



Charcot-Marie-Tooth Neuropathy Type 2 – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: Charcot-Marie-Tooth Disease, Axonal Type; CMT2; Hereditary Motor and Sensory Neuropathy 2; HMSN2

Thomas D Bird, MD¹

Created: September 24, 1998; Revised: April 14, 2016.

Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Charcot-Marie-Tooth hereditary neuropathy type 2 (CMT2) is an axonal (non-demyelinating) peripheral neuropathy characterized by distal muscle weakness and atrophy, mild sensory loss, and normal or near-normal nerve conduction velocities. CMT2 is clinically similar to CMT1, although typically less severe. Peripheral nerves are not enlarged or hypertrophic. The subtypes of CMT2 are similar clinically and distinguished only by molecular genetic findings.

Diagnosis/testing

The diagnosis is based on clinical and EMG/NCV findings, and in many instances by identification of diagnostic changes in one of the genes that determine the CMT2 subtypes.

Management

Treatment of manifestations: Treatment by a team including a neurologist, physiatrists, orthopedic surgeons, physical, and occupational therapist; special shoes and/or ankle/foot orthoses (AFO) to correct foot drop and aid walking; surgery as needed for severe pes cavus; forearm crutches, canes, wheelchairs as needed for mobility; exercise as tolerated; symptomatic treatment of pain, depression, sleep apnea, restless legs syndrome.

Prevention of secondary complications: Daily heel cord stretching to prevent Achilles' tendon shortening.

Surveillance: Monitoring gait and condition of feet to determine need for bracing, special shoes, surgery.

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

Agents/circumstances to avoid: Obesity, which makes ambulation more difficult; medications known to cause nerve damage (e.g., vincristine, isoniazid, nitrofurantoin).

Other: Career and employment counseling.

Genetic counseling

Most subtypes of CMT2 are inherited in an autosomal dominant manner; however, some are inherited in an autosomal recessive manner. Most probands with an autosomal dominant CMT2 subtype have inherited the pathogenic variant from an affected parent. The offspring of an individual with autosomal dominant CMT2 are at a 50% risk of inheriting the pathogenic variant.

Diagnosis

Establishing the Diagnosis

The diagnosis of Charcot-Marie-Tooth hereditary neuropathy type 2 (CMT2) is made clinically in individuals with the following findings:

- A progressive peripheral motor and sensory neuropathy
- Nerve conduction velocities (NCVs) that are usually within the normal range (>40-45 m/s), although occasionally in a mildly abnormal range (30-40 m/s)
- EMG testing that shows evidence of an axonal neuropathy with such findings as positive waves, polyphasic potentials, or fibrillations and reduced amplitudes of evoked motor and sensory responses
- Greatly reduced compound motor action potentials (CMAP)
- A family history that is typically (but not always) consistent with autosomal dominant inheritance. Note: Some subtypes are inherited in an autosomal recessive manner.

Note: Nerve biopsy is not required for diagnosis.

Establishing the genetic cause of CMT2 requires molecular genetic testing to identify diagnostic changes in one of the genes listed in Table 1a and Table 1b. Note that it has been estimated that a molecular diagnosis of CMT2 cannot be established in 75% of individuals with a clinical diagnosis of CMT2 [Rossor et al 2013].

Molecular testing approaches can include **serial single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**.

Serial single-gene testing can be considered based on the following:

- The order in which pathogenic variants most commonly occur (Table 1a)
- Ethnicity, if founder variants are present (Table 1a and Table 1b)
- Phenotypic findings that suggest specific CMT2 subtypes; for example:
 - Optic atrophy: CMT2A2 (*MFN2*)
 - Vocal cord paresis: CMT2C (*TRPV4*) and CMT2H/K (*GDAP1*)

A **multigene panel** that includes some or all of the genes included in Table 1a and Table 1b and other genes of interest (see Differential Diagnosis) may also be considered [Rossor et al 2013]. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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](#).

More comprehensive genomic testing (when available) including exome sequencing, mitochondrial sequencing, and genome sequencing may be considered if serial single-gene testing (and/or use of a multigene panel that includes some or all of the genes associated with CMT2) fails to confirm a diagnosis in an individual with features of CMT2. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation). For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

See Table 1a for the most common genetic causes (i.e., pathogenic variants of any one of the genes included in this table account for >2% of CMT2) and Table 1b for less common genetic causes (i.e., pathogenic variants of any one of the genes included in this table are reported in only a few families).

Table 1a. CMT2 Subtypes: Most Common Genetic Causes

CMT2 Subtype	Gene ¹	MOI	Comment
CMT2A2	<i>MFN2</i>	AD, AR	10%-30% of CMT2 [Rossor et al 2013, Rudnik-Schöneborn et al 2016] 16% of CMT in Spain [Casasnovas et al 2010] 3.4% of CMT in Norway [Braathen et al 2010] 8% of Germans w/CMT2 [Gess et al 2013] 18% of CMT2 in mainland China [Xie et al 2016] Deletion of exons 7 and 8 is a founder variant in the UK [Carr et al 2015].
CMT2I/J	<i>MPZ</i>	AD	8% [Rudnik-Schöneborn et al 2016] 2% of Germans with CMT2 [DiVincenzo et al 2014] 1% of CMT2 [Rossor et al 2013]
CMT2F	<i>HSPB1 (HSP27)</i>	AD	4% of CMT2 in Italy [Capponi et al 2011]

CMT2 subtypes/genes/loci accounting for >2% of the disorder; listed in order of frequency

MOI = mode of inheritance

AD = autosomal dominant

AR = autosomal recessive

1. See Molecular Genetics for information on the genes included in Table 1a.

Table 1b. CMT2 Subtypes: Less Common Genetic Causes

CMT2 Subtype	Gene ¹	MOI	Comment
CMT2A1	<i>KIF1B</i>	AD	Can mimic MS incl white-matter lesions on brain MRI [Genari et al 2011, Klein et al 2011b]
CMT2B	<i>RAB7A</i>	AD	Prominent sensory loss, reduced tendon reflexes, distal weakness w/distal ulceration. Also reported: onset > age 50 yrs [Shimizu et al 2010] & autonomic dysfunction [Manganelli et al 2012]. See also Auer-Grumbach et al [2000], Verhoeven et al [2003], Houlden et al [2004], Meggouh et al [2006].
CMT2B1	<i>LMNA</i>	AR	Primarily in Algeria; mean age of onset 14 yrs (range 6-27 yrs); functional disability ranging from mild to severe [Tazir et al 2004]
CMT2B2	<i>MED25</i>	AR	In a Costa Rican family w/adult onset [Leal et al 2001, Berghoff et al 2004, Leal et al 2009]

Table 1b. continued from previous page.

CMT2 Subtype	Gene ¹	MOI	Comment
CMT2C	<i>TRPV4</i>	AD	Frequent vocal cord & phrenic nerve paralysis that may require tracheotomy [Santoro et al 2002, McEntagart et al 2005, Chen et al 2010, Deng et al 2010, Landouré et al 2010]. Also reported: mild sensory loss [Chen et al 2010], scapular winging, elevated serum CK, respiratory insufficiency, hearing loss, skeletal dysplasia [Echaniz-Laguna et al 2014, Evangelista et al 2015]
CMT2D	<i>GARS</i>	AD	Mainly distal motor weakness w/wasting of hand muscles [Antonellis et al 2003]
CMT2E/1F	<i>NEFL</i>	AD	In multiple families w/a progressive SMN; phenotypic overlap w/CMT1 w/slow NCVs & overlap w/dominant intermediate CMT [Berciano et al 2016]
CMT2G	12q12-q13.3 (gene unknown)	AD	In 1 Spanish family [Nelis et al 2004]
CMT2H/K	<i>GDAP1</i>	AR	Incl pyramidal findings [Barhoumi et al 2001]
		AD	Zimoń et al [2011]
CMT2L	<i>HSPB8 (HSP22)</i>	AD	In 1 Chinese family; onset 15-33 yrs; normal NCV [Tang et al 2004, Tang et al 2005]; myofibrillar myopathy in some families [Ghaoui et al 2016]
CMT2M	<i>DNM2</i>	AD	
CMT2N	<i>AARS</i>	AD	In 3 families: 2 French & 1 Australian [Latour et al 2010, McLaughlin et al 2012]; hyperreflexia & myelopathy reported in a 4 th family [Motley et al 2015]
CMT2O	<i>DYNC1H1</i>	AD	In a 4-generation family w/childhood-onset delayed motor milestones w/progressive distal lower-limb weakness, pes cavus, variable sensory loss, nml CNVs; occasional proximal weakness, & waddling gait [Weedon et al 2011]. Also reported: arthrogryposis, SMA, cognitive impairment, spasticity [Scoto et al 2015, Strickland et al 2015]. HMSN in 1 family & SMA in an individual w/a <i>de novo</i> pathogenic variant [Peeters et al 2015].
CMT2P	<i>LRSAM1</i>	AR	1 family w/onset in 2 nd -3 rd decade; progressive distal muscle weakness & atrophy [Guernsey et al 2010]
		AD	2 families w/mild sensory loss [Weterman et al 2012, Nicolaou et al 2013].
CMT2Q	<i>DHTKD1</i>	AD	In a large Chinese family [Xu et al 2012]
CMT2R	<i>TRIM2</i>	AR	Early onset ± vocal cord paralysis [Ylikallio et al 2013, Pehlivan et al 2015]
CMT2S	<i>IGHMBP2</i>	AR	Axonal neuropathy [Cottenie et al 2014, Schottmann et al 2015]
CMT2T	<i>DNAJB2</i>	AR	Distal motor neuropathy [Gess et al 2014]
CMT2U	<i>MARS</i>	AD	In 2 families; onset age >50 yrs [Gonzalez et al 2013, Hyun et al 2014]
CMT2V	<i>NAGLU</i>	AD	Painful axonal neuropathy [Tétreault et al 2015]
CMT2W	<i>HARS</i>	AD	5 families, incl both axonal & demyelinating motor & sensory neuropathies [Safka Brozkova et al 2015]
Not assigned	<i>MME</i>	AR	Weakness, muscle atrophy, sensory loss, no dementia Late onset (4 th -6 th decades) [Higuchi et al 2016]

CMT2 subtypes accounting for ≤2% of the disorder; listed alphabetically by subtype.

MOI = mode of inheritance

AD = autosomal dominant

AR = autosomal recessive

1. Click [here](#) (pdf) for information on the genes included in Table 1b.

Clinical Characteristics

Clinical Description

Charcot-Marie-Tooth hereditary neuropathy type 2 (CMT2) is a disorder of peripheral nerves in which the motor system is more prominently involved than the sensory system, although both are involved [Pareyson & Marchesi 2009]. The affected individual typically has slowly progressive weakness and atrophy of distal muscles in the feet and/or hands usually associated with depressed tendon reflexes and mild or no sensory loss. The clinical syndrome overlaps extensively with CMT1. With the exception of CMT2B, CMT2 tends to be less disabling and to cause less sensory loss than CMT1 [Bienfait et al 2006, Pareyson et al 2006].

Affected individuals usually become symptomatic between ages five and 25 years [Bienfait et al 2006], though onset ranges from infancy with delayed walking to after the third decade. The typical presenting symptom is weakness of the feet and ankles. The initial physical findings are depressed or absent tendon reflexes with weakness of foot dorsiflexion at the ankle. Baets et al [2011] review the clinical presentations in the first year of life.

The adult with CMT2 typically has bilateral foot drop, symmetric atrophy of muscles below the knee (stork leg appearance) and absent tendon reflexes in the lower extremities. However, brisk tendon reflexes and extensor plantar responses have been reported as well as asymmetric muscle atrophy in up to 15% of affected individuals [Bienfait et al 2007].

Atrophy of intrinsic hand muscles is less frequently present and tendon reflexes may be intact in the upper limbs.

Proximal muscles usually remain strong. Brisk tendon reflexes and extensor plantar responses have been reported [Bienfait et al 2007].

