MAYO CLINIC

1-800-533-1710

Postmortem Cardiomyopathy/Arrhythm

PMCAG

PATIENT NAME				ORDER NUMBER
TESTRNV, TESTING A				**N425000324**
PATIENT ID X100430262	DATE OF BIRTH 02/19/1968	AGE 55 Y	SEX Male	REQUESTED BY CLIENT TESTING
COLLECTED 9/25/2023, 7:00 AM	RECEIVED 9/25/2023, 2:07 PM	REPORTED 10/1/2023, 2:34 PM		
The collected, received, and reported dates and times on the report are in the time zone of the performing location. 7028846 MCL RochesterCampus Rochester MN 55901				CLIENT ORDER NUMBER X100430262 CLIENT MRN 321

TEST DESCRIPTION

Evaluation of 105 genes associated with hereditary forms of cardiomyopathy and cardiac arrhythmia

SPECIMEN

Tissue Scroll

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
PLN (NM_002667.4)	c.40_42del p.Arg14del (p.R14del) Chr6(GRCh37):g.118880124_118880126del	Heterozygous	Pathogenic

The following PATHOGENIC variant was detected:
PLN (NM_002667.4), chr6(GRCh37):g.118880124_118880126del, c.40_42del, p.Arg14del (p.R14del), heterozygous

No additional reportable variants were detected within all other tested genes. See the Genes Analyzed section for a complete list of genes evaluated by this assay.

INTERPRETATION

PLN c.40_42del (p.Arg14del), PATHOGENIC
The heterozygous c.40_42del (p.Arg14del) deletion in the PLN gene (MIM:172405) is classified as pathogenic. The PLN gene encodes phospholamban, a protein found as a pentamer in the sarcoplasmic reticulum membrane which controls cellular calcium levels based on phosphorylation. Pathogenic variants in this gene are associated with autosomal dominant forms of hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy, also referred to collectively as intrinsic cardiomyopathy. This variant has been shown to segregate with disease in multiple families affected with DCM or ARVC (1-3). This variant has been reported as a founder variant in individuals of Dutch ancestry (3). Functional studies have demonstrated that this variant results in protein disruption due to a dominant negative effect (4,5). A mouse model of this variant closely mimics the human phenotype, further supporting the pathogenicity of this variant (6). The overall minor allele frequency for this variant (rs771044756) is approximately 0.0007% with a frequency up to 0.002% in Non-Finnish European sub populations (7,8). This result is supportive of a diagnosis of autosomal dominant PLN-associated intrinsic cardiomyopathy for this individual. Clinical correlation is recommended.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

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Consultation with a genetics professional is recommended for interpretation of this result and to determine whether reproductive risk assessment and familial testing may be of benefit to this family. Genetic testing for family members is available by ordering FMTT / Familial Mutation, Targeted Testing for the specific variant(s) detected. Please contact the laboratory at 1-800-533-1710 or the online test catalog at www.mayocliniclabs.com for information about FMTT.

REFERENCES:

1) Haghighi K, Kolokathis F, Gramolini AO, et al. A mutation in the human phospholamban gene, deleting arginine 14, results in lethal, hereditary cardiomyopathy. Proc Natl Acad Sci U S A. 2006;103(5):1388-1393. doi:10.1073/pnas.0510519103 (PMID 16432188)

2) van der Zwaag PA, van Rijsingen IA, Asimaki A, et al. Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy. Eur J Heart Fail. 2012;14(11):1199-1207. doi:10.1093/eurjhf/hfs119 (PMID 22820313)

3) van der Zwaag PA, van Rijsingen IA, de Ruiter R, et al. Recurrent and founder mutations in the Netherlands-Phospholamban p.Arg14del mutation causes arrhythmogenic cardiomyopathy. Neth Heart J. 2013;21(6):286-293. doi:10.1007/s12471-013-0401-3 (PMID 23568436)

4) Ceholski DK, Trieber CA, Holmes CF, Young HS. Lethal, hereditary mutants of phospholamban elude phosphorylation by protein kinase A. J Biol Chem. 2012;287(32):26596-26605. doi:10.1074/jbc.M112.382713 (PMID 22707725)

5) Haghighi K, Pritchard T, Bossuyt J, et al. The human phospholamban Arg14-deletion mutant localizes to plasma membrane and interacts with the Na/K-ATPase. J Mol Cell Cardiol. 2012;52(3):773-782. doi:10.1016/j.yjmcc.2011.11.012 (PMID 22155237)

