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Charcot-Marie-Tooth Neuropathy Type 1 – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonyms: CMT1, HMSN1, Hereditary Motor and Sensory Neuropathy 1

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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 THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.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 neuropathy type 1 (CMT1) is a demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity. It is usually slowly progressive and often associated with pes cavus foot deformity and bilateral foot drop. Affected individuals usually become symptomatic between age five and 25 years. Fewer than 5% of individuals become wheelchair dependent. Life span is not shortened.

Diagnosis/testing

CMT1A (70%-80% of all CMT1) involves duplication of *PMP22*. CMT1B (6%-10% of all CMT1) is associated with single-nucleotide variants in *MPZ*. CMT1C (1%-2% of all CMT1) is associated with pathogenic variants in *LITAF*, and CMT1D (<2% of all CMT1) is associated with pathogenic variants in *EGR2*. CMT1E (<5% of all CMT1) is associated with single-nucleotide variants in *PMP22*. CMT2E/1F (<5% of all CMT1) is associated with pathogenic variants in *NEFL*.

Management

Treatment of manifestations: Treatment by a multidisciplinary team including a neurologist, physiatrist, orthopedic surgeon, physical and occupational therapists; special shoes and/or ankle/foot orthoses 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.

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

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Surveillance: Regular foot examination for pressure sores.

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

Pregnancy management: Affected pregnant women may experience worsening symptoms during or after gestation; a higher occurrence of presentation anomalies, use of forceps, and operative delivery; and/or an increased incidence of post-partum bleeding.

Genetic counseling

CMT1 is inherited in an autosomal dominant manner. About two thirds of probands with CMT1A have inherited the *PMP22* duplication; about one third have CMT1A as the result of a *de novo* pathogenic variant. Similar data are not available for the other subtypes of CMT1. The offspring of an individual with any of the subtypes of CMT1 have a 50% chance of inheriting the altered gene. Prenatal testing is possible if the pathogenic variant has been identified in the family. Requests for prenatal testing for typically adult-onset diseases that do not affect intellect or life span are uncommon.

GeneReview Scope

Charcot-Marie-Tooth Neuropathy Type 1: Included Disorders
• CMT1A • CMT1B • CMT1C • CMT1D • CMT1E • CMT2E/1F

For synonyms and outdated names see Nomenclature.

Diagnosis

Clinical Diagnosis

Charcot-Marie-Tooth neuropathy type (CMT1) is diagnosed in individuals with the following:

- A progressive peripheral motor and sensory neuropathy
- Slow nerve conduction velocity (NCV). NCVs are typically 10-30 meters per second, with a range of 5-38 m/s (normal: >40-45 m/s).
- Palpably enlarged nerves, especially the ulnar nerve at the olecranon groove and the greater auricular nerve running along the lateral aspect of the neck
- A family history consistent with autosomal dominant inheritance

Molecular Genetic Testing

Genes. The CMT1 subtypes and the genes associated with them are summarized in Table 1. The complicated genetic diversity of hereditary neuropathies with emphasis on CMT syndrome has been addressed by Baets et al [2014], Pareyson et al [2014] and Bird [Charcot-Marie-Tooth Hereditary Neuropathy Overview.] Many genetic testing strategies have been proposed including that of Saporta et al [2011a].

Clinical testing

Table 1. Summary of Molecular Genetic Testing Used in Charcot-Marie-Tooth Neuropathy Type 1 (CMT1)

CMT1 Subtype	Gene [1]	Proportion of CMT1 Attributed to Pathogenic Variants in This Gene	Test Method
CMT1A	*PMP22*	70%-80%	Targeted analysis for pathogenic variants [2]
CMT1B	*MPZ* [3]	5%-10%	Sequence analysis [4]
			Deletion/duplication analysis [5]
CMT1C	*LITAF* [3] (previously known as *SIMPLE*)	1%-2%	Sequence analysis [4]
			Deletion/duplication analysis [5]
CMT1D	*EGR2* [3]	<2%	Sequence analysis [4]
			Deletion/duplication analysis [5]
CMT1E	*PMP22* [3]	<5%	Sequence analysis [4]
			Deletion/duplication analysis [5]
CMT2E/1F	*NEFL* [3]	<5%	Sequence analysis [4]
			Deletion/duplication analysis [5]
	Unknown [6]	NA	NA

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants detected in this gene.
2. Detects a1.5-Mb duplication at 17p11.2 that includes *PMP22* resulting in the presence of three copies of *PMP22* in all individuals with CMT1A. The test method is a deletion/duplication analysis targeted specifically at the *PMP22* duplication; a variety of test methods can be used (see footnote 5) in addition to FISH.
3. Each of these subtypes is identified based on detection of a pathogenic variant in the associated gene; hence, the variant detection rate is 100%.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
6. Høyer et al [2011]

Testing Strategy

To confirm/establish the diagnosis in a proband with slow nerve conduction velocities, one genetic testing strategy is serial single gene molecular genetic testing based on the order in which pathogenic variants most commonly occur.

1. Because CMT1A (caused by the 1.5-Mb duplication at 17p11.2 including *PMP22*) is by far the most common type of CMT1, it is appropriate to test a proband with very slow nerve conduction velocities for this duplication first [Klein & Dyck 2005].
2. If no *PMP22* duplication is identified, the next step is molecular genetic testing of *MPZ* and *GJB1* (a cause of X-linked CMT). Note: If the family history shows male to male transmission, testing of *GJB1,* mutation of which causes Charcot-Marie-Tooth Neuropathy X Type 1, is not appropriate.
3. If no *PMP22* duplication, *MPZ* pathogenic variant, or *GJB1* pathogenic variant is identified, consider sequence analysis of *LITAF, EGR2*, *PMP22* (single nucleotide variants) and *NEFL* [Saporta et al 2011a].

Note: This testing strategy is different from that for axonal neuropathies and autosomal recessive neuropathies.

An alternative genetic testing strategy is use of a multigene panel that includes *PMP22*, *MPZ*, *GJB1*, and other genes of interest (see Table 1 and Differential Diagnosis). Note: The genes included and the methods used in multigene panels vary by laboratory and over time. Success of this approach is demonstrated by Klein et al [2014], who were able to identify the genetic cause of CMT in five of 15 kindreds (using exome sequencing) who had escaped earlier detection by single-gene analysis. For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Clinical Characteristics

Clinical Description

Classic CMT1 Phenotype

Individuals with CMT1 usually become symptomatic between age five and 25 years [Marques et al 2005, Houlden & Reilly 2006, van Paassen et al 2014]; age of onset ranges from infancy (resulting in delayed walking) to the fourth and subsequent decades. Clinical severity is variable, ranging from extremely mild disease that goes unrecognized by the affected individual and physician to considerable weakness and disability.

