Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: TEST,

## Patient: POSITIVE, EXOME FRPT

**DOB**
**Sex:** Male
**Patient Identifiers:** 51723
**Visit Number (FIN):** 52110
**Collection Date:** 8/21/2023 07:39

## Exome Sequencing, Familial Control

ARUP test code 3016589

EXOME FRPT Int

Positive

INDICATION FOR TESTING
Familial control for exome 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 1 (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). This result is consistent with a diagnosis of familial hypercholesterolemia. This individual's offspring 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 exome sequencing even though these genes may not be related to the primary key clinical findings (Miller, 2022).

Evidence for variant classification: The LDLR 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.

H=High, L=Low, *=Abnormal, C=Critical

RECOMMENDATIONS
Genetic consultation is indicated, 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 code 3005867).

If there is clinical suspicion or family history of a genetic condition associated with 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
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.

BACKGROUND INFORMATION: Exome Sequencing, Familial Control

CHARACTERISTICS: The analyzed exome includes all exons from all known human nuclear genes and accounts for approximately 1-2 percent of the human genome. 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/3016589) 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. Mode of inheritance, reduced penetrance, and genetic heterogeneity can reduce the clinical sensitivity.

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

LIMITATIONS OF ANALYSIS: Not all pathogenic variants occur in the coding regions of genes. Some genes, or parts of genes, may not be adequately sequenced to allow for confident analysis. The following types of variants may not be detectable: those located in genes with corresponding pseudogenes, those in repetitive or high GC rich regions, large deletions / duplications / rearrangements, and mosaic variants. Rare variants in probe hybridization sites may compromise analytical 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.

VERIFIED/REPORTED DATES

| Procedure | Accession | Collected | Received | Verified/Reported |
|---|---|---|---|---|
| EXOME FRPT Int | 23-233-100749 | 8/21/2023 7:39:00 AM | 8/21/2023 7:39:52 AM | 8/21/2023 7:43:00 AM |

END OF CHART

H=High, L=Low, *=Abnormal, C=Critical