MAYO CLINIC

1-800-533-1710

Postmortem Arrhythmia Gene Panel

PMARG

PATIENT NAME				ORDER NUMBER
TESTRNV, TESTING A				**N425000322**
PATIENT ID X100430254	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, 2:01 PM	REPORTED 10/1/2023, 2:57 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 X100430254 CLIENT MRN 321

TEST DESCRIPTION

Evaluation of 44 genes associated with hereditary forms of cardiac arrhythmia

SPECIMEN

Tissue Scroll

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
SCN5A (NM_198056.2)	c.1936del p.Gln646Argfs*5 (p.Q646Rfs*5) Chr3(GRCh37):g.38640496del	Heterozygous	Pathogenic

The following PATHOGENIC variant was detected:
SCN5A (NM_198056.2), chr3(GRCh37):g.38640496del, c.1936del, p.Gln646Argfs*5 (p.Q646Rfs*5), 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

SCN5A c.1936del (p.Gln646Argfs*5), PATHOGENIC
The heterozygous c.1936del (p.Gln646Argfs*5) deletion in the SCN5A gene (MIM:600163) is classified as pathogenic. The SCN5A gene encodes the alpha subunit of the type V voltage-gated sodium channel. Pathogenic variants in this gene have been associated with numerous cardiac disorders including autosomal dominant Brugada syndrome (loss of function variants) and autosomal dominant long QT syndrome (gain of function variants). Other associations include cardiac conduction defects, sick sinus syndrome, dilated cardiomyopathy, and atrial fibrillation. This variant has been previously reported in at least seven unrelated individuals with either a diagnosis of or features consistent with Brugada syndrome or early repolarization syndrome (1-5). In addition, this variant was reported to segregate with disease (defined as either asymptomatic electrocardiographic changes (mild phenotype), or syncope, cardiac arrest, and sudden cardiac death (severe phenotype)) in 22 individuals from one family (3). The overall minor allele frequency for this variant (rs727505158) is approximately 0.003% with a frequency up to 0.006% in Non-Finnish European sub-populations (6,7). Lastly, other truncating variants in the SCN5A gene have been reported in association with Brugada syndrome and/or other cardiac arrhythmia phenotypes. This result is supportive of a diagnosis of Brugada syndrome or other SCN5A-related cardiac arrhythmia condition for this individual. Clinical correlation is recommended.

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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) Kapplinger JD, Tester DJ, Alders M, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. Heart Rhythm. 2010;7(1):33-46. doi:10.1016/j.hrthm.2009.09.069 (PMID 20129283)

2) Kanter RJ, Pfeiffer R, Hu D, Barajas-Martinez H, Carboni MP, Antzelevitch C. Brugada-like syndrome in infancy presenting with rapid ventricular tachycardia and intraventricular conduction delay. Circulation. 2012;125(1):14-22. doi:10.1161/CIRCULATIONAHA.111.054007 (PMID 22090166)

3) Park JK, Martin LJ, Zhang X, Jegga AG, Benson DW. Genetic variants in SCN5A promoter are associated with arrhythmia phenotype severity in patients with heterozygous loss-of-function mutation. Heart Rhythm. 2012;9(7):1090-1096. doi:10.1016/j.hrthm.2012.02.023 (PMID 22370247)

4) Wijeyeratne YD, Tanck MW, Mizusawa Y, et al. SCN5A Mutation Type and a Genetic Risk Score Associate Variably With Brugada Syndrome Phenotype in SCN5A Families. Circ Genom Precis Med. 2020;13(6):e002911. doi:10.1161/CIRCGEN.120.002911 (PMID 33164571)

5) Zhang ZH, Barajas-Martínez H, Xia H, et al. Distinct Features of Probands With Early Repolarization and Brugada Syndromes Carrying SCN5A Pathogenic Variants. J Am Coll Cardiol. 2021;78(16):1603-1617. doi:10.1016/j.jacc.2021.08.024 (PMID 34649698)

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

7) gnomAD Browser: gnomad.broadinstitute.org/

ADDITIONAL INFORMATION

TISSUE ID: Testing6-4-2912

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

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GENES ANALYZED

ABCC9, ANK2, CACNA1C, CACNA1D, CACNA2D1, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, CDH2, DES, DSC2, DSG2, DSP, EMD, FLNC, GNB5, HCN4, JUP, KCND2, KCND3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNJ8, KCNQ1, LMNA, NKX2-5, PKP2, PLN, PPA2, PRKAG2, RBM20, RYR2, SCN5A, SLC4A3, TECRL, TMEM43, TNNI3K, TRDN and TTN

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 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

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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 Arrhythmia Gene 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 PMARG) 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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