Client: UU University Division Validation
50 N. Medical Drive
Salt Lake City, UT 84132
UNITED STATES

Physician: ARUP,

Patient: PRODVAL2, HCM NGS

DOB	3/29/2021
Gender:	Female
Patient Identifiers:	593435
Visit Number (FIN):	617435
Collection Date:	3/30/2021 07:45

Hypertrophic Cardiomyopathy Panel, Sequencing

ARUP test code 3001579

Hypertrophic Cardiomyopathy Specimen	Whole Blood

Hypertrophic Cardiomyopathy Interp	Positive

INDICATION FOR TESTING
Hypertrophic cardiomyopathy

RESULT
One pathogenic variant was detected in the MYBPC3 gene.

PATHOGENIC VARIANT
Gene: MYBPC3 (NM_000256.3)
Nucleic Acid Change: c.772+1G>A Heterozygous
Inheritance: Autosomal dominant

INTERPRETATION
One pathogenic variant, c.772+1G>A, was detected in the MYBPC3 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic MYBPC3 variants are inherited in an autosomal dominant manner, and are associated with hypertrophic cardiomyopathy 4 (MIM: 115197), dilated cardiomyopathy 1MM and left ventricular noncompaction 10 (MIM: 615396). This result is consistent with a diagnosis of familial hypertrophic cardiomyopathy. Offspring of this individual have a 50 percent chance of inheriting the pathogenic variant.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification: The MYBPC3 c.772+1G>A variant (rs397516072), also published as IVS7+1G>A, is reported in the literature in multiple individuals affected with hypertrophic cardiomyopathy (Erdmann 2001, Walsh 2017). In one family, this variant was observed to segregate with disease in all affected members (Erdmann 2001). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant abolishes the canonical splice donor site of intron 6, which is likely to disrupt gene function. Indeed, RNA analyses of individuals with this variant exhibit skipping of exon 6 or exons 6 and 7 (Erdmann 2001). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Cardiology and genetic consultation are indicated, including a

discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report, but are available upon request.

REFERENCES
Erdmann J et al. Spectrum of clinical phenotypes and gene variants in cardiac myosin-binding protein C mutation carriers with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2001 Aug;38(2):322-30.

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.

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	21-089-101867	3/30/2021 7:45:00 AM	3/30/2021 7:46:27 AM	3/30/2021 7:55:00 AM
Hypertrophic Cardiomyopathy Interp	21-089-101867	3/30/2021 7:45:00 AM	3/30/2021 7:46:27 AM	3/30/2021 7:55:00 AM

END OF CHART

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