



1-800-533-1710

Peripheral Neuropathy Gene Panel

PEPAN

PATIENT NAME TEST, PEPAN A				ORDER NUMBER O304000536
PATIENT ID X100465813	DATE OF BIRTH 01/31/1972	AGE 52 Y	SEX Female	REQUESTED BY CLIENT 123
COLLECTED 6/4/2024, 10:15 AM	RECEIVED 6/5/2024, 2:13 PM	REPORTED 6/12/2024, 2:59 PM		
The collected, received, and reported dates and times on the report are in the time zone of the performing location.				CLIENT ORDER NUMBER X100465813
7028846 MCL RochesterCampus Rochester MN 55901				CLIENT MRN C7028846-0006053

TEST DESCRIPTION

Evaluation of 187 genes associated with peripheral neuropathy and deletion and duplication analysis for SMN1 and SMN2

SPECIMEN

WB Whole Blood

RESULT SUMMARY

Pathogenic Variants Detected

RESULT

Gene (Transcript)	Variant	Zygosity	Classification
PRX (NM_181882.2)	c.1102C>T p.Arg368* (p.R368*) Chr19(GRCh37):g.40903157G>A	Homozygous	Pathogenic

The following PATHOGENIC variant was detected:

PRX (NM_181882.2), chr19(GRCh37):g.40903157G>A, c.1102C>T, p.Arg368* (p.R368*), homozygous

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

PRX c.1102C>T (p.Arg368*), PATHOGENIC

The homozygous c.1102C>T (p.Arg368*) nonsense variant in the PRX gene (MIM:605725) is classified as pathogenic. Pathogenic variants in the PRX gene have been associated with autosomal recessive Charcot-Marie-Tooth disease type 4 and autosomal recessive Dejerine-Sottas disease (1). This variant is predicted to cause premature protein truncation. However, this variant occurs in the terminal region of the gene and the impact of truncation is unknown. Other truncating variants in the PRX gene have also been associated with disease. This variant has been reported previously as homozygous in affected siblings and as heterozygous in trans with (on the opposite chromosome) another likely pathogenic PRX variant (2,3). However, functional studies have not been performed to either support or refute the pathogenicity of this variant. 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 (4,5). This result is supportive of a diagnosis of a PRX-related disorder for this individual. Clinical correlation is recommended

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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) Bird TD. Charcot-Marie-Tooth Hereditary Neuropathy Overview. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. GeneReviews. Seattle (WA): University of Washington, Seattle; September 28, 1998. (PMID 20301532)
- 2) Candayan A, Çakar A, Yunisoğlu G, et al. Genetic Survey of Autosomal Recessive Peripheral Neuropathy Cases Unravels High Genetic Heterogeneity in a Turkish Cohort. *Neurol Genet.* 2021;7(5):e621. Published 2021 Aug 31. doi:10.1212/NXG.0000000000000621 (PMID 34476298)
- 3) Boerkoel CF, Takashima H, Stankiewicz P, et al. Periaxin mutations cause recessive Dejerine-Sottas neuropathy [published correction appears in *Am J Hum Genet* 2001 Feb;68(2):557]. *Am J Hum Genet.* 2001;68(2):325-333. doi:10.1086/318208 (PMID 11133365)
- 4) 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)
- 5) 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. 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. 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. 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 PEPAN) for details regarding genes with regions not routinely covered.

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GENES ANALYZED

AAAS, AARS1, ABCA1, ABCD1, AIFM1, ALDH18A1, AMACR, AP5Z1, APOA1, APTX, ARSA, ATL1, ATL3, ATM, ATP1A1, ATP7A, B4GALNT1, BAG3, BICD2, BSCL2, C12orf65 (MTRFR), C1orf194, CHCHD10, CLCF1, CLTCL1, CNTNAP1, COQ4, COQ7, COX10, COX20, COX6A1, CPOX, CRLF1, CTDP1, CYP27A1, CYP2U1, CYP7B1, DCTN1, DDHD1, DGAT2, DHH, DNAJB2, DNM2, DNMT1, DST, DYNC1H1, EGR2, ELP1, ERCC8, FA2H, FAM126A, FBLN5, FBXO38, FGD4, FGF14, FIG4, FLVCR1, FMR1, FXN, GALT, GAN, GARS1, GBA2, GBE1, GBF1, GDAP1, GJB1, GLA, GM2A, GNB4, GSN, HADHA, HADHB, HARS1, HEXA, HEXB, HINT1, HK1, HMBS, HSPB1, HSPB8, HSPD1, IARS2, IBA57, IGHMBP2, INF2, KARS1, KIF1A, KIF5A, LAMA2, LITAF, LMNA, LRSAM1, MARS1, MCM3AP, MFN2, MME, MORC2, MPC1, MPV17, MPZ, MTMR2, MTPP, MYH14, NAGLU, NDRG1, NEFH, NEFL, NF2, NGF, NIPA1, NTRK1, OPA1, PDK3, PDYN, PEX7, PHYH, PLA2G6, PLEKHG5, PLP1, PMP2, PMP22, PNKP, PNPLA6, POLG, PPOX, PRDM12, PRKCG, PRNP, PRPS1, PRX, PTRH2, RAB7A, REEP1, RETREG1, RNASEH1, RRM2B, RTN2, SACS, SBF1, SBF2, SCN10A, SCN11A, SCN9A, SCO2, SEPTIN9, SETX, SH3TC2, SIGMAR1, SLC12A6, SLC25A19, SLC25A46, SLC52A2, SLC52A3, SLC5A7, SMN1 (copy number variants in exon 7 only), SMN2, SNAP29, SOD1, SORD, SOX10, SPAST, SPG11, SPG21, SPG7, SPTAN1, SPTLC1, SPTLC2, SUCLA2, SURF1, TDP1, TFG, TRIM2, TRPV4, TSFM, TTPA, TTR, TUBB3, TWNK, TYMP, UBA1, VPS13D, VRK1, VWA1, WARS1, WASHC5, WNK1, YARS1 and ZFYVE26

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.

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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 upon request

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