

Patient REPORT, SAMPLE	Requesting Physician Not Provided	Accession Number 12345678
Date of Birth 04/15/1983	Report to QUEST DIAGNOSTICS	Family Number/Kindred Number
Sex F	Address 200 FOREST STREET	Patient Number 000000000
Specimen Type WHOLE BLOOD	2ND FLOOR	Specimen Collection Date 05/24/2021
Test Category Not Available	MARLBOROUGH, MA 01752	Date Received 05/25/2021
Test Requested SCN4A (Myotonia) DNA Sequencing Test	Additional Reports to:	Report Date 06/09/2021

SCN4A (Myotonia) DNA Sequencing Test

NEGATIVE

This test did not identify any variants associated with sodium channel myotonic disorder.

INTERPRETIVE RESULTS TABLE			
	Test	Technical Result	Clinical Relevance
Negative	SCN4A	No abnormal variants detected	See Limitations of Analysis

Comments: While this analysis did not identify any pathogenic or likely pathogenic variants associated with sodium channel myotonic disorder, the diagnosis cannot be completely ruled out due to variants not detected by this assay or variants in another gene.

Clinical limitations: Mutations in the *SCN4A* gene are the only reported cause of sodium channel myotonic disorder (1, 2, 3).

Other testing available: Other disorders may appear clinically similar to those caused by mutations in this gene. Athena Diagnostics recommends additional testing, if not already performed, based on this individual's clinical presentation and family history. Please contact the Athena Diagnostics Client Services Department or visit AthenaDiagnostics.com for information regarding additional testing.

Background information: The *SCN4A* gene encodes the voltage-gated sodium channel which functions as an initiator of muscle action potential (1). Mutations in the *SCN4A* gene have been associated with a number of hereditary sodium channel myotonic disorders (1). This group of disorders is predominantly characterized by myotonia which can present in various muscle groups including the face, tongue, neck, arms, and legs to varying degrees depending on the subtype (2, 3, 4). Subtypes include a form of congenital myasthenic syndrome (CMS) and the non-dystrophic disorders of skeletal muscle such as potassium-aggravated myotonia (PAM), paramyotonia congenita (PMC), hyperkalemic periodic paralysis (HyperPP), and hypokalemic periodic paralysis type 2 (HypoPP). Both loss and gain of function mutations have been observed (2, 3, 4).

SCN4A gene information: MIM ID: *603967; Chromosome Location: 17q23.3; NCBI Reference Sequence: NM_000334.4; In the cDNA, the initiator codon, ATG (methionine), is designated as codon number 1 and the "A" is designated as nucleotide +1. The initiator codon is located in exon 1 and all subsequent numbering is sequential.

Phenotype information: MIM ID: #608390 for myotonia congenita, atypical, acetazolamide-responsive, MIM ID: #168300 for paramyotonia congenita, MIM ID: # 170500 for hyperkalemic periodic paralysis, type 2, MIM ID: # 613345 for hypokalemic periodic paralysis, type 2 and MIM ID: # 614198 for myasthenic syndrome, acetazolamide-responsive

Methods:

DNA sequencing was performed using advanced ("next-generation") sequencing technology. Advanced sequencing was performed on sheared genomic DNA libraries enriched for target regions using in-solution hybrid capture. Target regions include coding regions in exons and at least ten non-coding nucleotides adjacent to each of these coding regions. Resulting sequences were then analyzed using bioinformatics tools in a standardized process that includes alignment to the GRCh37/hg19 genomic build and use of the Genome Analysis Toolkit 2.3-9 for variant detection. A mean coverage depth of at least 30 sequencing reads is obtained within each target region, with a minimum coverage depth of at least 20X. Target regions with coverage depths less than the minimum are not reported. Internal testing demonstrated approximately 99% sensitivity and approximately 99% specificity for detecting DNA sequence variation. In some limited circumstances, such as for regions that are difficult to sequence using advanced sequencing, Sanger sequencing of PCR-amplified target regions (using bi-directional sequence or alternate dye chemistries) may be performed in lieu of this process. Benign and likely benign variants, if identified, are considered normal and are not reported, but are available upon request.

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Limitations of DNA sequencing analysis: This method does not detect large deletions, insertions, or structural variations, and may not detect variants in patients exhibiting mosaicism. Furthermore, allele dropout cannot be detected in Sanger sequenced regions. Additionally, this test will not detect variants in low coverage regions, which may occur in an analysis of this scope. Regions with exceptionally high or low GC content, repetitive regions or regions having a high degree of similarity with other regions in the genome are more susceptible to low coverage and/or reduced sensitivity. Furthermore, this test does not detect variants in regions of the gene not analyzed (including promoter, 5' and 3' untranslated regions, introns, and certain regions having consistently low coverage). Although rare, false positive or false negative results may occur. All results should be interpreted in the context of clinical findings, relevant history, and other laboratory data.

Limitation of variant analysis: The classification and interpretation of the variant(s) identified reflect the current state of Athena Diagnostics' understanding at the time of this report. Variant classification and interpretation are subject to professional judgment, and may change for a variety of reasons, including but not limited to, updates in classification guidelines and availability of additional scientific and clinical information. This test result should be used in conjunction with the health care provider's clinical evaluation. Inquiry regarding potential changes to the classification of the variant is strongly recommended prior to making any future clinical decision. For questions regarding variant classification updates or our Family Insight Program, please call Athena Diagnostics at 800-394-4493 to speak to a genetic counselor or laboratory director, or visit <https://www.athenadiagnostics.com/athenainsight>.

For patients who are interested in sharing de-identified genetic and health information to improve understanding of genetics and health, please visit <https://GenomeConnect.org>. GenomeConnect is an online registry designed by the Clinical Genome Resource (ClinGen) and is not affiliated with Quest Diagnostics.

Background References

1. Graves, TD, et al. (2005) Postgrad Med J 81: 20-32. (PMID: 15640425)
2. Saperstein, DS. (2008) Semin Neurol 28: 260-9. (PMID: 18351527)
3. Trivedi, JR, et al. (2014) Exp Neurol 253: 28-30. (PMID: 24361411)
4. Jurkat-Rott, K, et al. (2010) Pflugers Arch 460: 239-48. (PMID: 20237798)
5. Furby, A, et al. (2014) Neuromuscul Disord:Jul 2. [Epub ahead of print] (PMID: 25088311)

This test was developed and its analytical performance characteristics have been determined by Athena Diagnostics. It has not been cleared or approved by the U.S. Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

Laboratory results and submitted clinical information reviewed by,

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Laboratory oversight provided by Vivekananda Datta, M.D., Ph.D., CLIA license holder, Athena Diagnostics (CLIA# 22D0069726)