

Inherited Peripheral Neuropathies

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KEYWORDS

• Charcot-Marie-Tooth • Inherited neuropathy • Genetic testing

KEY POINTS

- Identifiable genetic causes of neuropathy elucidate biologic pathways that cause demyelination or axonal loss.
- Charcot-Marie-Tooth (CMT) disease is genetically and clinically heterogeneous with more than 50 genes causing neuropathy that can vary in age of onset and severity.
- Mutations in just four genes (*PMP22*, *GJB1*, *MPZ*, and *MFN2*) cause more than 90% of the genetically identifiable cases of CMT in North America.
- Combining the clinical phenotype and nerve conduction velocities in the arm can further focus genetic testing among these four genes.
- Because CMT can affect family members other than the proband, the authors suggest that genetic counseling be considered for patients and their families.

INTRODUCTION

First described at the end of the nineteenth century by French neurologists Jean Martin Charcot and Pierre Marie and British neurologist Howard Henry Tooth, Charcot-Marie-Tooth (CMT) disease is now identified as the most common inherited neurologic condition, affecting approximately 1 in 2500 people.¹ CMT is frequently the final diagnosis of patients with previously unidentified (idiopathic or cryptogenic) peripheral neuropathies,² underscoring the need for better awareness and strategies to help general neurologists navigate through the clinical and molecular diagnosis of this fascinating group of neuropathies. Recent advances in molecular biology have demonstrated that CMT is genetically heterogeneous, with at least 50 genes known to cause CMT when mutated. Most patients have an autosomal dominant form of CMT, though X-linked and autosomal recessive (AR) inheritances are not uncommon. This article describes the characteristics of various forms of CMT, their biologic substrate, as well as the current strategy for genetic testing.

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THE BIOLOGY OF INHERITED PERIPHERAL NEUROPATHIES

A common feature of most genes mutated in CMT is the role they play in maintaining the structure or function of the two main cellular components of the peripheral nervous system, Schwann cells, and the axons of peripheral neurons (ventral horn spinal motor neurons and dorsal root ganglia sensory neurons) (Fig. 1).

The first genes identified to cause CMT express proteins that are essential for compact (peripheral myelin protein 22 [*PMP22*] and myelin protein zero [*MPZ*]) and non-compact (gap junction protein beta 1 [*GJB1*]) myelin structure³ and their altered expressions cause demyelination or dysmyelination. A novel concept derived from the identification of *PMP22* duplication as the basic pathomechanism in CMT type 1A (CMT1A) is that of gene-protein dosage. It became clear that the correct stoichiometry of *PMP22* is necessary to maintain compact myelin integrity. Too much *PMP22* (duplication) causes CMT1A; too little (haploinsufficiency) causes hereditary neuropathy with liability to pressure palsies (HNPP) (see later discussion).⁴ Abnormal expression of *MPZ* also causes demyelination, although in this case it is usually due to point mutations in the *MPZ* gene.

An important biologic feature common to both neurons and Schwann cells are their highly specialized and polarized cellular architecture.⁵ Although the polarization of neurons is a well-recognized feature of these cells, with their axons extending more than 1 m in humans, Schwann cells are also very polarized because their membranes have to expand while they concentrically wrap around axons. To overcome the long distances between the cell nucleus and the more distal segments of the membrane, Schwann cells have areas of non-compact myelin rich in gap junctions that provide a radial pathway directly across the layers of the myelin sheath. Connexin 32 (Cx32), the protein expressed by the *GJB1* gene, is the main component of gap junctions in the myelin of Schwann cells and this may explain, at least in part, why *GJB1* mutations cause CMT type 1X (CMT1X).⁶ The high polarization of neurons and Schwann cells may also explain why mutations in ubiquitously expressed genes, such as mitofusin 2 (*MFN2*), ganglioside-induced differentiation-associated protein 1 (*GDAP1*), or glycyl-tRNA synthetase (*GARS*), cause preferential dysfunction of the peripheral nervous system. The length-dependent neuropathy commonly found in patients with CMT seems to support the hypothesis that distal peripheral axons are especially susceptible to disruptions in organelle and metabolite axonal transport.

Schwann cells and axons interact at multiple points along the peripheral nerve, including the adaxonal membrane, paranodal myelin loops, microvilli, and

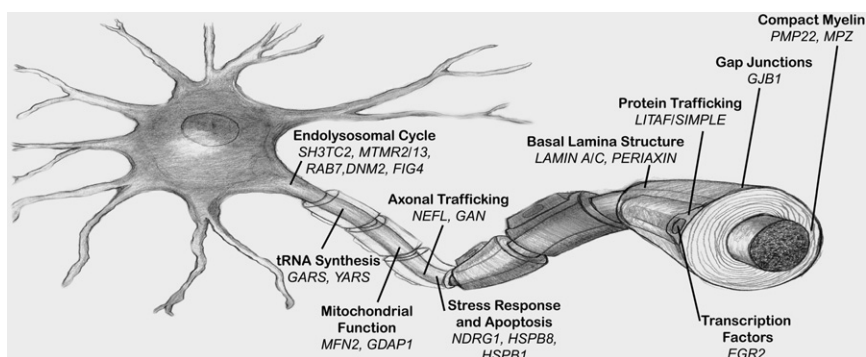


Fig. 1. A neuron: its axon and Schwann cells with the major genes associated with Charcot-Marie-Tooth disease with their respective function and cellular compartment.

juxtaparanodal basal lamina. These interactions are mutually beneficial, providing trophic support to the axon and myelinating cues to the Schwann cell. An example of this important interaction is the occurrence of secondary axonal degeneration in all forms of demyelinating CMT. This axonal degeneration is deemed to occur as a consequence of ineffective Schwann cell support to the axon and is actually more directly related to clinical functional impairment than the demyelination itself.⁷