The typical presenting symptom of CMT1 is weakness of the feet and ankles [Ferrarin et al 2012]. The initial physical findings are depressed or absent tendon reflexes with weakness of foot dorsiflexion at the ankle. The typical affected adult has bilateral foot drop, symmetric atrophy of muscles below the knee (stork leg appearance), atrophy of intrinsic hand muscles, and absent tendon reflexes in both upper and lower extremities.

Onset in the first year of life often suggests an autosomal recessive cause of CMT but autosomal dominant types of CMT caused by duplication of *PMP22* (CMT1A) and pathogenic missense variants in *PMP22* (CMT1E), *MPZ* (CMT1B), and *NEFL* have been reported in this age group [Baets et al 2011].

Proximal muscles usually remain strong.

Mild to moderate sensory deficits of position, vibration, and pain/temperature commonly occur in the feet, but many affected individuals are unaware of this finding. Pain, especially in the feet, is reported by 20%-30% of individuals [Carter et al 1998, Gemignani et al 2004, Carvalho et al 2005]. The pain is often musculoskeletal in origin but may be neuropathic in some cases [Pazzaglia et al 2010].

Poretti et al [2013] have shown that the vestibular impairment may contribute to the poor balance often present in CMT1.

In a study of 61 subjects with CMT1, Boentert et al [2014] found that 37% had obstructive sleep apnea and 40% had restless leg syndrome. If these findings are confirmed they would represent an important newly recognized aspect of the CMT1 phenotype.

Episodic pressure palsies have been reported [Kleopa et al 2004].

In CMT1A, prolonged distal motor latencies may already be present in the first months of life, and slow motor nerve conduction velocities (NCVs) have been found in some individuals by age two years [Krajewski et al 2000]. However, the full clinical picture may not occur until the second decade of life or later [García et al 1998]. In a study of 57 individuals with CMT1A, three had floppy infant syndrome, two had marked proximal and distal weakness (one requiring a wheelchair), one had severe scoliosis, five had calf muscle hypertrophy, and three had hand deformity [Marques et al 2005].

Some individuals with CMT1B have onset in the first decade of life; others have a much later onset. The age of onset trend tends to run true in families [Hattori et al 2003].

CMT1 is slowly progressive over many years. Affected individuals experience long plateau periods without obvious deterioration [Teunissen et al 2003]. NCVs slow progressively over the first two to six years of life and are relatively stable throughout adulthood. Early onset of symptoms and severity of disease show some correlation with slower NCVs, but this is only a general trend. Muscle weakness correlates with progressive decrease in the compound muscle action potential (CMAP) and suggests that developing axonal pathology is of considerable clinical relevance [Hattori et al 2003, Pareyson et al 2006].

In a study of persons with CMT1A over a five-year period, Verhamme et al [2009a] found increasing disability at least partially related to "a process of normal aging." In a study of a large family with CMT1A over two decades, Berciano et al [2010] found that deterioration varied from mild to marked. It remains unclear why such a wide range of severity is observed in persons with CMT1A with the same pathogenic variant (*PMP22* dup).

In CMT1A, Kim et al [2012] found that severity of weakness and sensory loss correlated with CMAPs and SNAPs (sensory nerve action potential), but not with conduction velocities.

The disease does not decrease life span.

Other findings in individuals with CMT1. A few men with CMT1 have reported impotence [Bird et al 1994].

Pes cavus foot deformity is common (>50%) and hip dysplasia may be under-recognized [Walker et al 1994, McGann & Gurd 2002].

Pulmonary insufficiency and sleep apnea are sometimes seen [Dematteis et al 2001].

Deafness has been occasionally reported in the CMT1 phenotype. Impaired auditory perception and processing has been reported as common (>60%) both in children with CMT1 and in those with CMT2 [Rance et al 2012]. Hearing loss has been associated with single-nucleotide variants in *PMP22* (CMT1E) [Kovach et al 1999, Sambuughin et al 2003, Postelmans & Stokroos 2006] and *MPZ* (CMT1B) [Starr et al 2003, Seeman et al 2004].

Vestibular abnormalities have been reported both in persons with CMT1A and in those with CMTX [Poretti et al 2013].

Lower-limb muscle atrophy and fatty infiltration can be demonstrated by MRI and followed longitudinally [Gallardo et al 2006].

Chanson et al [2013] reported MRI findings of decreased white matter volume in both CMT1A and hereditary neuropathy with liability to pressure palsies (HNPP). This was confirmed in one pathologic examination of a brain from a subject with CMT1A.

Colomban et al [2014] reported earlier onset of symptoms (8.6 vs 14 years) and higher deterioration of quality of life in affected women compared to affected men.

People with CMT1A can have symptoms that mimic those of HNPP [Mathis et al 2014].

Quality of life from the affected individual's perspective has been studied by Johnson et al [2014]. Foot and ankle weakness, impaired balance, pain, and fatigue were viewed as important disabling symptoms and tended to be more prevalent in affected women. Ramdharry et al [2012b] also reported a high prevalence of fatigue as a symptom in persons with CMT.

Pregnancy. See Pregnancy Management.

CMT1 Subtypes

The CMT1 subtypes, identified solely by molecular findings, are often clinically indistinguishable.

CMT1A. NCVs vary. Mean median motor NCVs were 21±5.7 m/s in one study [Hattori et al 2003] and 16.5 m/s (range: 5-26.5 m/s) in another [Carvalho et al 2005]. In a third study, the range was 12.6-35 m/s [Marques et al 2005]. CMAP is decreased [Hattori et al 2003].

CMT1B. The NCV shows a bimodal curve, with some families having slow median motor NCV (mean: 16.5 m/s) and others having normal or near-normal NCV (mean: 44.3 m/s). The individuals in this latter "normal" NCV group tend to have lower CMAP, later age of onset, and more frequent hearing loss and pupillary abnormalities. These findings suggest the existence of two types of CMT1B: primarily demyelinating and primarily axonal. The two types probably reflect functional differences (early onset gain of function versus late onset loss of function of the MPZ protein) caused by different pathogenic variants in *MPZ* (see Genotype-Phenotype Correlations) [Hattori et al 2003, Shy et al 2004, Grandis et al 2008].

CMT1C. This subtype appears to be clinically identical to CMT1A [Bennett et al 2004, Saifi et al 2005, Latour et al 2006]. NCVs range from 7.5 to 27 m/s with occasional temporal dispersion [Bennett et al 2004] and conduction block with variable age of onset including early childhood [Gerding et al 2009]. Using ultrasound, Luigetti et al [2015] found enlarged peripheral nerves in individuals with CMT1C.

