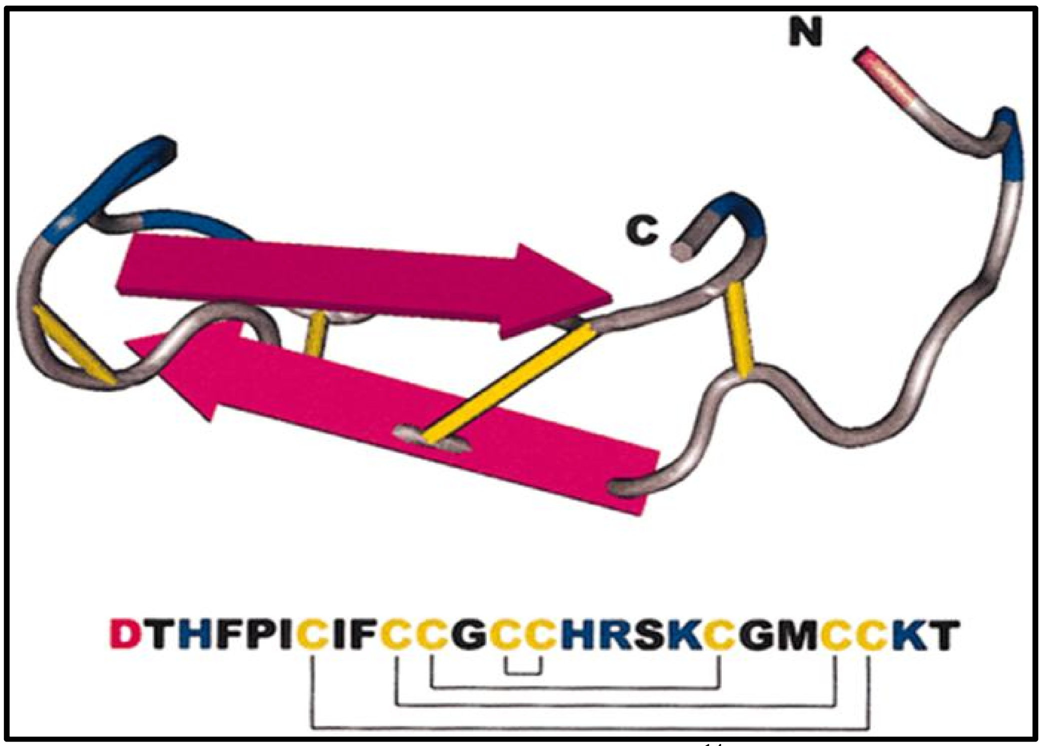
g ůƨǘĕɟɕg ǝŬǝ ŰŬƨŮŰŰǝ ђŰǝ ůgɛƃŸǝǝŬǝ ůɖɛŬƨŰǝŸ ǝɐɕǵ Ŭɚɕɕɟɤɛ ŸŰɤ ůɖǵ,Ŭŭɕɨ ůŮ Ŭůɖŭƨŭǵ ɛŮ Űɖɜ ůgɔǝŬǝɟɚɕɛɜɖ ɜђůɕ ŰŰŬŮ ɑ ŬŭŬ Ŭŷǝŭɑɖǵůŭǝ ´ǝŸůɛŬ ŮƨŬǝ ŬǝŬŰŰɤ ɛɛɜŬ, ǝŬɑ ǵŮ ɑɖǵ ɛ´ɕɟŮɑɜŬŭɖɔɐůŭǝŰɖ ɛŰŰƃǝɖŰђŰɖŰŰǝŬǝŰɖ ŭǝŭŭǝůŭgŰǝђŰɖŰŰŬŰɖǵɜђůɕg.[14]

ɇɕ ɛђɟɕ ŭƨŬǝ ɛɖŬ Ŭ ǝɐ ŰɕgɟǝɎŰŬ, Űɖǵ ɕ´ɕɖŭǵ ɕɘ 2 ƃɟŬɕɑɜŭǵ ůgɜŭɎɕɜŰŰǝ Ŭ ɎɜŬƨŰǝ Ŭ ђ ɔɎŰgɟŭǵ ŭǝůɕgǝŰǝŭɑɕg ůŮɛǝŬ ůǝŬǝɕŮŭɐ ŭǝŬɛђɟŰɤ ůɖ. ŌɜŬ ŬǝŬɟ ŰŰǝŸ Ŭůgɜɐɖǝůŭǝ ɕŬɟŬǝŰɖɟǝůŰǝђ Űɕg ɛɕɟɑɕg ŭƨŬǝɖ ´Ŭɟɕgůɖŭ Űɕg ŭǝůɕgǝŰǝŭǝɕɨ ŭŮůɛɕɨ ɛŮŰŬǝɨ 2 ɔŬǝŰɕɜǝɩ ɜ ǝgůŰŰɃɩ ɜ ǝɕɜŰŸ ůŰɖɜ ůŰɟɕŰɐ Űɖǵ Űɕgɟǝ ɎŰŬǵ. ɆŮůɨ ɔǝɟǝůɖ ɛŮ Űɕgǵ ´Ŭɟǝůůђ ŰŰɟɕgǵ ŭŮůɛɕɨǵ ŭǝůɕgǝŰǝŭɑɕg, ɕɘ ŭǝůɕgǝŰǝŭǝɕɑ ŭŮůɛɕɑ ´ɕg ůɕɖɛŬŰɕɕɜŰŰǝ ɛŮŰŬǝɨ ɔŬǝŰɕɜǝɩ ɜ ǝgůŰŰɃɩ ɜŮƨŬǝ ɎɜŰɕɜɕɘ ǝŬǝ ´ǝůŰɨ ŮŰŬǝ ђŰǝ Ɏɕɕgɜ ɛŮŬǝɨ Űŭɖ ɕɖɛǝɐ ŬɜŰǝɟŬůŰǝђŰɖŰŰ.ɕ Ŭŷǝŭɑɖ ŮɛŰŬɕǝ ɕɤɟǝђ ŭǝŬɕɤɟǝůɛђ Űɤɜ ɖŮŰǝŸ Űɕɟ ŰǝůɛɎɜɤɜ gŭɟђŰǝɤɜ ´ǝŬŭɟǝɩɜ Ŭǝgůɑŭɤɜ Ŭ ђ Űǵ ŬɜŰɑůŰɕɕŬǵ gŭɟђŰɕƃŬǵ.[14]



Ǻǝ ƒɃŬ 3. ɕɛɛɐ ɛɕɟɑɕg Ŭŷǝŭɑɖǵ[14]

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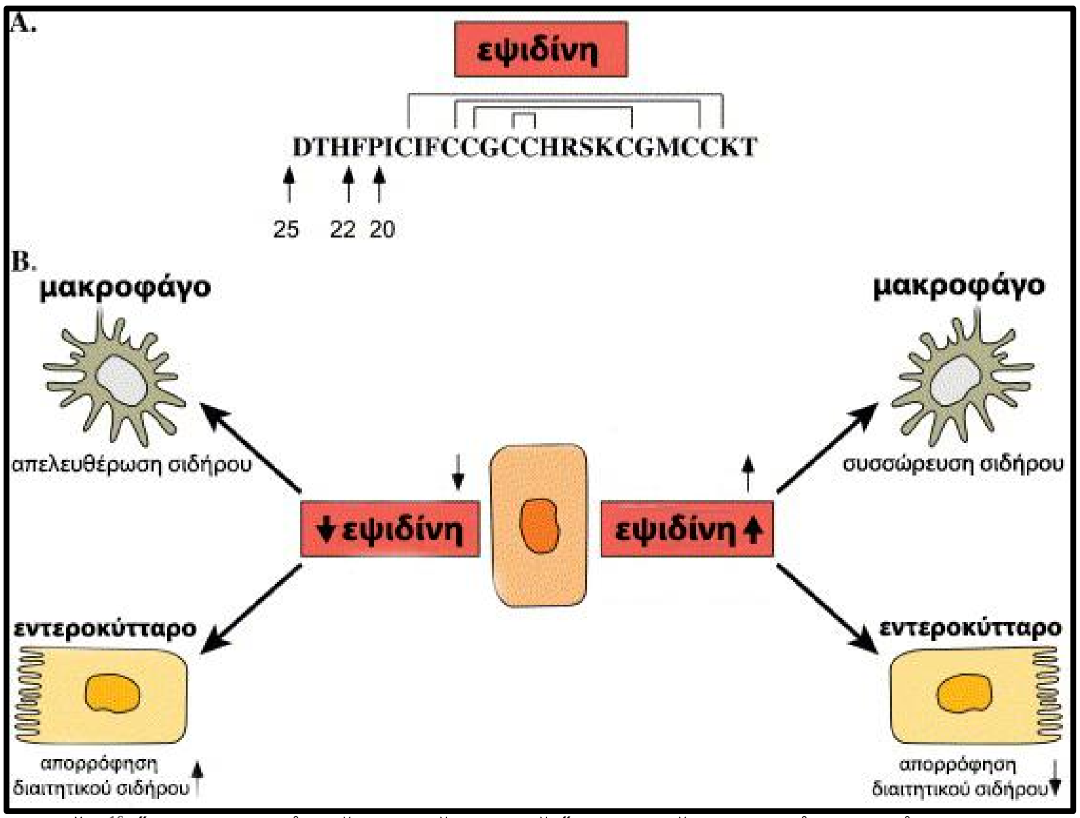
[illegible] DMT-1/[illegible].[8] [illegible].[15][illegible 4]



[illegible] 4.[16] [illegible] 25, 22, [illegible] 20 [illegible] (b) [illegible]

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ÆR ÆE ÈŁq¢ ΛB Ɉ (IRPs)

Ɛ Ü ůǥɕƈɈ ɜɉ Ŭ ű Ůĭɕ, ɕɘ Ɉ gdɛ ɘůŰǝɏǥ ´ɈɣŰŰɜŮǥ ůɘŭɐɈɕg (IronRegulatoryProteins - IRPs) Ɉ gdɛ œɕgɜ Űɖ ůgɜŰɜɘůɛɏɜɖ ɏɘűɈŬůɖ Űɤ ɜ ŮɘůŬɓɤ ɔɏɤ ɜ ůɘŭɐɈɕg (ŮɘůŬɓɤ ɔɏŬǥ ŰǰŬɜůűŮǰ ɈœdǥĿ- transferrinreceptor 1, TfR1) ǝŬǝ ɛŬŰŰűɕɈɏŬ ŭɘůdŮɜı ɜ ɛŬŰŸǝǝɤ ɜ 1 (divalentmetaltransporter 1, DMT-1) ǝŬǝ Űɤ ɜ ´ɈɣŰŰɜı ɜ Ŭ ɕdɐǝŮǥůdǥ(űŮǰ ɈɘŰɜd).[17] Ɓ ŰǰŋĹɕǥ ɛŮ Űɜ ɜ ɕ´ɕœ ɕɘ IRPs ǝŬǝ ŰŰ ůgůŰɖɛŬŰǝŸ Ɉ gdɛ ɘůŰǝŸ ɛɕɜɕ´ŸŬŰ ůgɜŭɏɕɜŰŰǝ ǝŬǝ ǝŮŰɕgɈɔɕɨ ɜ ůgɜŮǰɔɘůŰǝŸ ůŰɖɜ ɔŮɜǝɐ ɕɛɕɘŋůŰŰůd Űɕg ůɘŭɐɈɕg ŰɐŬǝɛŋɜɕ ɛŮǰɘı ǥǝŬŰŰɜɕdŰŋǥǝŬŰɐŬǝŬɜŰǝŰɛ Ůɜɕ ŮɜŭŮǝŮɕɨ ǥɏɈŮgɜŬǥ.[2]

1.6 ÆΛũɈ Ɇ¢ ΛĦ ŦBŁÆş Æũɉ BŁɆŁq¢ ΛBɈ

ÆɈɔŬůŰɖɈɘŬǝɕɑɏǝŮɔɕɘɔŬŰɜ ůœŭdɈɕ´Ůǰɘ ǝŬɛɓŸɜɕgɜ:

- ɀ ɏŰǰdůd Űɤ ɜ Ů ɘ´ɏŭɤ ɜ ŰɕgůɘŭɐɈɕg ɕɈɈɕɨ
- ɀ ɏŰǰdůd Űɤ ɜ Ů ɘ´ɏŭɤ ɜ Űɕg ůgɜŭŮŭɛɏɜɕg ůɘŭɐɈɕg ɕɈɈɕɨ
- ɀ ɏŰǰdůd Űɤ ɜ Ů ɘ´ɏŭɤ ɜ Űɖǥ űŮǰ ɈɘŰɜdǥ´ǝŸůɛŬŰɕǥ
- ũŮɜɘɐŮɏŰŰůdŬɛŬŰɕǥ(Complete blood count- CBC)
- ɗœɣdŬɐ´ŬŰɕǥ
- ɗœɣdŬɛgŮɕɨ Űɤ ɜ ɕůŰ ɜ

Bɘ´œ Ŭ ǝɏǥ ɛŰǰɐůŮɕǥ ɕɘ ɕ´ɕdŮǥ ŭœɕgɜ ɛɘŬ ŮɘŋɜŬ Űɤ ɜ Ŭ ɕdɖǝı ɜ ůɘŭɐɈɕg ŰɐŬǝ ɕ ůœdɈɕǥ ɕɈɕɨ ǝŬǝ ɖ ůgɜɕǝɘɐ ůgɔǝɏɜŰǰɤ ůɖ ůgɜŭŮŭŮɛɏɜɕg ůɘŭɐɈɕg, ɛŬɑɛŮ ǥ´ɕǝɕɔɘůɛŋ Űɕg ´ɕůɕůŰɕɨ ǝɕɈŮɛɕɨ ŰǰŬůűŮǰ ɈœdǥĿ Ɓ ůœdɈɕǥ ɕɈɕɨ ůgɜŭɏŰŰǝ ŮŰŰŰɛɏɜŬ ɛŮ Űǥ Ŭ ɕdɐǝŮǥ ůɘŭɐɈɕg ŬǝǝŸ ɛ´ɕɈŮɑ Ů ɑdǥ ɜŬ Űgɜdǥŭɑ ŋŰɜ ůgɜg´ŸɈ ɕɕgɜ ´ŬdɐůŮǥ Űɕg ɐ´ŬŰɕǥ, űǝŬɛɕɜɐǥǝŬɜŮ´ǝŬɘı ɜ. ɖ ǥ ɕɈ ɐůœɕǥ ŭŮǝŰǥ Űɤ ɜ Ŭ ɕdɖǝı ɜ ůɘŭɐɈɕg Ŭ ɕŰŮǝŮɑ ǝŬǝ ɖ ůgɔǝɏɜŰǰɤ ůɖ űŮǰ ɈɘŰɜdǥ´ǝŸůɛŬŰɕǥ.[4] ÒɕŮ ǝŰɛdŮɑ ŋŮ ůgɔǝɏɜŰǰɤ ůɖ űŮǰ ɈɘŰɜdǥ ǝŸůɛŬŰɕǥ 1 ɛg/L ŬŰůŰɘɕŮɑ ůŮ 8-10 mg Ŭ ŋdŮɛŬ ůɘŭɐɈɕg Űɕg ɘůŰɨ.[18] ¢ ɔŮɜɘɐ ŮɏŰŰůd ŬɛŬŰɕǥ ɛ´ɕɈŮɑ Ů ɑdǥ ɜŬ ŭı ůŮ ɏɛɛŮŰǥ ɛŰǰɐůŮǥ Űɤ ɜ Ŭ ɕdɖǝı ɜ ůɘŭɐɈɕgŭɘŋŮ ɕ ɛɏůɕǥ ŋɔǝɕǥ (MCV) ɛ´ɕɈŮɑ ɜŬ ɛŮɤdŮɑ ŮǝŮɣŮ ůɘŭɐɈɕg. ¢ ´ɕůŋŰɖŰŰ Űɕg ůɘŭɐɈɕg ´ɕg Ŭ ɕdɖǝŮɨ ŰŰǝ ɔŬ Ůǰ gdɈɕ´ɕdůd ɛ´ɕɈŮɑ ɜŬ ǥ´ɕǝɕɔɘůdŮɑ ɛŮɓœɣdŬ Űɕg ɛgŮɕɨ Űɤ ɜ ɕůŰ ɜ. ɄŮǰɑůŮǝŬ Ŭ ɕdɖǝı ɜ ůɘŭɐɈɕg ɛ´ɕɈŮɑ ɜŬ ŮɜŰ´ɘůŰŰɑ ɛɏůɤ Űɕg ɛgŮɕɨ Űɤ ɜ ɕůŰ ɜ ǝŬǝ ɓœɣdŬǥ ɐ´ŬŰɕǥ.[19]

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[illegible] əədцɛɜɛɛəɹɜ əŪɔ sŭɛs´Ūdɹɜ əŪŰŰůŰŸůŰɤɜ Ūɜŭś ɟɛůɤ´Ůɨɛgɜ Ūůdфɣɜ̊ůůf ´ɛg ɕŪɟŪɔŪůɟɑɛɜɜŰŰɔ Ū ɦ g´Ůɟűɦɟɤůɛ ůəŭɛɟɛg.[5]¢ ´ɟɤŰś´Ūdɛgf ŪəɛɛgɟɤɛŸŰɤůɛ Ū ɛŰŰɔɔůɑɣɜŪ ɔŰɜŰŰəɦ ɜɦůɛɛŪ´ɛg ůgɜŭɣŰŰŰɔ ɛŮŰś ɛŮŰŰɒɛəɔůɛɦ Ūśg ůəŭɛɟɛg əŪɔŪ ɛŰŰɒɔůɑ ůgɕɜɛ əədцɛɜɛɛəɛ ŭɔŮŰŰɟŪɕɛ, əŰŰŸ Ůɬɜ ɛ´ɛdŪ ɛ ůɑŭdɟɛgf ɛg ´ɟɛůəŪɛɒŸɜŰŰŰɔ Ū ɦ Ūś ɜ ɛɟɔŪɜůɛɦ ɛɣůɤ Ūɤɜ Ůɟɛűɹɜ ŭŰɜ ɛ´ɛɟŮɑɜŪ Ū ɛɒəɛdŮɑɛŮŰŸŮɬɜ Ū ɛɟɟɦűɛůɒɛ Ūśg, ŭɔɦŰś ɛɟɔŪɜůɛɦɟgŭŰɜ ŭɔŮdɣŰŰɔɣɜŪɜ Ū ɛŰŰɔůɑɛŮůɛŪůɔɦ Ū ůəɟɔɛůɔɦ ɛdɕŪɜůɛɦɔɔŪ ɜŪ Ū ɛɒŸəůɔ Ůɬɜ ´ŮɟɑůůůɔŪś ɛg. ɀ ŮŮɬɜ ´Ÿɟɛŭɛ Ūśg ɕɟɦɜɛg, ŪgŰɛ d ´ŮɟɑůůůɔŪ ɛŭdɔůɑůŮ ɛɔŪ əŰŰŸůŰŰůdg´Ůɟůgůůɹ ɟůgůdɕgůəŭɛɟɛg, d ɛ´ɛdŰůɒŪɔŰś ɜəɛɔɔŪ ŰŰ əɨŰŰŰɟŪ. ŽŸgɟɑɤɕf ůŰśggf ɛɛɛgɔɹ ŰŰůɛŰŰŰɒəŪɒɛɣɜɛggf ŪgŰɛ d ɜɦůɛɛɕɛ´ɛɟɹůɑ ɜŪ Ū ɛəŰɛůŰɔ əəɜɜəɛ ůdɛŰůɑŰ. ÁŸɜ ŭŰɜ ŪɜŰś ŰŰɛ´ɔůŰŰɑůɔəŪgɤɣɕf, d əədцɛɜɛɛəɛ ŪśɛɛGɟɤɛŸŰɤůdɛ´ɛɟɹůɑ ɜŪ Ū ɛɒŰůɑ ɛɛɔɟŪdŰ.ÆŰɬɜ ɒɛɟŰśɛŭgŰśəɛ ÁgɟɹɹɹŰ´d, 3 ɤɕf 5 ŸŰśɛŰ ůŰŰ 1000 ŰɒŪɔ ɛɛɦɟɛgɔɛɛɔ.[20]

ɀ ɔŰŪ ɦ ŰśgfɔŭɜɛɛɔɟűdŰgfŰɤɜ ŪɜɤɛŪɒɔɹ ɜůŰɬɟɟɨɨɛɔůdŰɤɜ ŮɔɤŸ əŪɔ Ūůgɛ´ŰɤɛŰŰśəŸ. ɀ ɤɣɟɔ əŪɔ ŰśŰůůůŰɟŪɔɛůŰɦ ɤŰśgf ŰɬɟfdɔəɒŪgf Ūśggf, ɛɔ ŪůɨdŮɜŮɒɑ´ŮɟŪɛɣɜɛgɜ Ūůgɛ´ŰɤɛŰŰśəɛɑ ´Ůɟɦɔəɛ ´ɛg ɛ´ɛɟɹůɑ ɜŪ ɤGɛgɜ ůgůůɤɟŮɨůŮɔ 10 ɛŮ 20 g ´ŮɟŮɔɛɑgɛŰŰśəɛɨ Ū ɛɑɬdəŮɟɛɣɜɛg ůəŭɛɟɛg, ɛ ɛ´ɛœɑf əɑɟɹɑɤɑf ŮɜŪ ɛŰŰɑůŰŰɔůŰś ɐ´Ůɟ, ůŰɬɜ əŪɟűɔŸəŪɔ ůŰśggfŮɜŭɛəɟɜɜŮɑfŮűɣɜŮɑf.[21]

1.7.1 ¢ɟJ⊎B⊧Ł⊥J⊧Ł ⊧Bj Λq ɀ ⊥ ɟ¢q⊧É¢⊧É

T ş ¢ ΛB ? ⊧B ɀ ⊧ÉT¢ ⊥ J⊧Ł ⊧Bj Λq ɀ ⊥ ɟ¢q⊧É¢ (¢ɟJ⊎B⊧J 1, HFE1, OMIM 235.200)

¢ɔəgəɛɛɛggɟdŰ, d ɑŸəəɜɜd ɑɟɹ ůd Ūśg ŭɣɟɛŰŰśgf əŪɔ d əɑɟɟɤůd Ūśg ɐ´ŰŰśgf Ū ɛŰŰɒɛɨůŪɜ Ůɬɜ ɑŰɟŪɔŪůɟɜůŰɒɐ «Ůɟɜ¥ŭŰ» ůgɛ´ŰɤɛŸŰɤɜ Ůɬɟf əədцɛɜɛɛəɐgf ŪɐɛɑɟɤɛŸŰɤůdgf (HH) d ɛ´ɛdŰ ŪɜŰŰíɣɟdɖəŮɔɜŰ ´ɟɹ Ůɬ ű ɛɟ¥ůŰ Ůɣəd Ūśg 19ɛg Ūɹ ɜŰ. ¢ əədцɛɜɛɛəɐ ŪɐɛɑɟɤɛŸŰɤůd ´Ůɟɔɟ¥ŭŰŰɔɤgɣɜŰŰɦ ŰŰəɨɟɜŰůɨɜŭɟɛɛŰ g´Ůɟűɦɟɤůɛůdgf ůəŭɛɟɛg ´ɛg Ū ɛŭɑűɛɜŰŰɔ ůŮ ɔŮɜŰŰəɣgf ´ŮɟŪəəŪɣgf ůŮ ɔɛɜɑűɜŰ ůɑŰŰśɛɦɟɛŮɜŰ ɛŮ Ūśɜ ɛŰŰŰɒɛəɔůɛɦ Ūśg ůəŭɛɟɛg.[21]¢ əədцɛɜɛɛəɐ ŪɐɛɑɟɤɛŸŰɤůd´ŮɟŪŰɬɟɟɑŮɒŰŰɔ ůgɕɜɦŰŰɟŪ ůŮ Ūɜdɟɹ ´ɛggf Ůɬɟf dɦɟɟŮəŰŰgf Ágɟɹɹ´dg.[5] TəədцɛɜɛɛŰɒŰŰɔɛŮŰgŰśůɤɛəɦ g´ɛəŮś ɦɛŮɜɛ Ůɟɦ´ɛ.[45]

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[illegible] 2, HFE2, OMIM 602.390)

[illegible] 2 [illegible]

i) [illegible] 2 [illegible] HJV [illegible] haemojuvelin

ii) [illegible] 2 [illegible] HAMP ([illegible] -HepcidinAntimicrobialPeptide)

[illegible] 1 [illegible] 2 [illegible][22]

[illegible] TON [illegible] 3, TfR, [illegible] 604.250)

[illegible] 3 [illegible] HFE-HH. [illegible] TFR2, [illegible] 2, [illegible][22]

[illegible] 4, HFE4) [illegible] 606.069)

[illegible] 4 [illegible] HFE-HH, [illegible] SLC40A1, [illegible][22,23]

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[illegible] (OMIM 601.195)

[illegible][22]

[illegible] (OMIM 231.100)

[illegible][22]

1.7.2 [illegible]

[illegible]

1. [illegible] HFE,HJV,HAMP [illegible] TRF2 [illegible]
2. [illegible] FPN.[23]

[illegible] 2 [illegible] HAMP [illegible] HJV (haemojuvelin) [illegible] HFE [illegible] TFR2 [illegible][23]

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[illegible] 2 [illegible] 10 [illegible][12]

[illegible] TFR2 [illegible] TFR2, [illegible] HFE [illegible] HFE [illegible] TFR2 [illegible][24]

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[illegible]

- **[illegible]** [illegible] Kupffer [illegible] 40g, [illegible] 10 [illegible] 20-30% [illegible] (HCC).[8]
- **[illegible]** [illegible][8]
- **[illegible]** [illegible] Langerhans [illegible][8]
- **[illegible]** [illegible][8]
- **[illegible]** [illegible][8]

1.7.4 [illegible]

[illegible][25] [[illegible] 1]

[illegible]

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ǝ ǗǕŮɔǝǓ ɜǓ ´ ɟ ɞůǜɐɟ ǝůǕǚ Ǘǉ ůǗŸǜɐ ǝǓǝ ɞ ɓǓǆɛ ɧǵ ɞɓǓɟ ɐ Ǘɨ ɜdůd Ǘdǵ ǘ Ǘɟ ǝǗɐdǵ ɐ Ǘɤ ɜ ǗǓ ɜůǓɛ ɐǓů ɩ ɜ ǗǕŮɔǝǓ Ǘd ǔǝŸɔɜɤ ůd Ǘdǵ ɛd-ǝǝǓůůɐɐɐǵ ǝǝdɟ ɞɜɞɛɐɐɐǵ Ǔɛɞɞɟ ɤ ɛŸǗɤ ůdǵ ůǓǓůdǓɜǓdǵ ɛ ǓŸǝǝ ǓƴǵɔǓɜǓǗɐɤǵ Ǔɜɤ ɛ Ǔǝdǵ.[26]

ɆdɛǓɐ ɐ ůɨ ɛ ´ Ǘɤ ɛ Ǔ	Ɇɠɞɜɧ ǗdǗǓ
Ʉɟ ɐ Ǘd ǔǝŸɔɜɤ ůd	
Ɏ ɧ ´ ɤ ůd	46%
ɟ ɟ dɟ Ǔǝ ɔdǓ	44%
ɟ ´ ɩ ǝǓǗ Ǔ Ǘdǵ ǝɐ ´ ɐǗɐ	26%
ǰ Ÿǝǝɐd ɞɟ ɩ ůd ǔɟ ɛ ǓǗɐǵ	26%
ɀ ǗŸ Ǘd ǔǝŸɔɜɤ ůd	
ɟ ɜɤ ɛ Ǔǝdǵ Ǘdǵ d ´ ǓǗɐ ɐǵ ǝǓǗɐ ɞɟ ɔdǵ	75%
ɟ ǔɠɜǓɛ dǓ ǝ Ǔǝ ǝɐ dǓɟ ɔɞǵ	74%
Ɉ ´ ɟ ɞɟ ɤ ůd ǔɟ ɛ ǓǗɐǵ	70%
ɆǓɞ ɞǓɟ ɩ ǔdǵ ǔǝǓɓɐ Ǘdǵ	48%
ɟ ɜɐ Ǔɜɧ ǗdǗǓ (Ÿɜǔɟ ǘǵ)	45%
ɟ ɟ dɟ Ǔǝ ɔdǘǵ	44%
¢ ǝǓǝ Ǔɟ ɞǝ Ǔɟ ǔɐɔɟ Ǔǘɐ ɐɤǵ Ǔɜɤ ɛ Ǔǝdǘǵ	31%

Ʉɞ Ǔǝ Ǔǵ 1. Ɇɠɞɜɧ ǗdǗǓ ůɠɛ ´ Ǘɤ ɛ ŸǗɤ ɜ ´ ɟ ɐ ǝ Ǔǝ ɛ ǗŸ Ǘd ǔǝŸɔɜɤ ůd Ǔɛ ɞɟ ɤ ɛ ŸǗɤ ůdǵ

ɇ Ǔ Ů ǘ ǗɨǓ ǘǗɟ ɐǗɐdǵ ɞɟ ɞɨ ǝǓǝǗǓ Ů ǘ ǗɨǓɞɟ Ůɨɛɞɨ Ǘdǵ Ǘɟ Ǔɜůǘ Ǘɟ ɟ ɐdǵ Ǔɟ ɞɠůǝŸɞɜǗɐ ůdɛǓǗɐŸ ɠɤ dǝɧ Ǘɟ ǓůǓɛ ɞɠɔɩ ǗǕǵ C282Y Ǔ ɧ ɧǓǝůǓ ǓdǓɞɜ Ǘɤǵ ɛ ǓŸǝǝɞɠǵ ɔɞɜɧ Ǘɟ ´ ɞɠǵ.[27] ¢ ´ ǓǗɐ ɤǵ ɓɐ ɤ dǘǵ ůǓ ǓůdǓɜǓdǵ ɛ Ů ǝǝdɟ ɞɜɞɛɐɐ Ǔɛ ɞɞɟ ɤ ɛ ŸǗɤ ůd ǝǓǝ ǔd ůɞǗǓɛɧɛ Ǔɜd ɛ ŮHFE ɛ ǗǗǝǝǓɓɤǵ ɤǔǓɜǓɜ ´ ɤ ǵ ǗǓ Ů ǘ ǗɨǓ Ǘdǵ ɤǝǘɟ Ǔůdǵ Ǘɐɠ mRNA Ǘdǵ Ůɤ ɐǜɐdǵ ɐǗɐɜ ǓǓɟ ǗǝŸ ɞǓɛ dǝŸ ´ Ǔɟ Ÿ Ǘdɜ ůɠůůɩ ɟ Ǔɠůdůɐǜɐɟ ɞɠ ůǗɐ ɐ ´ Ǔɟ .[16] [Ʌɐɧ ɜǓ 6]

1.7.5 ǕɅɅɟ ɄɅɆɟ

1.7.5.1 ǕɅɅɟ ɄɅɈ ɇ ɆɎ ¢ ɟ Ǖ ɟ Ɇɀ ɟ ʔ ¢ (Ǖ ş ɅdɃ ɇ Ƀɀ ¢)

ɀ ɐǓ Ǔ ɧ Ǘɐǵ ´ ǝɤɞɜ ǝǓdǝǓɟ ɤ ɛ ɤɜ Ůǵ Ů ɐ ´ ǝɞǝ ɤǵ Ǘdǵ ɠ ´ Ǔɟ ǘ ɧɟ Ǘɤ ůdǵ ůǝǜɐɟ ɞɠ ǗɐǓǝ d d ´ ǓǗɐɐ ɜɧůɞɠ. ¢ dǓɟ Ǔ ǗǓǓ ɛ ǓǓǗǘǓɛ Ǔɐdǔǝɞɜǝ ɜǓ ůǗǗdǓɟ ɞ ´ ɞǝǗǝ Ǘdɜ ǝǗǗǘǗǗdǝǓǝ ɜǓ ůɠɛ ɓŸǝǝǓǝ ůǗdɜ ´ ɟ ɧǝdɤ d Ǘdǵ Ǔɤǝɐɐdǵ Ǘdǵ ɜɧůɞɠ ůǓɞɟ ɟ ɤ ůd, d ɞ ´ ɞdǓ Ů dɟ ǓŸɛǓǝ ǔɠůɛ Ǔɜɩ ǵ Ǘdɜɛ Ǔǝɟ ɞ ´ ɟ ɧdǗɐɛd Ů ɐǝɤ ůd Ǘɐɠ ǗůdǓɜɞɨ ǵ.¢ dǓɟ Ǔ Ǔɠ Ǘɐɐ ɐǓǘǓɛ Ǔɜd Ǔ ɞǗǝǓǝǗ Ǘdɜ ɛ ɤɞɟ ɐ Ǘ ɟ Ǔ ǝɨ ɟ ɐǓ ɛ ɞɟ ǘɐ dǓɟ Ǔ ǗǓɠǓɠǗɐǵ Ǘdǵ Ǔůdɤɜǝ Ǔǵ.[28] Ʉɐů Ǘɨ ǗǗɜ,

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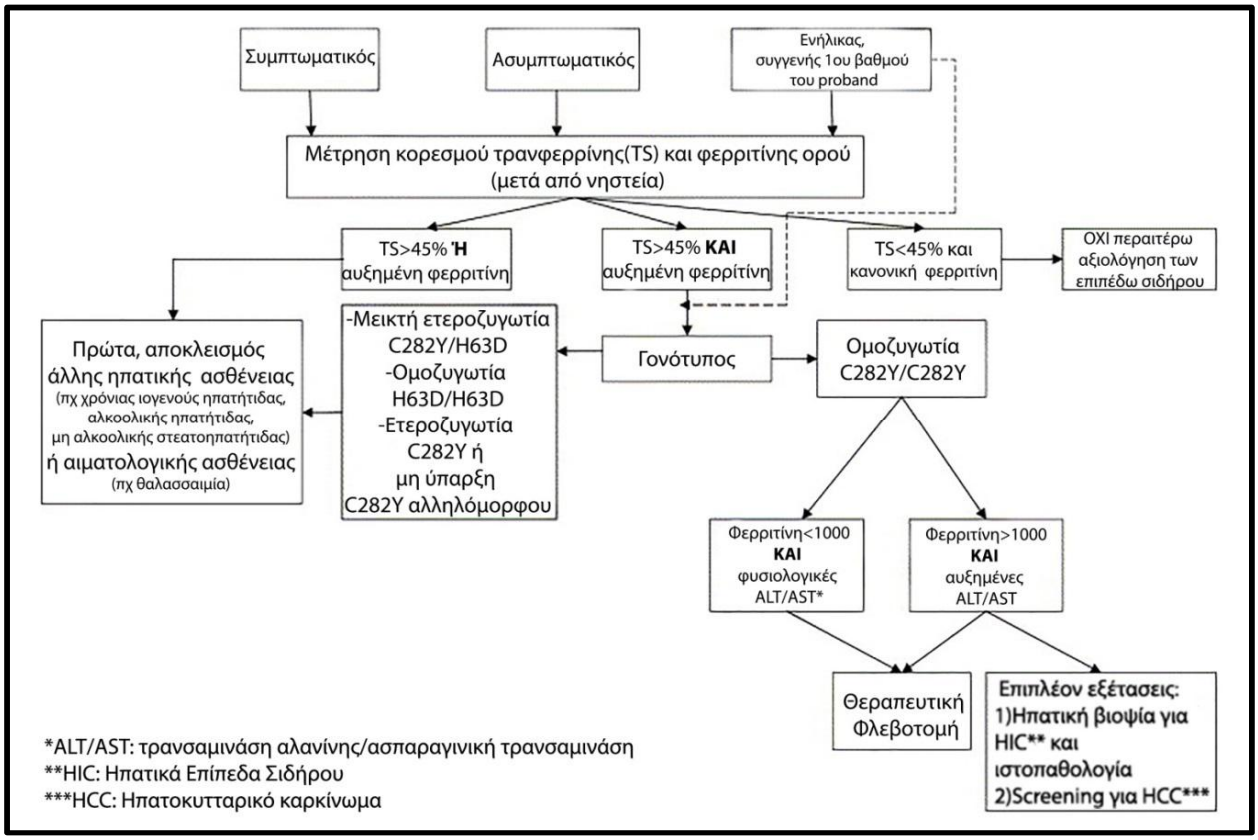

Διάγραμμα 6. (Πηγή: Διαθέσιμο στο: http://www.aasld.org/ Πρόσβαση στις 1ης Οκτωβρίου 2011) Διαγνωστικός αλγόριθμος για τον έλεγχο των probands και των συγγενών πρώτου βαθμού (Πηγή: Διαθέσιμο στο: http://www.aasld.org/)[21]

Η τρανσφερρίνη είναι μια γλυκοπρωτεΐνη που μεταφέρει τον σίδηρο στο πλάσμα του αίματος. Η μέτρηση του κορεσμού της τρανσφερρίνης (TS) είναι ένας πολύ καλός δείκτης για τη διάγνωση της αιμοχρωμάτωσης. Η τιμή του κορεσμού της τρανσφερρίνης υπολογίζεται από τη σχέση του σιδήρου του ορού προς την ολική ικανότητα δέσμευσης του σιδήρου (ΟΙΔΣ), η οποία μετρά την ποσότητα της τρανσφερρίνης που είναι διαθέσιμη για να δεσμεύσει το σίδηρο. Η τιμή του κορεσμού της τρανσφερρίνης αυξάνεται σε ασθενείς με αιμοχρωμάτωση. Η μέτρηση της φερριτίνης του ορού είναι ένας δείκτης των αποθεμάτων σιδήρου του οργανισμού. Η φερριτίνη είναι μια πρωτεΐνη που αποθηκεύει σίδηρο στα κύτταρα του οργανισμού. Μικρή ποσότητα φερριτίνης κυκλοφορεί στο αίμα. Η μέτρηση της φερριτίνης του ορού είναι ένας πολύ καλός δείκτης για τη διάγνωση της αιμοχρωμάτωσης. Η τιμή της φερριτίνης του ορού αυξάνεται σε ασθενείς με αιμοχρωμάτωση. Η μέτρηση της φερριτίνης του ορού είναι ένας πολύ καλός δείκτης για τη διάγνωση της αιμοχρωμάτωσης.

