Genetic Testing for Neuropathy: Hereditary Neuropathy Panel Sequencing and Exon-Level Deletion/Duplication Testing of 64 Genes

Panel Gene List: *AARS, AIFM1, ATL1, ATP7A, BSCL2, DNAJB2, DNM2, DNMT1, DYNC1H1, EGR2, FGD4, FIG4, GAN, GARS, GDAP1, GJB1, GLA, GNB4, HARS, HINT1, HSPB1, HSPB8, IGHMBP2, IKBKAP, INF2, KIF1A, KIF5A, LITAF, LMNA, LRSAM1, MFN2, MME, MORC2, MPZ, MTMR2, NDRG1, NEFL, NGF, NTRK1, PLEKHG5, PMP22, PRDM12, PRPS1, PRX, RAB7A, REEP1, RETREG1, SBF1, SBF2, SCN9A, SCN11A, SEPT9, SH3TC2, SLC12A6, SLC52A2, SLC52A3, SPTLC1, SPTLC2, TFG, TRIM2, TRPV4, TTR, WNK1*, YARS*

*(exon 10 "HSAN exon" only)

Clinical Features:

The inherited neuropathies are a large group of genetically and phenotypically heterogeneous disorders affecting the peripheral nervous system. The peripheral nervous system is divided into the somatic nervous system, which relays motor and sensory information to and from the central nervous system, and the autonomic nervous system, which regulates involuntary bodily functions, for example: heart rate, breathing and digestion. The inherited neuropathies are divided into three main groups based on primary symptoms: hereditary motor and sensory neuropathies, hereditary motor neuropathies, and hereditary sensory and autonomic neuropathies (HSAN).[1] The Hereditary Neuropathy Panel at GeneDx includes many genes from each of these different subgroups. Even though these groups are distinct, there is considerable phenotypic overlap among these disorders and patients commonly manifest a combination of sensory, motor, and autonomic features.

Collectively the Charcot-Marie-Tooth (CMT) neuropathies are the most common cause of hereditary neuropathy with a prevalence of approximately 1 in 2500.[2,3] 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.[2] 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 38m/s in the arms, while axonal forms of CMT primarily affect the axons of the peripheral nerves and are characterized by normal NCV of approximately 50m/s in the arms. Intermediate NCV of 35-45m/s can be difficult to classify as

axonal or demyelinating.[2] A subset of patients present with a severe CMT phenotype in the first year of life, often called Dejerine-Sottas syndrome (DSS) or congenital hypomyelinating neuropathy (CHN). These individuals with early-onset CMT commonly present with a severe demyelinating type and extremely slow NCV (<10m/s), delayed motor development or foot deformities. Many genes commonly associated with adult-onset CMT have been identified in individuals with DSS and CHN including: *PMP22*, *MPZ*, *EGR2*, *PRX*, *FIG4, GDAP1*.[3,4,5] The GeneDx Hereditary Neuropathy panel includes genes currently known to be associated with CMT, including *PMP22*, *GJB1*, *MPZ* and *MFN2*, which are implicated in over 90% of cases of CMT.[2] See table below for a complete list of genes.

As the name suggests, **hereditary motor neuropathies** are characterized by a predominately motor phenotype.[6] Distal hereditary motor neuropathies (dHMN) are further distinguished as a subset of disorders and common features include: progressive weakness and atrophy of the distal muscles, decreased or absent reflexes, reduced motor amplitude potentials on NCV and foot deformities.[7] Less common features include: vocal cord and diaphragm paralysis, pyramidal tract signs.[6] Some individuals report sensory and/or upper-motor neuron features and there can be significant phenotypic overlap with axonal forms of Charcot-Marie-Tooth, amyotrophic lateral sclerosis, and hereditary spastic paraplegia, making clinical diagnosis challenging.[7] Like CMT, most hereditary motor neuropathies are inherited in an autosomal dominant manner; autosomal recessive and X-linked forms are also described.[7] Seven subtypes of distal hereditary motor neuropathy have been described based on pattern of inheritance and main clinical features. To-date, genetic causes have been identified for dHMN types I, II, V, VI, VII, X-linked dHMN, dHMN with pyramidal features, and congenital distal spinal muscular atrophy.[7] The GeneDx Hereditary Neuropathy panel includes testing for each of these dHMN types. See table below for a complete list of genes.