Several recent studies have demonstrated a specific susceptibility of Schwann cells to mutations yielding misfolded proteins, as seen in certain *PMP22*⁸ and *MPZ*^{9,10} point mutations. Misfolded proteins accumulate in the endoplasmic reticulum (ER) of Schwann cells inducing a transitory unfolded protein response (UPR), a series of cellular events that help the ER to cope with the increased metabolic demand caused by misfolded protein retention. This, in turn, causes down-regulation of the myelination program genes and dedifferentiation of Schwann cells, a toxic gain of function that worsens the demyelination and is potentially amenable to therapeutic intervention.^{11,12}

CLINICAL AND NEUROPHYSIOLOGICAL FEATURES

CMT is clinically, as well as genetically, heterogeneous, with variability in the age of onset, speed of progression, and electrodiagnostic findings. Though both motor and sensory nerves are usually affected, the more prominent phenotypic characteristic is related to motor difficulty in most cases. The classic phenotype includes step-gate gait, pes cavus, sensory loss in a stocking or glove distribution, inverted champagne bottle legs, and atrophy in the hands.^{13–15} Physical examination also shows decreased or absent deep tendon reflexes, often diffusely but virtually always involving the Achilles tendon. Findings are usually symmetric.¹⁶ Onset is typically in the first to second decade in classic cases, though this may differ depending on the genetic subtype, including early-onset, infantile forms (historically designated Dejerine-Sottas syndrome) and late-onset, adult forms. Symptoms are usually slowly progressive, especially for the classic and late-onset phenotypes, but can be rather severe in early-onset forms. Patients usually have impaired proprioception with balance difficulty. Neuropathic pain affects around 20% of CMT patients.

Nerve conductions allow for classification into demyelinating, axonal, or intermediate groups, based on the motor nerve conduction velocities (MNCV) and compound muscle action potential amplitudes (CMAP). The standard cut off for demyelinating MNCV in the upper extremities is 38 m/s. Velocities between 35 and 45 m/s may be considered intermediately slowed, and greater than 45 m/s are considered axonal if there is a decrease in CMAP. Conduction velocities are performed in the arms because CMAP amplitudes are often unobtainable in the legs, even for demyelinating forms of CMT, due to impaired interactions between abnormal myelin and the underlying axon. CMT can be divided into subtypes based on electrodiagnostic features and inheritance pattern. Patients with autosomal dominant inheritance and a demyelinating phenotype are said to have CMT1. Patients with autosomal dominant inheritance and an axonal phenotype have CMT type 2 (CMT2) and patients with AR inheritance, regardless of the electrodiagnostic features, have CMT type 4 (CMT4). Patients with CMT inherited in an X-linked fashion have CMT type X (CMTX). The subtypes are further divided genetically based on the gene mutated. The gene, or the type of mutation in the gene that causes the condition, defines each genetic subtype, as shown on **Table 1**. The usual electrodiagnostic finding in demyelinating inherited neuropathies is widespread uniform slowing of conduction velocities, as opposed to the multifocal segmental slowing found in demyelinating acquired neuropathies in which temporal

Table 1
Classification of Charcot-Marie-Tooth disease

Type	Gene or Locus	Specific Phenotype
AD CMT1		
CMT1A	Dup 17p (PMP22) PMP22 (point mutation)	Classic CMT1 Classic CMT1, DSS, CHN, HNPP
CMT1B	MPZ	CMT1, DSS, CHN, intermediate, CMT2
CMT1C	LITAF	Classic CMT1
CMT1D	EGR2	Classic CMT1, DSS, CHN
CMT1E	NEFL	CMT2 but can have slow MNCVs in CMT1 range \pm early-onset severe disease
HNPP		
HNPP	Del 17p (PMP22) PMP22 (point mutation)	Typical HNPP Typical HNPP
X-linked CMT1 (CMT1X)		
CMT1X	GJB1	Intermediate \pm patchy MNCVs; male MNCVs less than female MNCVs
AR demyelinating CMT (CMT4)		
CMT4A	GDAP1	Demyelinating or axonal, usually early onset and severe vocal cord and diaphragm paralysis described Rare AD CMT2 families described
CMT4B1	MTMR2	Severe CMT1, facial, bulbar, focally folded myelin
CMT4B2	SBF2	Severe CMT1, glaucoma, focally folded myelin
CMT4C	SH3TC2	Severe CMT1, scoliosis, cytoplasmic expansions
CMT4D (HMSNL)	NDRG1	Severe CMT1, gypsy, deafness, tongue atrophy
CMT4E	EGR2	Classic CMT1, DSS, CHN
CMT4F	PRX	CMT1, more sensory, focally folded myelin
CMT4H	FGD4	CMT1
CMT4J	FIG4	CMT1
CCFDN	CTDP1	CMT1, gypsy, cataracts, dysmorphic features
HMSN-Russe	10q22–q23	CMT1
CMT1	PMP22 (point mutation)	Classic CMT1, DSS, CHN, HNPPs
CMT1	MPZ	CMT1, DSS, CHN, intermediate, CMT2
AD CMT 2		
CMT2A	MFN2	CMT2 Usually severe Optic atrophy
CMT2B	RAB7A	CMT2 with predominant sensory involvement and sensory complications
CMT2C	12q23–q24	CMT2 with vocal cord and respiratory involvement
CMT2D	GARS	CMT2 with predominant hand wasting, weakness, or dHMN V
CMT2E	NEFL	CMT2 but can have slow MNCVs in CMT1 range \pm early-onset severe disease

(continued on next page)

Table 1 (continued)		
Type	Gene or Locus	Specific Phenotype
CMT2F	HSPB1 (HSP27)	Classic CMT2 or dHMN II
CMT2G	12q12–q13.3	Classic CMT2
CMT2L	HSPB8 (HSP22)	Classic CMT2 or dHMN II
CMT2	MPZ	CMT1, DSS, CHN, intermediate, CMT2
CMT2 (HMSNP)	3q13.1	CMT2 with proximal involvement
AR CMT2 (also called CMT4)		
AR CMT2A	LMNA	CMT2 proximal involvement and rapid progression described Also causes muscular dystrophy, cardiomyopathy, or lipodystrophy
AR CMT2B	19q13.1–13.3	Typical CMT2
AR CMT2	GDAP1	CMT1 or CMT2 usually early onset and severe Vocal cord and diaphragm paralysis described Rare AD CMT2 families described
DI CMT (DI-CMT)		
DI-CMTA	10q24.1–25.1	Typical CMT
DI-CMTB	DNM2	Typical CMT
DI-CMTC	YARS	Typical CMT
Hereditary neuralgic amyotrophy (HNA)		
HNA	SEPT9	Recurrent neuralgic amyotrophy

