

# Charcot-Marie-Tooth Disease and Related Hereditary Neuropathies

## Indications for Ordering

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Confirm diagnosis and/or determine genetic etiology for hereditary neuropathies collectively referred to as Charcot-Marie-Tooth related disorders

- Charcot-Marie-Tooth (CMT) disease
  - Includes, among others, types 1 (CMT1), 1A (CMT1A), 2 (CMT2), and 4 (CMT4)
  - Also known as hereditary motor and sensory neuropathy (HMSN)
- Hereditary sensory neuropathies (HSN)/hereditary sensory and autonomic neuropathies (HSAN)
- Distal hereditary motor neuropathies (HMN)
- Hereditary neuropathy with liability to pressure palsies (HNPP)

## Test Description

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- Multiplex ligation-dependent probe amplification to detect large exonic deletions/duplications in *PMP22* gene
- Targeted capture of all coding regions and intron/exon boundaries followed by massively parallel sequencing of 78 genes (see table)
  - Sanger sequencing is performed as necessary to fill in regions of low coverage and confirm reported variants

## Tests to Consider

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### Typical testing strategy

For autosomal dominant or sporadic demyelinating CMT, suspected CMT1, or suspected HNPP

- Order *PMP22* deletion/duplication analysis
  - If negative, pursue testing for other genes causative for CMT1 or HNPP

### Primary tests

[Charcot-Marie-Tooth \(CMT\) and Related Hereditary Neuropathies, \*PMP22\* Deletion/Duplication with Reflex to Sequencing Panel 2012155](#)

- Recommended initial test to confirm a suspected diagnosis of CMT1 or CMT1A
- *PMP22* gene deletion/duplication analysis is performed first
  - If negative or inconclusive, reflexes to sequencing of 78 genes related to CMT and hereditary neuropathies
- 70-80% of cases are due to duplication of *PMP22*

[Charcot-Marie-Tooth Type 1A \(CMT1A\)/Hereditary Neuropathy with Liability to Pressure Palsies \(HNPP\), \*PMP22\* Deletion/Duplication 2012160](#)

- Acceptable initial test to confirm a suspected diagnosis of CMT1 or CMT1A
- Can be used to test for a known familial *PMP22* deletion or duplication associated with CMT1A or HNPP
- Use when testing for known familial *PMP22* deletion/duplication

[Charcot-Marie-Tooth \(CMT\) and Related Hereditary Neuropathies Panel, Sequencing 2012151](#)

- Order to confirm a suspected diagnosis of a hereditary neuropathy or CMT subtype other than CMT1/CMT1A
- To confirm a diagnosis of CMT1/CMT1A, *PMP22* gene deletion/duplication studies should be performed first

### Related test

[Familial Mutation, Targeted Sequencing 2001961](#)

- Useful when a pathogenic familial variant identifiable by sequencing is known

## Disease Overview

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**Prevalence of CMT hereditary neuropathy** – 1/3,300

**Age of onset** – first through third decade

## Diagnosis of hereditary neuropathy

- Based on combination of
  - Physical examination
  - Personal history
  - Family history
  - Electromyography
  - Nerve conduction velocity (NCV)
  - Nerve biopsy
  - Genetic testing
  - Exclusion of acquired neuropathies

## Subtypes of peripheral neuropathies

- Demyelinating (CMT1, CMT4)
  - Upper-limb motor NCV <38 meters/second (m/s)
  - Pathological evidence of myelin abnormalities
- Axonal/nondemyelinating (CMT2/HMSN, HMN, HSN)
  - Upper-limb motor NCV >38 m/s
  - Pathological evidence of axonal degeneration and regeneration
- Intermediate (dominant intermediate [DI-CMT], recessive intermediate [RI-CMT], X-linked type 1 [CMTX1])
  - Upper-limb motor NCV 25-45 m/s

## Symptoms

### CMT

- Progressive distal motor and sensory neuropathy
- Muscle weakness/atrophy
- Pes cavus foot deformity, foot drop

