NLM Citation: Bird TD. Charcot-Marie-Tooth Hereditary Neuropathy Overview. 1998 Sep 28 [Updated 2024 Aug 1]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Charcot-Marie-Tooth Hereditary Neuropathy Overview

Synonyms: Distal Hereditary Motor Neuropathy (dHMN), Hereditary Motor/Sensory Neuropathy (HMSN)

Thomas D Bird, MD[1]

Created: September 28, 1998; Revised: August 1, 2024.

Summary

The purpose of this overview is to increase the awareness of clinicians regarding Charcot-Marie-Tooth (CMT) hereditary neuropathy, its causes, and its management. The following are the goals of this overview.

Goal 1

Describe the clinical characteristics of CMT hereditary neuropathy.

Goal 2

Review the causes of CMT hereditary neuropathy.

Goal 3

Provide an evaluation strategy to identify the cause of CMT hereditary neuropathy in a proband (when possible).

Goal 4

Review management of CMT hereditary neuropathy.

Goal 5

Inform genetic counseling of family members of an individual with CMT hereditary neuropathy.

Author Affiliation: 1 Seattle VA Medical Center; Departments of Neurology and Medicine, University of Washington, Seattle, Washington; Email: tomnroz@u.washington.edu.

1. Clinical Characteristics of Charcot-Marie-Tooth (CMT) Hereditary Neuropathy

Charcot-Marie-Tooth (CMT) hereditary neuropathy refers to a group of disorders characterized by a chronic motor and sensory polyneuropathy, also known as hereditary motor and sensory neuropathy (HMSN).

Clinical Findings

Individuals with CMT manifest symmetric, slowly progressive distal motor neuropathy of the arms and legs usually beginning in the first to third decade and resulting in weakness and atrophy of the muscles in the feet and/or hands. The affected individual typically has distal muscle weakness and atrophy, weak ankle dorsiflexion, depressed tendon reflexes, and *pes cavus* foot deformity (i.e., high-arched feet).

Muscle weakness is often associated with mild to moderate distal sensory loss. Although usually described as "painless," the neuropathy can be painful [Azevedo et al 2018]. Sensory loss can most easily be demonstrated by a decreased appreciation of vibration, but can also include impaired sensation of pain/pinprick, temperature, and joint position.

Sensorineural hearing loss can occur.

The clinical diagnosis of CMT in a symptomatic person is based on characteristic findings of peripheral neuropathy on medical history and physical examination.

Classification of CMT Type

Traditional classification of CMT (e.g., CMT1, CMT2, and DI-CMT [dominant intermediate]) was based on peripheral neuropathy type as determined by nerve conduction velocity (NCV) and mode of inheritance as determined by family history. As understanding of the genetic basis of CMT gradually evolved, letters in alphabetic order were assigned to the CMT type to represent the gene involved (e.g., CMT1A).

In general the three autosomal dominant neuropathy types based on NCV (normal >40-45 meters/second) were the following [Stojkovic 2016]:

- **Demyelinating** (CMT1) defined as NCV <35 m/s. The clinical findings of distal muscle weakness and atrophy and sensory loss were usually slowly progressive and often associated with *pes cavus* foot deformity and bilateral foot drop. Affected individuals usually became symptomatic between ages five and 25 years. Fewer than 5% of individuals became wheelchair dependent. Life span was not shortened.
- **Axonal (non-demyelinating)** (CMT2) defined as NCV >45m/s. The clinical findings were distal muscle weakness and atrophy. Although axonal peripheral neuropathy shows extensive clinical overlap with demyelinating peripheral neuropathy, in general individuals with axonal neuropathy tended to be less disabled and have less sensory loss than individuals with demyelinating neuropathy.
- **Dominant intermediate CMT** (DI-CMT) defined as NCV 35-45 m/s. The clinical findings are a relatively typical CMT phenotype. NCVs are so variable that within a family some affected individuals fall in the demyelinating neuropathy range, whereas others fall in the axonal neuropathy range.

Newly proposed CMT naming system. As more genes causing CMT were identified and as the overlap of neuropathy phenotypes and modes of inheritance became apparent, the above alphanumeric classification system proved unwieldy and inadequate. In 2018, Magy et al [2018] proposed a gene-based classification of inherited neuropathies (see Table 4, which includes a comprehensive list of CMT-associated genes and correlation with the alphanumeric classification). An additional advantage of the Magy et al [2018] classification system is that an individual's findings can be described in terms of mode of inheritance, neuropathy type, and gene (see Evaluation Strategies).

Nomenclature

Distal hereditary motor neuropathy (dHMN) and distal spinal muscular atrophy (DSMA) = CMT. In their study of distal hereditary motor neuropathies (the clinically and genetically heterogeneous group of disorders characterized by lower motor neuron dysfunction), Bansagi et al [2017] reported that pathogenic variants in the same genes can cause the phenotypes known as dHMN and DSMA, leading them to conclude that dHMN and motor CMT should not be classified differently.

Dejerine-Sottas syndrome (DSS) originally referred to a severe demyelinating neuropathy of infancy and childhood associated with very slow NCVs, elevated CSF protein, marked clinical weakness, and hypertrophic nerves with onion bulb formation. Although the term "DSS" is still sometimes used to indicate a clinical phenotype, it does not imply an inheritance pattern or a specific genetic defect [Parman et al 2004].

Differential Diagnosis of CMT

CMT – the subject of this overview – needs to be distinguished from the following entities: systemic disorders with neuropathy, other types of hereditary neuropathy (Table1), distal myopathies (Table 2), hereditary sensory neuropathies (HSN), and acquired disorders. Note: These entities are not discussed elsewhere in this overview.

Systemic Disorders with Neuropathy

Blindness, seizures, dementia, and intellectual disability are not part of the CMT hereditary neuropathy phenotype discussed in this overview and suggest a different diagnosis, including childhood-onset disorders with significant CNS involvement such as metachromatic leukodystrophy, Krabbe disease, Pelizaeus-Merzbacher disease, and Lowe syndrome.

Other Hereditary Neuropathies

Table 1 includes multisystem disorders in which peripheral motor neuropathy may be a presenting feature (i.e., before multisystem involvement is appreciated) and/or one manifestation in a complex neurologic disorder.

Table 1. Other Hereditary Neuropathies

Gene [1]	MOI	Disorder	Other	*GeneReview* / OMIM
ABCD1	XL	Adrenomyeloneuropathy	Progressive stiffness & weakness of legs, sphincter disturbances, sexual dysfunction, & often, impaired adrenocortical function	X-Linked Adrenoleukodystrophy
ABHD12	AR	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, & cataract (PHARC)		OMIM 612674
FXN	AR	Friedreich ataxia	May present w/sensory loss, depressed tendon reflexes, & high-arched feet	Friedreich Ataxia
MT-ATP6	mt	NARP	Neurogenic muscle weakness, ataxia, & retinitis pigmentosa	Mitochondrial DNA-Associated Leigh Syndrome and NARP
PEX7 (*PHYH*)	AR	Refsum disease	Anosmia & early-onset retinitis pigmentosa ± neuropathy, deafness, ataxia, &/or ichthyosis	Refsum Disease
PMP22	AD	Hereditary neuropathy with liability to pressure palsies	Acute onset of recurrent, painless, focal sensorimotor neuropathy in a single nerve	Hereditary Neuropathy with Liability to Pressure Palsies
SCN9A	AD	*SCN9A*-related inherited erythromelalgia	Recurrent attacks of bilateral & symmetric intense pain, redness, warmth, & swelling involving feet & (less frequently) hands	*SCN9A*-Related Inherited Erythromelalgia

Table 1. continued from previous page.