Abbreviations: AD, autosomal dominant; CHN, congenital hypomyelinating neuropathy; CTDP1, CTD phosphatase subunit 1; Del, deletion; DMN2, dynamin 2; DSS, Dejerine-Sottas syndrome; Dup, duplication; EGR2, early growth response 2; FGD4, FYVE, RhoGEF, and PH domain containing 4; FIG4, FIG 4 homolog; HSP22, heat shock 22 kDa protein 8; HSP27, heat shock 27 kDa protein 1; KIF1Bb, kinesin family member 1B-b; LITAF, lipopolysaccharide-induced tumor necrosis factor; LMNA, lamin A and C; MCV, motor conduction velocity; MTMR2, myotubularin-related protein 2; MTMR13, myotubularin related protein 13; NDRG1, N-myc downstream regulated gene 1; NEFL, neurofilament, light polypeptide 68 kDa; PRX, periaxin; RAB7, RAB7, member RAS oncogene family; SEPT9, septin 9; SH3TC2, SH3 domain and tetratricopeptide repeats 2; YARS, tyrosyl tRNA synthetase.

From Reilly MM, Shy ME. Diagnosis and new treatments in genetic neuropathies. *J Neurol Neurosurg Psychiatry* 2009;80(12):1304–14. Copyright 2009, from BMJ Publishing Group Ltd; with permission.

dispersion and conduction block is frequently seen.^{17,18} Two exceptions to this rule are men with CMT1X and patients with HNPP. In these cases, focal demyelination with temporal dispersion or conduction block can be seen. In all other cases of demyelinating CMT the finding of focal slowing should raise the possibility of a superimposed inflammatory neuropathy, which can benefit from immunosuppressive therapy.¹⁹

GENETIC TESTING STRATEGIES

Strategies for focusing genetic testing have been in place since at least 2001, with flow charts to help guide testing.²⁰ The distribution of causal genes depends, at least in part, on the population tested. For European and North American populations, AR CMT comprises less than 10% of all cases and most patients have dominantly inherited CMT even if their cases are sporadic. Alternatively, populations in which consanguinity is high, such as in North Africa, may have up to 40% of their cases being

AR. Using MNCV and inheritance patterns, several strategies have been published since the 2001 study, mostly based on North American or European populations.²¹⁻²³ The authors have recently published testing guidelines which included age of onset of symptoms to help guide testing.²⁴ Age of onset classifications were infantile (delayed walking), childhood, or adult. These guidelines divided MNCV into four categories: less than or equal to 15 m/s (very slow), between 15 and 35 m/s (slow), between 35 and 45 m/s (intermediate), and greater than 45 m/s (axonal). Flow charts were provided using MNCV as the first level of evidence, with age of onset and inheritance patterns guiding the testing strategy within each category (Figs. 2 and 3). Of patients who had a genetic diagnosis, 92% were found to have changes in one of four genes: *PMP22*, *GJB1*, *MPZ*, and *MFN2*. Thus, the flow diagrams emphasize testing for these types of CMT, excepting HNPP, which has a distinctive nerve conduction study (NCS) pattern that differs from those of other forms of CMT and should be recognizable.

MNCV Less than or Equal to 15 m/s

All people with very slow MNCV who walked by 15 months of age had CMT1A; thus, genetic testing for the *PMP22* duplication is warranted for these individuals (see Fig. 2A). Of those patients who had delayed walking, most had CMT1A but 32% had CMT1B. Genetic testing for CMT1A and CMT1B is appropriate for people in this category. If these tests are negative, genetic testing for more rare forms of CMT may be reasonable.

MNCV Greater than 15 and Less than or Equal to 35 m/s

Approximately 89% of patients with slow MNCV who began walking by 15 months of age had CMT1A; thus, genetic testing should begin with *PMP22* duplication analysis (see Fig. 2B). CMT1X was the next most common type of CMT but should only be performed for people who do not have evidence of male-to-male transmission in their pedigree. CMT1B testing is much less likely to be the cause of the CMT for people in this category, but testing may be reasonable if testing for CMT1A and CMT1X are negative or if there is evidence of male-to-male transmission.

MNCV Greater than 35 and Less than or Equal to 45 m/s

Most people who had intermediate conduction velocities had either CMT1X or CMT1B (see Fig. 3A). If symptoms began in childhood, and no male-to-male transmission is present in the pedigree, it is most likely for the person to have CMT1X. If this testing is negative, CMT1B testing may be pursued. However, if the symptom onset was in adulthood, testing for CMT1B is more likely to elicit a positive genetic testing result, with CMT1X being a reasonable follow-up test.

MNCV Greater than 45 m/s or Unobtainable CMAP

People with normal velocities or unobtainable CMAP usually present with CMT1X (usually women), CMT1B, or CMT2A (see Fig. 3B). People with unobtainable CMAP were usually those with CMT2A, who are often severely affected in infancy and childhood.²⁵ Thus, for children with early onset or severe CMT, it is proposed to begin genetic testing for CMT2A. For people with axonal CMT who have a classic or adult onset of symptoms, testing should begin with CMT1X in the absence of male-to-male transmission in the pedigree. Testing should begin with CMT1B if male-to-male transmission is present or if CMT1X testing is negative. The authors propose using other clinical findings, such as the upper limbs being more severely affected than the lower limbs, to help guide additional genetic testing if necessary. For these patients, mutations in the *GARS* gene, causing CMT2D may be appropriate.