Mild sensory deficits of position, vibration, and pain/temperature may occur in the feet or sensation may be intact. Pain, especially in the feet, is reported by about 20%-40% of affected individuals [Gemignani et al 2004]. Hearing impairment has been reported [Bienfait et al 2006].

Vocal cord or phrenic nerve involvement resulting in difficulty with phonation or breathing has been observed [Dematteis et al 2001, Sulica et al 2001].

Restless legs and sleep apnea have been observed [Aboussouan et al 2007].

CMT2 is progressive over many years, but affected individuals experience long plateau periods without obvious deterioration. In some, the disease can be so mild as to go unrecognized by the affected individual and physician. The disease does not decrease life span.

Nerve biopsy shows:

- Loss of myelinated fibers with signs of regeneration, axonal sprouting, and atrophic axons with neurofilaments (not the hypertrophy or onion bulb formation seen in Charcot-Marie-Tooth hereditary neuropathy type 1 [CMT1]);
- Large nodal gaps and shorter internodal lengths than controls, suggesting a developmental abnormality of internode formation [Manganelli et al 2015].

Phenotype Correlations with Genes Included in Table 1a

MFN2

- [CMT2A](#) (also known as hereditary motor and sensory neuropathy VI [HMSN VI]) comprises CMT2A1 and CMT2A2. The phenotype is typical CMT with onset in the second or third decade of distal muscle

weakness and atrophy, less severe sensory loss, and depressed tendon reflexes [Züchner et al 2004a, Kijima et al 2005, Stuppia et al 2015].

CMT2A2 is characterized by early-onset, severe pure motor neuropathy [Feely et al 2011, Tufano et al 2015]. Optic atrophy has been observed [Verhoeven et al 2006, Züchner et al 2006].

- CMT with pyramidal signs is also known as hereditary motor and sensory neuropathy V (HMSN V) [Zhu et al 2005].

MPZ

- CMT2I is a late-onset (>45 years) axonal neuropathy [Auer-Grumbach et al 2003b].
- CMT2J is associated with deafness and/or pupillary abnormalities [Chapon et al 1999, Misu et al 2000, Gallardo et al 2009].

See also Differential Diagnosis, **Intermediate CMT neuropathy**.

HSPB1. CMT2F was initially reported in a Russian family with distal weakness, atrophy, and sensory loss beginning between ages 15 and 25 years. Primary motor neuropathy has been described [Solla et al 2010]; sensory loss can also occur [Rossor et al 2012]. CMT2F is similar to distal hereditary motor neuropathy (HMN), except that sensory loss does not occur in HMN [Irobi et al 2004].

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known for any of the genes known to cause CMT2.

Nomenclature

Editor's note: In *GeneReviews*, CMT1 refers to a demyelinating neuropathy and CMT2 refers to an axonal neuropathy. CMT1 and CMT2 are usually inherited in an autosomal dominant manner, although exceptions occasionally occur. CMT4 refers to autosomal recessive varieties of CMT. CMTX refers to X-linked forms.

Other experts in the field emphasize the physiology of the phenotypes such that all axonal varieties are classified as CMT2 regardless of mode of inheritance. Examples include:

- *IGHMBP2*-related CMT, described and classified by Cottenie et al [2014] as CMT2S (because it is axonal), whereas it could also be classified as CMT4 (because it is autosomal recessive);
- *MME*-related CMT, described and classified by Higuchi et al [2016] as CMT2 (because it is axonal), whereas it could also be classified as CMT4 (because it is autosomal recessive).

The nomenclature for all types of CMT is undergoing revision. A new nomenclature for CMT is likely to name the subtypes by gene.

Prevalence

The overall prevalence of hereditary neuropathies is estimated at 3:10,000 population, varying by country from 10:100,000 to 80:100,000 [Barreto et al 2016]. About 30% of these individuals (1:10,000) may have CMT2. The prevalence of the various subtypes of CMT2 is unknown.

In a study of 776 Germans with a CMT2 phenotype, Gess et al [2013] found the following: 11% had **CMTX1** (*GJB1*), 8% had CMT2A2 (*MFN2*) and 6% had **giant axonal neuropathy** (*GAN1*). Among those with CMT2, 35% had a genetic diagnosis.

Rossor et al [2013] show the prevalence of various subtypes of CMT2 and note that 75% of individuals with CMT2 have no known genetic cause.

Genetically Related (Allelic) Disorders

Other phenotypes associated with mutation of the genes in Table 1a and Table 1b.

Table 2. Allelic Disorders

Gene	Phenotype ¹
<i>AARS</i>	Early infantile epileptic encephalopathy 29 (OMIM 616339)
<i>DYNC1H1</i>	Autosomal dominant spinal muscular atrophy, lower extremity-predominant 1 (OMIM 158600)
<i>GARS</i>	<i>GARS1</i> -Associated Axonal Neuropathy
<i>GDAP1</i>	Charcot-Marie-Tooth neuropathy type 4A (CMT4A)
<i>HARS</i>	Usher syndrome type 3B (OMIM 614504)
<i>HSPB8</i>	Neuropathy, distal hereditary motor, type IIA (OMIM 158590)
<i>IGHMBP2</i>	Autosomal recessive distal spinal muscular atrophy 1 (OMIM 604320)
	Hutchinson-Gilford progeria syndrome
	Autosomal dominant Emery-Dreifuss muscular dystrophy type 2
	Autosomal recessive Emery-Dreifuss muscular dystrophy type 2
	Autosomal dominant familial dilated cardiomyopathy and conduction system defects
	Autosomal dominant Dunnigan-type familial partial lipodystrophy (OMIM 151660)
<i>LMNA</i>	Autosomal dominant limb-girdle muscular dystrophy 1B
	Benign variant associated with obesity-related traits in Canadian Oji-Cree [Hegele et al 2000]
	Autosomal recessive mandibuloacral dysplasia (OMIM 248370)
	Atypical Werner syndrome
	Familial partial lipodystrophy, type 2 (OMIM 151660)
	Co-occurrence of myopathy and neuropathy [Benedetti et al 2005]
<i>MFN2</i>	Multiple symmetric lipomatosis [Sawyer et al 2015]
<i>MPZ</i>	Charcot-Marie-Tooth neuropathy type 1B
<i>NEFL</i>	Associated with congenital myopathy and CMT in the same family [Agrawal et al 2014]
<i>TRPV4</i>	Neuromuscular disorders and skeletal dysplasias

1. See hyperlinked *GeneReview*, OMIM phenotype entry, or cited reference for more information.

Differential Diagnosis

See [CMT Overview](#), particularly to exclude potentially treatable causes of acquired neuropathy.

Charcot-Marie-Tooth hereditary neuropathy type 2 (CMT2) can sometimes be difficult to distinguish from chronic idiopathic axonal neuropathy.

Bienfait et al [2006] found extensive clinical overlap between individuals with CMT1A (caused by mutation of *PMP22*) and CMT2, while noting that people with CMT1A are more likely to have earlier-onset disease, foot deformity, and total areflexia.

A median motor NCV of 38 m/s is often used as a threshold for differentiating CMT1 from CMT2; however, the CMT2 phenotype can result from mutation of genes primarily associated with CMT1 (caused by mutation of *PMP22*) and [CMTX1](#) (caused by mutation of *GJB1*) [Gutierrez et al 2000, Young et al 2001, Shy et al 2004].

CMT2B1 (*LMNA*) can resemble several other types of autosomal dominant hereditary axonal neuropathy with predominantly sensory symptoms, including:

- The "burning feet syndrome" [Stögbauer et al 1999, Auer-Grumbach et al 2003a];
- Hereditary sensory neuropathy (including [hereditary sensory neuropathy type 1A](#) caused by mutation of *SPTLC1* [Bejaoui et al 2001]) which usually does not have motor symptoms such as muscle weakness, but can sometimes overlap with CMT2B.

CMT2C resembles phenotypes caused by mutation of the following genes:

- *SLC5A7* resulting in a similar, but pure motor syndrome without sensory loss, termed distal hereditary motor neuropathy VIIA (HMN7A; OMIM [158580](#))
- *DCTN1* resulting in autosomal dominant motor neuropathy with vocal paralysis (HMN7B; OMIM [607641](#)) [Puls et al 2003]

Bellone et al [2002] reported a family with autosomal dominant mutilating neuropathy that was not linked to the CMT2B locus or the HSN1A locus.

Table 3. Additional Disorders to Consider in the Differential Diagnosis of Charcot-Marie-Tooth Neuropathy Type 2

Gene	MOI	Overlapping Clinical Features	Distinguishing Clinical Features	GeneReview / OMIM
<i>DCAF8</i> ¹	AD		<ul style="list-style-type: none"> • Giant axons infrequently seen on nerve biopsy • Mild cardiomyopathy • Likely associated w/neurofilament degradation 	615820
<i>DCTN2</i>	AD		<ul style="list-style-type: none"> • Mixed axonal & mild demyelinating disease 	607376
<i>DGAT2</i>	AD		<ul style="list-style-type: none"> • Early onset • Sensory ataxia • Tremor • Slow disease progression 	606983
<i>DNM2</i> ²	AD		<ul style="list-style-type: none"> • Usually causes centronuclear myopathy • May be an overlap w/a predominantly CMT2 presentation 	602378
<i>DNMT1</i> ³	AD		<ul style="list-style-type: none"> • Sensory neuropathy associated w/hearing loss & later dementia 	DNMT1-Related Dementia, Deafness, and Sensory Neuropathy
<i>FBXO38</i> ⁴	AD		<ul style="list-style-type: none"> • Spinal muscular atrophy w/calf predominance (but also including triceps & hand weakness) • Onset ranges from age 13 to 48 yrs • Severity ranges from mild to severe • Nerve conduction shows reduced motor evoked amplitudes • May be referred to as distal hereditary motor neuropathy 2D (HMN2D) 	608533
<i>GJB1</i>	XL	CMT2 phenotype reported in some females	<ul style="list-style-type: none"> • Moderate to severe motor & sensory neuropathy in males • Usually mild to no symptoms in females • Sensorineural deafness & central nervous system symptoms in some families 	Charcot-Marie-Tooth Neuropathy X Type 1

Table 3. continued from previous page.

Gene	MOI	Overlapping Clinical Features	Distinguishing Clinical Features	GeneReview / OMIM
<i>GJB3</i> ⁵	AD	Nerve condition velocities not markedly slow, possibly suggesting a clinical diagnosis of CMT2	<ul style="list-style-type: none"> Sural nerve pathology shows demyelination compatible w/CMT1 Hearing impairment 	603324
<i>INF2</i> ⁶	AD		<ul style="list-style-type: none"> Childhood-onset CMT syndrome later complicated by renal glomerulosclerosis Nerve conduction vary from moderately slow to normal Intellectual disability & hearing loss reported⁷ 	610982
<i>MORC2</i>	AD		<ul style="list-style-type: none"> Asymmetric weakness Proximal weakness [Laššuthová et al 2016] Prominent sensory loss Pyramidal signs [Albulym et al 2016] Severe incapacity in adulthood [Sevilla et al 2016] 	616661
<i>SYT2</i> ⁸	AD		<ul style="list-style-type: none"> One family reported w/a CMT2 syndrome One family reported presynaptic neuromuscular junction disorder resembling Lambert-Eaton myasthenic syndrome [Whittaker et al 2015] 	600104
<i>TFG</i> ⁹	AD			602498
<i>VCP</i> ^{10, 11}	AD		<ul style="list-style-type: none"> One family reported w/mixed NCV CMT 	601023
<i>YARS</i>	AD		<ul style="list-style-type: none"> Mixed axonal & mild demyelinating phenotype [Thomas et al 2016] Also classified as dominant intermediate CMT (DI-CMTC) 	608323

MOI = mode of inheritance

XL = X-linked

AD = autosomal dominant

AR = autosomal recessive

1. Klein et al [2014]

2. Böhm et al [2012]

3. Klein et al [2011a]

4. Sumner et al [2013]

5. López-Bigas et al [2001]

6. Boyer et al [2011]

7. Mademan et al [2013]

8. Herrmann et al [2014]

9. Ishiura et al [2012], Lee et al [2013]

10. Gonzalez et al [2014]

11. Other pathogenic variants in *VCP* are associated with a specific type of inclusion body myopathy (see [Inclusion Body Myopathy with Paget Disease of Bone and/or Frontotemporal Dementia](#)).

