Whole Genome Sequence Analysis

CLIENT	SPECIMEN	PATIENT
Client Name:	Specimen Type:	Patient Name:
Hospital/Institution:	Collection Date:	Date of Birth:
Address:	Receive Date:	Gender:
Phone Number:	Report Date:	Patient's PKI ID:
Fax Number:		Accession ID:
		Cross Reference:

Test Performed: Whole Genome Sequencing, Proband Only
Reason for Testing: Clinical features of disease

RESULTS SUMMARY

Pathogenic variant detected.
Clinical and biochemical correlation is required.

DIAGNOSTIC FINDINGS RELATED TO PHENOTYPE

Phenotypic terms applied: Neuromuscular disorder

Gene	OMIM	Disease	Inheritance	Exon/ IVS	DNA change	Protein Change	Zygosity	Classification
GNE	603824	Hereditary inclusion body myopathy 2; Distal myopathy with rimmed vacuoles; Nonaka myopathy; Sialuria	Autosomal Dominant / Autosomal Recessive	4	c.816_820del	-	Heterozygous	Pathogenic
GNE	603824	Hereditary inclusion body myopathy 2; Distal myopathy with rimmed vacuoles; Nonaka myopathy; Sialuria	Autosomal Dominant / Autosomal Recessive	12	c.2179G>A	p.V727M	Heterozygous	Pathogenic

VARIANT INTERPRETATION

***GNE* c.816_820del – Pathogenic.** The c.816_820del variant results in the deletion of four nucleotides at positions c.816 through c.820 of the *GNE* gene, causing a frameshift in the protein reading frame. To our knowledge, this variant has not been reported in individuals with disease or as a variant in the general population, but it is of a type expected to cause disease. The c.816_*820del* GNE variant is classified as pathogenic. Clinical and biochemical correlation is required.

***GNE* c.2179G>A (p.V727M) – Pathogenic.** The c.2179G>A (p.V727M) missense variant results in the substitution of the valine codon at amino acid position 727 with a methionine codon. This variant is frequently reported in individuals of Asian ethnicity with GNE myopathy[1,2]. The c.2179G>A (p.V727M) *GNE* variant is classified as pathogenic. Clinical and biochemical correlation is required.

1. Celeste et al. Hum Mutat. 2014 Aug;35(8):915-26.
2. de Dios et al. Neuromuscul Disord. 2014 Dec;24(12):1063-7.

RECOMMENDATIONS

The detection of two pathogenic variants in the *GNE* gene is consistent with a diagnosis of disease in this individual; however, these must be interpreted in the context of this individual's clinical and biochemical profile. Genetic counseling is recommended.

Patient's Name: Accession ID: Cross Reference:

Sequence analysis cannot determine if two variants are on the same (in *cis*) or opposite (in *trans*) copies of a gene. Targeted testing of the parents of this individual to confirm that they each are carriers and that the c.816_820del and c.2179G>A (p.V727M) *GNE* pathogenic variants are on opposite chromosomes in this individual is available.

Targeted testing is available for family members at risk to carry the pathogenic variants identified in this individual. For more information, please contact the laboratory at 1-866-354-2910.

Identified data will be stored at PerkinElmer Genetics.

FINDINGS UNRELATED TO PHENOTYPE

Diagnostic findings not related to phenotype: No pathogenic variants in genes that are unrelated to the patient's phenotype were detected in this individual.

Carrier status in genes related to disease:

Gene	OMIM	Associated Disease	Inheritance	Exon/ Intron	DNA Change	Protein Change	Zygosity	Classification
PAH	**612349**	**Phenylketonuria**	**Autosomal Recessive**	**7**	**c.745C>T**	**p.L249F**	**Heterozygous**	**Pathogenic**

Carrier status in genes on ACMG recommended secondary list (Kalia et al. Genet Med. 2017 Feb;19(2):249-255. PMID: 27854360): No pathogenic variants in genes related on the ACMG recommended secondary list were detected in this individual.

Pharmacogenetic variants (only selected CPIC Class 1A alleles with clinical utility are evaluated):

Gene	Allele Haplotype	Predicted Metabolizer Status	Related Drugs
CYP2C19	CYP2C19*1/CPY2C19*2	Intermediate Metabolizer	***Clopidogrel, voriconazole, citalopram, escitalopram, sertraline, amitriptyline***

Consultation with a physician to discuss relevant Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines is recommended.

NOTES

A list of variants identified in this individual by whole genome sequencing is available upon request. Variants are evaluated by their reported frequency in databases such as the Genome Aggregation Database (gnomAD), Human Gene Mutation Database (HGMD), and ClinVar. Variants that have a population frequency greater than expected given the prevalence of the disease in the general population are considered to be benign variants. Silent variants of unknown significance and intronic variants of unknown significance beyond +/-3 are not reported unless known to be pathogenic or other evidence suggests potential disruption of splicing. The interpretation of variants is based on our current understanding of the genes involved. These interpretations may change over time as more information about the gene(s) and this individual's clinical phenotype becomes available. Raw sequencing data is available upon request.

Variant Statistics:

Gene	Transcript	DNA Change	Protein Change	Genomic Location	Coverage	Alternate Allele Fraction	dbSNP rsID
GNE	NM_001128227.2	c.816_820del	-	g.36236870-36236874	224	39.3%	-
GNE	NM_001128227.2	c.2179G>A	p.V727M	g.36217445	165	40.6%	rs121908627

Data Quality Statistics:

% Fully Covered Disease Causative Gene Target Bases	99.3%
% Fully Covered Disease Causative Gene Exons (>20X coverage)	99.1%

Patient's Name: Accession ID: Cross Reference:

No. of Variants Identified and Analyzed	>319,000
Average Coverage per Target Base	30

METHODS AND LIMITATIONS

Direct sequencing of genomic DNA was performed using 2X150bp reads on Illumina next generation sequencing (NGS) systems at a mean coverage of 30X in the target region. The target region includes exons and 10bp of flanking intronic sequence. In some cases, due to the complexity of the sequence, not all variants in the flanking intronic sequence are able to be analyzed. A base is considered to have sufficient coverage at 20X and an exon is considered fully covered if all coding bases plus three nucleotides of flanking sequence on either side are covered at 20X or more. Low coverage regions, if any, are limited to ~1% or less of the target nucleotides included in this panel. A list of these regions is available upon request. Alignment to the human reference genome (hg19) is performed and annotated variants are identified in the targeted region. Variants are called at a minimum coverage of 8X and an alternate allele frequency of 20% or higher. Single nucleotide variants (SNVs) meeting internal quality assessment guidelines are confirmed by Sanger sequence analysis for records after results are reported. Indels, and SNVs at director discretion, are confirmed by Sanger sequence analysis before reporting. This assay cannot detect variants in regions of the genome that are not amenable to NGS, such as areas containing large numbers of tandem repeats, and does not interrogate variants in mitochondrial DNA. This assay cannot detect single and multiple exon deletions or duplications. This assay is not designed to detect mosaicism; possible cases of mosaicism may be investigated at the discretion of the laboratory director.

Pursuant to the requirements of CLIA '88, this test was developed and its performance validated by PerkinElmer Genetics. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes

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