CMT1D. A few families with CMT1D have been identified [Warner et al 1998, Nelis et al 1999b, Numakura et al 2003, Shiga et al 2012].

CMT1E. An amino acid substitution in *PMP22* in exon 3 (p.Ala67Pro) is associated with deafness in a family with CMT1 previously reported by Kousseff et al [1982], Kovach et al [1999], Kovach et al [2002].

The amino acid substitution p.Trp28Arg was associated with profound deafness in one family [Boerkoel et al 2002].

The amino acid substitution p.Ser22Phe in *PMP22* is associated with pressure palsies as well as the CMT1 phenotype in a Cypriot family [Kleopa et al 2004].

In addition to the above, the following findings in affected families demonstrate further heterogeneity in the CMT1 phenotype:

- Pyramidal tract features
- Optic atrophy [Chalmers et al 1996, Dillmann et al 1997]
- Asymptomatic phrenic nerve involvement [Sagliocco et al 2003]
- Other distinctive signs such as keratitis, skeletal dysplasia, or tonic pupils

Neuropathology

CMT1A. Microscopically, the enlarged nerves show hypertrophy and onion bulb formation thought to result from repeated demyelination and remyelination of Schwann cell wrappings around individual axons [Carvalho et al 2005, Schröder 2006].

CMT1B. Individuals with slow NCVs tend to have demyelinating features on nerve biopsy, whereas those with normal NCVs have more axonal pathology with axonal sprouting [Hattori et al 2003]. Onion bulb formation has been seen [Bai et al 2006]. Excessive myelin folding and thickness were reported in a family with a c.336delA null variant in *MPZ* [De Angelis et al 2004].

Genotype-Phenotype Correlations

CMT1A. A relative gene dosage effect exists regarding genotype-phenotype correlation:

- One normal allele (as in HNPP with the 17p11.2 deletion) results in a mild phenotype.
- Two normal alleles represent the normal wild-type condition.

- Three normal alleles (as in the common CMT1A 17p11.2 heterozygous duplication) cause a more severe phenotype.
- Four normal alleles (as in homozygosity for the 17p11.2 duplication) result in the most severe phenotype.
- Taioli et al [2011] described a variety of microdeletions in *PMP22* associated with CMT1 or HNPP.
- Saporta et al [2011b] reported a child having a homozygous deletion of the entire *PMP22* gene associated with sensory neuropathy and facial weakness.
- Deletions or duplications of this same chromosomal region (17p11.2) can result in multiple congenital anomaly syndromes of Smith-Magenis or Potocki-Lupski (OMIM 610883) [Potocki et al 2007], respectively.

Severe neuropathy has been reported in persons with CMT1A and a second neuropathy-causing disease such as CMT1C [Meggouh et al 2005], CMTX1, myotonic dystrophy type 1 (DM1) or adrenomyeloneuropathy (see X-Linked Adrenoleukodystrophy) [Hodapp et al 2006].

CMT1B

- *MPZ* pathogenic variants with normal or near-normal NCVs include: p.Ser44Phe, p.Ser59Thr, p.Asp75Val, p.His81Arg, p.Tyr82His, p.Thr124Met, p.Lys130Arg, and p.Gly167Arg [Marrosu et al 1998, De Jonghe et al 1999, Young et al 2001, Hattori et al 2003, Bienfait et al 2006a, Finsterer et al 2006].
- The p.Thr124Met pathogenic variant in *MPZ* has been associated with late-onset sensorineural hearing loss, pupillary abnormalities, and motor NCVs ranging from slow (24-35 m/s) to normal (48-59 m/s) [Chapon et al 1999].
- Pupillary abnormalities have been reported in individuals with two *MPZ* pathogenic variants in *cis* configuration (p.[His81Tyr;Val113Phe]) [Bienfait et al 2002].
- Young et al [2013] reported sibs with CMT and pupillary abnormalities who were heterozygous for both CMT1A and CMT1B.
- Mild late onset (>40 years) neuropathy was associated with four pathogenic variants (p.Ser55Ile, p.Asn116Ser, p.Pro217Ser, c.645+1G>T) by Kleffner et al [2010].
- The p.Gly163Arg pathogenic variant in *MPZ* has been associated with a mild neuropathy and carpal tunnel syndrome [Street et al 2002].
- Severe Dejerine-Sottas syndrome phenotype is associated with the p.Ile30Thr and p.Met197TyrTer38 pathogenic variants [Floroskufi et al 2007, Zschüntzsch et al 2009].
- p.Asp104ThrfsTer14 is associated with a mild neuropathy in the heterozygous state and a severe neuropathy in the homozygous state [Steck et al 2006]. A similar phenomenon has been reported with p.Asp224Tyr [Fabrizi et al 2006].
- Høyer et al [2011] reported a Norwegian family with an autosomal dominant, early-onset (first decade), severe, demyelinating CMT syndrome associated with duplication of the entire *MPZ* gene.
- Maeda et al [2012] reported a family with CMT1 and increased gene dosage of *MPZ* estimated at five copies by chromosomal microarray; a similar family was also reported by Speevak & Farrell [2013].
- Yonekawa et al [2013] reported a boy age two years with severe congenital hypomyelinating neuropathy and a p.Asp61Asn pathogenic variant in *MPZ*.
- Brozková et al [2010] discuss the care which must be taken in sorting out the pathogenicity of ten different DNA variants in *MPZ*.

CMT1C

- The p.Gly112Ser pathogenic variant in *LITAF* has occurred in several different families [Bueno et al 2011].
- The p.Pro135Arg and p.Ala129Thr pathogenic variants have occurred in two unrelated Italian families [Ciotti et al 2014, Luigetti et al 2014].

CMT1D

- The p.Arg381His pathogenic variant in *EGR2* is associated with CMT1 with sensorineural hearing loss, third cranial nerve palsy, and vocal cord palsy [Pareyson et al 2000].
- The p.Asp383Tyr pathogenic variant is associated with a severe phenotype previously referred to as Dejerine-Sottas syndrome [Numakura et al 2003].
- More severe neuropathy was seen in a girl with a p.Arg359Trp pathogenic variant in *EGR2* and a p.Val136Ala pathogenic variant in *GJB1* (NM_000166.5), the gene associated with CMTX1 [Chung et al 2005].
- Szigeti et al [2007] have contrasted the findings of persons with autosomal dominant and recessive pathogenic variants in *EGR2*, noting cranial nerve involvement and respiratory compromise and a wide range of disability in one person with a dominant pathogenic variant (p.Arg359Trp). Scoliosis has also been noted in individuals with the p.Arg359Gln pathogenic variant [Mikesová et al 2005].
- A novel dominant *EGR2* pathogenic variant (p.Thr387Asn) has been associated with a mild demyelinating CMT1D phenotype [Shiga et al 2012].

