ARUP LABORATORIES
800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Jonathan R. Genzen, MD, PhD, Chief Medical Officer

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

Physician: Doctor, Example

Patient: Patient, Example

DOB	2/5/2013
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Familial Hypercholesterolemia Panel, Sequencing

ARUP test code 3002110

Familial Hypercholesterolemia Specimen	Whole Blood

Familial Hypercholesterolemia Interp	Positive

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

LIKELY PATHOGENIC VARIANT
Gene: LDLR (NM_000527.5)
Nucleic Acid Change: c.514G>A; Heterozygous
Amino Acid Alteration: p.Asp172Asn
Inheritance: Autosomal Dominant

INTERPRETATION
One likely pathogenic variant, c.514G>A; p.Asp172Asn, was detected in the LDLR gene by massively parallel sequencing. Pathogenic variants in LDLR are associated with autosomal dominant familial hypercholesterolemia 1 and LDL cholesterol level QTL2 (MIM: 143890). This result is consistent with a diagnosis of familial hypercholesterolemia. This individual's future offspring have a 50 percent chance of inheriting the likely pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The LDLR c.514G>A; p.Asp172Asn variant (rs879254554, ClinVar variation ID: 251266), also known as D151N, is reported in the literature in individuals with a diagnosis of familial hypercholesterolemia (Jensen 1999, Chater 2006) and in hypercholesterolemia cohorts (Benedek 2021, Di Taranto 2021, Leren 2021, Marco-Benedi 2022, Mozas 2004). This variant was also found to segregate with disease in three family members (Chater 2006). Computational analyses predict that this variant is deleterious (REVEL: 0.763). In vitro functional analyses of the LDLR cycle demonstrate no impact on protein expression, but significantly reduced LDL binding and uptake compared to wildtype cells (Etxebarria 2015). Based on available information, this variant is considered to be likely pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should undergo cholesterol screening using a lipid panel and be offered testing for the identified likely pathogenic LDLR variant (Familial Targeted Sequencing, ARUP test code 3005867).

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

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations: None

REFERENCES
Benedek P et al. Founder effects facilitate the use of a genotyping-based approach to molecular diagnosis in Swedish patients with familial hypercholesterolaemia. J Intern Med. 2021 Aug;290(2):404-415. PMID: 33955087.
Chater R et al. Mutational heterogeneity in low-density lipoprotein receptor gene related to familial hypercholesterolemia in Morocco. Clin Chim Acta. 2006 Nov;373(1-2):62-9. PMID: 16806138.
Di Taranto MD et al. Genetic spectrum of familial hypercholesterolemia and correlations with clinical expression: Implications for diagnosis improvement. Clin Genet. 2021 Nov;100(5):529-541. PMID: 34297352.
Etxebarria A et al. Activity-associated effect of LDL receptor missense variants located in the cysteine-rich repeats. Atherosclerosis. 2015 Feb;238(2):304-12. PMID: 25545329.
Jensen HK et al. Spectrum of LDL receptor gene mutations in Denmark: implications for molecular diagnostic strategy in heterozygous familial hypercholesterolemia. Atherosclerosis. 1999 Oct;146(2):337-44. PMID: 10532689.
Leren TP and Bogsrud MP. Molecular genetic testing for autosomal dominant hypercholesterolemia in 29,449 Norwegian index patients and 14,230 relatives during the years 1993-2020. Atherosclerosis. 2021 Apr;322:61-66. PMID: 33740630.
Marco-Benedi V et al. Lipoprotein(a) in hereditary hypercholesterolemia: Influence of the genetic cause, defective gene and type of mutation. Atherosclerosis. 2022 May;349:211-218. PMID: 34456049.
Mozas P et al. Molecular characterization of familial hypercholesterolemia in Spain: identification of 39 novel and 77 recurrent mutations in LDLR. Hum Mutat. 2004 Aug;24(2):187. PMID: 15241806.

This result has been reviewed and approved by [redacted]

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

BACKGROUND INFORMATION: Familial Hypercholesterolemia Panel, Sequencing

CHARACTERISTICS: Familial hypercholesterolemia (FH) is the most common inherited cardiovascular disease. It is characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) and premature atherosclerotic cardiovascular disease (ASCVD). Manifestations include coronary artery disease (CAD), cardiovascular disease (CVD), angina, myocardial infarction, xanthomas, and corneal arcus. Homozygous FH (HoFH) is a less common disorder, resulting from biallelic variants in a dominant FH-associated gene. HoFH is characterized by severe early-onset CAD, aortic stenosis, and high rate of coronary bypass surgery or death by teenage years.

EPIDEMIOLOGY: FH 1/250, HoFH 1/200,000 in the general population.

CAUSE: Pathogenic germline variants in genes associated with FH.

INHERITANCE: Autosomal dominant for LDLR, APOB and PCSK9-associated FH. Autosomal recessive for LDLRAP1-associated FH. HoFH results from biallelic variants in an autosomal dominant FH gene.

PENETRANCE: Estimated at 73-90 percent in individuals with molecularly confirmed FH; influenced by gene, variant, and non-genetic factors.

CLINICAL SENSITIVITY: Up to 85 percent for FH.

GENES TESTED: APOB, LDLR, LDLRAP1, PCSK9.

METHODOLOGY: 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 fill in regions of low coverage and to confirm reported variants. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a diagnosis of FH. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants, deep intronic variants, and large deletions/duplications/inversions will not be identified. Deletions/duplications/insertions of any size may not be detected by massive 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 may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US 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
Familial Hypercholesterolemia Specimen	24-121-123713	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Familial Hypercholesterolemia Interp	24-121-123713	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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