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

Physician: Doctor, Example

Patient: Patient, Example

DOB	8/14/1977
Gender:	Male
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 MYBPC3 gene.

PATHOGENIC VARIANT
Gene: MYBPC3 (NM_000256.3)
Nucleic Acid Change: c.26-2A>G; Heterozygous
Inheritance: Autosomal dominant/Autosomal recessive

INTERPRETATION
One copy of a pathogenic variant, c.26-2A>G, was detected in the MYBPC3 gene by massively parallel sequencing. Pathogenic variants in MYBPC3 are associated with autosomal dominant dilated cardiomyopathy 1MM and left ventricular noncompaction 10 (MIM: 615396) and autosomal dominant or recessive hypertrophic cardiomyopathy 4 (MIM: 115197). This result is consistent with a diagnosis of MYBPC3-associated cardiomyopathy. 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 MYBPC3 c.26-2A>G variant (rs376395543) is reported in the literature in multiple individuals affected with hypertrophic cardiomyopathy or left ventricular noncompaction and segregates with disease in several kindreds (Ehlermann 2008, Hathaway 2021, McGurk 2023, Sedaghat-Hamedani 2017, Van Driest 2004, Walsh 2017). This variant has been reported to be incompletely penetrant (McGurk 2023, Sedaghat-Hamedani 2017), and it is found in the general population with an overall allele frequency of 0.003% (7/255,378 alleles) in the Genome Aggregation Database (v2.1.1). This variant disrupts the canonical splice acceptor site of intron 1, which is likely to negatively impact gene function. 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 MYBPC3 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
Ehlermann P et al. Adverse events in families with hypertrophic or dilated cardiomyopathy and mutations in the MYBPC3 gene. BMC Med Genet. 2008 Oct 28;9:95. PMID: 18957093.

Hathaway J et al. Diagnostic yield of genetic testing in a heterogeneous cohort of 1376 HCM patients. BMC Cardiovasc Disord. 2021 Mar 5;21(1):126. PMID: 33673806.

McGurk KA et al. The penetrance of rare variants in cardiomyopathy-associated genes: A cross-sectional approach to estimating penetrance for secondary findings. Am J Hum Genet. 2023 Sep 7;110(9):1482-1495. PMID: 37652022.

Sedaghat-Hamedani F et al. Clinical genetics and outcome of left ventricular non-compaction cardiomyopathy. Eur Heart J. 2017 Dec 7;38(46):3449-3460. PMID: 29029073.

Van Driest SL et al. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004 Nov 2;44(9):1903-10. PMID: 15519027.

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	24-050-114829	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Hypertrophic Cardiomyopathy Interp	24-050-114829	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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