CMT1E

- Individuals with *PMP22* single-nucleotide variants tend to have more severe clinical disability than persons with a single 17p11.2 duplication, presumably because of a dominant-negative or loss of protein-function effect [Fabrizi et al 2001b].
- Deafness [Postelmans & Stokroos 2006], pressure palsies [Kleopa et al 2004] or vestibular loss [Jen et al 2005] may also occur.
- de Vries et al [2011] have reviewed 13 patients from seven families with the p.Arg95GlnfsTer128 pathogenic variant. Findings included cranial nerve involvement and often pressure palsies similar to HNPP.
- The pathogenicity of p.Thr118Met has been debated, but Shy et al [2006] present evidence that it causes a mild neuropathy.
- Abe et al [2010] reported a child with severe CMT and compound heterozygosity for complete deletion of *PMP22* on one allele and deletion of *PMP22* exon 5 on the other allele.
- Taioli et al [2012] have reported two sibs with early onset demyelinating CMT both heterozygous for a p.Trp39Cys pathogenic variant in PMP22 and their mother was mosaic (20% in blood) for the same variant and had mild signs of neuropathy.

CMT1F. Two different pathogenic variants in codon 22 of *NEFL* (p.Pro22Thr and p.Pro22Arg) have been reported with demyelinating autosomal dominant CMT1F [Shin et al 2008]. The p.Pro22Ser pathogenic variant in *NEFL* is associated with autosomal recessive CMT2E.

Penetrance

Penetrance of CMT1 is usually nearly 100%, but the wide range in age of onset and severity may result in under-recognition of individuals with mild or late-onset disease.

Nomenclature

CMT1A/CMT1E. CMT1A refers to CMT1 caused by duplication of *PMP22*; CMT1E refers to CMT1 caused by single-nucleotide variants in *PMP22*.

CMT2E/1F. Some individuals with pathogenic variants in *NEFL*, which typically cause CMT2E, may have slow NCVs, resulting in a diagnosis of CMT1F. To accommodate these two phenotypes associated with mutation of *NEFL*, the designation CMT2E/1F has been used.

Dejerine-Sottas syndrome (DSS). The severe phenotype associated with onset in early childhood has in the past been called Dejerine-Sottas syndrome (DSS). However, DSS is a confusing term because it no longer refers to a

specific phenotype caused by pathogenic variants in a specific gene. Pathogenic variants in at least three genes (*PMP22, MPZ*, and *EGR2*) have been associated with a severe early-onset phenotype:

- Heterozygosity for *de novo* autosomal dominant single-nucleotide variants in both *PMP22* and *MPZ* and homozygosity for *PMP22* pathogenic variants have been found in individuals with severe childhood-onset disease.
- Thirteen heterozygous missense variants in *PMP22* are associated with this phenotype.
- Three missense variants at codon 72 of *PMP22* are associated with this phenotype, suggesting that codon 72 pathogenic variants lead to a severe phenotype [Nelis et al 1999a].
- Pathogenic variants in *EGR2* may also cause the severe early-onset phenotype [Boerkoel et al 2002].
- Autosomal recessive forms of CMT may cause the DSS phenotype.
- Persons with pathogenic variants in two different neuropathy-causing genes may have a DSS phenotype [Hodapp et al 2006].

Prevalence

The overall prevalence of hereditary neuropathies is estimated at approximately 30:100,000 population. The prevalence of CMT1 is 15:100,000-20:100,000. The prevalence of CMT1A is approximately 10:100,000. These numbers hold true in a great variety of regions including China [Song et al 2006, Szigeti et al 2006].

CMT1A represents about 70% of CMT1 [Reilly & Shy 2009] and CMT1B represents about 6%-10% of CMT1 [Mandich et al 2009].

In a large study of German individuals with a CMT1 phenotype (776), Gess et al [2013] found the following percentages: CMT1A (51%), CMTX1 (9%), and CMT1B (5%). Among those with a CMT1 phenotype, 66% had a genetic diagnosis.

Figure 1 shows the frequency of various genetic causes of CMT [Rossor et al 2013], indicating that the *PMP22* duplication on chromosome 17p is responsible for approximately 31% of all CMT cases and approximately 70% of those with the CMT1 phenotype.

In a Chinese population Liu et al [2013] found pathogenic variants in *MPZ* in 3% of individuals with CMT1 and in 6% of those with CMT2.

Genetically Related (Allelic) Disorders

PMP22. Other phenotypes associated with mutation of *PMP22*:

- Hereditary neuropathy with liability to pressure palsies (HNPP), caused by deletions of *PMP22*
- The very rare autosomal recessive neuropathy CMT4 is caused by homozygosity for single-nucleotide variants in *PMP22* [Parman et al 1999, Numakura et al 2000]. Autosomal recessive CMT is sometimes referred to as Dejerine-Sottas syndrome (DSS) (see Nomenclature). In one family, sibs homozygous for a *PMP22* single-nucleotide variant (c.469C>T) are reported to have DSS, while their heterozygous parents are clinically normal [Parman et al 1999].

MPZ

- Mutation of *MPZ* is also associated with congenital hypomyelinating neuropathy and the CMT2 phenotype. One individual with the CMT2 phenotype and three separate pathogenic variants in *MPZ* has been described [Boerkoel et al 2002].
- The Roussy-Levy syndrome of CMT associated with ataxia or tremor has been shown to be caused by an *MPZ* pathogenic variant (c.393C>A) in the original family [Planté-Bordeneuve et al 1999].