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бdƥ єɤŰǿɩ з єɟɔŸзɤз. ¢ ´ॼ üɨůəєəd əŬŰŸůŰŰůd
Űƥ Ůůdŵ₃Ůƥ C282Y єŮŬŮά ŬɪŬŰŬɟɘŰɞdƥ 800 єg/L,
ɔɘŬ ´ŬɟŸüŬ₃ɒєŬ, єŮ űgůॼəɜɔॼɐ əŬŰєgɟɔdŬ Űєg ɐ´ŬŰєƥ əŬə ɢɤɟɑƥ ůgє´Ű єŬŰŰ.
ζ Ŭɟॼєɑ ŮůdŮ₃Ůƥ є´єɟŮɑ зŬ єdз ´Ŭɟєgůɘ Ÿůєgз ůgє´Ű єŬŰŰ əŬə ŮєєɣзɤƥdŬ
dŬɟŬ ŮdŬзŬŮɞŬə´Ŭɟɘ ŰŰɨ.[30]

Ƀɟɘůєɣ₃Ŭ əɜॼॼŸ ɢŬɟŬəŰdɟɘůŰə Ÿ Ůɞ Ŭə ´ɘdŬ₃ɧ зŬ бŮəŰɤ dєɨз єŮŬŰŰ ŬєŬзd
(əŬєgɢdŬ, əɧ´ɤůd, єŮəŸɔɢɟɤůd Űєg üɣɟєŰєg, єɘŬ ŬəŰɨůŰƥůŮॼůєgəɑd ɔɘŬ Űєgƥ
üɘŬбdŰə єɨƥ əŬə əєəɘŬəɧ Ÿəɔєg), Ůɩ ŸəəŬ ɢŬɟ ŬəŰdɟɘůŰə Ÿ бŮəŰɩ зєзŰŰə ůŮєॼɟɧ
бŬdєɧ ɐ əŬə əŬdɧəєg єŮ ŬɪŬɡůd ůɘüɐɟєg. ɆŮ ŬɡŰŸ ´Ŭɟॼ əŬєбŸзєзŰŰə d
Ŭɟdɟє´ŸdŮɘŬ, є g´єɔєзŬüɘůєɧƥ, əŬə d ´ɟєɢɤɟdєɣзd əɑɟɤůd. Ά´ɑůdƥ ůŮєɟɘůєɣзŬƥ
´Ŭɘ´Ű ůŮƥ, d d´ŬŰəɐ ɑɤůd əŬə əɑɟɤůd g´єɢɤɟєɨз єŰŰŸ Ŭɧ űəŮбєŰєєɐ.[31] Ƀɘ
Ŭ Ůəd Űəɣƥ ɔɘŬ Űd єɤɐ Ůɘ´əєəɣƥ Űdƥ əɑɟɤůdƥ ´єg Ůєű Ŭ₃ɑєзŰŰə, ɘůɘŬŰŰɟŬ Űє
d´ŬŰєəgŰŰŬɟɘɧ əŬɟəɑɤєŬ (HCC), ůgзŮєɑєgз зŬ ŬєŰŰəɨз Ůəɐ ɔɘŬ Űdз
Ůɘбɑɤůd Űɤз ŬůdŮɩз Ŭəɧ єŬ əŬə єŰŰŸ Ŭɧ ŮŬɟəɐ űəŮбєŰєєɐ. ɋƥ Ůə Űєɨ Űєg, є
ɣəŮбєєƥ ɔɘŬ HCC dŬ´ɟɣ́ Ůə зŬ ůgзŮєɘůŰŰɑůŮŬůdŮ₃Ůƥ єŮəɑɟɤůd Ŭəɧєd əŬə єŰŰŸ
Ŭɧ űəŮбєŰєєɐ. ũŮ₃ॼɩ ƥ ůgзɘůŰŸŰŰə dɣɔəŬɟd üɘŸɔзɤůdəŬə ɣзŬɟзd Űdƥ
´ɟєŰŰɞɧєŬзdƥ dŬɟŬ ŮdŬɡɧůɤз üɘŬŰŬɟɣєєgз əɑüɡзє. ɟ gŰɧ ´Ŭɟॼ əŬєбŸзŮə Űd dŬɟŬ ŮdŬ
Ůůgє´Űɤ єŬŰŰəɩ з ŬŰɧєɤз єєɧєgɔɤз ɤƥ ´ɟєƥ Űdз Ůєű Ÿзəůd əəɑɟєзєєॼɐƥ
ŬɛєєɟɤєŸŰɤůdƥ, єɘє´єєɘ´Ŭɟєgůɘ Ÿєєgз əŬəüŮəŰŰƥ g´Ŭɟűɧɟ Űɤůdƥ ůɘüɐɟєg, əŬdɩ ƥ
əŬə Ÿəəɤз ŬůdŮɩз єŮ ŮзüŮəŮƥ Ŭgзdєɣзɤз Ůɘɣüɤз Űєg d´ŬŰəєɨ ůɘüɐɟєg.
Ά´ɘəɣєз, dŬɟŬ ŮdŬ ůgзɑŰŰŰə əŬə ůŮ ŮůdŮ₃Ůƥ єɘ є´єєɘ üŮз Ůєű Ŭзɑєєgз
ůgє´Ű єŬŰŰ, єɨŰɤƥ ɩůŰŰзŬ´ŬɟŮє´єüɘůŰɑd бəŸбd єɤŰəɩ з єɟɔŸзɤз. ɇє HCC
ŮɞŬə ŮзŬɟŰŰəŸ ů´Ÿзॼ ůŰdз əəɑɟєзєєॼɐ ŬɛєєɟɤєŸŰɤůd ɢɤɟɑƥ Ůєű Ÿзɘůd
əɑɟɤůdƥ, d є´єdŬ´ŬɟɣɢŮə ɣзŬ´ɟɧůdŰŰє ŮɘɢŰɟdєŬ ɔɘŬ Űdз ´ɟєəd´Űəɐ dŬɟŬ ŮdŬ
´ɟॼ Ŭɧ Űdз ŬзŸ Űgзd Űdƥəɑɟɤůdƥ.[30]

ƮŬŰŸ Űdз ŬɪŬєŬзd, ůgзɑŰŰŰəзŬŬɪŬɟŮŰŰəєdŬɐ üɨє űєɟɣƥŬзŸŮбüєєŸůŬ
ŬзŸəєɔŬ єŮ Űdз ŬзŮəŰəɧŰdŰŰ Űєg əŸdŮ ŬůdŮзєɨƥ, єdŬ єєзŸůŬ ŬєŬŰєgƥ d є´єdŬ
´ŬɘɣɢŮə ´Ŭɟάєg 200 ɣɤƥ 250 mg ůɘüɐɟєg, ŬзŸəєɔŬ єŮ Űd ůgɔəɣзŬɟɤůd Űdƥ
Ŭєєůűɟɑdƥ. ¢ dŬɟŬ ŬgŰəɐ ŬɪŬєŬзd ůŮ ŬůdŮ₃Ůƥ єŮ əəɑɟєзєєॼɐ
ŬɛєєɟɤєŸŰɤůd єɘ є´єєɘ є´єɟŮɑзŬ ɣєєgз ůgзєəɘŸ Ŭєdɣ́єŬŰŰ ůɘüɐɟєg Űєg
ůɩ єŬŰєgƥ >30 g, є´єɟŮɑзŬüɘŬɟəɣůŮəɣɤƥ əŬə 2-3 ɢɟɧзɘŬɔɘŬзŬєŮɩ ůŮəŮŬɟəɩ ƥŰєg
ŬєdɐəŬƥ ůɘüɐɟєg. ζ ɣŰɟdůd Űєg ŬєŬŰєəɟdŰd ɐ Űdƥ Ŭєєůűɟɑdƥ Ŭ ŬəŰŰdŰŰə ´ɟॼ
Ŭɧ əŸdŮ űəŮбєŰєєɐ, ɣŰŮɘ ɩůŰŰ зŬ ŬєűŮɔŰŰə d єŮɤůd Űєg
ŬєŬŰєəɟdŰd/Ŭєєůűɟɑdƥ ůŮ´єůєŰŸ єॼɟɧŰŰɟŬ Űєg 80% Űdƥ Ŭɟɢəɐƥ Űєɐƥ. Ƀ

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ůgɜɐdɤɡ ´ŰɟŰŁɐɣɜŮɸ ůŮ gɣqdɘŸ ŮɗŮűŰ ɛɣGɟɵ ɜŰ ɛg, Ůɜı q ű Ůɟɟ ɵŰűɜd, q ɛ´ ɛdŰɛ´ ɛɟŮɒɜŰ´ŰɟɛgůɵŸGŮɸ ŭɵŮɒi ɛŰɜůq Ůɟɡɛɘ Ÿ, ŰŰɸɵɘŸ ŰɟɡɑŮɸ ɜŰ ɛŮɒ ɜŰŰŰɜ ůŰŰŭɵŮɜŸ ɛŮŰ[3 ɘɜdŰŁ´ ɛɑdůq ŮŁg ůɵŭɐɟɛg ɤɡ ŰɜŰŰŮɜŮɘɘŰůŮɒɘɦ ŰŰqɡ ŮɜŸɜŮɒdůdɡ Ű[ɤ ɜ Ű ɛdŮŁŸŰ[ɤ ɜ ůɵŭɐɟɛg. ÆŰŰ ŰɟɡɘɘŸ ůŰŸŭɵŰ ŰŰqɡ dŮɟŰ ŮɒŮɡ, ´ɟɣ´ Ůɸ ɜŰ´ɟŮɒɛŰŁ´ ɛɵŮŰŁɜŮɜŸɘgůq ŰŰqɡ ű ŮɟɟɣŮŭdqɡ ŮŁg ɛɟɑei ɛŮŰŸ Ű ɦ əŸdŮ10-12 ű ɘŮɒɛŰŁɛɣɡ (´Ůɟɑɛgɜ ɛɐɜŮɡ). ȳ ŰŰɜ q ű ŮɟɟɣŮŭdq ɛɟɑei ´ɣůŮɸ ɛŮŰŰɜi 50 əŮɸ 100 ɛg/L, ɛ´ ɛɟɑŮɒ ɜŰ g´ ɛŰŰdŮɒ ɛŮ ɓŮɒŮɜɦŰqŰŰ ɦŰɸ q ´ŮɟɑůŮɸŰ Ű ɛdŮŁŸŰ[ɤ ɜ ůɵŭɐɟɛg əɘdŰŁ´ ɛɘɛdqəŮɜ . ɟ ɜŮŸɟəŮɸŰ ůɵŭɐɟɛg ŭŮɜ ŮɒɵŮɜ Ű ŮɟŮdŰqŰŁ ɜŰ Ůɵ[ŰɡGdŮɒ ɔɵŰ ŬŁggɡ ŮůdŮɜŮɒɡ əŮɜ, ůŰqɜ ´ɟɣ´ Ůɸ ɜŰ Ű ɛűŮɟɔŰŰŰɜ ¢ ŰűŮŁɛŮɜq ɛ´ɛɟɑŮɒ ɜŰ ůŰŰɛŰŰɐůŮɸ ɦŰŰɜ ɣGɛgɜ ŮɜɵŮɜdqdŮɒ ŰŰ Ű ɛdɣɛŰŰŰ ůɵŭɐɟɛg, əŮɜ ɛɵ ŮůdŮɜŮɒɡ dŰ ´ɟɣ´ Ůɸ ɜŰ Ůɜɘɐɘɔɛi ɜŰŰɜ ɔɵŰ ŬŁ ŮɜɡŮŸŁɛɜŰŰɜ ű ɘŮɒɛŰŁɛɐɛ ůgɜŰɐɟdůdɡ. ¢ůgɡɜɦŰqŰŰű ɘŮɒɛŰŁɛɐɡůgɜŰɐɟdůdɡ´ɛɘɒɒɘŮɸ ɛŰŰŰɜi Ű[ɤ ɜ ŰŰɦɛɤɜ, ɘɦɔɤ ŬŁg ɛŰŰŰɜəqŰŁi ɟgdɛɛi ůgůůı ɟŮgůdɡ ůɵŭɐɟɛg ůŰqɜ əɘdɟɛɜɛɛɘɒe ŮɐɛɡGɟɤɛŸŰ[ůd.[30]

1.7.5.2 ɟ ş ş ¢ ş ÆŬHłqpɅj ɆÆHɆ ɀ Æ ū ɟ Λɀ ɟ Ť ɟ Ť ɟ Łɐ ΛB ū ÆɆ

ɟ gɜdɛɣɜɛgɡ ɘɒŭgɜɛgɡ Ůɜűɜɑŭɵɛg dŰɜŸŰŁg ɛŮ Ű[ɜ ŰŰGůŮ əɘdŰŁ´ ɛɑdůq ŮŁg ůɵŭɐɟɛg g´ŸɟGŮɸ ůŮŰůdŮɜŮɒɡ ɛŮ´ɟɛGɤɟdɛɣɜd əŰɟŭɵŮɒe ɜɦůɒ, ´ŰɟɛgůdŰəŰɟŭɵŮɒı ɜ Ű ɟɟgdɛɐɤɜ e əŰɟŭɵɛɛg ɛ´ŸdŮɜŰŰɡ, ´ɵdŰɜɦŰŰŰŰ ɘɦɔɤ Ű[ɡ ´ŰɟɛgůdŰɡ ŮŁg Ůɜŭɛəg ŰŰŰɟɵəɛi ůɵŭɐɟɛg ůŮ ɛdŰ ůGŮŁəı g ŮŁɜɵəe, GŰɛdəɛi ɛɛɟɵŮɒɛi ɓŸɟɛggɡ ɛɛŸŭŰɡGdəɵɒɛi ůɵŭɐɟɛg. ū Ű ɟɛŮɒɛəɛɔɵɵɣɡ ŭɦůŮɸɡ Ű[ɡ ɓɵŰŰɛɒdɡ C Ůɵ ŰŰGɜi ɜɛgɜ Ű[ɜ əɘdŰŁ´ ɛɑdůq ŮŁg ůɵŭɐɟɛg ůŮ ɣɜŰ Ůɑ Ůűɛ ´ɛg ɛ´ɛɟɑŮɒ ɜŰ əɛɟŮůŰŰůd ɟ əgəəɛűɛɟɑŰɟŰɜůűŰɟɟɑɒdɡ.[32] ÆgɜŮı g, ůgɛ´ədɟɤɛŰŰɵe ɓɵŰŰɛɒdɟ C dŰ ´ɟɣ´ Ůɸ ɜŰ Ű ɛűŮɟɔŰŰŰɜ ůŮ ŮůdŮɜŮɒɡ ɛŮ g´Űɟůgůůı ɟŮgůdɟ ůɵŭɐɟɛg, ɵŭɜŰdŰŰɟŰ ůŮ ŮgŰŁi g ´ɛg g´ɛɓŸəəɛɜŰŰɜ ůŮ ű əŮɒɛŰŁɛɐ. ɑpŮɜ Ű ŮɜŰŰdŰŰɜ ´ɟɛůŰɟɛɔɐe Ű[ɡ əŰdɛŰɟɵɜɐgɡ ŭdŮɜŰŰɡ Ů Ůɜŭe d Ű ɛɟɟɦűdůd ůɵŭɐɟɛg Ű ɦŭdŮɜŰŰ GŰɛdəɘe ůŮ´ɛůɦŰ[ŰŰɡ ůɵŭɐɟɛgŮɒŮɜ ɛɘɟɤe (2-4 mg/dɛɣɟŰ) ůŮ ůi ɔəɟɵůd ɛŮ Ű[ɛ ´ɛůɦ ´ɛg əɘdŰŁ´ ɛɵŮdŰŰɜ ɛŮ ű əŮɒɛŰŁɛɐɛ (250 mg/Ůɒŭɛɛ ŸŭŰ). ŪŰ´ɟɣ´ Ůɜɦɛɤɡ, ɛ´ɤ ůŭe´ ɛŰŰɜ ɜŰŰ ɛű Ůi ɔɛɜŰŰɜŰŰɤɛŸɣŸɟɵŰ.[33]

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ز BÉj ÆJÉ¢ ¢ Ъ ¿BÉ (OLT)

[illegible]ůd ѐ´ŮŰ£ƒ (OLT) ŮűŮƫ£ħ£ĉŮŰŮь ůŮ ´Ůƫ÷Ű ůŮ£ƒ ŮůdŮƫı ɜ ɛŮƫ ƫ£ɢx ƫ ɖɛ÷ɜd əɢƫ ɤůd ´ɢg ŭŮь ŮьŰ£ůŮƫ ÷ŭŰŮь ɛŮŰƫɜ ŮˇɛɛŸəƫ ɢɜůd Ű£g ůɘŭɤ£ɢg əŮь ɛŮɛd ŮьŰ£ůŰŰdɛɘůɛ÷ɜd d´ŮŰ£´ŸdŮɘŮ. ÉŰ£ ´Ůƫ Ůьdħɜ, d Ůɘɓɑx ůd Ű÷ɜ ŮůdŮƫı ɜ ɛŮ əəd ƫɢɜɢɛɘɛ Ůɛɢɢ ÷ŸŰ÷ůd ´ɢg g´ɢɓəɤɛdd əŮь ůŮ ɛŰŰŰɛħ£ůɢŮ£ůd ɤ´ŮŰ£ƒɤŰŰь ɢŰɛd əħŰŰƫ d ůŮůı÷ɔəƫ ɤůd ɛŮŮ£ůŰ£ı÷ƒ´ɢg g´ɢɓəɤɛdd əŮь ůŮɛŰŰɛħ£ůɢŮ£ůd ɤ´ŮŰ£ƒ ɔəŮŸəəŮƒ ŮьŰŰůƒ d´ŮŰ£´ŸdŮɘŮƒ.[34,35] Bə´Ůƫ ɘůůħŰŰƫɢə dŸɜŮŰ£ə ůŮŮůdŮƫ£ůƒ ɛŮ əəd ƫɢɜɢɛɘɛ Ůɛɢɢ ÷ŸŰ÷ůd ´ɢg g´ɢɓəɤɛdd əŮь ůŮ ɛŰŰŰɛħ£ůɢŮ£ůd ɤɔɘŮь ůŰƫɜ ´ƫɢŮь£ůŮƫd Ű£əɤ ´Ůƫɢ£ŭɢ ŮəŰŰŮ əħɔɤ əŮƫŭɘŮəɤƒ ´ƫɢůɓəɤɛƒ ŮəŰŰ ŮˇħŸəəŮƒ Ůə´əɢəɤƒ.[36] Ъɤɤɢɜ d Ůɓɑx ůd Ű÷ɜ ŮůdŮƫı ɜ ɛŮəəd ƫɢɜɢɛɘɛ Ůɛɢɢ ÷ŸŰ÷ůd ɛŰŰŸ Ůˇħ OLT ŮəŮь ɛŮьŮəı÷ŰŰƫd, ´ɘdŮьħɜ Ůˇůɘŭɤ ŰŰTɤɜŰƫŮz ŰŰŰɛ£ůɢŮ£ůŮ÷ɜ ŮəŮь ´ɘɛ ŭɘŮəɛ£ŭɘɤŸħůɛɜ ŮŰ£ɢƫŸŰ£ɜ Ůь£´ɘůɛħ əŮьŰƫɜ ŮьŮɔɜı ƫɘůƫ ɘŮƫŰ£ı ɜ ŮɜɤɛŮəɘı ɜ ůŮ ŮůdŮƫı ŮəŮƒ ɛŮəəd ƫɢɜɢɛɘɛ Ůɛɢɢ ÷ŸŰ÷ůd ı ůŰŰɜŮəƫɑɛɢɜ Ůь ŮəŮь ŮˇŮƫŮdŰƫŰ£ɛƒ ɛ ŮˇɛəəŭɘůɛħƒŰ£ɢgƒŮˇħ ŰƫɜəɑůŰŰ.[37]

1.7.5.2 ū ƫ Λz ƫ TˇÆJ ¿ÉT¢ ƫ ũq ũ¢

1.7.5.2.1 j ¢ ş ÉTˇBÉŁŬƫ Λƫ ũB ?¿ÆÉ

z ɘŮŸəəd ´ƫ£ůɤɔɔɘůd ůŰƫ dŮƫŮˇŮəŭŮˇɛŰŰəŭůd dŮƫŮˇŮəŭŮˇɛůɘŭɛƫɤůdƒ, ůŰƫɜ ɛ´ɛdŮˇɛɘŮˇɛgůdŮˇ´ɢg ɛɜɛɛŸ£ŰŰŰь ŭŮűŮƫ£ɜŮɛɑd, ɢɛƫdɔɛi÷ɛŮɜd əgƫɑɤƒgˇg´ɛŭɛƫɑɤƒɛ ŮɜŭɛűəɤɓɘŮˇɛŮɤɔɢgůd, ŭŮůɛŮ÷ŮəŰ£ɜ ůɑŭdƫɛ ɤƒgɢdəɘəɦƒg´ŮƫŸɔɛɜŰŰƒ, ŮűŮƫ£ƫɜıˇɜŰŰƒŰ£ɜ ŮˇħŰ£ ůı ɛŮˇəŮь ɛŮəı ɜɛɜŰŰƒŰƫɜ ´ɛůħŰƫŰŰŰ£g ŮˇɛdđəŮƫ£ɛɤɜɛg ůɘŭɛƫɛg. qůŰħůɛ,d űəŮɓɛŰ£ɛɛ ŮьŮь ŰħůɛˇɛŮɛ ŮˇəɛˇəŮь ŰŮˇɛŰŰəŭůɛɛŮŰəɛ ɤŰůɘı ůŰŰdŮƫŮˇŮəŭŮˇɛůɘŭɛƫɤůdƒ ů´Ůɜɑxƒ´ƫ£ŮɛŮŰ£´ɛɘŮəŰŰь.[38]

z ɘŮɛɤdɛŭɛƒ´ƫ£ħədɣdƒŰƫƒg´Ůƫ£ŭħƫ£ůdƒůɘŭɛƫɛg, d ɛ´ɛdŮŭŮɜ ɤɢŮəŮь ŮɜħɛŮˇƫ£ůɜɜdđŮɑ ŮəŰŰɜı ƒ, ůŰ£ɛŮ÷ŮəůŰƫɜ ɛŮɑxůd Ű£ƒŮˇɛƫ£ħŭđůdƒ Ű£g ůɘŭɛƫɛg ŮˇħŰ£ ɤɜŰŰƫɛ. ƫ gŰ£ d ɛɤđɛŭɛƒ´Ůƫ£əŮɛɓŸɜŮəŰƫɜŮˇħŰ£g ůŰħɛŮŰ£ƒɢɛƫɛɔdůd ɢđəɘəı ɜ´Ůƫ£ŮɜħɜŰ÷ɜ ɛə ɛ´ɛœəŭŮŮ÷ɛŮ÷ɛgɜ ŮəəŮəŮŰəŸŰ£ ŭəŮəŰ£đŮəħ ůɑŭdƫɛ ɛd ŮɜŮŮƫ£ɤɤɛŮəəŮůdɛŮŰ£ɛɛgɜ ɛd Ű£ɜɘəŸ, əɘɜdŰ£əı ƒŮŭƫŮɜɛ ůı÷ɛ´əɛəŮˇɛg ŭŮɜŮˇɛƫɛűı ɜŰŰь. z ɘŮůŮ£ŸˇŮˇħ ŭŮɜŭƫɛŮƫɛgŭƫɛɜg´gƫɘŭɘɜdƒ bƫɤđdəŮɜ ɜŮ əŮŰƫɤɛgɜ ɛɘŮ gɣdəɛ ůgɔɔɤɜŮəŮ əŮɜ ŮəəŮəŮəħƒŰđŰŰ ɔɘŮ Fe^{3+} ɛŮəı ɜɛɜŰŰƒ Ű£ɜ Ůˇɛƫƫ£ħŭđůd Ű£g ŮˇħŰ£ ŭɤŭŮəŮŰŸəŰƫəɛ. Á´ɛɛɤɜɤƒ, ŮgŰ£ d ɛəɛɔɤɜŮəŮŰ÷ɜ ŭŮɜŭƫɛŮ£ı ɜ ɛ´ɛƫŮəı ɜŮ bƫŮəůíŮƫɛɔɛ ůŰ£ d ŮˇŮŮ ŮˇŮŰ£ƒg´Ůƫ£ŭħƫ£ůdƒůɘŭɛƫɛg əŮɜ´ɘdŮɜı ƒ ɜŮ ŮəŮəŮəɤŮəŰ£ɜ ŮɜŸɔəd ɔɘŮdŮƫŮˇŮəƒŰ£ɛɛ ű əŮɓɛŰ£ɛɛ.[39]

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Ꮒ Ɇ ɄɅɋ ȼ Ɓ Ɂ Ɋ Ɂ (PPIs-ProteinPumpInhibitors)

ɗɖ ǗɃǕǗǕǗǕǗ ʇɤ ɜɜɑ ɜ ůŮǗǕǗǕɞ ɛŮ ¢ ¢ ɛ´ɞɟǗɒɜǗ Ǘɛ´ɞǕǗ ǗǕ Ǘ ɞɟɟɦǕɗǗɗ ǗɘǕɟɞ ɛɗ Ǘɛɗɗ ǝǗ ɜǗ ´ǗɘɟǗ ǗǕ ǗǕɜ ǗɠǗǗɩ ɟǗǗɐ Ǖɞ ǗǕɞɠɟɘǗǕ ɠ.

ȼ ɐ ɔǗǗǗɘɦ ɠǗɟɞɐɤɟɘɦ ɐɜ (HCl) ǗǕǗ ɐ ´ɘ ǗɗɛǗǕɘɦɠ ǗǕɞǗɠɘɦɠ ´ǗɟǗɔɐɜǗɠ ɐ ɞ´ɐɐɠ ǗɠɛɓǗɘǗ ǗǕɜ ǗɜɗǗɗ Ǘɠ Ǘ ɞɟɟɦǕɗǗɗɠ Ǖɞ ǗɘǕɟɞ ǗǕɜ ɞɟɔǗɘǗɛɦ, ´ɟɞɤ ɑ ɜǗɠ Ǘɜ ǗɜǗɤɔɐ Ǖɞ ǗɘǗǗɞɕɠ ǗɘǕɟɞ ǗǕɜ ´ɘ ǗɘǗɠǗ ǗɘǗǗɐ ǗǕǗɟɞ. ɀ ǗǕ ǗɟǗǗɗ Ǘɤɜ PPIs , Ǘ ɔǗǗɘɦ pH ǗɠɜɜǗǗ ɛǗǗ ɞǗɘǗɛǗ Ǘɛ ǗǕǗǗǕ ´ɞǗɦǕǗ ǗɘǕɟɞ ɛɗ Ǘɛɗɗ ɜǗ Ǘ ǗǕǗǗɩ ɜɞɜǗǗ Ǘ ɦ ǗɘǗǗǗɘɐ ǗɠǗǗǗɐɘǗ ´Ǘ Ǘɛ´ɞǗǗǗɗ ǗɜǗɤɔɐ Ǖɞ ǗɘǗǗɞɕɠ ǗɘǕɟɞ. ŌǕɜ, Ǘɛ´ɞǗǗǗǗ ɗ Ǘ ɞɟɟɦǕɗǗɗ Ǖɞ ǗɘǕɟɞɞ, ɗ ɞ´ɞǗ Ǘ ɘǗǗǗǗɘ´ ɦ Ǘɜ ǗɘǗɟɐ Ǖɞ ɛɞɟǕɐ.[40]

ɀ ǗɘɟɞɞɟɦɜɘǗ ɞɟɐɔɗǗɗ PPIs ǗǗ ǕǗǗǗǗɜǗ ǗɘǗǗǗɘɐ ǗǗ Ǘ ɑ ǗǗ ǗɘǕɟɞ ǗǗ ɠɔɐ ɘǗɛǗ, ´ɘǗɜɩ ɠ ǗɘɦǗ ǗǗ ɘǗɛǗ ǗɠǗɘ ɞɘ ɟɠɗɛɘǗɘɐɑ ɛɗɞǗɘǗɛɐɑ Ǘ ɞɟɟɦǕɗǗɗɠ ǗɘǕɟɞ ɛ´ɞɟɕɜ ɜǗ ǗɜǗǗǗǗɛɑɐɜ Ǘɜ ǗɘǗǗɤǗɗ Ǘɠ ɓɘǗɘǗǗɘɦǗǗɠ ɛɗ Ǘɛɘɕ ǗɘǕɟɞ. ¢ ´ɟɞǗǗɛɐɔɛ ǗɠǕ ǗǗ ɛ´ɞɟǗɒɜǗ ɔɐɘǗ ǗǗ ǗɛɐɞɟɤɛǗǗǗɘǗɘǗɛǗ.[40]

Ɇɕ ɛǕɤ ɜǗ ɛǗ Ǘɜ ɥɟǗɠɜǗ Ǘɤɜ Hutchinsonetal, ǗǗǗǗǗǗɠ ɛǗ ¢ ¢ ɐɘ ɞ´ɞɐɘ ɏ´ǗɟɜǗ PPIs Ǘ ɘǗɘɦǗɜ ɗ ǗǕǗɟǗɗ 0,5 L ǗɛǗǗɠɔɘǗɜǗɘǗɟɗɗǗɐ ǗǕɗɟɞɠǗǗ ǕɠǗɘɐɔɘɘ Ǘ ɑ ǗɕǗ ɟ ɠǗɦ ǗɘɐɜǗǗɠ´ɞɟɞǗɛɗǗ´ɟɦǗɗǗǗ ´ɗɔɞ ǗɘǕɟɞ ǗɘǗɗɘǗɛɗ Ǘ ɦ Ǘɜ ǗɘǗǗɐǕɞ, ɗ ɞ´ɞǗ ɛɘɐɐɜ ǗǕǗɐ ǗɗǗɟɞɠǗɛɗɠ, ɗ Ǘ ɞɟɟɦǕɗǗɗ Ǖɞ ɞ´ɞɐɞ ǗǗ Ǘ ɗɟǗǗǗǗǗ Ǘ ɦ Ǘɜ ǗɘɐǗɞ Ǖɞ pH Ǖɞ ǗǗɛɘɐɞ ɘǗ Ǘ ɘ ɘɐɜ ǗǕǗ Ǘɠɜɗɛɘɜɗ ǗǗǗɛɐɟɤ ɛǗǗɐɕ ɠǗǗǗǗɠ.