Gene [1]	MOI	Disorder	Other	*GeneReview* / OMIM
SEPTIN9	AD	Hereditary neuralgic amyotrophy	Recurrent sudden onset of shoulder or upper arm pain & weakness ± sensory loss; later atrophy of the upper extremity	OMIM 162100
SPART	AR	Troyer syndrome	Progressive spastic paraparesis, dysarthria, & pseudobulbar palsy; distal amyotrophy; motor & cognitive delays	Troyer Syndrome
TTR	AD	Transthyretin-associated amyloidosis	Sensorimotor & autonomic neuropathy; cardiomyopathy; nephropathy; CNS amyloidosis	Familial Transthyretin Amyloidosis
TYMP	AR	MNGIE	Progressive gastrointestinal dysmotility; cachexia; ptosis/ophthalmoplegia or ophthalmoparesis; leukoencephalopathy; demyelinating peripheral neuropathy	Mitochondrial Neurogastrointestinal Encephalopathy Disease

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; mt = mitochondrial; XL = X-linked
1. Genes are listed in alphabetic order.

Distal Myopathies

Some genetic myopathies that present with weakness in the distal lower and/or upper limbs can be confused with CMT (Table 2). In these so-called "distal myopathies" peripheral nerve electrophysiology is normal and EMG and muscle biopsy are myopathic.

Table 2. Distal Myopathies

Gene [1]	MOI	Disorder	Clinical Manifestations		*GeneReview* / OMIM
			Mean Age of Onset	Initial Muscle Group Involved	
ANO5	AR	Miyoshi dystrophy type 3			*ANO5*-Related Muscle Diseases
CAV3	AD AR	Distal myopathy			OMIM PS601419
CRYAB	AD	Distal myofibrillar myopathy	Adult	Distal leg & hands + cardiomyopathy	
DES	AD AR	Mesminopathy myofibrillar myopathy	15-40 yrs	Distal leg & forearm + cardiomyopathy	
DNAJB6	AD	Myofibrillar myopathy	Teens-adult	Distal leg	
DYSF	AR	Miyoshi early-adult-onset myopathy	15-20 yrs	Posterior compartment in legs	Dysferlinopathy
FLNC	AD	Distal myopathy 4			OMIM 614065
GNE	AR	Nonaka early-adult-onset distal myopathy	15-20 yrs	Anterior compartment in legs	*GNE*-Related Myopathy
LDB3	AD	Zaspopathy (Markesbery-Griggs late-onset distal myopathy)	>40 yrs	Anterior compartment in legs	OMIM PS601419
MATR3	AD	Amyotrophic lateral sclerosis 21 (Formerly MPD2)	35-60 yrs	Asymmetric lower leg & hands, dysphonia	Amyotrophic Lateral Sclerosis Overview, OMIM 606070
MYH7	AD	Laing early-onset distal myopathy	<20 yrs	Anterior compartment in legs & neck flexors	Laing Distal Myopathy

Table 2. continued from previous page.

Gene [1]	MOI	Disorder	Clinical Manifestations		*GeneReview* / OMIM
			Mean Age of Onset	Initial Muscle Group Involved	
MYOT	AD	Distal myotilinopathy	>40 yrs	Posterior > anterior in legs	OMIM PS601419
NEB	AR	Distal nebulin myopathy	2-15 yrs	Anterior lower leg	OMIM 256030
TIA1	AD AR	Welander distal myopathy	>40 yrs	Distal upper limbs (finger & wrist extensors)	OMIM 604454
TCAP	AR	Distal onset in telethoninopathy	Early	Lower leg	OMIM 601954
TTN	AD	Udd distal myopathy	>35 yrs	Anterior compartment in legs	Udd Distal Myopathy

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance
1. Genes are listed in alphabetic order.

Hereditary Sensory Neuropathy and Hereditary Sensory and Autonomic Neuropathy

Hereditary sensory neuropathy (HSN) and hereditary sensory and autonomic neuropathy (HSAN) can produce mild, moderate, or severe sensory loss without muscle weakness or atrophy. Rotthier et al [2012] have reviewed the clinical and genetic factors associated with six autosomal dominant and seven autosomal recessive types.

Table 3. Hereditary Sensory Neuropathy (HSN) and Hereditary Sensory and Autonomic Neuropathy (HSAN)

Gene [1]	MOI	Disorder	Other	*GeneReview* / OMIM
ATL1	AD	HSN1D		OMIM 613708
ATL3	AD	HSN1F		OMIM 615632
DNMT1	AD	HSN1E	Deafness, dementia	*DNMT1*-Related Dementia, Deafness, and Sensory Neuropathy
DST	AR	HSAN6		OMIM 614653
RETREG1	AR	HSAN2B	Hyperhidrosis, urinary incontinence	Hereditary Sensory and Autonomic Neuropathy Type II
ELP1	AR	HSAN3	Episodic hypertension, hyperhidrosis, cyclic vomiting	Familial Dysautonomia
KIF1A	AR	HSN2C		Hereditary Sensory and Autonomic Neuropathy Type II
NGF	AR	HSAN5		Congenital Insensitivity to Pain Overview
NTRK1	AR	HSAN4		Congenital Insensitivity to Pain with Anhidrosis
PRDM12	AR	HSAN8		Congenital Insensitivity to Pain Overview
SCN11A	AD	HSAN7	Gastrointestinal dysfunction	
SCN9A	AR	HSAN2D	Insensitivity to pain (also erythromelalgia)	Hereditary Sensory and Autonomic Neuropathy Type II
SPTLC1	AD	HSAN1A	Perforating ulcers	Hereditary Sensory Neuropathy Type IA
SPTLC2	AD	HSAN1C		OMIM 613640
WNK1	AR	HSAN2A		Hereditary Sensory and Autonomic Neuropathy Type II

HSAN = hereditary sensory and autonomic neuropathy; HSN = hereditary sensory neuropathy
1. Genes are listed in alphabetic order.

Acquired Neuropathies

Acquired (non-genetic) neuropathies include alcoholism, vitamin B_{12} deficiency, thyroid disease, diabetes mellitus, HIV infection, vasculitis, leprosy, neurosyphilis, amyloid deposition associated with chronic inflammation, occult neoplasm, heavy metal intoxication, and inflammatory and immune-mediated neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP).

2. Causes of Charcot-Marie-Tooth (CMT) Hereditary Neuropathy

More than 80 different genes are associated with CMT [Stojkovic 2016].

Table 4 presents information on 74 of the known CMT-associated genes including mode of inheritance and neuropathy type (axonal, demyelinating, and dominant intermediate). Organization of this table is modeled on the newly proposed classification system of Magy et al [2018]. Note that the column titled **Other Designations** includes designations used in other classification systems which include dominant intermediate CMT (DI-CMT), distal spinal muscular atrophy (DSMA), hereditary sensory and autonomic neuropathy (HSAN), and distal hereditary motor neuropathy (dHMN).