The CMT2 phenotype may sometimes be associated with signs of spasticity (e.g., hyperactive tendon reflexes and/or Babinski signs), a phenotype sometimes referred to as HMSN V. Mutation of two genes has been identified:

- *BSCL2* (see [BSCL2-Related Neurologic Disorders/Seipinopathy](#))
- *KIF5A*, associated with a form of spastic paraparesis (HSP10). Crimella et al [2012] and Liu et al [2014] identified pathogenic missense variants in *KIF5A* that may also cause an axonal neuropathy fitting the

CMT2 phenotype that sometimes includes pyramidal tract signs. See also [Hereditary Spastic Paraplegia Overview](#).

Intermediate CMT neuropathy inherited in an autosomal dominant manner has been described; affected individuals have a relatively typical CMT phenotype with nerve conduction velocities that overlap those observed in CMT1 (demyelinating form) and CMT2 (axonal form). Motor NCVs in these families usually range between 25 and 50 m/sec. Four genes (*DNM2*, *GNB4*, *MPZ*, and *YARS*) and one locus (10q24.1-q25.1) are included in this dominant intermediate category. See [CMT Overview](#).

Mitochondrial causes. Mitochondrial abnormalities are known to sometimes be associated with peripheral neuropathy.

- Mutation of the nuclear gene *MFN2* produces abnormal mitochondrial fusion/fission and resultant neuropathy (CMT2A).
- Mutation in the mitochondrial genome may also be associated with neuropathy (e.g., in [NARP](#)).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Charcot-Marie-Tooth hereditary neuropathy type 2 (CMT2), the following evaluations are recommended:

- Physical examination to determine extent of weakness and atrophy, pes cavus, gait stability, and sensory loss
- Nerve conduction velocity (NCV)
- Complete family history
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

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].

The following may be indicated:

- Special shoes, including those with good ankle support
- Ankle/foot orthoses (AFO) to correct foot drop and aid walking
- Orthopedic surgery to correct severe pes cavus deformity [Guyton & Mann 2000]
- Forearm crutches or canes for gait stability; fewer than 5% need wheelchairs.
- Treatment of sleep apnea or restless legs [Aboussouan et al 2007]
- Exercise within the individual's capability. In a systematic review of all reports of exercise for CMT, Sman et al [2015] identified the following significant improvements following exercise: strength, functional activities, and physiologic adaptations. The optimal exercise modality and intensity for people with CMT as well as the long-term safety of exercise remain unclear.

Pain and depression should be treated symptomatically [Gemignani et al 2004, Padua et al 2006].

Prevention of Secondary Complications

Daily heel cord-stretching exercises help prevent Achilles' tendon shortening.

Surveillance

Gait and condition of feet should be monitored to determine need for bracing, special shoes, or surgery.

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.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

A German study reviewed 63 pregnancies in 33 women with CMT and found no increase in the frequency of cesarean sections, forceps deliveries, premature births, or neonatal problems [Awater et al 2012].

Argov & de Visser [2009] reviewed pregnancy issues in hereditary neuromuscular disorders including CMT.

Greenwood & Scott [2007] have described the obstetric approach to women with mild and severe forms of CMT.

A Norway study found a higher than average rate of operative deliveries among women with CMT [Hoff et al 2005].

Therapies Under Investigation

Mathis et al [2015] have reviewed the future of therapeutic options in CMT.

Search [Clinical Trials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

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

Most CMT2 subtypes are inherited in an autosomal dominant manner. (Of note, CMT2 associated with pathogenic variants in *DNAJB2*, *IGHMBP2*, *LMNA*, *MED25*, *MME*, or *TRIM2* is inherited in an autosomal recessive manner.)

CMT2 associated with pathogenic variants in *MFN2*, *GDAP1*, or *LRSAM1* has been reported to be inherited both in an autosomal recessive manner and in an autosomal dominant manner.

Risk to Family Members – Autosomal Dominant CMT2

Parents of a proband

- Most individuals diagnosed with autosomal dominant CMT2 have an affected parent.
- A proband with autosomal dominant CMT2 may have the disorder as the result of a *de novo* pathogenic variant. The proportion of cases caused by a *de novo* pathogenic variant is unknown but likely very small.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include neurologic examination and molecular genetic testing if the pathogenic variant in the proband has been identified.
- Although most individuals diagnosed with autosomal dominant CMT2 have an affected parent, the family history 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.

Sibs of a proband

- The risk to sibs depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of parental germline mosaicism. (Although no instances of germline mosaicism have been reported, it remains a possibility.)

Offspring of a proband. Each child of an individual with autosomal dominant CMT2 has a 50% chance of inheriting the pathogenic variant.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or has a pathogenic variant, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, possible 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 testing is before pregnancy. Similarly, decisions regarding testing to determine the genetic status of at-risk asymptomatic family members are best made 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.

Testing of at-risk asymptomatic adult relatives of individuals with CMT2 is possible after molecular genetic testing has identified the specific pathogenic variant in the family. Such testing should be performed in the context of formal genetic counseling.

Testing of asymptomatic individuals younger than age 18 years who are at risk for adult-onset disorders for which no treatment exists is not considered appropriate, 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.

It is appropriate to consider testing symptomatic individuals regardless of age in a family with an established diagnosis of CMT2.

For more information, see the National Society of Genetic Counselors [Position Statement](#) on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics [Policy Statement](#): ethical and policy issues in genetic testing and screening of children.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for CMT2 are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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)**

PO Box 105

Glenolden PA 19036

Phone: 800-606-2682 (toll-free); 610-499-9264

Fax: 610-499-9267

Email: info@cmtausa.org

www.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, Inc.**

432 Park Avenue South

4th Floor

New York NY 10016

Phone: 855-435-7268 (toll-free); 212-722-8396

Fax: 917-591-2758

Email: info@hnf-cure.org

www.hnf-cure.org

- **My46 Trait Profile**

[Charcot Marie Tooth disease](#)

- **National Library of Medicine Genetics Home Reference**

[Charcot-Marie-Tooth disease](#)

- **NCBI Genes and Disease**

[Charcot-Marie-Tooth syndrome](#)

- **TREAT-NMD**

Institute of Genetic Medicine

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)**

1 Rue de l'International

BP59

Evry cedex 91002

France

Phone: +33 01 69 47 28 28

Email: dmc@afm.genethon.fr

www.afm-telethon.fr

- **European Neuromuscular Centre (ENMC)**

Lt Gen van Heutszlaan 6

3743 JN Baarn

Netherlands

Phone: 31 35 5480481

Fax: 31 35 5480499

Email: enmc@enmc.org

www.enmc.org

- **Muscular Dystrophy Association - USA (MDA)**

222 South Riverside Plaza

Suite 1500

Chicago IL 60606

Phone: 800-572-1717

Email: mda@mdausa.org

www.mda.org

- **Muscular Dystrophy UK**

61A Great Suffolk Street

London SE1 0BU

United Kingdom

Phone: 0800 652 6352 (toll-free); 020 7803 4800

Email: info@musceldystrophyuk.org

www.musceldystrophyuk.org

- **RDCRN Patient Contact Registry: Inherited Neuropathies Consortium**

Patient Contact Registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Charcot-Marie-Tooth Neuropathy Type 2: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CMT2A1	KIF1B	1p36.22	Kinesin-like protein KIF1B	KIF1B homepage - Leiden Muscular Dystrophy pages IPN Mutations, KIF1B	KIF1B	KIF1B
CMT2A2	MFN2	1p36.22	Mitofusin-2	MFN2 homepage - Leiden Muscular Dystrophy pages IPN Mutations, MFN2	MFN2	MFN2
CMT2B	RAB7A	3q21.3	Ras-related protein Rab-7a	RAB7A homepage - Leiden Muscular Dystrophy pages IPN Mutations, RAB7A	RAB7A	RAB7A

Table A. continued from previous page.

CMT2B1	<i>LMNA</i>	1q22	Prelamin-A/C	Human Intermediate Filament Database LMNA (lamin C1) Human Intermediate Filament Database LMNA (lamin A) Human Intermediate Filament Database LMNA (lamin C2) LMNA homepage - Leiden Muscular Dystrophy pages IPN Mutations, LMNA The UMD-LMNA mutations database	LMNA	LMNA
CMT2B2	<i>MED25</i>	19q13.33	Mediator of RNA polymerase II transcription subunit 25	MED25 database	MED25	MED25
CMT2C	<i>TRPV4</i>	12q24.11	Transient receptor potential cation channel subfamily V member 4	TRPV4 database	TRPV4	TRPV4
CMT2D	<i>GARS</i>	7p14.3	Glycine--tRNA ligase	alsod/GARS genetic mutations GARS homepage - Leiden Muscular Dystrophy pages IPN Mutations, GARS	GARS	GARS
CMT2E	<i>NEFL</i>	8p21.2	Neurofilament light polypeptide	Human Intermediate Filament Database NEFL NEFL homepage - Leiden Muscular Dystrophy pages IPN Mutations, NEFL	NEFL	NEFL
CMT2F	<i>HSPB1</i>	7q11.23	Heat shock protein beta-1	HSPB1 homepage - Leiden Muscular Dystrophy pages IPN Mutations, HSPB1	HSPB1	HSPB1
CMT2G	Unknown	12q12-q13.3	Unknown			
CMT2H/2K	<i>GDAP1</i>	8q21.11	Ganglioside-induced differentiation-associated protein 1	GDAP1 homepage - Leiden Muscular Dystrophy pages IPN Mutations, GAPD1	GDAP1	GDAP1
CMT2I	<i>MPZ</i>	1q23.3	Myelin protein P0	MPZ homepage - Leiden Muscular Dystrophy pages IPN Mutations, MPZ	MPZ	MPZ
CMT2J	<i>MPZ</i>	1q23.3	Myelin protein P0	MPZ homepage - Leiden Muscular Dystrophy pages IPN Mutations, MPZ	MPZ	MPZ

Table A. continued from previous page.

CMT2L	<i>HSPB8</i>	12q24.23	Heat shock protein beta-8	HSPB8 homepage - Leiden Muscular Dystrophy pages IPN Mutations, HSPB8	HSPB8	HSPB8
CMT2N	<i>AARS</i>	16q22.1	Alanine--tRNA ligase, cytoplasmic	AARS @ LOVD	AARS	AARS
CMT2O	<i>DYNC1H1</i>	14q32.31	Cytoplasmic dynein 1 heavy chain 1	alsod/DYNC1H1 genetic mutations	DYNC1H1	DYNC1H1
CMT2P	<i>LRSAM1</i>	9q33.3-q34.1	E3 ubiquitin-protein ligase LRSAM1		LRSAM1	LRSAM1
CMT2Q	<i>DHTKD1</i>	10p14	Probable 2-oxoglutarate dehydrogenase E1 component DHKT1D1, mitochondrial		DHTKD1	DHTKD1
CMT2R	<i>TRIM2</i>	4q31.3	Tripartite motif-containing protein 2		TRIM2	TRIM2
CMT2S	<i>IGHMBP2</i>	11q13.3	DNA-binding protein SMUBP-2	IGHMBP2 homepage - Leiden Muscular Dystrophy pages IPN Mutations, IGHMBP2	IGHMBP2	IGHMBP2
CMT2T	<i>DNAJB2</i>	2q35	DnaJ homolog subfamily B member 2		DNAJB2	DNAJB2
CMT2U	<i>MARS</i>	12q13.3	Methionine--tRNA ligase, cytoplasmic		MARS	MARS
CMT2V	<i>NAGLU</i>	17q21.2	Alpha-N-acetylglucosaminidase	NAGLU database	NAGLU	NAGLU
CMT2W	<i>HARS</i>	5q31.3	Histidine--tRNA ligase, cytoplasmic	HARS @ LOVD	HARS	HARS
	<i>MME</i>	3q25.2	Neprilysin		MME	MME

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for Charcot-Marie-Tooth Neuropathy Type 2 ([View All in OMIM](#))

120520	MEMBRANE METALLOENDOPEPTIDASE; MME
150330	LAMIN A/C; LMNA
156560	METHIONYL-tRNA SYNTHETASE; MARS
159440	MYELIN PROTEIN ZERO; MPZ
162280	NEUROFILAMENT PROTEIN, LIGHT POLYPEPTIDE; NEFL
600112	DYNEIN, CYTOPLASMIC 1, HEAVY CHAIN 1; DYNC1H1
600287	GLYCYL-tRNA SYNTHETASE; GARS
600502	IMMUNOGLOBULIN MU-BINDING PROTEIN 2; IGHMBP2
600882	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2B; CMT2B
601065	ALANYL-tRNA SYNTHETASE; AARS
601472	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2D; CMT2D

Table B. continued from previous page.