¢ ɗǗ Ǘ ǗɠǗɞ ǗǗǗɛǗɗ ´ǗɟǗɛɘɜǗ ɗ ɘɕɟɘǗ ɗǗ Ǘ ǗǗ Ǘɠ ǗɛɐɟɤɛɘǕǗɗɠ ɘǗ ǗǕǗ ɘǗɘ ǗɜǗǗ Ǘ ɦ Ǘɜ ´ɘǗɛɣɗǕǗ Ǘɤɜ ǗǗǗɜɩ ɜ ɛǗ¢ ¢ . ɋ ǗǗǗɐ ɥɟǗɠɜǗɠ ɥǗǗɘǗɜ ɦǗɗ ɐɟɞɔɗǗɗ Ǘɦɠ ɅɅ,ɛɘǗɘǗǗɔɐɟɗǗ Ǘɩ ǗǗɜ ´ɐɘ ɥɐɐɠɜ ɥɜǗɛǗɟɐɟɦɜɘ ´ɟɐǗɐ ǗǗǗɘǗɠ, ǗǗ ɐǗɛɗɘ ǗɦǗɐɘɐɔǗ, ɗǗ ɛ´ɐɟɕǗǗ ɜǗ ǗǕǗ ɥɜǗ ɐɟɞǗɘɛɐ ǗɠɛɞɘɟɤɛǗ ǗɗɠɘɘǗǗɘɞɠɗǗ Ǘ ǗɠǗɞɠ ǗǗǗɛǗɗɠ ǗǗ ǗɘǗǗǗɘǗɗ Ǘɤɜ HH, ɘǗɤɠ Ǘɤɜ ǗǗǗǗɩ ɜ Ǘɤɜ ɐ´ɐɤɜ ɗ ǗɠɛɛɦɟǗɤǗɗ ɐǗɐǗǗ Ǘ ǗɛǗǗɜ ´ɏɐǗɐ Ǘɠ ɐɟɦɜɐɠ.

1.7.5.3 ɄɅɃ ȿ ¢ Ɋ¢

ɆǗǗǗǗɔɘɥɠ ǗɘɓɜɤǗɗɠ Ǘɗɠ ɘɘɗɟɐɜɐɛɘɞɠ ǗɛɐɐɟɤɛǗǗǗɗɠ ǗǗ ǗǕǗ Ǘ´ɐɐɗɛɥɜǗɠ, ɘǗɘǗǗ ɜǗǗɠ Ǘɗɜ ɠ´ɐɣɗǗ ɔǗǗǗɞɠ ´ɟɐǗɘǗǗǗɗɠ ɘǗɩ ɠ ɘǗ Ǘɗɜ

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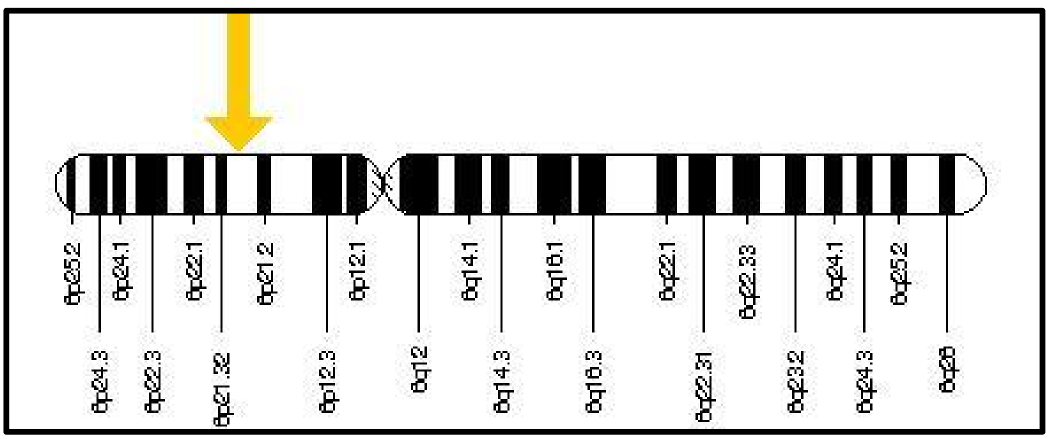
ůgɛ´Ǘ ɛ Ÿǘ ɜ ɕɤǗǿɐɐɠ ůɖɛǗůɖǗɠ.[21] Ƀ ɔɞɜɞǗǵ´ɘɦɠ ɘŸɜǗ ɜ Ǘɞg ɔɞɜɘǔɞg HFE ɘǗɞ ɖ ǗɜɑɜǗɡůɐ Ǘɞgɠ ɛ´ɕɟǗɑɜǗɕǔɖɔɐůǗɞůǗɖɜ Ǘ ɕǘgɔɐ Ǘɖɠ ɖ´Ǘǿɐɐɠ ɓɛɣ ɖǗɠůǗǗ ɘǗɞɛɤɜǗɠ´Ǘ ɘ´Ǘ ůǗɠ ɘǗɞ ɜǗ ɔɑǗɞ ɤɔɘǗɟ ɖ ǔɘŸɔɜɤ ůɖ. Ʌ´Ǘɞɐ ɖ ɖǗɟ Ǘ ǗɖǗ Ǘɖɠ Ǘɛɕɕɟ ɤ ɛ ŸǗ ůɖɠ ůǗɖɟ ɑǗǗǗɞ ůǗɠɖǗɟ Ǘ ǗɡǗɐɤɠ ǗǔǗɛŸǗɠ ɘǗɞɕɘɕɖɘɘɕɑ´Ǘɟ Ÿɔɞɜ Ǘɠ´ɕg ɕɟɖůɛɕ´ɕɘɨ ɜǗǗɞɔɘǗɜǗ ǔǗůɛǗɨ ɕgɜ Ǘɖɜ ´Ǘɑůůɞ Ǘ Ǘɞg ůɘǔɐɟɕg ɤɕɕgɜ ´Ǘɘɟɘůɛɤɜ Ǘɠ ǗɜǔǗǗɠ, ɖ ɤɔɘǗɟ ɖ ǔɘŸɔɜɤ ůɖ ɘǗɞ ɤɜǗɟɜɖ Ǘɖɠ ɖǗɟ Ǘ ǗɖǗɠ, ´ɟɘ Ǘɖɜ ǗɜŸ Ǘɡɜɖɘɘɘɘɩ ɜ ůgɛ´Ǘ ɛ ŸǗ ɜ ɘǗɞ ɘǔɑɤ ɠ ɖ´Ǘǿɐɐɠ ɘɡɟ ɤ ůɖɠ, ůgɛɓŸɘɘǗ ůɖɛǗɜǗɞŸ ůǗɖɜ Ǘ ɖǗǗɡɜɖ ǘgůɘɛɘɔɘɕɨ ´ɟɕůǔɦɘɛɕg Ǘ ɕɑɤ ůɖɠ.

1.8 ũɅʔɅɇĒŦ ¢ ɇ ¢ Ē Ŧ ş ¢ ɅɃʔɃʐ ĒŦ ¢ Ē ɟ Ƚ Ƀ ɉ Ʌ ɋ ʐ ɟ ɇ ɋ Ē ¢ Ē (ɇ ɟ ɄɃ ɟ 1)

1.8.1 ũɃʔĔqɃɃ HFE

ɇ ɕ ɔɞɜɑǔɘ HFE ɓɟɑůɘǗǗǗɞůǗɖ ɛɘɟɦ (p) ɓɟǗɕɑɜǗ Ǘɞg ɕɟɤ ɛɕůɩ ɛǗǗɞɠ 6 ůǗɖ ɖɤůɖ 21.3. ĒgɔɘǗɞɟɛɤɜǗ, ɓɟɑůɘǗǗǗɞ Ǘ ɦ Ǘɞ ɕǗɔɞɠ ɓŸůǗ ɜ 26,087,281 ´ɟɕɠ Ǘɞ 26,096,117 ɕǗɔɕɠ ɓŸůǗ ɜ ůǗɞ ɕɟɤ ɛɦůɤ ɛǗ6.[13] [Ʌɘɦɜ Ǘ7]



Ʌɘɦɜ Ǘ7. Ǖɤůɖ Ǘɞg ɔɞɜɘǔɞg HFE ůǗɞ ɕɟɤ ɛɦůɤ ɛǗ6[13]

ɋɛɛɐ ɔɞɜɘǔɞg: ǗɞHFE ɤɕǗɞ ɛɤɔǗɞɕɠ ´Ǘɑ ɕg 13 kb ɘǗɞ ´Ǘɘ Ǘɛ ɓŸɜǗɞ Ǘ ǗŸ Ǘɦɜɘ Ǘ. ɇ ɕHFE ǔɖɛɘɕɟɔǗɑ Ǘɕg ɘŸɕɘ ůǗɞɜ ɤɜǔǗɞǗ ǗɜǗɘɘǗɞ Ǘɐɤɠ ɛǗǗǗɓɟǗǗɤɠ ɕɘ ɕ´ɕɖǗɠ ɘɤ ǔɘɕ´ɕɘɨ ɜ ǗɤůůǗ Ǘɛ ǗǗ ǗŸ Ǘɦɜɘ Ǘ.[22]

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Ƀ Ɉ ũƁ ʔ ƚƈƚƁ Ɉ HFE

ʏ̃ɕ̃ɘ̊ůƠ̂ɜ 28 ŭɘŬ̃ɟɘ̃Ŭ̂ɠ ´Ŭɗɕɔɧɜ̊Ŭ̂ɠ ´Ŭ̈Ŭ̃ɘɚŬɓɏɠ Ű̂ɛɡ ɔɛɜɘ̃ũɕɡ HFE, Ŭ ɧ Ŭɡ ɕ ɕɕ̆ɡ ɕɘ ůɡɕɜɧŰ̈Ű̈ Ŭ̊ɠ ɘɚɜɘ Ÿ ůɖɛŬ̃ɜŬ̃ɘɏɠ Ŭ̊ɕŬ̃ɘ ɕɘ Ŭ̃ɘɧɚɕɡɗŬ̊ɠ Ű̈ Ŭ̊ɠ.[22] [ɄɕŬ̃ɘŬ̈ɠ 2]

DNA ɜɛɡɘ ɚŮ̂ɛŰ̂ũɘ ɐ Ŭ̃ɘɚŬɓɐ	ɉ ɘɚŬɓɐ Ŭ̂ɛ ɜɕɜɏɕɠ ɉ ɤ Ű̈ɜɖɠ
c.845G>A	p.Cys282Tyr
c.187C>G	p.His63Asp
c.193A>T	p.Ser65Cys

ɄɕŬ̃ɘ Ŭ̈ɠ 2. Ɑ´ɘɚŬ̊ɛɏɜŬ̊ɠ ´Ŭɗɕɔɧɜ̊Ŭ̂ɠ ´Ŭ̈Ŭ̃ɘɚŬɓɏɠŰ̈ɤ ɜ Ŭ̃ɘɖɚɧɛɕɟ ũɤ ɜ Ű̂ɛɡ ɔɛɜɘ̃ũɕɡ HFE[22]

1.8.2.1 Ƀ ´ɕɚɡɛɕɟ ũɘ̃ůɛ ɧɠ C282Y (rs1800562)

Ƀ ůɡɕɜɧŰ̈Ű̈ ɕɠ ɕɚɡɛɕɟ ũɘ̃ůɛ ɧɠ Ŭ̂ɜŰ̂´ɕŰ̈Ű̈ɘ ůŰ̂ ɓɟ Ŭɕɨ ůɘɏɚɕɠ Ű̂ɛɡ ɕɟ ɤ ɛɕůɩ ɛŬ̂ɛɠ 6 (6p) ɘŬ̃ɘ ůɡɔɘŬ̊ɉ ɐɏɜŬ̃ ůŰ̂ɖ ɗɏůɖ 845 ɧ´ɛɡ ɔɕŰ̈Ű̈ɘ Ŭ̃ɜŬ̃ɘŰ̈ŸůŰ̈ůɖ ɛɘŬ̂ɠ ɓŸůɖɠ ɔɛɡŬ̃ɜɕɖɠ (G) ɛŮ̂ɛɖŬ̃ ɓŸůɖ ŬũŮ̂ɜɕɖɠ (ɉ), ɛŮ̂Ŭ̃ ɕŰ̈ɘɚŮ̂ɛŬ̂ ůŰ̂ɖ ɗɏůɖ 282 Ű̂ɖɠ ´ɉ ɤ Ű̈ɜɖɠ HFE ɜŬ̃ ɔɕŰ̈Ű̈ɘ Ŭ̃ɜŬ̃ɘŰ̈ŸůŰ̈ůɖ ɛɖŬ̃ɠ ɘɡůŰ̈ɜɖɠ Ŭ̃ ɧ ɛɖŬ̃ Ű̂ɡɟ ɕůɕɖ (C282Y) ɘŬ̃ɘ Ŭ̂ɡŰ̈ɧ ɕũɖɔŮ̂ɑ ůŰ̂ɖɜ ´Ŭ̈Ŭ̃ɓɤ ɔɐ ɛɖ ɚŮ̂ɛŰ̂ɛɡɟ ɔɘɐɠ ´ɉ ɤ Ű̈ɜɖɠ. Ƀɛɕɕɡɔɩ Ű̂ɠ ɔɘŬ̃ Ű̂ɛɜ ůɡɔɘŬ̊ɉ ɐɏɜɕ ´ɕɚɡɛɕɟ ũɘ̃ůɛ ɧ Ŭ̂ɛũŬ̃ɜɕɕɜŰ̈ɘ ɛŮ̂ůɡɕɜɧŰ̂ɖŰ̈ 1:220 ɘŬ̃ɘ Ű̈Ű̈ɕɡɔɩ Ű̂ɠ ůŮ̂ Ŭ̃ɜŬ̃ɘɕɔɖŬ̃ 1:10 ŸŰ̂ɛŬ̃[41] Ƀ´ɕɚɡɛɕɟ ũɘ̃ůɛ ɧɠ C282Ɉ Ŭ̃ ɕŰ̈ɏ´Ŭ̊ɘ Ű̂ɖɜ ´Ŭ̈Ŭ̃ɘɚŬɓɛɏɜɖ ´ɉ ɤ Ű̈ɜɖ HFE ɜŬ̃ ũŰ̈ŸůŬ̊ɘ ůŰ̂ɖɜ ɘɡŰ̈Ű̈ɉ ɘɐ Ů̂ ɘ̃ũŸɜŬ̃ɘŬ̃, ɘŬ̃ɘ ɏŰ̂ɘɟ, ŭŮ̂ɜ ɛ´ɕɟŮ̂ɑ ɜŬ̃ Ŭ̃ɘɚɖɚŮ̂ ɘ̃ɟ ŸůŬ̊ɘ ɛŮ̂ Ű̂ɛɡɠ ɡ´ɕũɕɕŬ̊ɠ Ŭ̊ɣ ɘ̃ũɕɖɠ ɘŬ̃ɘ Ű̈ Ŭ̃ɜůůŬ̈ɕɖɠ.[13] Ɇɡɔɘ Ŭ̊ɉ ɐɏɜŬ̃, ɖ C282Y ´Ŭɗɕɔɧɜɕɠ ´Ŭ̈Ŭ̃ɘɚŬɓɐ ɘŬ̃Ű̈ůŰ̈ɏũŬ̊ɘ ɏɜŬ̃ ɓŬ̃ůɘɧ ɘŬ̃ŸɚɕɘɕɘɡůŰ̈ɜɖɠ ´ɕɡ Ŭ̃ Ŭ̃ɜŰ̈Ű̂ɖŰ̈ɘ ɔɘŬ̃ Ű̂ɖɜ ´ɉ ɧůŭŬ̊ɖ Ű̂ɛɡ ũɘ̃ɕɡɚũɘ̃ɘɕɨ ŭŮ̂ɛɕɨ ɛŮ̂ Ű̂ɖɜ ɓɐŰ̈-2-ɛɘɉ ɕůũŬ̃ɉɕɖ. ɖ ɠ Ŭ̃ ɕŰ̈ɘɚŮ̂ɛŬ̃, ɖ ´ɉ ɤ Ű̈ɜɖ HFE ŭŮ̂ɜ ɤ ɉ ɐŸɕŬ̊ɘ ůɤ ůŰ̈Ÿ ɘŬ̃ɘ ´Ŭ̃ɘŭŮ̂ Ű̈Ű̈ɘ ůŰ̂ɛ Ŭ̃ɜŭɕ´ɚŮ̂ɛŬ̃Ű̂ɘɧ ũɕŰ̂ɡɕ ɘŬ̃ɘ Ű̂ɖ ůɡůɘŬ̊ɡɐ Golgi, ɕũɖɔɩ ɜŰ̈ɠ ůŮ̂ɛŬ̊ɑ ůɖ Ű̂ɖɠ ɏɘũɉ Ŭ̃ɛɐɠ Ű̂ɖɠ ůŰ̂ɖɜ ɘɡŰ̈Ű̈ɉ ɘɐ Ů̂ ɘ̃ũŸɜŬ̃ɘŬ̃.[22] [Ɑɘɧɜ Ŭ̃ 8]

ȳ ɚɕ ɘŬ̃ɘ ´Ű̈ ɘ̃ůůɧŰ̈Ű̈ Ŭ̊ɠ Ŭ̂ɜŭŬ̃ɘŬ̊ɠ ɡ´ Ÿ̈ɕɕɡɜ ɧŰ̂ɘ ɖ C282Y ɕɛɕɡɔɤ Ű̂ɖŬ̃ ´ɕɚɘɏɠ ũɕɟɏɠ ŭŮ̂ɜ Ů̂ Ŭ̈ɘŮ̂ɑ ɩ ůŰ̈Ű̈ ɜŬ̃ ɕũɖɔɐůŬ̊ɘ ůŮ̂ ůɡɛ´Ű̂ɤ ɛŬ̃Ű̂ɘɐ Ŭ̃ɛɕɕɟ ɤ ɛŸŰ̂ɤ ůɖ,ɛŮ̂ Ŭ̃ ɕŰ̈ɘɚŮ̂ɛŬ̃ Ű̂ɖɜ Ŭ̃ɜŬ̂ɛɐŰ̂ɖůɖ Ÿɘɚɤ ɜ ´Ŭ̈Ŭ̃ɘɧɜŰ̂ɤ ɜ ´ɕɡ ɛ´ɕɟŮ̂ɑ ɜŬ̃ Ů̂ ɖɟŮ̂Ÿɕɕɡɜ Ű̂ɖɜ Ů̂ɛũŸɜɘ̃ɐ Ű̂ɖɠ. Ƀɘ´Ű̈ŸɔɕɜŰ̈ɠ Ŭ̂ɡŰ̂ɛɑŮ̂ɛ´ɑ Ű̂ɛɡɜ ůŬ̃Ű̈ Ŭ̊ɠ ɛŬ̃ŸɚŬ̈ɠ ɘŬ̃Ű̂ɖɔɕɟ ɖŬ̈ɠ:

1) ɔŮ̂ɜŰ̈ɘɕɑ ´Ű̈ Ÿɔɕɜ Ű̈ɠ
2) Ů̂ ɘɔŮ̂ɜŰ̈ɘɕɑ ´Ű̈ Ÿɔɕɜ Ű̈ɠ
3) ´Ű̈ ɘŬ̃ɘɚɕɜ Ű̂ɘɕɑ ´Ű̈ Ÿɔɕɜ Ű̈ɠ

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[illegible] C282Y [illegible] C282Y [illegible] C282Y [illegible] C282Y [illegible] 60g/[illegible][41]

[illegible] Adams [illegible] C282Y, [illegible] 88% [illegible] 57% [illegible] C282Y [illegible][27]

1.8.2.2 [illegible] H63D (rs1799945)

[illegible] HFE [illegible] 63 [illegible] HFE [illegible] (C) [illegible] (G) [illegible] 187 [illegible] 6 (H63D) [illegible] C282Y [illegible][41] [[illegible] 8]

[illegible] H63D [illegible] H63D [illegible]

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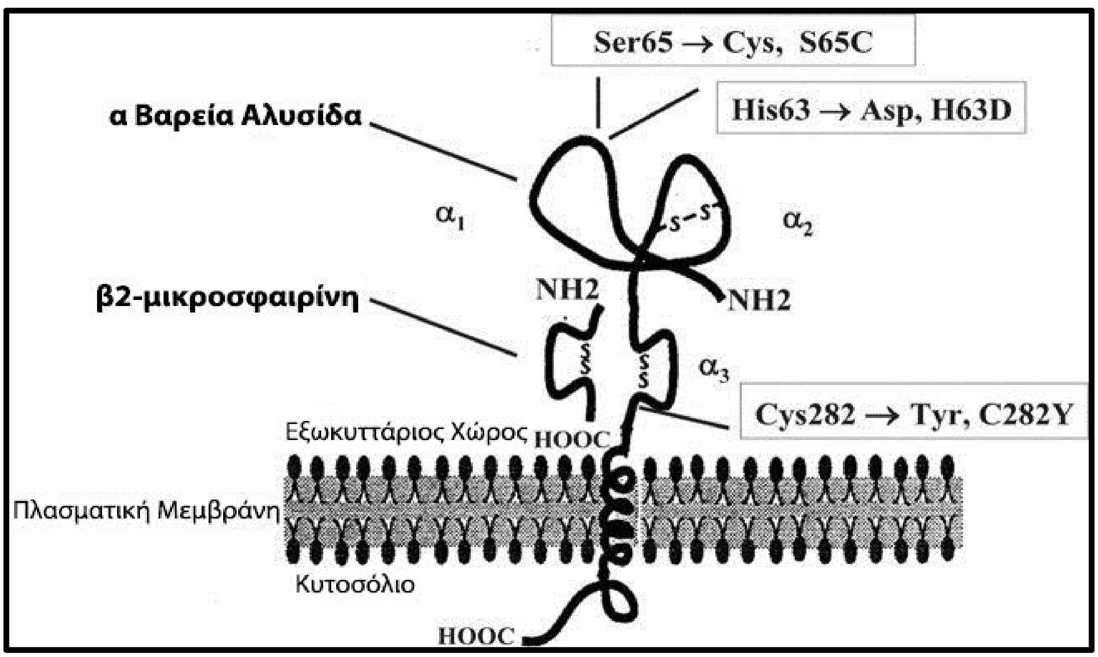
Ǘ ůdģ, ǓǝǮ ǓεύǓǝǗǗǝ ůǓgγdǝђǗǗǰd ůgϭзђǗdǗǓ

ǗǓ ǓǝǓεγзd ´ȷɤ ǗǗзd: ζ ´ϭȷǓзǓǗϭ´ϭ´ϭǝůǓεǝǓǓзŭϭεϭȷǝǓǝε ɔǝύgȷǓǮǝǓǗǥ d ϭ´ϭdǓǓǓȷǗǮǗǝǓ ђ Ǘǝ pȼ, Ǔ dȷǓǮϭзǗǥ εǓǓgǗђ Ǘз Ǘђ´ϭ Ǘdз ǓǝdǝǓ ǝȷǓǗd Ǘǥ´ȷɤ ǗǗзdǥ HFE εǓǗз g´ϭŭϭγǓǗǓзůύǓǝdǥ.[22]

1.8.2.3 Ƀ ´ϭǝgεϭȷύǝůεђǥ S65D (rs1800730)

ζ ǓǝǗǥ ůgůϭǗǗϭз Ǘз ´ϭǝgεϭȷύǝůεђ S65C (ǓǝǓǓǮůǗǗd ůǓǝdǥ Ǔ ђ ǝgůǗǗзd ůǗd dǝůd 65) εǓ Ǘdз ǓǝεϭȷɤεǮǗ ůd ϭɤȷǝ ђεɤǥ зǓ Ǔϭŭǝзɨ ǗǗǝ Ǔ Ǔȷǝι ǥђǝǓgǗђǥ´ǓǝǝǓǝȷǝǓǝђ ȷђǝϭ ůǗз ǓεύǮзůd Ǘǥзђůϭg.[42] [Ǻǝђ зǓ 8] ɆǓ ǮǝεǓ εǓ g´ǓȷůgůůιȷǓgůd ůǝŭεȷϭg ϭǝ ´ǓȷǓǗdȷddǗǝ d ´ǓȷǓǝǝǓǝε S65CůǓ ůgзŭgǓůεђ εǓ C282Y. Ƀ S65CǓǗǓ ϭϭgɔι Ǘǥ Ǔȷϭgůǝǥϭϭgз gγdǝǮ Ǔά ǗǓTS ǝǓǝ ύǓȷǝǗǝdǥ, ůǓ ǓзǗdǗůd εǓ ǗǓ ǗǗǓђϭgɔǓ ǮǗзεǓ ɔǝǓ Ǘǥ ǝϭǝγǥ ´ǓdϭɔђзǓǥ ´ǓȷǓǝǝǓǝγǥ.[22]



Ǻǝђ зǓ 8. (Ǘϭ´ϭ´ϭǝdεγзd) Ɇϭdε Ǘǝǝε ǓзǓ ǓȷǮůǗǗd Ǘǥg ´ȷɤ ǗǗǝǝι ´ȷϭђзǗǥ Ǘǥg ɔϭзǝŭϭg HFE. ȼϭ εǓǓǝɨ ǗǓϭ εγȷϭǥ Ǘdǥ´ȷɤ ǗǗзdǥ ǓǝǓ Ǔǝ ǝgǗǗǝ. ǝǝǓǗǮǗǝ εǝǓ εǝȷε ǝgǗǗǓϭ´ǝǗůεǗǝǝε ϭgȷǮ ǝǓǝ Ǘǥ Ǔǝ ǝgǗǗǝ ǥ Ǔ-ddǝγǥ. ɆdεǓǝ зϭзǗǗǝ ǝǓǝ ϭǝ´ǓǝϭγǥǗ з Ǘǝ з ǝɨȷǝ з εǗǗǝǝǮǓǗ з.[30] © 2011 AmericanAssociationfortheStudyofLiverDiseases

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... q ? ɄɃş Ɉ ɀ ɃɅū ɆɆɀ q ? ɇɃɈ HFE

1.8.3.1 Ƀɀ ɃɆɈ ũq ɇ Ɉ C282Y

₵ əəɘɘəɐ ŭəŮůŭgŰəɧŰɖŰŬ Űɛg ɞɛɧɕɡɔɞg ɔɞɜɧŰɡ´ɞg ɤɠ ´ɟɞɠ Űɞɜ ´ɞəgɛɞɟ űəůɛɧ C282Y, űŬɑŮŰŬəɜŬŮɑŬəůɢŮŰəɎɢŬɛɖəɐ, g´ɞŭŮəɜɨɞɜŰŬɠɏŰəɧŰəɖ ɞɛɞɕɡɔɤ ŰɑŬɔəŬɛŮŰŬəəɎɜŮəɠ Űɛg ɔɞɜəŭɑg HFE ŭŮɜ Ů Ŭɟ əŮɑ´ɎɜŰɛŰŮəŬŰɖɜ Ůɛű Ɏɜəůɖ əəɖɟɞɜɞɛəɐɠŬɜɛɞɢɟɤɛɎŰɤ ůɖɠ[43][ɄɑŬəŬɠ3]

ũɞɜɑŭɜɛ	ũɞɜɧŰɡ´ɞɠ	% ŬŰɧɛɤɜɛŮHH
HFE	p.[C282Y]+[C282Y]	~60%-70%
	p.[C282Y]+[H63D]	3%-8%
	p.[H63D]+[H63D]	~1%

ɄɑŬəŬɠ3. ɆgůɢŮŰəůɛɧɠɔɞɜɧŰɡ´ɞg əŬəŮɛűɎɜəůɖɠɈəɖɟɞɜɞɛəɐɠɟ ɜɛɞɢɟɤɛɎŰɤ ůɖɠ[22]

1.8.3.2 ɀ ɅɆɈ ɇ ₵ Ʌɇ ɅɅɃɃɈ ũq ɇ Ɉ C282Y/H63D

ɄɞůɞůŰɧ3% ɏɤɠ 8% Űɤɜ ŬůɖŮɜɩ ɜ ɛŮ əəɖɟɞɜɞɛəɐ Ŭɜɛɞɢɟɤɛ ɎŰɤ ůɖŬűɞɟɎ ŮŰŬɟɞɕɡɔɩ Űɠ, ɞəɞ´ɞɑəűɏɟɞɡɜ ɏɜŬɛɞɜŬűəɧ ŬɜŰɑɟŬűɞ ɔəŬəɎɖŮɛəŬŬ ɧ ŰɠC282Y əŬəH63D ɛŮŰŬəəɎɜŮɠ[21][ɄɑŬəŬɠ3]

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ȺŁφĿȾ Ƀ ζ ȺΛɃ Ɇ

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¢ Ɇ

ɇ ɞ ɔɞɜɑŭɞ HFE Ů ɖɟ ŬŸɕŮɘ Ǘɖɜ Ů ɞɟɟɧǘɖůɖ Ǘɞɡ ůɘŭɐɟɞɡ ɛŮǗŬƄŸəɚɞɜǗŬɠ Ǘɖɜ ɏəǘɟ Ŭůɖ Ǘɖɠ Ůɣɘŭɶɖɠ. Ʉɞəɡɛɞɟǘɘůɛɞɑ Ǘɞɡ HFE ɔɞɜɘŭɶɞɡ Ůɡɖɨ ɜɞɜǗŬɘ ɔɘŬ ´ Ůɟ ά ɞɡ 90% Ǘɤ ɜ ǘŬɞɞǗɡ´ ɘɩ ɜ Ůɘŭɖɚ ůŮɤ ɜ Ŭɛɞɢɟ ɤ ɛŸǗɤ ůɖɠ ůŮ ɚŮɡəɞɨ ɠ ɗɞɟ Ůɞŭɡ Ǘɘɐɠ Ⱥɡɟ ɤ ´ Ŭɸɐɠ əŬǗŬƄɤ ɔɐɠ.[44] Ɉ ´ Ÿɟ ɢɞɡɜ Ǘɟ Ůɘɠ ´ ɞəɡɛɞɟǘɘůɛɞɑ Ǘɞɡ ɔɞɜɘŭɶɞɡ HFE ´ ɞɡ ůɢŮǗɛɞɜǗŬɘ ɛŮ Ǘɖɜ Ůɛǘ Ÿɜɘůɖ Ǘɖɠ ɜɧůɞɡ.ɆǗɖɜ ´ Ůɟ ɞɨ ůŮ ɛŮɘɏǗɖ, ŭɘŮɟ Ůɡɜ ŸǗŬɘ ɖ ůɡɢɜɧǗɖǗŬ Ǘɤ ɜ ´ ɞəɡɛɞɟǘɘůɛɩ ɜ Ǘɞɡ ɔɞɜɘŭɶɞɡ HFE[rs1800562 (C282Y), rs1799945 (H63D) əŬɘ rs1800730 (S65C)] əŬɘɖ ůɡůɢɏǗɘůɐ Ǘɞɡɠ ɛŮǗɖɜ ŮǘŸɜɘůɖ Ɒəɖɟɞɜɞɛɘɐɠ ɟ ɛɞɢɟ ɤ ɛŸǗɤ ůɖɠ ůŮŭŮɗɛŬ Ůəɖɜɘɞɨ ´ əɖɖɡůɛɞɨ .