Table 4. CMT: Genes, Mode of Inheritance, Neuropathy Phenotype

Gene [1]	MOI	Neuropathy Type			Other Phenotypic Features / Comments	*GeneReview* / OMIM / Reference	Other Designations [2]
		Ax	De	In			
Most commonly involved genes [3]							
GDAP1	AR	●			Vocal cord paresis [4]	*GDAP1*-Related Hereditary Motor and Sensory Neuropathy	CMT2K
	AR	●	●	●			CMT4A CMT2H CMT2K CMTRIA
	AD, AR	●				OMIM 607831	
GJB1	XL	●	●	●	Family history may appear to be AD as females can be as severely affected as males; CNS myelin may be affected.	Charcot-Marie-Tooth Neuropathy X Type 1	CMT1X
HINT1	AR	●			Neuromyotonia	OMIM 601314	
MFN2	AD, AR	●			Optic atrophy	Charcot-Marie-Tooth Neuropathy Type 2A	CMT2A2A/B
MPZ	AD	●	●	●		OMIM 118200	CMT1B CMT2I/J DI-CMTD
PMP22	AD		●			OMIM 601097	CMT1A CMT1E
SH3TC2	AR	●				*SH3TC2*-Related Hereditary Motor and Sensory Neuropathy	CMT4C
SORD	AR	●		●	Distal muscle atrophy & weakness	Cortese et al [2020]	
Other genes							
AARS1	AD	●				Setlere et al [2022]	CMT2N

Table 4. continued from previous page.

Gene [1]	MOI	Neuropathy Type			Other Phenotypic Features / Comments	*GeneReview* / OMIM / Reference	Other Designations [2]
		Ax	De	In			
ABHD12	AR		●		Deafness, cataract, retinitis pigmentosa	OMIM 613599	PHARC
AIFM1	XL	●			Deafness, intellectual disability	OMIM 300169	CMTX4
ARHGEF10	AD		●			OMIM 608136	
ATP1A1	AD	●				Lassuthova et al [2018]	
ATP7A [5]	XL	●			Distal lower extremities	*ATP7A*-Related Copper Transport Disorders, OMIM 300011	
BAG3	AD	●			Myofibrillar myopathy, cardiomyopathy	OMIM 603883	
BSCL2	AD	●			Distal lower extremities; UMN involvement can cause spastic paraplegia	*BSCL2*-Related Neurologic Disorders / Seipinopathy	dHMN5A
CADM3	AD	●			Forearm & hand atrophy as well as lower limb	Rebelo et al [2021]	
CNTNAP1	AR	●	●		Arthrogryposis, leukodystrophy	OMIM 602346	
COA7	AR	●				Higuchi et al [2018]	
DCTN1	AD				Distal lower extremities	OMIM 601143	dHMN7B
DCTN2	AD	●			Vocal cord paresis [4]	OMIM 607376	
DGAT2	AD	●				OMIM 606983	
DHTKD1	AD	●				OMIM 614984	CMT2Q
DNAJB2	AR	●			Distal motor neuropathy	Frasquet et al [2016], Lupo et al [2016]	DSMA5
DNMT1	AD	●			Hearing loss, dementia	*DNMT1*-Related Dementia, Deafness, and Sensory Neuropathy	DMNT1
DNM2	AD			●		OMIM 606482	CMT2M DI-CMTB
DRP2	XL			●	Autism	OMIM 300052	
DYNC1H1	AD	●			SMA	*DYNC1H1*-Related Disorders	CMT2O
EGR2	AD		●			OMIM 129010	CMT1D
	AR		●				CMT4E
FGD4	AR		●			OMIM 609311	CMT4H
FIG4	AR		●			OMIM 611228	CMT4J
GARS1	AD	●			Onset in hands	*GARS1*-Associated Axonal Neuropathy	CMT2D dHMN5A
GNB4	AD			●		OMIM 610863	DI-CMTF
HARS1	AD	●	●			OMIM 142810	CMT2W

Table 4. continued from previous page.

Gene [1]	MOI	Neuropathy Type			Other Phenotypic Features / Comments	*GeneReview* / OMIM / Reference	Other Designations [2]
		Ax	De	In			
HSPB1	AD	●				OMIM 602195	CMT2F dHMN2B
HSPB3	AD					OMIM 604624	dHMN2C
HSPB8	AD	●			Adult onset	OMIM 608014	CMT2L dHMN2A
IGHMBP2	AR	●				OMIM 600502	CMT2S DSMA1
INF2	AD			●	Glomerulosclerosis	OMIM 610982	
ITPR3	AD		●		Marked variability in onset age & severity	Beijer et al [2024]	
KIF1B	AD	●				OMIM 605995	CMT2A1
KIF5A	AD	●			Spasticity	OMIM 602821	
LITAF	AD		●			OMIM 603795	CMT1C
LMNA	AR	●				OMIM 150330	CMT2B1
LRSAM1	AD, AR	●				OMIM 610933	CMT2G CMT2P
MARS1	AD	●				OMIM 156560	CMT2U
MCM3AP	AR	●	●		Childhood onset, severe	OMIM 603294	
MME	AR, AD	●				OMIM 120520	CMT2T
MORC2	AD	●				OMIM 616661	CMT2Z
MPV17	AR	●			Navaho neurohepatopathy	OMIM 137960	
MPZ	AD	●	●	●		OMIM 118200	CMT1B CMT2I/J DI-CMTD
MTMR2	AR		●		Vocal cord paresis [4]	OMIM 603557	CMT4B1
NAGLU	AD	●				OMIM 609701	CMT2V
NDRG1	AR		●			OMIM 605262	CMT4D
NEFH	AD	●				OMIM 162230	
NEFL	AD, AR	●	●			OMIM 162280	CMT1F/2E
PDK3	XL	●				OMIM 300906	CMTX6
PLEKHG5	AR			●	Distal predominant	OMIM 611101	DSMA4
PMP2	AD		●			OMIM 618279	CMT1G
PNKP	AR	●				OMIM 605610	CMT2B2
PRPS1	XL				Retinopathy, deafness	Charcot-Marie-Tooth Neuropathy X Type 5 (See Phosphoribosylpyrophosphate Synthetase Deficiency.)	CMTX5
PRX	AR	●				OMIM 605725	CMT4F

Table 4. continued from previous page.

Gene [1]	MOI	Neuropathy Type			Other Phenotypic Features / Comments	*GeneReview* / OMIM / Reference	Other Designations [2]
		Ax	De	In			
PTRH2	AR				Hearing loss	OMIM 608625	
RAB7A	AD	●			Prominent sensory loss	OMIM 602298	CMT2B
SARS1	AD			●	Sensorimotor neuropathy, distal muscle atrophy	He et al [2023]	
SBF1	AR	●				OMIM 603560	CMT4B3
SBF2	AR		●			OMIM 607697	CMT4B2
SCO2	AR	●			Motor neuropathy	Rebelo et al [2018]	
SETX	AD				Distal lower extremities	OMIM 608465	FALS
SIGMAR1	AR	●			Motor neuropathy	OMIM 601978	
SGPL1	AR	●			Recurrent mononeuropathy	Sphingosine Phosphate Lyase Insufficiency Syndrome	
SPG11	AR	●			Spasticity, cognitive decline	OMIM 610844	CMT2X ALS5
SPTLC1	AD	●			May be assoc w/a juvenile ALS syndrome [6]	OMIM 605712	HSAN1A
TRIM2	AR	●			Vocal cord paresis [4]	OMIM 614141	CMT2R
TRPV4	AD	●			Vocal cord paresis, [4] skeletal dysplasia	Autosomal Dominant *TRPV4* Disorders	CMT2C
VCP	AD	●			Inclusion body myopathy, dementia	Inclusion Body Myopathy with Paget Disease of Bone and/or Frontotemporal Dementia	CMT2Y
VWA1	AR	●			Motor neuropathy, *pes cavus*, & proximal muscle weakness	OMIM 619216	
WARS	AD	●			Motor neuropathy	OMIM 191050	dHMN9
YARS1	AD			●		OMIM 603623	DI-CMTC
Unknown [7]	XL		●		Rapid progression, severe hand weakness	OMIM 302802	CMTX3