### HSN/HSAN

- Predominant sensory neuropathy with motor involvement in advanced disease

### HMN

- Distal motor neuropathy without sensory loss

### HNPP

- Transient/recurring focal pressure neuropathies (eg, carpal tunnel syndrome)
- Mild to moderate peripheral neuropathy

## Diagnostic issues

- Clinical phenotype is often indistinguishable among CMT subtypes
  - Genetic testing is needed to determine subtype
- Acquired neuropathies can present similarly to hereditary neuropathies
  - Acquired forms should be excluded prior to diagnosing hereditary neuropathy

## Genetics

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### Genes – see table

- CMT disease is comprised of multiple subtypes defined by phenotype and/or inheritance pattern
  - CMT1 – demyelinating neuropathy, autosomal dominant
  - CMT2 – axonal motor and sensory neuropathy, autosomal dominant and recessive
  - CMT4 – demyelinating neuropathy, autosomal recessive
  - CMTX – variable neuropathy, X-linked
  - DI-CMT – dominant intermediate neuropathy
  - RI-CMT – recessive intermediate neuropathy
- CMT subtypes are further divided based on specific causative gene
  - eg, CMT1A is caused by variants in *PMP22*, and CMT1B is caused by variants in *MPZ*
  - Genetic testing to determine subtype can be performed
    - Sequentially, based on phenotype and inheritance pattern **OR**
    - With large panels that test multiple genes simultaneously
    - *PMP22* duplication testing is typically performed first for cases of suspected CMT1
      - CMT1A is the most common subtype
    - *PMP22* deletion testing is typically performed first for cases of suspected HNPP

### Inheritance – gene dependent (see table)

### De novo variants

- 10-20% of *PMP22* duplications causing CMT1A
- ~One-third of point mutations in *PMP22*, *GJB1*, and *MPZ*

## Test Interpretation

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### Sensitivity/specificity

- *PMP22* deletion/duplication analysis
  - Clinical sensitivity (GeneReviews)
    - 70-80% for CMT1
    - 80% for HNPP
  - Analytical sensitivity/specificity – 99%
- Sequencing of 78 genes
  - Clinical sensitivity – disorder dependent (see table)
  - Analytical sensitivity/specificity – 99%

## Results

- Positive – one or more pathogenic variants detected
  - Genes with autosomal dominant inheritance
    - One pathogenic variant predicts a CMT-related disorder
  - Genes with autosomal recessive inheritance
    - One pathogenic variant predicts carrier status for a CMT-related disorder
    - Two pathogenic variants on opposite chromosomes predicts a CMT-related disorder
  - Genes with X-linked inheritance
    - In females, one pathogenic variant predicts carrier status
    - In males, one pathogenic variant predicts a CMT-related disorder
- Negative – no pathogenic variants associated with a CMT-related disorder identified
  - Does not exclude a diagnosis of CMT or related hereditary neuropathies
- Inconclusive – variants of unknown clinical significance may be identified

## Limitations

- Not detected
  - Variants in genes not tested
  - Large exonic deletions/duplications (other than *PMP22*, if tested)
  - Deep intronic or regulatory region mutations
- Small deletions or insertions may not be detected
- Diagnostic errors can occur due to rare sequence variations