The **hereditary sensory and autonomic neuropathies** (HSAN) are a phenotypically diverse group of disorders, as some individuals only have sensory symptoms; others have a combination of sensory, autonomic and motor abnormalities, while others have purely autonomic findings.[1] Clinical features include: Distal sensory loss, particularly related to pain and temperature, chronic ulcerations of the hands and feet, soft tissue infections, osteomyelitis, and skin and nail changes are seen in some individuals. Additionally, autonomic features can include: anhidrosis, fever, fluctuations in blood pressure, and gastrointestinal issues.[1] Axonal nerve damage is most frequently observed in patients with HSAN; however, some patients also have demyelinating features.[1] Subtypes of HSAN are broken down based on age of onset, mode of inheritance, and main clinical findings.[1,8] HSAN I is characterized by autosomal dominant inheritance, a predominance of sensory symptoms, and onset of symptoms in childhood or adulthood. [1,8] HSAN II-V and HSAN VIII are characterized by autosomal recessive inheritance and congenital or early childhood onset of symptoms.[1,8,9] These subtypes tend to have primarily autonomic involvement without motor symptoms. Due

to severe autonomic involvement and increased risk of sepsis associated with HSAN III and HSAN IV, life expectancy of these patients is lower than in the other types.[1] HSAN VII is an autosomal dominant disorder characterized by congenital inability to experience pain, delayed motor development, mild weakness, hyperhidrosis, and gastrointestinal dysfunction[10] (Leipold et al., 2013). Small fiber neuropathy is typically an adult-onset disorder characterized by neuropathic pain and autonomic symptoms, and has been associated with pathogenic variants in *SCN9A* and *SCN11A*[11,12]. See table below for a complete list of genes.

In addition, **hereditary recurrent, focal neuropathies** demonstrate some clinical overlap with the previously mentioned disorders. Hereditary neuropathy with liability to pressure palsy (HNPP) is characterized by recurrent episodes of sensory and motor neuropathy in a single nerve. While any nerve in the peripheral nervous system can be affected, the ulnar, peroneal, median, brachial plexus and radial nerves are most commonly affected[13]. The most common cause of HNPP is a 1.5 Mb deletion on the short arm of chromosome 17, which includes the *PMP22* gene. While approximately 80% of individuals with HNPP have this recurrent deletion, the remaining 20% have sequence variants in the *PMP22* gene[1]. Hereditary neuralgic amyotrophy (HNA) is an episodic disorder of intense pain and muscle weakness/paralysis affecting the arms and shoulders and is associated with variants involving the *SEPT9* gene.[15]

Genetics:
The Hereditary Neuropathy Panel at GeneDx includes sequencing and deletion/duplication analysis of genes causing 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. A genetic diagnosis is identified in approximately 50-70% of individuals with CMT[3], 20-30% of individuals with HSAN[1;14], and 20% of individuals with distal motor neuropathy.[7]

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). For the WNK1 gene, only exon 10 in the neuronal specific transcript associated with hereditary sensory neuropathy type II (NM_213655) is analyzed. 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; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or

confirm regions with inadequate sequence or copy number data by NGS. 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.

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 table below. 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. Gene specific exclusions for exon-level deletion/duplication testing for this panel are: *NGF* gene, no copy number testing, *PRDM12* gene only whole gene deletions or duplications may be detected.

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Disorder	Gene	Protein	Inh.	Diagnostic Yield in Selected Population(s)
Hereditary Motor and Sensory Neuropathies	*AARS*	alanyl-tRNA synthetase	AD	Unknown[1,2]
	AIFM1	Apoptosis-inducing factor, mitochondria-associated, 1	XL	Rare[3]
	BSCL2	seipin	AD	Unknown in CMT2[38]