602195	HEAT-SHOCK 27-KD PROTEIN 1; HSPB1
602298	RAS-ASSOCIATED PROTEIN RAB7; RAB7
604139	DNAJ/HSP40 HOMOLOG, SUBFAMILY B, MEMBER 2; DNAJB2
605427	TRANSIENT RECEPTOR POTENTIAL CATION CHANNEL, SUBFAMILY V, MEMBER 4; TRPV4
605588	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2B1; CMT2B1
605589	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2B2; CMT2B2
606071	HEREDITARY MOTOR AND SENSORY NEUROPATHY, TYPE IIC; HMSN2C
606595	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2F; CMT2F
606598	GANGLIOSIDE-INDUCED DIFFERENTIATION-ASSOCIATED PROTEIN 1; GDAP1
607677	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2I; CMT2I
607684	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2E; CMT2E
607731	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2H; CMT2H
607736	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2J; CMT2J
607831	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2K; CMT2K
608014	HEAT-SHOCK 22-KD PROTEIN 8; HSPB8
608507	MITOFUSIN 2; MFN2
608591	none found
608673	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2L; CMT2L
609260	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, AUTOSOMAL DOMINANT, TYPE 2A2A; CMT2A2A
610197	MEDIATOR COMPLEX SUBUNIT 25; MED25
610933	LEUCINE-RICH REPEAT- AND STERILE ALPHA MOTIF-CONTAINING 1; LRSAM1
613287	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2N; CMT2N
614228	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2O; CMT2O
614436	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2P; CMT2P
614984	DEHYDROGENASE E1 AND TRANSKETOLASE DOMAINS-CONTAINING PROTEIN 1; DHTKD1
615025	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2Q; CMT2Q
616155	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2S; CMT2S
616233	none found
616280	CHARCOT-MARIE-TOOTH DISEASE, AXONAL, TYPE 2U; CMT2U

Molecular Pathogenesis

The relationship of myelin and axon pathology to the pathogenesis of CMT is discussed in detail in several reviews [Züchner & Vance 2006a, Züchner & Vance 2006b, Manganelli et al 2015]. Rossor et al [2013] show the molecular and anatomic relationships of the various genes and proteins associated with CMT.

Information on the three genes that account for more than 2% of CMT2 (Table 1a) follows.

Click [here](#) (pdf) for molecular genetic information on genes less commonly associated with CMT2 (Table 1b).

MFN2

Gene structure. *MFN2* has 19 exons with a 2274-bp open reading frame. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Züchner et al [2004b] and Verhoeven et al [2006] have reported more than 25 pathogenic missense variants in *MFN2*. See also Table A.

Deletion of exons 7 and 8 in *MFN2* represent a founder variant in the UK [Carr et al 2015].

Normal gene product. Mitofusin-2, encoded by *MFN2*, is involved in mitochondrial network architecture and mediates mitochondrial fusion.

Abnormal gene product. Mutation of *MFN2* may disrupt the mitochondrial fusion-fission balance in peripheral nerve. Diminished axonal mitochondrial transport has been described [Baloh et al 2007].

HSPB1 (HSP27)

Gene structure. *HSPB1* contains three exons with a central HSP20- α -crystallin domain. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. See Table A.

Normal gene product. The heat shock protein beta-1 (also referred to as heat-shock protein 27) has many possible functions including antiapoptotic and cytoprotective properties, inhibition of caspase activation, prevention of aggresome formation, and involvement in the neurofilament network.

Abnormal gene product. Pathogenic variants in *HSPB1* result in altered neurofilament assembly [Evgrafov et al 2004].

MPZ

Gene structure. *MPZ* spans approximately 7 kb and contains six exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. See Table A.

Table 4. Selected *MPZ* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change (Alias ¹)	Reference Sequences
c.254A>T	p.Asp85Val (p.Asp75Val)	NM_000530.5 NP_000521.1
c.401C>T	p.Thr134Met (p.Thr124Met)	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

Normal gene product. Myelin protein P₀ is a major structural component of peripheral myelin representing about 50% of peripheral myelin protein by weight and about 7% of Schwann cell message. It is a homophilic adhesion molecule of the immunoglobulin family that plays an important role in myelin compaction. It has a single transmembrane domain, a large extracellular domain, and a smaller intracellular domain.

Abnormal gene product. Different pathogenic variants affect all portions of the protein and may alter myelin adhesion. Either demyelinating or axonal phenotypes can result.

References

Published Guidelines / Consensus Statements

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available [online](#). 2013. Accessed 4-30-18.

National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available [online](#). 2018. Accessed 4-30-18.

Literature Cited

Aboussouan LS, Lewis RA, Shy ME. Disorders of pulmonary function, sleep, and the upper airway in Charcot-Marie-Tooth disease. *Lung*. 2007;185:1–7. PubMed PMID: 17294338.

Agrawal PB, Joshi M, Marinakis NS, Schmitz-Abe K, Ciarlini PD, Sargent JC, Markianos K, De Girolami U, Chad DA, Beggs AH. Expanding the phenotype associated with the NEFL mutation: neuromuscular disease in a family with overlapping myopathic and neurogenic findings. *JAMA Neurol*. 2014;71:1413–20. PubMed PMID: 25264603.

Albulym OM, Kennerson ML, Harms MB, Drew AP, Siddell AH, Auer-Grumbach M, Pestronk A, Connolly A, Baloh RH, Zuchner S, Reddel SW, Nicholson GA. MORC2 mutations cause axonal Charcot-Marie-Tooth disease with pyramidal signs. *Ann Neurol*. 2016;79:419–27. PubMed PMID: 26659848.

Antonellis A, Ellsworth RE, Sambuughin N, Puls I, Abel A, Lee-Lin SQ, Jordanova A, Kremensky I, Christodoulou K, Middleton LT, Sivakumar K, Ionasescu V, Funalot B, Vance JM, Goldfarb LG, Fischbeck KH, Green ED. Glycyl tRNA Synthetase Mutations in Charcot-Marie-Tooth Disease Type 2D and Distal Spinal Muscular Atrophy Type V. *Am J Hum Genet*. 2003;72:1293–9. PubMed PMID: 12690580.

Argov Z, de Visser M. What we do not know about pregnancy in hereditary neuromuscular disorders. *Neuromuscul Disord*. 2009;19:675–9. PubMed PMID: 19692244.

Auer-Grumbach M, De Jonghe P, Verhoeven K, Timmerman V, Wagner K, Hartung HP, Nicholson GA. Autosomal dominant inherited neuropathies with prominent sensory loss and mutilations: a review. *Arch Neurol*. 2003a;60:329–34. PubMed PMID: 12633143.

Auer-Grumbach M, Strasser-Fuchs S, Robl T, Windpassinger C, Wagner K. Late onset Charcot-Marie-Tooth 2 syndrome caused by two novel mutations in the MPZ gene. *Neurology*. 2003b;61:1435–7. PubMed PMID: 14638973.

Auer-Grumbach M, De Jonghe P, Wagner K, Verhoeven K, Hartung HP, Timmerman V. Phenotype-genotype correlations in a CMT2B family with refined 3q13-q22 locus. *Neurology*. 2000;55:1552–7. PubMed PMID: 11094113.

Awater C, Zerres K, Rudnik-Schöneborn S. Pregnancy course and outcome in women with hereditary neuromuscular disorders: comparison of obstetric risks in 178 patients. *Eur J Obstet Gynecol Reprod Biol*. 2012;162:153–9. PubMed PMID: 22459654.

Baets J, Deconinck T, De Vriendt E, Zimoń M, Yperzeele L, Van Hoorenbeeck K, Peeters K, Spiegel R, Parman Y, Ceulemans B, Van Bogaert P, Pou-Serradell A, Bernert G, Dinopoulos A, Auer-Grumbach M, Sallinen SL, Fabrizi GM, Pauly F, Van den Bergh P, Bilir B, Battaloglu E, Madrid RE, Kabzińska D, Kochanski A, Topaloglu H, Miller G, Jordanova A, Timmerman V, De Jonghe P. Genetic spectrum of hereditary neuropathies with onset in the first year of life. *Brain*. 2011;134:2664–76. PubMed PMID: 21840889.

- Baloh RH, Schmidt RE, Pestronk A, Milbrandt J. Altered axonal mitochondrial transport in the pathogenesis of Charcot-Marie-Tooth disease from mitofusin 2 mutations. *J Neurosci*. 2007;27:422–30. PubMed PMID: 17215403.
- Barhoumi C, Amouri R, Ben Hamida C, Ben Hamida M, Machghoul S, Gueddiche M, Bentati F. Linkage of a new locus for autosomal recessive axonal form of Charcot-Marie-Tooth disease to chromosome 8q21.3. *Neuromuscul Disord*. 2001;11:27–34. PubMed PMID: 11166163.
- Barreto LC, Oliveira FS, Nunes PS, de França Costa IM, Garcez CA, Goes GM, Neves EL, de Souza Siqueira Quintans J, de Souza Araújo AA. Epidemiologic Study of Charcot-Marie-Tooth Disease: A Systematic Review. *Neuroepidemiology*. 2016;46:157–65. PubMed PMID: 26849231.
- Bejaoui K, Wu C, Scheffler MD, Haan G, Ashby P, Wu L, de Jong P, Brown RH Jr. SPTLC1 is mutated in hereditary sensory neuropathy, type 1. *Nat Genet*. 2001;27:261–2. PubMed PMID: 11242106.
- Bellone E, Rodolico C, Toscano A, Di Maria E, Cassandrini D, Pizzuti A, Pigullo S, Mazzeo A, Macaione V, Girlanda P, Vita G, Ajmar F, Mandich P. A family with autosomal dominant mutilating neuropathy not linked to either Charcot-Marie-Tooth disease type 2B (CMT2B) or hereditary sensory neuropathy type I (HSN I) loci. *Neuromuscul Disord*. 2002;12:286–91. PubMed PMID: 11801401.
- Benedetti S, Bertini E, Iannaccone S, Angelini C, Trisciani M, Toniolo D, Sferrazza B, Carrera P, Comi G, Ferrari M, Quattrini A, Previtali SC. Dominant LMNA mutations can cause combined muscular dystrophy and peripheral neuropathy. *J Neurol Neurosurg Psychiatry*. 2005;76:1019–21. PubMed PMID: 15965218.
- Berciano J, Peeters K, García A, López-Alburquerque T, Gallardo E, Hernández-Fabián A, Pelayo-Negro AL, De Vriendt E, Infante J, Jordanova A. NEFL N98S mutation: another cause of dominant intermediate Charcot-Marie-Tooth disease with heterogeneous early-onset phenotype. *J Neurol*. 2016;263:361–9. PubMed PMID: 26645395.
- Berghoff C, Berghoff M, Leal A, Morera B, Barrantes R, Reis A, Neundorfer B, Rautenstrauss B, Del Valle G, Heuss D. Clinical and electrophysiological characteristics of autosomal recessive axonal Charcot-Marie-Tooth disease (ARCMT2B) that maps to chromosome 19q13.3. *Neuromuscul Disord*. 2004;14:301–6. PubMed PMID: 15099588.
- Bienfait HM, Baas F, Koelman JH, de Haan RJ, van Engelen BG, Gabreels-Festen AA, Ongerboer de Visser BW, Meggouh F, Weterman MA, De Jonghe P, Timmerman V, de Visser M. Phenotype of Charcot-Marie-Tooth disease Type 2. *Neurology*. 2007;68:1658–67. PubMed PMID: 17502546.
- Bienfait HM, Verhamme C, van Schaik IN, Koelman JH, de Visser BW, de Haan RJ, Baas F, van Engelen BG, de Visser M. Comparison of CMT1A and CMT2: similarities and differences. *J Neurol*. 2006;253:1572–80. PubMed PMID: 16941080.
- Böhm J, Biancalana V, Dechene ET, Bitoun M, Pierson CR, Schaefer E, Karasoy H, Dempsey MA, Klein F, Dondaine N, Kretz C, Haumesser N, Poirson C, Toussaint A, Greenleaf RS, Barger MA, Mahoney LJ, Kang PB, Zanoteli E, Vissing J, Witting N, Echaniz-Laguna A, Wallgren-Pettersson C, Dowling J, Merlini L, Oldfors A, Bomme Ousager L, Melki J, Krause A, Jern C, Oliveira AS, Petit F, Jacquette A, Chaussenot A, Mowat D, Leheup B, Cristofano M, Poza Aldea JJ, Michel F, Furby A, Llona JE, Van Coster R, Bertini E, Urtizberea JA, Drouin-Garraud V, Béroud C, Prudhon B, Bedford M, Mathews K, Erby LA, Smith SA, Roggenbuck J, Crowe CA, Brennan Spital A, Johal SC, Amato AA, Demmer LA, Jonas J, Darras BT, Bird TD, Laurino M, Welt SI, Trotter C, Guicheney P, Das S, Mandel JL, Beggs AH, Laporte J. Mutation spectrum in the large GTPase dynamin 2, and genotype-phenotype correlation in autosomal dominant centronuclear myopathy. *Hum Mutat*. 2012;33:949–59. PubMed PMID: 22396310.
- Boyer O, Nevo F, Plaisier E, Funalot B, Gribouval O, Benoit G, Cong EH, Arrondel C, Tête MJ, Montjean R, Richard L, Karras A, Pouteil-Noble C, Balafréj L, Bonnardeaux A, Canaud G, Charasse C, Dantal J, Deschenes G, Deteix P, Dubourg O, Petiot P, Pouthier D, Leguern E, Guiochon-Mantel A, Broutin I, Gubler

