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

Laboratory for Molecular Medicine
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www.partners.org/personalizedmedicine/lmm

Lab Accession: **PM-13-X00000**
Patient Name: **DOE, GENE**
Birth Date: **01/01/1950**
Age Sex: **61 year old Female**

MOLECULAR DIAGNOSTICS REPORT

Specimen Type:	Blood, Peripheral	**Received Date:**	08/07/2008
Related Accession(s):		**Referring Facility:**	UNIV OF AMERICA
Referring Physician:	DR. SMITH	**Referring Fac. MRN:**	12345678
Copies To:	OTHER CONTACTS, MS, CGC SENDOUT UNIVERSITY OF AMERICA	**Lab Control Number:** **Family Number:**	00-222-55555 F000000

TEST DESCRIPTION – HCM Panel (18 Genes)
Sequence Confirmation Test
Copy Number Variation Analysis

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

INDICATION FOR TEST – Clinical diagnosis and family history of HCM

RESULTS

DNA VARIANTS:
Heterozygous c.1504C>T (p.Arg502Trp), Exon 17, MYBPC3, Pathogenic

INTERPRETATION:
Positive. DNA sequencing and copy number assessment of the coding regions and splice sites of ACTC1, ACTN2, CSRP3, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, MYOZ2, NEXN, PLN, PRKAG2, TNNC1, TNNI3, TNNT2, TPM1 and TTR identified the variant listed above.

SUMMARY (see below for variant interpretations): This individual carries a pathogenic variant in MYBPC3, which is consistent with the clinical diagnosis of HCM.

Cardiomyopathy due to pathogenic variants in the MYBPC3 gene is typically inherited in an autosomal dominant pattern. Each first-degree relative has a 50% (or 1 in 2) chance of inheriting a variant and its risk for cardiomyopathy. 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 www.partners.org/personalizedmedicine/lmm.

VARIANT INTERPRETATIONS:
The **Arg502Trp** variant in MYBPC3 has been well reported in multiple individuals across multiple studies and is known to be pathogenic. This variant meets our criteria for pathogenicity (www.partners.org/personalizedmedicine/lmm) based upon extensive segregation studies and functional evidence (Richard 2003, Van Driest 2004, Carballo 2005, Ingles 2005, Maron 2008, Kaski 2009, Marston 2009, Saltzman 2010). It is also the most common pathogenic HCM variant identified by our laboratory.

RECOMMENDATION:

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Genetic counseling is recommended for this individual and their relatives. Familial variant testing is available for other relatives if desired. For assistance in locating genetic counseling services or disease specialists, please call the laboratory at 617-768-8500 or email at LMM@partners.org.

COMMENTS:

Common sequence variants of unlikely clinical significance that are classified as benign are not included in this report but are available upon request.

In addition, the following less common sequence variant has been identified. Although it is likely benign we cannot rule out that it may be pathogenic or contribute to disease.

864+12T>A in intron 8 of NEXN: This variant is not expected to have clinical significance because it is not located within the splice consensus sequence. It has been identified in 0.2% (13/6568) of European American chromosomes from a broad population by the NHLBI Exome Sequencing Project (http://evs.gs.washington.edu/EVS).

INCIDENTAL VARIANTS:

Heterozygous c.864+12T>A, Intron 8, NEXN, Likely Benign

TEST INFORMATION

BACKGROUND:

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left ventricular hypertrophy (LVH) in a non-dilated ventricle. With a prevalence estimated to be ~1/500 in the general population, HCM is the most common monogenic cardiac disorder. To date, over 1000 variants have been identified in genes causative of HCM, most of which affect the sarcomere, the contractile unit of the cardiac muscle. In addition, defects in genes involved in storage diseases, such as LAMP2, PRKAG2 and GLA, typically cause systemic disease but may also result in predominant cardiac manifestations, which can mimic hypertrophic cardiomyopathy (HCM).

METHODOLOGY:

The HCM Panel includes the following 18 genes: ACTC1, ACTN2, CSRP3, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, MYOZ2, NEXN, PLN, PRKAG2, TNNC1, TNNI3, TNNT2, TPM1, and TTR. For reference sequences and exons covered, please visit our website (www.partners.org/personalizedmedicine/lmm).

This test is performed by next generation sequencing using Agilent SureSelect capture followed by sequencing of the coding regions and splice sites using Illumina sequencing technologies. Variant calls are generated using the Burrows-Wheeler Aligner followed by GATK analysis. Detection of copy number variants (CNVs) encompassing 1 or more exons is performed using VisCap™ analysis. Sanger sequencing is used to fill in regions with insufficient 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 does not detect variants in non-coding regions, aside from the splice junctions, that could affect gene expression and a few exons have been excluded due to technical difficulties. CNV analysis is only performed when data meets necessary quality standards and may not be available for all cases.

Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen).

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This test was developed and its performance characteristics determined by the Laboratory for Molecular Medicine at the 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.

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