Disorder	Gene	Protein	Inh.	Diagnostic Yield in Selected Population(s)
(Charcot-Marie-Tooth Neuropathies)	*DNAJB2*	DNAJ/HSP40 homolog subfamily B member 2	AR	Rare[39]
	DNM2	dynamin 2	AD	~3% of CMT[4]
	DYNC1H1	cytoplasmic dynein 1 heavy chain 1	AD	Unknown; reported in 3 families with spinal muscular atrophy with lower extremity predominance[5]; and in 5.5% of patients with malformations of cortical development[6]
	EGR2	early growth response 2	AD/AR	<2% of patients with CMT1[7]
	FGD4	Fyve, RhoGEF and PH domain-containing protein 4	AR	~3% of autosomal recessive CMT[8]
	FIG4	FIG4 homolog, SAC1 lipid phosphatase domain containing S. cerevisiae	AR	<1% of patients with CMT[8,9]
	GAN	gigaxonin	AR	6% of patients with CMT2[10]
	GARS	glycyl-tRNA synthetase	AD	~3% of patients with CMT2[9]
	GDAP1	ganglioside-induced differentiation-associated protein 1	AD/AR	1-5% of autosomal recessive CMT[8]
	GJB1	gap junction protein B1; connexin 32	XL	~90% of X-linked CMT[9,11]
	GNB4	G protein, beta-4 subunit	AD	Rare[12]
	HARS	Histidyl tRNA synthetase	AD	Unknown[13]
	HINT1	histidine triad nucleotide binding protein 1	AR	Up to 11% of autosomal recessive neuropathies in patients from Czech Republic, Austria, Serbia, Bulgaria and

Disorder	Gene	Protein	Inh.	Diagnostic Yield in Selected Population(s)
				Turkey[14]
	HSPB1	heat shock 27 kDa protein 1	AD	~4% of patients with CMT2[15]
	HSPB8	heat shock 22 kDa protein 8	AD	Unknown[15,16]
	IGHMBP2	immunoglobulin u binding protein 2	AR	~33% of patients with SMARD[17]; ~2% of CMT2[18]
	INF2	inverted formin 2	AD	~75% of patients with CMT and FSGS[19]
	KIF5A	kinesin heavy chain, neuron-specific	AD	~3% of familial HSP[20]; ~10% of complicated HSP in French European population[21]
	LITAF	lipopolysaccharide-induced TNF factor gene	AD	1-2% CMT1[7]
	LMNA	lamin A/C nuclear-envelope proteins	AR	Rare in CMT2[22]
	LRSAM1	leucine-rich repeat and sterile alpha motif-containing 1	AD/AR	Rare in CMT2[23,24]
	MFN2	mitofusin 2	AD/AR	10-30% of CMT2[11;22]
	MME	Membrane metalloendopeptidase	AD/AR	~13% of patients with a clinical diagnosis of autosomal recessive CMT undergoing exome sequencing[25]
	MORC2	MORC family CW-type zinc finger protein 2	AD	Rare in CMT2[26,27]
	MPZ	myelin protein zero	AD	6-10% of patients with CMT1[9;28]; Rare in CMT2[22]
	MTMR2	mytotubularin-related protein 2	AR	Rare in autosomal recessive CMT[8]
	NDRG1	N-myc downstream-regulated gene 1	AR	Rare in autosomal recessive CMT[8]

Disorder	Gene	Protein	Inh.	Diagnostic Yield in Selected Population(s)
	NEFL	neurofilament light	AD	~1% of CMT with onset during the first year of life[29]; 2%-5% of CMT2[9;29]
	PLEKHG5	Pleckstrin homology domain-containing family C member 5	AR	Unknown[41,42]
	PMP22	peripheral myelin protein 22	AD	Duplication: ~70% of CMT1[11;30] Sequence variants: <5% of CMT1[7]
	PRPS1	phosphoribosylpyrophosphate synthetase 1	XL	Unknown[31]
	PRX	periaxin	AR	~5% of autosomal recessive CMT[8]
	RAB7A	RAS-associated protein 7	AD	Rare in CMT2[22;32]
	SBF1	SET binding factor 1; mytotubularin-related protein 5	AR	Rare in autosomal recessive CMT[33]
	SBF2	SET binding factor 2; mytotubularin-related protein 13	AR	~4% of autosomal recessive CMT[8]
	SH3TC2	SH3 domain and tetratricopeptides repeats 2	AR	~18% of CMT4[34]
	SLC12A6	solute carrier family 12 member 6	AR	Carrier frequency of 1/23 in the Charlevoix and Saguenay-Lac-St-Jean regions of Quebec[45]
	TRIM2	Tripartite motif-containing protein 2	AR	Rare in axonal neuropathy[35]
	TRPV4	transient receptor vallanoid 4	AD	Rare in CMT2[22]
	YARS	tyrosyl-tRNA synthetase	AD	Unknown[36]
Hereditary Motor	*ATP7A*	ATPase, Cu2+ transporting alpha polypeptide	XL	85% of Menkes disease and occipital