- MC, Saunier S, Ronco P, Vallat JM, Alonso MA, Antignac C, Mollet G. INF2 mutations in Charcot-Marie-Tooth disease with glomerulopathy. *N Engl J Med.* 2011;365:2377–88. PubMed PMID: 22187985.
- Braathen GJ, Sand JC, Lobato A, Hoyer H, Russell MB. MFN2 point mutations occur in 3.4% of Charcot-Marie-Tooth families. An investigation of 232 Norwegian CMT families. *BMC Med Genet.* 2010;11:48. PubMed PMID: 20350294.
- Safka Brozkova D, Deconinck T, Griffin LB, Ferbert A, Haberlova J, Mazanec R, Lassuthova P, Roth C, Pilunthanakul T, Rautenstrauss B, Janecke AR, Zavadakova P, Chrast R, Rivolta C, Zuchner S, Antonellis A, Beg AA, De Jonghe P, Senderek J, Seeman P, Baets J. Loss of function mutations in HARS cause a spectrum of inherited peripheral neuropathies. *Brain.* 2015;138:2161–72. PubMed PMID: 26072516.
- Carr AS, Polke JM, Wilson J, Pelayo-Negro AL, Laura M, Nanji T, Holt J, Vaughan J, Rankin J, Sweeney MG, Blake J, Houlden H, Reilly MM. MFN2 deletion of exons 7 and 8: founder mutation in the UK population. *J Peripher Nerv Syst.* 2015; 2015;20:67–71. PubMed PMID: 26114802.
- Capponi S, Geroldi A, Fossa P, Grandis M, Ciotti P, Gulli R, Schenone A, Mandich P, Bellone E. HSPB1 and HSPB8 in inherited neuropathies: study of an Italian cohort of dHMN and CMT2 patients. *J Peripher Nerv Syst.* 2011;16:287–94. PubMed PMID: 22176143.
- Casasnovas C, Banchs I, Cassereau J, Gueguen N, Chevrollier A, Martínez-Matos JA, Bonneau D, Volpini V. Phenotypic spectrum of MFN2 mutations in the Spanish population. *J Med Genet.* 2010;47:249–56. PubMed PMID: 19889647.
- Chapon F, Latour P, Diraison P, Schaeffer S, Vandenberghe A. Axonal phenotype of Charcot-Marie-Tooth disease associated with a mutation in the myelin protein zero gene. *J Neurol Neurosurg Psychiatry.* 1999;66:779–82. PubMed PMID: 10329755.
- Chen DH, Sul Y, Weiss M, Hillel A, Lipe H, Wolff J, Matsushita M, Raskind W, Bird T. CMT2C with vocal cord paresis associated with short stature and mutations in the TRPV4 gene. *Neurology.* 2010;75:1968–75. PubMed PMID: 21115951.
- Cottenie E, Kochanski A, Jordanova A, Bansagi B, Zimon M, Horga A, Jaunmuktane Z, Saveri P, Rasic VM, Baets J, Bartsakoulia M, Ploski R, Teterycz P, Nikolic M, Quinlivan R, Laura M, Sweeney MG, Taroni F, Lunn MP, Moroni I, Gonzalez M, Hanna MG, Bettencourt C, Chabrol E, Franke A, von Au K, Schilhabel M, Kabzińska D, Hausmanowa-Petrusewicz I, Brandner S, Lim SC, Song H, Choi BO, Horvath R, Chung KW, Zuchner S, Pareyson D, Harms M, Reilly MM, Houlden H. Truncating and missense mutations in IGHMBP2 cause Charcot-Marie Tooth disease type 2. *Am J Hum Genet.* 2014;95:590–601. PubMed PMID: 25439726.
- Crimella C, Baschirotto C, Arnoldi A, Tonelli A, Tenderini E, Airoldi G, Martinuzzi A, Trabacca A, Losito L, Scarlato M, Benedetti S, Scarpini E, Spinucci G, Bresolin N, Bassi MT. Mutations in the motor and stalk domains of KIF5A in spastic paraplegia type 10 and in axonal Charcot-Marie-Tooth type 2. *Clin Genet.* 2012;82:157–64. PubMed PMID: 21623771.
- Dematteis M, Pepin JL, Jeanmart M, Deschaux C, Labarre-Vila A, Levy P. Charcot-Marie-Tooth disease and sleep apnoea syndrome: a family study. *Lancet.* 2001;357:267–72. PubMed PMID: 11214130.
- Deng H-X, Klein CJ, Yan J, Shi Y, Wu Y, Fecto F, Yau H-J, Yang Y, Zhai H, Siddique N, Hedley-Whyte ET, DeLong R, Martina M, Dyck PJ, Siddique T. Scapuloperoneal spinal muscular atrophy and CMT2C are allelic disorders caused by alterations in TRPV4. *Nat Genet.* 2010;42:165–9. PubMed PMID: 20037587.
- DiVincenzo C, Elzinga CD, Medeiros AC, Karbassi I, Jones JR, Evans MC, Braastad CD, Bishop CM, Jaremko M, Wang Z, Liaquat K, Hoffman CA, York MD, Batish SD, Lupski JR, Higgins JJ. The allelic spectrum of Charcot-Marie-Tooth disease in over 17,000 individuals with neuropathy. *Mol Genet Genomic Med.* 2014;2:522–9. PubMed PMID: 25614874.
- Echaniz-Laguna A, Dubourg O, Carlier P, Carlier RY, Sabouraud P, Péréon Y, Chapon F, Thauvin-Robinet C, Laforêt P, Eymard B, Latour P, Stojkovic T. Phenotypic spectrum and incidence of TRPV4 mutations in patients with inherited axonal neuropathy. *Neurology.* 2014;82:1919–26. PubMed PMID: 24789864.

- Evangelista T, Bansagi B, Pyle A, Griffin H, Douroudis K, Polvikoski T, Antoniadi T, Bushby K, Straub V, Chinnery PF, Lochmüller H, Horvath R. Phenotypic variability of TRPV4 related neuropathies. *Neuromuscul Disord.* 2015;25:516–21. PubMed PMID: 25900305.
- Evgrafov OV, Mersiyanova I, Irobi J, Van Den Bosch L, Dierick I, Leung CL, Schagina O, Verpoorten N, Van Impe K, Fedotov V, Dadali E, Auer-Grumbach M, Windpassinger C, Wagner K, Mitrovic Z, Hilton-Jones D, Talbot K, Martin JJ, Vasserman N, Tverskaya S, Polyakov A, Liem RK, Gettemans J, Robberecht W, De Jonghe P, Timmerman V. Mutant small heat-shock protein 27 causes axonal Charcot-Marie-Tooth disease and distal hereditary motor neuropathy. *Nat Genet.* 2004;36:602–6. PubMed PMID: 15122254.
- Feely SM, Laura M, Siskind CE, Sottile S, Davis M, Gibbons VS, Reilly MM, Shy ME. MFN2 mutations cause severe phenotypes in most patients with CMT2A. *Neurology.* 2011;76:1690–6. PubMed PMID: 21508331.
- Gallardo E, García A, Ramón C, Maraví E, Infante J, Gastón I, Alonso Á, Combarros O, De Jonghe P, Berciano J. Charcot-Marie-Tooth disease type 2J with MPZ Thr124Met mutation: clinico-electrophysiological and MRI study of a family. *J Neurol.* 2009;256:2061–71. PubMed PMID: 19629567.
- Gemignani F, Melli G, Alfieri S, Inglesi C, Marbini A. Sensory manifestations in Charcot-Marie-Tooth disease. *J Peripher Nerv Syst.* 2004;9:7–14. PubMed PMID: 14871449.
- Genari AB, Borghetti VH, Gouvêa SP, Bueno KC, dos Santos PL, dos Santos AC, Barreira AA, Lourenço CM, Marques W Jr. Characterizing the phenotypic manifestations of MFN2 R104W mutation in Charcot-Marie-Tooth type 2. *Neuromuscul Disord.* 2011;21:428–32. PubMed PMID: 21531138.
- Gess B, Auer-Grumbach M, Schirmacher A, Strom T, Zitzelsberger M, Rudnik-Schöneborn S, Röhr D, Halfter H, Young P, Senderek J. HSJ1-related hereditary neuropathies: novel mutations and extended clinical spectrum. *Neurology.* 2014;83:1726–32. PubMed PMID: 25274842.
- Gess B, Schirmacher A, Boentert M, Young P. Charcot-Marie-Tooth disease: Frequency of genetic subtypes in a German neuromuscular center population. *Neuromuscul Disord.* 2013;23:647–51. PubMed PMID: 23743332.
- Ghaoui R, Palmio J, Brewer J, Lek M, Needham M, Evilä A, Hackman P, Jonson PH, Penttilä S, Vihola A, Huovinen S, Lindfors M, Davis RL, Waddell L, Kaur S, Yiannikas C, North K, Clarke N, MacArthur DG, Sue CM, Udd B. Mutations in HSPB8 causing a new phenotype of distal myopathy and motor neuropathy. *Neurology.* 2016;86:391–8. PubMed PMID: 26718575.
- Gonzalez MA, Feely SM, Speziani F, Strickland AV, Danzi M, Bacon C, Lee Y, Chou TF, Blanton SH, Weihl CC, Zuchner S, Shy ME. A novel mutation in VCP causes Charcot-Marie-Tooth Type 2 disease. *Brain.* 2014;137:2897–902. PubMed PMID: 25125609.
- Gonzalez M, McLaughlin H, Houlden H, Guo M, Yo-Tsen L, Hadjivassiliou M, Speziani F, Yang X-L, Antonellis A, Reilly M M, Zuchner S. Inherited Neuropathy Consortium. Exome sequencing identifies a significant variant in methionyl-tRNA synthetase (MARS) in a family with late-onset CMT2. *J Neurol Neurosurg Psychiatr.* 2013;84:1247–9. PubMed PMID: 23729695.
- Grandis M, Shy ME. Current therapy for Charcot-Marie-Tooth disease. *Curr Treat Options Neurol.* 2005;7:23–31. PubMed PMID: 15610704.
- Greenwood JJ, Scott WE. Charcot-Marie-Tooth disease: peripartum management of two contrasting clinical cases. *Int J Obstet Anesth.* 2007;16:149–54. PubMed PMID: 17275278.
- Guernsey DL, Jiang H, Bedard K, Evans SC, Ferguson M, Matsuoka M, Macgillivray C, Nightingale M, Perry S, Rideout AL, Orr A, Ludman M, Skidmore DL, Benstead T, Samuels ME. Mutation in the gene encoding ubiquitin ligase LRSAM1 in patients with Charcot-Marie-Tooth disease. *PLoS Genet.* 2010 Aug 26;6(8) PubMed PMID: 20865121.

