ARUP LABORATORIES | aruplab.com
500 Chipeta Way, Salt Lake City, Utah 84108-1221
phone: 801-583-2787, toll free: 800-522-2787
Jonathan R. Genzen, MD, PhD, Chief Medical Officer

PATIENT REPORT

Patient Age/Sex: Male

Specimen Collected: 01-May-23 15:11

WGS Seq, Familial Control with Report | **Received: 01-May-23 15:12** | **Report/Verified: 01-May-23 15:14**

Procedure	Result	Units	Reference Interval
WGS FRPT Int	Positive f1 i1		

Result Footnote

f1: WGS FRPT Int
INDICATION FOR TESTING
Familial control for whole genome sequencing; report of secondary findings requested.

RESULT
One likely pathogenic variant was detected in the LDLR gene.

LIKELY PATHOGENIC VARIANT
Gene: LDLR (NM_000527.4)
OMIM disease: Familial hypercholesterolemia (MIM: 143890)
Inheritance pattern: Autosomal dominant
Variant: c.337G>A; p.Glu113Lys - heterozygous
Chr19(GRCh37):g.11215919
Frequency: gnomAD: 8 out of 281,964 chromosomes, overall MAF 0.0028%
Computational prediction programs: Uncertain (REVEL: 0.658)

INTERPRETATION
One likely pathogenic variant, c.337G>A; p.Glu113Lys, was detected in the LDLR gene by massively parallel sequencing. Pathogenic germline variants in LDLR are associated with autosomal dominant familial hypercholesterolemia-1 (MIM: 143890). Offspring of this individual have a 50 percent chance of inheriting the likely pathogenic variant.

The American College of Medical Genetics and Genomics (ACMG) recommends analysis of specific genes in all individuals undergoing genome sequencing even though these genes may not be related to the primary key clinical findings (Miller, 2022).

Evidence for variant classification:
The identified c.337G>A; p.Glu113Lys variant, also known as E92K, segregates with elevated LDL cholesterol but not elevated triglycerides in a large three-generation pedigree, and it has been reported in two additional probands who were affected with hypercholesterolemia (Fouchier, 2005; Taylor, 2007; Wu, 2000). This variant is also reported in ClinVar (Variation ID: 237872). Based on available information, this variant is considered to be likely pathogenic.

No additional pathogenic variants in the v3.1 list of ACMG-recommended genes were detected. This does not exclude the possibility this individual may carry another pathogenic variant because the ACMG genes are only analyzed to the extent standard massively parallel sequencing will allow. Note that single pathogenic variants in autosomal recessive ACMG genes are not reported. See the background information below for a list of the ACMG genes reviewed.

RECOMMENDATIONS
Genetic consultation is recommended, including a discussion of medical screening and management. At-risk family members should be offered targeted testing for the identified likely pathogenic LDLR variant (Familial Targeted Sequencing, ARUP test 3005867). If there is clinical suspicion or a family history of a genetic condition associated with another one of the ACMG-recommended genes, additional targeted testing should be considered as exome sequencing will not identify all pathogenic variants in these genes.

REFERENCES

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

Result Footnote

f1: WGS FRPT Int

Fouchier SW, et al. Update of the molecular basis of familial hypercholesterolemia in The Netherlands. Hum Mutat. 2005;26(6):550-556. PMID: 16250003.

Miller DT, et al. ACMG SF v3.1 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2022;24(7):1407-1414. PMID: 35802134 .

Taylor A, et al. Multiplex ARMS analysis to detect 13 common mutations in familial hypercholesterolaemia. Clin Genet. 2007;71(6):561-568. PMID: 17539906.

Wu LL, et al. Co-segregation of elevated LDL with a novel mutation (D92K) of the LDL receptor in a kindred with multiple lipoprotein abnormalities. J Hum Genet. 2000;45(3):154-158. PMID: 10807540.

Test Information

i1: WGS FRPT Int

BACKGROUND INFORMATION: Whole Genome Sequencing, Familial Control with Report

CHARACTERISTICS: The analyzed genome includes all exons from all known human nuclear genes and all intronic variants suspected of influencing splicing. These regions are sequenced to identify the cause(s) of a disorder in a family member. The American College of Medical Genetics (ACMG) recommends analysis of certain genes for secondary findings in all individuals undergoing genome sequencing. Please refer to ACMG Secondary Findings Gene List (http://ltd.aruplab.com/Tests/Pub/3016497) for an up-to-date list of genes analyzed. Note that this gene list is updated periodically and is only accurate for this sample at the time of reporting. Please contact an ARUP genetic counselor (800-242-2787 ext. 2141) for clarification regarding genes analyzed.

INHERITANCE: Varies depending on the specific gene and variant

CLINICAL SENSITIVITY: Varies by gene

METHODOLOGY: Genomic DNA is extracted from whole blood, prepared into libraries, then sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]). Variant calling is performed using a custom bioinformatics pipeline that includes phenotype-based scores. Human genome build 19 (Hg 19) is used for data analysis.

LIMITATIONS OF ANALYSIS: Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay is not designed to detect low-level somatic variants associated with disease. Interpretation of this test result may be impacted if this individual has had an

Test Information

i1: WGS FRPT Int

allogeneic stem cell transplantation. Mode of inheritance, reduced penetrance, and genetic heterogeneity could reduce the clinical sensitivity.

LIMITATIONS OF REPORTING: Secondary pathogenic findings, including variants identified in genes on the ACMG-recommended panel or other medically actionable variants at ARUP's discretion, are reported. Variants of unknown significance will not be reported. Single pathogenic variants in autosomal recessive genes will not be reported.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. Food and Drug Administration. This test was performed in a CLIA-certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.