MAYO CLINIC

1-800-533-1710

Spastic Paraplegia Gene Panel

ISPP

PATIENT NAME				ORDER NUMBER
TESTRNV, IMPLEMENTATION				**M312000322**
PATIENT ID X100399586	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, 3:32 PM	REPORTED 10/17/2022, 2:09 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
X100399586

CLIENT MRN
321

TEST DESCRIPTION

Evaluation of 128 genes associated with hereditary spastic paraplegia

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variants Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
B4GALNT1 (NM_001478.4)	c.263dup p.Leu89Profs*13 (p.L89Pfs*13) chr12(GRCh37):g.58025103dup	homozygous	PATHOGENIC

The following homozygous PATHOGENIC variant was detected:
B4GALNT1 (NM_001478.4), chr12(GRCh37):g.58025103dup, c.263dup, p.Leu89Profs*13 (p.L89Pfs*13)

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

B4GALNT1 c.263dup (p.Leu89Profs*13), PATHOGENIC
The homozygous c.263dup (p.Leu89Profs*13) duplication in the B4GALNT1 gene (MIM:601873) is classified as pathogenic. Pathogenic variants in the B4GALNT1 gene have been associated with autosomal recessive spastic paraplegia. This variant is predicted to cause premature protein truncation due to a frameshift and is expected to result in loss-of-function. Other truncating variants in the B4GALNT1 gene have also been associated with disease. This variant has been reported in the homozygous state in patients with spastic paraplegia (1-3). Furthermore, functional studies have been performed to support the pathogenicity of this variant. Cell lines carrying this variant showed absent enzyme activity compared to wild-type cells and immunoblotting for B4GALNT1 protein showed no band of protein (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 (5,6). This result is supportive of a diagnosis of B4GALNT1-related spastic paraplegia 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) Boukhris A, Schule R, Loureiro JL, et al. Alteration of ganglioside biosynthesis responsible for complex hereditary spastic paraplegia. Am J Hum Genet. 2013;93(1):118-123. doi:10.1016/j.ajhg.2013.05.006 (PMID 23746551)
2) Hengel H, Buchert R, Sturm M, et al. First-line exome sequencing in Palestinian and Israeli Arabs with neurological disorders is efficient and facilitates disease gene discovery [published correction appears in Eur J Hum Genet. 2022 Feb;30(2):248]. Eur J Hum Genet. 2020;28(8):1034-1043. doi:10.1038/s41431-020-0609-9 (PMID 32214227)
3) Rose L, Hall K, Tang S, Hasadsri L, Kimonis V. Homozygous B4GALNT1 mutation and biochemical glutaric acidemia type II: A case report. Clin Neurol Neurosurg. 2020;189:105553. doi:10.1016/j.clineuro.2019.105553 (PMID 31812852)
4) Bhuiyan RH, Ohmi Y, Ohkawa Y, et al. Loss of Enzyme Activity in Mutated B4GALNT1 Gene Products in Patients with Hereditary Spastic Paraplegia Results in Relatively Mild Neurological Disorders: Similarity with Phenotypes of B4galnt1 Knockout Mice. Neuroscience. 2019;397:94-106. doi:10.1016/j.neuroscience.2018.11.034 (PMID 30521973)
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. 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 ISPP) for details regarding genes with regions not routinely covered.

GENES ANALYZED

ABCD1, ACO2, AFG3L2, ALDH18A1, AMPD2, AP4B1, AP4E1, AP4M1, AP4S1, AP5Z1, APOPT1 (COA8), ARG1, ARL6IP1, ASNS, ATL1, AUH, B4GALNT1, BICD2, BOLA3, BSCL2, C12orf65 (MTRFR), COQ7, CPT1C, CTC1, CTSD, CYP27A1, CYP2U1, CYP7B1, DARS1, DARS2, DDHD1, DDHD2, DLD, EARS2, ENTPD1, ERLIN1, ERLIN2, EXOSC3, FA2H, FAR1, FARS2, FUCA1, FXN, GALC, GBA2, GBE1, GJC2, GLB1, GM2A, GPT2, HACE1, HEXA, HIBCH, HSPD1, HTRA1, IBA57, IFIH1, IRF2BPL, ISCA2, KDM5C, KIDINS220, KIF1A, KIF5A, L1CAM, L2HGDH, LYRM7, MAG, MARS2, MED17, MTFMT, NIPA1, NT5C2, NUBPL, OPA3, PANK2, PDHX, PEX16, PGAP1, PLA2G6, PLP1, PNP, PNPLA6, PNPLA8, PRF1, PRUNE1, PSAP, PYCR2, RAB18, RAB3GAP1, RAB3GAP2, RARS1, REEP1, REEP2, RNASEH2A, RNASEH2B, RNASEH2C, RTN2, SACS, SAMHD1, SDHAF1, SERAC1, SLC12A6, SLC16A2, SLC19A3, SLC33A1, SLC6A8, SOX2, SPART, SPAST, SPG11, SPG21, SPG7, SPTAN1, SUMF1, TACO1, TBC1D20, TECPR2, TFG, TREX1, TTC19, TYROBP, UBAP1, UBQLN2, VAMP1, VPS13D, WASHC5, ZFYVE26 and ZFYVE27

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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 Spastic Paraplegia 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 ISPP) 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.

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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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