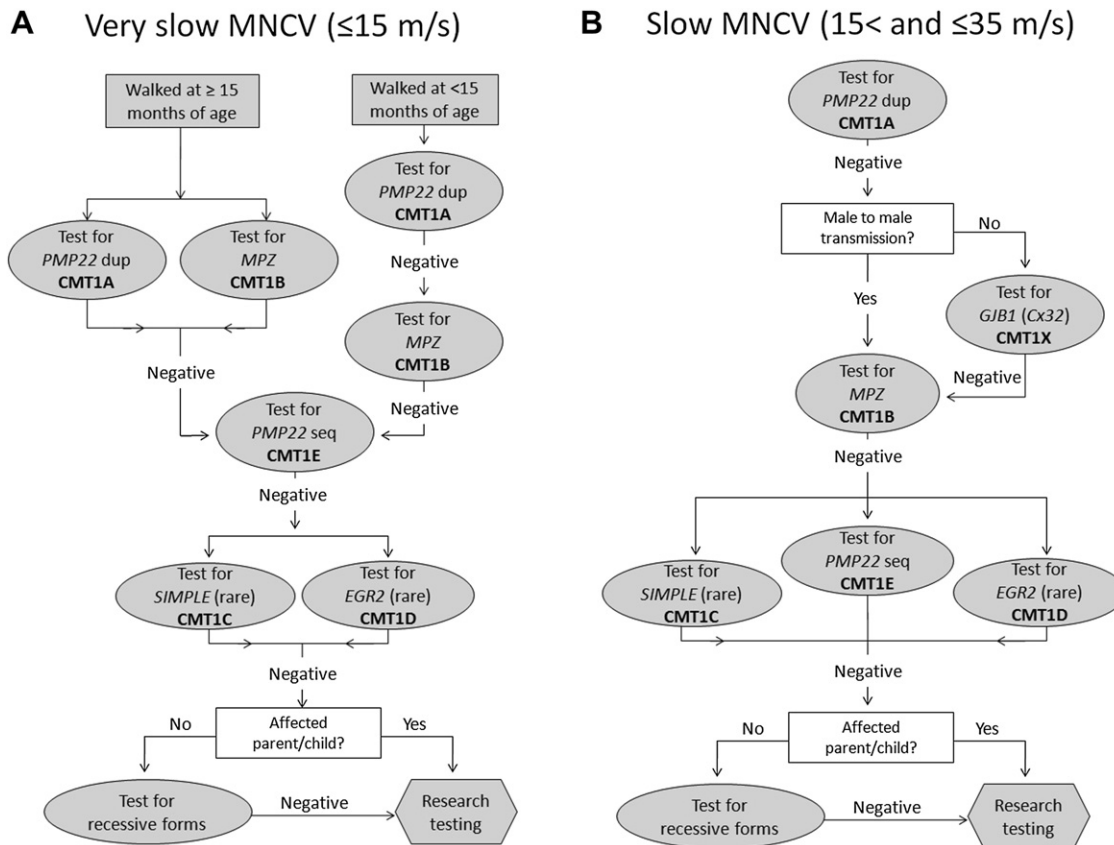


Fig. 2. Algorithm for the genetic diagnosis of patients with Charcot-Marie-Tooth disease and very slow (A) or slow (B) upper extremity motor nerve conduction velocities. dup, duplication; *EGR2*, early growth response 2; *LITAF*, lipopolysaccharide-induced TNF factor; seq, sequencing. (From Saporta AS, Sottile SL, Miller LJ, et al. Charcot-Marie-Tooth disease subtypes and genetic testing strategies. *Ann Neurol* 2011;69(1):22–33; with permission.)

Although a detailed review of the pros and cons for testing is beyond the scope of this article, the authors think it reasonable to provide some information about how we pursue genetic testing.²⁶ Clearly, not every patient with a genetic neuropathy wants or needs testing to identify the genetic cause of their disease. We believe that the ultimate decision to undergo genetic testing rests with the patient or the patient's parents if a symptomatic child is younger than 18 years of age. Reasons that patients give for obtaining testing include identifying the inheritance pattern of their CMT, making family planning decisions, and obtaining knowledge about the cause and natural history of their form of CMT. Natural history data is available for some forms of CMT such as CMT1A²⁷ and CMT1X,²⁸ which can provide guidance for prognosis, recognizing that there can be phenotypic variability in these subtypes. Patients with other forms of CMT frequently choose to undergo genetic testing to contribute to the natural history data collection for other patients with the same subtype. There are also reasons why patients do not want genetic testing. These include the high cost of commercial testing and fears of discrimination in the workplace or in obtaining health insurance. Because there are currently no medications to reverse any form of CMT, many patients decide against testing because their therapies will not depend on the results. We maintain that is always the patient's decision whether or not to pursue genetic testing.

Once a genetic diagnosis has been made in a patient, other family members usually do not need genetic testing but can be identified by clinical evaluation with neurophysiology. We do not typically test patients for multiple genetic causes of CMT simultaneously, although we did identify 11 patients with multiple genetic causes of CMT. It is our current policy to only consider performing genetic testing in clinically affected family members of a proband if their phenotype is atypical for the type of CMT in the family. In addition, we do not test asymptomatic minors with a family history of CMT, either by electrophysiology or genetic testing owing to the chance for increased psychological harm to the child.²⁹ We do routinely perform limited NCSs, though not needle electromyogram (EMG), on symptomatic children with CMT. Because nerve conduction changes, including slowing, are often uniform and detectable in early childhood in CMT,^{17,18} testing of a single nerve is often adequate to guide genetic testing or determine whether a symptomatic child is affected in a family with CMT.