## References

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Gene Symbol	Gene Description	NM #	OMIM	Associated Disorder(s)	Inheritance	Clinical Sensitivity <sup>a</sup>
AARS	Alanyl-tRNA synthetase	001605	601065	CMT 2N	AD	Unknown
AIFM1	Apoptosis-inducing factor, mitochondrion-associated, 1	004208	300169	CMT X4/Cowchock syndrome	XL-R	Unknown
ARHGEF10	Rho guanine nucleotide exchange factor (GEF) 10	014629	608136	Slowed nerve conduction velocity	AD	Unknown
ATL1	Atlantin GTPase 1	015915	606439	HSN 1D, SPG 3A	AD	Unknown
ATP7A	ATPase, Cu <sup>++</sup> transporting, alpha polypeptide	000052	300011	ATP7A-related distal motor neuropathy, X-linked distal SMA 3, Menkes disease	XL-R	Unknown
BAG3	BCL2-associated athanogene 3	004281	603883	Giant axonal neuropathy; BAG3-associated myofibrillar myopathy	AD	Unknown
BICD2	Bicaudal D homolog 2 (Drosophila)	001003800	609797	SMA, lower extremity-predominant 2 (SMALED2)	AD	Unknown
BSCL2	Berardinelli-Seip congenital lipodystrophy 2 (seipin)	032667	606158	BSCL2-related neurological disorders/seipinopathies – dHMN/HMN 5A, CMT 2, Silver syndrome, SPG 17, Berardinelli-Seip congenital lipodystrophy (BSCL)	HMN – AD BSCL – AR	HMN – 2-7%
CCT5	Chaperonin containing TCP1, subunit 5 (epsilon)	012073	610150	HSN with SPG	AR	Unknown
DCTN1	Dynactin 1	004082	601143	dHMN 7B, Perry syndrome	AD	Unknown
DHTKD1	Dehydrogenase E1 and transketolase domain containing 1	018706	614984	CMT 2Q, aminoadipic aciduria	CMT2Q – AD Aminoadipic aciduria – AR	Unknown
DNAJB2	DnaJ (Hsp40) homolog, subfamily B, member 2	001039550	604139	CMT 2T, distal SMA 5	AR	Unknown
DNM2	Dynamin 2	001005360	602378	DI-CMT B	AD	CMT – <3%
DNMT1	DNA (cytosine-5)-methyltransferase 1	001130823	126375	DNMT1-related dementia, deafness, and sensory neuropathy (HSAN 1E)	AD	Unknown
DYNC1H1	Dynein, cytoplasmic 1, heavy chain 1	001376	600112	CMT 2O, SMA with lower-extremity predominance	AD	Unknown
EGR2	Early growth response 2	000399	129010	CMT1D, CMT4E	CMT1D – AD CMT4E – AR	CMT 1 – <2% CMT 4 – unknown
FAM134B	Family with sequence similarity 134, member B	001034850	613114	HSAN 2B	AR	HSN – ~1%
FBLN5	Fibulin 5	006329	604580	CMT 1, dHMN with macular degeneration and hyperelastic skin	AD	Unknown
FGD4	FYVE, RhoGEF and PH domain containing 4	139241	611104	CMT 4H	AR	Unknown
FIG4	FIG4 phosphoinositide 5-phosphatase	014845	609390	CMT 4J, ALS	CMT4J – AR ALS – AD	Unknown
GAN	Gigaxonin	022041	605379	Giant axonal neuropathy 1 (GAN)	AR	GAN – 70-90%
GARS	Glycyl-tRNA synthetase	002047	600287	CMT 2D, distal SMA 5, dHMN 5	AD	HMN – ~2%
GDAP1	Ganglioside induced differentiation associated protein 1	018972	606598	CMT 2H, CMT 2K, CMT 4A, RI-CMT A	AR	CMT 2 – 5% CMT 4 – 25%
GJB1	Gap junction protein, beta 1, 32kDa	000166	304040	CMT X1	XL-D	CMT – ~8% CMT X – 90%
GNB4	Guanine nucleotide binding protein (G protein), beta polypeptide 4	021629	610863	DI-CMT 1F	AD	Unknown
HARS	Histidyl-tRNA synthetase	002109	142810	Probable CMT 2, Usher syndrome 3B	AD	Unknown
HEXA	Hexosaminidase A (alpha polypeptide)	000520	606869	Tay-Sachs disease/hexosaminidase A deficiency	AR	Unknown
HINT1	Histidine triad nucleotide binding protein 1	005340	601314	Gamstorp-Wohlfart syndrome/neuromyotonia and axonal neuropathy	AR	Unknown
HK1	Hexokinase 1	000188	142600	CMT 4G, HSAN Russe type	AR	Unknown
HOXD10	Homeobox D10	002148	142984	Isolated congenital vertical talus	AD	Unknown