AD = autosomal dominant; ALS = amyotrophic lateral sclerosis; AR = autosomal recessive; Ax = axonal; De = demyelinating; dHMN = distal hereditary motor neuropathy; DI-CMT = dominant intermediate CMT; DSMA = distal spinal muscular atrophy; HSAN = hereditary sensory and autonomic neuropathy; In = intermediate; UMN = upper motor neuron; XL = X-linked

1. Genes are listed in alphabetic order.

2. Designations used in other classification systems

3. Based on Cornett et al [2016] and Cornett et al [2017]

4. Can be the first manifestation of CMT. Typically presents as hoarse voice and stridor associated with use of accessory inspiratory muscles [Zambon et al 2017].

5. *ATP7A*-CMT shares none of the clinical or biochemical abnormalities characteristic of the allelic disorders Menkes disease and occipital horn syndrome (see *ATP7A*-Related Copper Transport Disorders).

6. Johnson et al [2021]

7. A 78-kb interchromosomal insertion into the CMTX3 locus at Xq26.3-q27.3 requiring a custom-targeted assay [Brewer et al 2016, Kanhangad et al 2018]

3. Evaluation Strategies to Identify the Genetic Cause of Charcot-Marie-Tooth (CMT) Hereditary Neuropathy in a Proband

Establishing a specific genetic cause of CMT hereditary neuropathy can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling.

Establishing the specific cause of CMT hereditary neuropathy for a given individual involves obtaining a medical history and performing a physical examination to exclude disorders that differ from CMT as defined in this overview; these include systemic disorders with neuropathy, other hereditary neuropathies (Table1), distal myopathies (Table 2), hereditary sensory neuropathies (HSN) and hereditary sensory and autonomic neuropathies (HSAN) (Table 3), and acquired disorders.

For those individuals with CMT (as defined in this overview) a detailed family history and the use of molecular genetic testing are essential to establishing a specific genetic cause.

Family History

A three-generation family history with attention to other relatives with neurologic signs and symptoms should be obtained. Documentation of relevant findings in relatives can be accomplished either through direct examination of those individuals or review of their medical records, including the results of molecular genetic testing and EMG and NCV studies.

Individuals with CMT may have a negative family history for many reasons, including mild subclinical expression in other family members, autosomal recessive inheritance, or a *de novo* heterozygous pathogenic variant in a gene associated with autosomal dominant inheritance [Rudnik-Schöneborn et al 2016] or X-linked inheritance.

Molecular Genetic Testing

Health care providers ordering genetic testing should be familiar with the genetics of CMT. Given the complexity of interpreting genetic test results and their implications for genetic counseling, health care providers should consider referral to a neurogenetics center or a genetic counselor specializing in neurogenetics (see NSGC – Find a Genetic Counselor).

Molecular genetic testing approaches can include gene-targeted testing (single-gene testing, multigene panel) and comprehensive genomic testing (exome sequencing, exome array). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

Step 1

Single-gene testing for *PMP22* duplication/deletion is recommended as the first test in all probands with CMT as defined in this *GeneReview*. *PMP22* duplication (a 1.5-Mb duplication at 17p11.2 that includes *PMP22*) accounts for as much as 50% of all CMT and, thus, *PMP22* deletion/duplication analysis is recommended as the first test for all probands with CMT. Note: (1) Because the methodology to detect *PMP22* duplication differs from that used in many multigene panels, this test needs to be ordered separately unless a laboratory explicitly states that *PMP22* deletion/duplication analysis is included in its multigene panel. (2) Conversely, if *PMP22* deletion/duplication analysis has already been performed and is normal, and if the next step in testing an individual is use of a multigene panel, it is appropriate to request that the laboratory not include *PMP22* deletion/duplication analysis.

Step 2

A multigene panel that includes the eight most commonly involved genes (i.e., *GDAP1*, *GJB1*, *HINT1*, *MFN2*, *MPZ*, *PMP22*, *SH3CT2,* and *SORD*) as well as some or all of the other genes listed in Table 4 is most likely to identify the genetic cause of the neuropathy while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with CMT as defined in this *GeneReview*. Of note, given the rarity of some of the genes associated with CMT some panels may not include all the genes in Table 4. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Step 3

Comprehensive genomic testing – which does not require the clinician to determine which gene(s) are likely involved – may be considered if a genetic cause has not been identified in Step 1 and Step 2. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Expressing the particular type of CMT in a given individual based on the results of molecular genetic testing in the context of inheritance, neurologic examination, and gene involved as proposed by Magy et al [2018] is illustrated for *GDAP1*-related hereditary motor and sensory neuropathy (Table 5).

Table 5. *GDAP1*-Related CMT Classification

Historical CMT Classification	MOI	Type Based on NCV	Magy et al [2018] Classification
CMT2H	AR	Ax	AR-CMTAx-*GDAP1*
CMT2K	AD	Ax	AD-CMTAx-*GDAP1*
CMT4A	AR	De	AR-CMTDe-*GDAP1*
CMTRIA	AR	In	AR-CMTIn-*GDAP1*

AD = autosomal dominant; AR = autosomal recessive; Ax = axonal; De = demyelinating; In = intermediate; MOI = mode of inheritance; NCV = nerve conduction velocity

4. Management of Charcot-Marie-Tooth (CMT) Hereditary Neuropathy

Treatment of Manifestations

Reviews of treatment approaches to CMT [Carter et al 2008, Young et al 2008, Reilly & Shy 2009, Corrado et al 2016] as well as reviews of the diagnosis, natural history, and management of CMT [Pareyson & Marchesi 2009a, Pareyson & Marchesi 2009b, Cornett et al 2017, Sivera Mascaró et al 2024] are available. Guidelines for the management of the pediatric population with CMT have been published [Yiu et al 2022].

Treatment is symptomatic. Affected individuals are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists [Grandis & Shy 2005, McCorquodale et al 2016].

Quality of life and defining disability have been measured and compared among various groups of individuals with CMT [Burns et al 2010, Ramchandren et al 2015]. Persistent weakness of the hands and/or feet has important career and employment implications; anticipatory counseling is appropriate.

Special shoes, including those with good ankle support, may be needed. Affected individuals often require ankle/foot orthoses (AFOs) to correct foot drop and aid walking. Night splints have not improved ankle range of motion [Refshauge et al 2006, Kenis-Coskun & Matthews 2016].

Some individuals require forearm crutches or canes for gait stability; fewer than 5% of individuals need wheelchairs.

Daily heel cord stretching exercises to prevent Achilles tendon shortening are desirable, as well as gripping exercises for hand weakness [Vinci et al 2005b].

Exercise is encouraged within the individual's capability and many individuals remain physically active [Sman et al 2015].