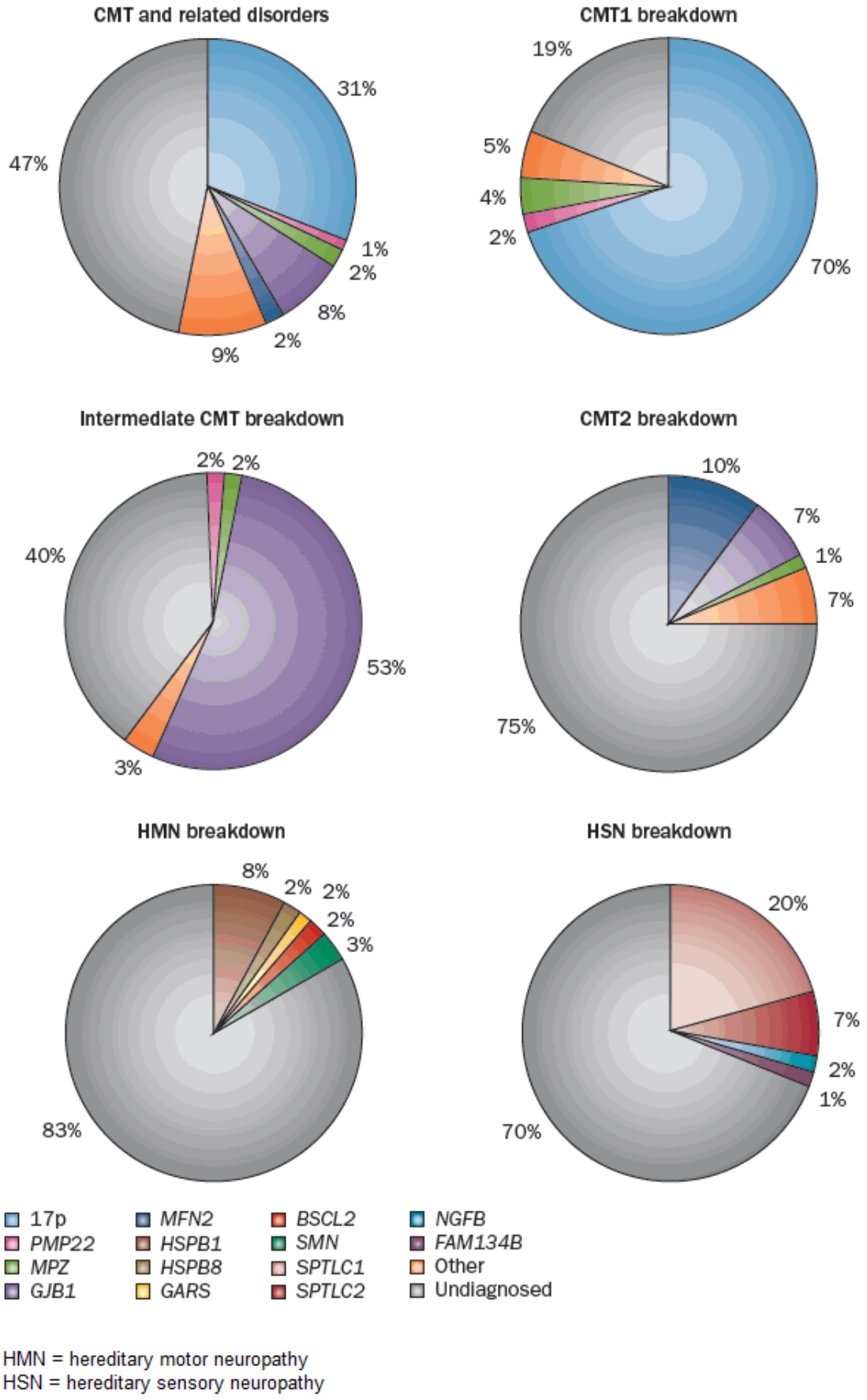

Figure 1. Genetic diagnoses in CMT and related disorders

From Rossor et al [2013]; reprinted with permission

LITAF. No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *LITAF*.

EGR2. Mutation of *EGR2* is also associated with autosomal recessive CMT4 [Warner et al 1998, Timmerman et al 1999, Warner et al 1999, Boerkoel et al 2002].

NEFL. Some individuals with pathogenic variants in *NEFL*, which typically cause CMT2E, may have slow NCV [Jordanova et al 2003], causing them to have been diagnosed with CMT1F [Fabrizi et al 2007]. To accommodate these two phenotypes associated with mutation of *NEFL*, the designation CMT2E/1F has been used.

Differential Diagnosis

Acquired causes of neuropathy and other inherited neuropathies need to be considered (see CMT Overview). The differential diagnosis includes other genetic neuropathies, especially CMTX, CMT2, CMT4, and HNPP, all of which show considerable phenotypic overlap [Bienfait et al 2006b].

FBLN5. Auer-Grumbach et al [2011] found pathogenic variants in *FBLN5* in families with features of CMT1; *FBLN5* pathogenic variants were additionally associated with age-related macular degeneration and cutis laxa. Šafka Brozková et al [2013] have found the same pathogenic missense variant in *FBLN5* in a Czech family with CMT1 and a different background haplotype compared with the Austrian family reported by Auer-Grumbach.

GJB3. López-Bigas et al [2001] have described an autosomal dominant neuropathy associated with hearing impairment caused by a pathogenic variant in *GJB3*. Although the sural nerve pathology showed demylination compatible with CMT1, the nerve conduction velocities (NCVs) were not markedly slow and may suggest an axonal neuropathy.

Familial slow NCV (OMIM 608236). Verhoeven et al [2003] have described a family with no symptoms or signs, but with slow NCVs associated with a pathogenic variant in *ARHGEF10*, encoding the protein rho guanine nucleotide exchange factor 10.

In the autosomal dominant **intermediate forms** of CMT, individuals have a relatively typical CMT phenotype with NCVs that overlap those observed in CMT1 (demyelinating neuropathy) and CMT2 (axonal neuropathy) [Villanova et al 1998]. Motor NCVs in these families usually range between 25 and 50 m/s. Five types are recognized to date:

- DI-CMTA, linked to 10q24 [Verhoeven et al 2001]
- DI-CMTB caused by pathogenic variants in *DNM2*. The phenotype is a classic, mild to moderately severe Charcot-Marie-Tooth hereditary neuropathy that often includes pes cavus foot deformity, depressed tendon reflexes, distal muscle weakness and atrophy, and sensory loss.
- DI-CMTC caused by pathogenic variants in *YARS* (formerly *TyrRS*), linked to 1p35.5 [Jordanova et al 2006]
- DI-CMTD caused by pathogenic variants in *MPZ*
- DI-CMTF caused by pathogenic variants in *GNB4*. Soong et al [2013] reported heterozygous pathogenic variants in *GNB4* in a family previously reported by Lee et al [2010] and a *de novo* case. NCV varied widely from slow to normal.

It is usually not possible to differentiate between intermediate forms of CMT and most CMT2 subtypes based on clinical findings [Nicholson & Myers 2006] unless cataract and/or neutropenia (occasional findings in DI-CMTB) are present.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Charcot-Marie-Tooth neuropathy type 1 (CMT1), the following evaluations are recommended:

- Physical examination to determine extent of weakness and atrophy, *pes cavus*, gait stability, and sensory loss
- NCV to help distinguish demyelinating, axonal, and mixed forms of neuropathy
- Detailed family history
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Individuals with CMT1 are often evaluated and managed by a multidisciplinary team that includes neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists [Carter 1997, Grandis & Shy 2005].

