FirmaLab™ Bio-Diagnostics

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Patient Name: **Jane Doe**

DOB	Gender	Ethnicity
02/18/1979	F	Jewish, Middle-Eastern

Test Ordered	Test Result	Expected (Negative) Value
GNE Sequencing	***Carrier (Heterozygous)***	Negative (No variations found)

Result Note: Two variations found in GNE gene.

1. Heterozygous variation found in exon 12 c.2135 T>C p.M712T.
This variation, when homozygous, is confirmatory for diagnosis of GNE Myopathy (formerly Nonaka Myopathy, or HIBM).

2. Intronic heterozygous variation found in Intron 1a c.+34 T>C. This variation is unknown significance

34 bp after end of exon 1a or 27463 bp before start of exon 2.
Reference SNP (refSNP) Cluster Report: rs7875447 , A/G (FWD)
A=0.2725/32726 (ExAC)
A=0.3482/1744 (1000 Genomes)
A=0.2139/2203 (GO-ESP)

Result Interpretation: Heterozygous variation found in GNE gene region. This result is consistent with an individual who is a carrier for HIBM or GNE myopathy, usually a family member of an HIBM or GNE myopathy patient. Amino acid numbering is based on GNE variant 2, encoding 722 Amino Acids (Gene Bank NP_005467). See additional information attached.

Electronically signed by: Daniel Darvish, MD, on 06/19/2016 21:42
Report Type: Complete

Specimen ID	Specimen Type	Collection Date Time	Date Received	Report Date
1020006	Whole Blood (EDTA)		06/07/2016 09:30	06/15/2016 17:07

Test Requested: HIBM genetic confirmation, sequencing of the *GNE* gene.

Appropriate genetic counseling should be utilized to explain the implications of the test result, its residual risks and uncertainties. The results are characterized as heterozygous, or homozygous for each DNA variation found. A negative result from this analysis cannot eliminate the possibility that an individual carries a non-coding mutation that may affect the expression or splicing of the gene. Only those with mutations on both alleles of the *GNE* gene are at risk for myopathy. The disease penetrance of homozygous *GNE*: p.M712T (atg>acg) "Iranian-Jewish" mutation is roughly 97%. The disease penetrance of other mutations are not known but are believed to be slightly below 100%. This interpretation is based on the clinical information provided and the current understanding of the molecular genetics of *GNE* related myopathy. Although DNA-based testing is highly accurate, rare diagnostic errors may occur. Examples include misinterpretation because of genetic variants, blood transfusion, bone marrow transplantation, gene therapy, cell therapy, erroneous representation of family relationships, or contamination of a fetal sample with maternal cells.

Method of Analysis: *GNE* coding region translates to a 722 amino acid protein, which is the rate-limiting enzyme (GNE/MNK) for sialic acid biosynthesis. *GNE* coding region is located at exons 2-12. Genomic DNA is isolated from the sample and exons 2-12 of the *GNE* gene are amplified enzymatically and analyzed using automated sequencing. DNA segments are tested by multiple forward and reverse sequence runs to obtain a consensus sequence. The readability of each sequence result is ranked and poorly readable or questionable sequences are repeated. The resulting sequence reads are blasted against human *GNE* genomic sequence on chromosome 9p13 (Chromosome 9, GenBank accession NW_924062, base range from 36032542 to 36076499). Following exons, and flanking intronic regions were sequenced. Multiple sequence runs of the same DNA strand are used to confirm positive or negative findings.

GNE-Exon 2 (5' UTR and coding region, Amino Acids M1-G55)
GNE-Exon 3 (Amino Acids N56-L205)
GNE-Exon 4 (Amino Acids G206-A256)
GNE-Exon 5, (Amino Acids G257-T327)
GNE-Exon 6, (Amino Acids G328-C357)
GNE-Exon 7, (Amino Acids S358-K427)
GNE-Exon 8, (Amino Acids G428-V470)
GNE-Exon 9, (Amino Acids G471-T544)
GNE-Exon 10, (Amino Acids G545-D605)
GNE-Exon 11, (Amino Acids E606-T644)
GNE-Exon 12, (Amino Acids A645-Y722, and 3' UTR)

This test was developed and its performance characteristics determined by FirmaLab. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA), or the FDA has determined that such clearance of approval is not necessary. The laboratory is accredited by College of American Pathologists (CAP), and certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity molecular testing.