- Gutierrez A, England JD, Sumner AJ, Ferer S, Warner LE, Lupski JR, Garcia CA. Unusual electrophysiological findings in X-linked dominant Charcot-Marie-Tooth disease. *Muscle Nerve*. 2000;23:182–8. PubMed PMID: 10639608.
- Guyton GP, Mann RA. The pathogenesis and surgical management of foot deformity in Charcot-Marie-Tooth disease. *Foot Ankle Clin*. 2000;5:317–26. PubMed PMID: 11232233.
- Hegele RA, Cao H, Harris SB, Zinman B, Hanley AJ, Anderson CM. Genetic variation in LMNA modulates plasma leptin and indices of obesity in aboriginal Canadians. *Physiol Genomics*. 2000;3:39–44. PubMed PMID: 11015599.
- Herrmann DN, Horvath R, Sowden JE, Gonzalez M, Sanchez-Mejias A, Guan Z, Whittaker RG, Almodovar JL, Lane M, Bansagi B, Pyle A, Boczonadi V, Lochmüller H, Griffin H, Chinnery PF, Lloyd TE, Littleton JT, Zuchner S. Synaptotagmin 2 mutations cause an autosomal-dominant form of lambert-eaton myasthenic syndrome and nonprogressive motor neuropathy. *Am J Hum Genet*. 2014;95:332–9. PubMed PMID: 25192047.
- Higuchi Y, Hashiguchi A, Yuan J, Yoshimura A, Mitsui J, Ishiura H, Tanaka M, Ishihara S, Tanabe H, Nozuma S, Okamoto Y, Matsuura E, Ohkubo R, Inamizu S, Shiraishi W, Yamasaki R, Ohyagi Y, Kira JI, Oya Y, Yabe H, Nishikawa N, Tobisawa S, Matsuda N, Masuda M, Kugimoto C, Fukushima K, Yano S, Yoshimura J, Doi K, Nakagawa M, Morishita S, Tsuji S, Takashima H. Mutations in MME cause an autosomal-recessive Charcot-Marie-Tooth disease type 2. *Ann Neurol*. 2016 Mar 17. PubMed PMID: 26991897.
- Hoff JM, Gilhus NE, Daltveit AK. Pregnancies and deliveries in patients with Charcot-Marie-Tooth disease. *Neurology*. 2005;64:459–62. PubMed PMID: 15699375.
- Houlden H, King RH, Muddle JR, Warner TT, Reilly MM, Orrell RW, Ginsberg L. A novel RAB7 mutation associated with ulcero-mutilating neuropathy. *Ann Neurol*. 2004;56:586–90. PubMed PMID: 15455439.
- Hyun YS, Park HJ, Heo S-H, Yoon BR, Nam SH, Kim S-B, Park CI, Choi B-O, Chung KW. Rare variants in methionyl- and tyrosyl-tRNA synthetase genes in late-onset autosomal dominant Charcot-Marie-Tooth neuropathy. *Clin. Genet*. 2014;86:592–4. (Letter). PubMed PMID: 24354524.
- Irobi J, De Jonghe P, Timmerman V. Molecular genetics of distal hereditary motor neuropathies. *Hum Mol Genet*. 2004;13(Spec No 2):R195–202. PubMed PMID: 15358725.
- Ishiura H, Sako W, Yoshida M, Kawarai T, Tanabe O, Goto J, Takahashi Y, Date H, Mitsui J, Ahsan B, Ichikawa Y, Iwata A, Yoshino H, Izumi Y, Fujita K, Maeda K, Goto S, Koizumi H, Morigaki R, Ikemura M, Yamauchi N, Murayama S, Nicholson GA, Ito H, Sobue G, Nakagawa M, Kaji R, Tsuji S. The TRK-fused gene is mutated in hereditary motor and sensory neuropathy with proximal dominant involvement. *Am J Hum Genet*. 2012;91:320–9. PubMed PMID: 22883144.
- Kijima K, Numakura C, Izumino H, Umetsu K, Nezu A, Shiiki T, Ogawa M, Ishizaki Y, Kitamura T, Shozawa Y, Hayasaka K. Mitochondrial GTPase mitofusin 2 mutation in Charcot-Marie-Tooth neuropathy type 2A. *Hum Genet*. 2005;116:23–7. PubMed PMID: 15549395.
- Klein CJ, Botuyan MV, Wu Y, Ward CJ, Nicholson GA, Hammans S, Hojo K, Yamanishi H, Karpf AR, Wallace DC, Simon M, Lander C, Boardman LA, Cunningham JM, Smith GE, Litchy WJ, Boes B, Atkinson EJ, Middha S, B Dyck PJ, Parisi JE, Mer G, Smith DI, Dyck PJ. Mutations in DNMT1 cause hereditary sensory neuropathy with dementia and hearing loss. *Nat Genet*. 2011a;43:595–600. PubMed PMID: 21532572.
- Klein CJ, Kimmel GW, Pittock SJ, Engelstad JE, Cunningham JM, Wu Y, Dyck PJ. Large kindred evaluation of mitofusin 2 novel mutation, extremes of neurologic presentations, and preserved nerve mitochondria. *Arch Neurol*. 2011b;68:1295–302. PubMed PMID: 21987543.
- Klein CJ, Wu Y, Vogel P, Goebel HH, Bönnemann C, Zukosky K, Botuyan MV, Duan X, Middha S, Atkinson EJ, Mer G, Dyck PJ. Ubiquitin ligase defect by DCAF8 mutation causes HMSN2 with giant axons. *Neurology*. 2014;82:873–8. PubMed PMID: 24500646.

- Landouré G, Zdebik AA, Martinez TL, Burnett BG, Stanescu HC, Inada H, Shi Y, Taye AA, Kong L, Munns CH, Choo SS, Phelps CB, Paudel R, Houlden H, Ludlow CL, Caterina MJ, Gaudet R, Kleta R, Fischbeck KH, Sumner CJ. Mutations in TRPV4 cause Charcot-Marie-Tooth disease type 2C. *Nat Genet.* 2010;42:170–4. PubMed PMID: 20037586.
- Laššuthová P, Šafka Brožková D, Krútová M, Mazanec R, Züchner S, Gonzalez MA, Seeman P. Severe axonal Charcot-Marie-Tooth disease with proximal weakness caused by de novo mutation in the MORC2 gene. *Brain.* 2016;139:e26. PubMed PMID: 26912637.
- Latour P, Thauvin-Robinet C, Baudelet-Méry C, Soichot P, Cusin V, Faivre L, Locatelli MC, Mayençon M, Sarcey A, Broussolle E, Camu W, David A, Rousson R. A major determinant for binding and aminoacetylation of tRNA(Ala) in cytoplasmic Alanyl-tRNA synthetase is mutated in dominant axonal Charcot-Marie-Tooth disease. *Am J Hum Genet.* 2010;86:77–82. PubMed PMID: 20045102.
- Leal A, Huehne K, Bauer F, Sticht H, Berger P, Suter U, Morera B, Del Valle G, Lupski JR, Ekici A, Pasutto F, Endele S, Barrantes R, Berghoff C, Berghoff M, Neundörfer B, Heuss D, Dorn T, Young P, Santolin L, Uhlmann T, Meisterernst M, Sereda MW, Stassart RM, Zu Horste GM, Nave KA, Reis A, Rautenstrauß B. Identification of the variant Ala335Val of MED25 as responsible for CMT2B2: molecular data, functional studies of the SH3 recognition motif and correlation between wild-type MED25 and PMP22 RNA levels in CMT1A animal models. *Neurogenetics.* 2009;10:275–87. PubMed PMID: 19290556.
- Leal A, Morera B, Del Valle G, Heuss D, Kayser C, Berghoff M, Villegas R, Hernandez E, Mendez M, Hennies HC, Neundorfer B, Barrantes R, Reis A, Rautenstrauß B. A second locus for an axonal form of autosomal recessive Charcot-Marie-Tooth disease maps to chromosome 19q13.3. *Am J Hum Genet.* 2001;68:269–74. PubMed PMID: 11112660.
- Lee HS, Kim MJ, Ko DS, Jeon EJ, Kim JY, Kang IS. Preimplantation genetic diagnosis for Charcot-Marie-Tooth disease. *Clin Exp Reprod Med.* 2013;40:163–8. PubMed PMID: 24505562.
- Liu YT, Laurá M, Hersheson J, Horga A, Jaunmuktane Z, Brandner S, Pittman A, Hughes D, Polke JM, Sweeney MG, Proukakis C, Janssen JC, Auer-Grumbach M, Zuchner S, Shields KG, Reilly MM, Houlden H. Extended phenotypic spectrum of KIF5A mutations: From spastic paraparesis to axonal neuropathy. *Neurology.* 2014;83:612–9. PubMed PMID: 25008398.
- López-Bigas N, Olive M, Rabionet R, Ben-David O, Martinez-Matos JA, Bravo O, Banchs I, Volpini V, Gasparini P, Avraham KB, Ferrer I, Arbones ML, Estivill X. Connexin 31 (GJB3) is expressed in the peripheral and auditory nerves and causes neuropathy and hearing impairment. *Hum Mol Genet.* 2001;10:947–52. PubMed PMID: 11309368.
- Mademan I, Deconinck T, Dinopoulos A, Voit T, Schara U, Devriendt K, Meijers B, Lerut E, De Jonghe P, Baets J. De novo INF2 mutations expand the genetic spectrum of hereditary neuropathy with glomerulopathy. *Neurology.* 2013;81:1953–8. PubMed PMID: 24174593.
- Manganelli F, Nolano M, Pisciotta C, Provitera V, Fabrizi GM, Cavallaro T, Stancanelli A, Caporaso G, Shy ME, Santoro L. Charcot-Marie-Tooth disease: New insights from skin biopsy. *Neurology.* 2015;85:1202–8. PubMed PMID: 26362287.
- Manganelli F, Pisciotta C, Provitera V, Taioli F, Iodice R, Topa A, Fabrizi GM, Nolano M, Santoro L. Autonomic nervous system involvement in a new CMT2B family. *J Peripher Nerv Syst.* 2012;17:361–4. PubMed PMID: 22971099.
- Mathis S, Magy L, Vallat JM. Therapeutic options in Charcot-Marie-Tooth diseases. *Expert Rev Neurother.* 2015;15:355–66. PubMed PMID: 25703094.
- 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.