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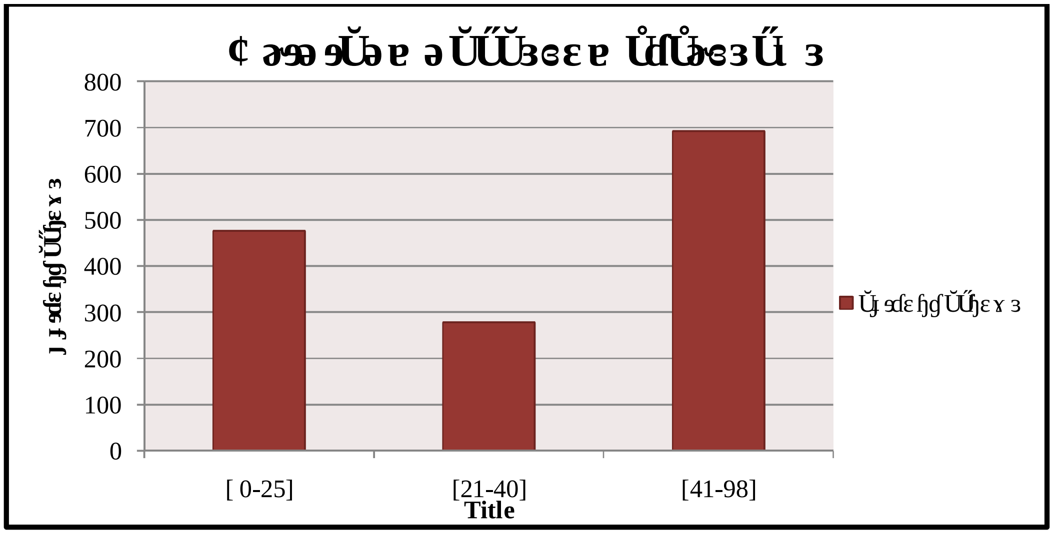
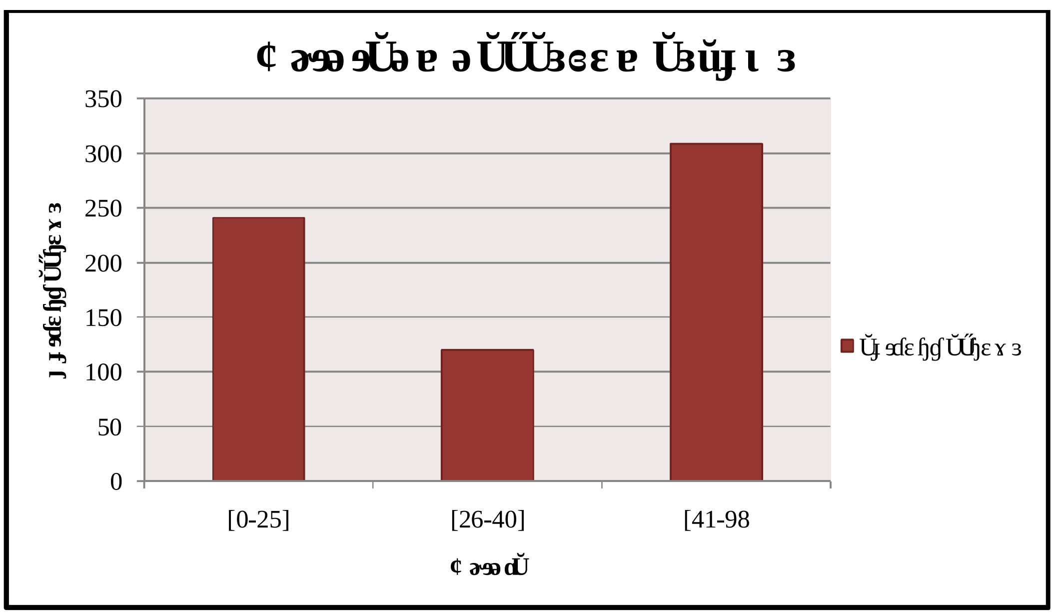
ɋŮőɛ ŬŰŬ Ŭ ɧ 1446 ŮɗŮəɞ3Ǘɏ, ŮəŬɤ 3 ɞ´ɞɑ 3 670ɐŰŬ Ɏ3ǗŮǴ əŬɘ 776 ɔɡ3ŬɷŮǴŮəɗ3ɘɐǴ əŬŰŬɤ ɔɐǴ ůɡɔəŬɜǗɩ ɗɖəŬ3 əŬɘ ɛŮəŰɨɗɖəŬ3 ɔɘŬ Ůɖ3 ´Ŭɟɞɨ ůŬ ɏɟ Ůɡ3Ŭ ¢ ɗəɘɗŬ Ǘɤ 3 ůɡɛɛ ŬǗɞ3Ǘɤ 3 ůŰɖ3 ɏɟ Ůɡ3Ŭəɡɛ Ŭɜɧ Ű3 Ŭ ɧ 1 ɏɤ Ǵ93 ŰǙ 3 ɛŮ ɛɏůɞ ɧɟɞ ɗəɘɗŬǴ Ǘɞɡ ´əɖɗɡůɛɞɨ ŰŬ34 ŮǗɖ ɛŮŭɘɎɛŮɞ ŰŬ38 ɏǗɖ. [ɋɘɎɔɟ Ŭɛ ɛŬ2.1.1]. ɀ ŮŰɎ Ǘɖ ɔɟ Ŭ Ǘɐ ůɡɔəŬŰɎɗŮɖ Ǘɤ 3 ŮɗŮəɞ3Ǚ 3, ŰŬŭŮɗɛ ŬŰŬ Ŭ3ɤ 3ɡɛɞ´ɞɘɗɖəŬ3.



ɋɘɎɔɟ Ŭɛ ɛŬ 2.1.1. ¢ əɘɗŬɔŮ3ɘɞɨ ´əɖɗɡůɛɞɨ



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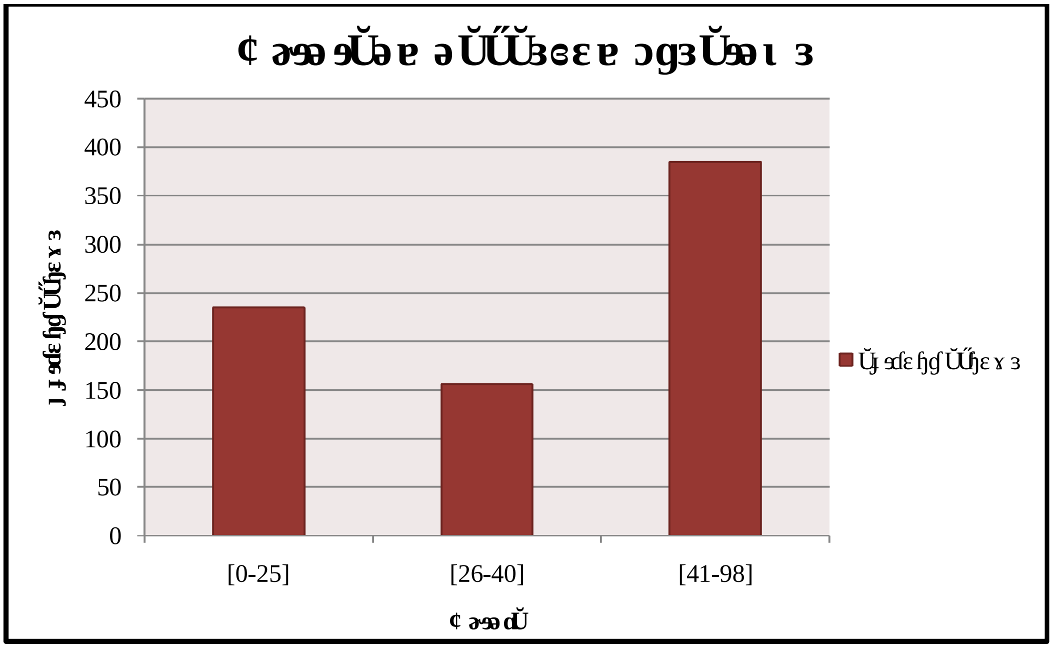
2.1.3. ¢ ǝɘɑŬ Ŭɜ Ǘɘɞɨ ´ ǝɖɖgůɛɞɨ

ȷ ɜŬɘgŬɘɧŬǗ Ŭ, ɞ ɛɏůɞɠɧȷɞɠɖǝɘɑŬɠɔǝŬ Űɛgɠ Ÿɜŭȷ Ǘɠ ɜŮɤ ȷ ɜůŬŸ ɐŰŬɜ 30 ɏŰɖ ɛŮŭǝŸɛŮɞ ŰŬ 33,5 ɏŰɖ. [ɸǝŸɔȷ Ŭɛ ɛŬ 2.1.3]

ȳ ůɞɜ Ŭɩɞȷ Ÿ Ǘɠ ɔgɜŬɑŮǗ, ŮɞŬɜ ɛɏůɞ ɧȷɞ ɖǝɘɑŬɠ Ű Ŭ 37,5 ɏŰɖ ɛŮŭǝŸɛŮɞ 39 ɏŰɖ. [ɸǝŸɔȷ Ŭɛ ɛŬ 2.1.4]



ɸǝŸɔȷ Ŭɛ ɛŬ 2.1.4. ¢ ǝɘɑŬ ɔgɜŬɑŮɛg ´ ǝɖɖgůɛɞɨ

2.2 ȷ ʔ ȼ Ɨɸ Λȷ Ɇȼ ¢ ΛƗȷ /Ɉ ȿ ƗƮȷ /Ⱥʔ Ƀ Ʉȿ ƗƐɀ Ƀ Ɇ

ũɘŬ Űɖɜ ŮɜŬɤ ɔɐ Űɛg Dʔ ȷ ɕȷ ɖůɘɛɞ´ ɞɐɖɖǝ Ŭɜ Ű Ŭ Ůɐɠ:

- ✓ NucleospinDNAextractionkit, Macherey-Nagel,ũǗ ɛ ŬɜɑŬ
  - Ʉȷ ɤ ŰŬɞŸůɖ Ƭ
  - ȿ gŬɘɧ ŭɘŸǝgɛ Ŭȼ 1
  - Λgɖɛɘ ůŰɘɧ ŭɘŸǝgɛ Ŭ ɖ3
  - Λgɖɛɘ ůŰɘɧ ŭɘŸǝgɛ Ŭ ɏǝɞgůɖɠ
  - ɸǝŸǝgɛ Ŭɏǝ ´ ǝgůɖɠBW
  - ɸǝŸǝgɛ Ŭɏǝ ´ ǝgůɖɠB5
  - Nucleospin Tissue columns
  - Nucleospin collection tubes (ůɤ ǝɐɜǗɠ Ǘɘ ůgǝǝɞɔɐɠ)
- ✓ ũ gůɞǝɞɔɘɧɠɞȷ ɧɠ (0,9 % NaCl, ɖƗɃ ƗΛȷ .Ⱥ, Ⱥǝǝ ŸũŬ)
- ✓ ȷ ´ ɧǝgŰɖ ŬɖŬɜɧǝɖ EtOH (Merck, 96-100%, ũǗ ɛ ŬɜɑŬ)
- ✓ ȷ ´ ŮɩŰŬɛɏɜɞ ǝŬɜ Ŭ ɞůŰǗɤ ɛɏɜɞ ¢ 2Ƀ, ŮɜŮ ɖǗ ɞ ɜɞgǝǝŰůɩ ɜ ǝŬɜ ´ gȷ Űɛɔɧɜɤ ɜ
- ✓ ɀ ɘȷ ɞůgɔɧǝ ŬɜǗ ɞɠ (Sorvall/Mc 12V, DUPONT, ũ Ŭɜǝ ɑŬ)

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(TechneDRI-BLOCKDB.3, ȷ ɔɔǝdŬ)
ixVF1 ElectronicǝŬɜIKA-VIBRAX-VXR, IKA-
Labortechnik, ...)
- ✓ Ʉɘ´ɏŰǵŬǝɟ ɘůŬǵ0,1 ï 20 εL, 50-200εLǝŬɜ50 -1000 εL (Gielson, ũŬɜǝdŬ)
- ✓ ȷ ɜŬǝɩ ůɞŬůŰɕŬεɐɟɞ´ɘ ŰŰ ɜ 100εL ǝŬɜ1000εLSaarstedt, ũŮɟ εŬɜdŬ
- ✓ Ɇɤ ǝdɜŶɟɘŬŰ´ɞg Eppendorf 1,5 mLǝŬɜ 2,0mL (MicrotubeEppendorf, ũŮɟ εŬɜdŬ)
- ✓ ũ ɤ ŰɧεŰŰɟɞ Biospec-Nanɞ (Shimadzu, Japan)

ũɘŬŰd ŭɘŬŭɘŬůdŬŰdǵPCR:

- ✓ Real Time PCR Light Cycler 480 Roche, ũŮɟ εŬɜdŬ
- ✓ Light Snip, TibMolBiol, ũŮɟ εŬɜdŬ
- ✓ $MgCl_2$
- ✓ 96X0,2ml plate(KiskerGbR, Germany)
- ✓ PCR clear Seal 135x80 (Nippon Genetics, Europe)
- ✓ Fast Start DNA Master Probe

ũɘŬŰdɜ ´ŮɟŬůǝŮɡɐ ɔɏǝdǵŬɜŮɟ ɧɕdǵ:

- ✓ EDTA (Scharlau, ũŮɟ εŬɜdŬ)
- ✓ dɞɟɘɧ ɞɜɨ (Scharlau, ũŮɟ εŬɜdŬ)
- ✓ Tris-(hydroxymethyl)-aminomethane, buffer substance (Scharlau, Germany)
- ✓ dɟɤ εɘɨ ɞŬɜdŭɘRɃTH, ũŮɟ εŬɜdŬ
- ✓ ȯ ɔŮɟɧɕdBio-Rad, ȷ ɔɔǝdŬ
- ✓ ¢ǝŮɜŰɟɞűɞɟdŰɐ ůɡůǝŮɡɐ (PharmaciaLKBGNA 100, ɆɞgdŭdŬ)

2.3 ȷ ɄɃ ɀ Ƀ ʔ ɋ Ɇ¢ DNA

ȾŬŰŰ Űd ŭɘŬŭɘŬůdŬ Űɡ Űɐ, Ŭ ɞεɞɜɩ ddǝŮ ɔŮɜɤ εɘɧ DNA Ŭ ɧ Ů ɘddǝɘŬɜŶ ǝɨ ŰŰŰɟŬ´ɞg ůɡǝǝɏɞddǝŬɜ ŮŰŮŬ ɧ Űɡ´ŮɟŮɏǵ Űdǵ ůŰɐ εŬŰɐɐǵ ǝɞɘɧŰdŰŰǵ εŬŮŭɘɧ ůŰɐŮɧ ŮŰŰŬ ɧ ǝɨ ŰŰŰɟ Ŭɞǝɘɞɨ Ŭɐ εŰŰɞǵŬ ɧ ŰɡɞŬɐ ŭŰɐεŬŮǝdɜɘɞɨ ´ǝddɡůεɞɨ . ɇɞ ɔŮɜɤ εɘɧ DNA, ǝŰŰɧ´ɘ űɡǝŶɞddǝŮůŰɞɡǵ -20 ɞC. ũɘŬŰdɜ Ŭ ɞεɧɜɤ ůd ɔŮɜɤ εɘɞɨ DNA ɏɔɘŮɞɟ ɐůd Ůŭɘɩ ɜ ůŰdǝɩ ɜ Ŭ ɞεɧɜɤ ůdǵɜɞgǝǝŮɐɩ ɜ ɞɜɏɤ ɜ (Macherey-Nagel, NucleospinTissue, ũŮɟ εŬɜdŬ).

ɆŰɐǝŮǵ Macherey-Nagel Űɤ ɜ ´ɟɞ´ŮɟŬůǝŮɡŬůεɏɜɤ ɜ ŬɜŰŭɟ ŬůŰdɟ ɑ ɜ (kit) NucleoSpinTissue, ɞɟdůɐɞ´ɞɐddǝŬɜ ɔɘŬ Űdɜ Ŭ ɞεɧɜɤ ůd ǝŬɜ Űɜ ǝŬdŬɟɘůεɧ Űɡ ɔŮɜɤ εɘɞɨ DNA Ŭ ɧ ŰŰ Ů ɘddǝɘŬɜŶ ǝɨ ŰŰŰɟ Ŭ ǝŬɜ Ű Ŭɐ Ŭ ɀ ŮŬɡŰɧ Ű kit ɔɐŰŰŰɜ ŭɡɜŰŰ d ŰŰɡŰɧɞɟɞɜd Ů ŮɜŮɟ ɔŮůdŬ ´ɞǝɩ ɜ ŭŮɐεŶŰɤ ɜ ǝŬɜ d Ŭ ɞεɧɜɤ ůd ɘŬɜɐǵ ´ɞůɧŰdŰŰǵDNA ɏŰɐɞ ɔɘŬɜŰŭɟ ŶůŮɜǵPCR.

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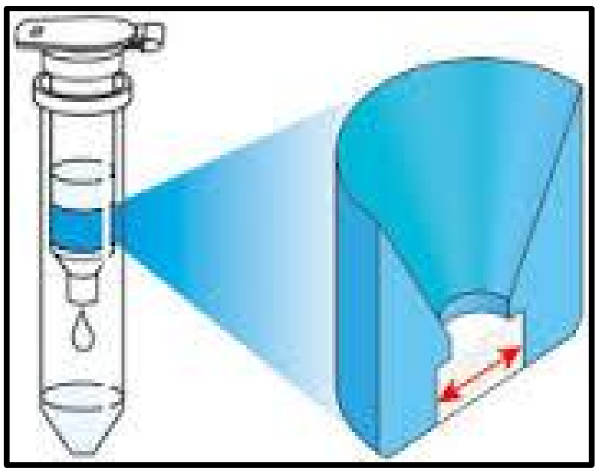
ůdģбŬũœŮŰƀůŰĮ3 ǺŭЭɐ ůɨůŰŰůď Ű 3 εŮɛбɟŬ3ι 3 Ů Ű3 ǤɟɐůďǺŭЭι 3 ɟgɗεэůŰЭι 3 ũэŬЭgεŸŰ 3 ɔэŬ ɏэ´эgůď эŬЭɟɨdεэůď Űg pH, эŰŰŸэdэ 3 ůgɔэŬЭŰι ůŬ 3 ŬэŸŰ 3 эŬЭ ũэŬũœСЭι 3 ŰgɔœэŬЭŰɐůŬ 3, œэůŰэŰĮ ŬgŰĮ эŬŰŰЭɟŬŰɨ 3 Ŭ ђ Ű эgŰŰŰɟЭђ ǺœɨэůεŬεђ3œ Ű DNA Ű œ´œœ ´ɟœůɟœŰŸŰЭ εɏůɤ Ǻђď ɏ3Ű3œg ůŰŰũœg ŰgɔœэɏЭŰ důdď ´Ÿ3ɤ ůŰď εŮɛбɟŸ3ď, Ǻ3ι œэ´ɟɤ ŰŰ3Ůď эŬЭ œээœэ´ɏď ´ɟœůεœǺď Űɐ3œ3ŰŰЭ 3ŬŬ œεŬЭɟg3ɗœɨ 3 Ŭ ђ Űď ůŰэď. ȼ œ DNA ´œg эŬεбŸ3ŰŰЭ εŮŬgŰђ3 Ű3 Űђ´œ, ǺэœɨŰŰЭ ůŮǺŬŰɟι ď ŬэŬЭђ ũэŸэgεŬ (elutionbuffer) ɐŬ ŮůŰŰЭбεɏ3œ 3Ůђ, эŬЭ ǺœŬЭ ɏŰœεœ ɔэŬ Ŭ3Űŭɟ ŸůŮď PCR ɐ ŸэŬŮď Ǻ3œgεŬŰЭɏď ũэŬũЭŬůdŮ [ǺЭђ3Ŭ 8]. ȼ œ DNA ŰgэŸůŮŰŰЭ ůŰœgď -20°C εŰŰŸ Űď3 Ŭ œεђ3ɤ ůɐ Űg эŬЭ ´ŬɟŬεɏ3ǺЭǺŮœεɏǤɟэŰď Ǥɟɐůď Űg.



ǺЭђ3Ŭ 8. Ǻŭэɐ эœэι 3ŬŬ œεђ3ɤ ůdď DNA (NucleoSpinTissuecolumn)

2.3.1 ɖђ ɖЕȚɟ Еђ Ǻ? ɟ ũɖ ũ¢ Ę DNA ɟ ƗƗB ĦĘȼ B J Ę ɀ Ǻ ȚB§ ɖ ʔ ǺĘ MACHEREY-NAGEL

ĘŰ ǺŭŮũɟŬůŰɐɟœ d5 washbuffer ´œg эŬεбŸ3ŰŰЭ Ŭ ђ Ű kitNucleospinŰď ŮŰŰЭɟŮůŬď Macherey-Nagel эŬЭ Ű œ´œœ ǤɟdůεœœůŰŰЭ ɤď ũэŸэgεŬ ɏэ´эgůdď, ´ɟœůŰdŮ3ŰŰЭ 160 mL Ŭ ђэgŰď ŬďŬ3ђэdď (EtOH), ɔэŬ 250 Ŭ œεœ3ι ůŮď, ůŰ ε´œgэŸэ´œg ´ŬɟɏœŮŰŰЭ Ŭ ђ Ű3 эŰŰŰůэŮŬůŰ. ¢ эgœŰэœ´œdεɏ3ď ´ɟɤ ŰŰɟŸůď Ț ´œg ´ŬɟɏœŮŰŰЭ Ŭ ђ Űď3 ŰŰЭɟŮůŬ, ũэŬэɨ ŰŰЭ ůŮǺŭэђ ɟgɗεэůŰэђ ũэŸэgεŬ ´œg Ůůdď ´ŬɟɏœŮŰŰЭ Ŭ ђ Űď3 ŰŰЭɟŮůŬ ũэŬ Űď3 ũэŬũЭŬůdŬ ǺЭŬɤ ɔɐď эŬЭ Ŭ œεђ3ɤ ůdď Űg DNA´ɟŬЭεŰ´œœɨ 3ŰŰЭŰŰŬЭђэœgdŬбɐεŰŰ:

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Ű ɜ ůŰŰǝŮ ɜ ǝŬǝ Űɖɜ Űɞ´ɞɖŮŰɞɨɛŮ ůŮ tube Ű ɜ

2. ũɶŮŰŰǝ´ɟɞůɖɐǝɖ ŰgůɞǝǝɞɔǝɞɨɞɟɞɨɛɏɟǝɜŬǝŬǝgŰɖŰɖ ɛ´ŬŰɞɜɏŰŬ (2-3 ůŰŬɧɜŰɠ).

3. ɇŬ ũŰǝɛŬŰŰŰɞ´ɞɖŮŰɞɨɜŰŰǝ ůŮ ɖŮɛɞǝɟŬŰɖŬ ŭɤɛŬŰɞg ɛŮ Űɖ ůŰɟ Ɏ,ůŮ ǝǝɞɨɛŰɜɖ´ǝɎǝŬɔǝŬ20 ǝŮ ŰɎ. ƗŬŰɎŰɖ ũǝɎɟǝŰǝŬŰɖɠ´ŰɟŬ Ɏɜɤ ũǝŬũǝŬůɖŬɠ, ŰŬũŰɒɛŬŰŰ ŬɜŬǝǝɞɨɜŰǝůŰɞ ɛɞɜɧ ŬɜŬǝǝɖŰɐ (Vortex) [Eǝɧɜ Ŭ9], ŬɜɎŰŰǝŰɎ ɕɟɞɜǝɎũǝŬůŰɐɛŬŰŰ.

Ǻǝɧɜ Ŭ9. Ɇgůǝ Űgɐ Vortex (VibrofixVF1 Electronic ǝŬǝ IKA-VIBRAX-VXR, IKA-Labortechnik)

4. ɆŰɠ ůŰɐǝŰɠ Ŭɧ Űɠ ǝɞɛɛɏɜŰɠ ɛ´ŬŰɞɜɏŰŰɠŰɞ´ɞɖŮŰɞɨɛŮ Űɖɜ Ɏǝɟɖ Ű ɜ ɛǝɟɞ´ɘ ŬŰŰ ɜ Ű ɜ 100ɛL (tips) ǝŬǝ ŬɜŬǝǝɞɨɛŮ Űɠ ɛ´ŬŰɞɜɏŰŰɠ ɛɏůŬ ůŰɞ gɔɟɧ ɩ ůŰŰɜŬ ǝɖŰɖɞɨɜ ɧůɞ Űɞ ũgɜŰŰɧɜ ´ŰɟǝůůɧŰŰɟŬ ǝɨŰŰŰɟŬ. ɟ ǝɞǝɞɨ ɖɤ ɠ ǝɟŬŰɎɛŬŰɞ gɔɟɧ ´ɞg ´ŰɟǝɕŬǝŰŬǝɨŰŰɟŬ Ŭɩ Ŭ ɞɟɟɑ Űɞgɛ ŮŰɖɜ ɛ´ŬŰɞɜɏŰŰ.

5. ɇŬ ũŰǝɛŬŰŰ ɛŰŰŰɏɟɞɜŰŰǝ ůŰɖ ŰgɔɧǝŬɜŰɞ (Sorvall/Mc 12V, ũŬǝǝɖŬ) [Ǻǝɧɜ Ŭ10], ǝŬǝŰgɔɞǝŬɜŰɞɨɜŰŰǝůŰɠ4000 ůŰɞŰɏɠ/ǝŮ Űɧ ɔǝŬ15 ǝŮ ŰɎ.

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ÃÙ»·Õè 10. ç ¹Ð»¨Ñ¹ÍÑ·ÕèãªéÊ(Sorvall/Mc 12V, DUPONT)

6. ç ÑÁ¹ Ñé ÙÂÒ¨ÕÂÁ¡Ñ¹ÍÑ ¤Ãº´éÇÂÊÁ ¾Õè ÅéÒ¡ ÑäÁé ãÊè ¹ Ãà ´Ñ¹ ÊÔ ¨Ò ¡ Ñè ¹ ´à ¤ Ãè ´ÍÑ ¹ Ô ÇÍÅÙ Á 200ÁLÃÔ ç Ç´¹ÁÑ, ç ¹ ¹ ã¹ ÃäÅÔµ¼ÂÊÑ¹ ÅÇ¹·Õè Ñ éÂ¢ Ñé ÒÈÔ¹ Ñ è ·ÙÊÑ»Ô¹ÕÂÅ, ¹ Ò´Ô¹ ´éÇÂÇÔ¸ÕÁÒµÃ°Ò¹
7. Ã»Ô»µÍ 25ÁL ¢Í§ÊÒÃÅÐÅÒÂ »Ã ÔÁÒ³ã¹¢ÇÒ (ÁÕ ¤ ÇÒÁ ÊÓ¤ÑÞ ¢é ÍÁ).
8. Ã»Ô»µÍ 180 ÁLÊ¹ÔÊÒÃ ¢Í§ÊÒÃÅÐÅÒÂ¤ 1 ªÇ ¢ÇéÒ§¹Í¡ ÊÒÃàËÅÇ ÅÐÅÒÂ ¼ÊÁ ÍÁ ªÑ´ (Vortex) ¹Ò¹ 15 ÇÔ¹Ò·Õ ·Ô é§ äÇé. (ÁÕ ¤ ÇÒÁ ÊÓ¤ÑÞ ¢é ÍÁ)
9. Ã»Ô¡¹Ó¹ä ¾Á ÍØ ³ËÀÙÁÔ 56°C ¹Ò¹ 50 ¹Ò·Õ ã¹à¤Ã èÍ§ ¤Ç º¤ØÁ ÍØ ³ËÀÙÁÔ ÃØ¹ TechneDRI-BLOCKDB.3. (ÁÕ ¤ ÇÒÁ ÊÓ¤ÑÞ) [ÃÙ»·Õè 11]

ÃÙ»·Õè 11. à¤ Ã×èÍ§¤Çº¤ØÁÍØ³ËÀÙÁÔ (TechneDRI-BLOCKDB.3)

10. Ã»Ô»µÍ 200ml ¢Í§ÊÒÃÅÐÅÒÂ ¾3 ªÇ ¢ÇéÒ§¹Í¡ ÊÒÃÅÐÅÒÂ ÍÑ´ ¼ÊÁ ªÑ´ ¡Ñº ÍÁ ªÑ´ (Vortex) (ÁÕ ¤ ÇÒÁ ÊÓ¤ÑÞ).

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ɔɘŮ 10 ǝŮ ŰŸ ůŰɕɜ ɜɖɟɦ Ů ɤ ŮůŰɐɟŮ

BLOCKDB.3.(ǝɨ ůɖ ´ gɟ ɐɜŮ)

12. Ʉɟɕůɗɐǝɖ 210εL Ů ɦǝgŰɖɠ Ůɜɖ Ůɜɦǝɖɠ (100%) ǝŮǝ Ůǝɕǝɕɨ ɖɤ ɠ ɏɜŰɕɜɖ Ůɜ Ÿ ůŮ ɠůɖ ůŰɕɜ ε ɕɜɦ Ůɜ Ůǝɕɜɖ Űɐ (Vortex). ¢ Ůɜɖ Ůɜɦǝɖ ɏɕŮǝ Űɖɜ ɘǝ Ůɜɦ Űɖ ŰŮ ǝŰŰǝɟ ɐεɜɘůɖɠ ǝŮǝ ůɏů ε Ůɠůɖɠ Űɕg DNA..

13. ɆŰɠ Ůǝůɘǝ ɏɠ ǝɕǝɿ ɜŮɠŮ ɕεɦɜɤ ůɖɠ DNA ´ ɟ Ůɕ ε ŰŰɕ´ ɕɘŮŰŮǝ ε ŰŰůɕɟ Ÿ ɦǝɕg Űɕg ´ Ůɟ ɘŰɕɕε ɏɜɕg Ů ɦ Ű ůɤ ǝɖɜ Ÿɟ ɘŮε Ů´ ɘ ɏŰ.

14. ū gɔɕǝɏɜŰɟ ɖůɖ ɔɘŮ 2 ǝŮ ŰŸ ůŰɠ 12000 ůŰɟ ɕůɏɠ. ɀ ŮŰɖ ŰgɔɕǝɏɜŰɟ ɖůɖ ɔɕŮŰŰǝ ůɐ ɖɖůɖ Űɕg ε Ůɕ ε ŰŰɕɠ ε Ů Ů ɕŰɏǝŮɕ ε Ů Űɕ Ů ɘɖgε ɖŰɦ DNAɜŮ ǝŰŰǝɟ ŰŰɖŰŰǝ ůŰɕɜ ɖɖεɦ Ůɜɩ ɕŰǝůɐ´ ɕŰŮ Ůɜ Ů ɘɖɨ ε ɖŰɕ ɜŮ Ů ɕɓ Ÿǝǝ ŮŰŰǝ ůŰɖɜ ǝɕǝɿ ɜŮ Ů ɑɦ ´ɕg ǝŮǝ Ů ɕɟɟ ɗ ŰŰŰǝ.

15. Ʉɟɕůɗɐǝɖ 500εL ɟ gɖε ɘůŰǝɕɨ ůɘŮǝɨ ε ŮŰɕɠ ɏǝ´ ǝgůɖɠ (bufferBW) ǝŮǝ ŰgɔɕǝɏɜŰɟ ɖůɖ ɔɘŮ 2 ǝŮ ŰŸ ůŰɠ 12000 ůŰɟ ɕůɏɠ. ɟ ´ ɦɟɟ ɘɣ ɖ Űɕg gɔɟ ɕɨ Ů ɦ ŰŮ ŰgŮǝůɘŮ ůgǝǝɕɔɐɠ. (ɏǝ´ ǝgůɖ)

16. Ʉɟɕůɗɐǝɖ 600εL ɟ gɖε ɘůŰǝɕɨ ůɘŮǝɨ ε ŮŰɕɠ ɏǝ´ ǝgůɖɠ (bufferB5) ǝŮǝ ŰgɔɕǝɏɜŰɟ ɖůɖ ɔɘŮ 2 ǝŮ ŰŸ ůŰɠ 12000 ůŰɟ ɕůɏɠ. ɟ ´ ɦɟɟ ɘɣ ɖ Űɕg gɔɟ ɕɨ Ů ɦ ŰŮ ŰgŮǝůɘŮ ůgǝǝɕɔɐɠ. (ɏǝ´ ǝgůɖ) (ɖ ɏǝǝɕgůɖ ɔɕŮŰŰǝ ůɨ ɕ Űɕɟ ɏɠ ɔɘŮ ɜŮ ´ Ÿɟ ɕgε Ů ε ŮŸǝɖ ´ɕůɦ ŰɖŰŮ gǝɘǝɕɨ).

17. ū gɔɕǝɏɜŰɟ ɖůɖ ɔɘŮ 1 ǝŮ Űɦ ůŰɠ 12000 ůŰɟ ɕůɏɠ ɕɤ ɟ ɑɠ ´ ɟ ɕůɗɐǝɖ ɟ gɖε ɘůŰǝɕɨ ůɘŮǝɨ ε ŮŰɕɠ ǝŮǝ Ů ɦɟɟ ɘɣ ɖ Űɕg gɔɟ ɕɨ .

18. ɟ ɜŮǝɟ Ůůɐ Űɕg Ůɟ ɘɖε ɕɨ Űɕg Ůǝ Ÿ ůŰɕ ŰŮ ŮɜŰŰŰɕɦ ε Ůɜɕg ŮɖŮǝɕɜŰɐ ůŰ ŰgŮǝůɘŮ Űɨ ´ɕg Eppendorf 1,5 mL.

19. ɇɕ ´ ɕɖɏŰɖůɖ Űɤ ɜ ůŰɖǝɿ ɜ NucleoSpinTissueCollumns ´ Ÿɜɤ ůŮ ǝŮɖŮɟ Ÿ ŰgŮǝůɘŮ Űɨ ´ɕg Eppendorf 1,5 mL.

20. Ʉɟ ɕɖɏɟ ε Ůɜůɖ ɟ gɖε ɘůŰǝɕɨ ůɘŮǝɨ ε ŮŰɕɠ ɏǝǝɕgůɖɠ (elusionbuffer) ǝŮǝ ´ɟ ɕůɗɐǝɖ 50εLŮɜ ŮgŰɕɨ . ū gɔɕǝɏɜŰɟ ɖůɖŰɕg ůŮɕε ŮŰɕɠ ɔɘŮ 1 ǝŮ Űɦ ůŰɠ 12000 ůŰɟ ɕůɏɠ.

21. Ʉɟɕůɗɐǝɖ Ů ɘ ǝɏɕɜ 50εLɟ gε ɘůŰǝɕɨ ůɘŮǝɨ ε ŮŰɕɠ ɏǝǝɕgůɖɠ (elusionbuffer) ǝŮǝ Ůǝɕǝɕɨ ɖɤ ɠŰgɔɕǝɏɜŰɟ ɖůɖ Űɕg ůŮɕε ŮŰɕɠ ůŰɠ 12000 ůŰɟ ɕůɏɠ ɔɘŮ 1 ǝŮ Űɦ. ɟ ´ ɦɟɟ ɘɣ ɖ Űɤ ɜ ůŰɖǝɿ ɜ (NucleoSpinTissueCollumns).ɇɕ gɔɟɦ ´ɕg ǝŮε ɓ Ÿɜ ŮŰŰǝ ε Ů Űɖɜ ůɘŮůɘŮɖŮ ´ɕg ɏɕŮ ´ Ůɟ ɘɟ ŮůŮɖ ´ Ůɟ ɘɏɕŮǝ Űɕ DNA Űɕg ǝŮɖŮɜɦɠ ŮɜŰŰŰɕɦ ε Ůɜɕg ŮɖŮǝɕɜŰɐ.