SPECIFIC FORMS OF CMT

CMT1

CMT1 includes five types of CMT that are caused by four genes when mutated. This group includes most people with CMT (over 70%). These genes are essential to Schwann cell function and the formation of myelin sheaths surrounding the axon, though they interact in different ways and thus are phenotypically heterogeneous.³⁰

CMT1A

CMT1A is the most common type of CMT, affecting 55% of genetically defined patients.²⁴ It is caused by a 1.4 megabase (Mb) duplication at 17p11.2 including the *PMP22* gene, created by unequal crossing over of homologous chromosomes.^{31,32} People with CMT1A typically have the classic CMT phenotype, with normal age of onset for walking, development of symptoms in the first two decades, pes cavus, and slowly progressive motor and sensory neuropathy, which rarely progresses to wheelchair use later in life.^{24,33} People with CMT1A have distinctive length dependent sensorimotor demyelinating neuropathies. One study found that more than 90% of patients with CMT1A had MNCV in the ulnar nerve between 16 and 35 m/s or less.²⁴

CMT1A is an autosomal dominant condition, and most patients will have a family history. However, there is a de novo rate of about 10%.³⁴ Therefore, people without family history with ulnar MNCV under 35 m/s should first be screened for the *PMP22* duplication before proceeding with other genetic testing.²⁴ Once one person in a family has been genetically shown to have CMT1A, first and second-degree family members can be screened by MNCV. If other family members are shown to have the characteristically slowed conduction velocities, it can be assumed that that person also has CMT1A without needing genetic testing.

HNPP

HNPP is caused by the reciprocal deletion of the 1.4 Mb stretch of chromosome 17p11.2 containing the *PMP22* gene.³⁵ A small percentage of people with HNPP have this phenotype due to a frameshift, splice site, or point mutation of the *PMP22* gene (www.molgen.ua.ac.be/cmtmutations). HNPP is the third most common type of CMT, affecting about 9.1% of genetically diagnosed patients,²⁴ with a de novo rate of about 20%.³⁶ The hallmark feature of HNPP is transient and recurrent motor and sensory mononeuropathies. These typically occur at entrapment sites, such as the carpal tunnel, ulnar groove, and fibular head.³⁷ These palsies may last hours, days, or weeks, or occasionally longer. For some people, HNPP can progress to long-term peripheral neuropathy phenotypically indistinguishable from CMT1, in which patients may require ankle-foot orthoses or wrist splints.³⁷ HNPP can be distinguished electrophysiologically by marked slowing of the ulnar and sural sensory nerve conduction velocities, with or without reduced SNAP, and relatively preserved MNCV.³⁸ Distal motor latencies, particularly in the median and peroneal nerves, are typically prolonged, often out of proportion with the reduction of velocity.³⁹ Conduction block and focal slowing often occur at entrapment sites, particularly during a palsy episode.³⁷

CMT1B

CMT1B is caused by mutations in the *MPZ* gene⁴⁰ located at chromosome 1q22, which encodes for *MPZ*, a major component of the myelin sheath. It affects about 8.5% of people with genetically defined CMT.²⁴ People with CMT1B usually present in a bimodal distribution. One group develops a severe, early onset, demyelinating neuropathy and the other group develops a late onset, milder, axonal neuropathy. Age of onset of symptoms is useful in determining the subtype of CMT. Most people with early onset CMT1B will have delayed walking and MNCV less than 15 m/s.²⁴ Those with late onset CMT1B will walk at a normal age and usually have MNCV greater than 35 m/s.²⁴

CMT1C

CMT1C is caused by mutations in the *SIMPLE* gene at chromosome 16p13.3-p12.⁴¹ The phenotype of CMT1C seems similar to that of CMT1A, with onset between the first and third decades and MNCV between 16 and 25 m/s,^{42,43} as well as progressive sensorimotor nerve involvement. *SIMPLE* mutations are a rare cause for CMT, making up 0.6% to 1.2% of demyelinating CMT cohorts.^{24,42}

CMT1D

CMT1D is caused by mutations in the *EGR2* gene at chromosome 10q21.1-q22.1.⁴⁴ Patients typically present in infancy with severe symptoms and may have congenital hypomyelination (hypotonia, delayed motor milestones, MNCV < 10 m/s).⁴⁵ Cranial nerve involvement may also be present.^{45,46} Recessive inheritance has also been described with this gene causing CMT4E, which seems to have a similar phenotype.

CMT1E

Point mutations in the *PMP22* gene cause CMT1E or HNPP, depending on the function of the mutation. Those with CMT1E tend to have earlier onset and more severe symptoms than those with CMT1A, but this is not invariable.^{47,48} MNCV in severely affected patients are markedly reduced, usually less than 10 m/s.⁴⁷ Onset within the first 2 years of life presenting with delayed walking is not uncommon. CMT1E is a rare form of CMT, accounting for about 1% of people with genetically confirmed CMT.²⁴

CMT2**CMT2A**

CMT2A is caused by mutations in the *MFN2* gene.⁴⁹ This is the most common type of CMT2, accounting for approximately 21% of axonal CMT.²⁵ People with CMT2A usually, though not always, have a severe phenotype, with onset in infancy or early childhood and usually needing a wheelchair for ambulation by 20 years of age.^{25,49} It may be difficult to perform NCSs and obtain responses for those with severe muscle atrophy and thus people who have severe symptoms without recordable potentials should be screened for CMT2A. The minority of patients may present with a mild or moderate axonal phenotype.²⁵ There are many polymorphisms in *MFN2* so that care must be taken to ensure that mutations are disease-causing. Most disease-causing mutations are in the GTPase domain, coiled-coil domains, or in other evolutionary conserved regions of the protein.²⁵

CMT2B

CMT2B is caused by mutations in the *RAB7* gene.⁵⁰ This type of CMT is distinguished by distal sensory loss that often leads to foot ulcerations and subsequently infections and amputations^{50–53} in addition to typical motor signs. Nerve conduction often have reduced amplitude with normal or near-normal velocities.^{50–53} Sensory loss is often severe such that patients may be clinically indistinguishable from those with hereditary sensory and autonomic neuropathy (HSAN) type 1.