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<i>HSPB1</i>	Heat shock 27kDa protein 1	001540	602195	CMT 2F, dHMN 2B	AD (rarely AR)	HMN – ~8%
<i>HSPB3</i>	Heat shock 27kDa protein 3	006308	604624	dHMN 2C	AD	Unknown
<i>HSPB8</i>	Heat shock 22kDa protein 8	014365	608014	CMT 2L, dHMN 2A	AD	HMN – ~2%
<i>IGHMBP2</i>	Immunoglobulin mu binding protein 2	002180	600502	CMT 2S, HMN 6, SMA with respiratory distress (SMARD)	AR	Unknown
<i>IKBKAP</i>	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein	003640	603722	Familial dysautonomia, HSAN 3	AR	Unknown
<i>INF2</i>	Inverted formin, FH2 and WH2 domain containing	001031714	610982	DI-CMT E	AD	Unknown
<i>KARS</i>	Lysyl-tRNA synthetase	001130089	601421	RI-CMT B	AR	Unknown
<i>KIF1A</i>	Kinesin family member 1A	004321	601255	HSAN 2C, spastic paraplegia 30	AR	Unknown
<i>KIF1B</i>	Kinesin family member 1B	015074	605995	CMT 2A1	AD	Unknown
<i>KIF5A</i>	Kinesin family member 5A	004984	602821	SPG 10, axonal neuropathy	AD	Unknown
<i>LAS1L</i>	LAS1-like ( <i>S. cerevisiae</i> )	031206		Spinal muscular atrophy with respiratory distress (SMARD)	XL	Unknown
<i>LITAF</i>	Lipopolysaccharide-induced TNF factor	004862	603795	CMT 1C	AD	CMT 1 – 1-2%
<i>LMNA</i>	Lamin A/C	005572	150330	CMT 2B1 and other phenotypes	AR	Unknown
<i>LRSAM1</i>	Leucine rich repeat and sterile alpha motif containing 1	138361	610933	CMT 2P	AD	Unknown
<i>MARS</i>	Methionyl-tRNA synthetase	004990	156560	CMT 2	AD	Unknown
<i>MED25</i>	Mediator complex subunit 25	030973	610197	CMT 2B2	AR	Unknown
<i>MFN2</i>	Mitofusin 2	014874	608507	CMT 2A2, HMSN 6, HMSN 7	AD	CMT – ~2% CMT 2 – 10-20%
<i>MPZ</i>	Myelin protein zero	000530	159440	CMT 1B, CMT 2I, CMT 2J, DI-CMT D	AD	CMT 1 – 5-10% CMT 2 – ~1% DI-CMT – 1-2%
<i>MTMR2</i>	Myotubularin related protein 2	016156	603557	CMT 4B1	AR	Unknown
<i>MYH14</i>	Myosin, heavy chain 14, non-muscle	024729	608568	Peripheral neuropathy, myopathy, hoarseness, and hearing loss	AD	Unknown
<i>NDRG1</i>	N-myc downstream regulated 1	006096	605262	CMT 4D	AR	Unknown
<i>NEFL</i>	Neurofilament, light polypeptide	006158	162280	CMT 1F, CMT 2E	AD	CMT 1 – <5% CMT 2 – 4%
<i>NGF</i>	Nerve growth factor (beta polypeptide)	002506	162030	HSAN 5	AR	HSN – ~2%
<i>NTRK1</i>	Neurotrophic tyrosine kinase, receptor, type 1	001012331	191315	HSAN 4/congenital insensitivity to pain with anhidrosis	AR	Unknown
<i>PDK3</i>	Pyruvate dehydrogenase kinase, isozyme 3	001142386	300906	CMT X6	XL-R	Unknown
<i>PLEKHG5</i>	Pleckstrin homology domain containing, family G (with RhoGef domain) member 5	020631	611101	RI-CMT C, distal SMA	AR	Unknown
<i>PMP22</i>	Peripheral myelin protein 22	000304	601097	Gene duplication – CMT 1A	AD	CMT 1 – 70-80%
				Gene deletion – HNPP	AD	HNPP – 80%
				Sequence mutations – CMT 1E, HNPP	AD	CMT 1 – <5%, HNPP – 20%
<i>PRNP</i>	Prion protein	000311	176640	Hereditary prion diseases	AD	Unknown
<i>PRPS1</i>	Phosphoribosyl pyrophosphate synthetase 1	002764	311850	CMT X5, <i>PRPS1</i> -related disorders	XLR	Unknown
<i>PRX</i>	Periaxin	181882	605725	CMT 4F	AR	Unknown
<i>RAB7A</i>	RAB7A, member RAS oncogene family	004637	602298	CMT 2B	AD	Unknown
<i>REEP1</i>	Receptor accessory protein 1	022912	609139	dHMN 5B, SPG 31	AD	Unknown
<i>SBF1</i>	SET binding factor 1	002972	603560	CMT 4B3	AR	Unknown
<i>SBF2</i>	SET binding factor 2	030962	607697	CMT 4B2	AR	Unknown

