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

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Hypertrophic Cardiomyopathy Panel, Sequencing

ARUP test code 3001579

Hypertrophic Cardiomyopathy Specimen	Whole Blood

Hypertrophic Cardiomyopathy Interp

Positive

RESULT
One pathogenic variant was detected in the MYH7 gene.

PATHOGENIC VARIANT
Gene: MYH7 (NM_000257.4)
Nucleic Acid Change: c.2156G>A; Heterozygous
Amino Acid Alteration: p.Arg719Gln
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.2156G>A; p.Arg719Gln, was detected in the MYH7 gene by massively parallel sequencing. Pathogenic variants in MYH7 are associated with autosomal dominant hypertrophic cardiomyopathy 1 (MIM: 192600), dilated cardiomyopathy 1S (MIM: 613426), left ventricular noncompaction 5 (MIM: 613426), and Laing distal myopathy (MIM: 160500). This result is consistent with a diagnosis of a MYH7-related disorder. This individual's offspring have a 50 percent chance of inheriting the 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 MYH7 c.2156G>A; p.Arg719Gln variant (rs121913641) is reported in the literature in multiple individuals and families with hypertrophic cardiomyopathy, and shown to co-segregate with disease (Burns 2017, Consevage 1994, Gonzalez-Quereda 2020, Robyns 2020, Walsh 2017). This variant is classified as pathogenic by an expert review panel in ClinVar (Variation ID: 14107). It is absent from the Genome Aggregation Database, indicating it is not a common polymorphism. The arginine at codon 719 is highly conserved, and computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.694). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Cardiology and genetic consultations are indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic MYH7 variant (Familial Targeted Sequencing, ARUP test code 3005867).

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

COMMENTS
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
Burns C et al. Multiple Gene Variants in Hypertrophic Cardiomyopathy in the Era of Next-Generation Sequencing. Circ Cardiovasc Genet. 2017 Aug;10(4):e001666. PMID: 28790153.
Consevage MW et al. A new missense mutation, Arg719Gln, in the beta-cardiac heavy chain myosin gene of patients with familial hypertrophic cardiomyopathy. Hum Mol Genet. 1994 Jun;3(6):1025-6. PMID: 7848441.
Gonzalez-Quereda L et al. Targeted Next-Generation Sequencing in a Large Cohort of Genetically Undiagnosed Patients with Neuromuscular Disorders in Spain. Genes (Basel). 2020 May 11;11(5):539. PMID: 32403337.
Robyns T et al. Clinical and ECG variables to predict the outcome of genetic testing in hypertrophic cardiomyopathy. Eur J Med Genet. 2020 Mar;63(3):103754. PMID: 31513939.
Walsh R et al. Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. Genet Med. 2017 Feb;19(2):192-203. PMID: 27532257.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Hypertrophic Cardiomyopathy Panel, Sequencing

CHARACTERISTICS: Familial hypertrophic cardiomyopathy (HCM) is a genetically heterogeneous disorder characterized by unexplained left ventricular hypertrophy (LVH). Common symptoms include shortness of breath, chest pain, palpitations, orthostasis, and syncope. Individuals with HCM may remain asymptomatic. Affected individuals are at risk for arrhythmias, outflow tract obstruction, thromboembolic complications, heart failure, and sudden cardiac death. Onset of familial HCM is often in adolescence or early adulthood. Syndromic forms of HCM, which include extracardiac manifestations, can present as isolated LVH.
EPIDEMIOLOGY: Prevalence of HCM is 1:500.

CAUSE: Pathogenic germline variants in sarcomeric genes and other genes associated with HCM.

INHERITANCE: Typically autosomal dominant for familial HCM. Genes with X-linked, autosomal recessive, and mitochondrial inheritance are also associated. De novo variation, compound heterozygous, or digenic heterozygous variants have been reported.

PENETRANCE: Variable.

CLINICAL SENSITIVITY: 50-60 percent for familial HCM, 20-30 percent for isolated HCM.

GENES TESTED: ACTC1, ACTN2, AGL, ALPK3, BRAF*, CACNA1C, CSRP3, DES, FHL1, FLNC*, GAA, GLA, HRAS, JPH2, KRAS, LAMP2, MAP2K1, MAP2K2, MYBPC3, MYH7, MYL2, MYL3, NRAS, PLN, PRKAG2*, PTPN11, RAF1, RIT1, SOS1, TNNC1, TNNI3, TNNT2, TPM1, TTR
* One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

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 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 heritable form of hypertrophic cardiomyopathy. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Mitochondrial genes are not interrogated. Regulatory region variants, large deletions/duplications/inversions, and deep intronic variants 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 are not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
BRAF(NM_004333) exon(s) 5,18
FLNC(NM_001458) exon(s) 47,48
PRKAG2(NM_016203) exon(s) 10,13

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
Hypertrophic Cardiomyopathy Specimen	22-301-105001	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Hypertrophic Cardiomyopathy Interp	22-301-105001	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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