Patient ID	Patient Name		Birth Date	Sex	Age
SA00154748	ABNORMAL, HYPBG		1987-11-25	F	34
Order Number	**Client Order Number**	**Ordering Physician**	**Report Notes**		
SA00154748	SA00154748	CLIENT,CLIENT			
Account Information		**Collected**			
C7028846 DLMP Rochester		07 Oct 2022 08:00			

Hypobetalipoproteinemia Gene Panel

Interpretation

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SARB1: c.409G>A (p.Asp137Asn): The homozygous c.409G>A (p.Asp137Asn) variant in the SAR1B gene (MIM: 607690) is classified as pathogenic. The SAR1B gene encodes secretion associated RAS-related GTPase 1B, a protein involved in the assembly and transport of chylomicrons from the endoplasmic reticulum to the Golgi apparatus. Pathogenic variants in this gene are associated with autosomal recessive chylomicron retention disease, also known as Anderson disease. This variant has been reported in the homozygous and compound heterozygous in several individuals with chylomicron retention disease and has been shown to segregate with disease in at least three families with (1–5). This variant has been observed at a low frequency in individuals of non-Finnish European descent (0.005%, 6/112452 alleles) (6). This amino acid is highly conserved across species and there is a small physicochemical difference between aspartic acid (Asp) and asparagine (Asn). An in silico meta-predictor suggests that this amino acid change may impact protein function. However, computational tools are not sufficient to determine the biological impact (or lack thereof) of a variant, and functional studies have not been performed to confirm the pathogenicity of this variant. Taken together, this result is supportive of a diagnosis of chylomicron retention disease for this individual. Clinical correlation is recommended.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

Consultation with a genetics professional is recommended for interpretation of this result and to determine whether reproductive risk assessment and familial testing may be of benefit to this family. Genetic testing for family members is available by ordering FMTT / Familial Mutation, Targeted Testing for the specific variant(s) detected. Please contact the laboratory at 1–800–533–1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

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3. Peretti N, Roy CC, Sassolas A, et al. Chylomicron retention disease: a long term study of two cohorts. Mol Genet Metab. 2009;97(2):136–142. doi:10.1016/j.ymgme.2009.02.003 (PMID: 19285442)

4. Blanco-Vaca F, Martin-Campos JM, Beteta-Vicente A, et al. Molecular analysis of APOB, SAR1B, ANGPTL3, and MTTP in patients with primary hypocholesterolemia in a clinical laboratory setting: Evidence supporting polygenicity in mutation-negative patients. Atherosclerosis. 2019;283:52–60. doi:10.1016/j.atherosclerosis.2019.01.036 (PMID: 30782561)

5. Simone ML, Rabacchi C, Kuloglu Z, et al. Novel mutations of SAR1B gene in four children with chylomicron retention disease. J Clin Lipidol. 2019;13(4):554–562. doi:10.1016/j.jacl.2019.05.013 (PMID: 31253576)

6. gnomAD Browser: gnomad.broadinstitute.org/; Karczewski K, Francioli LC, MacArthur DG, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020; 581(7809):434–443 (PMID 32461654)

Result Summary

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Pathogenic Variants Detected

Result

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The following homozygous PATHOGENIC variant was detected:

LPL (NM_000237.2), Chr8(GRCh37):g.19813411C>G, c.835C>G, p.Leu279Val (p.L279V)

No additional reportable pathogenic variants, likely pathogenic variants, or variants of uncertain significance were detected within all other tested genes. See the Genes Analyzed section for a complete list of genes evaluated by the assay.

Test Description

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Evaluation of 5 genes associated with familial hypobetalipoproteinemia.

Specimen

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WB Whole Blood

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905	William G. Morice M.D. Ph.D	24D0404292

MAYO CLINIC LABORATORIES

Patient ID	Patient Name		Birth Date	Sex	Age
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Method

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Next generation sequencing (NGS) and/or Sanger sequencing was performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known pathogenic variants. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for indels less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. NGS, and/or a polymerase chain reaction (PCR)-based quantitative method was performed to test for the presence of deletions and duplications in the genes analyzed. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria. See www.mayocliniclabs.com (TEST ID HYPBG) for details regarding genes with regions not routinely covered.

Genes Analyzed

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ANGPTL3, APOB, MTTP, PCSK9, and SAR1B

Disclaimer

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Clinical Correlations
An online research opportunity called GenomeConnect (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects de-identified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

If testing was performed because of a clinically significant family history it is often useful to first test an affected family member. Detection of a reportable variant(s) in an affected family member would allow for more informative testing of at risk individuals.

To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1–800–533–1710.

Technical Limitations
Next generation sequencing may not detect all types of genomic variants. In rare cases, false negative or false positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

Additionally, low level mosaic variants may not be detected.

This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the Hypobetalipoproteinemia Gene Panel in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID HYPBG) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation
Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely

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benign are not reported.

Results from in silico evaluation tools may change over time and should be interpreted with caution and professional clinical judgment.

Released By MCR

Linnea M. Baudhuin, Ph.D.

Received: 10 Oct 2022 10:13 **Reported:** 10 Oct 2022 15:19

Laboratory Notes

[1] This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

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