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Charcot-Marie-Tooth Disease and Related Hereditary Neuropathies

Charcot-Marie-Tooth (CMT) disease is a hereditary neuropathy with many types and subtypes, including types 1 (CMT1), 1A (CMT1A), 2 (CMT2), and 4 (CMT4), among others. Disorders with similar clinical findings include hereditary motor neuropathy (HMN), hereditary motor and sensory neuropathy (HMSN), hereditary sensory neuropathies (HSN), hereditary sensory and autonomic neuropathies (HSAN), and hereditary neuropathy with liability to pressure palsies (HNPP). Diagnostic testing for these conditions can be performed to confirm the diagnosis in symptomatic individuals or to identify family members at risk for developing the condition; genetic etiology generally determines the CMT type and subtype.

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

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

Types of Peripheral Neuropathies

- Demyelinating
  - Upper-limb motor NCV <38 meters/second (m/s)
  - Pathological evidence of myelin abnormalities
- Axonal/nondemyelinating

TESTS TO CONSIDER

Charcot-Marie-Tooth (CMT) and Related Hereditary Neuropathies, PMP22 Deletion/Duplication with Reflex to Sequencing Panel 2012155
Method: Multiplex Ligation-dependent Probe Amplification/Massively Parallel Sequencing

- Recommended test for suspected autosomal dominant or sporadic demyelinating CMT, CMT1 or CMT1A.
- Deletion/duplication of *PMP22* gene is performed first. If no large deletions or duplications are detected and/or results do not explain the clinical scenario, sequencing of hereditary neuropathy genes is performed (see Genes Tested table for gene list).
- Deletion/duplication and sequencing components are also orderable separately, see below.

Charcot-Marie-Tooth Type 1A (CMT1A)/Hereditary Neuropathy with Liability to Pressure Palsies (HNPP), PMP22 Deletion/Duplication 2012160
Method: Multiplex Ligation-dependent Probe Amplification

- Recommended test for suspected HNPP, appropriate first-tier test for suspected autosomal dominant or sporadic demyelinating CMT, CMT1 or CMT1A; does not detect sequence variants.
- Recommended test if there is a known familial *PMP22* deletion or duplication previously identified in a family member. A copy of the family member's test result documenting the known familial variant is required.

Charcot-Marie-Tooth (CMT) and Related Hereditary Neuropathies Panel, Sequencing 2012151
Method: Massively Parallel Sequencing

- Upper-limb motor NCV >38 m/s
- Pathological evidence of axonal degeneration and regeneration

- Intermediate
  - Upper-limb motor NCV 25-45 m/s

Types of CMT

- CMT disease is comprised of multiple types 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.
  - CMT1A, for example, is caused by variants in *PMP22,* and CMT1B is caused by variants in *MPZ*
  - Symptoms are often indistinguishable among CMT subtypes
  - Genetic testing to determine subtype can be performed
    - Sequentially, based on phenotype and inheritance pattern **OR**
    - With large panels that test multiple genes simultaneously

- Recommended test for hereditary neuropathies or CMT subtype **other than** CMT1/CMT1A (see Genes Tested table for gene list).
- Appropriate second-tier test for suspected CMT1 after result of *PMP22* deletion/duplication analysis is negative.

Familial Mutation, Targeted Sequencing 2001961
Method: Polymerase Chain Reaction/Sequencing

- Recommended test for a known familial sequence variant previously identified in a family member.
- A copy of the family member's test result documenting the known familial variant is required.

TEST DESCRIPTION

See Genes Tested table for genes included in the panel.

Sensitivity/Specificity

- *PMP22* deletion/duplication analysis
  - Clinical sensitivity (GeneReviews)
    - 70-80% for CMT1
    - 80% for HNPP
  - Analytical sensitivity/specificity – 99%
- Sequencing panel
  - Clinical sensitivity is disorder dependent.

Limitations

- A negative result does not exclude a heritable form of neuropathy.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplantation.
- The following will not be evaluated:
  - Variants outside the coding regions and intron-exon boundaries of the targeted genes
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications in *PMP22*
  - Large deletions/duplications in genes other than *PMP22*
  - Noncoding transcripts
- The following exons are not sequenced due to technical limitations of the assay:
  - *SPTLC1* (NM_006415) 3
  - *DNMT1* (NM_001130823) 5
  - *SETX* (NM_001351528) 26
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

Analytical Sensitivity

- For MLPA: 99%
- For massively parallel sequencing:

Variant Class	Analytical Sensitivity (PPA) Estimate[a] (%)	Analytical Sensitivity (PPA) 95% Credibility Region[a] (%)
SNVs	99.2	96.9-99.4
Deletions 1-10 bp	93.8	84.3-98.2
Deletions 11-44 bp	100	87.8-100
Insertions 1-10 bp	94.8	86.8-98.5
Insertions 11-23 bp	100	62.1-100

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived.