Orthopedic surgery may be required to correct severe *pes cavus* deformity [Guyton 2006, Casasnovas et al 2008, Ward et al 2008]. Clinical assessment and management approaches to foot deformities that may be associated with CMT are reviewed in Laurá et al [2024]. Management regarding surgery referral and intervention ideally involves multidisciplinary input (i.e., neurology, physical therapy, and orthopedics). Surgery is sometimes required for hip dysplasia [Chan et al 2006].

The cause of any pain should be identified as accurately as possible [Padua et al 2006].

- Musculoskeletal pain may respond to acetaminophen or nonsteroidal anti-inflammatory agents [Carter et al 1998].
- Neuropathic pain may respond to tricyclic antidepressants or drugs such as carbamazepine or gabapentin.

Modafinil has been used to treat fatigue [Carter et al 2006].

Those at increased risk for vocal cord paralysis (see Table 4) warrant consultation with specialists in otolaryngology at the time of diagnosis; evidence of vocal cord paralysis (hoarseness and/or stridor) at any time warrants periodic monitoring by specialists in otolaryngology to detect vocal cord hypomotility and quantify the degree of airway obstruction, a potentially lethal complication [Zambon et al 2017].

In a study of five individuals with CMT-associated sensorineural hearing loss and auditory neuropathy spectrum disorder, Farber et al [2024] found that cochlear implants were safe and reliable and improved both hearing and speech. Note: Four of the described individuals were from a family with the *PMP22* pathogenic variant c.199G>C (p.Ala67Pro) [Kovach et al 1999].

Agents/Circumstances to Avoid

Obesity is to be avoided because it makes walking more difficult.

Medications that are toxic or potentially toxic to persons with CMT comprise a spectrum of risk ranging from definite high risk to negligible risk. See the Charcot-Marie-Tooth Association website (pdf) for an up-to-date list.

Chemotherapy for cancer that includes vincristine may be especially damaging to peripheral nerves and severely worsen CMT [Graf et al 1996, Nishikawa et al 2008].

Pregnancy Management

CMT appears to be an independent risk factor for maternal complications during pregnancy and delivery [Pisciotta et al 2020]. In a study of 157 deliveries in 193 pregnancies Pisciotta et al found that:

- In 9.3% of pregnancies, new manifestations of CMT can appear and existing manifestations (including reduced strength and sensitivity, cramps, and pain) can worsen, and may persist following pregnancy;
- Placenta previa (1.6%) abnormal nonvertex presentation (8.4%), and preterm delivery (20.3%) occurred more frequently in the pregnancies of mothers with CMT.

5. Genetic Counseling of Family Members of an Individual with Charcot-Marie-Tooth (CMT) Hereditary Neuropathy

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

CMT hereditary neuropathy can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner.

Genetic counseling regarding risk to family members depends on accurate diagnosis, determination of the mode of inheritance in each family, and results of molecular genetic testing. Given the complexity of the genetics of CMT, health care providers should consider referring at-risk relatives to a neurogenetics center or genetic counselor specializing in neurogenetics (see NSGC – Find a Genetic Counselor search tool).

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with autosomal dominant CMT have an affected parent.
- Some individuals diagnosed with autosomal dominant CMT have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant varies depending on the involved gene. In a study of 1,206 index cases, Rudnik-Schöneborn et al [2016] identified *de novo* variants in 1.3% of individuals with a *PMP* duplication and 25% of those with *MPZ* variants.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Germline mosaicism has been reported [Fabrizi et al 2001].
- The family history of some individuals diagnosed with autosomal dominant CMT may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known CMT-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism.
- If the parents have not been tested for the pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for CMT because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant CMT has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an individual diagnosed with autosomal recessive CMT are obligate heterozygotes (i.e., carriers of one pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with autosomal recessive CMT are obligate heterozygotes (carriers) for a pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the CMT-related pathogenic variants in the family.

X-Linked Inheritance – Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., represents a simplex case), the mother may be a heterozygote or the affected male may have a *de novo* pathogenic variant, in which case the mother is not heterozygous. The frequency of males with a *de novo* pathogenic variant is not known.

Parents of a female proband

- A female proband may have inherited the pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*.
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother (and possibly the father, or subsequently the father) can determine if the pathogenic variant was inherited.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother.

- If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may or may not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the recurrence risk to sibs is low but greater than that of the general population because of the theoretic possibility of germline mosaicism.

Sibs of a female proband. The risk to sibs depends on the genetic status of the parents.

- If the mother of the proband has a pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes (carriers) and may or may not be affected.
- If the father of the proband has a pathogenic variant, he will transmit it to all of his daughters and none of his sons.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is low but greater than that of the general population because of the theoretic possibility of germline mosaicism.

Offspring of a proband

- Affected males transmit the pathogenic variant to all of their daughters and none of their sons.
- Heterozygous females have a 50% chance of transmitting the pathogenic variant to each child; sons who inherit the pathogenic variant will be affected; daughters may or may not be affected.

Other family members. If a parent of the proband also has a pathogenic variant, the parent's female family members may be at risk of being heterozygotes (asymptomatic or symptomatic) and the parent's male family members may be at risk of being affected depending on their genetic relationship to the proband.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote detection. Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Related Genetic Counseling Issues

Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the CMT-related pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years). For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.

In a family with an established diagnosis of CMT it is appropriate to consider testing of symptomatic individuals regardless of age.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant or X-linked condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the CMT-related pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Association CMT France**
  France
  Phone: 820 077 540; 2 47 27 96 41
  www.cmt-france.org

- **Charcot-Marie-Tooth Association (CMTA)**
  Phone: 800-606-2682
  Email: info@cmtausa.org
  cmtausa.org

- **European Charcot-Marie-Tooth Consortium**
  Department of Molecular Genetics
  University of Antwerp
  Antwerp Antwerpen B-2610
  Belgium
  Fax: 03 2651002
  Email: gisele.smeyers@ua.ac.be
- **Hereditary Neuropathy Foundation**
  Phone: 855-435-7268 (toll-free); 212-722-8396
  Fax: 917-591-2758
  Email: info@hnf-cure.org
  www.hnf-cure.org
- **Medical Home Portal**
  Charcot-Marie-Tooth Disease (Hereditary Motor Sensory Neuropathy)
- **National Library of Medicine Genetics Home Reference**
  Charcot-Marie-Tooth disease
- **NCBI Genes and Disease**
  Charcot-Marie-Tooth syndrome
- **TREAT-NMD**
  Institute of Translational and Clinical Research
  University of Newcastle upon Tyne
  International Centre for Life
  Newcastle upon Tyne NE1 3BZ
  United Kingdom
  Phone: 44 (0)191 241 8617
  Fax: 44 (0)191 241 8770
  Email: info@treat-nmd.eu
  Charcot-Marie-Tooth Disease
- **Association Francaise contre les Myopathies (AFM)**
  France
  Phone: +33 01 69 47 28 28
  Email: dmc@afm.genethon.fr
  afm-telethon.fr
- **CMT Research Foundation**
  Phone: 404-806-7180
  Email: info@cmtrf.org
  www.cmtrf.org
- **European Neuromuscular Centre (ENMC)**
  Netherlands
  Phone: 31 35 5480481
  Email: enmc@enmc.org
  enmc.org
- **Muscular Dystrophy Association (MDA) - USA**

Phone: 833-275-6321
Email: ResourceCenter@mdausa.org
mda.org

- **Muscular Dystrophy UK**
  United Kingdom
  Phone: 0800 652 6352
  musculardystrophyuk.org
- **RDCRN Patient Contact Registry: Inherited Neuropathies Consortium**
  Patient Contact Registry