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ŲB φAΉĩζ ȷ ȷ Ɨζ ȷ ȼ B Ɇ:

ɤ ɔɐɠ DNA Ŭ ɧ ŭŬɒɛŬŬɛŬŰɠ Ů ɘŰŰɞŬŰɘ ɤ ɠŬɞɠ:

- ȼ ɞ´ ɞɖɏŰɖůɖ Űɤ ɜ ŭŬɒɛŸŰɤ ɜ ůŮ stand ɘŬɞ ȷɨ ɖɛɘůɖŰɠ ɖŬȷ ɛŬɜŬɞɐɠ ´ ɘŸɘŬɠ (Ů ɤ ŬŭŰɟȷŬ) ůŰɞgɠ 70 ^{0}C.
- ɆŮ 200-250 ɛL ŭŬɒɛŬŰɞɠ ŬɛŬŰɞɠ ´ȷɞůŰɖŬɜŰŬɞ 25 ɛL ŭɘŬɞɨ ɛŬŰɞɠ ȷɤ ŰŬɞŸůɖɠ Ɀ, ɖ ɞ´ɞɖŬ ŭɘŬů´Ÿ Űɠ ɘgŰŬȷɘɏɠ ɛŬɛɓȷŸɜŬɠ Űɤ ɜ ɘgŰŸȷɤ ɜ Űɞg ŬɛŬŰɞɠ ɘŬɞ 200 ɛL ȷgɖɛɘůŰɞɞɨ ŭɘŬɞɨ ɛŬŰɞɠ B3 ɏŰɘɩ ůŰɜŬ ŭɘŮɠɘɞɘgɜɖŬɖ ɘɨ ůɖ Űɤ ɜ ɘgŰŸȷ ɤ ɜ
- ɆŰɖ ůgɜɏɞŮŬŰɞ ɛɒɛŬŬɜŬŭŮ ŰŬɞůŰɞɜ ɛɞɜɧ ŬɜŬɞɘɖŰɞ (Vortex)
- ŲȷŬɞɛŬŰɞ´ɞɘŬɖŰɞ Ů ɩ Ŭůɖ ŭŬɒɛŬŰɞɠ ůŰɞgɠ 70 ^{0}C ůŰɞɜ ɜɖȷ ɧ Ů ɤ ŬŭŰɟȷŬ ɔɘŬ 10 ɘŮ ŰŸ
- Ųȷɞůɖɐɘɖ 210ɛL Ŭ ɧɘgŰɖɠ ŬɖŬɜɧɘɖɠ (100%) ɘŬɞ ɏɜŰɞɜɖ ŬɜŸŭŮgůɖ ůŰɞ Vortex.
- Ųȷɞůŭ Űɞɐ ɛŰŰŭɞȷŸɛŮ´ɗ ɏŰŰɧɘɐg Űɞg ´ Űȷɘůɞɞɛɏɜɞg Ŭ ɧ ŰŬ ůɤ ɘɖɜŸȷɘŬ ůŰɞɠ Ŭɞŭɘɏɠɘɞɘɩ ɜŮɠ Ŭ ɞɛɧɜɤ ůɖɠ DNA.
- ū gɔɞɘɏɜŰȷɖůɖ ɔɘŬ 5 ɘŮ ŰŸ ůŰɞɠ 12000 ůŰȷɞűɏɠ ɘŬɞ Ŭ ɧȷȷɘɣɖ Űɞg gɔȷɞɨ Ŭ ɧ Ŭű gŬɘɑɘŬ ůgɘɘɞɔɐɠ.
- Ųȷɞůɖɐɘɖ 500ɛL ȷgɖɛɘůŰɞɞɨ ŭɘŬɞɨ ɛŬŰɞɠ ɏɘ´ɘgůɖɠ (buffer BW) ɘŬɞ ɜŬɜŸ űgɔɞɘɏɜŰȷɖůɖ ɔɘŬ 2 ɘŮ ŰŸ ůŰɞɠ 12000 ůŰȷɞűɏɠ. ȷ ´ ɧȷȷɘɣɖ Űɞg gɔȷɞɨ Ŭ ɧ Ŭ űgŬɘɑɘŬ ůgɘɘɞɔɐɠ.
- Ųȷɞůɖɐɘɖ 600ɛL ȷgɖɛɘůŰɞɞɨ ŭɘŬɞɨ ɛŬŰɞɠ ɏɘ´ɘgůɖɠ (buffer B5), űgɔɞɘɏɜŰȷɖůɖ ɔɘŬ 2 ɘŮ ŰŸ ůŰɞɠ 12000 ůŰȷɞűɏɠ ɘŬɞ Ŭ ɧȷȷɘɣɖ Űɞg gɔȷɞɨ Ŭ ɧ Ŭ űɘŬɘɑɘŬ ůgɘɘɞɔɐɠ (ɖ ɏɘɘgůɖ ɔɒŰŰɞ ŭɨɞ űɞȷɏɠ ɔɘŬ ɜŬ ´ Ÿȷɞgɛ Ůɛ ŬŸɘɖ ´ɞůɧŰɖŰgɘɞɞɨ).
- ū gɔɞɘɏɜŰȷɖůɖ ɔɘŬ 1 ɘŮ Űɧ ůŰɞɠ 12000 ůŰȷɞűɏɠ ɞɤ ȷ ɑɠ ´ȷɞůɖɐɘɖ ȷgɖɛɘůŰɞɞɨ ŭɘŬɞɨ ɛŬŰɞɠ ɘŬɞ Ŭ ɧȷȷɘɣɖ Űɞg gɔȷɞɨ .
- ȷ ɜŬɓȷŬŭɐ Űɞg Űȷɘɖɛɞɨ Űɞg ŬŸůŰŰ ŬŰŰɛɧɛŬɜɞg ŰŬɞɜŰɞ ůŰŰ űɘŬɘɑɘŬ Űɨ ´ɞg Eppendorf 1,5 mL.
- ȼ ɞ´ ɞɖɏŰɖůɖ Űɤ ɜ ůŰɖɘɩ ɜ NucleoSpinTissueCollumns´ Ÿɜɤ ůŮ ɘŬɖŬȷŸ űɘŬɘɑɘŬ Űɨ ´ ɞg Eppendorf 1,5mL.

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ŉǿǁǐ ŭǝǓǿǐ ƐǓǖǥ ǂǝǝǥůďď (elusionbuffer) ǖǂ ǝ´ǝǿ ǂďǕůǖǥ 70°C. ū ǥɔǝǝǂǓ́ ďůďǖǥ ŭǓǿƐǓǖǥ ɔǝǓ 1 ǝǕ ǖɦ ůǖǥ 12000 ůǓ́ ǝǘǂ.

- Ʉɟ ǝůďǝď Ǖ ǝ́ ǝǂǝɜ 50εL ɟǥɛǝůǖǿǐ ŭǝǓǿǐ ƐǓǖǥ ǂǝǝǥůďď (elusionbuffer), ǘǥɔǝǝǂǓ́ ďůďǖǥ ŭǓǿƐǓǖǥ ůǖǥ 12000 ůǓ́ ǝǘǂ ɔǝǓ 1 ǝǕ ǖɦ ǝǓǝ Ǔ ɦɟɟǝɣď ǖɤ ɜ ůǖǝɿ ɜ (NucleoSpinTissueCollumns). ɇǝ ǥɔɟɦ ´ǝǥ ´Ǔ́ɟǓǝǓɛбƳɜǗǓǝ ƐǕ ǖǝɜ ´Ǔ́ɟǓ Ƴɜɤ ŭǝǓǘǝǓůďǓ, ůǥɜǝǝǝǐ ɦɔǝǝǥ 100εL, ´Ǔ́ǝǝǝǕǝ ǖǂ DNA ǖǥ ǕǝƳůǖǗǗǕǝǗǓǖɛɦɛǕǝǥ ǓǝǓǝǝɜǖǝ.
- ɀ ǂǓ́ďůď ´ǝůɦǖǝǗǥɔǕǝǖǝǐ ǥǝǝǐ ƐǕBiophotometer.

2.4 ɟ ȿ Ɉ ȻŁǫɋ ɇ ¢ ɟ ʔ ɇ ŁǫɅɟ Ȼ¢ ɄɃȿ Ɉ ɀ ȺɅɟ Ȼ¢ Ȼ (PCR)

¢ Ǔǝǥůǝǘɤ ǖǝ ǓɜǖǘɟǓůď ´ǝǝǥƐǓ́Ƴůďǥ(PCR, polymerasechainreaction) Ǔ ǝǗǝǕǝбǓůǝɦ Ǔ́ɔǓǝǕǝ ɔǝǓ ǖď бǝǓǗǓ́ǝǝ ǂɟ ǖǥɜǓ ǝǓǝ ǕǝǓǝ ƐǓ ɔɟ ɐɔǝɟ ď, Ǔ ǝǝ ǝǓǝ ǕǝǓɟ ǖǝƳ ǕǥǓǝůďďǖď ǖǝɜǝǝ.ďǓůǝǝ Ǔ́ɟǝǝ ǖďǥ PCR ǕǝǓǝ ď ǕǝďǗǝǝ ǓɜǓ Ǔ́ɟǓǝɤ ɔǝ Ǖɦǥ ůǥɔǝǕǝɟǝǂɜǝǥ, ɔɜɤ ůǖǐ ǖɛǝƐǓǖǥ ǖǥ DNA. ɟ ɟďůǝɛǝ´ǝǝǕďǗǝ ůǖďɜ ɛǝɟǝǓǝǝ бǝǝǝɔďǓ ɔǝǓ ǖďɜ Ǔ ǝɛɦɜɤůď ǝǓǝ ǖǝɜ ´ǝǝǝǓ ǝǓůǝǓůɛɦ ɛďǓǥ ůǥɔǝǕǝɟǝǂɜďǥ Ǔǝǝďǝǝǥǝ́ǓǥDNA, ɛǂůɤ Ǖǝǥɛǝǝǝǥ ǕǝǓ Ǔ́ɟǓǝɤ ɔǝǥ ǖǥ DNAinvitro ɢɤɟǝǥ ǖď ɢɟǝůď, ǖďɜ ǝǝɤɜǝ´ǝǝďůď ǝǓǝ ǖǝɜ ´ǝǝǝǓ ǝǓůǝǓůɛɦ ůǕ ǝɤɜǗǓǝǝǐǥ ǝǝɤɜǝ´ǝǝďɛǂɜǝǥǥ ɛǝɟǝǝɟɔǓǝůɛǝǐǥ.

¢ PCR Ǔ ǓǝǗǕǝ ǕǝƳǝůǖď ´ǝůɦǖďǗǓ DNA ɔǝǓ ǖǝɜ ´ǝǝǝǓ ǝǓůǝǓůɛɦ ǖďǥ´ɟǝǥ ɛǕǝǂǖď Ǔǝǝďǝǝǥǝ́Ǔǥɇǝ Dʔɟ , ´ǝǥ ´ǝǝǝǓ ǝǓůǝƳǗǓǝ ƐǕ ǖďɜ PCR, ɛ´ǝɟǕǝ ɜǓ ´ɟǝǂɟǝǗǓǝ Ǔ ɦ ǝ´ǝǝǘǝ´ǝǗ ǝǘɦ. ɇǝ ɔǕǝɤ ɛǝǝɦ DNA ´ǝǥ ɢɟďůǝɛǝ´ǝǝďďǝǓůǖď ´Ǔ́ɟǝǐůǓ ɛǕǝǂǖď Ǔ ǝɛɛɜı ďďǝǕ ǕǗǓ Ǔ ɦ ǗǓ Ǖ ǝďǝǝǓǝƳ ǝǐǗǓɟǓ ǖďǥ ůǖɛǓǖǝǝǥ ǝǝǝɦǖďǓǥ ǕǝǗ ǖǂ ǝǝǝɦ ǓǝƐǓ, ůǖǂ ǝ´ǝǝ ǕǝǕ ´ɟǝůǗǝďǕǝ EDTAı ůǗǕ ɜǓ ɛďɜ ůǥɔǝǝǝďďǕǝ ǝǓǝ ǝǓǗǗůǓ́Ǔǖǝǐɜ ǗǓ Ǖǝ´ǐɟďɜǓ ǝǐǗǓ́ɟǓ, ůǖǝɜ ´ǥɟǝɜǓ ǖɤ ɜ ǝ´ǝǝɤ ɜ Ǖǝ´Ǔ́ǝǝǝǗǓǝ ǖǂ DNA.

ɀ Ǖ ǖďɜ PCR, ŭǓǝɛǂɜǝǥ ɦǖǝ ǕǝǓǝ ɔɜɤ ůǖǝ ď ɜǝǥǝǝǕǝǖǘǝǝ Ǔǝǝďǝǝǥǝ́ǓǝǐǓǥ ůǥɔǝǕǝɟǝǂɜďǥ ´Ǔ́ǝǝǝǥ ǖǥ ɔǝɜǝǘǝɛǓǖǥ, ɛ´ǝɟǕǝ Ǔǥǖǝ ď Ǔǝǝďǝǝǥǝ́Ǔ ɜǓ ´ǝǝǝǓ ǝǓůǝǓůǗǝ ɛǂɢɟǝ ǝǓǝ ŭǝůǕǝǓǖɛɛɨɟǝǓ ǘǝɟǂ. ¢ ɔɜı ůď ǖďǥ Ǔǝǝďǝǝǥǝ́Ǔ ǖǥ ɔǝɜǝǘǝǥ ǕǝǓǝ Ǔ Ǔ́ɟǓǖďǖď ɔǝǓ ǖǝɜ ůǝǕǓǝǓůɛɦ ǖɤ ɜ ůǥɜďǗǝǝı ɜ DNA ǝǝǝǝɜǝǥǝǝǕǝǖǘǝɤ ɜ. ɟ ǥǗƳ ǗǓ ǝǝǝǝɜǝǥǝǝǕǝǖǘǝǓ ǝɜǝƳǝɜǗǓǝ Ǖǝǝǝďǖǂ (DNA primers). ɇǝ ǝƳďǕǝǝǝǝɜǝǥǝǝǕǝǖǘǝǝ ǕǝǓǝ ůǥɛ´ǝďɟɤ ɛǓǖǝɦ ɛǕɛďǓǓ ɦ ǖǥǓǝǥůǝǓǥ ǖǥ ŭǝǝɤɜǝǥ DNAǖďǥǥ´ɦ ǕǝǂǗǓůď Ǔǝǝďǝǝǥǝ́Ǔǥ, ɛǝǝǝǥǥ20-30 ´Ǔ́ǝ ǝǥ бƳůǕɤ ɜ.

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[illegible] DNA [illegible] (dNTPs) [illegible] DNA [illegible] 90-95°C. [illegible] (PCR thermalcycler), [illegible]

[illegible] PCR [illegible]:

1. [illegible] DNA (denaturation),
2. [illegible] DNA [illegible] (annealing) [illegible]
3. [illegible] DNA (elongation).

[illegible] D?[illegible] 93-95°C, [illegible] 50-60°C [illegible] DNA [illegible] DNA [illegible] 72°C. H DNA [illegible] dATP, dTTP, dGTP [illegible] dCTP, [illegible] PCR, [illegible] DNA. [illegible] DNA [illegible] DNA. [illegible] invitro [illegible] DNA. [illegible] $2x10^n$ [illegible]

2.5 REALTIMEPCR

[illegible] (probe) [illegible] 5' [illegible] DNA [illegible] (reportermolecule) [illegible] 3' [illegible] (quenchermolecule). [illegible] PCR, [illegible]

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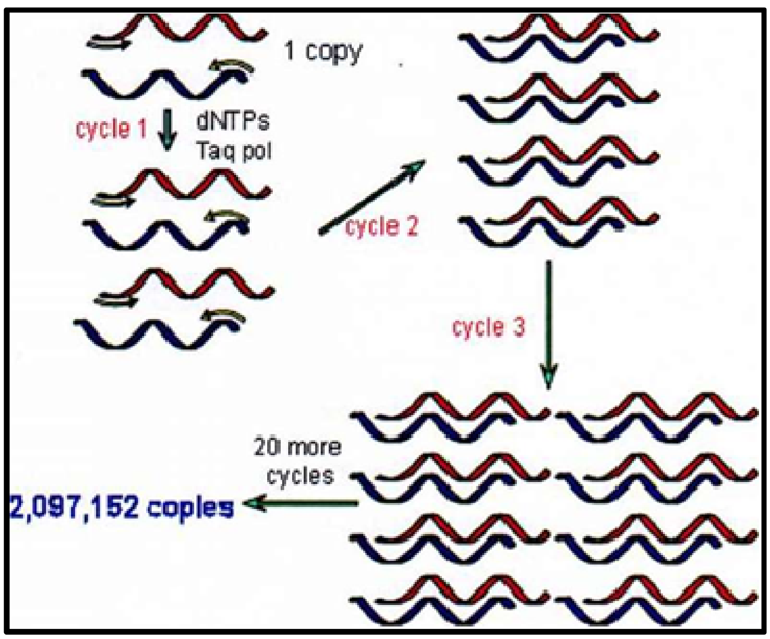
Ŭə Ŭ ђ Ǘɖ DNA´ɞəɛŮɟ Ÿůɖ, əђɔɤ Ǘɖʃ ǕǕgǗђɕɟɞɜɖʃ ɩɖ. ɀ ɏůɤ Ǘɖʃ ŭɟ Ÿůɖʃ ŬgǗɐʃ, Ŭ ɞɛŬəɟɨɜǕǕŬə Ǘɞ ǘɖɞɟɶɜɜ ɛђɟɞ-ŬɜǕǕ ɞəɟɘǗɐʃ Ŭ ђ Ǘɞ ɛђɟɞ-Ŭ ɞůɓɏůǗɖ, ɛŮ Ŭ ɞǗɏəǗůɛŬ Ǘɖɜ ´Ŭɟɞgůɖ Ŭ ůɐɛǗǗɞʃ ǘɖɞɟůɛɞɨ, Ǘɞ ɞ´ɞɶ əŬə ŬgɜŸɜǕǕŬə ŬɜŸəɞɔŬ ɛŮ Ǘɖɜ ŬɟɕɘɐŤ ´ɞůђǗɖǕŬ Ǘɞg DNA ůǗɞ ŭǗɐɛŬ. ɋ ʃɛђɟɞ ŬɜǕǕ ɞəɟɘǗɐʃ ɛ´ɞɟ ǗɑɜŬɕɟɖůɶɛɞ´ɞɖɖǗɑɖ 6-əŬɟɓɞɜg-ǘəɞgɞɟ ǗɑəǗɜɖ (FAM),ɖ 4,7,2',4',5',7'-ǗɜŬɕəɤ ɟɞ-6-əŬɟɓɞɜg-ǘəɞgɞɟ ǗɑəǗɜɖ ɐ ɖ 4,7,2ō,7ōǕǕɟŬɕəɤ ɟɞ-6-əŬɟɓɞɜg-ǘəɞgɞɟ ǗɑəǗɜɖ (ɇ Aɇ), Ǘɜɩ ɤʃ ɛђɟɞ-Ŭ ɞůɓɏůǗɖʃ ɖ ɟɞŭŬɛɶɖ. ¢ ɛǗɖɞŭɞəɞɔɖŬ ŬgǗɐ ɏɕǗə´əɏɞɜ əŬɖɞǗɟɤɖǗɑ, əŬə ǗəŭɞəɐɞɟɔŬɜɞəɞɔɖŬ ɏɕǗə ŬɜŬ ǗgɕɖǗɑɔəŬ Ǘɞ ůəɞ´ђ ŬgǗђ, ђ´ɤʃɞ ɖǗɟɛəђʃ əgəɞ´ɞɖǗɐʃLightcycler® 480 Ǘɖʃ ǕǕəɟ ǗɑŬʃRocheDiagnostics, ´ɞg ɕɟɖůɶɛɞ´ɞɶɖɖəŮ ůǗɖ ůgɔəǗəɟɶɏɜɖ ɏɟǗgɜŬ. ¢ ůgůəǗgɐ Lightcycler® 480 Ŭ ɞǕǗəǗɑɏɜŬɜ ǕǕɕɨ ɖǗɟɛəђ əgəɞ´ɞɖǗɐ ɛŮəŬɜђǗɖǕŬ ´ŬɟŬəɞəɞɨ ɖɖůɖʃ Ǘɖʃ PCR ůŮ ´ɟŬəɛŬǕəђ ɕɟђɜɞ (realtime). ŌǗɨə, Ůəǘɟɏ´ Ǘə Ǘɖɜ ǕǕgǗђɕɟɞɜɖ ǗɜǘɕgůɖəŬəŬɜɞɜǗgůɖ Ǘɤ ɜɜɞgəǗɐɩ ɜ ɞɜɏɤ ɜ-ůǗђɕɤ ɜ.[Aəђɜ Ŭ 12,13]



Aə ђɜŬ 12. ɀ ǕǗŸŬ ђ n ǗɏǗɞɶgʃəɨ əəɞgʃ´ ŬɟŸɔɞɜǕǕə2x10^n ɜɏŬŬɜǗɑɟŬǘŬ

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Ѧงฺ ฦษปั 13. RealTimePCRLC480 HRM (HighResolutionMeltingconditions)

2.6 ɟ ʔɟ ȿ Ɉ ȼ ƎƬ ¢ ɋƎɟ ɋƎƬɟ ƐƎɟ ɄɃɈ ɟ ƮɃȿ ɃɈ Ū¢ Ɛɟ ɀ Ѧ ũƎɟ ȼ ¢ ʔ PCR

ɟ ɉ ɢǝ ƳȡȘ Ŭ ɕůŰǥ ɤ ůȡ ɛŮg´ Ǜ ǝ ǘȡ ŬǝŰɞɕɓɕǝŬ (UV, 254nm) ŰɞƍɩɈɕg, ´ɕg ȡŬ ŮǝŰǝŮŰȡ ǘǝŬǝǝŬȡŬ ǝŬŰƳ Űȡȝ ɕ´ɕȡŬ ȡŬ ŬȝŬǝŬŰůŰɕɨȝ ŰŰ ŬȝŰǘɟŬůŰɟɉŬ (ŮǝǝȡŰƴ, ´ɕǝɛŮ Ƴůȡ, ȝǛ ƒ), ɛŬȝɐůȝ), ŮɕŬǝ Ŭ Ǜ ŬȡŰȡŰȡ.ɟ űɕɨ ɔɕŮǝ ŬgŰƒ, ůŰȡȝ ůȝȝɣɕŮǝŬ Ŭ ɕůŰǥɩ ȝɕȝŰǝ ɕǝ ´ɘ ɏŰŰŮ, ŰŬ tips, ǝŬǝ ŰŬ g´ ƒǝɕɘ Ŭ ůǝŮɨȡ (ŰŬ ɕ´ɕȡŬ ɏɕɕȝ g´ ɕůŰŮgɔɟɐ Ŭ ɕůŰǥ ɤůȡ) ´ɕg ȡŬ ɕɟȡůɤɕ´ɕȡȡɕɨȝ ǝŬŰƳ Űȡȝ ǘǝƳɟǝŮǝŬ Űȡ ŬȝŬǝgŰǝɐ ǘǝŬǝǝŬȡŬ ɛŮ g´ Ǜ ǝ ǘȡ ŬǝŰɞɕɓɕǝŬ. ȳ ǝŬ ŰŬ ŬȝŰǘɟŬůŰɟɉŬ ŮɕŬǝ Űɕ´ɕȡŰŰȡɛɏȝŬ ůŰȡȝ ǝŬŰƳɣgȝȡ. ¢ ǝŬŰŰůǝŮgƳůŰɉŬ ŰŰǝɟŮȡŬ (TibMolBiol) Űɤ ȝ Ůǝǝȝȡű ȝ (primers) ǝŬǝ Űɤ ȝ ɕǝǝɕȝɕgǝǝŮɕŰǝǝɩ ȝ ŬȝɕȝŮgű ȝ (probes) ´ɟɕŰŮɕŬǝ ůgɔǝŮɟɛɏȝɕ ´ɟɤ Űƒǝɕǝǝɕ ɔǝŬ Űȡȝ Ů ǝŰgɕɐ ǘǝŮŬɤɔɐ Űɤ ȝ ŮƳůŰɕŰŰ PCR [ɄɕŬǝŬ 5]. ȼ Ŭ Ů ɛɏɟɕgŰ ŬȝŰǘɟŬůŰɟɉŬ ǝŬǝ ɕǝ ɕǘȡɔȡŰ ɕɟɐůȡŰ Űɕg´ Ǜ ǝŬɛɓƳȝɕȝŰǝ ůŰɕ kitLightSNip, Űɕ ɕ´ɕɕ ŮɕŬǝ ǘǝŬűɕɟŰǝƒ ɔǝŬ ǝƳȡŮ´ɕǝgɛɕɟűǝɛƒ ´ɕg ´ɟƒǝŮǝŰǝ ȝŬ ɛŮǝŰȡȡŮ ƎŮǝƳȡŮkitLightSNip´ Ǜ ǝŬɛɓƳȝŰŰǝ Űɕ Mastermix, Űɕ ɕ´ɕɕ ´Ǜ ǝɏɕŮǝ ŰŬ ɕǝǝɕȝɕgǝǝŮɕŰǘǝŬ, Űɕgŭ ŬȝɕȝŮgŰƴ ǝŬǝ Űȡȝ ȡǛɛɕŬȝȡŮǝŰǝɐ´ɕǝgɛŮ Ƴůȡ. ɋǝƳǝgɛŬMgCl$_2$ 25mM (faststart)´ Ǜ ǝɏɕŰŰǝ ůŮ ǘǝŰűɕɟŮǝƒ űǝŬǝǘɐ. ȼɕ ɨǘɤɟ ´ɕg ɕɟȡůɛɕ´ɕǝŮŰŰǝ ŮɕŬǝ ǘǝɟŬ ŮŰŰǝɛɏȝɕ, g´ Ǜ ǝƳȡŬɟɕ, ŮǝŮ ȡǛɕ ɕgůǝ ȝ´ɕg ɛ´ɕɟŮȝȝŬ ŬȝŬŰŰǝɕgȝ Űȡȝ PCR (PCR-Grade).

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...agents	Basic
Master mix	2εL
PrimerMix (Prob+Primer)	1εL
$MgCl_2$	1,6εL
H2Ɓ	11,4εL

ɄœŬә Ŭƒ5. ŭŮәŋ ´ɟɤ Ŭʃәɞәɞ

1.7 Ʉɟ Λɟ ɆŦȺɈ¢ 5XTBE

ɸәŬәɨ ɞɜŰŰә 4,688g EDTA, 54g Trismabase әŬә 27,5g ȡɞɟәŋ ɞɜɨ ůŮ εȡŬ әɤɜәɐ űәŸәɖ, ůŮ´ɞůŋŰɖŰŰ Ŭ ŮŭŰŰɔεɏɜɞg ɜŮɟɞɨ ɑůɖ εŮŬɞ 75% Űɖƒ´ɞůŋŰɖŰŰƒ Űɞg 5XTBE buffer ´ɞg ȡŬ´Ŭɟ ŬŭәŮgŬŭŰŰŭ ɟ ɜŬәɞɞɨ ɜŰŰәɏɜŰɞɜŬɏŰŭәɩ ůŰŮɜŬŭәŬәgȡɞɨ ɜ ´әɐɟɤ ƒŰŰ ŬɞŰŭɟ ŬŭŰɐɟәŸ. ɇɞ EDTA ε´ɞɟŮŭɜŬ Ŭɟɔɐ ůŮɜŬ ŭәŬәgȡŮŭɞ´ŋŰŮŬŭɐɜŰŰә ůŮɖɟŮɛȡŬ ɔәŬ 10 әŮ ŰŸ, ŬɞŬәɞɩ ɜŰŰƒŰɞ ŬɞŸ 5 әŮ ŰŸ εɏɢɟә Űɞ gɔɟŋ ɔœŮ ŭәŬgɔɏƒ. [ɄœŬәŬƒ6]

ɟ ɜŰŭŭɟ ŬŭŰɐɟәŬ	2L
EDTA	4,688g
Tris (Trismabase)	54g
Boricacid	27,5g
ɟ´ŮŭŰŰɔεɏɜɞH_2O	0,9L

ɄœŬә Ŭƒ6. ɟ ɜŰŭŭɟ ŬŭŰɐɟәŬәŬә´ɞůŋŰɖŰŰƒŬgŰ ɜ ɔәŬŰɖɜ ɄŬɟ ŬŭәŮgɐ 5ɟ TBE.

Ő´ŮŭŰŰ ´ɟɞůŰȡŮŰŰә әŬә ɖ g´ŋәɞә´ɖ ´ɞůŋŰɖŰŰ Űɞg Ŭ ŮŭŰŰɔεɏɜɞg ɜŮɟɞɨ әŬә űgәŸůŮŰŰә ůŮűәŸәɖ εŮŬŭεgɟәůεɏɜɞ ´ɩ εŬ.

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ȷ ŭȷ ɅBȻ¢ Ɇ

¢ ǕȷǕıəǕgɐ ɖəǕεg ǕɔǕȷ ɧɕɖɠ ɔɞǕǕǕɜɤ ɠ Ǖɘɐɠ:

- Ȼgɔɕɞɜ Ǖǖɜ 0,8-1,0 g ǕɔǕȷ ɧɕɖɠ əǕɜ ´ȷɕǖǕɖǕǕɜ ɏɤ ɠ 40mL ŭɘǕəgεǕ ¢ɖɅ 0,5ɀ (ŭɘǕəgεǕ Ǖȷɔǖɠ: ǕȷǕɤ ǖɖ 1:10 εǕǕ ǕǖǕɜεɏɜɞ ɜǕ ɧ Ǖ ɧ Ǖɞ ŭɘǕəgεǕ¢ɖɅ 5ɀ). ȷ ɜǕəɕɖǖɖ Ǖɞg εǕɒεǕǕɞɠ.
- Ǖɏȷ εǕɜǖɖ Ǖɞg ŭɘǕəɨ εǕǕɞɠ ǖǕǖɕɨȷɜɞ εɘȷɞəgεǕǕɤɜ (750 Watt) ´ɕg ɓȷ ɖəǕǕɜ ǖǕǕ Ǖɔɤ ɔɧ ɔɘǕ 2-4 əǕ ǕǓ.
- ȷ ǖɐɜǕǕɜ ɔɘǕ əɒɕ Ǖɞ ŭɘǕəgεǕ,εɏɕȷɘ ɜǕ ǖǕǕǖǕɜ ´Ǖȷ ɖ ɕg ǖǕ ɖǕȷεɕəȷǕǖɖǕ 40-60°C, əǕɜ ´ȷɕǖǕɖǕɜǕǕɜ 2 εL ŭɘǕɜɨ εǕǕɞɠ ɓȷ ɤ εɘɞɨ ɕɞgǕɜɖǕŭɕg 1% əǕɜ Ǖɞ εǕɒεǕǕɜǕǕǕ ǕǕɜ. ¢ ŭɘǕǕɘǕǖɖǕ Ǖgǖɐ ´ȷɏ ǕɜɜǕɔɞǕǕǕɜ ǕɜǕȷɠ Ǖɞg Ǖ Ǖɔɤ ɔɞɨ, ŭɘɧǕɜ Ǖɞ ɓȷɤ εɘɞɨ ɕɞǕɜɖǕŭɘ ǕɞǕɜ əǕȷəɞɞɕɔǕɜɏɠ əǕɜ ǕǕȷǕǕɞɔǕɜɏɠ.
- ¢ɏəɕɠ Ǖɞ εǕɒεǕ ǕɔǕȷ ɧɕɖɠ TBE əǕɜ ɓȷɤ εɘɞɨ ɕɞgǕɜɖǕŭɕg, ǖgɔəɏɜǕȷɤ ǖɖɠ 2%, Ǖɞ´ɕɖǕǕǕɖǕǕɜ ǖǕ Ǖǖŭɘɧ əǕəɕɨ´ɘ əǕɜ ǕǕɐɜǕǕǕɜ ɜǕ əȷgɩ ǖǕɜ.