bp, base pairs; PPA, positive percent agreement; SNVs, single nucleotide variants

Genes Tested

Gene	MIM Number	Disorder and Subtype (Abbreviation)	Inheritance
AARS	601065	CMT disease, axonal, type 2N (CMT 2N)	AD
AIFM1	300169	Cowchock syndrome (CMT X4)	XL
ATL1	606439	Spastic paraplegia 3A, autosomal dominant (SPG 3A) Neuropathy, hereditary sensory, type ID (HSN 1D)	AD
ATP7A	300011	Menkes disease Occipital horn syndrome Spinal muscular atrophy, distal, X-linked 3	XL
BAG3	603883	Myopathy, Myofibrillar, 6 Giant axonal neuropathy	AD
BICD2	609797	Spinal muscular atrophy, lower extremity-predominant, 2	AD
BSCL2	606158	*BSCL2*-related neurologic disorders/seipinopathy neuropathy, distal hereditary motor, type VA (dHMN/HMN 5A) Silver spastic paraplegia syndrome Charcot-Marie-Tood disease type 2 (CMT 2)	AD
CCT5	610150	Neuropathy, hereditary sensory, with spastic paraplegia (HSN with SPG)	AR
DCTN1	601143	Neuropathy, distal hereditary motor, type VIIB (dHMN 7B) Perry syndrome	AD
DHTKD1	614984	CMT disease type 2Q (CMT 2Q)	AD
DNAJB2	604139	Spinal muscular atrophy, distal, autosomal recessive, 5	AR
DNM2	602378	CMT disease, axonal type 2M (CMT 2M) CMT disease, dominant intermediate B (DI-CMT B) Centronuclear myopathy 1	AD
DNMT1	126375	Neuropathy, hereditary sensory, type IE (HSAN 1E) Cerebellar ataxia, deafness, and narcolepsy	AD
DYNC1H1	600112	CMT disease, axonal, type 2O (CMT 2O) Spinal muscular atrophy, lower extremity-predominant 1	AD
EGR2	129010	CMT disease, type 1D (CMT 1D)	AD
		Dejerine-Sottas disease Neuropathy, congenital hypomyelinating, 1 (CMT 4E)	AD or AR

Gene	MIM Number	Disorder and Subtype (Abbreviation)	Inheritance
ELP1 (IKBKAP)	603722	Familial dysautonomia Hereditary sensory and autonomic neuropathy type III (HSAN 3)	AR
FBLN5	604580	Neuropathy, hereditary, with or without age-related macular degeneration	AD
FGD4	611104	CMT disease, type 4H (CMT 4H)	AR
FIG4	609390	CMT disease, type 4J (CMT 4J)	AR
		Amyotrophic lateral sclerosis 11	AD
GAN	605379	Giant axonal neuropathy-1	AR
GARS	600287	CMT disease, type 2D (CMT 2D) Neuropathy, distal hereditary motor, type VA (dHMN 5A)	AD
GDAP1	606598	CMT disease, type 4A (CMT 4A) CMT disease, axonal, with vocal cord paresis CMT disease, axonal, type 2K (CMT 2K) CMT disease, recessive intermediate, A (RI-CMT A)	AR
GJB1	304040	CMT neuropathy, X-linked dominant, 1 (CMT X1)	XL
GNB4	610863	CMT disease, dominant intermediate F (DI-CMT 1F)	AD
HARS	142810	CMT disease, axonal, type 2W (CMT 2W)	AD
HEXA	606869	Tay-Sachs disease/ hexosaminidase A deficiency	AR
HINT1	601314	Neuromyotonia and axonal neuropathy	AR
HOXD10	142984	Isolated congenital vertical talus	AD
HSPB1	602195	CMT disease, axonal, type 2F (CMT 2F) Neuropathy, distal hereditary motor, type IIB; (dHMN 2B)	AD
HSPB3	604624	Neuronopathy, distal hereditary motor, type IIC (dHMN 2C)	AD
HSPB8	608014	CMT disease, axonal, type 2L (CMT 2L) Neuropathy, distal hereditary motor, type IIA (dHMN 2A)	AD
IGHMBP2	600502	Neuronopathy, distal hereditary motor, type VI (HMN 6) Charcot-Marie-Tooth disease, axonal, type 2S (CMT 2S)	AR
INF2	610982	CMT disease, dominant intermediate E (DI-CMT E)	AD
KARS	601421	CMT disease, recessive intermediate, B (RI-CMT B)	AR
KIF1A	601255	Neuropathy, hereditary sensory, type IIC (HSAN 2C SPG 30)	AR
KIF1B	605995	CMT disease, type 2A1 (CMT 2A1)	AD
KIF5A	602821	SPG 10	AD
LAS1L	300964	Spinal muscular atrophy with respiratory distress (SMARD)	XL
LITAF	603795	CMT disease, type 1C (CMT 1C)	AD
LMNA	150330	CMT disease, type 2B1 (CMT 2B1)	AR
LRSAM1	610933	CMT disease, axonal, type 2P (CMT 2P)	AD or AR
MARS	156560	CMT disease, axonal, type 2U (CMT 2U)	AD
MED25	610197	CMT disease, type 2B2 (CMT 2B2)	AR
MFN2	608507	Hereditary motor and sensory neuropathy VIA (HMSN 6A) CMT disease, axonal, type 2A2A (CMT 2A2A)	AD
		CMT disease, axonal, type 2A2B (CMT 2A2B)	AR
MORC2	616661	CMT disease, axonal, type 2Z (CMT 2Z)	AD

