Charcot-Marie-Tooth Disease and Related Hereditary Neuropathies

Indications for Ordering

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

- 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
  - Confirms presence of all reported sequence variants
  - Provides data for bases with insufficient coverage by massively parallel sequencing

Tests to Consider

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

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

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

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***
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	Atlastin GTPase 1	015915	606439	HSN 1D, SPG 3A	AD	Unknown
ATP7A	ATPase, Cu++ 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
HSPB1	Heat shock 27kDa protein 1	001540	602195	CMT 2F, dHMN 2B	AD (rarely AR)	HMN – ~8%

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HSPB3	Heat shock 27kDa protein 3	006308	604624	dHMN 2C	AD	Unknown
HSPB8	Heat shock 22kDa protein 8	014365	608014	CMT 2L, dHMN 2A	AD	HMN – ~2%
IGHMBP2	Immunoglobulin mu binding protein 2	002180	600502	CMT 2S, HMN 6, SMA with respiratory distress (SMARD)	AR	Unknown
IKBKAP	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein	003640	603722	Familial dysautonomia, HSAN 3	AR	Unknown
INF2	Inverted formin, FH2 and WH2 domain containing	001031714	610982	DI-CMT E	AD	Unknown
KARS	Lysyl-tRNA synthetase	001130089	601421	RI-CMT B	AR	Unknown
KIF1A	Kinesin family member 1A	004321	601255	HSAN 2C, spastic paraplegia 30	AR	Unknown
KIF1B	Kinesin family member 1B	015074	605995	CMT 2A1	AD	Unknown
KIF5A	Kinesin family member 5A	004984	602821	SPG 10, axonal neuropathy	AD	Unknown
LAS1L	LAS1-like (S. cerevisiae)	031206		Spinal muscular atrophy with respiratory distress (SMARD)	XL	Unknown
LITAF	Lipopolysaccharide-induced TNF factor	004862	603795	CMT 1C	AD	CMT 1 – 1-2%
LMNA	Lamin A/C	005572	150330	CMT 2B1 and other phenotypes	AR	Unknown
LRSAM1	Leucine rich repeat and sterile alpha motif containing 1	138361	610933	CMT 2P	AD	Unknown
MARS	Methionyl-tRNA synthetase	004990	156560	CMT 2	AD	Unknown
MED25	Mediator complex subunit 25	030973	610197	CMT 2B2	AR	Unknown
MFN2	Mitofusin 2	014874	608507	CMT 2A2, HMSN 6, HMSN 7	AD	CMT – ~2% CMT 2 – 10-20%
MPZ	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%
MTMR2	Myotubularin related protein 2	016156	603557	CMT 4B1	AR	Unknown
MYH14	Myosin, heavy chain 14, non-muscle	024729	608568	Peripheral neuropathy, myopathy, hoarseness, and hearing loss	AD	Unknown
NDRG1	N-myc downstream regulated 1	006096	605262	CMT 4D	AR	Unknown
NEFL	Neurofilament, light polypeptide	006158	162280	CMT 1F, CMT 2E	AD	CMT 1 – <5% CMT 2 – 4%
NGF	Nerve growth factor (beta polypeptide)	002506	162030	HSAN 5	AR	HSN – ~2%
NTRK1	Neurotrophic tyrosine kinase, receptor, type 1	001012331	191315	HSAN 4/congenital insensitivity to pain with anhidrosis	AR	Unknown
PDK3	Pyruvate dehydrogenase kinase, isozyme 3	001142386	300906	CMT X6	XL-R	Unknown
PLEKHG5	Pleckstrin homology domain containing, family G (with RhoGef domain) member 5	020631	611101	RI-CMT C, distal SMA	AR	Unknown
PMP22	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%
PRNP	Prion protein	000311	176640	Hereditary prion diseases	AD	Unknown
PRPS1	Phosphoribosyl pyrophosphate synthetase 1	002764	311850	CMT X5, *PRPS1*-related disorders	XLR	Unknown
PRX	Periaxin	181882	605725	CMT 4F	AR	Unknown
RAB7A	RAB7A, member RAS oncogene family	004637	602298	CMT 2B	AD	Unknown
REEP1	Receptor accessory protein 1	022912	609139	dHMN 5B, SPG 31	AD	Unknown
SBF1	SET binding factor 1	002972	603560	CMT 4B3	AR	Unknown
SBF2	SET binding factor 2	030962	607697	CMT 4B2	AR	Unknown
SCN9A	Sodium channel, voltage-gated, type IX, alpha subunit	002977	603415	HSAN 2D	AR	Unknown

Gene Symbol	Gene Description	NM #	OMIM	Associated Disorder(s)*	Inheritance**	Clinical Sensitivity***
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

* CMT = Charcot-Marie-Tooth disease; DI-CMT = dominant-intermediate Charcot-Marie-Tooth; RI-CMT = recessive-intermediate Charcot-Marie-Tooth; HSN = hereditary sensory neuropathy; dHMN/HMN = (distal) hereditary motor neuropathy; HMSN = hereditary motor and sensory neuropathy; HSAN = hereditary sensory and autonomic neuropathy; HNPP = hereditary neuropathy with liability to pressure palsies; SPG = spastic paraplegia; SMA = spinal muscular atrophy; SCA = spinocerebellar ataxia; ALS = amyotrophic lateral sclerosis

** AD = autosomal dominant; AR = autosomal recessive; XL = X-linked (unknown if dominant or recessive); XL-R = X-linked recessive; XL-D = X-linked dominant

*** Percentage of the specified disorder that is attributable to variants in gene (see references)