Gene Symbol	Gene Description	NM #	OMIM	Associated Disorder(s)	Inheritance	Clinical Sensitivity <sup>a</sup>
SCN9A	Sodium channel, voltage-gated, type IX, alpha subunit	002977	603415	HSAN 2D	AR	Unknown
SETX	Senataxin	015046	608465	dHMN, ALS, SCA	AD	
SH3TC2	SH3 domain and tetratricopeptide repeats 2	024577	608206	CMT 4C	AR	Unknown
SLC12A6	Solute carrier family 12 (potassium/chloride transporter) member 6	133647	604878	HMSN with agenesis of the corpus callosum (ACC)	AR	HMSN/ACC – 90%
SLC5A7	Solute carrier family 5 (sodium/choline co-transporter), member 7	021815	608761	dHMN 7A	AD	Unknown
SOX10	SRY (sex determining region Y)-box 10	006941	602229	Peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease	AD	Unknown
SPTLC1	Serine palmitoyltransferase, long chain base subunit 1	006415	605712	HSAN 1A	AD	HSN – ~20%
SPTLC2	Serine palmitoyltransferase, long chain base subunit 2	004863	605713	HSAN 1C	AD	HSN – ~7%
TDP1	Tyrosyl-DNA phosphodiesterase 1	018319	607198	SCA with axonal neuropathy 1 (SCAN1)	AR	Unknown
TFG	TRK-fused gene	006070	602498	HMSN, Okinawa type (HMSNO), SPG 57	HMSNO – AD SPG57 – AR	Unknown
TRIM2	Tripartite motif containing 2	001130067	614141	CMT 2R	AR	Unknown
TRPV4	Transient receptor potential cation channel, subfamily V, member 4	021625	605427	CMT 2C and other phenotypes	AD	Unknown
WNK1	WNK lysine deficient protein kinase 1	018979	605232	HSAN 2A, pseudohypoaldosteronism type 2C	HSAN2A – AR PHA – AD	Unknown
YARS	Tyrosyl-tRNA synthetase	003680	603623	DI-CMT C	AD	Unknown

<sup>a</sup>Percentage of the specified disorder that is attributable to variants in gene (see references)

AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; AR, autosomal recessive; CMT, Charcot-Marie-Tooth disease; dHMN/HMN, (distal) hereditary motor neuropathy; DI-CMT, dominant-intermediate Charcot-Marie-Tooth; HMSN, hereditary motor and sensory neuropathy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; HSN, hereditary sensory neuropathy; RI-CMT, recessive-intermediate Charcot-Marie-Tooth; SCA, spinocerebellar ataxia; SMA, spinal muscular atrophy; SPG, spastic paraplegia; XL, X-linked (unknown if dominant or recessive); XL-D, X-linked dominant; XL-R, X-linked recessive