Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/20/2021
Sex:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Exome Sequencing, Familial Control

ARUP test code 2006340

Exome Sequencing, Familial Control

Positive

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

LIKELY PATHOGENIC VARIANT
Gene: LDLR (NM_000527.4)
Variant: c.337G>A; p.Glu113Lys - Heterozygous
Chr19(GRCh37):g.11215919
Frequency: rs769383881; gnomAD: 8 out of 281,964 chromosomes, overall MAF 0.0028%
Conservation: Highly conserved amino acid (Alamut software v2.11.0)
Computational prediction programs: Uncertain (REVEL: 0.658)
Inheritance pattern: Autosomal dominant

INTERPRETATION
One likely pathogenic variant, c.337G>A; p.Glu113Lys, was detected in the low density lipoprotein receptor (LDLR) gene by massively parallel sequencing. Pathogenic germline variants in LDLR are associated with autosomal dominant familial hypercholesterolemia-1 (MIM: 143890). Offspring of this individualhave 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 indication for testing (Miller 2021).

No additional pathogenic variants in the v3.0 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.

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, and Wu 2000). This variant is also reported in ClinVar (Variation ID: 237872). Based on available information, this variant is considered to be likely pathogenic.

RECOMMENDATIONS

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

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 Mutation, Targeted Sequencing, ARUP test code 2001961).

If there is clinical suspicion or 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

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

Miller et al. ACMG SF v3.0 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. 2021 May 20.

Taylor et al. Multiplex ARMS analysis to detect 13 common mutations in familial hypercholesterolaemia. Clin Genet. 2007 Jun;71(6):561-8.

Wu 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):154-8.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Exome Sequencing, Familial Control

CHARACTERISTICS: DNA coding regions and intron/exon boundaries of the human exome are sequenced to identify the cause(s) of a disorder in a family member. The American College of Medical Genetics (ACMG) recommends analysis of the following genes for pathogenic mutations in all individuals undergoing exome sequencing:

GENES ASSOCIATED WITH AN INCREASED RISK FOR TUMORS/CANCER: hereditary breast and ovarian cancer (BRCA1, BRCA2), Li-Fraumeni syndrome (TP53) Peutz-Jeghers syndrome (STK11) Lynch syndrome (MLH1, MSH2, MSH6, PMS2), familial adenomatous polyposis (APC), MUTYH-associated polyposis, Von Hippel Lindau syndrome (VHL), multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2/familial medullary thyroid cancer (RET), PTEN hamartoma tumor syndrome (PTEN), retinoblastoma (RB1), hereditary paraganglioma-pheochromocytoma syndrome (SDHD, SDHAF2, SDHC, SDHB), tuberous sclerosis complex (TSC1, TSC2), WT1-related Wilms (WT1), neurofibromatosis type 2 (NF2). GENES ASSOCIATED WITH CARDIOVASCULAR (HEART) PROBLEMS: EDS IV (COL3A1), Marfan syndrome (FBN1), Loeys-Dietz syndrome (TGFBR1 and TGFBR2), familial thoracic aortic aneurysms and dissections (SMAD3, ACTA2, MYLK, MYH11), hypertrophic cardiomyopathy/dilated cardiomyopathy (MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA ,MYL2, LMNA), catecholaminergic polymorphic ventricular tachycardia (RYR2), arrhythmogenic right ventricular cardiomyopathy (PKP2, DSP, DSC2, TMEM43, DSG2), Romano-Ward long QT syndromes types 1, 2, and 3, Brugada syndrome (KCNQ1, KCNH2, SCN5A), familial hypercholesterolemia (LDLR, APOB, PCSK9).

GENES INFLUENCING RESPONSE TO ANESTHESIA: malignant hyperthermia (RYR1, CACNA1S).

INHERITANCE: Varies depending on the specific gene and variant.

CLINICAL SENSITIVITY: Varies by gene.

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 mutations. Rare variants in probe hybridization sites may compromise analytical sensitivity. Mode of inheritance, reduced penetrance,and genetic heterogeneity could reduce the clinical sensitivity.

LIMITATIONS OF REPORTING: Only known pathogenic variants identified in genes on the ACMG-recommended panel are reported. Variants of unknown significance will not be reported. Single pathogenic variants in autosomal recessive genes will not be reported.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Exome Sequencing, Familial Control	21-326-117748	11/22/2021 3:52 00 PM	11/22/2021 3:53:16 PM	11/22/2021 3:55:00 PM

END OF CHART

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