CMT2C

CMT2C is caused by mutations in the *TRPV4* gene.^{54–56} CMT2C is characterized by a predominantly motor axonal neuropathy and vocal cord and diaphragmatic paresis, often presenting with hoarseness or stridor.^{54–57} Sensorineural hearing loss and bladder urgency and incontinence have been reported.⁵⁴ CMT2C is allelic with spondylometaphyseal dysplasia, metatropic dysplasia, and brachyolmia, and thus may have some overlapping characteristics such as short statures and scoliosis.^{55,58}

CMT2D

CMT2D is an axonal neuropathy caused by mutations in the *GARS* gene.⁵⁹ People with CMT2D typically have upper extremity weakness greater than and/or before lower extremity weakness and wasting, with a split-hand appearance of more atrophy in the FDI and thenar eminences and less so in the hypothenar eminence.^{59,60} CMT2D is allelic with distal spinal muscular atrophy type V (dSMA-V), with the distinguishing feature being lack of sensory involvement in dSMA-V.⁶⁰

CMT2E

CMT2E is caused by mutations in the neurofilaments light polypeptide (*NEFL*) gene.⁶¹ NCSs may be axonal or in the demyelinating range.^{62–64} Those with demyelinating conduction may have a severe early onset or a childhood presentation.⁶⁴ This is

considered an axonal form of CMT because neurofilaments are components of the axon, not myelin.⁶⁵

CMT2F

CMT2F is caused by mutations in the *HSPB1* gene, a member of the heat shock protein (HSP)-27 superfamily.⁶⁶ Most people with mutations in this gene have distal hereditary motor neuropathy (dHMN), a pure motor phenotype,^{67,68} though some will have sensory findings on examination and electrophysiology.⁶⁹ Impairment typically begins in the distal legs and progresses slowly to the distal arms and then proximal legs.⁶⁸ There has been one report of presumed AR inheritance with mutations in this gene.⁶⁸

CMT2L

CMT2L is caused by mutations in the *HSPB8* gene, also a member of the *HSP* superfamily, and is also known as *HSP22*.⁷⁰ Mutations in this gene have also been found to cause dHMN type II.⁷¹ Scoliosis and proximal weakness have been reported.⁷² Mutations in this gene are a rare cause of CMT.

CMT2K

CMT2K is caused by heterozygous mutations in the *GDAP1* gene, though recessive forms of CMT with mutations in this gene are called CMT4A and are likely more common.⁷³ Thus far, five mutations have been found to cause CMT2K: 358 C>T (p. R120W),^{74,75} 469A>C (p.T157P)^{75,66} 678A>T (p.R226S),⁷⁶ 101C>G (p.S34C),⁷⁶ and 23delAG (p.G10fs).⁷⁶ Phenotypes range from mild adult onset and slowly progressive to severe childhood onset.⁷³⁻⁷⁶ One study found that 3 out of 11 families with CMT2 had a dominantly inherited mutation in *GDAP1*,⁷⁶ indicating that this may be a significant cause of axonal CMT.

CMT4

CMT4A

CMT4A is caused by two recessive mutations in the *GDAP1* gene.⁷³ People with CMT4A typically have an early onset and severe sensorimotor neuropathy^{73,77} that may be demyelinating or axonal in presentation.^{78,79} Phenotype is typically severe, with first symptoms being noted in childhood and eventual progression to wheelchair not uncommon.^{79,80} Vocal cord paralysis or hoarseness has also been reported.^{79,80} Nerve conductions have been described as axonal or demyelinating, which has led to some confusion about the cell type of origin for the disease. *GDAP1* is a nuclear encoded gene that plays a role in mitochondrial fission or fragmentation, as opposed to *MFN2*, the causal gene for CMT2A, which plays an important role in mitochondrial fusion.

CMT4B1

CMT4B1 is caused by mutations in the myotubularin-related protein (*MTMR*)-2 gene.⁸¹ Patients typically have demyelinating MNCV.⁸² Onset is usually in childhood and causes distal weakness that progress proximally, often leading to wheelchair use by adulthood.⁸³ Diaphragmatic and facial weakness may occur.^{84,85}

CMT4B2

CMT4B2 is caused by mutations in *SBF2*, also known as *MTMR13*.^{86,87} Nerve conductions are usually demyelinating.^{86,87} Onset is typically in childhood, though later than in CMT4B1.⁸⁷ Nerve biopsies showing focally folded myelin are characteristic of CMT4B1 (*MTMR2* mutations) and CMT4B2 (*MTMR13* mutations).

CMT4C

CMT4C is caused by mutations in the *SH3TC2* gene.⁸⁸ In addition to demyelinating sensorimotor neuropathy, scoliosis or kyphoscoliosis are hallmark features of this condition,^{88–92} though not universally present. Patients often present in childhood with delayed walking, distal weakness, foot deformities, or scoliosis.^{88–91,93} Cranial nerve involvements may also be present.^{90,91,93} Although prevalence numbers are not known in all populations, there is evidence that CMT4C may be the most common of the AR-inherited neuropathies.⁹²

CMT4F

CMT4F is caused by mutations in the *PERIAXIN* gene (*PRX*).^{94,95} Patients have demyelinating conduction and severe early onset sensorimotor neuropathy.^{94,96} Sensory ataxia may be present,^{94,96,97} as might scoliosis.⁹⁶ Many sequence changes in the *PRX* gene have been found to be benign variants (www.molgen.ua.ac.be/cmtmutations), and variants of uncertain significance within the gene should be further investigated before determining if they are disease-causing mutations.