- McEntagart ME, Reid SL, Irrthum A, Douglas JB, Eyre KE, Donaghy MJ, Anderson NE, Rahman N. Confirmation of a hereditary motor and sensory neuropathy IIC locus at chromosome 12q23-q24. *Ann Neurol.* 2005;57:293–7. PubMed PMID: 15668982.
- McLaughlin HM, Sakaguchi R, Giblin W. NISC Comparative Sequencing Program, Wilson TE, Biesecker L, Lupski JR, Talbot K, Vance JM, Züchner S, Lee YC, Kennerson M, Hou YM, Nicholson G, Antonellis A. A recurrent loss-of-function alanyl-tRNA synthetase (AARS) mutation in patients with Charcot-Marie-Tooth disease type 2N (CMT2N). *Hum Mutat.* 2012;33:244–53. PubMed PMID: 22009580.
- Meggouh F, Bienfait HM, Weterman MA, de Visser M, Baas F. Charcot-Marie-Tooth disease due to a de novo mutation of the RAB7 gene. *Neurology.* 2006;67:1476–8. PubMed PMID: 17060578.
- Misu K, Yoshihara T, Shikama Y, Awaki E, Yamamoto M, Hattori N, Hirayama M, Takegami T, Nakashima K, Sobue G. An axonal form of Charcot-Marie-Tooth disease showing distinctive features in association with mutations in the peripheral myelin protein zero gene (Thr124Met or Asp75Val). *J Neurol Neurosurg Psychiatry.* 2000;69:806–11. PubMed PMID: 11080237.
- Motley WW, Griffin LB, Mademan I, Baets J, De Vriendt E, De Jonghe P, Antonellis A, Jordanova A, Scherer SS. A novel AARS mutation in a family with dominant myeloneuropathy. *Neurology.* 2015;84:2040–7. PubMed PMID: 25904691.
- Nelis E, Berciano J, Verpoorten N, Coen K, Dierick I, Van Gerwen V, Combarros O, De Jonghe P, Timmerman V. Autosomal dominant axonal Charcot-Marie-Tooth disease type 2 (CMT2G) maps to chromosome 12q12-q13.3. *J Med Genet.* 2004;41:193–7. PubMed PMID: 14985381.
- Nicolaou P, Cianchetti C, Minaidou A, Marrosu G, Zamba-Papanicolaou E, Middleton L, Christodoulou K. A novel LRSAM1 mutation is associated with autosomal dominant axonal Charcot-Marie-Tooth disease. *Eur J Hum Genet.* 2013;21:190–4. PubMed PMID: 22781092.
- 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.* 2009;8:654–67. PubMed PMID: 19539237.
- Pareyson D, Scaioli V, Laura M. Clinical and electrophysiological aspects of Charcot-Marie-Tooth disease. *Neuromolecular Med.* 2006;8:3–22. PubMed PMID: 16775364.
- Peeters K, Bervoets S, Chamova T, Litvinenko I, De Vriendt E, Bichev S, Kancheva D, Mitev V, Kennerson M, Timmerman V, De Jonghe P, Tournev I, MacMillan J, Jordanova A. Novel mutations in the DYNC1H1 tail domain refine the genetic and clinical spectrum of dyneinopathies. *Hum Mutat.* 2015;36:287–91. PubMed PMID: 25512093.
- Pehlivan D, Coban Akdemir Z, Karaca E, Bayram Y, Jhangiani S, Yildiz EP, Muzny D, Uluc K, Gibbs RA. Baylor-Hopkins Center for Mendelian Genomics, Elcioglu N, Lupski JR, Harel T. Exome sequencing reveals homozygous TRIM2 mutation in a patient with early onset CMT and bilateral vocal cord paralysis. *Hum Genet.* 2015;134:671–3. PubMed PMID: 25893792.
- Pitceathly RD, Murphy SM, Cottenie E, Chalasani A, Sweeney MG, Woodward C, Mudanohwo EE, Hargreaves I, Heales S, Land J, Holton JL, Houlden H, Blake J, Champion M, Flinter F, Robb SA, Page R, Rose M, Palace J, Crowe C, Longman C, Lunn MP, Rahman S, Reilly MM, Hanna MG. Genetic dysfunction of MT-ATP6 causes axonal Charcot-Marie-Tooth disease. *Neurology.* 2012;79:1145–54. PubMed PMID: 22933740.
- Puls I, Jonnakuty C, LaMonte BH, Holzbaur EL, Tokito M, Mann E, Floeter MK, Bidus K, Drayna D, Oh SJ, Brown RH, Ludlow CL, Fischbeck KH. Mutant dynactin in motor neuron disease. *Nat Genet.* 2003;33:455–6. PubMed PMID: 12627231.

- Rosser AM, Davidson GL, Blake J, Polke JM, Murphy SM, Houlden H, Innes A, Kalmar B, Greensmith L, Reilly MM. A novel p.Glu175X premature stop mutation in the C-terminal end of HSP27 is a cause of CMT2. *J Peripher Nerv Syst.* 2012;17:201–5. PubMed PMID: 22734906.
- Rosser AM, Polke JM, Houlden H, Reilly MM. Clinical implications of genetic advances in Charcot-Marie-Tooth disease. *Nat Rev Neurol.* 2013;9:562–71. PubMed PMID: 24018473.
- 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.
- Santoro L, Manganelli F, Di Maio L, Barbieri F, Carella M, D'Adamo P, Casari G. Charcot-Marie-Tooth disease type 2C: a distinct genetic entity. Clinical and molecular characterization of the first European family. *Neuromuscul Disord.* 2002;12:399–404. PubMed PMID: 12062259.
- Sawyer SL, Cheuk-Him Ng A, Innes AM, Wagner JD, Dyment DA, Tetreault M. Care4Rare Canada Consortium, Majewski J, Boycott KM, Sreaton RA, Nicholson G. Homozygous mutations in MFN2 cause multiple symmetric lipomatosis associated with neuropathy. *Hum Mol Genet.* 2015;24:5109–14. PubMed PMID: 26085578.
- Schottmann G, Jungbluth H, Schara U, Knierim E, Morales Gonzalez S, Gill E, Seifert F, Norwood F, Deshpande C, von Au K, Schuelke M, Senderek J. Recessive truncating IGHMBP2 mutations presenting as axonal sensorimotor neuropathy. *Neurology.* 2015;84:523–31. PubMed PMID: 25568292.
- Scoto M, Rosser AM, Harms MB, Cirak S, Calissano M, Robb S, Manzur AY, Martínez Arroyo A, Rodriguez Sanz A, Mansour S, Fallon P, Hadjikoumi I, Klein A, Yang M, De Visser M, Overweg-Plandsoen WC, Baas F, Taylor JP, Benatar M, Connolly AM, Al-Lozi MT, Nixon J, de Goede CG, Foley AR, Mcwilliam C, Pitt M, Sewry C, Phadke R, Hafezparast M, Chong WK, Mercuri E, Baloh RH, Reilly MM, Muntoni F. Novel mutations expand the clinical spectrum of DYNC1H1-associated spinal muscular atrophy. *Neurology.* 2015;84:668–79. PubMed PMID: 25609763.
- Sevilla T, Lupo V, Martínez-Rubio D, Sancho P, Sivera R, Chumillas MJ, García-Romero M, Pascual-Pascual SI, Muelas N, Dopazo J, Vilchez JJ, Palau F, Espinós C. Mutations in the MORC2 gene cause axonal Charcot-Marie-Tooth disease. *Brain.* 2016;139:62–72. PubMed PMID: 26497905.
- Shimizu H, Oka N, Kawarai T, Taniguchi K, Saji N, Tadano M, Bernardi G, Orlacchio A, Kita Y. Late-onset CMT2 associated with a novel missense mutation in the cytoplasmic domain of the MPZ gene. *Clin Neurol Neurosurg.* 2010;112:798–800. PubMed PMID: 20800346.
- Shy ME, Jani A, Krajewski K, Grandis M, Lewis RA, Li J, Shy RR, Balsamo J, Lilien J, Garbern JY, Kamholz J. Phenotypic clustering in MPZ mutations. *Brain.* 2004;127:371–84. PubMed PMID: 14711881.
- 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.
- Solla P, Vannelli A, Bolino A, Marrosu G, Coviello S, Murru MR, Tranquilli S, Corongiu D, Benedetti S, Marrosu MG. Heat shock protein 27 R127W mutation: evidence of a continuum between axonal Charcot-Marie-Tooth and distal hereditary motor neuropathy. *J Neurol Neurosurg Psychiatry.* 2010;81:958–62. PubMed PMID: 20660910.
- Stögbauer F, Young P, Kuhlenbaumer G, Kiefer R, Timmerman V, Ringelstein EB, Wang JF, Schroder JM, Van Broeckhoven C, Weis J. Autosomal dominant burning feet syndrome. *J Neurol Neurosurg Psychiatry.* 1999;67:78–81. PubMed PMID: 10369826.
- Strickland AV, Schabihüttl M, Offenbacher H, Synofzik M, Hauser NS, Brunner-Krainz M, Gruber-Sedlmayr U, Moore SA, Windhager R, Bender B, Harms M, Klebe S, Young P, Kennerson M, Garcia AS, Gonzalez MA, Züchner S, Schule R, Shy ME, Auer-Grumbach M. Mutation screen reveals novel variants and expands the phenotypes associated with DYNC1H1. *J Neurol.* 2015;262:2124–34. PubMed PMID: 26100331.

