

Hereditary Neuropathy Panel

PANEL GENE LIST

AARS, ABHD12*, AIFM1, ATL1, ATL3, ATP7A, BAG3, BICD2, BSCL2, CHCHD10, CNTNAP1*, COX6A1*, CYP27A1, DNAJB2, DNM2, DNMT1, DST, DYNC1H1, EGR2, ELP1, FBXO38, FGD4, FIG4, GAN, GARS, GDAP1, GJB1, GLA, GNB4, HADHA, HARS, HINT1, HSPB1, HSPB8, IGHMBP2, INF2, KARS, KIF1A, KIF5A, LITAF, LMNA, LRSAM1, MFN2, MME, MORC2, MPV17, MPZ, MTMR2, NDRG1, NEFH, NEFL, NGF*, NTRK1, PDK3, PLEKHG5, PMP22, PNKP, PRDM12**, PRPS1, PRX, RAB7A, REEP1, RETREG1, SBF1, SBF2, SCO2*, SCN9A, SCN11A, SEPT9, SETX, SH3TC2, SIGMAR1, SLC12A6, SLC25A46, SLC52A2, SLC52A3, SLC5A7, SPG11, SPTLC1, SPTLC2, TFG, TRIM2, TRPV4, TTR, VAPB, VCP, VRK1, WNK1***, YARS

** Sequence analysis only

** Only whole gene deletions or duplications may be detected

*** Analysis of 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 Xlinked forms are also described.⁷ Seven subtypes of distal hereditary motor neuropathy have been described in the original classification of dHMN based on pattern of inheritance and main clinical features. To-date, genetic causes have been identified for a number of dHMN types, dHMN with pyramidal features, and congenital distal spinal muscular atrophy.⁷ The GeneDx Hereditary Neuropathy panel includes testing for genes currently known to be associated with dHMN. 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 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 affected¹³. 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 gene¹. 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 CMT³, 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). 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.

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: ABHD12, CNTNAP1, COX6A1, NGF, SCO2 genes, no copy number testing; PRDM12 gene only whole gene deletions or duplications may be detected. For the WNK1 gene, only exon 10 in the neuronal specific transcript associated with hereditary sensory neuropathy type II (NM_213655) is analyzed. Additionally, this analysis would not detect a variant in/near the Alanine repeat at the 3' end of the PRDM12 gene.

CLINICAL 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.

Hereditary Neuropathy Panel

Gene	Disorder	Inh.	Diagnostic Yield in Selected Population
AARS	CMT2N; Developmental and epileptic encephalopathy 29	AD /AR	Unknown ^{15,16}
ABHD12	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract	AR	Rare ^{17,18}
AIFM1	CMT4X/Cowchock syndrome; Deafness 5; Combined oxidative phosphorylation deficiency 6; Spondyloepimetaphyseal dysplasia with hypomyelinating leukodystrophy	XL	Rare ¹⁹
ATL1	HSN type ID; Spastic paraplegia 3A	AD/AR	Unknown in HSN ²⁰ ; 10-15% of AD HSP and 80% of early onset AD HSP ²¹
ATL3	HSN type IF	AD	Rare ²²
ATP7A	Menkes disease; Occipital horn syndrome; ATP7A-related distal motor neuropathy	XL	85% of Menkes disease and occipital horn syndrome ²³
BAG3	Myofibrillar myopathy 6; Dilated cardiomyopathy 1HH	AD	Rare ²⁴

