Genetic Testing for Neuropathy: Axonal Charcot-Marie-Tooth Panel Sequencing and Exon-Level Deletion/Duplication Testing of 32 Genes

Disorder also known as: Hereditary motor and sensory neuropathy (HMSN), CMT2

Panel Gene List: *AARS, AIFM1, BSCL2, DNAJB2, DNM2, DYNC1H1, GAN, GARS, GDAP1, GJB1, GNB4, HARS, HINT1, HSPB1, HSPB8, IGHMBP2, INF2, KIF5A, LMNA, LRSAM1, MFN2, MME, MORC2, MPZ, NEFL, PLEKHG5, PRPS1, RAB7A, SLC12A6, TRIM2, TRPV4, 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 Axonal CMT Panel at GeneDx includes sequencing and deletion/duplication analysis of genes associated with axonal 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 Axonal 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 Populations
CMT2N	AARS	alanyl-tRNA synthetase	AD	Unknown[1,2]
Cowchock syndrome/CMTX 4; Combined oxidative phosphorylation deficiency 6; X-Linked deafness 5	AIFM1	apoptosis inducing factor, mitochondria-associated 1	XL	Rare[3]
dHMN VA; Silver syndrome	BSCL2	seipin	AD	~7% of dHMN; unknown in CMT2[4]
Distal SMA type 5	DNAJB2	DNAJ/HSP40 homolog; subfamily B, member 2	AR	Rare[5]
CMT2M; CMTDIB	DNM2	dynamin 2	AD	~3% of CMT[6]
CMT2O; Spinal muscular atrophy with lower extremity predominance	DYNC1H 1	cytoplasmic dynein 1 heavy chain 1	AD	Unknown; reported in 3 families with spinal muscular atrophy with lower extremity predominance and in 5.5% of patients with malformations of cortical development[7,8]
Giant axonal neuropathy 1	GAN	gigaxonin	AR	~6% of patients with CMT2[9]
CMT2D; dHMN VA	GARS	glycyl-tRNA synthetase	AD	~3% of patients with CMT2[10]
CMT4A;CMT2K; CMTRIA; Axonal CMT with vocal	GDAP1	Ganglioside-induced differentiation-associated protein 1	AD/ AR	~1-5% autosomal recessive CMT[11]

cord paresis				
CMTX1	GJB1	gap junction protein beta-1; connexin 32	XL	~90% of X-linked CMT[10;12]
CMTDIF	GNB4	guanine nucleotide-binding protein, beta-4	AD	Rare[13]
CMT2W	HARS	Histidyl-tRNA synthetase	AD	Unknown[14]
Neuromyotonia and axonal neuropathy	HINT1	histidine triad nucleotide binding protein 1	AR	Up to 11% of autosomal recessive neuropathies in patients from Czech Republic, Austria, Serbia, Bulgaria and Turkey[15]
CMT2F; dHMN IIB	HSPB1	heat shock 27 kDa protein 1	AD	~8% of patients with dHMN; ~4% of patients with CMT2[16]
CMT2L; dHMN IIA	HSPB8	heat shock 22 kDa protein 8	AD	Unknown in CMT2 and dHMNII[16,17]
CMT2S; SMARD/HMNVI	IGHMBP 2	immunoglobulin u binding protein 2	AR	~33% patients with SMARD[18]; ~2% of CMT2[19]
CMTDIE; FSGS	INF2	inverted formin 2	AD	~75% of patients with CMT and focal segmental glomerulosclerosis (FSGS)[20]
Spastic paraplegia 10	KIF5A	kinesin family member 5A	AD	~ 3% of familial HSP[21]; ~ 10% of complicated HSP in French European population[22]
CMT2B1	LMNA	lamin A/C nuclear-envelope proteins	AR	Rare in CMT2[23]
CMT2P	LRSAM1	leucine-rich repeat and sterile alpha motif-containing 1	AD/ AR	Rare in CMT2[24,25]

CMT2A2A (AD); CMT2A2B (AR); HMSN VIA (AD)	MFN2	mitofusin 2	AD/ AR	10-30% of CMT2[12;23]
CMT2T	MME	membrane metalloendopeptidase	AD/ AR	~13% of patients with a clinical diagnosis of autosomal recessive CMT undergoing exome sequencing[26]
CMT2Z	MORC2	MORC family CW-type zinc finger protein 2	AD	Rare in CMT2[27,28]
CMT1B; CMT2I; CMT2J; CMTDID; DSD; CHN	MPZ	myelin protein zero	AD	6-10% of patients with CMT1[10;29]; Rare in CMT2[23]
CMT1F; CMT2E	NEFL	neurofilament protein light chain	AD	~1% of CMT neuropathy onset within the first year of life[30]; 2%-5% of CMT2[10]
CMTRIC; dSMA4	PLEKHG5	pleckstrin homology domain-containing protein family G, member 5	AR	Unknown[31,32]
CMTX5	PRPS1	phosphoribosylpyrophosphate synthetase 1	XL	Unknown[33]
CMT2B	RAB7A	RAS-associated protein 7	AD	Up to 7% HSAN patients[34]; rare in CMT2[23]
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[35]

CMT2R	TRIM2	tripartite motif-containing protein 2	AR	Rare in axonal neuropathy[36]
CMT2C; congenital distal SMA	TRPV4	transient receptor potential cation channel V, member 4	AD	Rare in CMT2[23]
CMTDIC	YARS	tyrosyl-tRNA synthetase	AD	Unknown[37]

Abbreviations: AD – autosomal dominant; AR – autosomal recessive; CMT – Charcot-Marie-Tooth neuropathy; dHMN – distal hereditary motor neuropathy; FSGS – focal segmental glomerulosclerosis; HSAN – hereditary sensory and autonomic neuropathy; HSP – hereditary spastic paraplegia; SMARD – spinal muscular atrophy with respiratory distress; XL – X-linked

Table References:

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