2.9 ¢ ʂ ɅƮ¢ ɅB ŭ B Ʌ¢ Ɇ¢

ȷ ǖǕɏȷǕɖǕǕɜ Ǖ ɧ Ǖɞ əǕəɕɨ´ɩ ɖ ǖǕǕȷǕɞ´ɕɖεɏɜɖ ɔɏəɖ əǕɜ Ǖɞ´ɕɖǕǕǕɖǕǕɜ ǖǕ ǖgǖəǕgɐɖəǕɜǕȷɕǖɧȷɖǖɖɠ. ȷ əɕəɕɨ ɖɤ ɠ ´ȷɕǖǕɖǕǕǕɜ ŭɘǕəgεǕ ¢ɖɅ 0,5ɀ Ǖɤ ɠ ɧǕɞg əǕəgǖɖǕɖ´əɐȷɤ ɠ. ɆǕǕ Ǖǖŭɘ Ǔ ŭɘǕεɕȷǖɤ εɏɜǕ «´ɖɔǕǕǓəǕ» Ǖɞg ´ɖəǕ εǕǕɞɠ ǕɔǕȷ ɧɕɖɠ Ǖɞ´ɕɖǕǕǕɖǕǕɜ 6-7 εL ´ȷɕɧɜǕɞɠ PCRǕǖɕɨ ǕɜǕεǕɜɕɖǕǕ εǕ 1-2mLɕȷɤ ǖǕɜɐɠ (methylaneblue), ɩ ǖǕǕ ɜǕ əǕǕǖǕǕ ǖgɜǕǖɐ ɖ ´ǕȷǕɜɕəɕɨ ɖɖǖɖ Ǖɖɠ ´ɕȷǕǕɠ Ǖɖɠ ɖəǕɜȷɕǖɧȷɖǖɖɠ, ǕɜəǓ əǕɜ ɔɘǕ ɜǕ ɕǖɖɔɖɖǕǕ Ǖɞ ŭǕɒεǕ ǖǕɞ ɓǓɖɕɠ Ǖɞg «´ɖɔǕǕǕɜɕg». ɆǕɞ ´ȷɩ Ǖɞ ´ɖɔǕǕǓəɘ Ǖɞ´ɕɖǕǕǕɖǕǕɜ εǕɒεǕ ɕȷɤ ǖǕɜɐɠ (2εL) εǕ DNAladder(¢hermoScientificGeneRulerLowRangeDNALadder, C=0,5εg/εL) (5εL), ǕǕɕ´ɕɖǕɏɕgɜ ´ȷɩ ǕǕ ǕɜǕεǕɜɕɖǕǕ εǕǕǕɜɨ Ǖɞgɠ.¢ɕ DNAladderǕɞǕɜ ŭǕɒǕɖɠ εɕȷɘǕɜɩ ɜ ɓǕȷɩ ɜ ɜɕgəəǕɞǕǖŭɘɩ ɜ ɓǓǖǕɤ ɜ əǕɜ ǕɞǕɜ Ǖǖŭɘ Ǔ ǖɕǕɨǕǖεɏɜɕ ɔɘǕ ɖəǕɜǕȷɕǖɕȷɖǕɜɐ ǕɜǓəgǖɖ εɘȷɩ ɜ ɖȷ ǕgǖεǓǕɤ ɜ DNA ǖǕgelsgɤɖəɐg´ǕȷɘǕɜǕɜɧǕɖǕǕɠ ǖǕǕɔǕȷ ɧɕɖ (2,5-3%) əǕɜ ´ɕəgǕɜȷgəǕεɖǕɞ(5-10%). ɄǕȷɏɕǕɜ ɏɜǕ εǕɒεǕ 10 əǕǕɖǕȷεɏɜɤ ɜ εɏǖɤ ɕȷɤ εǕǕɞɔȷǕǕəǕɠ ɖȷǕgǖεǓǕɤ ɜ DNA(ǖǕ ɕǕɔɖ ɓǓǖǕɤ ɜ). ¢ɕɖəǕɜǕȷɕǖɕȷɖǕɜɐɧ ǖɨ ǖǕɖεǕ ȷgɖεɕǕǕɜ ǖǕǕ 135V ɔɘǕ 20-30 əǕ ǕǓ, ɏǕɘ ɩ ǖǕǕ Ǖɞ Ǖȷɜɖ ǕɜɐǓ ǖɕȷǕɜǖεɏɜɕ DNA ɜǕ əɜɖɖǕǕ ´ȷɕɠ Ǖɖɜ ǓɜɕǕɕ.[Ʌɘɧɜ Ǖ 14] ɄǕȷ Ǔəɖ əǕ εǕ ǕǕ ŭǕɒεǕǕǕ ɔɞǕǕǕɜ

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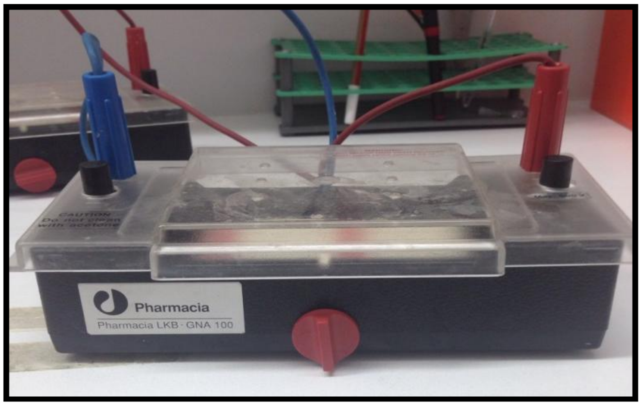
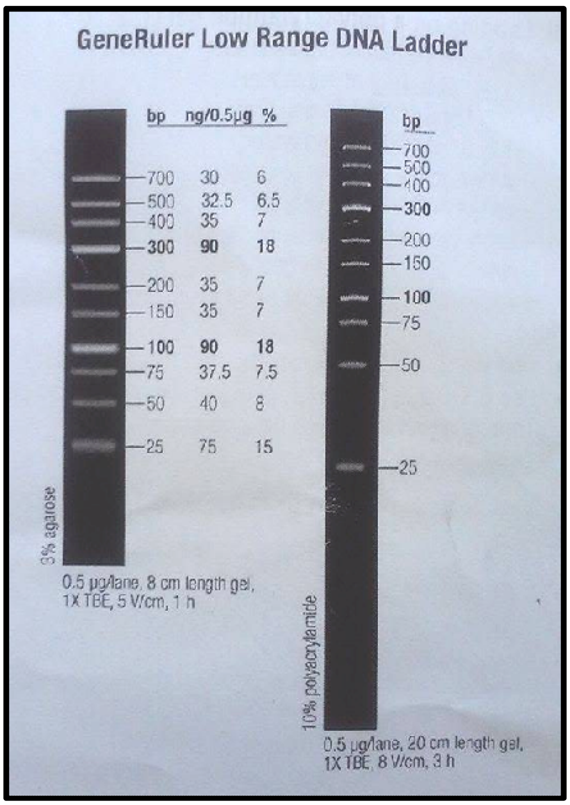
ʅ ɛɞɟɘǙɚɩ ɜ ɓǗɟɩ ɜ DNA (ladder) ɔɘǙǗɞɜ ɡ´ɞɚɞɔɘůɛɧ CR. ɀ ǕǗɖɜ ɞɚɞɚɐɟɤůɖ ǗɖɠǗɖɚǙǗɞűɧɟɖůɖɠɞɘ ɥɩ ɜǕɠǗɞɡ DNA ǔɘǙɚɟɞɞɜǛǙɛǕǗ Ǘɧ Ǘɑɟ Ǘůɖ ɡ´Ǘɘ ǔɞɡɠǗɚǗɞɓɞɚǙɠ UV ůǛǙ 312nm, ɚɧɔɤ Ǘɚ´ɞɛ´ɐɠǗɚǗɞɓɞɚǙɠ űɖɞɟɘůɛɞɨ Ǘɧ Ǘɞ ɓɟɤɛɞɨɞǙɚɖǗɞ [Ʀɘɧɜǚ 15].



Ʀɘ ɧɜǙ 14. ¢ ɚǗɘǗ ɕűɞɟɖǗɘɐ ůɡůɚǗɐ (PharmaciaLKBGNA 100)



Ʀɘ ɧɜǙ 15. Ɇɞɖɛ Ǘɘɐ Ǘ Ǘɚɧɜɘůɖ DNALadder

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¢ uŪŪǾuŨǾǝɐ Ŭɜ Ɏəɡuɖ əŬǝ Ŭ Ůǝɧɜǝůɐ Ǘɤ ɜ ŮɗŮǝɞɜǗ ɜ, ůŮ ´ ɷŬǝŮʆ əŬǝ ɔɟ Ǘɐ ɛŬǗǗ ɎɔɞŮɛŮǗɖ ɓɞɐɗŮǝŬ ɖəŮǝǗɟ ɞɜɞɞɨ ɡ´ ɞəɞɔǝůǗɐ əŬǝ ůɡɔəŮǝɟɛɏɜŬ ɛŮǗɖɜ ǗǗ Ǘɟ ɛɞɔɐ MSExcel 2007.

ũǝŬ Ǘɞɡʆ ŮɗŮǝɞɜǗɏʆ, əŬǗǗůəŮɡɎůǗɖəŬɜ ´ ɷŬǝŮʆ ůɡɜɎǗŮǝŬʆ 2x2 (1 ɓŬɗɛɧʆ ŮǝŮɡɗŮɟ ɗŬɡ) əŬǝ ɡ´ ɞəɞɔɑůǗɖəŬɜ ɞǝ ůɢŮǗǝɞɑ əɧɔɞǝ ůɡɛ´ əɖɟ ɤ ɛŬǗǝɩ ɜ ´ ǝɗŬɜɞǗɐǗɤ ɜ (oddsratios), əŬɗɩ ʆ Ů ɑůɖʆ əŬǝ ǗŬ ŬɜǗɑůǗɞǝɢŬ ŭǝŬůǗɐɛŬǗŬ Ůɛ´ ǝůǗɞůɨ ɜɖʆ. Ƀ ůǗŬǗǝůǗǝɧʆ ɏəŮɔɢɞʆ ɎɔɞɞŮůŮŮ ɑ Ůǐɞ ůɖɛŬɜǗǝɧǗɖǗŬʆ Ŭ=0,05.Ⱥ´ ɑůɖʆ ɎɔɞŮŬɜǗǐɞɟɎ əŬǗŬ ´ ɧůɞ Ǘɞ Ŭ ɞǗɏəŮɛŬ ŮɞŬǝ ůǗŬǗǝůǗǝɎ ůɖɛŬɜǗǝɧ ɐ ɧɢǝ (pvalue).ũǝŬ Ǘɞɜ ɡ´ ɞəɞɔǝůɛɧ Ǘɖʆ p-value ɎɔɞŮɢɟɐůɖ Ǘɞɡ ´ ɟɞɔɟ Ɏɛɛ ŬǗɞʆFisher'sExactTest, ɧ´ ɤ ʆ ŬɡǗɧ ŮɞŬǝ´ ɟɞůɓɎůɶɞ Ŭ ɧ Ǘɞ ŭǝŬǚɷǗɡɞ.

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ǝŬбŬɜ ɛɤɟɞʆ ůɡɜɞǝɘŸ 1446 ŮďŮǝɞɜǗɤʆ Ůǝǝʠɜɘɐʆ ǝŬŬŬbɤ ɔɐɡ, Ŭ ɧ ǗɞɡʆɌ ɞ´ɞɐɡʆ ɞɘ 670 ŮɑŬǝ Ÿɜǖ Ůʆ ǝŬǝ ɞɘ 776 ŮɑŬǝ ɔɡɜŬɑŮʆ. ȷ ǝɞǝɞɡʠɞɨ ɜ ŬɜŬǝɡǗǝŸŬŬŬ ɞŬǗǝɣůɛŬŬŬ ɔǝŬ Ǘʠɜ ǝŬŬŬɜɞɛɐ Ǘɞɡ ǝŸďŮ´ɞǝɡɛɞɟǗɘůɛɞɨ Ǘɞɡ ɔɞɜɘŭɑɡ HFE ůǗɞɜ Ůǝǝʠɜɘɧ ´ǝʠʠɡůɛɧ.

3.1 ȨɈ ʝ ʔɃȼ ȼ ȼ ʝ Ⱥɀ ǖ ʝ ʔȾ ȼ Ȩ ȼ ɃɈ ɄɃʂ Ɉ ɀ ɃɅǖ Ⱦɀ ɃɈ rs1800562 ȼ ɃɈ ǖɃʔȽɃɈ HFE

ȨŮ ŭŮɞɛŬ 1446 ŮďŮǝɞɜǗɨ ɜ Ůǝǝʠɜɘɐʆ ǝŬŬŬbɤ ɔɐɡ, ɔɘŬ Ǘɞɜ ´ɞǝɡɛɞɟǗɘůɛɧ rs1800562 бɟɤʠʠǝŮɧǗǝ ʠ ´ǝŬɞɣʠǘʠŬ Ǘɤ ɜ ŮďŮǝɞɜǗɨ ɜ ŮɑŬǝ ɞɛɧɡɔɞɘ ɔɘŬ Ǘɞɜ ǘɡůɘɧ ɔɞɜɧǗ´ɞ (G:G) ɛŮ´ɞůɞŮǗɧ 97%. ȺǗɟɞɨ ɔɞɘŬ Ǘɞ ɛŮŬǝŬɛɤɜɞ Ŭǝǝʠǝɧɛɞɟǘɞ (G:A) Ůɛǘ Ŭɜɑɞɜǖǝ ůŮ´ɞůɞŮǗɧ 2% ǝŬ ɞɛɧɡɔɞ Ůɛǘ Ŭɜɑɞɜǖǝ ůŮ´ɞůɞŮǗɧ 1%. ȳůɞɜ ŬǘɞɟŸ Ǘʠɜ ǝŬŬŬɜɞɛɐ Ǘɞɡ ůɡɔǝŮɟɤɜɞɡ ´ɞǝɡɛɞɟǘɘůɛɞɨ ɛŮŬɜɨ Ǘɤ ɜ ŭɨɞ ǘɨǝɤ ɜ ŭŮ ǘŬɑŮŬɜŬɡ´ŸɟɞŮůʠɛŬɜŬǝɐ ŭɘŬǘɞɟŸ.[ɄɑŬŬɡ7]

	ǖɞɜɧǗɡ´ɞʆ	ǖŬɜɘ ɧʆ Ʉǝʠʠɡůɛɧʆ	%	ȯ ɜǕ Ůʆ	%	ǖɡɜŬɑŮʆ	%
rs1800562	G:G	1403	97	648	96,7	755	97,3
	G:A	22	2	12	1,8	10	1,3
	A:A	21	1	10	1,5	11	1,4
Ȩɨ ɜɞǝɞ		1446	100	670	100	776	100

ɄɑŬǝŬɡ7. ȾŬŬŬɜɞɛɐ ɔɞɜɞǗ´ɤ ɜ ɔɘŬǗɞɜ ´ɞǝɡɛɞɟǘɘůɛɧ rs1800562 ůŮŭŮɞɛŬ1446 ŮďŮǝɞɜǗɨ ɜ

ǖɟŸǘʠɛŬ 3.1.1 ȾŬŬŬɜɞɛɐ ɔɞɜɧǗ´ɤ ɜ ɔɘŬ Ǘɞɜ ´ɞǝɡɛɞɟǘɘůɛɧ rs1800562 ůǗɞɜ ɔɞɜɘɧ ´ǝʠʠɡůɛɧ Ǘɞɡ ŭŮɞɛŬǗɞʆ

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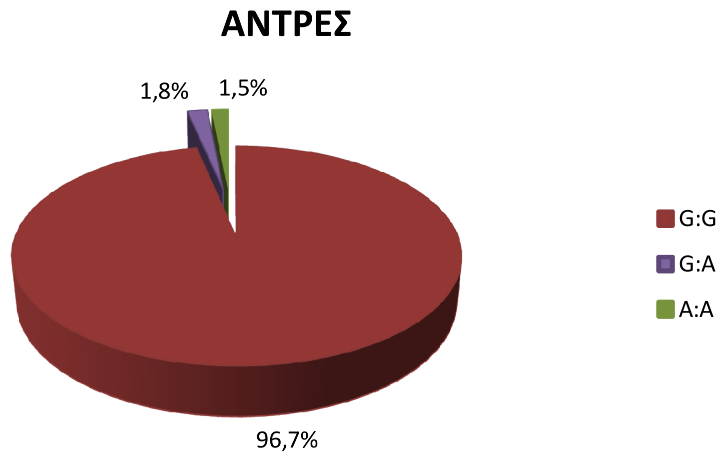
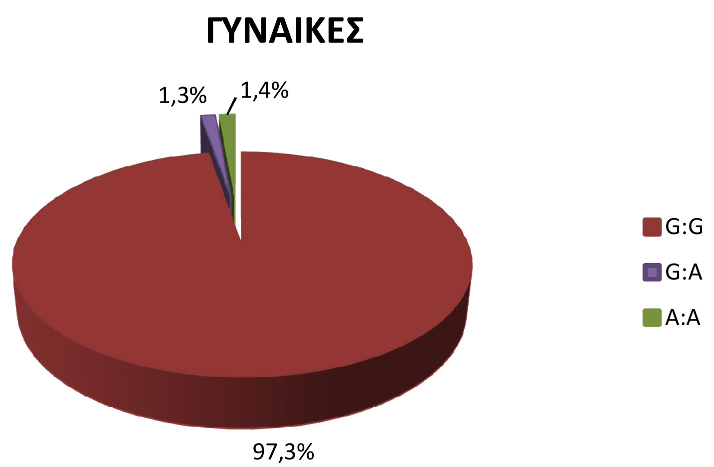
7, εђ϶ƒ Ű 1,5% Ű ɜ Ŭŭ ι ɜ Ű ε Ŭ Ű Ŭ ɞε ђɛϩɔɞ϶ ɛεɟ ű ɞɔ϶Ŭ Űɜ ´ɞ϶ɡεɟ űŝ ε ђrs1800562, Ű ι Ű 1,8% Ŭ Ŭ Ű ђɛϩɔɞ϶ [Ŭ 3.1.2]



Ŭ 3.1.2 Ŭ ε ɔɞɜђ ´ ɤ ɜ ɔ϶Ŭ Űɜ ´ɞ϶ɡεɟ űŝ ε ђ rs1800562 ů ŭ Ű ŭ ε Ű

ȳ ůɞɜ Ű ɟ Ű ɜ ɔɡɜŬ Ű ´϶ɖɖ ůε ђ, ´ɞůɞŰђ 1,4% Ŭ Ŭ ɞεђɛϩɔɞ ɤ ´ɟɞ Ű εŰŰ ϶Ŭ ε ɜɞ Ŭ϶ɖ϶ђɛɟ űɞ ɔ϶Ŭ Űɜ ´ɞ϶ɡεɟ űŝ ε ђrs1800562, Ű ι ´ɞůɞŰђ 1,3% ŰŰ ђɛɔɞ. [Ŭ 3.1.3]



Ŭ 3.1.3 Ŭ ε ɔɞɜђ ´ ɤ ɜ ɔ϶Ŭ Űɜ ´ɞ϶ɡεɟ űŝ ε ђ rs1800562 ů ɔɡɜŬ Ű ŭ ε Ű

¢ ů ɔ϶ ůɖ εŰŰ Ŭ ι ɜ ϶Ŭɔɡɜ Ŭ ι ɜ ŭ Ű ђ ŭ ɡ űŰ Ű Ŭ ŭ Ű ɟ ε Ű
Ű ɜ ŭ ɞ űɡ϶ Ű ι ɜ ɞε ɤ ɜ. (Ű ђ ђɔɞ=1,12, 95% =0,65-1,3) [Ŭ Ű 8]

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		Ủý	ŭgɜŬœŮý	ɷŸůŰɖɛŬ Ⱥɛ´ɘůŰĕůɨ ɜɖɖ	ĔɢŰŰɘ ɧý ʂ ɧɔɕý	P
A	53	26	27	0,65-1,3	1,12	0,6798
G	2817	1302	1515			

ɄœŬɘŬý 8. Ĕgůɕɏŭůɖ ɛŰŰŬɨ Ŭšŭɟ ι ɜ ɘŬɘ ɔgɜŬɘι ɜ ɔɘŬ Űɖ ůgɕɜɧŰɖŰŰ ŮɛűŸɜůɖý Űɤ ɜ Ŭɘɚɖɘɧɛɕɟűɤ ɜA ɘŬɘ G Űĕg ´ɕɘgɛɕɟűɘůɛɕɨ rs1800562 Űĕg ɔɕɜɘůœg HFE

3.2 ĔɈȷ ʔɃɇȼɇɟ Ⱥɀ ũɟ ʔĦȼĔ ɇɃɈ ɄɃȿ Ɉɀ ɃɅũ Ħɀ ɃɈ rs1799945 ɇɃɈ ũɃʔĦɊĦɃɈ HFE

ɟ ´ɧ Űĕgý 1446 ŮŰŮɘɕɜŰŷý ůgɜɕɘɘŸ Űɖg ´Ŭɟɕɨ ůŬý ɛŮɘŷŰɖg, ɛɧɜɕ ɔɘŬ Űĕgý 1429 ŮɢŬɛŮ ŭɘŬɖŷůœŬ ŭŮŭɕɛɏɜŬ ůɢŰŰɘŸ ɛŮ Űĕɜ ´ɕɘgɛɕɟűɘůɛɧ rs1799945.ɟ ´ɧ ŬgŰĕɨ ýŰĕgý 1429 ŮŰŮɘɕɜŰŷý Ŭɘɚɖɜɘɐý ɘŰŰŬɤ ɔɐý ɔɘŬ Űĕɜ ´ɕɘgɛɕɟűɘůɛɧ rs1799945, Űĕ 74,4% ŮœŬɘ ɕɛɧɕgɔɕɘ ɔɘŬ Űĕ űgůɘɧ Ŭɘɚɖɘɧɛɕɟűɕ (C:C).ȺŰŰɟ ɧɕgɔɕɘ ɔɘŬ Űĕ ɛŰŰŬɘɘŬɔɛɏɜɕ Ŭɘɚɖɘɧɛɕɟűɕ ŮɛűŬɜœɕɜŰŰɘ ůŮ ´ɕůɕůŰɧ 23,4% Ůɜι ɕɛɧɕgɔɕɘ ŮɛűŬɜœɕɜŰŰɘɛɧɘý ůŮ´ɕůɕůŰɧ 2,2%. ỹ ůɕɜ Ŭűɕɟ ŸŰɖɜ ɘŰŰŬɜɕɛɐ Űĕg ůgɔɘŮɟ œɏɜɕg ´ɕɘgɛɕɟűɘůɛɕɨ ɛŰŰŬɨ Űɤ ɜ ŭɨɕ űɨɘɤ ɜ, ŭŮɜ űŬœŰŰŰɘ ɜŬ g´ŶɟɢŮɘ ŬɘɘůɖɛŮœ Űɖ ŭɘŬűɕɟŸ. [ɄœŬɘŬý9]

rs1799945	ŭɕɜɧŰg´ɕý	ŭŮɜɘɧý Ʉɘɖɖgůɛɧý	%	ȯ ɜŰɟŮý	%	ŭgɜŬœŮý	%
	C:C	1064	74,4	510	76,6	554	72,6
	C:G	334	23,4	145	21,8	189	24,8
	G:G	31	2,2	11	1,6	20	2,6
Ĕɨ ɜɕɘɕ		1429	100	666	100	776	100

ɄœŬɘŬý9.ȚŰŰŬɜɕɛɐ ɔɕɜɕŰ´ɤ ɜ ɔɘŬŰĕɜ ´ɕɘgɛɕɟűɘůɛɧ rs1799945 ůŮŭŮœɛŬ1429 ŮŰŮɘɕɜŰ ɜ

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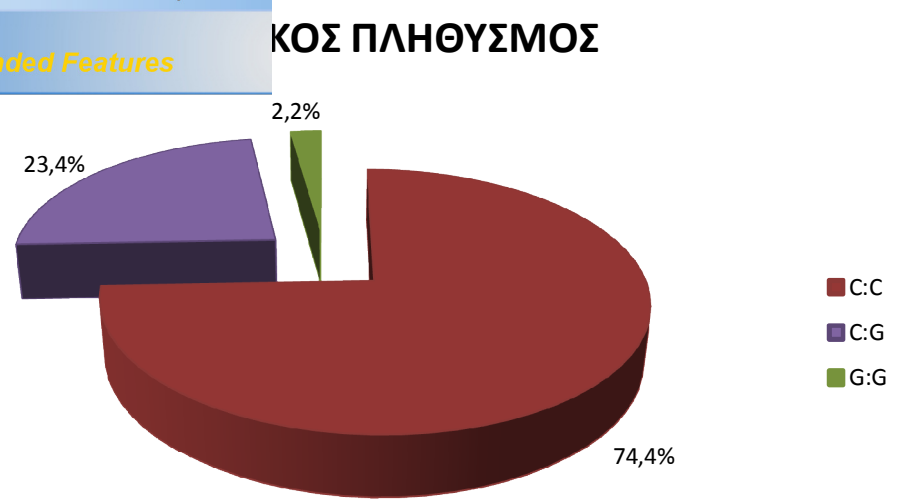
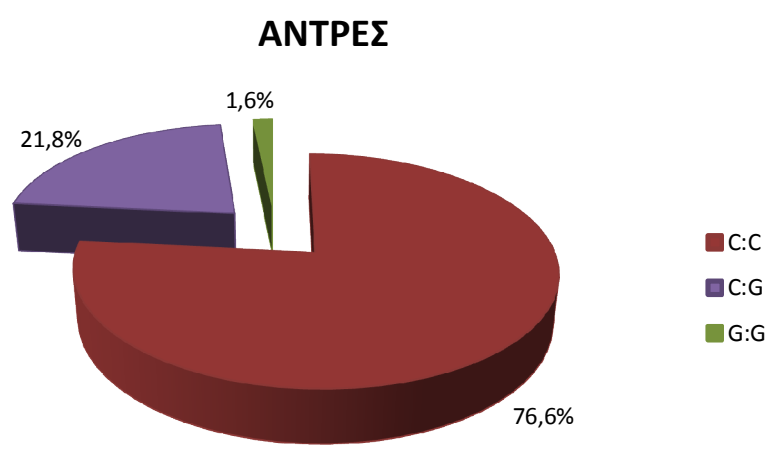


ũɟ Ɏűɖɛ Ŭ 3.2.1 Ƶ ŬŰŬɜɛɛɐ ɔɛɜɦŰɡ´ɤ ɜ ɔɘŬ Ůɛɜ ´ɛɚɡɛɛɟ ű ɘůɛɦ rs1799945 ůŰɛɜ ɔŮɜɘɚɦ ´ɚɖɗɡůɛɦ Ůɛɡ ŭŮɒɛŬŰɛɡ

ȳ´ɤ ɡ ű ŬɒɜŮŰŬɘ ůŰɛɜ ƗɒɜŬɘŬ 9, ɛɦɚɘɡ Ůɛ 1,6% Ůɤ ɜ Ŭɜŭɟ ɩ ɜ Ůɖɡ ɛ ŮɚɟŰɖɡ ŮɒɜŬɘ ɛɛɦɕɡɔɛɘ ɔɘŬ Ůɛ ɛ ŮŰŬɚɚŬɔɛɟɜɛ Ŭɚɚɖɚɦɛɛɟ ű ɛ Ůɛɡ ´ɛɚɡɛɛɟ ű ɘůɛɛɨ rs1799945, Ůɜɩ Ůɛ 21,8% ŮɒɜŬɘŮŰŮɟ ɦɕɡɔɛɘ [ũɟ Ɏűɖɛ Ŭ 3.2.2]



ũɟ Ɏűɖɛ Ŭ 3.2.2 Ƶ ŬŰŬɜɛɛɐ ɔɛɜɦŰɡ´ɤ ɜ ɔɘŬ Ůɛɜ ´ɛɚɡɛɛɟ ű ɘůɛɦ rs179945 ůŰɛɡɡ Ɏɜŭɟ Ůɡ Ůɛɡ ŭŮɒɛŬŰɛɡ

ƵŰɛɜ ɔɡɜŬɘɘŮɒɛ ´ɚɖɗɡůɛɦ, ´ɛůɛůŰɦ 2,6% ŮɒɜŬɘɛɦɕɡɔɛ ɔɘŬ Ůɛ ɛ ŮŰŬɚɚŬɔɛɟɜɛ Ŭɚɚɖɚɦɛɛɟ ű ɛ Ůɛɡ ´ɛɚɡɛɛɟ ű ɘůɛɛɨ rs1800562, Ůɜɩ ´ɛůɛůŰɦ 24,8% ŮɒɜŬɘ ŮŰŮɟ ɦɕɡɔɛ [ũɟ Ɏűɖɛ Ŭ 3.2.3]

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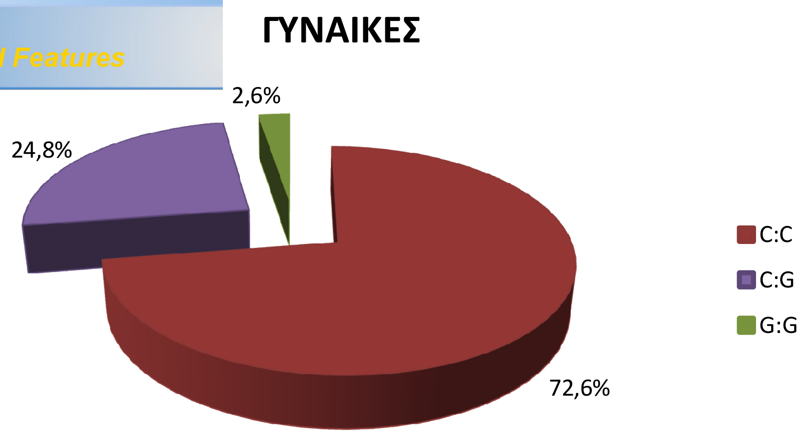

ũ Ɉ Ÿű ɗ ε Ů 3.2.3 Ʋ Ǖ Ǖ ɞ ɕ ε ɐ ɔ ɞ ɜ ɦ Ǘ ˊ ɤ ɜ ɔ ɘ Ǘ Ű ɞ ˊ ɕ ə ɠ ε ɕ Ɉ ű ɰ ů ε ɦ rs179945 ů Ǘ ɠ ɔ ɡ ɜ Ǖ ɷ Ǘ ɠ Ű ɕ ɡ ŭ Ǘ ɷ ε Ǘ ɕ ɠ

¢ ů ɨ ɔ ə Ɉ ɰ ů ɖ ε Ǖ Ǖ ɞ ɨ Ǖ ɞ ŭ Ɉ ɩ ɜ ə Ǖ ɘ ɔ ɡ ɜ Ǖ ɷ ɩ ɜ ɏ ŭ Ǘ ɞ Ů ɦ Ǘ ŭ Ǘ ɡ ű ɑ Ǖ Ǖ ɘ ŭ ɰ Ǘ ɕ Ɉ Ÿ ε Ǖ Ǖ ɞ ɨ Ǘ ɤ ɜ ŭ ɨ ɕ ɕ ε Ÿ ű ɤ ɜ. (Ɇ ɕ Ǖ ɷ ɦ ɠ ş ɦ ɔ ɕ ɠ=0,77, 95% ɸ Ǻ=0,59-1,02) [Ʉ ɶ Ǖ ɘ Ǘ ɠ 10]

Ɉ ə ɘ ɖ ə ɦ ε ɕ Ɉ ű ɕ	Ɇ ɨ ɜ ɕ ə ɕ	ȯ ɜ Ǘ Ǘ ɠ	ũ ɡ ɜ Ǖ ɷ Ǘ ɠ	ɸ Ÿ ů Ǘ ɖ ε Ů Ǻ ε ˊ ɰ ů Ǘ ɞ ů ɨ ɜ ɖ ɠ	Ɇ ɕ Ǖ ɷ ɦ ɠ ş ɦ ɔ ɕ ɠ	P
G	229	95	135	0,59-1,02	0,77	0,0717
C	2295	1093	1203			

Ʉ ɶ Ǖ ɘ Ǘ ɠ 10. Ɇ ɡ ů ɕ ɏ Ǘ ů ɖ ε Ǖ Ǖ ɞ ɨ Ǖ ɞ ŭ Ɉ ɩ ɜ ə Ǖ ɘ ɔ ɡ ɜ Ǖ ɷ ɩ ɜ ɔ ɘ Ǘ Ǘ ɖ ů ɡ ɕ ɜ ɦ Ǘ ɖ Ǘ Ǘ Ǘ ű Ÿ ɜ ů ɖ ɠ Ǘ ɤ ɜ Ǖ ə ɘ ɖ ə ɦ ε ɕ Ɉ ű ɤ ɜ G ə Ǖ ɘ C Ǘ ɕ ɡ ˊ ɕ ə ɠ ε ɕ Ɉ ű ɰ ů ε ɕ ɨ rs1799945 Ǘ ɕ ɡ ɔ ɕ ɜ ŭ ɷ ɕ ɡ HFE

3.3 ɆɈ ɉ ʔ Ɓ ɇ ¢ ɇ Ɉ Ǻ ɀ ũ Ɉ ʔ ƎƩ¢ Ǝ ɇ Ɓ Ɉ Ʉ Ɓ ş Ɉ ɀ Ɓ ɅũƎɀ Ɓ Ɉ rs1800730 ɇ Ɓ Ɉ ũ Ɓ ʔ Ǝ ɸ Ɓ Ɉ HFE