Gene	Disorder	Inh.	Diagnostic Yield in Selected Population
BICD2	Lower extremity-predominant SMA 2A; Lower extremity-predominant SMA 2B	AD	~8% of dHMN in limited study ²⁵
BSCL2	dHMN type VC; Silver spastic paraplegia syndrome; Progressive encephalopathy with or without lipodystrophy; Congenital generalized lipodystrophy type 2	AD/AR	~7% of dHMN ²⁶
CHCHD10	SMA Jokela type; FTLN and/or ALS2	AD	Rare ²⁷
CNTNAP1	Congenital hypomyelinating neuropathy 3; Lethal congenital contracture syndrome 7	AR	Rare ²⁸
COX6A1	CMTRID	AR	Rare ²⁹
CYP27A1	Cerebrotendinous xanthomatosis	AR	Rare ³⁰
DNAJB2	Distal SMA 5	AR	6.7% of dHMN in limited study ²⁵
DNM2	CMT2M; CMTDIB; Centronuclear myopathy 1	AD	~3% of CMT ³¹
DNMT1	HSN type IE; Cerebellar ataxia, deafness, and narcolepsy	AD	Rare ³²
DST	HSAN VI; Epidermolysis bullosa simplex 2	AR	Rare ³³
DYNC1H1	CMT2O; Mental retardation 13; SMA, lower extremity predominant 1	AD	Unknown; reported in 3 families with SMA with lower extremity predominance ³⁴ ; and 5.5% of patients with malformations of cortical development ³⁵
EGR2	CMT1D; Dejerine-Sottas disease; Congenital hypomyelinating neuropathy 1	AD/AR	Rare ³⁶
ELP1	Familial dysautonomia	AR	Carrier frequency of 1/32-1/36 in Ashkenazi Jewish population ³⁷
FBXO38	dHMN type IID	AD	Rare ³⁸
FGD4	CMT4H	AR	~3% of autosomal recessive CMT ³⁹
FIG4	CMT4J; Yunis-Varon syndrome; ALS 11	AD/AR	<1% of patients with CMT ³⁶
GAN	Giant axonal neuropathy 1	AR	6% of patients with CMT ⁴⁰
GARS	CMT2D; dHMN type VA; Infantile SMA, James type	AD	~3% of patients with CMT2; 9.8% of dHMN in limited study ²⁵
GDAP1	CMT2K; Axonal CMT with vocal cord paresis; CMTRIA; CMT4A	AD/AR	<1% of patients with CMT ³⁶
GJB1	CMTX1	XL	~10-20% of CMT ^{41,42}
GLA	Fabry disease	XL	>98% of males with Fabry disease ⁴³
GNB4	CMTDIF	AD	Rare ⁴⁴
HADHA	LCHAD deficiency; mitochondrial trifunctional protein deficiency; Acute	AR	Rare ^{45,46}

Gene	Disorder	Inh.	Diagnostic Yield in Selected Population
	fatty liver of pregnancy; maternal HELLP syndrome of pregnancy		
HARS	CMT2W	AD	Unknown ⁴⁷
HINT1	Neuromyotonia and axonal neuropathy	AR	Up to 11% of autosomal recessive neuropathies in patients from Czech Republic, Austria, Serbia, Bulgaria and Turkey ⁴⁸
HSPB1	CMT2F; dHMN type IIB	AD	~4% of patients with CMT2 and ~8-10% of patients with dHMN ²⁵
HSPB8	CMT2L; dHMN type IIA	AD	Rare ^{6,49}
IGHMBP2	CMT2S; dHMN type VI	AR	~33% of patients with SMARD ⁵⁰ ; ~2% of CMT2 ⁵¹
INF2	CMTDIE; FSGS 5	AD	~75% of patients with CMT and FSGS ⁵²
KARS	CMTRIB; Deafness 89	AR	Rare ⁵³
KIF1A	HSN type IIC; NESCAV syndrome; Spastic paraplegia 30	AD/AR	Rare in HSN; 5-6% of AD HSP ^{21,54}
KIF5A	Spastic paraplegia 10; Neonatal intractable myoclonus; KIF5A-related ALS	AD	1-2% of AD HSP; 5-8% of complicated AD HSP ²¹
LITAF	CMT1C	AD	<1% of CMT2
LMNA	CMT2B1; Hutchinson-Gilford progeria; Mandibuloacral dysplasia; Dilated cardiomyopathy 1A; Emery-Dreifuss muscular dystrophy 2, Emery-Dreifuss muscular dystrophy 3; Restrictive dermopathy, lethal; Lipodystrophy	AD/AR	Rare in CMT ²⁵⁵
LRSAM1	CMT2P	AD/AR	Rare in CMT ^{256,57}
MFN2	CMT2A2A; CMT2A2B; CMT6A	AD/AR	8-33% of CMT ^{258,59}
MME	CMT2T	AD/AR	~13% of patients with a clinical diagnosis of autosomal recessive CMT undergoing exome sequencing ⁶⁰
MORC2	CMT2Z	AD	Rare in CMT ^{261,62}
MPV17	CMT2EE; Mitochondrial DNA depletion syndrome 6	AR	Rare ⁶³
MPZ	CMTDID; CMT1B; CMT2I; CMT2J; DejerineSottas disease; Congenital hypomyelinating neuropathy 2; Roussy-Levy syndrome	AD	6-10% of patients with CMT1; Rare in CMT ²⁴¹
MTMR2	CMT4B1	AR	Rare in autosomal recessive CMT ⁶⁴
NDRG1	CMT4D	AR	Rare in autosomal recessive CMT ⁶⁵
NEFH	CMT2CC	AD	Rare ^{66,67}