Disorder	Gene	Protein	Inh.	Diagnostic Yield in Selected Population(s)
Neuropathies (distal)				horn syndrome[37]
	BSCL2	seipin	AD	~7% of dHMN[38]
	DNAJB2	DNAJ/HSP40 homolog subfamily B member 2	AR	Rare[39]
	GLA	galactosidase alpha	XL	>98% of males with Fabry disease[40]
	HSPB1	heat shock 27 kDa protein 1	AD	~8% of patients with dHMN[15]
	HSPB8	heat shock 22 kDa protein 8	AD	Unknown in dHMN[15,16]
	PLEKHG5	Pleckstrin homology domain-containing family C member 5	AR	Unknown[41,42]
	REEP1	receptor expression enhancing protein 1	AD	3-6.5% of patients with hereditary spastic paraplegia[43,44]
	SLC52A2	Solute carrier family 52 (riboflavin transporter) member 2	AR	Unknown in Brown-Vialetto-Van Laere syndrome[46]
	SLC52A3	Solute carrier family 52 (riboflavin transporter) member 3	AR	Unknown in Brown-Vialetto-Van Laere syndrome[47]
	TFG	TRK-fused gene	AD	Unknown[48]
	TTR	transthyretin	AD	Val122Ile variant identified in 3-4% of African Americans; Val130Met variant identified in 1 in 100,000 Northern European individuals in the United States[49]
Hereditary Sensory and Autonomic Neuropathies	*ATL1*	atlastin-1	AD	Unknown in HSAN[50];~7% of familial and ~4% of sporadic HSP[20]
	DNMT1	DNA methyltransferase 1	AD	Rare[51]
	IKBKAP	inhibitor of kappa light	AR	Carrier frequency of

Disorder	Gene	Protein	Inh.	Diagnostic Yield in Selected Population(s)
		polypeptide gene enhancer in B cells, kinase complex-associated protein		1/27-1/32 in Ashkenazi Jewish population[52]
	KIF1A	kinesin family member 1A	AR/AD	Rare[53]
	NGF	nerve growth factor, beta subunit	AR	Rare in HSAN[32]
	NTRK1	neurotrophic tyrosine kinase receptor type 1	AR	Up to 7% of patients with HSAN[32]
	PRDM12	PR domain-containing protein 12	AR	Rare in HSAN[54]
	RAB7A	RAS-associated protein 7	AD	Up to 7% HSAN patients[55]
	RETREG1 aka FAM134B	family with sequence similarity 134, member B	AR	<2% of HSAN patients[32]
	SCN9A	sodium channel voltage gated type IX alpha subunit	AD/AR	Unknown in HSAN II[56]; ~28% of Dutch Caucasian patients with biopsy confirmed small fiber neuropathy[57]
	SCN11A	Sodium channel voltage gated type XI alpha subunit	AD	Rare[58,59]
	SPTLC1	serine palmitoyltransferase, long chain base subunit 1	AD	Up to 12% of patients with HSAN with a founder mutation noted in the United Kingdom[32,55]
	SPTLC2	serine palmitoyltransferase, long chain base subunit 2	AD	<5% of patients with HSAN[60]
	WNK1	WNK1/HSN2 isoform	AR	<3% of HSAN patients[32]
Hereditary Recurrent,	*PMP22*	peripheral myelin protein 22	AD	Deletion: ~80% of HNPP[61]

Disorder	Gene	Protein	Inh.	Diagnostic Yield in Selected Population(s)
Focal Neuropathies				Sequence variants: ~20% of HNPP[61]
	SEPT9	Septin 9	AD	~55% of individuals with hereditary neuralgic amyotrophy[62]

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; HSAN – hereditary sensory and autonomic neuropathy; HSP – hereditary spastic paraplegia; SMARD – spinal muscular atrophy with respiratory distress; XL – X-linked

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