CMT4J

CMT4J is caused by mutations in the *FIG4* gene.⁹⁸ Patients may have demyelinating conduction and a severe motor phenotype, possibly asymmetric, with onset in early childhood. Rapid progression to a wheelchair in adulthood has been described for patients who were only mildly affected in their first two decades of life.^{98,99} Early death has been reported (47 years of age).⁹⁹ Abnormalities on EMG may be similar to those seen in motor neuron disease, including fibrillations, positive waves, and reduced motor unit action potentials of long durations. However (see previous discussion), NCS may be in the demyelinating range despite these EMG changes.⁹⁹

CMTX**CMT1X**

CMT1X is caused by mutations in the *GJB1* gene, encoding the protein Cx32.⁶ CMT1X is the second most common form of CMT, found in at least 10% of all patients.²⁴ Men typically have more severe symptoms than women with the condition,¹⁰⁰ and tend to have marked atrophy of the intrinsic hand muscles and all compartments of the calf muscles. Most men will have symptoms in childhood, though about 20% have a later age of onset.²⁴ Men with CMT1X have been reported to have transient stroke-like episodes with MRI changes following a stressor.¹⁰¹ Whereas two out of three women with CMT1X will have slowly progressive mild symptoms, one out of three do have moderate neuropathy more similar to men with the condition.¹⁰⁰ Men with MNCV often present between 25 and 45 m/s, whereas women usually have MNCV greater than 35 m/s.²⁴

HSAN

The HSANs are characterized by a predominant (although not always exclusive) sensory presentation. Patients may develop distinct clinical phenotypes according to the genetic abnormality, including distal lower limb sensory loss and neuropathic pain, congenital insensitivity to pain, or pure autonomic dysfunction. Most HSAN syndromes are AR and early-onset, although some can be autosomal dominant. HSAN subtypes are described in **Table 2**.

dHMNs

The dHMNs are inherited neuropathies that are exclusively motor in nature but are similar to CMT in any other way. Specifically, they are also length-dependent and

Type	Inheritance	Gene or Locus	Specific Phenotype
HSAN I	AD	SPTLC1	Mainly sensory, sensory complications, motor involvement variable, men may be more severely affected
CMT2B	AD	RAB7A	Sensorimotor, sensory complications, no pain
HSAN IB	AD	3p22–p24	Sensory, cough, gastroesophageal reflux
HSAN II	AR	WNK1	Severe sensory complications, mutilations, onset first 2 decades
HSAN III	AR	IKBKAP	Familial dysautonomia or Riley-Day syndrome, prominent autonomic, absence fungiform papillae of the tongue
HSAN IV	AR	NTRK1	Congenital insensitivity to pain with anhidrosis, severe sensory, anhidrosis, mental retardation, unmyelinated fibers mainly affected
HSAN V	AR	NTRK1	Congenital insensitivity to pain with mild anhidrosis, no mental retardation, small myelinated fibers mainly affected
HSAN V	AR	NGFB	Congenital insensitivity to pain, minimal autonomic, no mental retardation, mainly unmyelinated fibers affected
Channelopathy-associated insensitivity to pain	AR	SCN9A	Congenital insensitivity to pain

Abbreviations: AD, autosomal dominant; IKBKAP, inhibitor of kappa light polypeptide gene enhancer in B cells, kinase complex-associated protein; NGFB, nerve growth factor beta polypeptide; NTRK1, neurotrophic tyrosine kinase receptor type 1; RAB7, RAB7, member RAS oncogene family; SCN9A, sodium channel, voltage-gated, type IX, alpha subunit; SPTLC1, serine palmitoyl-transferase, long-chain base subunit-1.

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usually slowly progressive. Some of the dHMNs are actually caused by mutation in genes that are also related to CMT. **Table 3** is a description of dHMN subtypes and their main features.

Inherited Neuropathies in Multisystem Genetic Disorders

Inherited neuropathies can be part of a more generalized genetic disease that affects other neurologic and nonneurologic systems. Examples of genetic neurologic disorders that can present with peripheral neuropathies are the spinocerebellar ataxias and the hereditary spastic paraplegias. Metabolic disorders are another cause of multisystem diseases that also affect the peripheral nervous system. This group includes some leukodystrophies (metachromatic, Krabbe, adrenoleukodystrophy),

Table 3
Classification of the dHMNs

Type	Inheritance	Gene or Locus	Specific Phenotype
dHMN I	AD	Unknown	Juvenile-onset dHMN
dHMN II	AD	HSPB1 (HSP27)	Adult-onset typical dHMN, CMT2F
dHMN II	AD	HSPB8 (HSP22)	Adult-onset typical dHMN, CMT2L
dHMN III	AR	11q13	Early onset, slowly progressive
dHMN IV	AR	11q13	Juvenile onset, diaphragmatic involvement
dHMN V	AD	GARS	Upper limb onset, slowly progressive, CMT2D
dHMN V	AD	BSCL2	Upper limb onset, ± spasticity lower limbs, Silver-Russell syndrome
dHMN VI	AR	IGHMBP2	Spinal muscle atrophy with respiratory distress, infantile-onset respiratory distress
dHMN VIIA	AD	2q14	Adult onset, vocal cord paralysis
dHMN VIIB	AD	DCTN1	Adult onset, vocal cord paralysis, facial weakness
dHMN, ALS4	AD	SETX	Early onset, pyramidal signs
dHMN J	AR	9p21.1–p12	Juvenile onset, pyramidal features, Jerash
Congenital distal SMA	AD	12q23–12q24	Antenatal onset, arthrogryposis

Abbreviations: AD, autosomal dominant; BSCL2, Berardinelli-Seip congenital lipodystrophy 2 (seipin); DCTN1, dynactin1; IGHMBP2, immunoglobulin mu binding protein 2; SETX, sentaxin; SMA, spinal muscular atrophy.

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peroxisomal diseases (Fabry, Refsum), lipoprotein deficiencies (Tangier, Cerebrotendinous xanthomatosis), porphyrias, mitochondrial diseases, and the familial amyloid neuropathies. A comprehensive review of these conditions is beyond the scope of this article; however, it is important to include this group of diseases in the differential diagnosis of patients with inherited neuropathies and signs of dysfunction beyond the peripheral nervous system.

THERAPEUTIC STRATEGIES AND FUTURE DIRECTIONS

Despite the great improvement in our biologic understanding of inherited neuropathies, derived mostly from developments in molecular biology and transgenic animal models in the last 25 years, there is still no treatment available for any type of CMT. Physical therapy, occupational therapy, and a few orthopedic procedures are still the cornerstone of CMT treatment.