Gene	MIM Number	Disorder and Subtype (Abbreviation)	Inheritance
MPZ	159440	CMT disease, dominant intermediate D (DI-CMT D) CMT disease, type 1B (CMT 1B) CMT disease, type 2I (CMT 2I) CMT disease, type 2J (CMT 2J) Roussy-Levy syndrome	AD
		Neuropathy, congenital hypomyelinating (CMT 4) Dejerine-Sottas disease	AD or AR
MTMR2	603557	CMT disease, type 4B1 (CMT 4B1)	AR
NDRG1	605262	CMT disease, type 4D (CMT 4D)	AR
NEFL	162280	CMT disease, type 2E (CMT 2E) CMT disease, dominant intermediate G (DI-CMT G)	AD
		CMT disease, type 1F (CMT 1F)	AD or AR
NGF	162030	Neuropathy, hereditary sensory and autonomic, type V (HSAN 5)	AR
NTRK1	191315	Insensitivity to pain, congenital, with anhidrosis (HSAN 4)	AR
PDK3	300906	CMT disease, X-linked dominant, 6 (CMT X6)	XL
PLEKHG5	611101	CMT disease, recessive intermediate C (RI-CMT C) Spinal muscular atrophy, distal, autosomal recessive, 4	AR
PMP22	601097	CMT disease, type 1A (CMT 1A) *(Gene duplication)* Neuropathy, recurrent, with pressure palsies (HNPP) *(Gene deletion and sequence variants)* CMT disease, type 1E (CMT 1E) *(Sequence variants)*	AD
PRNP	176640	Hereditary prion diseases	AD
PRPS1	311850	CMT disease, X-linked recessive, 5 (CMT X5)	XL
PRX	605725	CMT disease, type 4F (CMT 4F)	AR
RAB7A	602298	CMT disease, type 2B (CMT 2B)	AD
REEP1	609139	Neuronopathy, distal hereditary motor, type VB (dHMN 5B) Spastic paraplegia 31, autosomal dominant	AD
RETREG1 (FAM134B)	613114	Neuropathy, hereditary sensory and autonomic, type IIB (HSAN 2B)	AR
SBF1	603560	CMT disease, type 4B3 (CMT 4B3)	AR
SBF2	607697	CMT disease, type 4B2 (CMT 4B2)	AR
SCN9A	603415	Small fiber neuropathy Paroxysmal extreme pain disorder	AD
		Hereditary sensory and autonomic neuropathy type IID (HSAN 2D) Insensitivity to pain, congenital	AR
SETX	608465	Amyotrophic lateral sclerosis 4, juvenile	AD
		Spinocerebellar ataxia, autosomal recessive 1	AR
SH3TC2	608206	Mononeuropathy of the median nerve, mild	AD
		CMT disease, type 4C (CMT 4C)	AR
SLC12A6	604878	Agenesis of the corpus callosum with peripheral neuropathy	AR
SLC5A7	608761	Neuronopathy, distal hereditary motor, type VIIA (dHMN 7A)	AD
SPTLC1	605712	Neuropathy, hereditary sensory and autonomic, type IA (HSAN 1A)	AD

Gene	MIM Number	Disorder and Subtype (Abbreviation)	Inheritance
SPTLC2	605713	Neuropathy, hereditary sensory and autonomic, type IC (HSAN 1C)	AD
TDP1	607198	Spinocerebellar ataxia, autosomal recessive with axonal neuropathy	AR
TFG	602498	Hereditary motor and sensory neuropathy, Okinawa type	AD
TRIM2	614141	CMT disease, type 2R (CMT 2R)	AR
TRPV4	605427	Hereditary motor and sensory neuropathy, type IIC (HMSN 2C)	AD
TTR	176300	Amyloidosis, hereditary, transthyretin-related Carpal tunnel syndrome, familial	AD
WNK1	605232	Neuropathy, hereditary sensory and autonomic, type II (HSAN 2A)	AR
YARS	603623	CMT disease, dominant intermediate C (DI-CMT C)	AD

AD, autosomal dominant; AR, autosomal recessive; dHMN/HMN, (distal) hereditary motor neuropathy; DI-CMT, dominant-intermediate CMT; 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 CMT; SPG, spastic paraplegia; XL, X-linked

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