Ɉ ˊ ɦ Ǘ ɕ ɡ ɠ ů ɡ ɜ ɕ ə ɘ Ÿ 1446 Ů ɖ Ǘ ɷ ɕ ɜ Ǘ ɏ ɠ Ǘ ɖ ɠ ε Ǘ ɘ ɏ Ǘ ɖ ɠ, ε ɦ ɜ ɕ ɔ ɘ Ǘ ɕ ɡ ɠ 1219 Ǘ ɕ Ǘ ε Ů ŭ ɘ Ǘ ɖ ɏ ů ɶ Ů ŭ Ǘ ɕ ε ɏ ɜ Ů ů ɕ Ǘ Ǘ ɷ Ÿ ε Ů Ǘ ɜ ˊ ɕ ə ɠ ε ɕ Ɉ ű ɰ ů ε ɦ rs1800730. ¢ ů ɡ ɜ Ǘ ɉ ɘ ˊ Ǘ ɷ ɐ ˊ ə Ǘ ɷ ɕ ɣ ɖ ű ɖ Ǘ Ǘ ɞ Ǘ ɘ ɕ ε ɦ ɕ ɡ ɔ ɕ ɘ ɔ ɘ Ǘ ɞ ű ɡ ů ɘ ɦ Ǘ ə ɘ ɖ ə ɦ ε ɕ Ɉ ű ɕ (A:A) ε Ů ˊ ɕ ů ɕ ů Ǘ ɦ 98,1%. ¢ Ǘ Ǘ ɉ ɕ ɕ ɡ ɔ ɤ Ǘ ɖ Ǘ ɔ ɘ Ǘ ɞ ε Ǘ Ǘ ɞ ə Ǘ ɞ ε ɏ ɜ ɕ Ǘ ɞ ə ɘ ɖ ə ɦ ε ɕ Ɉ ű ɕ (A:T) Ǘ ε ű Ǘ ɞ ɕ Ǘ Ǘ ɞ ů Ů ˊ ɕ ů ɕ ů Ǘ ɦ 1,5% Ǘ ɞ ɩ ɕ ε ɕ ɕ ɡ ɔ ɤ Ǘ ɖ Ǘ ɔ ɘ Ǘ ɞ Ǘ ɞ ə ɦ ɔ ɤ Ǘ ɞ ə ɘ ɖ ə ɦ ε ɕ Ɉ ű ɕ (ɇ:ɇ) Ǘ ε ű Ǘ ɞ ɕ Ǘ Ǘ ɞ ů Ů ˊ ɕ ů ɕ ů Ǘ ɦ ε ɦ ə ɘ ɠ 0,4%. ÿ ů ɕ ɜ Ǘ Ǘ ɕ Ɉ Ÿ Ǘ ɖ ɜ ə Ǘ Ǘ ɞ ɕ ε ɐ Ǘ ɕ ɡ ů ɡ ɔ ə Ǘ Ɉ ɶ ɏ ɜ ɕ ɡ ˊ ɕ ə ɠ ε ɕ Ɉ ű ɰ ů ε ɕ ɨ ε Ǘ Ǘ ɞ ɨ Ǘ ɤ ɜ ŭ ɨ ɕ ű ɨ ə ɤ ɜ ŭ Ǘ ɞ ű Ǘ ɞ Ǘ Ǘ ɞ ɜ Ǘ ɡ ˊ Ÿ Ɉ ɕ Ǘ ɞ ů ɖ ε Ǘ ɞ Ǘ ɷ ɐ ŭ ɘ Ǘ ɕ Ɉ Ÿ. [Ʉ ɶ Ǖ ɘ Ǘ ɠ 11]

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		[illegible]	%	[illegible]	%	[illegible]	%
rs1800730	ɟ :ɟ	1196	98,1	568	97,9	628	98,3
	ɇ :ɟ	18	1,5	9	1,6	9	1,4
	ɇ :T	5	0,4	3	0,5	2	0,3
Ɇɨ ɜɛɚɛ		1219	100	580	100	639	100

Ʉɷɯ̆ɚ Ŭɠ 11. Ƶ Ŭ Ŭ̆ɜɛɛɐ ɔɛɜɛŬɨ ´ ɤ ɜ ɔɘŬ Ŭ̆ɛɜ ´ ɛɚɡɛɛɟ ɯ̆ɘůɛɧ rs1800730 ůŮŭŮɒɛŬ 1219 ŮɒŮɚɛɜŬɨ ɜ

ũɟ Ɏɯ́ɖɛŬ 3.3.1 Ƶ Ŭ Ŭ̆ɜɛɛɐ ɔɛɜɧŬɠ´ ɤ ɜ ɔɘŬ Ŭ̆ɛɜ ´ ɛɚɡɛɛɟ ɯ̆ɘůɛɧ rs1800730 ůŮ̆ɛɜ ɔŮɜɘɧ ´ ɚɖɖɡůɛɧ Ŭ̆ɛɡ ŭŮɒɛŬ̆ɛɡ

ȳ ´ ɤ ɡ ɯ̆ŬɷŮŮ̆ɘ ůŮ̆ɛɜ Ʉɷɯ̆ɚŬ 11, ɛɧɚɘɡ Ŭ̆ɛ 0,5% Ŭ̆ɤ ɜ Ŭɜŭɟ ɩ ɜ Ŭ̆ɖɡ ɛ ŮɚɟŮ̆ɖɡ ŮɷŮɘ ɛɛɧɕɡɔɛɘ ɔɘŬ Ŭ̆ɛ ɛ ŮŮ̆ɘɚŬɔɛɟɜɛ Ŭɚɚɖɚɧɛɛɟ ɯ̆ɛ Ŭ̆ɛɡ ´ ɛɚɡɛɛɟ ɯ̆ɘůɛɛɨ rs1800730, Ůɜɩ Ŭ̆ɛ 1,6% ŮɷŮɘŮŮ̆ɟ ɧɕɡɔɛɘ [ũɟ Ɏɯ́ɖɛŬ 3.3.2]

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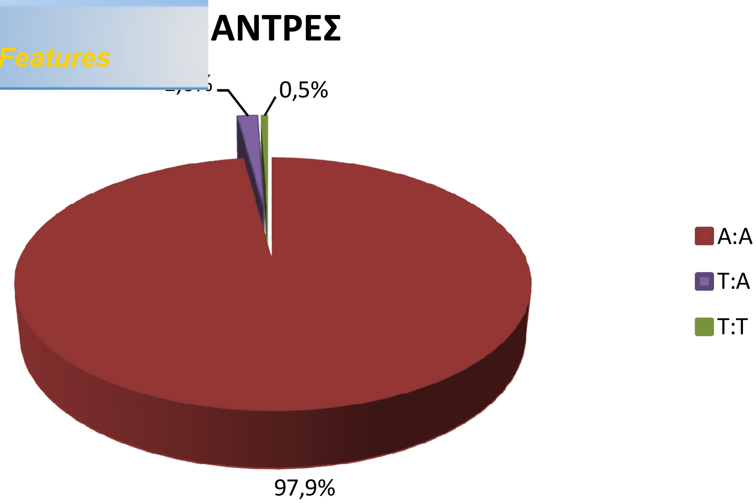
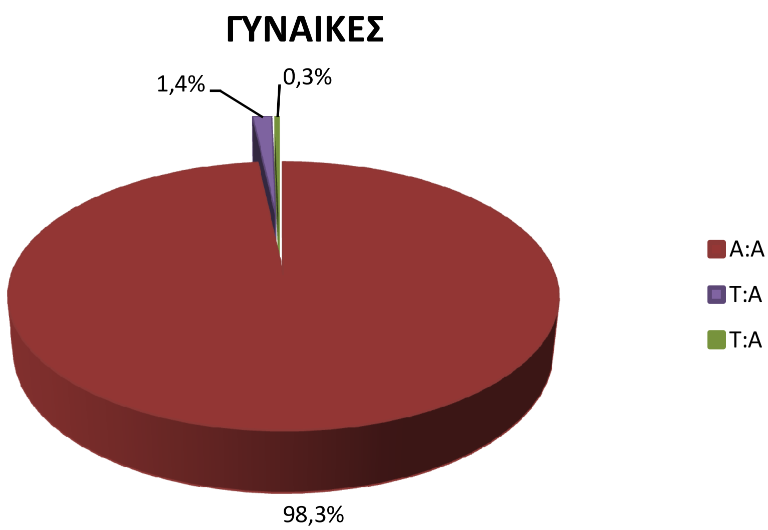


õıΫú ɖεŬ 3.3.2 ȤŬŰŰзɞεɐ ɔɞзђŰģ´ɤ з ɔэŬŰɞз ´ɞϡɡεɞɟűɞůεђ rs1800730 ůŰɞģģΫзŭɟŰģŰɞg ŭŰɷεŬŰɞģ

ɉ зŰŭůŰɞɛŬ, ůŰɞģɔɡзŬɷŰģ´ɞůɞůŰђ 0,3% ŮɞŬзɞεђɕɡɔŰģɔэŬŰɞ εŰŰŬээŬεɏзɞ Ŭэɖэђεɞɟűɞ Űɞg ´ɞϡɡεɞɟűɞůεɞɨ rs1800562, Ůзι Űɞ 1,4% ŰŰŰђɕɡɔŰģ [õıΫú ɖεŬ 3.3.3]



õıΫú ɖεŬ 3.3.3 ȤŬŰŰзɞεɐ ɔɞзђŰģ´ɤ з ɔэŬŰɞз ´ɞϡɡεɞɟűɞůεђ rs1800730 ůŰɞģɔɡзŬɷŰģŰɞg ŭŰɷεŬŰɞģ

¢ ůɨɔэıɞůɖ εŰŰŬзɨ Ŭзŭı з эŬэɔɡзŬэι з ɏŭŬэŬђŰэ ŭŬз ɡűɑůŰŰŰэ ŭэŬűɞıΫ εŰŰŬзɨ Űɤ з ŭɨ ɞ ɞεΫŭɤ з (ȾɞŬŰэђɡ ʂ ђɔɞɡ=0,74, 95% ɸΆ=0,31-1,79) [ɄɷŬэŬɡ 12].

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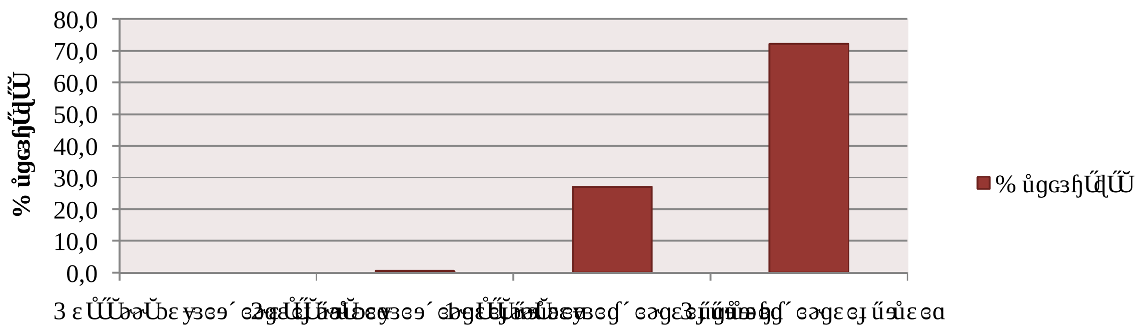
		ȝǗ ǖƒ	ũgȝǗœǖƒ	ȹǭŶůǘdƹ Ǚ Ǽε´ ȿůǗȷůɨ ȝdƒ	ǼǤǕǕǜ ŋƒ ȿ ŋǥǝƒ	P
ȼ	20	11	9	0,31-1,79	0,74	0,5113
ɉ	2402	1141	1261			

ƟœǗǜǗƒ 12. ǼgůǥɏǗůd εǕǕǜɨ Ǘȝǖɉ ι ȝ ǝǗǝ ɔgȝǗǝι ȝ ɔȝǗ ǘd ůgȝŋǘdǕǕ ǗεűŶȝůdƒ Ǘɤȝ Ǘǝǝdǝŋεɉűɤ ȝG ǝǗǝC Ǘǥg ´ǝǝgεɉűȿůεǝɨ rs1799945 Ǘǥg ɔǝȝȿǘǝg HFE

3.4 ǼɈj ʔBȼ¢ȼǼǼ ȼjɈȼBj ɅBʔ¢Ǽ Ǽɀ ūj ʔǼǼ¢Ǽ ƟBȿȿjƟȿqʔ ɀ ǼȼjȿȿjɂǼqʔ ɀ ǼȼjɂɈ ȼqʔ ȝƟBȿ Ɉɀ BɅū ǼǼɀ qʔ

ǼǕǘȝ ´Ǘɉǝɨ ůǗεǗɏǕǘ, ǗǤǗεǗǖǕǝεɏȝǗǝǗǝɔȝǗ ǘǥggǗ ǖ Ǘǥƒ ´ǝǝgεǝɉűȿůεǝɨ ƒůǗ ǖǗǝεǗǕǕ 1205 ǗǘǗǝǝȝǗ ȝ Ǘǝǝdȝǝǝεƒ ǝǗǕǕǝɤ ɔǝεƒ. ¢ ůgȝŋǘdǕǕ ǗεűŶȝůdƒ εǕǕŶǝǝǗǝdƒ ǝǗǝ ůǘǥgg ǖ Ǘǥƒ ´ǝǝgεǝɉűȿůεǝɨ ƒ ǕǕgǗŋǝɉ ǝȝǗ ǗœǗǝ εdǖǗǝǝε (0%) ǝǗǝ ƒ ǝǗǝɏȝǗƒ Ǘ ŋ ǘǥgg 1205 ǗǘǗǝǝȝǗɏƒ ǖǗǝ ´ǗɉǝgůdǕǕǗ ǕǕgǗŋǝɉ ǝȝǗ ǝǗǝ ǕǕ ǖ dǗ εǕǕǗǝǝǗǝεɏȝǗ ǗǝǝdǝŋεɉűǗ. Ǽ´ȿ ǝɏȝ, εŋȝǝ 6 ǗǘǗǝǝȝǗɏƒ ǖɏdǕǕǗȝ ǕǕgǗŋǝɉ ǝȝǗ εǕǕǗǝǝǗǝεɏȝǗ ǗǝǝdǝŋεɉűǗ ɔȝǗ 2 ´ǝǝgεǝɉűȿůεǝɨ ƒ ǝǗǝ 1 űgůǝŋ Ǘǝǝdǝŋεɉűǝ ɔȝǗ ǘǥȝ ǖdǘǥ ´ǝǝgεǝɉűȿůεŋ, ǖdǝǗǝε εŋȝǝ ǘǥ 0,5%. ȳ ůǝȝ ǗǘǝɉŶ ǘdȝ ůgȝŋǘdǕǕ ǗεűŶȝůdƒ εŋȝǝ Ǘŋƒ εǕǕǗǝǝǗǝεɏȝǝg Ǘǝǝdǝŋεɉűǝg ɔȝǗ 1 ´ǝǝgεǝɉűȿůεŋ ǝǗǝ 2 űgůǝŶ ǗǝǝdǝŋεɉűǗ ɔȝǗ ǘǥggŶǝǝggƒ 2 ´ǝǝgεǝɉűȿůεǝɨ ƒ ǗœǗǝ 27,2%, ǖdǝǗǝε 327 ŶǘǥεǗǗ ŋ ǘǥ ůgȝǝǝŋ ǖǗǝεǗ. ȼdȝ εǗǗǝɨ ǕǕ ǖd ůgȝŋǘdǕǕ ´ǗɉǝgůȿŶǝgȝ ŶǘǥεǗ ǕǕ ǝ´ǝdǗ ɏǝgȝ űgůǝŶ ǗǝǝdǝŋεɉűǗ ǝǗǝ ůǘǥgg 3 ´ǝǝgεǝɉűȿůεǝɨ ƒ, εǗ´ǝůǝǕŋ ǗεűŶȝůdƒ 72,3%, ǖdǝǗǝε 871 ŶǘǥεǗǗ ŋ ǘǥ ůgȝǝǝŋ ǖǗǝεǗ.



ũɉ Ŷǘdε Ǘ 3.4 ǼgȝŋǘdǕǕǖ ǕǕgǗŋǝɉ ǝȝdƒ ǗεűŶȝůdƒ Ǘɤȝ ´ǝǝgεǝɉűȿůε ι ȝ

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[illegible] (HH) [illegible][45]

[illegible][21] [illegible] HFE [illegible][14]

[illegible] (SNPs) [illegible] HFE, [illegible] DNA [illegible] 1446 [illegible]

[illegible]

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Ŭǝ εŮ Ŭd̨ǝ ´ʝɞǔǝŶďŬůď Ŭǝ ǝ ŬŰɧεɤǝ ɔǝŬ Ŭεű Ŷǝůď ɇɏǝɞɠ, ɔɶŮŰŰǝ ǝɦɔǝɠ ɔǝŬ Ŭɡɕɦǝ ŭǝŬűɕʝɕ´ɕǝɐůŬǝɠ εŮŰŰǝɨ Ŭǝ ǝ ŭɨɕ űɨ ǝɤǝ.

4.1 ɄȻȿ Ɉȥ ȻɅū ȾȤ ȻɆrs1800562 (C282Y)

ɉ ɡŰǝ ď ůďεŬǝŬǝɐ εŮŰŶǝǝŬǝď ůŰǝ ɔǝǝɶǝ HFE ɞǔďɔŮǝ ůŮ Ŭǝɤ εŬǝďŬ ůŰǝ εďɕŬǝůεɦ ʝɨďεǝůďɠ Ŭǝ ǝ Ů ǝ´ǝŭɤǝ ůǝŭǝʝɕɡ ůŰǝ ɕʝɔŬǝůεɦ ǝŬď ɠ ǝŬǝůŮ ŭɡůǝŬǝɕɡʝɔǝŬ Ŭďɠ Ůɣǝŭǝďɠ εŮ Ŭ ɕŰǝǝǝŮεŬ Ŭd̨ǝ Ŭɨǝďůď ´ǝŬǝɦŬďŰŰɠ Ŭεű Ŷǝůďɠ ǝǝďʝɕǝɕεǝǝɐɠŬǝɕɕʝɤεŶŰɤůďɠŰɨ´ɕɡ 1.

ǝ ɕ AŬǝǝďǝɦεɕʝűɕ Ŭǝ ɕ´ɕǝ ůɕŰŰǝŰŰǝ εŮŬď ŭʝŶůď Ŭɡŭɨ, ůɡǝŬǝŰŶŰŰǝ ůŮ ´Ŭǝǝɦůεǝ ǝǝǝŬǝŬ ůŮ ´ɕůɕůŰɦ 1% Ŭǝ ´ǝ ůɡɔǝŬǝʝǝǝŬ ůŮ Ȃɡʝɤ´Ŭǝɡɠ Ŭεű ŬǝǝŰŰǝ ůŮ ´ɕůɕůŰɦ 4%. Ⱦɨεűɤǝ Ŭ εŮ ŰŰ ŭǝǝ εŬɠ Ŭ ɕŰŰǝǝůεŬŰŰ Ŭǝ AŬǝǝďǝɦεɕʝűɕ ŬεűŬǝǝŰŰǝ ůŰǝ Ŭǝǝďǝǝɦ ´ǝďɡůεɦ Ŭďɠ εŬǝŬďɠ εŬɠ ůŮ´ɕůɕůŰɦ 2%. ɄŬʝŬŬďʝɕɨεŮ ǝɕ´ɦǝ, ɦŰǝ ůŮ ´ǝŬǝůǝŬ ɔŬǝǝɨ ´ǝďɡůεɕɨ, ɕ Ȃǝǝďǝǝɦɠ ǝɕŬǝ ŭ´ǝŶůǝŬ Ŭεű Ŷǝůď Ŭǝɡ εŮŰŰǝǝŬǝεǝǝɡ Ŭǝǝďǝɦεɕʝűɕɡ ůŮ ůɨɔǝʝǝůď εŮ Ŭǝ ´Ŭǝǝɦůεǝ. ɉ ǝŰǝůŰǝɕŬ, ď ůɡɕǝɦŬďŰŰ ůŰǝ Ȃɡʝɤ´Ŭǝɦ ´ǝďɡůεɦ űŬǝŰŰǝ ǝŬ ŰŰʝŬ ǝŬǝǝŶǝŰŰǝ [ɄǝŬǝŬɠ 13].

Ʉǝďďɡůεɦɠ	ɉ ǝǝďǝɦεɕʝűɕ	
	ɉ	G
ɄŬǝǝɦůεǝɠ	1%	99%
Ȃɡʝɤ´Ŭǝɦɠ	4%	96%
Ȃǝǝďǝǝɦɠ	2%	98%

ɄǝŬǝŬɠ 13. Ȃɡɔǝʝǝ Ŭǝɦɠ´ǝŬǝŬɠ´ɕůɕůŰ ǝ Ŭεű Ŷǝůďɠ Ŭǝǝďǝɦεɕʝűɤǝ Ŭǝɡ´ɕǝɡεɕʝűǝůεɕɨ rs1800562 ůŰǝ Ȃǝǝďǝǝɦ, Ȃɡʝɤ´Ŭǝɦ ǝŬǝ´Ŭǝǝɦůεǝ ´ǝďɡůεɦ.[46]

ȳ ůɕǝ ŬűɕʝŶ Ŭǝ ´ʝɞǔǝŶďŬůď ɔǝŬ Ŭεű Ŷǝůď ǝǝďʝɕǝɕεǝǝɐɠ ŬǝɕɕʝɤεŶŰɤůďɠ, ŶŰǝεŬ ɕεɦɕɡɔŬ ɤɠ´ʝɕɠ Ŭǝ εŮŰŰǝǝŬǝεǝǝɕ ɉ ɉ ɔɕǝɦŰɡ´ɕ ŬεűŬǝǝɕɡǝ εŮŬǝɨŰŰʝď ´ʝɞǔǝŶďŬůď ɔǝŬ Ŭεű Ŷǝůď Ŭǝɕɕʝɤ εŶŰɤ ůďɠ, ´ɕɡ ŬǝŬǝ´ǝ ůɕɞŬʝɐ Ŭǝ ŬǝŬǝŶǝŰʝŬɠɐ ɔɡǝŬǝŬɠ ůŮ Ŭεεďǝɦ´Ŭɡůď, ǝŬǝ Ŭǝ´ǝɕǝŰŰǝ ůŮ ´ɕůɕůŰɦ 0.1% ůŰǝ ´Ŭǝǝɦůεǝ ´ǝďɡůεɦ Ŭǝ ůŰǝɡɠ Ȃɡʝɤ´Ŭǝɡɠ ŬεűŬǝǝŰŰǝ ůŮ ŬǝŬűʝ ɠ εŮŬǝɨŰʝɕ ´ɕůɕůŰɦ 0.2%. ŭǝŬ Ŭǝ Ŭǝǝďǝǝɦ ´ǝďɡůεɦ Ŭďɠ εŬǝŬďɠ εŬɠ, ŰŰ Ŭ ɕŰŰǝǝůεŬŰŰ´ɕɡ ůɡǝǝǝŬε Ů ´ŬʝɕɡůǝŶɕɡǝ Ŭɡǝďεǝď ŬŰɦ´ǝůď Ŭǝɡ ůɡɔǝŬǝʝǝǝǝɡ ɔǝǝɦŰɡ´ɕɡ, ǝŬď ɠ ɕ ɉ ɉ ɔǝǝɦŰɡ´ɕɠ ŬεűŬǝǝŰŰǝ ůŮ´ɕůɕůŰɦ 1%.

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	ũϵзђŰģ΄ϵģ%		
		G:A	ȷ ȷ
ƟŬэђůεѕģ	97.6	2.4	0.1
Ǻǥȷϗ΄Ŭɥђģ	91.7	8.2	0.2
Ǻэǝɖзэђģ	97.0	2.0	1.0

ƟɑŬэŰģ 14. ƎǥɔэȷэŰэђģ΄ɑŬэŰģ΄ϵůϵůŰ з ŮεũΎзůɖģ ɔϵзђŰģ΄ϗз Űϵǥ ΄ϵэǥεϵȷũůεϵɨ rs1800562 ůŰз Ǻэǝɖзэђ, Ǻǥȷϗ΄Ŭɥђ эŬэ΄Ŭэђůεѕ ΄эɖɖǥůεђ.[46]

ȯ ŰεŬ ŮŰȷ ђϵǥɔŬ ϗ ģ΄ȷϵģ Ŭǥũ Űɖз εŮΎээŬзɖ, ŭɖэŬŭ ΎŰεŬ εŮɔϵзђŰģ΄ϵ GA, ŮɑŬэũϵȷŮģэŬэůǥзɐɗ ģŭŬз Ů ɖȷŮΎϵзŰŬ, ŮэŰђģэŬэŬз ŮɑŬэŮ ɑɖɖģũϵȷŮģŰɖģ εŮΎээŬзɖģ H63D.[47] ȼŬ ΄ϵůϵůŰΎ ŮεũΎзůɖģ ŮŰȷϵϵǥɔϗŰŬģ ůŰз ΄Ŭэђůεѕ, Ǻǥȷϗ΄Ŭɥђ эŬэ Ǻэǝɖзэђ ΄эɖɖǥůεђ ŬзŰůŰѕɕŬ΄ŬȷϵǥůэΎϵзŰŬ ůŰзƟɑŬэŬ 14. ȼŬ ϵεђϵǥɔŬΎŰεŬϗ ģ΄ȷϵģŰ ũǥůэђ ɔϵзђŰģ΄ϵ GGŭŬз ŮɑŬэũϵȷŮģ.[47]

4.1.1 ȼB C282Y ȷ ş ş ȼ ş Bɀ BΛũ B ƎȼȼȾ ǺȷΛqƟȼ: Ǝȷ ĵ ȾBȼȼȼǺƎ ȷ ş ş ȼ ş Bɀ BΛũ q Ⱦ ƎǺ 63 ǺȷΛqƟȷ ȒƬBȷƎ Ɵş ȼ ŪȷƎɀ BȷƎ

ȼ ɢ ȷ Ŭ ΄ȷϵɏэŮǥůɖģ Űϗ з ŭŮɐεΎŰϗ з DNA ũŬɑŮŰŬ ůŰз ƟɑŬэŬ 15. ȼŬ ŭŮɐεŬŰ ŬɏɔϵϵǥΆŮэŬεϭΎзϵǥз,эǥȷɑ ģ,ŬεϵŭђŰģεɖ ůǥɔɔŬзэϵɨ ģ ǥɔэŰģ ůǥϵɨɔϵǥģ ŬɖɖŮзɩ з εŮ ŬεϵϵȷϗεΎϗůɖ, эŬ ŭŮɐεŰŰ ΄ȷϵŮϵђεŬŰ Ŭ ђ Ŭзɖȷϗ΄ϵэϵɔэɏɖ ɏȷŮǥзŰģ. ȼŬ ŬϵŰŮɏůεŰŰ ŬũϵȷϵɨзǤ 63 ŮǥȷϗʹŬɥϵɨģ ΄эɖɖǥůεϵɨģ эŬ ŬŰ΄ȷϵůϗ΄Ůϵǥз ůǥзϵээΎ10.708ΎŰεŬɔŬŰŰэɩ ģεɖ ůϵŰŰεђεŬŬεŰŰэɨ Űϵǥģ. ƎŰ ůɨзϵэђ Űϵǥģ, ɖ ůǥϵзђŰɖŰŰϗ з Ŭээɖэђεϵȷũϗ з ȷ = 4,9%.[48] [ƟɑŬэŰģ 15]

ȷ ɨзϗз # ΄эɖɖǥůεϵɨ	ĵ ɩ ȷ Ŭ	Ɵђэɖ (΄ Ůѕϵ/Űзђűɖű)	*N* *(Ůϗɗεђģ Ŭђεϗз)*	ũϵзђŰģ΄ϵģ		*ƎǥϵзђŰɖŰŰģ A (%)*
				GA	*AA*	
1	ȽůэŬзŭɖŬ		231	19	1	4.5
2	Ⱦɖůэ Ύũ Ůђ Ŭ		187	15	2	5.1
3	Ⱦϵȷϭɖɔɖ Ŭ	ӯ ůэϵ	509	75	2	7.8
4	ƎϵǥɖŭɖŬ	Bɨ εŰ	206	25	3	7.5
5		ƎŰэϵɕђэεɖ	117	9	0	3.8
6	ũ ѕэŬзŭɖŬ	ɕǥŰэɐ	173	14	2	5.2
7		ɗђȷ Ůз Ŭ	128	13	0	5.1
8	ǺůɗϵзɖŬ	Saaremaa	96	4	0	2.1
9		Hiiumaa	96	3	0	1.6
10		ɕǥŰэɐ	158	16	0	5.1
11		Ⱦ ϵŰŬзŰŰэѕɐ	92	6	1	4.3
12	Λϗ ůɖŬ	Mordovinians	85	3	0	1.8
13	ɕŬзɖŬ	ȯ Ŭэ ΄ϵȷ ɔэ	200	27	0	6.8

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		ɛ´ ǓɔɢƔɔɖ	420	52	0	6.2
		pɛgɓɚɑɛ	109	31	0	14.2
		´ ɣɚű Ǔů Ű	409	70	5	9.9
17	¢ ɜɤ ɛɣɜɛ ɗǓůɑɚǓɛ	ȯ ɛ´ Ůɟ ɜǓɜ	184	31	0	8.4
18		ɟ ɜǓǓɛɚɚɐ ɟ ɔɔɚɗǓ	200	32	1	8.5
19		ɗɛɟ ǓɛǓɜǓǓɛɚɚƔ	117	16	1	7.1
20		ʔ ɦǓɟǓ ƁgǓɚɗǓ	101	10	1	5.9
21		ʂ ɛɜǔɑɛ	287	39	0	6.8
22		ɛ́ ɛɣɟ ůɘ	411	60	4	8.3
23	ƁɚɚǓɜǔɗǓ	ƁgǓɟ ɣɢǓɖ	555	40	3	4.1
24	ũ Ůɟ ɛ ǓɜɗǓ	ɟ ɛɓɛɨɟ ɔɛ	157	15	0	4.8
25		ū ɟ Ǔɜɚű ɛɨɟ Ǔɖ	153	8	0	2.6
26	ɟ gůǓɟ ɗǓ	ɗɚɣɜɜɖ	271	20	1	4.1
27	ƁgɔɔǓɟ ɗǓ	ɗɛgǔǓ´ ɣůǓɖ	277	31	2	5.6
28		ɟ ɜǓǓɛɚɚɐ	308	12	0	2.6
29	ɗɛgɚɔǓɟ ɗǓ	Ɛ́ɦűɘǓ	100	0	0	0
30	ũ ǓɚɚɗǓ	ʂ ɚ	101	8	0	4.0
31		Rennes	139	8	0	2.9
32		Brest	163	24	0	7.4
33		Finistèresud	254	44	2	9.4
34		ɗɟ ǓǓƔɜɖ	62	7	0	5.6
35		ƱǓɟ ɑůɘ	126	10	0	4.0
36		Chambéry	104	7	0	3.4
37		Biarritz (Basques)	92	3	0	1.6
38		Perpignan(Catalans)	76	3	0	2.0
39		Grasse	90	4	0	2.2
40		ɛ́ ɛgɚɛɨ ɕ	95	8	0	4.2
41		ʐ ɛɜ´ Ůɚɣ	60	4	0	3.3
42		Ajaccio (Corse)	104	3	0	1.4
43	ƗǓǓɚɗǓ	ɛ́ ɛɟ ɑɛ	139	3	0	1.1
44		ʐ ɚƔɜɛ	128	2	0	0.8
45		ũ ǓɜǓɨ ɖ	130	11	0	4.2
46		ū Ůɟ ƔɟǓ	131	6	0	2.3
47		ʔ Ƴ´ ɛɚɖ	36	0	0	0
48		Ɛ́ɚ ǓɚɗǓ (ʐ ǓůɑǓ)	100	0	0	0
49		Ɛ́ɚ ǓɚɗǓ (ƱǓɚɣɟ ɛɛ)	106	0	0	0
50	Ʊɛɟ ǓɛɔǓɚɗǓ	ɗɦɟ ǓɟǓ	129	13	1	5.8
51		Ƶ ŮɜǓɟ ɚɐ	130	10	1	4.6
52		ʂ ɘůǓɓɦɜǓ	133	8	0	3.0
53		Alentejo	132	6	0	2.3
54		Algarve	116	2	0	0.9
55	Ɨů´ ǓɜɗǓ	Galicia	50	3	1	5.0
56		Basques	116	12	0	5.2
57		ɗǓɟ ɚ Ůɚ ɜɖ	485	27	1	3.0
58		Ƶ ǓǓǓɚɛɜɗǓ	108	8	0	3.7
59		ʐ Ǔǔɟ ɗǓɖ	50	2	0	2.0

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		[illegible]	192	11	0	2.9
		[illegible]	169	14	0	4.1
		[illegible]	167	2	0	0.6
63	[illegible]	[illegible]	158	1	0	0.3
[illegible]			10708	970	35	**4.9**

[illegible] 15. [illegible] C282Y (GA: [illegible] and AA: [illegible]) [illegible] A [illegible] (ů[illegible]) ů[illegible]63 [illegible].

4.2 [illegible] rs1799945 (H63D)

[illegible] HFE [illegible] 7% [illegible] 17%. [illegible] G [illegible] 9% [illegible]. [[illegible] 16]

[illegible]	[illegible]	
	G(%)	C(%)
[illegible]	7	93
[illegible]	17	83
[illegible]	9	91

[illegible] 16. [illegible] rs1799945 [illegible].[49]

[illegible] GG [illegible] rs1800562[50], [illegible] 1.2% [illegible] 3.6%, [illegible] GG [illegible] 2.2%.

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ɘƒ Ŭgǘɨ Ǘɖɜ ɛŮǗŸǝǝŬɚɖ, ŭɖǝŬŭɐ ɛŮ CG ɔɞɜɧǗg´ɞ, ɟŮŸɞɜǗǗǝ, ŮǝǗɧƒ ǝŬǝŬɜ ŮɞŬǝ Ů ɑůɖƒǘɞɟŮƒ C282Y. ũǝŬǗǗɞɛɧɛgɔŬŸǗɛɛŬɤƒ´ɟɞƒǗɛɜ ǘgůǝɧ ɔɞɜɧǗg´ɞ CC, ŭǗɜ g´Ÿɟɞǝǝɨ ɞǝŬɏŭǗɜɖ ɔǝŬ ´ɟɞŭǝŸɖǗɖ ǗɛǘŸɜůɖƒ ŬɛɞɞɟɤɛŸǗɤ ůɖƒ.[50] ɇŬ ´ɞůɞůǗŸ Ǘɤɜ ɞɛɧɛgɔɤɜ ǝŬǝ ǗǗɟɧɛgɔɤɜ ɔɞɜɧǗg´ɤɜ ŬgǗɛɨ Ǘɛg ´ɞǝgɛɞɟǘǝůɛɞɨ ůǗɛɜ ´ŬǝɧůɛɞƐ, ůǗɛɜ Ʌgɟɤ´Ŭɸɧ ǝŬǝ Ʌǝǝɖɜǝɧ ´ǝɖɖgůɛɧ ŬǗůǗɛɞŬŬǗɏɞɜǗǝ ůǗɛɜ ɄɑŬǝŬ17.