Gene	Disorder	Inh.	Diagnostic Yield in Selected Population
NEFL	CMTDIG; CMT1F; CMT2E	AD/AR	~1% of CMT with onset during the first year of life; 2%-5% of CMT241,68
NGF	HSAN V	AD/AR	Rare in HSAN ⁶⁹
NTRK1	Congenital insensitivity to pain with anhidrosis	AR	Rare except in Japanese and Israeli Bedouin populations where there are common founder mutations ⁷⁰
PDK3	CMTX6	XL	Rare ⁷¹
PLEKHG5	CMTRIC; Distal SMA type 4	AR	Rare ^{7,72}
PMP22	CMT1A; CMT1E; HNPP; Roussy-Levy syndrome; Dejerine-Sottas disease	AD/AR	>50% of all inherited CMT; Duplication: ~70% of CMT1; Sequence variants: <5% of CMT1; Deletion: ~80% of HNPP; Sequence variants: ~20% of HNPP ^{2,13,73}
PNKP	CMT2B2; Ataxia-oculomotor apraxia 4; Microcephaly, seizures and developmental delay	AR	Rare ⁷⁴
PRDM12	HSAN type VIII	AR	Rare ⁷⁵
PRPS1	CMTX5; Arts syndrome; X-linked deafness 1; PRPS-related gout; Phosphoribosylpyrophosphate synthetase superactivity	XL	Unknown ⁷⁶
PRX	CMT4F; Dejerine-Sottas disease	AR	~5% of demyelinating CMT ⁷⁷
RAB7A	CMT2B	AD	Rare ⁷⁸
REEP1	dHMN type VB; Spastic paraplegia type 31	AD	3-6.5% of patients with hereditary spastic paraplegia ^{79,80}
RETREG1	HSAN type IIB	AR	<2% of HSAN patients ⁸¹
SBF1	CMT4B3	AR	Rare in autosomal recessive CMT ⁸²
SBF2	CMT4B2	AR	Rare in autosomal recessive CMT ⁸²
SCN11A	HSAN type VII; Familial episodic pain syndrome 3; Small fiber neuropathy	AD	Rare ^{83,84}
SCN9A	HSAN type IID; Congenital insensitivity to pain; Primary erythermalgia; Paroxysmal extreme pain disorder; Small fiber neuropathy	AD/AR	~5% of patients with SFN ⁸⁶ ; ~28% of Dutch Caucasian patients with biopsy confirmed small fiber neuropathy ¹¹
SCO2	Myopia 6; Mitochondrial complex IV deficiency, nuclear type 2	AD/ AR	Rare ⁸⁷
SETX	Juvenile ALS 4; Spinocerebellar ataxia with axonal neuropathy 2	AD/AR	Rare overall; Frequent cause (~60%) of juvenile-to-adult cases with cerebellar ataxia, sensorimotor neuropathy and increased AFP ⁸⁸
SEPT9	Hereditary neuralgic amyotrophy	AD	~55% of individuals with hereditary neuralgic amyotrophy ⁸⁹
SH3TC2	CMT4C	AR	~18% of CMT4 ⁹⁰