Treatment is symptomatic and may include the following:

- Special shoes, including those with good ankle support; affected individuals often require ankle/foot orthoses (AFOs) to correct foot drop and aid walking [Ramdharry et al 2012a].
- Orthopedic surgery to correct severe pes cavus deformity [Guyton & Mann 2000, Ward et al 2008, Boffeli & Tabatt 2015]
- Forearm crutches or canes for gait stability for some individuals; fewer than 5% of individuals need wheelchairs.
- Exercise within the individual's capability; many remain physically active. Exercise is **not** detrimental to persons with CMT [Piscosquito et al 2014].
- Serial night casting to help increase ankle flexibility [Rose et al 2010]
- Accurate identification, as far as possible, of the cause of pain:
  - 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.
- Career and employment counseling to address persistent weakness of hands and/or feet
- Interventions designed to improve leg cramps, tremor, agility, endurance, and ankle flexibility, thereby improving quality of life; see Burns et al [2010] study of children with CMT1A.

Prevention of Primary Manifestations

No treatment reverses or slows the natural progression of CMT.

Prevention of Secondary Complications

Daily heel cord stretching exercises to prevent Achilles' tendon shortening are desirable.

Surveillance

Individuals should be evaluated regularly by a team comprising physiatrists, neurologists, and physical and occupational therapists to determine neurologic status and functional disability.

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

Rudnik-Schöneborn et al [1993] evaluated 45 pregnancies in 21 women with CMT1. Worsening of the CMT1 symptoms during or after gestation was reported in about half of pregnancies. A follow-up study of 63 pregnancies in 33 women with CMT showed no serious complications but 20% of women reported a worsening of symptoms during pregnancy [Awater et al 2012]. In a study of affected pregnant women in Norway, deliveries involved a higher occurrence of presentation anomalies, use of forceps, and operative delivery; the women also experienced increased post-partum bleeding [Hoff et al 2005].

Therapies Under Investigation

Reilly & Shy [2009], Roberts [2012], and Patel & Pleasure [2013] have reviewed research on potential new treatments of CMT.

Dyck et al [1982], Ginsberg et al [2004], and Carvalho et al [2005] have described a few individuals with CMT1 and sudden deterioration in whom treatment with steroids (prednisone) or IVIg has produced variable levels of improvement. Nerve biopsy has shown lymphocytic infiltration. One such family had a specific *MPZ* pathogenic variant (p.Ile99Thr) [Donaghy et al 2000].

Sahenk et al [2005] studied the effects of neurotrophin-3 (NT3) on individuals with CMT1A. This same group has shown benefit of NT3 delivered by adeno-associated virus (AAV) gene therapy in a mouse model of CMT1A [Sahenk et al 2014].

Passage et al [2004] reported benefit from ascorbic acid (vitamin C) in a mouse model of CMT1. Similar benefit was reported with a progesterone receptor antagonist in a rat model of CMT [Meyer zu Horste et al 2007]. Two high-dose (1,000-1,500 mg/day) treatment trials of ascorbic acid in CMT1A have found no beneficial effect over a period of one to two years [Verhamme et al 2009b, Pareyson et al 2011]. Lewis et al [2013] also could not find a positive treatment response to ascorbic acid vs. placebo in 110 subjects with CMT1A.

Patzkó et al [2012] provided evidence for the potential use of curcumin in the treatment of individuals with CMT1B who have pathogenic variants in *MPZ*.

Fledrich et al [2014] suggested neuregulin-1 as a potential treatment for CMT1A based on experiments in a rat model of the disease.

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.

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

Charcot-Marie-Tooth neuropathy type 1 (CMT1) is inherited an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 67%-80% of individuals with CMT1A have inherited the *PMP22* duplication from an affected parent and about 20% [Marques et al 2005] to 33% [Boerkoel et al 2002] have a *de novo* pathogenic variant.
- Similar data are not available for the other subtypes of CMT1.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include neurologic examination and molecular genetic testing.

Note: Although most individuals diagnosed with CMT1 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. If the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the pathogenic variant and may be mildly/minimally affected.

Sibs of a proband

- The risk to the sibs depends on the genetic status of the proband's parents.
- If a parent has the *PMP22*, *MPZ*, *LITAF*, or *EGR2* pathogenic variant, the risk to 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 cannot be detected in leukocyte DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism [Fabrizi et al 2001a].

Offspring of a proband. Every child of an individual with CMT1 has a 50% chance of inheriting the *PMP22*, *MPZ*, *LITAF*, or *EGR2* 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 has the pathogenic variant, his or her family members are at risk.

Related Genetic Counseling Issues

Testing of at-risk asymptomatic adult relatives of individuals with CMT1 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. This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. Testing of asymptomatic at-risk individuals with nonspecific or equivocal symptoms is predictive testing, not diagnostic testing.

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.

In a family with an established diagnosis of CMT1, testing is appropriate to consider in symptomatic individuals regardless of age.

See also 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.

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 or clinical evidence of the disorder, it is likely that the variant occurred *de novo* in the proband. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or 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.
- 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 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

If the *PMP22*, *MPZ*, *LITAF*, *or EGR2* pathogenic variant has been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing of the gene or custom prenatal testing.

Requests for prenatal testing for typically adult-onset conditions which (like CMT1) do not affect intellect or life span are not common. 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. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic testing (PGT) may be an option for some families in which the *PMP22*, *MPZ*, *LITAF*, or *EGR2* pathogenic variant has been identified. Successful use of PGT for CMT1A has been reported [Lee et al 2013].

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@musculardystrophyuk.org
  www.musculardystrophyuk.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 1: Genes and Databases

Locus Name	Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CMT1A	*PMP22*	17p12	Peripheral myelin protein 22	PMP22 homepage - Leiden Muscular Dystrophy pages IPN Mutations, PMP22	PMP22	PMP22
CMT1B	*MPZ*	1q23.3	Myelin protein P0	MPZ homepage - Leiden Muscular Dystrophy pages IPN Mutations, MPZ	MPZ	MPZ
CMT1C	*LITAF*	16p13.13	Lipopolysaccharide-induced tumor necrosis factor-alpha factor	LITAF homepage - Leiden Muscular Dystrophy pages IPN Mutations, LITAF	LITAF	LITAF
CMT1D	*EGR2*	10q21.3	E3 SUMO-protein ligase EGR2	EGR2 homepage - Leiden Muscular Dystrophy pages IPN Mutations, EGR2	EGR2	EGR2
CMT1E	*PMP22*	17p12	Peripheral myelin protein 22	PMP22 homepage - Leiden Muscular Dystrophy pages IPN Mutations, PMP22	PMP22	PMP22
CMT1F	*NEFL*	8p21.2	Neurofilament light polypeptide	Human Intermediate Filament Database NEFL NEFL homepage - Leiden Muscular Dystrophy pages IPN Mutations, NEFL	NEFL	NEFL

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 1 (View All in OMIM)

118200	CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1B; CMT1B
118220	CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1A; CMT1A
118300	CHARCOT-MARIE-TOOTH DISEASE AND DEAFNESS
129010	EARLY GROWTH RESPONSE 2; EGR2
159440	MYELIN PROTEIN ZERO; MPZ
162280	NEUROFILAMENT PROTEIN, LIGHT POLYPEPTIDE; NEFL
601097	PERIPHERAL MYELIN PROTEIN 22; PMP22
601098	CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1C; CMT1C
603795	LIPOPOLYSACCHARIDE-INDUCED TUMOR NECROSIS FACTOR-ALPHA FACTOR; LITAF

Table B. continued from previous page.

