# Genetic Testing for Neuropathy: Demyelinating Charcot-Marie-Tooth Panel Sequencing and Exon-Level Deletion/Duplication Testing of 23 Genes

**Disorder also known as**: Hereditary motor and sensory neuropathy (HMSN), CMT1

**Panel Gene List:** *DNM2, EGR2, FGD4, FIG4, GDAP1, GJB1, GNB4, INF2, LITAF, MFN2, MPZ, MTMR2, NDRG1, NEFL, PLEKHG5, PMP22, PRPS1, PRX, SBF1, SBF2, SH3TC2, SLC12A6, YARS*

**Clinical Features:**
Collectively the Charcot-Marie-Tooth (CMT) neuropathies are the most common cause of hereditary neuropathy with a prevalence of approximately 1 in 2,500[1,2]. Charcot-Marie-Tooth neuropathies are also known as hereditary motor and sensory neuropathies (HMSN) because they are characterized by predominately motor and sensory symptoms. The “classic” CMT presentation is characterized by progressive distal muscle weakness with the feet and legs being most severely affected, paresthesia and/or loss of sensation, a “drop foot” gait, depressed deep tendon reflexes, hammer toes, and pes cavus. Most types of CMT exhibit autosomal dominant inheritance; however, autosomal recessive and X-linked forms are well described in the literature[1]. Historically CMT neuropathies have been classified as demyelinating or axonal based on nerve conduction studies. Demyelinating forms of CMT primarily affect the myelin sheath of the peripheral nerve and are characterized by slow nerve conduction velocities (NCV) of less than 38 m/s in the arms, while axonal forms of CMT primarily affect the axons of the peripheral nerves and are characterized by normal or almost normal NCV of greater than 38 m/s in the arms[3, 4]. Axonal neuropathies are also typically associated with a decrease of compound muscle action potential (CMAP) [1]. Intermediate NCV of 25-45 m/s can be difficult to classify as axonal or demyelinating[1, 3, 4].

**Genetics:**
Neuropathy can be caused by a genetic disorder, metabolic disease, trauma, infection, or other inflammatory and immune related events, and in some cases the cause is not known. A genetic etiology can be identified in approximately 50-70% of individuals with CMT[4]. Specifically, a molecular diagnosis can be identified in approximately 80-95% of individuals with demyelinating neuropathy (CMT1) and a molecular diagnosis can be identified in approximately 25-35% of individuals with axonal neuropathy (CMT2)[5,6]. The Demyelinating CMT Panel at GeneDx includes sequencing and deletion/duplication analysis of genes associated with demyelinating neuropathy. The complete list of genes and associated disorders is included in the table below. The inherited neuropathies show a great deal of

genetic and phenotypic heterogeneity, and can be inherited in an autosomal dominant, autosomal recessive or X-linked manner.

**Test Methods:**

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

Sequencing and deletion/duplication analysis of the remaining genes on the Hereditary Neuropathy Panel is available as a reflex test if the Demyelinating CMT panel is negative.

**Test Sensitivity:**

The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel depends in part on the patient's clinical phenotype. Specific information about the diagnostic yield for each gene in selected populations is summarized in the following table. The technical sensitivity of sequencing is estimated to be > 99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

**References:**

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| Disease Associations | Gene | Protein | Inh. | Diagnostic Yield in Selected Population(s) |
|---|---|---|---|---|
| CMT2M; CMTDIB | *DNM2* | dynamin 2 | AD | ~3% of CMT[1] |
| CMT1D; DSD; CHN | *EGR2* | early growth response 2 protein | AD/AR | <2% of patients with CMT1[2] |
| CMT4H | *FGD4* | frabin; Fyve, RhoGEF and PH domain-containing protein 4 | AR | ~3% of autosomal recessive CMT[3] |
| CMT4J | *FIG4* | SAC domain-containing inositol phosphatase 3; SAC3 | AR | <1% of patients with CMT[3,4] |
| CMT4A; CMT2K; CMTRIA; Axonal CMT with vocal cord paresis | *GDAP1* | ganglioside-induced differentiation-associated protein 1 | AD/AR | ~1-5% autosomal recessive CMT[3] |
| CMTX1 | *GJB1* | gap junction protein beta-1; connexin 32 | XL | ~90% of X-linked CMT[4,5] |
| CMTDIF | *GNB4* | guanine nucleotide-binding protein, beta-4 | AD | Rare[6] |
| CMTDIE; FSGS | *INF2* | inverted formin 2 | AD | ~75% of patients with CMT-FSGS[7] |

| | | | | |
|---|---|---|---|---|
| CMT1C | *LITAF* | lipopolysaccharide-induced TNF-alpha factor gene; small integral membrane protein of lysosome/late endosome (SIMPLE) | AD | 1-2% of CMT1[2] |
| CMT2A2A (AD); CMT2A2B (AR); HMSN VI | *MFN2* | mitofusin 2 | AD/AR | 10-30% of CMT2[5;8] |
| CMT1B; CMT2J; CMTDID; DSD; CHN | *MPZ* | myelin protein zero | AD | 6-10% of patients with CMT1[4;9]; Rare in CMT2[8] |
| CMT4B1 | *MTMR2* | mytotubularin-related protein 2 | AR | Rare in autosomal recessive CMT[3] |
| CMT4D | *NDRG1* | N-myc downstream-regulated gene 1 | AR | Rare in autosomal recessive CMT[3] |
| CMT1F; CMT2E | *NEFL* | neurofilament protein, light chain | AD | ~1% of CMT neuropathy onset within the first year of life[10]; 2%-5% of CMT2[4] |
| CMTRIC; dSMA4 | *PLEKHG5* | pleckstrin homology domain-containing protein family G, member 5 | AR | Unknown[11,12] |

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|---|---|---|---|---|
| CMT1A; CMT1E; HNPP; DSD | *PMP22* | peripheral myelin protein 22 | AD | Duplication: ~70% of CMT1[5;13]; Deletion: ~80% of HNPP[14]; Point mutation: <5% of CMT1[2]; 20% of HNPP[14] |
| CMTX5 | *PRPS1* | phosphoribosyl pyrophosphate synthetase 1 | XL | Unknown[15] |
| CMT4F; DSD | *PRX* | periaxin | AR | ~5% of autosomal recessive CMT[3] |
| CMT4B3 | *SBF1* | SET binding factor 1; mytotubularin-related protein 5 | AR | Rare in autosomal recessive CMT[16] |
| CMT4B2 | *SBF2* | SET binding factor 2; mytotubularin-related protein 13 | AR | ~4% of autosomal recessive CMT[3] |
| CMT4C | *SH3TC2* | SH3 domain and tetratricopeptide repeats 2 | AR | ~18% of CMT4[17] |
| Agenesis of the corpus callosum with peripheral neuropathy | *SLC12A6* | solute carrier family 12 member 6 | AR | Carrier frequency of 1/23 in the Charlevoix and Saguenay-Lac-St-Jean regions of Quebec[18] |
| CMTDIC | *YARS* | tyrosyl-tRNA synthetase | AD | Unknown[19] |

Abbreviations: AD – autosomal dominant; AR – autosomal recessive; CMT – Charcot-Marie-Tooth neuropathy; dHMN – distal hereditary motor neuropathy; FSGS – focal segmental glomerulosclerosis; HNPP – hereditary neuropathy with liability to pressure palsy

## Table References:

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