MAYO CLINIC

1-800-533-1710

Brugada Syndrome, SCN5A Full Gene

SCN5A

PATIENT NAME				ORDER NUMBER
ABNORMAL, SCN5A				**M213000131**
PATIENT ID SA00154386	DATE OF BIRTH 11/25/1986	AGE 35 Y	SEX Female	REQUESTED BY CLIENT CLIENT
COLLECTED 9/12/2022, 8:00 AM	RECEIVED 9/22/2022, 10:02 AM	REPORTED 9/28/2022, 9:16 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 SA00154386 CLIENT MRN SA00154386

TEST DESCRIPTION

Evaluation of the SCN5A gene associated with Brugada syndrome

SPECIMEN

DNA (ul)

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 heterozygous PATHOGENIC variant was detected: SCN5A (NM_198056.2), Chr3 (GRCh37):g.38640496del, c.1936del, p.Gln646Argfs*5 (p.Q646Rfs*5)

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.

INTERPRETATION

SCN5A c.1936del (p.Gln646Argfs*5): The heterozygous c.1936del (p.Gln646Argfs*5) variant 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). This variant has been observed at a very low frequency in individuals of non-Finnish European (0.006%, 1/15412 alleles) descent (6). Lastly, other truncating variants in the SCN5A gene have been reported in association with Brugada syndrome and/or other cardiac arrhythmia phenotypes. Taken together, this result is supportive of a diagnosis of Brugada syndrome or other SCN5A-related cardiac arrhythmia condition 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

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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. gnomAD Browser: gnomad.broadinstitute.org/; Karczewski K, Francioli LC, MacArthur DG, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020; 581(7809):434-443 (PMID 32461654)

RESOURCES

DNR

METHOD

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. 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. 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. 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 SCN5A) for details regarding genes with regions not routinely covered.

GENES ANALYZED

SCN5A

DISCLAIMER

Clinical Correlations

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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 Brugada Syndrome, SCN5A Full Gene 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 SCN5A) 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.

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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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