MAYO CLINIC

1-800-533-1710

Neuromuscular Gene Panel

MUPAN

PATIENT NAME				ORDER NUMBER
TESTING, MUPAN_ABNORMAL				**M311000204**
PATIENT ID SA00154798	DATE OF BIRTH 08/08/2002	AGE 20 Y	SEX Male	REQUESTED BY CLIENT CLIENT
COLLECTED 10/11/2022, 12:00 AM	RECEIVED 10/13/2022, 3:31 PM	REPORTED 10/14/2022, 4:46 PM		
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TEST DESCRIPTION

Evaluation of 215 genes associated with neuromuscular disorders and deletion and duplication analysis for SMN1 and SMN2

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variants Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
CPT2 (NM_000098.2)	c.338C>T p.Ser113Leu (p.S113L) chr1(GRCh37):g.53668099C>T	homozygous	PATHOGENIC

The following homozygous PATHOGENIC variant was detected:
CPT2 (NM_000098.2), chr1(GRCh37):g.53668099C>T, c.338C>T, p.Ser113Leu (p.S113L)

Negative for SMN1 exon 7 deletion.

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

CPT2 c.338C>T (p.Ser113Leu), PATHOGENIC
The homozygous c.338C>T (p.Ser113Leu) missense variant in the CPT2 gene (MIM:600650) is classified as pathogenic. Pathogenic variants in the CPT2 gene have been associated with autosomal recessive CPT II deficiency (1). This variant has been reported previously in CPT2-deficient individuals with the adult form of the disease (2). Furthermore, functional studies have been performed to support the pathogenicity of this variant and have shown that the c.338C>T variant depresses the catalytic activity of CPT II (3,4). The overall minor allele frequency for this variant (rs74315294) is approximately 0.139% with a frequency up to 0.752% in Ashkenazi Jewish sub-populations (5,6). This result is supportive of a diagnosis of CPT II deficiency 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) GeneReviews: Carnitine Palmitoyltransferase II Deficiency (https://www.ncbi.nlm.nih.gov/books/NBK1253/) (PMID: 20301431)
2) Bonnefont JP, Djouadi F, Prip-Buus C, Gobin S, Munnich A, Bastin J. Carnitine palmitoyltransferases 1 and 2: biochemical, molecular and medical aspects. Mol Aspects Med. 2004;25(5-6):495-520. doi:10.1016/j.mam.2004.06.004 (PMID 15363638)
3) Wataya K, Akanuma J, Cavadini P, et al. Two CPT2 mutations in three Japanese patients with carnitine palmitoyltransferase II deficiency: functional analysis and association with polymorphic haplotypes and two clinical phenotypes. Hum Mutat. 1998;11(5):377-386. doi:10.1002/(SICI)1098-1004(1998)11:5<377::AID-HUMU5>3.0.CO;2-E (PMID 9600456)
4) Taroni F, Verderio E, Dworzak F, Willems PJ, Cavadini P, DiDonato S. Identification of a common mutation in the carnitine palmitoyltransferase II gene in familial recurrent myoglobinuria patients. Nat Genet. 1993;4(3):314-320. doi:10.1038/ng0793-314 (PMID 8358442)
5) 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)
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)

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. Additionally, droplet digital PCR was utilized to detect copy number for SMN1 and SMN2 exon 7. Of note, only exon 7 copy number was assessed for these 2 genes. 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 MUPAN) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ABHD5, ACAD9, ACADM, ACADS, ACADVL, ACTA1, ADSS1, AGK, AGL, AGRN, ALDOA, ALG14, ALG2, ANO5, ASAH1, ASCC1, ATP1A2, ATP2A1, B3GALNT2, B4GAT1, BAG3, BIN1, BVES, CACNA1S, CAPN3, CASQ1, CAV3, CAVIN1, CFL2, CHAT, CHCHD10, CHKB, CHRNA1, CHRNB1, CHRND, CHRNE, CLCN1, COL12A1, COL13A1, COL6A1, COL6A2, COL6A3, COLQ, COQ2, COQ4, COQ6, COQ8A, COQ9, CPT2, CRPPA, CRYAB, CTDP1, DAG1, DES, DGUOK, DMD, DNA2, DNAJB6, DNM2, DOK7, DPAGT1, DPM1, DPM2, DPM3, DYSF, EMD, ENO3, ETFA, ETFB, ETFDH, FAM111B, FBXL4, FDX2, FHL1, FKBP14, FKRP, FKTN, FLAD1, FLNC, GAA, GBE1, GFER, GFPT1, GMPPB, GNE, GOSR2, GYG1, GYS1, HADHA, HADHB, HNRNPA1, HNRNPA2B1, HNRNPDL, HRAS, INPP5K, ISCU, ITGA7,

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JAG2, KBTBD13, KCNJ2, KLHL40, KLHL41, KY, LAMA2, LAMB2, LAMP2, LARGE1, LDB3, LDHA, LMNA, LMOD3, LPIN1, LRP4, MAP3K20, MATR3, MB, MEGF10, MGME1, MICU1, MRPS25, MSTO1, MTM1, MTO1, MUSK, MYBPC1, MYH2, MYH7, MYMK, MYOT, MYPN, NEB, OPA1, ORAI1, PAX7, PDSS1, PDSS2, PFKM, PGAM2, PGK1, PGM1, PHKA1, PLEC, PNPLA2, PNPLA8, POGLUT1, POLG, POLG2, POMGNT1, POMGNT2, POMK, POMT1, POMT2, PREPL, PRKAG2, PUS1, PYGM, PYROXD1, RAPSN, RBCK1, RNASEH1, RRM2B, RXYLT1, RYR1, SCN4A, SDHA, SELENON, SGCA, SGCB, SGCD, SGCG, SIL1, SLC18A3, SLC22A5, SLC25A1, SLC25A20, SLC25A3, SLC25A4, SLC25A42, SLC5A7, SMN1 (copy number variants in exon 7 only), SMN2 (copy number variants in exon 7 only), SPEG, SQSTM1, STAC3, STIM1, SUCLA2, SUCLG1, SUN1, SUN2, SYNE1, SYT2, TANGO2, TAZ (TAFAZZIN), TBCD, TCAP, TFG, TIA1, TK2, TMEM43, TMEM65, TNNT1, TNPO3, TOR1AIP1, TPM2, TPM3, TRAPPC11, TRIM32, TRIP4, TSFM, TTC19, TTN, TWNK, UBA1, VAMP1, VCP, VMA21 and YARS2

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.

Testing doesn't rule out silent carrier (2+0) status for spinal muscular atrophy. SMN1 g.27134T>G variant status available

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upon request.

Genes may be added or removed based on updated clinical relevance. Please refer to the Targeted Genes and Methodology Details for the Neuromuscular 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 MUPAN) 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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