

Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB: 3/23/1957
Gender: Male
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
Collection Date: 00/00/0000 00:00

**Charcot-Marie-Tooth (CMT) and Related Hereditary Neuropathies, PMP22
Deletion/Duplication with Reflex to Sequencing Panel**

ARUP test code 2012155

Charcot-Marie-Tooth Reflex Specimen whole blood

Charcot-Marie-Tooth (CMT) Reflex Interp Positive

H=High, L=Low, *=Abnormal, C=Critical

Unless otherwise indicated, testing performed at:

ARUP LABORATORIES | 800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Jonathan R. Genzen, MD, PhD, Laboratory Director

Patient: Patient, Example
ARUP Accession: 24-057-401601
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
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4848

RESULT

One pathogenic variant was detected in the PMP22 gene.

PATHOGENIC VARIANT

Gene: PMP22 (NM_000304.3)
Nucleic Acid Change: Deletion of exons 1-5 (whole gene deletion); Heterozygous
Inheritance: Autosomal dominant

INTERPRETATION

One pathogenic variant, deletion of the entire PMP22 gene, was detected by deletion/duplication analysis. This result is consistent with a diagnosis of hereditary neuropathy with liability to pressure palsies (HNPP), an autosomal dominant neurological disorder characterized by repeated focal pressure neuropathies and peripheral neuropathy. This individuals offspring have a 50 percent chance of inheriting the causative variant.

Because a pathogenic deletion was identified in PMP22, sequencing of genes associated with Charcot-Marie-Tooth (CMT) disease and other hereditary neuropathies was not performed. Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:

The PMP22 whole gene deletion is reported in the literature in individuals with hereditary neuropathy with liability to pressure palsies (HNPP; Zhang 2010) and loss of function is a disease mechanism for HNPP (Li 2013). Considering available information, this deletion is classified as pathogenic.

RECOMMENDATIONS

Genetic consultation is indicated, including a discussion of medical screening and management. At-risk adult relatives and symptomatic family members should be offered targeted testing for the detected deletion (Charcot-Marie-Tooth 1A (CMT1A)/Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) (PMP22) Deletion/Duplication; ARUP test code 2012160).

COMMENTS

Likely benign and benign variants are not included in this report [remove the following phrase for non-NY cases], but are available upon request.

REFERENCES

Li J et al. The PMP22 gene and its related diseases. Mol Neurobiol. 2013 Apr;47(2):673-98. PMID: 23224996.
Zhang F et al. Mechanisms for nonrecurrent genomic rearrangements associated with CMT1A or HNPP: rare CNVs as a cause for missing heritability. Am J Hum Genet. 2010 Jun 11;86(6):892-903. PMID: 20493460.

This result has been reviewed and approved by [REDACTED]

BACKGROUND INFORMATION: Charcot-Marie-Tooth (CMT) and Related Hereditary Neuropathies, PMP22 Deletion/Duplication with Reflex to Sequencing Panel

CHARACTERISTICS: Charcot-Marie-Tooth (CMT), hereditary sensory neuropathies (HSN), hereditary sensory and autonomic neuropathy (HSAN), distal hereditary motor neuropathies (dHMN), and hereditary neuropathy with liability to pressure palsies (HNPP).

EPIDEMIOLOGY: Incidence of hereditary neuropathy is approximately 1/3,000; CMT is 1/5,000.

INHERITANCE: Gene-dependent; autosomal dominant, autosomal recessive, or X-linked.

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CLINICAL SENSITIVITY: greater than 70-80 percent for CMT1; 20-30 percent for CMT2; greater than 25 percent for CMT4; greater than 90 percent for CMTX; 15-20 percent for HMN; approximately 30 percent for HSN; approximately 99 percent for HNPP.

GENES TESTED:

Deletion/duplication Analysis: PMP22
Sequencing Panel: AARS, AIFM1, ATL1, ATP7A, BAG3, BICD2, BSCL2, CCT5, DCTN1, DHTKD1, DNAJB2, DNM2, DNMT1*, DYNC1H1, EGR2, ELP1, FBLN5, FGD4, FIG4, GAN, GARS, GDAP1, GJB1, GNB4, HARS, HEXA, HINT1, HOXD10, HSPB1, HSPB3, HSPB8, IGHMBP2, INF2, KARS, KIF1A, KIF1B, KIF5A, LAS1L, LITAF, LMNA, LRSAM1, MARS, MED25, MFN2, MORC2, MPZ, MTMR2, NDRG1, NEFL, NGF, NTRK1, PDK3, PLEKHG5, PMP22, PRNP, PRPS1, PRX, RAB7A, REEP1, RETREG1, SBF1, SBF2, SCN9A, SETX*, SH3TC2, SLC12A6, SLC5A7, SPTLC1*, SPTLC2, TDP1, TFG, TRIM2, TRPV4, TTR, WNK1, YARS

* - One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Multiplex ligation-dependent probe amplification (MLPA) of the PMP22 gene. If results were negative or inconclusive, testing reflexed to targeted capture of all coding regions and intron-exon boundaries of the genes listed above followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY: 99 percent for MLPA. The analytical sensitivity of this for sequencing is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a heritable form of neuropathy. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will not be determined. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Non-coding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:

SPTLC1(NM_006415) exon(s) 3
DNMT1(NM_001130823) exon(s) 5
SETX(NM_001351528) exon(s) 26

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

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VERIFIED/REPORTED DATES				
Procedure	Accession	Collected	Received	Verified/Reported
Charcot-Marie-Tooth Reflex Specimen	24-057-401601	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Charcot-Marie-Tooth (CMT) Reflex Interp	24-057-401601	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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Unless otherwise indicated, testing performed at: