MAYO CLINIC

1-800-533-1710

Postmortem Myasthenia Panel

PCMSP

PATIENT NAME				ORDER NUMBER
TESTRNV, TESTING A				**N425000328**
PATIENT ID X100430256	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, 2:03 PM	REPORTED 10/2/2023, 11:45 AM		
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 X100430256 CLIENT MRN 321

TEST DESCRIPTION

Evaluation of 28 genes associated with congenital myasthenia

SPECIMEN

Tissue Scroll

RESULT SUMMARY

Pathogenic Variants Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
DOK7 (NM_173660.5)	c.1124_1127dup p.Ala378Serfs*30 (p.A378Sfs*30) Chr4(GRCh37):g.3494837_3494840dup	Homozygous	Pathogenic

The following PATHOGENIC variant was detected:
DOK7 (NM_173660.5), chr4(GRCh37):g.3494837_3494840dup, c.1124_1127dup, p.Ala378Serfs*30 (p.A378Sfs*30), homozygous

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

DOK7 c.1124_1127dup (p.Ala378Serfs*30), PATHOGENIC
The homozygous c.1124_1127dup (p.Ala378Serfs*30) duplication in the DOK7 gene (MIM:610285) is classified as pathogenic. Pathogenic variants in the DOK7 gene have been associated with autosomal recessive congenital myasthenic syndrome (1). This variant is predicted to cause protein truncation and is expected to be an inactivating (loss of function) mutation. This variant has been reported in numerous affected patients in the literature and has been reported to co-segregate with disease in an affected family (2-4). Functional data in cultured myotubes demonstrates this variant is associated with impaired maturation of the postsynaptic structure (2). Other truncating variants in the DOK7 gene have also been associated with disease. This variant has been observed at a low frequency in exome and/or genome sequencing data gathered from large, multi-ethnic cohorts, suggesting it is a rare variant (5,6). This result is supportive of a diagnosis of DOK7-related congenital myasthenic syndrome for this individual. Clinical correlation is recommended.

This result should be interpreted in the context of clinical findings, family history, and other laboratory testing.

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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) Beeson D, Higuchi O, Palace J, et al. Dok-7 mutations underlie a neuromuscular junction synaptopathy. Science. 2006;313(5795):1975-1978. doi:10.1126/science.1130837 (PMID 16917026)
3) Cossins J, Liu WW, Belaya K, et al. The spectrum of mutations that underlie the neuromuscular junction synaptopathy in DOK7 congenital myasthenic syndrome. Hum Mol Genet. 2012;21(17):3765-3775. doi:10.1093/hmg/dds198 (PMID 22661499)
4) Evangelista T, Hanna M, Lochmüller H. Congenital Myasthenic Syndromes with Predominant Limb Girdle Weakness. J Neuromuscul Dis. 2015;2(Suppl 2):S21-S29. doi:10.3233/JND-150098 (PMID 26870666)
5) dbSNP: www.ncbi.nlm.nih.gov/snp
6) gnomAD Browser: gnomad.broadinstitute.org/

ADDITIONAL INFORMATION

TISSUE ID: Testing5-398285

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 PCMSP) 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

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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 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 Myasthenia 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 PCMSP) 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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