Chapter Notes

Revision History

- 11 July 2024 (tb) Revision: *ITPR3* added to Table 4 [Beijer et al 2024]
- 25 April 2024 (tb) Revision: Laurá et al [2024] added to Management
- 14 March 2024 (tb) Revision: information regarding cochlear implants added to Management; clinical practice guidelines [Sivera Mascaró et al 2024] added to Management
- 23 February 2023 (tb) Revision: *SARS1* added to Table 4 [He et al [2023]
- 29 September 2022 (tb) Revision: Setlere et al [2022] added to Table 4 (*AARS1*)
- 24 February 2022 (tb) Revision: added Yiu et al [2022] guidelines for pediatric management
- 9 September 2021 (tb) Revision: added comment on *SPTLC1* in Table 4 [Johnson et al 2021]
- 20 May 2021 (tb) Revision: *CADM3* added to Table 4 [Rebelo et al 2021]
- 18 March 2021 (tb) Revision: *VWA1* added to Table 4
- 4 March 2021 (tb) Revision: Pregnancy Management section added [Pisciotta et al 2020]
- 14 May 2020 (tb) Revision: *SORD* added to Table 4 [Cortese et al 2020]
- 2 January 2020 (tb) Revision: correction (*PNKP*) to Table 4 [Leal et al 2018]
- 12 December 2019 (aa) Revision: information on *GJB1* added to Table 4
- 24 January 2019 (aa) Revision: gene (*PMP2*) added to Table 4
- 28 June 2018 (bp) Comprehensive update posted live
- 31 May 2011 (me) Comprehensive update posted live
- 31 August 2007 (me) Comprehensive update posted live
- 27 April 2005 (me) Comprehensive update posted live
- 28 March 2003 (me) Comprehensive update posted live
- 20 June 2001 (me) Comprehensive update posted live
- 28 September 1998 (pb) Overview posted live
- April 1996 (tb) Original submission

References

Literature Cited

Azevedo H, Pupe C, Pereira R, Nascimento OJM. Pain in Charcot-Marie-Tooth disease: an update. Arq Neuropsiquiatr. 2018;76:273-6. PubMed PMID: 29742248.

Bansagi B, Griffin H, Whittaker RG, Antoniadi T, Evangelista T, Miller J, Greenslade M, Forester N, Duff J, Bradshaw A, Kleinle S, Boczonadi V, Steele H, Ramesh V, Franko E, Pyle A, Lochmüller H, Chinnery PF, Horvath R. Genetic heterogeneity of motor neuropathies. Neurology. 2017;88:1226-34 PubMed PMID: 28251916.

Beijer D, Dohrn MF, Rebelo A, Danzi MC, Grosz BR, Ellis M, Kumar KR, Vucic S, Vais H, Weissenrieder JS, Lunko O, Paudel U, Simpson LC, Raposo J, Saporta M, Arcia Y, Xu I, Feely S, Record CJ, Blake J, Reilly MM, Scherer S, Kennerson M, Lee YC, Foskett JK, Shy M, Zuchner S. A recurrent missense variant in ITPR3 causes demyelinating Charcot-Marie-Tooth with variable severity. Brain. 2024. Epub ahead of print. PubMed PMID: 38938188.

Brewer MH, Chaudhry R, Qi J, Kidambi A, Drew AP, Menezes MP, Ryan MM, Farrar MA, Mowat D, Subramanian GM, Young HK, Zuchner S, Reddel SW, Nicholson GA, Kennerson ML. Whole genome sequencing identifies a 78 kb insertion from chromosome 8 as the cause of Charcot-Marie-Tooth neuropathy CMTX3. PLoS Genet. 2016;12:e1006177 PubMed PMID: 27438001.

Burns J, Ramchandren S, Ryan MM, Shy M, Ouvrier RA. Determinants of reduced health-related quality of life in pediatric inherited neuropathies. Neurology. 2010;75:726–31. PubMed PMID: 20733147.

Carter GT, Han JJ, Mayadev A, Weiss MD. Modafinil reduces fatigue in Charcot-Marie-Tooth disease type 1A: a case series. Am J Hosp Palliat Care. 2006;23:412–6. PubMed PMID: 17060310.

Carter GT, Jensen MP, Galer BS, Kraft GH, Crabtree LD, Beardsley RM, Abresch RT, Bird TD. Neuropathic pain in Charcot-Marie-Tooth disease. Arch Phys Med Rehabil. 1998;79:1560–4. PubMed PMID: 9862301.

Carter GT, Weiss MD, Han JJ, Chance PF, England JD. Charcot-Marie-Tooth disease. Curr Treat Options Neurol. 2008;10:94–102. PubMed PMID: 18334132.

Casasnovas C, Cano LM, Albertí A, Céspedes M, Rigo G. Charcot-Marie-tooth disease. Foot Ankle Spec. 2008;1:350–4. PubMed PMID: 19825739.

Chan G, Bowen JR, Kumar SJ. Evaluation and treatment of hip dysplasia in Charcot-Marie-Tooth disease. Orthop Clin North Am. 2006;37:203–9. PubMed PMID: 16638451.

Cornett KM, Menezes MP, Bray P, Halaki M, Shy RR, Yum SW, Estilow T, Moroni I, Foscan M, Pagliano E, Pareyson D, Laurá M, Bhandari T, Muntoni F, Reilly MM, Finkel RS, Sowden J, Eichinger KJ, Herrmann DN, Shy ME, Burns J, Inherited Neuropathies Consortium. Phenotypic variability of childhood Charcot-Marie-Tooth disease. JAMA Neurol. 2016;73:645-51. PubMed PMID: 27043305.

Cornett KMD, Menezes MP, Shy RR, Moroni I, Pagliano E, Pareyson D, Estilow T, Yum SW, Bhandari T, Muntoni F, Laura M, Reilly MM, Finkel RS, Eichinger KJ, Herrmann DN, Bray P, Halaki M, Shy ME, Burns J, CMTPedS Study Group. Natural history of Charcot-Marie-Tooth disease during childhood. Ann Neurol. 2017;82:353-9. PubMed PMID: 28796392.

Corrado B, Ciardi G, Bargigli C. Rehabilitation management of the Charcot-Marie-Tooth syndrome: a systematic review of the literature. Medicine (Baltimore). 2016;95:e3278. PubMed PMID: 27124017.

Cortese A, Zhu Y, Rebelo AP, Negri S, Courel S, Abreu L, Bacon CJ, Bai Y, Bis-Brewer DM, Bugiardini E, Buglo E, Danzi MC, Feely SME, Athanasiou-Fragkouli A, Haridy NA, Isasi R, Khan A, Laurà M, Magri S, Pipis M, Pisciotta C, Powell E, Rossor AM, Saveri P, Sowden JE, Tozza S, Vandrovcova J, Dallman J, Grignani E, Marchioni E, Scherer SS, Tang B, Lin Z, Al-Ajmi A, Schüle R, Synofzik M, Maisonobe T, Stojkovic T, Auer-Grumbach M, Abdelhamed MA, Hamed SA, Zhang R, Manganelli F, Santoro L, Taroni F, Pareyson D, Houlden H, Herrmann DN, Reilly MM, Shy ME, Zhai RG, Zuchner S, et al. Biallelic mutations in SORD cause a common and potentially treatable hereditary neuropathy with implications for diabetes. Nat Genet. 2020;52:473-81. PubMed PMID: 32367058.

