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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

Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication

ARUP test code 2010183

Cardiomyopathy/Arrhythmia Panel Specimen	Whole Blood

Cardiomyopathy/Arrhythmia Panel 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: Cardiomyopathy and Arrhythmia Panel, Sequencing and Deletion/Duplication
CHARACTERISTICS: Inherited cardiomyopathy and arrhythmia disorders are genetically and phenotypically heterogeneous. Phenotypes include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular noncompaction (LVNC), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), long QT syndrome (LQTS), and short QT syndrome (SQTS).

EPIDEMIOLOGY: The prevalence of HCM is 1 in 500, DCM is 1 in 250 to 1 in 2,500, ARVC is 1 in 1,000, LQTS is 1 in 2,500, CPVT is 1 in 10,000, and it is unknown for BrS, LVNC, and SQTS.

CAUSE: Pathogenic germline variants in genes associated with cardiomyopathy and arrhythmia such as nuclear genes encoding sarcomeric or desmosomal proteins, cardiac ion channel components and cytoskeletal proteins, or pathogenic variants within the mitochondrial genome

INHERITANCE: Gene dependent and can be autosomal recessive, autosomal dominant, X-linked, or mitochondrial

PENETRANCE: Variable; dependent on gene and variant

CLINICAL SENSITIVITY: Dependent on clinical phenotype. Estimated at 50 percent for ARVC, 15-30 percent for BrS, 60 percent for CPVT, 25-40 percent for familial DCM, 50-60 percent for nonsyndromic familial HCM, and 60-75 percent for LQTS.

GENES TESTED: ABCC9; ACTC1; ACTN2; AGL; ALMS1; ALPK3; BAG3; BRAF*; CACNA1C; CALM1*; CALM2; CALM3; CASQ2; CRYAB; CSRP3*; DES*; DMD; DOLK; DSC2; DSG2; DSP; EMD; FHL1*; FKTN*; FLNC*; GAA; GLA; HCN4; HRAS; JPH2; JUP; KCNE1; KCNE2; KCNH2*; KCNJ2; KCNQ1; KRAS; LAMP2; LDB3; LMNA; MAP2K1; MAP2K2*; MYBPC3; MYH6*; MYH7*; MYL2; MYL3; NEXN; NKX2-5; NRAS; PKP2*; PLN; PRDM16; PRKAG2*; PTPN11**; RAF1*; RBM20; RIT1*; RYR2; SCN5A; SOS1*; TAFAZZIN; TCAP; TECRL*; TMEM43; TNNC1; TNNI3; TNNI3K; TNNT2; TPM1*; TRDN*; TTN*; TTR; VCL

*One or more exons are not covered by sequencing and/or deletion duplication analysis for the indicated gene; see limitations section below.

**Deletion/duplication detection is not available for this gene.

METHODOLOGY: Probe hybridization-based 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 that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of 2 exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of 3 exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a heritable form of cardiomyopathy or arrhythmia. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of 2 or fewer exons in size, though these may be identified. Single exon deletions are reported but called at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
BRAF (NM_004333, NM_001378468, NM_001378469, NM_001378473, NM_001378474) exon(s) 5,18
BRAF (NM_001354609, NM_001378472, NM_001378467) exon(s) 5,18,19
BRAF (NM_001374244) exon(s) 5,10,19
BRAF (NM_001374258) exon(s) 5,10,19,20
BRAF (NM_001378470, NM_001378475) exon(s) 4,17,18
BRAF (NM_001378471) exon(s) 5,17,18
CALM1 (NM_001363670) exon(s) 1
CSRP3 (NM_001369404) partial exon(s) 5(Chr11:19204180-19204196)
DES (NM_001382712) exon(s) 9
FKTN (NM_001351497) exon(s) 6
FKTN (NM_001351498) partial exon(s) 9(Chr9:108382363-108382373)
FLNC (NM_001458) exon(s) 47,48
FLNC (NM_001127487) exon(s) 46,47
PRKAG2 (NM_016203, NM_001040633) exon(s) 13
PRKAG2 (NM_001304527, NM_001363698) exon(s) 11
PRKAG2 (NM_001304531) exon(s) 10
PRKAG2 (NM_024429) exon(s) 9
RAF1 (NM_001354689) exon(s) 8

RAF1 (NM_001354694) exon(s) 7
SOS1 (NM_001382394) exon(s) 1
TECRL (NM_001363796) exon(s) 12
TPM1 (NM_001365777) partial exon(s) 9(Chr15:63358119-63358186)
TPM1 (NM_001365780) partial exon(s) 8(Chr15:63358119-63358186)
TTN (NM_001267550) exon(s)
172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,1
88,189,190,191,192,193,194,195,196,197
TTN (NM_001256850) exon(s) 154,155,156
TTN (NM_133378) exon(s) 153,154,155

Single exon deletions/duplications will not be called for the following exons:
BRAF (NM_004333) 3,18; BRAF (NM_001354609) 3,18-19; BRAF (NM_001374244) 3,10,19; BRAF (NM_001374258) 3,10,19-20; BRAF (NM_001378467) 3,18-19; BRAF (NM_001378468) 3,18; BRAF (NM_001378469) 3,18; BRAF (NM_001378470) 2,17-18; BRAF (NM_001378471) 3,17-18; BRAF (NM_001378472) 3,18-19; BRAF (NM_001378473) 3,18; BRAF (NM_001378474) 3,18; BRAF (NM_001378475) 17-18; CALM1 (NM_001363670) 1; DES (NM_001382712) 9; FHL1 (NM_001449) 7; FHL1 (NM_001159699) 6; FHL1 (NM_001159700) 7; FHL1 (NM_001159701) 6; FHL1 (NM_001159702) 8; FHL1 (NM_001159703) 6; FHL1 (NM_001159704) 6; FHL1 (NM_001167819) 7; FHL1 (NM_001330659) 5; FHL1 (NM_001369326) 8; FHL1 (NM_001369327) 8; FHL1 (NM_001369328) 8; FHL1 (NM_001369329) 7; FHL1 (NM_001369330) 7; FHL1 (NM_001369331) 6; FKTN (NM_001351497) 6; FLNC (NM_001458) 44-48; FLNC (NM_001127487) 43-47; KCNH2 (NM_000238) 6; KCNH2 (NM_001204798) 2; KCNH2 (NM_172056) 6; KCNH2 (NM_172057) 2; MAP2K2 (NM_030662) 1; MYH6 (NM_002471) 26; MYH7 (NM_000257) 27; PKP2 (NM_004572) 1; PKP2 (NM_001005242) 1; PRKAG2 (NM_016203) 13; PRKAG2 (NM_001040633) 13; PRKAG2 (NM_001304527) 11; PRKAG2 (NM_001304531) 10; PRKAG2 (NM_001363698) 11; PRKAG2 (NM_024429) 9; RAF1 (NM_001354689) 8; RAF1 (NM_001354694) 7; RIT1 (NM_001256821) 1; SOS1 (NM_001382394) 1; TECRL (NM_001363796) 12; TRDN (NM_006073) 5; TRDN (NM_001251987) 5; TRDN (NM_001256020) 5; TRDN (NM_001256021) 5; TRDN (NM_001256022) 5; TTN (NM_001267550) 172-197,201; TTN (NM_001256850) 154-156; TTN (NM_133378) 153-155

This test was developed and its performance characteristics determined by ARUP Laboratories. The U.S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use. The results are not intended to be used as the sole means for clinical diagnosis or patient management decisions.

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

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Cardiomyopathy/Arrhythmia Panel Specimen	22-294-118072	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cardiomyopathy/Arrhythmia Panel Interp	22-294-118072	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