Gene	Disorder	Inh.	Diagnostic Yield in Selected Population
SIGMAR1	Distal SMA type 2; Juvenile ALS type 16	AR	Rare ⁹¹
SLC12A6	Agenesis of the corpus callosum with peripheral neuropathy	AR	Carrier frequency of 1/23 in the Charlevoix and Saguenay-Lac-St-Jean regions of Quebec ⁹²
SLC5A7	dHMN VIIA; Congenital myasthenic syndrome presynaptic 20	AD/AR	Rare ¹⁰⁹
SLC25A46	CMT6B	AR	Rare ⁹³
SLC52A2	Brown-Vialetto_Van Laere syndrome 2	AR	Unknown ⁹⁴
SLC52A3	Brown-Vialetto-Van Laere syndrome	AR	Unknown ⁹⁵
SPG11	CMT2X; Juvenile ALS 5; Spastic paraplegia 11	AR	43% (12/28) of families with autosomal recessive CMT2 in one study ⁹⁶ ; 40% of autosomal recessive juvenile ALS ⁹⁷
SPTLC1	HSAN type IA	AD	Up to 12% of patients with HSAN with a founder mutation noted in the United Kingdom ⁸¹
SPTLC2	HSAN type IC	AD	<5% of patients with HSAN ⁹⁹
TFG	Hereditary motor and sensory neuropathy, Okinawa type; Spastic paraplegia 57	AD/AR	Unknown ¹⁰⁰
TRIM2	CMT2R	AR	Rare in axonal neuropathy ¹⁰¹
TRPV4	CMT2C; TRPV4-related skeletal dysplasias	AD	Up to 7% of axonal neuropathy in European countries and Australia ¹⁰²
TTR	Hereditary transthyretin-related amyloidosis; Familial euthyroid hyperthyroxinemia	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 ¹⁰³
VAPB	Late-onset SMA Finkel type; ALS 8	AD	Rare ^{104,105}
VCP	CMT2Y; ALS with or without FTLD 6; Inclusion body myopathy with early-onset Paget disease with FTLD	AD	Rare ¹⁰⁶
VRK1	Pontocerebellar hypoplasia type 1A	AR	Rare ¹⁰⁷
WNK1	HSAN type II	AR	Rare ⁹
YARS	CMTDIC; YARS multisystem disease	AD/AR	Unknown ¹⁰⁸

Abbreviations: AD – autosomal dominant; AR – autosomal recessive; XL – X-linked ; CMT – Charcot-Marie-Tooth neuropathy; dHMN – distal hereditary motor neuropathy/neuronopathy; 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; SMA – spinal muscular atrophy; ALS - amyotrophic lateral sclerosis FTLD – Frontotemporal lobar degeneration

REFERENCES:

1. Roththier et al. (2012) Nature Reviews. Neurology 8 (2):73-85 (PMID: 22270030).
2. Siskind et al. (2013) J Genet Couns 22 (4):422-36 (PMID: 23604902).
3. Vallat et al. (2013) Current Opinion In Neurology 26 (5):473-80 (PMID: 23945280).
4. Reilly et al. (2009) Journal Of Neurology, Neurosurgery, And Psychiatry 80 (12):1304-14 (PMID: 19917815)
5. Mathis et al. (2015) J. Med. Genet. : (PMID: 26246519)
6. Irobi et al. (2004) Hum. Mol. Genet. 13 Spec No 2:R195-202 (PMID: 15358725).
7. Rossor et al. (2012) Journal Of Neurology, Neurosurgery, And Psychiatry 83 (1):6-14 (PMID: 22028385).
8. Auer-Grumbach et al. (2006) Neuromolecular Medicine 8 (1-2):147-58 (PMID: 16775373).
9. Kurth (Updated February 2015). Hereditary Sensory and Autonomic Neuropathy Type II. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2010.
10. Leipold et al. (2013) Nature Genetics 45 (11):1399-404 (PMID: 24036948).
11. Faber et al. (2012) Annals Of Neurology 71 (1):26-39 (PMID: 21698661).
12. Huang et al. (2014) Brain : A Journal Of Neurology 137 (Pt 6):1627-42 (PMID: 24776970).
13. Chrestian (Updated August 2020). Hereditary Neuropathy with Liability to Pressure Palsies. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2010.
14. Murphy et al. (2012) Journal Of Neurology, Neurosurgery, And Psychiatry 83 (7):706-10 (PMID: 22577229).van Alfen et al. (2011) Nat Rev Neurol 7 (6):315-22 (PMID: 21556032).
15. Latour et al. (2010) American Journal Of Human Genetics 86 (1):77-82 (PMID: 20045102).
16. McLaughlin et al. (2012) Human Mutation 33 (1):244-53 (PMID: 22009580).
17. Fiskerstrand et al. (2010) American Journal of Human Genetics 87 (3):410-7 (PMID: 20797687).
18. Frasnquet et al. (2018). J. Neurol. Sci. 387:134-138 (PMID: 29571850).
19. Rinaldi et al. (2012) Am. J. Hum. Genet. 91 (6):1095-102 (PMID: 23217327)
20. Guelly et al. (2011) Am. J. Hum. Genet. 88 (1):99-105 (PMID: 21194679)
21. Hedera P. Hereditary Spastic Paraplegia Overview. 2000 Aug 15 [Updated 2021 Feb 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
22. Fischer et al. (2014) Brain 137 (Pt 7):e286 (PMID: 24736309).
23. Moizard et al. (2011) Clin. Genet. 79 (3):243-53 (PMID: 21208200).
24. Noury et al. (2018) Muscle Nerve 57 (2):330-334 (PMID: 28224639).
25. Frasnquet et al. (2020) Eur J Neurol : (PMID: 33369814).
26. Ito D. BSCL2-Related Neurologic Disorders/Seipinopathy. 2005 Dec 6 [Updated 2018 May 24]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