Fabrizi GM, Ferrarini M, Cavallaro T, Jarre L, Polo A, Rizzuto N (2001) A somatic and germline mosaic mutation in MPZ/P(0) mimics recessive inheritance of CMT1B. Neurology. 57:101-5. PubMed PMID: 11445635.

Farber NI, Chin OY, Mills DM, Diaz RC, Brodie HA, Sagiv D. Cochlear implantation in Charcot-Marie-Tooth patients: speech perception and quality of life. Ann Otol Rhinol Laryngol. 2024;133:469-75. PubMed PMID: 38361273.

Frasquet M, Chumillas MJ, Vílchez JJ, Márquez-Infante C, Palau F, Vázquez-Costa JF, Lupo V, Espinós C, Sevilla T. Phenotype and natural history of inherited neuropathies caused by HSJ1 c.352+1G>A mutation. J Neurol Neurosurg Psychiatry. 2016;87:1265-8. PubMed PMID: 27083531.

Graf WD, Chance PF, Lensch MW, Eng LJ, Lipe HP, Bird TD. Severe vincristine neuropathy in Charcot-Marie-Tooth disease type 1A. Cancer. 1996;77:1356–62. PubMed PMID: 8608515.

Grandis M, Shy ME. Current therapy for Charcot-Marie-Tooth disease. Curr Treat Options Neurol. 2005;7:23–31. PubMed PMID: 15610704.

Guyton GP. Current concepts review: orthopaedic aspects of Charcot-Marie-Tooth disease. Foot Ankle Int. 2006;27:1003–10. PubMed PMID: 17144969.

He J, Liu XX, Ma MM, Lin JJ, Fu J, Chen YK, Xu GR, Xu LQ, Fu ZF, Xu D, Chen WF, Cao CY, Shi Y, Zeng YH, Zhang J, Chen XC, Zhang RX, Wang N, Kennerson M, Fan DS, Chen WJ. Heterozygous Seryl-tRNA synthetase 1 variants cause Charcot-Marie-Tooth disease. Ann Neurol. 2023;93:244-56. PubMed PMID: 36088542.

Higuchi Y, Okunushi R, Hara T, Hashiguchi A, Yuan J, Yoshimura A, Murayama K, Ohtake A, Ando M, Hiramatsu Y, Ishihara S, Tanabe H, Okamoto Y, Matsuura E, Ueda T, Toda T, Yamashita S, Yamada K, Koide T, Yaguchi H, Mitsui J, Ishiura H, Yoshimura J, Doi K, Morishita S, Sato K, Nakagawa M, Yamaguchi M, Tsuji S, Takashima H. Mutations in COA7 cause spinocerebellar ataxia with axonal neuropathy. Brain. 2018;141:1622-36 PubMed PMID: 29718187.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Johnson JO, Chia R, Miller DE, Li R, Kumaran R, Abramzon Y, Alahmady N, Renton AE, Topp SD, Gibbs JR, Cookson MR, Sabir MS, Dalgard CL, Troakes C, Jones AR, Shatunov A, Iacoangeli A, Al Khleifat A, Ticozzi N, Silani V, Gellera C, Blair IP, Dobson-Stone C, Kwok JB, Bonkowski ES, Palvadeau R, Tienari PJ, Morrison KE, Shaw PJ, Al-Chalabi A, Brown RH Jr, Calvo A, Mora G, Al-Saif H, Gotkine M, Leigh F, Chang IJ, Perlman SJ, Glass I, Scott AI, Shaw CE, Basak AN, Landers JE, Chiò A, Crawford TO, Smith BN, Traynor BJ, et al. Association of variants in the SPTLC1 gene with juvenile amyotrophic lateral sclerosis. JAMA Neurol. 2021;78:1236-48. PubMed PMID: 34459874.

Kanhangad M, Cornett K, Brewer MH, Nicholson GA, Ryan MM, Smith RL, Subramanian GM, Young HK, Züchner S, Kennerson ML, Burns J, Menezes MP. Unique clinical and neurophysiologic profile of a cohort of children with CMTX3. Neurology. 2018;90:e1706-10 PubMed PMID: 29626178.

Kenis-Coskun O, Matthews DJ. Rehabilitation issues in Charcot-Marie-Tooth disease. J Pediatr Rehabil Med. 2016;9:31-4. PubMed PMID: 26966798.

Kovach MJ, Lin JP, Boyadjiev S, Campbell K, Mazzeo L, Herman K, Rimer LA, Frank W, Llewellyn B, Jabs EW, Gelber D, Kimonis VE. A unique point mutation in the PMP22 gene is associated with Charcot-Marie-Tooth disease and deafness. Am J Hum Genet. 1999;64:1580-93. PubMed PMID: 10330345.

Lassuthova P, Rebelo AP, Ravenscroft G, Lamont PJ, Davis MR, Manganelli F, Feely SM, Bacon C, Brožková DŠ, Haberlova J, Mazanec R, Tao F, Saghira C, Abreu L, Courel S, Powell E, Buglo E, Bis DM, Baxter MF, Ong RW, Marns L, Lee YC, Bai Y, Isom DG, Barro-Soria R, Chung KW, Scherer SS, Larsson HP, Laing NG, Choi BO, Seeman P, Shy ME, Santoro L, Zuchner S. Mutations in ATP1A1 cause dominant Charcot-Marie-Tooth type 2. Am J Hum Genet. 2018;102:505-14. PubMed PMID: 29499166.

Laurá M, Barnett J, Benfield J, Ramdharry GM, Welck MJ. Foot surgery for adults with Charcot-Marie-Tooth disease. Pract Neurol. 2024;24:275-84. PubMed PMID: 38631902.

Leal A, Bogantes-Ledezma S, Ekici AB, Uebe S, Thiel CT, Sticht H, Berghoff M, Berghoff C, Morera B, Meisterernst M, Reis A. The polynucleotide kinase 3'-phosphatase gene (PNKP) is involved in Charcot-Marie-Tooth disease (CMT2B2) previously related to MED25. Neurogenetics. 2018;19:215-25. PubMed PMID: 30039206.

Lupo V, Aguado C, Knecht E, Espinós C. Chaperonopathies: spotlight on hereditary motor neuropathies. Front Mol Biosci. 2016;3:81. PubMed PMID: 28018906.

Magy L, Mathis S, Le Masson G, Goizet C, Tazir M, Vallat JM. Updating the classification of inherited neuropathies: results of an international survey. Neurology. 2018;90:e870-6 PubMed PMID: 29429969.

McCorquodale D, Pucillo EM, Johnson NE. Management of Charcot-Marie-Tooth disease: improving long-term care with a multidisciplinary approach. J Multidiscip Healthc. 2016;9:7-19. PubMed PMID: 26855581.

Nishikawa T, Kawakami K, Kumamoto T, Tonooka S, Abe A, Hayasaka K, Okamoto Y, Kawano Y. Severe neurotoxicities in a case of Charcot-Marie-Tooth disease type 2 caused by vincristine for acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2008;30:519–21. PubMed PMID: 18797198.

Padua L, Aprile I, Cavallaro T, Commodari I, La Torre G, Pareyson D, Quattrone A, Rizzuto N, Vita G, Tonali P, Schenone A, Italian CMT. QoL Study Group. Variables influencing quality of life and disability in Charcot Marie Tooth (CMT) patients: Italian multicentre study. Neurol Sci. 2006;27:417–23. PubMed PMID: 17205227.