A dedicated, multidisciplinary rehabilitation team can significantly contribute to the management of patients with CMT and improve functionality and quality of life. Physical therapy strategies to maintain muscle strength and tone, prevent muscle contractures, and improve balance are a common need for most patients with CMT. Orthotics are also an important component of treating these patients, providing support and improving balance for ambulation. Occupational therapy focused on developing tools and strategies to help patients with activities of daily living will benefit patients with CMT, especially those with hand weakness. Tendon lengthening and tendon transfers can benefit a subset of CMT patients with muscle contractures and tendon shortening and patients with significant weakness in functionally relevant muscles, respectively; however, the optimal timing of such procedures is still controversial.

Reducing the expression of *pmp22* in Schwann cells (hence treating the overexpression of *pmp22*) is a biologic strategy being tested to treat CMT1A. High-dose ascorbic acid (vitamin C) was shown to decrease *pmp22* levels and symptoms in mice with CMT1A, so that they were able to stay on a rotating rod longer, cross a beam more rapidly, and grip for longer than untreated mice.¹⁰² Several studies have been performed in humans with CMT1A, testing different doses of vitamin C (1–4 g/d) for up to 2 years. Unfortunately, all studies failed to meet their primary outcome measures and did not show a significant effect on phenotype.^{103–106} Progesterone antagonists have also been shown to decrease *pmp22* expression in a rat model of CMT1A, improving their phenotype (specifically, the axonal loss seen during disease progression).^{107,108} Unfortunately, onapristone, the compound shown to have therapeutic effects in this study, is toxic to humans. Efforts to develop bioequivalent compounds with a better safety profile are ongoing.

Recent studies have demonstrated the role of ER accumulation of misfolded proteins and UPR activation in the pathogenesis of several animal models of CMT associated with point mutations in myelin-related genes, including *pmp22*⁸ and *MPZ*.^{9,10} Furthermore, treatment with an agent that relieves ER stress (curcumin) improved the phenotype of both models.^{11,12} Therefore, compounds that either relieve ER stress or reduced UPR activation are promising therapeutic strategies to treat patients with mutations that cause misfolded proteins to accumulate in the ER of Schwann cells.

Treatment strategies for axonal forms of CMT have not been as easily identified as for demyelinating forms. Recently, histone deacetylase-6 inhibitors have been shown to correct axonal transport defects in a mouse model of CMT2F associated with point mutations in the *HSPB1* gene, rescuing the axonal loss and clinical phenotype of these mice.¹⁰⁹ It remains to be shown whether this same strategy could be useful in other forms of axonal CMT, but correcting axonal transport defects may be a common treatment option for most of these CMT types.

Two new technologies recently developed hold enormous potential in the search for compounds to treat CMT: cellular reprogramming and high-throughput drug screening. Cellular reprogramming is a technique that allows the generation of specific cell types (including stem cell-like cells, neurons, and glia) by genetically modifying readily available somatic cells such as fibroblasts or lymphocytes.^{110,111} Using this technology, researchers are able to generate unlimited supplies of patient-specific cell lines for use in mechanistic studies and drug development.¹¹² These patient-specific cell lines will be particularly useful when combined with high-throughput screening of drug libraries containing thousands of compounds. In these highly automated platforms, the process of identifying compounds capable of correcting certain disease-related cell phenotypes is streamlined, allowing for a faster target selection of compounds to be tested in phase 1 animal studies. The use of patient-derived human cells offer the theoretical advantage of a more translational platform, which could facilitate the process of moving from phase 1 studies to human clinical trials. Whether this is actually true, remains to be proven. A recent study using cellular reprogramming successfully generated human neural crest progenitors derived from a patient with HSAN type III.¹¹³ These cells are the precursors of sensory and autonomic neurons, the cell types most affected by this condition. Interestingly, patient-derived neural crest precursors expressed very low levels of normal inhibitor of kappa light polypeptide gene enhancer in B cells, kinase complex-associated protein (*IKBKAP*) transcript, while also displaying marked defects in neuronal differentiation and migration. The investigators were also able to find compounds that, at least partially, rescued this phenotype, validating this platform for drug discovery in inherited neuropathies.

SUMMARY

Although CMT is a genetically heterogeneous condition, it is often possible to determine the type of CMT a person has by distinguishing characteristics. The prevalence of the various mutations, inheritance pattern, nerve conduction, and age of onset should be taken into account when deciding what genetic testing should be ordered. New genes causing CMT continue to be found, prevalence continues to be studied, and recommendations for testing will continue to evolve over time. Our increasing understanding of biologic processes involved in CMT has offered new therapeutic targets for drug development and new tools recently developed hold the promise of even faster drug discovery in CMT.

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Case study

A 25-year-old man with no family history of neuropathy had been weak since infancy. He was able to stand independently by 3 years of age but was never able to run normally and always had an abnormal gait. He is currently only able to walk if wearing ankle-foot orthoses. He also has pronounced weakness with fine movements of his fingers and is unable to button his clothes, cut his own food or perform activities such as turning a key in his front door. His neurological function has been relatively stable since his teenage years. Nerve conduction studies showed markedly slowed NCVs (<10 m/s) in his upper extremities; NCV in his legs were unobtainable at routine recording sites. Compound muscle amplitude potentials were significantly reduced in the arms and absent in the legs. Sensory nerve action potentials were absent in the arms and legs. Genetic testing revealed an Arg98Cys mutation in *MPZ* (myelin protein zero) leading to a diagnosis of severe CMT1B.

Comment: In North America, if one has a genetically diagnosable form of CMT it is likely that the causal mutation is in one of four genes (PMP22, MPZ, GJB1 or MFN2) unless the family history strongly suggests an autosomal recessive inheritance pattern (multiple affected siblings with no parents affected). CMT1A, the most common form of CMT typically has NCV around 20 m/sec in the arms and a classic CMT phenotype with normal early milestones and gradual weakness developing in the first two decades of life. Delayed early milestones and NCV<10 m/s are suggestive of an early onset form of CMT1B. GJB1 mutations causing CMT1X typically have intermediately slowed NCV (35-45 m/s) with an x-linked inheritance. MFN2 mutations cause the most frequent form of CMT2. Another group of patients with CMT1B often present symptoms in adulthood, with intermediate to normal NCV.

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