607678	CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1D; CMT1D
607734	CHARCOT-MARIE-TOOTH DISEASE, DEMYELINATING, TYPE 1F; CMT1F

PMP22 (CMT1A, CMT1E)

Gene structure. *PMP22* transcript variant 1 (NM_000304.2) has 1828 nucleotides and five exons, four of which encode amino acids [Patel et al 1992]. It is similar to a growth arrest-specific gene in mouse and rat. For a detailed summary of gene and protein information for the following genes, see Table A, **Gene**.

Pathogenic variants

- **CMT1A.** The molecular defect in CMT1A is a 1.5-Mb duplication at 17p11.2 that includes *PMP22* [Lupski et al 1991, Raeymaekers et al 1991]. This duplication results from unequal crossing over of homologous chromosomes at regions of repetitive elements that flank the duplicated region.
- **CMT1E.** More than 30 single-nucleotide variants in *PMP22* can cause the CMT1E phenotype and the mouse ortholog of the human mutated allele p.Leu16Pro is found in the Trembler-J mouse [Devaux & Scherer 2005]. (For more information, see Table A.)

Table 2. Selected *PMP22* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.47T>C	p.Leu16Pro	NM_000304.2 NP_000295.1
c.65C>T	p.Ser22Phe	
c.82T>C	p.Trp28Arg	
c.117G>C	p.Trp39Cys	
c.199G>C	p.Ala67Pro	
c.353C>T [2]	p.Thr118Met	
c.469C>T [3]	p.Arg157Trp	
c.281dupG [3]	p.Arg95GlnfsTer128 (Gly94fsTer222)	
(1.5-Mb duplication at 17p11.2)	--	

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
2. See Genotype/Phenotype Correlations.
3. See Genetically Related Disorders.

Normal gene product. Peripheral myelin protein 22 is a 160-amino acid protein that is present in compact myelin and has four transmembrane domains.

Abnormal gene product. Duplication of *PMP22* is associated with increased mRNA message for *PMP22* in peripheral nerve and by an unknown mechanism that results in abnormal myelination [Gabriel et al 1997].

Most pathogenic missense variants are localized in the transmembrane domains of peripheral myelin protein 22, indicating the functional importance of these domains. Individuals with *PMP22* single-nucleotide variants tend

to have more severe clinical disability than those with a single 17p11.2 duplication, presumably because of a dominant-negative or loss-of-protein function effect [Sereda & Nave 2006].

A mouse containing eight copies of human *PMP22* shows a phenotype similar to but more severe than that seen in individuals with CMT1A, while mice containing 16 and 30 additional copies of mouse *PMP22* show severe hypomyelination [Nelis et al 1999a]. This supports the hypothesis that more copies of *PMP22* result in a more severe phenotype [Giambonini-Brugnoli et al 2005].

Perea et al [2001] have generated a transgenic mouse model in which mouse *PMP22* over-expression can be regulated, possibly providing a system for evaluation of potential therapeutic approaches.

MPZ (CMT1B)

Gene structure. *MPZ* spans approximately seven kilobases and contains six exons. The reference sequence was updated in 2010 to encode the 248 amino acid protein NM_000530.6, which should be considered when referring to *MPZ* pathogenic variants (for detailed information, see entry for *MPZ* at Inherited Peripheral Neuropathies Mutation Database).

Pathogenic variants. Nearly 100 pathogenic variants in *MPZ* have been reported [De Jonghe et al 1997, Nelis et al 1999a, Kochański et al 2004, Lee et al 2004, Shy 2006]. More than 70% of the pathogenic variants are localized in exons 2 and 3 of *MPZ*, which code for the extracellular domain, indicating the functional importance of this domain. Intronic variants affecting *MPZ* splicing have been reported [Sabet et al 2006]. (For more information, see Table A.) A duplication of the entire *MPZ* gene was detected in a Norwegian family with an autosomal dominant, early onset (first decade), severe, demyelinating CMT syndrome [Høyer et al 2011].

Table 3. Selected *MPZ* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.89T>C [2]	p.Ile30Thr	NM_000530.6 NP_000521.2
c.131C>T [2]	p.Ser44Phe	
c.164G>T [2]	p.Ser55Ile	
c.181G>A	p.Asp61Asn	
c.175T>A [2]	p.Ser59Thr	
c.224A>T [2]	p.Asp75Val	
c.241C>T	p.His81Tyr	
c.[241C>T;337G>T] [2, 3]	p.[His81Tyr;Val113Phe]	
c.244T>C	p.Tyr82His	
c.296T>C [4]	p.Ile99Thr	
c.306delA [2, 5]	p.Asp104ThrfsTer14	
c.347A>G	p.Asn116Ser	
c.337G>T [2]	p.Val113Phe	
c.371C>T [2]	p.Thr124Met	
c.389A>G [2]	p.Lys130Arg	
c.393C>A [6]	p.Asn131Lys	
c.487G>A	p.Gly163Arg	
c.499G>A [2]	p.Gly167Arg	

Table 3. continued from previous page.

DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.588dupT	p.Met197TyrTer38 (Met207TyrfsTer38)	
c.670G>T [2]	p.Asp224Tyr	
c.645+1G>T [2]	NA	
c.649C>T [2]	p.Pro217Ser	

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.
NA = not applicable
1. Variant designation that does not conform to current naming conventions
2. See Genotype-Phenotype Correlations.
3. Nomenclature for variants in *cis* configuration
4. See Therapies Under Investigation.
5. See Neuropathology.
6. See Genetically Related Disorders.

Normal gene product. P_0 myelin protein is a major structural component of peripheral myelin, representing about 50% of peripheral myelin protein by weight and about 7% of Schwann cell message [Wells et al 1993]. 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. It is also expressed in glomerular epithelial cells of the kidney [Plaisier et al 2005].

Abnormal gene product. Different pathogenic variants affect all portions of the protein and may alter myelin adhesion or produce an unfolded protein response [Wrabetz et al 2006]. Either demyelinating or axonal phenotypes can result. Grandis et al [2008] found that pathogenic variants associated with late-onset disease cause a partial loss of function in transfected cells, whereas pathogenic variants associated with early-onset disease cause abnormal gain of function. Abnormal *MPZ* is retained in the endoplasmic reticulum of Schwann cells causing a transitory canonic unfolded protein response [Pennuto et al 2008, Saporta et al 2012].

