



1-800-533-1710

Muscle Channelopathy Gene Panel

SMCP

PATIENT NAME TESTING, SMCP_ABNORMAL				ORDER NUMBER M311000142
PATIENT ID SA00154781	DATE OF BIRTH 04/04/2004	AGE 18 Y	SEX Male	REQUESTED BY CLIENT CLIENT
COLLECTED 10/11/2022, 12:00 AM	RECEIVED 10/13/2022, 3:30 PM	REPORTED 10/17/2022, 1:58 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 SA00154781 CLIENT MRN SA00154781

TEST DESCRIPTION

Evaluation of 5 genes associated with skeletal muscle channelopathies

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variant Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
SCN4A (NM_000334.4)	c.3877G>A p.Val1293Ile (p.V1293I) chr17(GRCh37):g.62022068C>T	heterozygous	PATHOGENIC

The following heterozygous PATHOGENIC variant was detected:

SCN4A (NM_000334.4), chr17(GRCh37):g.62022068C>T, c.3877G>A, p.Val1293Ile (p.V1293I)

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

SCN4A c.3877G>A (p.Val1293Ile), PATHOGENIC

The heterozygous c.3877G>A (p.Val1293Ile) missense variant in the SCN4A gene (MIM:603967) is classified as pathogenic. Pathogenic variants in the SCN4A gene have been associated with autosomal dominant hypokalemic and hyperkalemic periodic paralysis, autosomal dominant paramyotonia congenita, autosomal dominant atypical acetazolamide-responsive myotonia congenita and autosomal recessive congenital myasthenic syndrome. This variant has been reported as heterozygous in individuals with paramyotonia congenita and myotonia congenita (1-3). Additionally, the p.V1293I variant was shown to co-segregate with disease in multiple families (1,3). Furthermore, functional studies have been performed to support the pathogenicity of this variant. Functional studies indicate that the p.V1293I variant alters the voltage-dependent gating properties of SCN4A (4,5). This variant is absent from large control databases (6,7). Given the evidence above, this result is likely supportive of a diagnosis of a SCN4A-related disorder 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.



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REFERENCES:

- 1) Chung KW, Yoo DH, Lee SJ, Choi BO, Lee SS. A Large Dominant Myotonia Congenita Family with a V1293I Mutation in SCN4A. J Clin Neurol. 2016;12(4):509-511. doi:10.3988/jcn.2016.12.4.509 (PMID 27486940)
- 2) Magot A, David A, Sternberg D, Pereon Y. Focal and abnormally persistent paralysis associated with congenital paramyotonia. BMJ Case Rep. 2014;2014:bcr2014204430. Published 2014 Jun 17. doi:10.1136/bcr-2014-204430 (PMID 24939454)
- 3) Koch MC, Baumbach K, George AL, Ricker K. Paramyotonia congenita without paralysis on exposure to cold: a novel mutation in the SCN4A gene (Val1293Ile). Neuroreport. 1995;6(15):2001-2004. doi:10.1097/00001756-199510010-00012 (PMID 8580427)
- 4) Farinato A, Altamura C, Imbrici P, et al. Pharmacogenetics of myotonic hNav1.4 sodium channel variants situated near the fast inactivation gate. Pharmacol Res. 2019;141:224-235. doi:10.1016/j.phrs.2019.01.004 (PMID 30611854)
- 5) Green DS, George AL Jr, Cannon SC. Human sodium channel gating defects caused by missense mutations in S6 segments associated with myotonia: S804F and V1293I. J Physiol. 1998;510 (Pt 3)(Pt 3):685-694. doi:10.1111/j.1469-7793.1998.685bj.x (PMID 9660885)
- 6) dbSNP: www.ncbi.nlm.nih.gov/snp; Sherry ST, Ward M and Sirotkin K. dbSNP-Database for Single Nucleotide Polymorphisms and Other Classes of Minor Genetic Variation. Genome Res. 1999;9:677-679 (PMID 10447503)
- 7) 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)

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

GENES ANALYZED

ATP1A2, CACNA1S, CLCN1, KCNJ2 and SCN4A

DISCLAIMER

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.

PATIENT NAME TESTING, SMCP_ABNORMAL

22-40879



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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 Muscle Channelopathy 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 SMCP) 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

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requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

RELEASED BY

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