27. Pasanen et al. (2016) Acta Neurol. Scand. 133 (5):361-6 (PMID: 26224640).
28. Lesmana et al. (2019) Pediatr. Neurol. 93 :43-49 (PMID: 30686628).
29. Tamiya et al. (2014) Am. J. Hum. Genet. 95 (3):294-300 (PMID: 25152455).
30. Nie et al. (2014) Orphanet J Rare Dis 9 :179 (PMID: 25424010).
31. Claeys et al. (2009) Brain: A Journal Of Neurology 132 (Pt 7):1741-52 (PMID: 19502294).
32. Klein CJ. DNMT1-Related Disorder. 2012 Feb 16 [Updated 2019 Jan 31]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
33. Manganelli et al. (2017) Neurology 88 (22):2132-2140 (PMID: 28468842).
34. Harms et al. (2012) Neurology 78 (22):1714-20 (PMID: 22459677).
35. Poirier et al. (2013) Nat. Genet. 45 (6):639-47 (PMID: 23603762).
36. DiVincenzo et al. (2014) Mol Genet Genomic Med 2 (6):522-9 (PMID: 25614874).
37. Shohat M, Weisz Hubshman M. Familial Dysautonomia. 2003 Jan 21 [Updated 2014 Dec 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
38. Sumner et al. (2013) Am. J. Hum. Genet. 93 (5):976-83 (PMID: 24207122).
39. Dohrn et al. (2017) J. Neurochem. : (PMID: 28902413).
40. Gess et al. (2013) Neuromuscul. Disord. 23 (8):647-51 (PMID: 23743332)
41. Saporta et al. (2011) Annals Of Neurology 69 (1):22-33 (PMID: 21280073).
42. Abrams CK. GJB1 Disorders: Charcot Marie Tooth Neuropathy (CMT1X) and Central Nervous System Phenotypes. 1998 Jun 18 [Updated 2020 Feb 20]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
43. Mehta (Updated January 2017). Fabry Disease. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2010.
44. Soong et al. (2013) Am. J. Hum. Genet. 92 (3):422-30 (PMID: 23434117).
45. Khani et al. (2021) J Neurol 268 (2):640-650 (PMID: 32897397).
46. Diebold et al. (2019) Mol. Cell. Probes 44 :14-20 (PMID: 30682426).
47. Saffa et al. (2015) Brain 138 (Pt 8):2161-72 (PMID: 26072516).
48. Horga et al. (2015) J. Neurol. 262 (8):1984-6 (PMID: 26194197).
49. Capponi et al. (2011) Journal Of The Peripheral Nervous System: Jpns 16 (4):287-94 (PMID: 22176143).
50. Guenther et al. (2007) Human Mutation 28 (8):808-15 (PMID: 17431882).
51. Yuan et al. (2017) J. Hum. Genet. 62 (6):599-604 (PMID: 28202949).
52. Boyer et al. (2011) The New England Journal Of Medicine 365 (25):2377-88 (PMID: 22187985).
53. McLaughlin et al. (2010) Am. J. Hum. Genet. 87 (4):560-6 (PMID: 20920668).
54. Rivière et al. (2011) American Journal Of Human Genetics 89 (2):219-30 (PMID: 21820098).
55. Worman et al. (2007) Experimental Cell Research 313 (10):2121-33 (PMID: 17467691).

