MAYO CLINIC

1-800-533-1710

Congenital Myasthenia Gene Panel

CMSP

PATIENT NAME				ORDER NUMBER
TESTRNV, IMPLEMENTATION				**M312000314**
PATIENT ID X100399593	DATE OF BIRTH 02/19/1968	AGE 54 Y	SEX Male	REQUESTED BY CLIENT TEST
COLLECTED 10/12/2022, 7:33 AM	RECEIVED 10/13/2022, 3:35 PM	REPORTED 10/17/2022, 2:02 PM		
The collected, received, and reported dates and times on the report are in the time zone of the performing location.				CLIENT ORDER NUMBER X100399593
7028846 MCL RochesterCampus Rochester MN 55901				CLIENT MRN 321

TEST DESCRIPTION

Evaluation of 28 genes associated with congenital myasthenic syndromes

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Likely Pathogenic Variants Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
CHRNE (NM_000080.3)	c.1033-1G>C chr17(GRCh37):g.4802680C>G	heterozygous	LIKELY PATHOGENIC
CHRNE (NM_000080.3)	c.794C>T p.Pro265Leu (p.P265L) chr17(GRCh37):g.4804293G>A	heterozygous	LIKELY PATHOGENIC

The following heterozygous LIKELY PATHOGENIC variants were detected:
CHRNE (NM_000080.3), chr17(GRCh37):g.4802680C>G, c.1033-1G>C
CHRNE (NM_000080.3), chr17(GRCh37):g.4804293G>A, c.794C>T, p.Pro265Leu (p.P265L)

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

CHRNE c.1033-1G>C, LIKELY PATHOGENIC and c.794C>T (p.Pro265Leu), LIKELY PATHOGENIC
The heterozygous c.1033-1G>C and heterozygous c.794C>T (p.Pro265Leu) variants in the CHRNE gene (MIM:100725) are classified as likely pathogenic. Pathogenic variants in the CHRNE gene have been associated with autosomal dominant and autosomal recessive forms of congenital myasthenic syndrome (1). This test cannot determine whether the detected variants are in cis (on the same chromosome) or in trans (on different chromosomes). Genetic testing of this individual's parents and/or other first-degree relatives could help to clarify this result.

The c.1033-1G>C splice variant in the CHRNE gene was detected. This variant alters a canonical splice site and may cause skipping of the adjacent exon or use of a cryptic splice site, leading to premature protein truncation. To our knowledge, this variant has not been reported in affected individuals. This variant has been observed at a very low frequency in exome and/or genome sequencing data gathered from large, multi-ethnic cohorts, suggesting it is a rare variant (2,3).

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The c.794C>T (p.Pro265Leu) missense variant in the CHRNE gene was detected. This variant has been reported in siblings with congenital myasthenic syndrome who carried a second variant in trans that caused premature protein truncation. Furthermore, functional studies have shown this variant impacts protein function (4). This variant has been observed at a very low frequency in exome and/or genome sequencing data gathered from large, multi-ethnic cohorts, suggesting it is a rare variant (2,3). An in silico meta-predictor suggests that this amino acid change may impact protein function.

Due to the multiple established inheritance patterns for the condition(s) associated with this gene, this result may be supportive of a diagnosis of CHRNE-related congenital myasthenic syndrome. However, establishing if the variants are in cis (on the same chromosome) or in trans (on opposite chromosomes) could help to clarify this result. 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) GeneReviews: Congenital Myasthenic Syndromes Overview (https://www.ncbi.nlm.nih.gov/books/NBK1168/) (PMID: 20301347)
2) 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)
3) 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)
4) Ohno K, Quiram PA, Milone M, et al. Congenital myasthenic syndromes due to heteroallelic nonsense/missense mutations in the acetylcholine receptor epsilon subunit gene: identification and functional characterization of six new mutations. Hum Mol Genet. 1997;6(5):753-766. doi:10.1093/hmg/6.5.753 (PMID 9158150)

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.

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Confirmation of select reportable variants was performed by alternate methodologies based on internal laboratory criteria. See www.mayoclinicslabs.com (TEST ID CMSP) for details regarding genes with regions not routinely covered.

GENES ANALYZED

AGRN, ALG14, ALG2, CHAT, CHRNA1, CHRNB1, CHRND, CHRNE, COL13A1, COLQ, DNM2, DOK7, DPAGT1, GAA, GFPT1, GMPPB, LAMB2, LRP4, MUSK, PLEC, PREPL, RAPSN, SCN4A, SLC18A3, SLC25A1, SLC5A7, SYT2 and VAMP1

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.

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 Congenital Myasthenia Gene Panel in the Special Instructions section of the Test Catalog for the most up to date list of genes included in this test.

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Reclassification of Variants Policy
See www.mayocliniclabs.com (TEST ID CMSP) 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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