LITAF (CMT1C)

Gene structure. *LITAF* has three coding exons. For a detailed summary of gene and protein information for the following genes, see Table A, **Gene**.

Benign variants. A benign variant was reported by Bennett et al [2004].

Pathogenic variants. Missense variants have been reported in *LITAF* [Street et al 2003, Bennett et al 2004, Saifi et al 2005, Latour et al 2006] (Table 4). (For more information, see Table A.) The pathogenicity of some DNA changes is difficult to determine [Kochański 2006].

Table 4. Selected *LITAF* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.332C>G	p.Ala111Gly	NM_004862.3 NP_004853.2
c.334G>A [1]	p.Gly112Ser	
c.344C>A	p.Thr115Asn	
c.346T>G	p.Trp116Gly	
c.385G>A	p.Ala129Thr	
c.403C>T	p.Pro135Ser	
c.403C>A	p.Pro135Thr	
c.404C>G	p.Pro135Arg	

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. See Genotype-Phenotype Correlations.

Normal gene product. The protein product of *LITAF* has two names: lipopolysaccaride-induced tumor necrosis factor-α factor (LITAF) and small integral membrane protein of the lysosome/late endosome (SIMPLE) [Saifi et al 2005]. The gene may play a role in the lysosomal sorting of plasma membrane proteins [Shirk et al 2005].

Abnormal gene product. Mutation may alter the ability of the Schwann cell to degrade proteins.

EGR2 (CMT1D)

Gene structure. *EGR2* spans 4.3 kb and contains two coding exons. For a detailed summary of gene and protein information for the following genes, see Table A, **Gene**.

Pathogenic variants. Selected autosomal dominant pathogenic variants are listed in Table 5 [Timmerman et al 1999, Pareyson et al 2000]. (For more information, see Table A.) The pathogenicity of some DNA changes is difficult to determine [Kochański 2006].

Table 5. Selected *EGR2* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1075C>T [1]	p.Arg359Trp	NM_000399.3 NP_000390.2
c.1076G>A [1]	p.Arg359Gln	
c.1142G>A [1]	p.Arg381His	
c.1144A>C or c.1146T>A	p.Ser382Arg	
c.1147G>T [1]	p.Asp383Tyr	
c.1160C>A [1]	p.Thr387Asn	
c.1225C>T	p.Arg409Trp	

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. See Genotype-Phenotype Correlations.

Normal gene product. Early growth response-2 protein is a zinc finger transcription factor. It is the ortholog of the murine Krox-2 protein. EGR2 induces expression of several proteins involved in myelin sheath formation and maintenance.

Abnormal gene product. *Krox-2* null mice show a block in Schwann cell differentiation.

***NEFL* (CMT2E/1F)**

Gene structure. Both the mouse and human *NEFL* have four coding exons; the 5' UTRs are highly conserved. For a detailed summary of gene and protein information for the following genes, see Table A, **Gene**.

Pathogenic variants. See Table 6. (For more information, see Table A.)

Table 6. Selected *NEFL* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Reference Sequences
c.23C>G	p.Pro8Arg	NM_006158.3 NP_006149.2
c.64C>T	p.Pro22Ser	
c.64C>A [2]	p.Pro22Thr	
c.65C>G [2]	p.Pro22Arg	
c.1001A>C	p.Gln334Pro (Gln333Pro)	
c.293A>G	p.Asn98Ser (Asn97Ser)	
c.446C>T	p.Ala149Val (Ala148Val)	

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
2. See Genotype-Phenotype Correlations.

Normal gene product. The protein encoded by *NEFL* contains 543 amino acids with a head, rod, and tail domain. Neurofilaments form the cytoskeletal component of myelinated axons.

Abnormal gene product. Knockout mice lacking neurofilments have diminished axon caliber and delayed regeneration of myelinated axons following crush injury. A mouse with a single-nucleotide variant in *NEFL* has massive degeneration of spinal motor neurons and abnormal neurofilament accumulation with severe neurogenic skeletal muscle atrophy.

References

Published Guidelines / Consensus Statements

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National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2017. Accessed 4-30-18.

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Suggested Reading

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Chapter Notes

Revision History

- 5 July 2018 (ma) Chapter retired: covered in Charcot-Marie-Tooth Hereditary Neuropathy Overview
- 26 March 2015 (ks) Revision: *MPZ* pathogenic variants renamed to correspond with RefSeq NM_000530.6
- 18 December 2014 (me) Comprehensive update posted live
- 20 February 2014 (tb) Revision: Lee et al 2013 added to Preimplantation genetic diagnosis
- 7 November 2013 (tb) Revision: additions to Prevalence; figure added [Rossor et al 2013]
- 11 July 2013 (tb) Revision: additions to Prevalence and Natural History
- 18 October 2012 (me) Comprehensive update posted live
- 18 August 2011 (tb) Revision: Høyer et al 2011; see Testing, Genotype-Phenotype Correlations, Molecular Genetics
- 16 June 2011 (tb) Revision: additions to Differential Diagnosis – *FBLN5*
- 1 March 2011 (cd) Revision: edits to Testing Strategy
- 14 September 2010 (me) Comprehensive update posted live
- 18 December 2007 (cd) Revision: prenatal diagnosis available for CMT1D
- 30 March 2007 (me) Comprehensive update posted to live Web site
- 20 October 2006 (cd) Revision: targeted mutation analysis, mutation scanning, and prenatal diagnosis for CMT1D no longer available
- 30 December 2005 (cd) Revision: prenatal diagnosis and mutation scanning clinically available for CMT1C
- 26 April 2005 (me) Comprehensive update posted live
- 9 September 2004 (tb,cd) Revision: addition of *LITAF*; sequence analysis clinically available
- 10 May 2004 (tb) Author revisions
- 29 December 2003 (tb) Author revisions
- 22 April 2003 (tb) Author revisions
- 27 March 2003 (me) Comprehensive update posted live
- 10 May 2002 (tb) Author revisions
- 20 December 2001 (tb) Author revisions
- 12 September 2001 (tb) Author revisions
- 24 July 2001 (tb) Author revisions
- 27 June 2001 (tb) Author revisions
- 1 June 2001 (tb) Author revisions
- 16 January 2001 (tb) Author revisions
- 25 August 2000 (ca) Comprehensive update posted live
- 15 June 2000 (tb) Author revisions
- 15 May 2000 (tb) Author revisions
- 14 January 2000 (tb) Author revisions
- 31 August 1999 (tb) Author revisions
- 18 June 1999 (tb) Author revisions
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