Patient ID	Patient Name		Birth Date	Sex	Age
SA00155413	ABNORMAL, ARVGG		1986-11-25	F	35
Order Number	**Client Order Number**	**Ordering Physician**	**Report Notes**		
SA00155413	SA00155413	CLIENT,CLIENT			
Account Information		**Collected**			
C7028846 DLMP Rochester		16 Nov 2022 08:00			

Arrhythmogenic Cardiomyopathy Panel

Interpretation

MCR

PLN c.40_42del (p.Arg14del), PATHOGENIC
The heterozygous c.40_42del (p.Arg14del) variant 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 PLN have been associated with autosomal dominant forms of hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). 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). Taken together, this result is supportive of a diagnosis of a hereditary form of 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.

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)
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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)

Result Summary

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Pathogenic Variant Detected

Result

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The following heterozygous PATHOGENIC variant was detected:

PLN (NM_002667.4), Chr6(GRCh37):g.118880124_118880126del, c.40_42del, p.Arg14del (p.R14del)

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

Test Description

MCR

Evaluation of 18 genes associated with hereditary forms of arrhythmogenic cardiomyopathy

Specimen

MCR

WB Whole Blood

Performing Site Legend

Code	Laboratory	Address	Lab Director	CLIA Certificate
MCR	Mayo Clinic Laboratories - Rochester Main Campus	200 First Street SW, Rochester, MN 55905	William G. Morice M.D. Ph.D	24D0404292

Patient ID	Patient Name		Birth Date	Sex	Age
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Method

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Next generation sequencing (NGS) and/or Sanger sequencing was performed to test for the presence of variants in coding regions and intron/exon boundaries of the genes analyzed, as well as some other regions that have known pathogenic variants. NGS and/or a polymerase chain reaction (PCR)-based quantitative method was performed to test for the presence of deletions and duplications in the genes analyzed. The human genome reference GRCh37/hg19 build was used for sequence read alignment. At least 99% of the bases are covered at a read depth over 30X. Sensitivity is estimated at above 99% for single nucleotide variants, above 94% for indels less than 40 base pairs (bp), above 95% for deletions up to 75 bp and insertions up to 47 bp. See the Genes Analyzed field for a list of genes tested.

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria. See www.mayocliniclabs.com (TEST ID ARVGG) for details regarding genes with regions not routinely covered.

Genes Analyzed

MCR

CDH2, DES, DSC2, DSG2, DSP, EMD, FLNC, JUP, LMNA, NKX2–5, PKP2, PLN, PPA2, PRKAG2, RBM20, RYR2, TMEM43 and TTN

Disclaimer

1 MCR

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

There may be regions of genes that cannot be effectively evaluated for sequencing or deletion and duplication analysis as a result of technical limitations of the assay, including regions of homology, high GC content, and repetitive sequences. Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria.

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 Arrhythmogenic Cardiomyopathy Panel 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 ARVGG) for information regarding the laboratory's policy for reclassification of variants.

Variant Evaluation
Variant curation is performed using published ACMG-AMP

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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.

Released By MCR

Linnea M. Baudhuin, Ph.D.

Received: 17 Nov 2022 13:10 **Reported:** 18 Nov 2022 12:26

Laboratory Notes

1 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.

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