- Stuppia G, Rizzo F, Riboldi G, Del Bo R, Nizzardo M, Simone C, Comi GP, Bresolin N, Corti S. MFN2-related neuropathies: Clinical features, molecular pathogenesis and therapeutic perspectives. *J Neurol Sci.* 2015;356:7–18. PubMed PMID: 26143526.
- Sulica L, Blitzer A, Lovelace RE, Kaufmann P. Vocal fold paresis of Charcot-Marie-Tooth disease. *Ann Otol Rhinol Laryngol.* 2001;110:1072–6. PubMed PMID: 11713921.
- Sumner CJ, d'Ydewalle C, Wooley J, Fawcett KA, Hernandez D, Gardiner AR, Kalmar B, Baloh RH, Gonzalez M, Züchner S, Stanescu HC, Kleta R, Mankodi A, Cornblath DR, Boylan KB, Reilly MM, Greensmith L, Singleton AB, Harms MB, Rossor AM, Houlden H. A dominant mutation in FBXO38 causes distal spinal muscular atrophy with calf predominance. *Am J Hum Genet.* 2013;93:976–83. PubMed PMID: 24207122.
- Tang BS, Luo W, Xia K, Xiao JF, Jiang H, Shen L, Tang JG, Zhao GH, Cai F, Pan Q, Dai HP, Yang QD, Xia JH, Evgrafov OV. A new locus for autosomal dominant Charcot-Marie-Tooth disease type 2 (CMT2L) maps to chromosome 12q24. *Hum Genet.* 2004;114:527–33. PubMed PMID: 15021985.
- Tang BS, Zhao GH, Luo W, Xia K, Cai F, Pan Q, Zhang RX, Zhang FF, Liu XM, Chen B, Zhang C, Shen L, Jiang H, Long ZG, Dai HP. Small heat-shock protein 22 mutated in autosomal dominant Charcot-Marie-Tooth disease type 2L. *Hum Genet.* 2005;116:222–4. PubMed PMID: 15565283.
- Tazir M, Azzedine H, Assami S, Sindou P, Nouioua S, Zemmouri R, Hamadouche T, Chaouch M, Feingold J, Vallat JM, Leguern E, Grid D. Phenotypic variability in autosomal recessive axonal Charcot-Marie-Tooth disease due to the R298C mutation in lamin A/C. *Brain.* 2004;127:154–63. PubMed PMID: 14607793.
- Tétreault M, Gonzalez M, Dicaire MJ, Allard P, Gehring K, Leblanc D, Leclerc N, Schondorf R, Mathieu J, Zuchner S, Brais B. Adult-onset painful axonal polyneuropathy caused by a dominant NAGLU mutation. *Brain.* 2015;138:1477–83. PubMed PMID: 25818867.
- Thomas FP, Guergueltcheva V, Gondim FA, Tournev I, Rao CV, Ishpekova B, Kinsella LJ, Pan Y, Geller TJ, Litvinenko I, De Jonghe P, Scherer SS, Jordanova A. Clinical, neurophysiological and morphological study of dominant intermediate Charcot-Marie-Tooth type C neuropathy. *J Neurol.* 2016;263:467–76. PubMed PMID: 26725087.
- Tufano M, Cappuccio G, Terrone G, Manganelli F, Pisciotta C, Geroldi A, Capponi S, Del Giudice E. Early onset Charcot-Marie-Tooth neuropathy type 2A and severe developmental delay: expanding the clinical phenotype of MFN2-related neuropathy. *J Peripher Nerv Syst.* 2015;20:415–8. PubMed PMID: 26307494.
- Verhoeven K, Claeys KG, Züchner S, Schroder JM, Weis J, Ceuterick C, Jordanova A, Nelis E, De Vriendt E, Van Hul M, Seeman P, Mazanec R, Saifi GM, Szigeti K, Mancias P, Butler IJ, Kochanski A, Ryniewicz B, De Bleecker J, Van den Bergh P, Verellen C, Van Coster R, Goemans N, Auer-Grumbach M, Robberecht W, Milic Rasic V, Nevo Y, Tournev I, Guergueltcheva V, Roelens F, Vieregge P, Vinci P, Moreno MT, Christen HJ, Shy ME, Lupski JR, Vance JM, De Jonghe P, Timmerman V. MFN2 mutation distribution and genotype/phenotype correlation in Charcot-Marie-Tooth type 2. *Brain.* 2006;129:2093–102. PubMed PMID: 16714318.
- Verhoeven K, De Jonghe P, Coen K, Verpoorten N, Auer-Grumbach M, Kwon JM, FitzPatrick D, Schmedding E, De Vriendt E, Jacobs A, Van Gerwen V, Wagner K, Hartung HP, Timmerman V. Mutations in the small GTPase late endosomal protein RAB7 cause Charcot-Marie-Tooth type 2B neuropathy. *Am J Hum Genet.* 2003;72:722–7. PubMed PMID: 12545426.
- Weedon MN, Hastings R, Caswell R, Xie W, Paszkiewicz K, Antoniadi T, Williams M, King C, Greenhalgh L, Newbury-Ecob R, Ellard S. Exome sequencing identifies a DYNC1H1 mutation in a large pedigree with dominant axonal Charcot-Marie-Tooth disease. *Am J Hum Genet.* 2011;89:308–12. PubMed PMID: 21820100.
- Weterman MA, Sorrentino V, Kasher PR, Jakobs ME, van Engelen BG, Fluiter K, de Wissel MB, Sizarov A, Nürnberg G, Nürnberg P, Zelcer N, Schelhaas HJ, Baas F. A frameshift mutation in LRSAM1 is responsible for a dominant hereditary polyneuropathy. *Hum Mol Genet.* 2012;21:358–70. PubMed PMID: 22012984.

- Whittaker RG, Herrmann DN, Bansagi B, Hasan BA, Lofra RM, Logigian EL, Sowden JE, Almodovar JL, Littleton JT, Zuchner S, Horvath R, Lochmüller H. Electrophysiologic features of SYT2 mutations causing a treatable neuromuscular syndrome. *Neurology*. 2015;85:1964–71. PubMed PMID: 26519543.
- Xie Y, Li X, Liu L, Hu Z, Huang S, Zhan Y, Zi X, Xia K, Tang B, Zhang R. MFN2-related genetic and clinical features in a cohort of Chinese CMT2 patients. *J Peripher Nerv Syst*. 2016;21:38–44. PubMed PMID: 26801520.
- Xu WY, Gu MM, Sun LH, Guo WT, Zhu HB, Ma JF, Yuan WT, Kuang Y, Ji BJ, Wu XL, Chen Y, Zhang HX, Sun FT, Huang W, Huang L, Chen SD, Wang ZG. A nonsense mutation in DHTKD1 causes Charcot-Marie-Tooth disease type 2 in a large Chinese pedigree. *Am J Hum Genet*. 2012;91:1088–94. PubMed PMID: 23141294.
- Ylikallio E, Pöyhönen R, Zimon M, De Vriendt E, Hilander T, Paetau A, Jordanova A, Lönnqvist T, Tyynismaa H. Deficiency of the E3 ubiquitin ligase TRIM2 in early-onset axonal neuropathy. *Hum Mol Genet*. 2013;2013;22:2975–83. PubMed PMID: 23562820.
- Young P, Grote K, Kuhlenbaumer G, Debus O, Kurlemann H, Halfter H, Funke H, Ringelstein EB, Stogbauer F. Mutation analysis in Chariot-Marie Tooth disease type 1: point mutations in the MPZ gene and the GJB1 gene cause comparable phenotypic heterogeneity. *J Neurol*. 2001;248:410–5. PubMed PMID: 11437164.
- Zimoń M, Baets J, Fabrizi GM, Jaakkola E, Kabzińska D, Pilch J, Schindler AB, Cornblath DR, Fischbeck KH, Auer-Grumbach M, Guelly C, Huber N, De Vriendt E, Timmerman V, Suter U, Hausmanowa-Petrusewicz I, Niemann A, Kochański A, De Jonghe P, Jordanova A. Dominant GDAP1 mutations cause predominantly mild CMT phenotypes. *Neurology*. 2011;77:540–8. PubMed PMID: 21753178.
- Zhu D, Kennerson ML, Walizada G, Züchner S, Vance JM, Nicholson GA. Charcot-Marie-Tooth with pyramidal signs is genetically heterogeneous: families with and without MFN2 mutations. *Neurology*. 2005;65:496–7. PubMed PMID: 16087932.
- Züchner S, De Jonghe P, Jordanova A, Claeys KG, Guergueltcheva V, Cherninkova S, Hamilton SR, Van Stavern G, Krajewski KM, Stajich J, Tournev I, Verhoeven K, Langerhorst CT, de Visser M, Baas F, Bird T, Timmerman V, Shy M, Vance JM. Axonal neuropathy with optic atrophy is caused by mutations in mitofusin 2. *Ann Neurol*. 2006;59:276–81. PubMed PMID: 16437557.
- Züchner S, Mersiyanova IV, Muglia M, Bissar-Tadmouri N, Rochelle J, Dadali EL, Zappia M, Nelis E, Patitucci A, Senderek J, Parman Y, Evgrafov O, Jonghe PD, Takahashi Y, Tsuji S, Pericak-Vance MA, Quattrone A, Battaloglu E, Polyakov AV, Timmerman V, Schroder JM, Vance JM. Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. *Nat Genet*. 2004a;36:449–51. PubMed PMID: 15064763.
- Züchner S, Vance JM. Mechanisms of disease: a molecular genetic update on hereditary axonal neuropathies. *Nat Clin Pract Neurol*. 2006a;2:45–53. PubMed PMID: 16932520.
- Züchner S, Vance JM. Molecular genetics of autosomal-dominant axonal Charcot-Marie-Tooth disease. *Neuromolecular Med*. 2006b;8:63–74. PubMed PMID: 16775367.
- Züchner S, Vorgerd M, Sindern E, Schroder JM. The novel neurofilament light (NEFL) mutation Glu397Lys is associated with a clinically and morphologically heterogeneous type of Charcot-Marie-Tooth neuropathy. *Neuromuscul Disord*. 2004b;14:147–57. PubMed PMID: 14733962.

Chapter Notes

Revision History

- 5 July 2018 (ma) Chapter retired: covered in [Charcot-Marie-Tooth Hereditary Neuropathy Overview](#)
- 14 April 2016 (tb) Revision: MME and related reference added

- 24 March 2016 (bp) Comprehensive update posted live
- 30 April 2015 (tb) Revision: heterozygous mutation of *IGHMBP2* as causative of CMT2S, of *DNAJB2* as causative of CMT2T, and of *MARS* as causative of CMT2U
- 12 March 2015 (tb) Revision: discussion of CMT nomenclature; additions to Differential Diagnosis; references added [Cottenie et al 2014, Gess et al 2014, Gonzalez et al 2014, Mathis et al 2015, Schottmann et al 2015, Scoto et al 2015]
- 2 October 2014 (tb) Revision: edits to Differential Diagnosis
- 31 July 2014 (tb) Revision: addition of *KIF5A* to Differential Diagnosis [Crimella et al 2012, Liu et al 2014]
- 3 April 2014 (tb) Revision: addition of *DCAF8* to Differential Diagnosis [Klein et al 2014]
- 20 February 2014 (tb) Revision: Lee et al 2013 added to Preimplantation genetic diagnosis
- 30 January 2014 (tb) Revision: Sumner et al [2013]; edits to Testing Strategy
- 14 November 2013 (tb) Revision: figure added to Prevalence and Molecular Genetics [Rossor et al 2013]
- 11 July 2013 (tb) Revision: additions to Prevalence and Differential Diagnosis
- 3 January 2013 (cd) Revision: sequence analysis of select exons of *LRSAM1* available clinically
- 13 December 2012 (tb) Revision: mutations in *DHTKD1* identified as causative of a form of CMT2 [Xu et al 2012]
- 13 September 2012 (tb) Revision: addition of Ishiura et al [2012], Pitceathly et al [2012], Nicolaou et al [2013]
- 30 August 2012 (cd) Revision: sequence analysis for *MED25* and *DYNC1H1* available clinically
- 5 July 2012 (me) Comprehensive update posted live
- 9 February 2012 (tb) Revision: mutations in *DYNC1H1* reported to be associated with CMT2O; mutation in *LRSAM1* associated with CMT2P
- 22 December 2011 (tb) Revision: mutations in *AARS* cause CMT2N.
- 15 September 2011 (tb) Revision: Differential Diagnosis — intermediate form of CMT
- 18 August 2011 (cd) Revision: targeted mutation analysis for p.Ala335Val in *MED25* associated with CMT2B2
- 1 March 2011 (cd) Revision: edits to Testing Strategy
- 27 January 2011 (cd) Revision: testing available clinically for CMT2C
- 27 May 2010 (cd) Revision: edits to Agents/Circumstances to Avoid
- 11 March 2010 (me) Comprehensive update posted live
- 7 January 2008 (cd) Revision: prenatal diagnosis for CMT2D available
- 16 August 2007 (me) Comprehensive update posted live
- 30 January 2007 (tb) Revision: sequence analysis clinically available on a limited basis for CMT2D
- 30 December 2005 (cd) Revision: testing and prenatal diagnosis for CMT2B clinically available; prenatal diagnosis for CMT2A clinically available
- 21 December 2005 (tb) Revision: Differential Diagnosis — HMSN-V
- 14 June 2005 (tb) Revision: CMT2K added
- 4 May 2005 (me) Comprehensive update posted live
- 6 December 2004 (tb) Revision: testing
- 9 September 2004 (tb,cd) Revision: *MFN2* added; sequence analysis clinically available
- 9 August 2004 (tb,cd) Revision: CMT2B1
- 21 June 2004 (tb) Revision: CMT2F
- 10 May 2004 (tb) Author revisions
- 1 April 2004 (tb) Revision: prenatal diagnosis available for CMT2E
- 7 April 2003 (me) Comprehensive update posted live
- 12 September 2001 (tb) Author revisions
- 24 July 2001 (tb) Author revisions
- 27 June 2001 (tb) Author revisions
- 19 June 2001 (tb) Revision: CMT2A gene found

- 23 March 2001 (tb) Author revisions
- 16 January 2001 (tb) Author revisions
- 25 August 2000 (me) Comprehensive update posted live
- 15 June 2000 (tb) Author revisions
- 15 May 2000 (tb) Author revisions
- 3 February 2000 (tb) Author revisions
- 12 October 1998 (tb) Author revisions
- 24 September 1998 (pb) Review posted live
- April 1996 (tb) Original submission

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the [GeneReviews® Copyright Notice and Usage Disclaimer](#). No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the [GeneReviews® Copyright Notice and Usage Disclaimer](#).

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.