Pareyson D, Marchesi C. Diagnosis, natural history, and management of Charcot-Marie-Tooth disease. Lancet Neurol. 2009a;8:654–67. PubMed PMID: 19539237.

Pareyson D, Marchesi C. Natural history and treatment of peripheral inherited neuropathies. Adv Exp Med Biol. 2009b;652:207–24. PubMed PMID: 20225028.

Parman Y, Battaloglu E, Baris I, Bilir B, Poyraz M, Bissar-Tadmouri N, Williams A, Ammar N, Nelis E, Timmerman V, De Jonghe P, Najafov A, Deymeer F, Serdaroglu P, Brophy PJ, Said G. Clinicopathological and genetic study of early-onset demyelinating neuropathy. Brain. 2004;127:2540–50. PubMed PMID: 15469949.

Pisciotta C, Calabrese D, Santoro L, Tramacere I, Manganelli F, Fabrizi GM, Schenone A, Cavallaro T, Grandis M, Previtali SC, Allegri I, Padua L, Pazzaglia C, Saveri P, Quattrone A, Valentino P, Tozza S, Gentile L, Russo M, Mazzeo A, Trapasso MC, Parazzini F, Vita G, Pareyson D, et al. Pregnancy in Charcot-Marie-Tooth disease: data from the Italian CMT national registry. Neurology. 2020;95:e3180-e3189. PubMed PMID: 32928981.

Ramchandren S, Shy M, Feldman E, Carlos R, Siskind C. Defining disability: development and validation of a mobility-Disability Severity Index (mDSI) in Charcot-Marie-tooth disease. J Neurol Neurosurg Psychiatry. 2015;86:635-9. PubMed PMID: 25157034.

Rebelo AP, Cortese A, Abraham A, Eshed-Eisenbach Y, Shner G, Vainshtein A, Buglo E, Camarena V, Gaidosh G, Shiekhattar R, Abreu L, Courel S, Burns DK, Bai Y, Bacon C, Feely SME, Castro D, Peles E, Reilly MM, Shy ME, Zuchner S. A CADM3 variant causes Charcot-Marie-Tooth disease with marked upper limb involvement. Brain. 2021;144:1197-213. PubMed PMID: 33889941.

Rebelo AP, Saade D, Pereira CV, Farooq A, Huff TC, Abreu L, Moraes CT, Mnatsakanova D, Mathews K, Yang H, Schon EA, Zuchner S, Shy ME. SCO2 mutations cause early-onset axonal Charcot-Marie-Tooth disease associated with cellular copper deficiency. Brain. 2018;141:662-72. PubMed PMID: 29351582.

Refshauge KM, Raymond J, Nicholson G, van den Dolder PA. Night splinting does not increase ankle range of motion in people with Charcot-Marie-Tooth disease: a randomised, cross-over trial. Aust J Physiother. 2006;52:193–9. PubMed PMID: 16942454.

Reilly MM, Shy ME. Diagnosis and new treatments in genetic neuropathies. J Neurol Neurosurg Psychiatry. 2009;80:1304–14. PubMed PMID: 19917815.

Rotthier A, Baets J, Timmerman V, Janssens K. Mechanisms of disease in hereditary sensory and autonomic neuropathies. Nat Rev Neurol. 2012;8:73–85. PubMed PMID: 22270030.

Rudnik-Schöneborn S, Tölle D, Senderek J, Eggermann K, Elbracht M, Kornak U, von der Hagen M, Kirschner J, Leube B, Müller-Felber W, Schara U, von Au K, Wieczorek D, Bußmann C, Zerres K. Diagnostic algorithms in Charcot-Marie-Tooth neuropathies: experiences from a German genetic laboratory on the basis of 1206 index patients. Clin Genet. 2016;89:34-43 PubMed PMID: 25850958.

Setlere S, Jurcenko M, Gailite L, Rots D, Kenina V. Alanyl-tRNA synthetase 1 gene variants in hereditary neuropathy: genotype and phenotype overview. Neurol Genet. 2022;8:e200019. PubMed PMID: 36092982.

Sivera Mascaró R, García Sobrino T, Horga Hernández A, Pelayo Negro AL, Alonso Jiménez A, Antelo Pose A, Calabria Gallego MD, Casasnovas C, Cemillán Fernández CA, Esteban Pérez J, Fenollar Cortés M, Frasquet Carrera M, Gallano Petit MP, Giménez Muñoz A, Gutiérrez Gutiérrez G, Gutiérrez Martínez A, Juntas Morales R, Ciano-Petersen NL, Martínez Ulloa PL, Mederer Hengstl S, Millet Sancho E, Navacerrada Barrero FJ, Navarrete Faubel FE, Pardo Fernández J, Pascual Pascual SI, Pérez Lucas J, Pino Mínguez J, Rabasa Pérez M, Sánchez González M, Sotoca J, Rodríguez Santiago B, Rojas García R, Turon-Sans J, Vicent Carsí V, Sevilla Mantecón T. Clinical practice guidelines for the diagnosis and management of Charcot-Marie-Tooth disease. Neurologia (Engl Ed). 2024. Epub ahead of print.

Sman AD, Hackett D, Fiatarone Singh M, Fornusek C, Menezes MP, Burns J. Systematic review of exercise for Charcot-Marie-Tooth disease. J Peripher Nerv Syst. 2015;20:347-62. PubMed PMID: 26010435.

Stojkovic T. Hereditary neuropathies: an update. Rev Neurol (Paris). 2016;172:775-8 PubMed PMID: 27866730.

Vinci P, Villa LM, Castagnoli L, Marconi C, Lattanzi A, Manini MP, Calicchio ML, Vitangeli L, Di Gianvito P, Perelli SL, Martini D. Handgrip impairment in Charcot-Marie-Tooth disease. Eura Medicophys. 2005b;41:131–4. PubMed PMID: 16200028.

Ward CM, Dolan LA, Bennett DL, Morcuende JA, Cooper RR. Long-term results of reconstruction for treatment of a flexible cavovarus foot in Charcot-Marie-Tooth disease. J Bone Joint Surg Am. 2008;90:2631–42. PubMed PMID: 19047708.

Yiu EM, Bray P, Baets J, Baker SK, Barisic N, de Valle K, Estilow T, Farrar MA, Finkel RS, Haberlová J, Kennedy RA, Moroni I, Nicholson GA, Ramchandren S, Reilly MM, Rose K, Shy ME, Siskind CE, Yum SW, Menezes MP, Ryan MM, Burns J. Clinical practice guideline for the management of paediatric Charcot-Marie-Tooth disease. J Neurol Neurosurg Psychiatry. 2022;93:530-8. PubMed PMID: 35140138.

Young P, De Jonghe P, Stögbauer F, Butterfass-Bahloul T. Treatment for Charcot-Marie-Tooth disease. Cochrane Database Syst Rev. 2008;(1):CD006052. PubMed PMID: 18254090.

Zambon AA, Natali Sora MG, Cantarella G, Cerri F, Quattrini A, Comi G, Previtali SC, Bolino A. Vocal cord paralysis in Charcot-Marie-Tooth type 4b1 disease associated with a novel mutation in the myotubularin-related protein 2 gene: a case report and review of the literature. Neuromuscul Disord. 2017;27:487-91 PubMed PMID: 28190646.

License