PARTNERS HEALTHCARE | PERSONALIZED MEDICINE
MASSACHUSETTS GENERAL HOSPITAL | BRIGHAM AND WOMEN'S HOSPITAL

Laboratory for Molecular Medicine
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Unit Number(s):

Lab Accession: **PM-20-N00116**
Patient Name: **P.T.970, HCM 2020 PT1**
Birth Date: **1/1/1900**
Age Sex: **120 Year old Unspecified**

MOLECULAR DIAGNOSTICS REPORT

Specimen Type: DNA, Isolated - Blood, Peripheral (edit)
DNA, Isolated - Blood, Peripheral (edit)
Related Accession(s):
Referring Physician: LMM DR
Copies To:

Received Date: 1/31/2020
Referring Facility:
Referring Fac. MRN:
Lab Control Number:
Family Number: FABC123

TEST DESCRIPTION – Copy Number Variation Analysis
Sequence Confirmation Test
Pan Cardiomyopathy Panel (62 Genes)

TEST PERFORMED – CNV-a; SeqConfirm; PCM-pnlAv5

INDICATION FOR TEST – PROFICIENCY TESTING

RESULTS

DNA VARIANTS:
Heterozygous c.49C>T (p.Arg17Cys), Exon 3, MYH7, Uncertain significance

INTERPRETATION:
Inconclusive. DNA sequencing and copy number analysis of the coding regions and splice sites of 62 cardiomyopathy genes (see methodology section below) identified the variant listed above.

INTERPRETATION SUMMARY:
One heterozygous variant of uncertain significance was identified in the MYH7 gene and though the available data is limited, it suggests that the MYH7 variant may be disease-causing. Specific variant information is described in the variant interpretation sections below.

Genetic testing of this individual's biological relatives, particularly the parents or those who are affected, may help to clarify the significance of this variant or determine whether this variant has occurred de novo.

Disease penetrance and severity can vary due to modifier genes and/or environmental factors. The significance of a variant should therefore be interpreted in the context of the individual's clinical manifestations. For a list of disease-gene associations, please visit our website at http://personalizedmedicine.partners.org/Laboratory-For-Molecular-Medicine/Tests/Cardiomyopathy/.

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VARIANT INTERPRETATIONS:

p.Arg17Cys, c.49C>T (MYH7; NM_000257.2; Chr14g.23902893G>A; GRCh37):
The p.Arg17Cys variant in MYH7 has been identified in 3 individuals with HCM, 1 of whom was a child who carried an additional MYH7 variant in trans (LMM data, Walsh 2017, Alfares 2015). It has also been identified in 0.007% (4/251344) of South Asian chromosomes by gnomAD. Computational prediction tools and conservation analyses suggest that this variant may impact the protein, though this information is not predictive enough to determine pathogenicity. In summary, while there is some suspicion for a pathogenic role, the clinical significance of this variant is uncertain. ACMG/AMP Criteria Applied: PM2, PP3, PS4_Supporting.

RECOMMENDATION:
Genetic counseling is recommended for this individual and their relatives. For assistance in locating genetic counseling services or disease specialists please call the laboratory at 617-768-8500 or email at LMM@partners.org. Please note that variant classification, particularly of uncertain significance, may change over time if more information becomes available. Please contact us at 617-768-8500 or LMM@partners.org.

COMMENTS:
An online research opportunity called GenomeConnect is available for any recipient of genetic testing to advance knowledge of genetic variants by sharing de-identified genetic and health information. Please visit genomeconnect.org to learn more.

TEST INFORMATION

BACKGROUND:
Inherited cardiomyopathies are a group of genetically heterogeneous cardiac diseases that are relatively common in the general population They are associated with heart failure and sudden cardiac death and have a substantial genetic component. Familial inheritance is common and typically follows an autosomal dominant pattern, though other inheritance are also observed. The predominant forms are hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), followed by arrhythmogenic right ventricular cardiomyopathy (ARVC) and left ventricular non-compaction (LVNC).