56. Weterman et al. (2012) Human Molecular Genetics 21 (2):358-70 (PMID: 22012984).
57. Guernsey et al. (2010) PLoS Genetics 6 (8): (PMID: 20865121).
58. Züchner S. MFN2 Hereditary Motor and Sensory Neuropathy. 2005 Feb 18 [Updated 2020 May 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
59. Morena et al. (2019) Int J Mol Sci 20 (14): (PMID: 31336816)
60. Higuchi et al. (2016) Ann. Neurol. 79 (4):659-72 (PMID: 26991897).
61. Sevilla et al. (2016) Brain 139 (Pt 1):62-72 (PMID: 26497905).
62. Albulym et al. (2016) Ann. Neurol. 79 (3):419-27 (PMID: 26659848).
63. Baumann et al. (2019) Clin. Genet. 95 (1):182-186 (PMID: 30298599).
64. Wang et al. (2019) Front Neurosci 13 :974 (PMID: 31680794).
65. Tazir et al. (2013) J. Peripher. Nerv. Syst. 18 (2):113-29 (PMID: 23781959)
66. Rebelo et al. (2016) Am. J. Hum. Genet. 98 (4):597-614 (PMID: 27040688);
67. Jacquier et al. (2017) Acta Neuropathol Commun 5 (1):55 (PMID: 28709447)
68. Baets et al. (2011) Brain 134 (Pt 6):1587-90 (PMID: 21616967).
69. Capsoni et al. (2014) The European Journal Of Neuroscience 39 (3):392-400 (PMID: 24494679).
70. Indo Y. NTRK1 Congenital Insensitivity to Pain with Anhidrosis. 2008 Aug 5 [Updated 2020 Apr 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
71. Kennerson et al. (2016) J. Peripher. Nerv. Syst. (1):45-51 (PMID: 26801680).
72. Kim et al. (2013) Orphanet Journal Of Rare Diseases 8:104 (PMID: 23844677).
73. Li et al. (2013) Molecular Neurobiology 47 (2):673-98 (PMID: 23224996).
74. Leal et al. (2018) Neurogenetics 19 (4):215-225 (PMID: 30039206).
75. Drissi et al. (2020) Br Med Bull 133 (1):65-78 (PMID: 32219415).
76. Kim and Kim (Updated June 2013). Charcot-Marie-Tooth Neuropathy X Type 5 In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2010.
77. Hayashi et al. (2013) Journal Of Human Genetics 58 (5):273-8 (PMID: 23466821).
78. Cogli et al. (2009) Biochem. Soc. Trans. 37 (Pt 5):1027-31 (PMID: 19754445).
79. Züchner et al. (2006) American Journal Of Human Genetics 79 (2):365-9 (PMID: 16826527).
80. Beetz et al. (2012) American Journal Of Human Genetics 91 (1):139-45 (PMID: 22703882).
81. Davidson et al. (2012) Journal Of Neurology 259 (8):1673-85 (PMID: 22302274).
82. Nakhro et al. (2013) Neurology 81 (2):165-73 (PMID: 23749797).
83. Leipold et al. (2013) Nature Genetics 45 (11):1399-404 (PMID: 24036948).
84. Huang et al. (2014) Brain: A Journal Of Neurology 137 (Pt 6):1627-42 (PMID: 24776970).
85. Faber et al. (2012) Annals Of Neurology 71 (1):26-39 (PMID: 21698661).
86. Hisama FM, Dib-Hajj SD, Waxman SG. SCN9A Neuropathic Pain Syndromes. 2006 May 6 [Updated 2020 Jan 23]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
87. Rebelo et al. (2018) Brain 141 (3):662-672 (PMID: 29351582).
88. Nanetti et al. (2013) Orphanet J. Rare Dis. 8 :123 (PMID: 23941260).
89. van Alfen et al. (2011) Nat Rev Neurol 7 (6):315-22 (PMID: 21556032).
90. Azzedine, Bontoux, and LeGuern (Updated October 2015). Charcot-Marie-Tooth Neuropathy Type 4C. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2010.
91. Ma et al. (2020) Neuromuscul. Disord. 30 (7):572-575 (PMID: 32600828).
92. Howard et al. (2002) Nature Genetics 32 (3):384-92 (PMID: 12368912).
93. Abrams et al. (2015) Nat. Genet. 47 (8):926-32 (PMID: 26168012).
94. Foley et al. (2014) Brain: A Journal Of Neurology 137 (Pt 1):44-56 (PMID: 24253200).
95. Green et al. (2010) American Journal Of Human Genetics 86 (3):485-9 (PMID: 20206331).
96. Montecchiani et al. (2016) Brain 139 (Pt 1):73-85 (PMID: 26556829)
97. Orlicchio et al. (2010) Brain: A Journal Of Neurology 133 (Pt 2):591-8 (PMID: 20110243)
98. Davidson et al. (2012) Journal Of Neurology 259 (8):1673-85 (PMID: 22302274).
99. Rothier et al. (2010) Am. J. Hum. Genet. 87 (4):513-22 (PMID: 20920666).
100. Ishiura et al. (2012) American Journal Of Human Genetics 91 (2):320-9 (PMID: 22883144).
101. Ylikallio et al. (2013) Hum. Mol. Genet. 22 (15):2975-83 (PMID: 23562820).
102. Deng et al. (2020) Neuromolecular Med. 22 (1):68-72 (PMID: 31468327).
103. Sekijima Y. Hereditary Transthyretin Amyloidosis. 2001 Nov 5 [Updated 2018 Dec 20]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021.
104. Garg et al. (2017) J Neurol Neurosurg Psychiatry 88 (6):474-483 (PMID: 28003344).
105. Chen et al. (2010) The Journal of biological chemistry 285 (51):40266-81 (PMID: 20940299).
106. Gite et al. (2020) Neuromuscul. Disord. 30 (3):232-235 (PMID: 32165109)
107. Greenbaum et al. (2020) Muscle Nerve 61 (3):395-400 (PMID: 31837156).
108. Jordanova et al. (2006) Nature Genetics 38 (2):197-202 (PMID: 16429158).
109. Salter et al. (2018) Neurol. Genet. 4 (2):e222 (PMID: 29582019).