6) Eijgenraam TR, Boukens BJ, Boogerd CJ, et al. The phospholamban p.(Arg14del) pathogenic variant leads to cardiomyopathy with heart failure and is unreponsive to standard heart failure therapy [published correction appears in Sci Rep. 2020 Oct 2;10(1):16710]. Sci Rep. 2020;10(1):9819. Published 2020 Jun 17. doi:10.1038/s41598-020-66656-9 (PMID 32555305)

7) dbSNP: www.ncbi.nlm.nih.gov/snp

8) gnomAD Browser: gnomad.broadinstitute.org/

ADDITIONAL INFORMATION

TISSUE ID: Testing5-3092045

METHOD

Next generation sequencing (NGS) was performed to test for the presence of sequence variants in coding regions and intron/exon boundaries of the genes analyzed. The human genome reference GRCh37/hg19 build was used for sequence read alignment. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. See www.mayocliniclabs.com (TEST ID

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PMCAG) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ABCC9, ACAD9, ACADVL, ACTC1, ACTN2, AGL, ALMS1, ALPK3, ANK2, BAG3, BRAF, CACNA1C, CACNA1D, CACNA2D1, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, CDH2, CPT2, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, ELAC2, EMD, FHL1, FKRP, FKTN, FLNC, GAA, GLA, GNB5, HCN4, HRAS, JPH2, JUP, KCND2, KCND3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ8, KCNQ1, KRAS, LAMP2, LMNA, LZTR1, MAP2K1, MAP2K2, MRAS, MTO1, MYBPC3, MYH7, MYL2, MYL3, MYLK3, MYPN, NEXN, NKX2-5, NRAS, PCCA, PCCB, PKP2, PLN, PPA2, PPCS, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RIT1, RYR2, SCN5A, SGCD, SHOC2, SLC22A5, SLC4A3, SOS1, SOS2, TAZ (TAFAZZIN), TBX20, TCAP, TECRL, TMEM43, TMEM70, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TRDN, TRIM63, TTN, TTR and VCL

DISCLAIMER

Sample Quality:

This test is intended for use when EDTA whole blood is not available and formalin-fixed, paraffin-embedded (FFPE) tissue is the only available sample. DNA extracted from FFPE tissue can be degraded, which results in a higher failure rate for next-generation sequencing when compared to DNA extracted from whole blood. Due to the quality of DNA extracted from FFPE, the acceptable coverage threshold may be lower than that of the equivalent blood assays. Coverage of at least 20X is expected for most regions assessed but may be adjusted on a case-by-case basis at the discretion of the laboratory director.

Clinical Correlations

An online research opportunity called GenomeConnect (genomeconnect.org), a project of ClinGen, is available for the recipient of this genetic test. This patient registry collects de-identified genetic and health information to advance the knowledge of genetic variants. Mayo Clinic is a collaborator of ClinGen. This may not be applicable for all tests.

If testing was performed because of a clinically significant family history it is often useful to first test an affected family member. Detection of a reportable variant(s) in an affected family member would allow for more informative testing of at-risk individuals.

To discuss the availability of further testing options or for assistance in the interpretation of these results, Mayo Clinic Laboratory genetic counselors can be contacted at 1-800-533-1710.

Technical Limitations

Next generation sequencing may not detect all types of genomic variants. In rare cases, false negative or false positive results may occur. The depth of coverage may be variable for some target regions, but assay performance below the minimum acceptable criteria or for failed regions will be noted. Given these limitations, negative results do not rule out the

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diagnosis of a genetic disorder. If a specific clinical disorder is suspected, evaluation by alternative methods can be considered.

Deletion/duplication analysis is not performed due to technical limitations of the FFPE sample type. In addition, there may be regions of genes that cannot be effectively evaluated for sequencing analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of NGS results by Sanger sequencing is typically not performed for this test. Additionally, low level mosaic variants may not be detected.

This test is not designed to differentiate between somatic and germline variants. If there is a possibility that any detected variant is somatic, additional testing may be necessary to clarify the significance of results.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the Postmortem Cardiomyopathy/Arrhythm in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

Reclassification of Variants Policy

See www.mayocliniclabs.com (TEST ID PMCAG) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation

Variant curation is performed using published ACMG-AMP recommendations as a guideline. Other gene-specific guidelines may also be considered. Variants classified as benign or likely benign are not reported.

Results from in silico evaluation tools may change over time and should be interpreted with caution and professional clinical judgment.

TEST CLASSIFICATION

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

RELEASED BY

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