METHODOLOGY:
The Pan Cardiomyopathy Panel includes 62 genes: ABCC9, ACTC1, ACTN2, ANKRD1, BAG3, CASQ2, CAV3, CHRM2, CRYAB, CSRP3, DES, DMD, DOLK, DSC2, DSG2, DSP, DTNA, EMD, FHL2, GATAD1, GLA (includes deep intronic c.639+919G>A variant), ILK, JPH2, JUP, LAMA4 (excludes exon 2A* in NM_001105209.1 and exon 8 in NM_002290.3), LAMP2, LDB3, LMNA (excludes exons 1B* and 13B* in NM_001257374.2), CAVIN4, MYBPC3, MYH6 (excludes exon 37 in NM_002471.3), MYH7, MYL2, MYL3, MYLK2, MYOM1, MYOZ2, MYPN, NEBL, NEXN, PDLIM3, PKP2, PLN, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RYR2, SCN5A, SGCD, TAZ, TCAP, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TRDN, TTN, TTR, VCL. For TTN, all of the coding exons in the NM_133378.4 transcript are included. *Exon from an alternate transcript. For additional information on reference sequences and exon coverage, please visit our website (www.partners.org/personalizedmedicine/lmm).

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This assay is performed using the PerkinElmer Sciclone® G3 Workstation combined with the Agilent SureSelect Clinical Research Exome capture kit (#G9496A 5190-7344; targeting coding regions (exons) and canonical splice sites) followed by sequencing on the Illumina NextSeq 550 (High-Output v2 kit). Reads are aligned to the GRCh37 reference sequence using the Burrows-Wheeler Aligner (BWA 0.7.17), and variant calls are made using the Genomic Analysis Tool Kit (GATK v4.0.3.0). Detection of copy number variants (CNVs) encompassing 2 or more exons is performed using next-generation sequencing read data and the VisCap algorithm. CNV analysis is only performed when data meets necessary quality standards and may not be available for all cases. Variant calls are limited bioinformatically to the associated region of interest for the assay (see above for details). Sanger sequencing is used for fill in when bases have <12x coverage. All clinically significant variants are confirmed by Sanger sequencing or droplet digital PCR; variants classified as likely benign or benign are not confirmed.

This test is 99.93% sensitive (95% CI =99.92-99.94%) to detect variants changing a single base and 96.75% sensitive to detect insertion/deletions (95% CI =96.28-97.22%) within covered regions. Technical positive predictive value for single nucleotide variant changes is 99.42% (95% CI = 99.37-99.48%) and 94.16% (95% CI = 93.34-94.97%) for insertion/deletion changes within covered regions. There is demonstrated reduced detection for larger indels, especially in low complexity regions with corresponding low sequence coverage and in regions with high homology.

Variant classifications are based on ACMG/AMP criteria (Richards et al. 2015) with ClinGen rule specifications (https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation/). Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen). Likely benign and benign variants are not included in this report but are available upon request.

This test does not routinely detect variants in non-coding regions (aside from the canonical splice sites), triplet repeat expansions, translocations, inversions, and copy number variants encompassing less than 2 consecutive exons. There is reduced detection for larger indels, variants in low complexity regions, and variants in regions with high homology.

This test was developed, and its performance characteristics determined by the Laboratory for Molecular Medicine at Partners HealthCare Personalized Medicine (LMM, 65 Landsdowne St, Cambridge, MA 02139; 617-768-8500; CLIA#22D1005307). It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

REFERENCES:

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Jordan DM, Kiezun A, Baxter SM, Agarwala V, Green RC, Murray MF, Pugh T, Lebo MS, Rehm HL, Funke BH, Sunyaev SR. 2011. Development and validation of a computational method for assessment of missense variants in hypertrophic cardiomyopathy. Am. J. Hum. Genet. 88(2):183-92. PMID: 21310275.

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Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, ACMG Laboratory Quality Assurance Committee. 2015. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet. Med. 17(5):405-24. PMID: 25741868.

Walsh R, Thomson KL, Ware JS, Funke BH, Woodley J, McGuire KJ, Mazzarotto F, Blair E, Seller A, Taylor JC, Minikel EV, Exome Aggregation Consortium null, MacArthur DG, Farrall M, Cook SA, Watkins H. 2017. Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples. Genet. Med. 19(2):192-203. PMID: 27532257.

REPORT PREPARATION by Andrea Muirhead Oza MS, CGC, on Thursday March 12, 2020 at 11:16:35AM
REPORT by Hana Zouk Ph.D., FACMG, on Monday March 16, 2020 at 10:32:41AM
Final Diagnosis by **Hana Zouk Ph.D., FACMG,** Electronically signed on Monday March 16, 2020 at 10:34:29AM