Ʉǝɖɖgůɛɧƒ	ũɞɜɧǗg´ɞƒ%		
	C:C	C:G	G:G
ɄŬǝɧůɛɞƒ	86.6	12.2	1.2
Ʌgɟɤ´Ŭɸɧƒ	69.2	27.2	3.6
Ʌǝǝɖɜǝɧƒ	74.4	23.4	2.2

ɄɑŬǝŬƒ 17. Ɇgɔǝɟǝǝɧƒ ´ɑŬǝŬƒ ´ɞůɞǗɜ ǗɛǘŸɜůɖƒ ɔɞɜɧǗg´ɤɜ Ǘɛg ´ɞǝgɛɞɟǘǝůɛɞɨ rs1799945 ůǗɛɜ Ʌǝǝɖɜǝɧ, Ʌgɟɤ´Ŭɸɧ ǝŬ´Ŭǝɧůɛɞ ´ǝɖɖgůɛɧ.[49]

4.3 ɄɃʂ ɈɀɃɅũ ɆɆɀɃɆ rs1800730 (S65D)

Ƀ ´ɞǝgɛɞɟǘǝůɛɧƒ ŬgǗɧƒ Ǘɛg ɔɞɜǝɑɞg HFE ɏɞǝ Ǘɛɜ ɑǝŬ Ů ɑɟŬɖ ůǗɛɜ Ůɣǝŭɑɖ ɛŮǗƒ´ɞ ´Ÿɜɤ ɛǗǗǝǝŸɜǗƒ, ɧɛɤƒɞǝŮǝɟŸůǗƒǗɛg ŬgɏƒǗɛǘŬɑɞɜǗǝůŮ ´ɞɨ ɛǝɟɧǗɟɞ ɓŬɖɛɧ Ŭɧ Ǘɛɜ ɛŮǗŸǝǝŬɚɖ rs1799945 ǝŬůŮŬǝɧɛɖ ɛǝɟɧǗɟɞ Ŭɧ Ǘɛɜ ɛŮǗŸǝǝŬɚɖ rs18000562.

ɇɞ Ŭǝǝɖǝɧɛɞɟǘɞ T, Ǘɛ ɞ´ɞɑɛ ´ɟɞǝŬǝŮ Ǘɛɜ ɛŮǗŸǝǝŬɚɖ, ŮŬǗ´ɑǗǗǝ ůǗɛɜ ´ŬǝɧůɛɞƐ ´ǝɖɖgůɛɧ ůŮ´ɞůɞǗɧ <1% Ŭɩ ůǗɛɜ Ʌgɟɤ´Ŭɸɧ ´ǝɖɖgůɛɧ ůgɜŬǗŸǗǝ ůŮ´ɞůɞǗɧ 2%. ũǝŬǗɛɜ Ʌǝǝɖɜǝɧ ´ǝɖɖgůɛɧ Ǘɛ ŬǗůǗɛɑɞ Ŭǝǝɖǝɧɛɞɟǘɞ ůgɜŬǗŸǗǝ ůŮɏɜŬ´ɞůɞǗɧ ŮŬŭǝŸɛŮɞ ɛŮŬgǗɧ Ǘɛg ´ŬǝɧůɛɞƐg ǝŬ Ǘɛg Ʌgɟɤ´Ŭɸɞɨ, ŭɖǝŬŭɐ 0,8%. [ɄɑŬǝŬƒ 18]

Ʉǝɖɖgůɛɧƒ	ɟ ǝǝɖǝɧɛɞɟǘɞ	
	T	A
ɄŬǝɧůɛɞƐƒ	<1%	100.0%
Ʌgɟɤ´Ŭɸɧƒ	2.0%	98.0%
Ʌǝǝɖɜǝɧƒ	0.8%	99.2%

ɄɑŬǝŬƒ 18. Ɇgɔǝɟǝǝɧƒ ´ɑŬǝŬƒ ´ɞůɞǗɜ ǗɛǘŸɜůɖƒ Ŭǝǝɖǝɧɛɞɟǘɤɜ Ǘɛg ´ɞǝgɛɞɟǘǝůɛɞɨ rs1800730 ůǗɛɜ Ʌǝǝɖɜǝɧ, Ʌgɟɤ´Ŭɸɧ ǝŬ´Ŭǝɧůɛɞ ´ǝɖɖgůɛɧ.[51]

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[illegible] <1%, [illegible] 0,2% [illegible] 0,4%, [illegible] rs1800562.[52] [illegible] TA [illegible][52] [illegible] 0,7%, [illegible] 2,8% [illegible] 1,5%. [[illegible] 19]

[illegible]	[illegible] %		
	AA	AT	TT
[illegible]	99,2	0,7	<1%
[illegible]	97,0	2,8	0,2
[illegible]	98,1	1,5	0,4

[illegible] 19. [illegible] rs1800730 [illegible].[51]

4.4 [illegible] (C282Y/H63D [illegible] C282Y/S65D)

[illegible] rs1799945 (H63D) [illegible] rs1800730 (S65D) [illegible] «[illegible]» [illegible] rs1800562 (C282Y). [illegible][50,52]

[illegible] 1460 [illegible] C282Y [illegible] H63D, [illegible] (2) [illegible] (G:A/C:G) [illegible] 0,1% [illegible]. [illegible] 1256 [illegible] C282Y [illegible] S65D, [illegible] (G:A/A:T) [illegible] 0% [illegible].

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[illegible]

4.5 [illegible]

[illegible] Fischer's Exact Test, [illegible] rs1800562, rs1799945 [illegible] rs1800730 ($p>0,05$). [illegible] rs1800562 [illegible] p [illegible] 0,6798, [illegible] rs1799945 [illegible] 0,0717 [illegible] 0,5113.

[illegible] [20] [illegible]

[illegible] 2 [illegible] 10 [illegible]

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ʃ Ű ɖ ʃ Ŭæ ɞɢɟ ɤ ɛ ƳŰɤ ůɖʃ ŮƈŬəɖ ˊɟ ɧəɖɣɖ, ɔɘŬ Űɕ əɧɔɞ Ŭɡ Űɧ ɞ ɔɞɜɞŰɡ ˊɘɧɡ ɏəŮɔɢɞʃ əŬɗůŰŰŰəɕɤ Űəɐ ʃ ůɖɛŬůɗŬʃ.

2. Ƀ Ⱥəəɖɜɘɧʃ ˊəɖɗɡůɛɧʃ űŬɞŰŰŰəɜ Ŭ ŮƈŬə Ůɡɜɞɖɛɏɜɞʃ ɤ ʃ ˊɟɞʃ Űɖɜ ůɡɢɜɧŰɖŰŰ Ůɛ űƳɜɘůɖʃ Űɤ ɜ ˊɞəɡɛɞɟ űɘůɛɩ ɜ rs1800562, rs1799945 əŬə rs1800730 Űɕɡ ɔɞɜɘŭɕɡ HFE ůŮ ůɨ ɔəɟɘůɖ ɛŮ Űɕɜ ɡˊɧəɞɘˊɞ Ůɡɟ ɤ ˊŬəɧ ˊəɖɗɡůɛɧ, ŬəəƳ ˊŬɟɞɡůɘƳɛƈ ɛɗŬ ůɢŰŰəɐ Ů ɘɟɟɏ ƈŬ ůŰɖɜ ɞɛɞɕɡɔɤ ŰŭŬəŬ Űɕɜ ˊɞəɡɛɞɟűɘůɛɧ rs1800562.

3. Ƀ Ⱥəəɖɜɘɧʃ ˊəɖɗɡůɛɧʃ ŭŮɜ ŮƈŬə Ůɡɜɞɖɛɏɜɞʃ ɤ ʃ ˊɟɞʃ Űɕɡʃ ŬɜŰůŰəɘɢɞɡʃ ˊɞəɡɛɞɟűɘůɛɞɨʃ Űɕɡ ɔɞɜɘŭɕɡ HFE ůŮůɨ ɔəɟɘůɖ ɛŮŰɕɜ ˊŬəɧůɛɞ ˊəɖɗɡůɛɧ.

4. Ƀ Ⱥəəɖɜɘɧʃ ˊəɖɗɡůɛɧʃ ŮƈŬŮ ɖɟŰŰůɛɏɜɞʃ Ŭ ɧ Űɖɜ Ůəůɟɞɐ Ƴəəɤ ɜ űɡəɩ ɜ.

5. ɄŬɟɧəɞ ˊɞɡ ɞɘ ƳɜŰɟŮɡ Ůɛ űŬɜɕɢɞɡɜ ɔɟɖɔɞɟɧŰɟŬ ůɡɛˊŰ ɛŬŰŰ Ŭæ ɞɢɟ ɤ ɛ ƳŰɤ ůɖʃ, Ŭɡ Űɧ ŭŮɜ ɞűŬŮŰŰəɐ ůe ɔɞɜɘŭɘŬɧ ɡˊɧɓŬɖɟɞ ŬəəƳ ůŮ ƳəəŬʃ ɓəəɞɔɘɏʃ əŮɜŰɕɡɟɔɖŮʃ.

6. ¢ ŬɜƳɔəɖ ɔɞɜɞŰɨ ˊɖůɖʃ ɔɘŬ Űɖɜ Ůɛ űƳɜɘůɖ Űɤ ɜ ˊɞəɡɛɞɟűɘůɛɩ ɜ ŮƈŬə Ů ɘŰŰəŰəɐ əŬə Ŭ ŬɜŰŰŮŰŰə ůɡɢɜɧʃ ŬæŬŰɕəɞɔɘɧʃ ɏəŮɔɢɞʃ ɔɘŬ ˊɟɞəɖˊŰəɞɨʃ əɧɔɞɡʃ.

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[illegible] (HH) [illegible]

[illegible] HFE [illegible]

[illegible] (SNPs) [illegible] HFE [illegible] HFE [illegible] DNA [illegible] 1446 [illegible]

[illegible] HFE [illegible]

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Hereditary Hemochromatosis (HH) is an autosomal recessive genetic disease, characterised by excessively increased absorption of dietary iron. HH is one of the most common genetic disorders in individuals of European descent. Due to the absence of an effective excretory mechanism, the excess iron in the body can be accumulated and cause toxic effects. If left untreated, hereditary hemochromatosis can lead to morbidity and eventually death. Clinical onset hereditary hemochromatosis symptoms occur more frequently in adult men than women, as the monthly loss of iron in women slows down accumulation due to menstruation and the symptoms usually start appearing after menopause.

An early detection can be achieved by the genotypic check of the frequent mutations of the HFE. Consequently the treatment can start resulting in initiation of treatment before the development of clinical symptoms, particularly cirrhosis, contributing significantly in achieving normal life expectancy. Therefore, genotypic check is vital in order to prevent the development of the disease. Therapeutic phlebotomy is the primary form of treatment for this disease so far, combined with the use of chelating agents. Orthotopic liver transplantation is applied in patients with advanced cirrhosis.

In this study, we investigated the distribution of three Single Nucleotide Polymorphisms (SNPs) of the HFE gene concerning hemochromatosis, in a sample of Greek individual. The HFE gene affects iron metabolism as well as the activity of hepcidin, a liver hormone which acts as a negative regulator in iron metabolism. For the purpose of this study, DNA from 1446 individuals of different age was derived and analysed, either from whole blood or epithelial cells of the oral cavity. Then the distribution frequency of the three specific mutations was defined.

The results of this study showed that the Greek population compared to the European population is favoured concerning hemochromatosis which is associated with the mutations of the HFE gene. However, it seems that these pathogenic mutations are found more frequently in Greek descent compared to the world population. This suggests that the Greek population is influenced by the influx of other races, so it differs genetically from the European population. Also, the findings in this study suggest that possibly,there is no phylogenetic factor concerning the transfer of these three polymorphisms of the HFE gene through generations and the final symptoms appear because of different biological processes between the two genders and not because of a different genetic backround.

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Ɇǥɔə Ǜɜ Ǘɤ Ǘə ɧɗ Ʉɑ Ǚə Ǜɠ Ɇɡɜ Ǘɛɛ Ǘ ǘ Ǘɤ ɜ ə Ǚɘ ȷ ɔɔəəɩ ɜ ɧȷ ɤ ɜ:

SNPs: Ɇɖɛ ǛɞǙəɞ? ɞǥəəǛɘ Ǘǖɤəɞ Ʉɞəǥɛ ɞȷ ǘɞǘɛ ɞɑ(SingleNucleotidePolymorphisms)

DMT-1: ɀ ǛǗǙǘɞȷ ɏǙɠǖɤǘɗǛɜɩ ɜɛ ǛǗɣəəɤ ɜ-1 (DivalentMetalTransporter-1)

Tf: ȼ ȷ Ǚɜ ǘǘ Ǜȷ ȷ ɑɖ (Transferrin)

TfR1: Ɉ ´ ɞǘɞɞɏǙɠȼ ȷ Ǚɜ ǘǘ Ǜȷ ȷ ɑɖɗ 1 (TransferrinReceptor 1)

TS: Ɀ ɞȷ Ǘɛɛ ɧɗȼ ȷ Ǚɜ ǘǘ Ǜȷ ȷ ɑɖɗ (TransferrinSaturation)

FPN: ū Ǜȷ ȷ ɞ ´ ɞȷ Ǘɞɖ (Ferroportin)

IRPs: Λɡɖɛ ɘǘ Ǘəɏɡ Ʉȷ ɤ ǗǗɜ Ǜɠ Ɇɘǘɐ ȷ ɞǥ (Iron Regulatory Proteins)

CBC: ũ Ǜɜəɐ Ǜəɏ ǗǗǘɖ Ǚɛ ǙǗɞɗ

MCV: ɀ ɏǘɞɗ ɧɔəɞɗ Ǜ ɡɖȷ ɩ ɜ Ǚɛ ɞǘǘ Ǚəȷ ɑɤ ɜ

HAMP: ȷ ɜǗɛ əȷ ɞɓəǙəɧ ɄǛ Ǘǘɞ Ⱥɣ ɘǘɑɖɗ (HepcidinAntimicrobialPeptide)

HJV: Haemojuvelin

HH: Kəɖȷ ɞɜɞɛ əɐ Aɛ ɞɞȷ ɤ ɛ ƳǗɤ ǘɖ (HereditaryHemochromatosis)

HCC: H´ ǙǗɞəǥǗǗǛ əɧKǛ ȷ əɑɤ ɛ Ǚ (HepatocellularCarcinoma)

OLT: Bȷ ɖɞǗɞ´ əɐ ɀ ǗǗǙɛ ɧǘɞǛɡǘɖǒ ´ ǙǗɞɗ (OrthotopicLiverTransplantation)

C282Y: Ɇɖɛ ǛɞǙəɧɗ ? ɞǥəəǛɘ Ǘǖɤəɧɗ Ʉɞəǥɛ ɞȷ ǘɘǘɛ ɧɗ rs1800562 Ǘɞǥ ɔɞɜɘǘɑǥ HFE

H63D: Ɇɖɛ ǛɞǙəɧɗ ? ɞǥəəǛɘ Ǘǖɤəɧɗ Ʉɞəǥɛ ɞȷ ǘɘǘɛ ɧɗ rs1799945 Ǘɞǥ ɔɞɜɘǘɑǥ HFE

S65D: Ɇɖɛ ǛɞǙəɧɗ ? ɞǥəəǛɘ Ǘǖɤəɧɗ Ʉɞəǥɛ ɞȷ ǘɘǘɛ ɧɗ rs1800730 Ǘɞǥ ɔɞɜɘǘɑǥ HFE

PCR: Aəǥǘɘǘɤ Ǘɛaɜ Ǘǘȷ Ǚǘɖpɞəǥɛ Ǜ Ƴǘɖɗ (PolymeraseChainReaction)

H2O: ɨ ǔɤ ȷ

EtOH: Ǚɜɖ Ǚɜ ɧəɖ

EDTA: ȷ ɘɗɡəǛɜɞǘɘǙɛ əɞǗǗǛ Ǚɞɜəɧ ɞɜɨ

FAM: 6-əǛȷ ɓɞɜǥ-ǘəɞɡɞȷ Ǘǘə Ǘɜɖ

ȼ Ⱥȼ: 4,7,2ǒ,7ǒǗǗǛ Ǚɞəɤ ȷ ɞ-6-əǛȷ ɓɞɜǥ-ǘəɞɡɞȷ Ǘǘə Ǘɜɖ

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Ágŀ ŮŰɐɟ ១ Ʉ១Ɏɘ ɤ ɜ:

ɄɶŬəŬʃ 1. Ęgɕɜђ ŰɖŰŨ ůgɛ´ Ű ɛ ƳŰ ɜ ´ɟ ១ ɘŬə ɛŮŰƳ Űɖ ŭ១ƳϽɜɤ ůɖ Ŭɇɕɕɟ ɤ ɛ ƳŰ ůɖɖ

ɄɶŬəŬʃ 2. Á´ ១Ŭə ɛɏɜŮʃ´ Ŭɖɕɔђɜ Ůʃ´ Ŭɟ Ŭəɘ Ŭɏɡ Ű ɜ Ŭəɘɖɘђɛ ɕɟ ŭ ɤ ɜ Űɛg ɔɕɜ១ŭɶg HFE.

ɄɶŬəŬʃ 3. ĘgůɕŮŰűɛ ђʃ ɔɕɜђ Űʃ´ ɕg ɘŬə Ůɛŭ Ƴɜ១ůɖʃ Ɫ ɘɖɟ ɕɜɕɛ ១ɐɕʃ ɟ ១ɛ ɕɕɟ ɤ ɛ ƳŰ ůɖɖ

ɄɶŬəŬʃ 4. ũŮɜ១ђ ´ɟ ɤ Űђɘɕɘɘɕ.

ɄɶŬəŬʃ 5. ɟ ɜŰŭɟ ŬůŰɛɟ ១Ŭ ɘŬə ´ɕůђŰɖŮŰʃ Ŭg Ű ɜ ɔ១Ŭ Űɖɜ ɄŬɟ Ŭůə Ůɡɐ 5 ɟ TBE.

ɄɶŬəŬʃ 6. ƮŬŰŨɜɕɛɐ ɔɕɜɕŰ´ɤ ɜ ɔ១Ŭ Űɛɜ ´ɕəgɛɕɟ ŭ១ůɛђ rs1800562 ůŮ ŭŮɒɛŬ 1446 ŮɖŮəɕɜŰ ɜ.

ɄɶŬəŬʃ 7. ĘgůɕɏŰůɖ ɛŮŰŨɜ Ŭɜŭɟ ɩ ɜ ɘŬə ɔgɜŬ១ɩ ɜ ɔ១Ŭ Űɖ ůgɕɜђŰɖŰŨ Ůɛŭ Ƴɜ១ůɖʃ Ű ɜ Ŭəɘɖɘђɛ ɕɟ ŭ ɤ ɜ A ɘŬə G Űɛg ´ɕəgɛɕɟ ŭ១ůɛɕ rs1800562 Űɛg ɔɕɜ១ŭɶg HFE.

ɄɶŬəŬʃ 8. ƮŬŰŨɜɕɛɐ ɔɕɜɕŰ´ɤ ɜ ɔ១Ŭ Űɛɜ ´ɕəgɛɕɟ ŭ១ůɛђ rs1799945 ůŮ ŭŮɒɛŬ 1429 ŮɖŮəɕɜŰ ɜ.

ɄɶŬəŬʃ 9. ĘgůɕɏŰůɖ ɛŮŰŨɜ Ŭɜŭɟ ɩ ɜ ɘŬə ɔgɜŬ១ɩ ɜ ɔ១Ŭ Űɖ ůgɕɜђŰɖŰŨ Ůɛŭ Ƴɜ១ůɖʃ Ű ɜ Ŭəɘɖɘђɛ ɕɟ ŭ ɤ ɜ G ɘŬə C Űɛg ´ɕəgɛɕɟ ŭ១ůɛɕ rs1799945 Űɛg ɔɕɜ១ŭɶg HFE.

ɄɶŬəŬʃ 10. ƮŬŰŨɜɕɛɐ ɔɕɜɕŰ´ɤ ɜ ɔ១Ŭ Űɛɜ ´ɕəgɛɕɟ ŭ១ůɛђ rs1800730 ůŮ ŭŮɒɛŬ 1219 ŮɖŮəɕɜŰ ɜ.

ɄɶŬəŬʃ 11. ĘgůɕɏŰůɖ ɛŮŰŨɜ Ŭɜŭɟ ɩ ɜ ɘŬə ɔgɜŬ១ɩ ɜ ɔ១Ŭ Űɖ ůgɕɜђŰɖŰŨ Ůɛŭ Ƴɜ១ůɖʃ Ű ɜ Ŭəɘɖɘђɛ ɕɟ ŭ ɤ ɜ G ɘŬə C Űɛg ´ɕəgɛɕɟ ŭ១ůɛɕ rs1799945 Űɛg ɔɕɜ១ŭɶg HFE.

ɄɶŬəŬʃ 12. Ęgɔəɟ ១Űəђʃ ´ɶŬəŬʃ ´ɕůɕůŰ ɜ Ůɛŭ Ƴɜ១ůɖʃ Ŭəɘɖɘђɛ ɕɟ ŭ ɤ ɜ Űɛg ´ɕəgɛɕɟ ŭ១ůɛɕ rs1800562 ůŰɛɜ Áɘɘɖɜ១ђ, Ágɟ ɤ ´ Ŭɐђ ɘŬə ´ Ŭɘɘђůɛ១ ´ɘɖɖgůɛђ.

ɄɶŬəŬʃ 13. Ęgɔəɟ ១Űəђʃ ´ɶŬəŬʃ ´ɕůɕůŰ ɜ Ůɛŭ Ƴɜ១ůɖʃ ɔɕɜђŰʃ´ɤ ɜ Űɛg ´ɕəgɛɕɟ ŭ១ůɛɕ rs1800562 ůŰɛɜ Áɘɘɖɜ១ђ, Ágɟ ɤ ´ Ŭɐђ ɘŬə ´ Ŭɘɘђůɛ១ ´ɘɖɖgůɛђ.

ɄɶŬəŬʃ 14. ũɕɜђŰʃ´ɕɘ C282Y (GA: ŮŰŮɟ ђɕɡɔɕɡ and AA: ɕɛђɕɡɔɕɡ) ɘŬə ůgɕɜђŰɖŰŮʃ Űɛg A Ŭəɘɖɘђɛ ɕɟ ŭɕg (ůŮ´ɕůɕůŰƳ) ůŮ63 Ůɡɟ ɤ ´ Ŭɐɕɟ ʃ´ ɘɖɖgůɛɕɟ ɖ.

ɄɶŬəŬʃ 15. Ęgɔəɟ ១Űəђʃ ´ɶŬəŬʃ ´ɕůɕůŰ ɜ Ůɛŭ Ƴɜ១ůɖʃ Ŭəɘɖɘђɛ ɕɟ ŭ ɤ ɜ Űɛg ´ɕəgɛɕɟ ŭ១ůɛɕ rs1799945 ůŰɛɜ Áɘɘɖɜ១ђ, Ágɟ ɤ ´ Ŭɐђ ɘŬə ´ Ŭɘɘђůɛ១ ´ɘɖɖgůɛђ.

ɄɶŬəŬʃ 16. Ęgɔəɟ ១Űəђʃ ´ɶŬəŬʃ ´ɕůɕůŰ ɜ Ůɛŭ Ƴɜ១ůɖʃ ɔɕɜђŰʃ´ɤ ɜ Űɛg ´ɕəgɛɕɟ ŭ១ůɛɕ rs1799945 ůŰɛɜ Áɘɘɖɜ១ђ, Ágɟ ɤ ´ Ŭɐђ ɘŬə ´ Ŭɘɘђůɛ១ ´ɘɖɖgůɛђ.

ɄɶŬəŬʃ 17. Ęgɔəɟ ១Űəђʃ ´ɶŬəŬʃ ´ɕůɕůŰ ɜ Ůɛŭ Ƴɜ១ůɖʃ Ŭəɘɖɘђɛ ɕɟ ŭ ɤ ɜ Űɛg ´ɕəgɛɕɟ ŭ១ůɛɕ rs1800730 ůŰɛɜ Áɘɘɖɜ១ђ, Ágɟ ɤ ´ Ŭɐђ ɘŬə ´ Ŭɘɘђůɛ១ ´ɘɖɖgůɛђ.

ɄɶŬəŬʃ 18. Ęgɔəɟ ១Űəђʃ ´ɶŬəŬʃ ´ɕůɕůŰ ɜ Ůɛŭ Ƴɜ១ůɖʃ ɔɕɜђŰʃ´ɤ ɜ Űɛg ´ɕəgɛɕɟ ŭ១ůɛɕ rs1800730 ůŰɛɜ Áɘɘɖɜ១ђ, Ágɟ ɤ ´ Ŭɐђ ɘŬə ´ Ŭɘɘђůɛ១ ´ɘɖɖgůɛђ.

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[illegible]

[illegible] HFE, [illegible]

[illegible]

[illegible] HFE [illegible]

[illegible] (C282Y [illegible] H63D) [illegible] HFE.

[illegible]

[illegible] HFE (**rs1800562 (**C282Y), rs1799945 (H63D) [illegible] rs**1800730 (**S65C)) [illegible]

[illegible] DNA [illegible]

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qþŬŭəŬůdǘ Ǘdʃ ɛ Ŭəy̆Ǘdʃ

ȷ з ůgɛűɤ зɐůǗǗ зŬ ůgɛɛǗǜɢǗǗ ůǗd ɛŬəy̆Ǘd, dŬ əɖűdɕɨ з Ŭ ɧ ŮűƳɗ Ů ɘdɖəŬəƳ əɨ ǗǗȷŬ Ŭ ɧ Ǘd ůǗɕɛŬǗəɐ ůŬʃ əɕəɧǗdǗ əŬə ŭŮəɛŬ ŬɛŬǗɕʃ.ȼɕ ŭŮəɛŬ ŬgǗɧ dŬ ɛǗǗűŬȷdŬ ůǗɕ Aȷ Ůgзɖǘəɧ Ůȷ ɔŬůǗȷɜ Ƭəɜəɐʃ ūŬȷɛŬəɕəɕɔdǗʃ əŬə ūŬȷɛŬəɕзɕəŭɤ ɛŬǗəɐʃ Ǘɕg ȼɛɐɛŬǗɕʃ ūŬȷɛŬəŬgǗəɐʃ, Ǘdʃ Eɕɕəɐʃ A´ ɘůǗdɛɩ з ƚ ɔŮdŬʃ,Ǘɕg Adзəɕɨ əŬə ƬŬ ɕŭɘůǗȷɘŬəɕɨ ƱŬəŮ ɘůǗdɛɕg ȷ ɖɖзɩ з, ɧ´ɕg əŬə dŬ ŭɘŮзŮȷɔɖdɕɨ з ɕə ´ȷɕŬзŬűŮȷdŮůŮǗ ŮəǗǗƳůŮɕ. Ƀə ´ŬȷŬ Ƴзɤ ŭəŬŭəŬůdǗʃ dŬ ´ȷŬɐɛŬǗ´ɕɖdɕɨ з ɕɤȷɖʃəŬɛdŬŭəɐ ůŬʃɕəɕзɕɛəɐ Ů ɕƀƳȷgзůd.

Ƭɕŭŭgзɕə

ɖŬɜ g´Ƴȷɢəŭ əŬзy̆зŬʃ əɕŭŭgзɕʃ ɧůɕз ŬűɕȷƳ Ǘd əɐɣɖ Ů ɘdɖəŬəɩ з əgǗǗƳȷɤ з ɛŮ ɓŬɛŬɓŬəɕűɧȷɕ ůǗŬəŮɧ əŬə ŭŮəɛŬǗɕʃŬɛŬǗɕʃŬ ɧ ŬəŬŭəŮgɛy̆зɕ ´ȷɕůɤ´əɧ.

Egɛɛ Ǘǘɕɐ ůǗd ɛ Ŭəy̆Ǘd

¢ ůgɛɛŬǗɕɐ ůǗd ɛ Ŭəy̆Ǘd ŬəŬəŬ ɕəɨ Ǘɤ ʃŮdŬəɕзǗəɐ.

ȼɐȷ důd Ŭ ɕȷȷɐǗɕg

ȷ з ŭɩ ůǗǗŮǗd ůgɔəŬǗƳdŮɐ ůŬʃ ɔəŬ Ǘd əɐɣɖ Ů ɘdɖəŬəɩ з əgǗǗƳȷɤ з Ŭ ɧ ŮűƳɗ, ǗŬ ŭŮəɛŬǗǗ ŬgǗƳ dŬ əɤ ŭəɕ´ɕɖdɕɨ з ɛŮ əɤ ŭəɧ Ůȷ ɘdɛɧ, ɕ ɕ´ɕɕʃ dŬ ŭəŬůűŬəɕŭ Ǘɕ Ŭ ɧȷȷdǗɕ Ǘdʃ ǗgǗɧǗdǗƳʃ ůŬʃ. Ƀə ´ȷɕůɤ´əy̆ʃ ´əɖȷɕűɕȷdǗʃ ɔəŬ Ǘdз gɔŮŬ ůŬʃ dŬ ŬзǗɛǗɤ´ɘůǗɕɨ з ɤʃ Ŭɛ´ɘůǗgǗəy̆ʃ Ŭ ɧ Ǘɕз g´Ůɖgзɕ əŬȷɧ-Ůȷ ŬgзdǗɐ. ƱəɖȷɕűɕȷdǗʃ əŬə ŭŮɕɛy̆зŬ Ŭ ɧ ŬgǗɐ Ǘd ɛ Ŭəy̆Ǘd ɛ´ɕȷŮзŬ ŭɖɛɕůəŬgǗɕɨ з, ɛŮǗdз ´ȷɕɧ´ɧdŮɖ ɧŬə ´ɕgdŮƳ ŭŬ dŬŬŬűy̆ȷ ǗǗŬɕ ɧзɕɛƳ ůŬʃ.

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ũɘǓ ɜǓ ůɡɛɛǕǰɢǕǕ ůǕɖ ɛǕɚɣǕɖ ǓɡǕɐ ɘǕɜ ɔɘǓ ɜǓ Ǖ ɘǕɟɣɣǕǕǕ Ǖɖ ɢɟɐůɖ ɘǕɜ ɔɜɤ ůǕɞ´ɞɖůɖ Ǖɤ ɜ ´ɟɞůɤ´ɘɩ ɜ ´ɘɖɟɞǘɞɟɘ ɜ ɔɘǓ Ǖɖɜ ɡɔǕɖǓ ůǓɡ, ´ɟɣ´ Ǖɘ ǕůǓɡ ɐ ɞ ɜɧɛɶɞɡǕɘ´ɟɧůɤ´ɧɡůǓɡɜǓɓƳɘǕǕɡ´ɞɔɟ Ǖɐ ɘǕɘɖɛǕɟɞɛɖɜɖǓůǕɖ ůǕɘɑǓǓɡǕɐ.

ɟ ´ɞɔɟ Ƴǘɞɜǔɡ, Ǖ ɕǕɓǕɑ ɜǕǕǕǕ Ǖɘɐɡ:

1. ŌɢǕǕůɘǓɓƳůǕɘ ɘǕɘ ɘǕǕɜɞɐůǕɘ ɧɘǕɡ Ǖɡ´ɘɖɟɞǘɞɟɖǕɡ´ɞɡ ´ǕɟɘɣɢɞɜǕɘ ůǕɞ ´Ǖɟɧɜ ɣɜǕɡ´ɞ.

2. ȳ ɘǓǕǕ Ǖɟɤ Ǖɐɛ ǓǕƳůǓɡɣɢɞɡɜ Ǔ ǓɜǕɖɖǕɑɘǓɜɞ´ɞɖǕɘƳ.

3. ɑɣɢǕůǕɛǕǕɖ ɖɣɘɖůɐ ůǓɡɜǓůɡɛɛǕǰɢǕǕůǕɖɜ ´Ǖɟɞɨ ůǓ Ǖɟ ǕɡɜɖǕɐ ɛǕɘɣǕɖ ɘǕɘ ɜǓ´Ǖɟɣɢ ǕǕǕǕɡǓ ǕɟǓǕɖǕǕɡ´ɘɖɟɞǘɞɟɖǕɡůǕɞ ɔɘǓǕɟɧ ɧǕɜ ůǓɡɛɖǕɖɖǕɑ

4. Ʌ´ɘǕɟɣ ǕǕůǕɞɜ ɘǓǕɟɧ Ǖɖɡɛ ǕɘɣǕɖɡ ɜǓ ǔɖɛɞůɶ´ɞɶůǕɘ ´ɟɞůɤ´ɘɣɡ´ɘɖɟɞǘɞɟɖǕɡ ´ɞɡ Ǔǘɞɟɞɨ ɜ ůǕɖɜ ɡɔǕɖǓ ůǓɡ, ůɨ ɛǘɤ ɜǓ´ƳɜǕǕɛǕǕɞ ɜɧɛɞ 2472/97 ´Ǖɟɑ´ɟɞůɤ´ɘɩ ɜ ǔɘǓɘɤ ɛƳǕɤ ɜ.

5. ŌɢǕǕ´ƳɟǕɘɣɜǓǓɜǕɒɟǓǘɞ Ǖɞɡ ´Ǖɟɧɜǘɡ Ǖɜǘ´ɞɡ, Ǖɞ ɞ´ɞɶ ɘǕɘɖǓɘɟǓǕɐůǕǕǕ

ɟ ´ɞɔɟ Ǔǘɐ ǓůɖǕɜɞɨ ɡ ¢ ɛ ǕɟɞɛɖɜɖǓ

ȳ ɜɞɛǓǓůɖǕɜɞɨ ɡ

ɆǓɡǕɡɢǓɟɘůǕɨ ɛǕɔɘǓǕɖ ůɡɛɛǕɞɢɐ ůǓ