Inherited Neuropathies

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Abstract

Hereditary neuropathies (HNs) are among the most common inherited neurologic disorders and are diverse both clinically and genetically. Recent genetic advances have contributed to a rapid expansion of identifiable causes of HN and have broadened the phenotypic spectrum associated with many of the causative mutations. The underlying molecular pathways of disease have also been better delineated, leading to the promise for potential treatments. This chapter reviews the clinical and biological aspects of the common causes of HN and addresses the challenges of approaching the diagnostic workup of these conditions in a rapidly evolving genetic landscape.

Keywords

- hereditary neuropathy
- Charcot-Marie-Tooth disease
- hereditary sensory and motor neuropathy
- hereditary sensory and autonomic neuropathy

Hereditary neuropathies (HN) are among the most common inherited neurologic diseases, with a prevalence of 1 in 2,500 individuals.[1,2] They encompass a clinically heterogeneous set of disorders and vary greatly in severity, spanning a spectrum from mildly symptomatic forms to those resulting in severe disability. The most common form of HN, Charcot-Marie-Tooth disease (CMT; also called hereditary motor and sensory neuropathy [HMSN]), manifests with slowly progressive muscle weakness and sensory loss—with symptoms emerging in a length-dependent fashion. There are also motor and sensory predominant forms of HN, referred to as hereditary motor neuropathy (HMN) and hereditary sensory neuropathy (HSN), respectively. These diseases can be viewed along a spectrum of motor and sensory involvement, from purely motor and motor predominant (HMN) neuropathies, through motor *and* sensory (CMT) neuropathies, to sensory predominant and pure sensory (HSN) neuropathies; for simplicity, we designate all diseases along the spectrum as "CMT and related disorders." In addition to the sensory or motor or both symptoms, patients with HN often develop foot deformities including pes cavus and pes planus, as well as other musculoskeletal complications such as scoliosis and hip dysplasia. Select forms of HN also involve cranial nerves and respiratory function. Nevertheless, in the majority of patients with HN there is no shortening of life expectancy.

Historically, hereditary neuropathies have been classified based on the primary site of nerve pathology (myelin vs. axon) and the inheritance pattern (autosomal dominant, recessive, or X-linked). The distinction between demyelinating and axonal forms is defined by motor nerve conduction velocities (CV) in the upper extremities. Demyelinating forms of HN are those with median motor nerve CVs below 38 m/s, whereas in axonal forms CVs are greater than 38 m/s.[3] In recent years, it has become increasingly recognized that certain mutations are associated with CV slowing to an intermediate range (25–45 m/s); hence, "intermediate CMT" was designated as a separate category.[4,5] Incorporating both primary pathology and mode of inheritance, the subtypes of CMT can be divided as follows: autosomal dominant demyelinating CMT (AD CMT1), autosomal dominant axonal CMT (AD CMT2), autosomal recessive demyelinating CMT (CMT4), autosomal recessive axonal CMT (AR CMT2), X-linked CMT, dominant intermediate CMT (DI CMT), recessive intermediate CMT (RI CMT), hereditary neuropathy with liability

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to pressure palsies (HNPP), hereditary motor neuropathy (HMN), and hereditary sensory neuropathy (HSN). A letter designation follows the subtype representing the specific gene abnormality; for example, CMT1A refers to autosomal dominant CMT1 due to a duplication of the *PMP22* gene (►**Table 1**). The classification is complex and constantly evolving and not everyone agrees with the classification above, especially with regards to CMT4, where some prefer to use CMT4 for all autosomal recessive forms of CMT (demyelinating and axonal).

Since the discovery of the first CMT gene (*PMP-22*) over two decades ago, the field of HN has witnessed an explosion of gene discovery that has been facilitated by the development of advanced diagnostic techniques including next-generation sequencing. At this time, over 80 causative genes have been identified.[6] Despite this, large studies from neuromuscular centers have shown that a genetic diagnosis is being achieved in only 54% to 67% of patients.[5,7,8] Among the known forms of hereditary neuropathy, demyelinating forms are more common, with axonal forms comprising only 25% to 30% of all HN.[5,9] More causative genes have also been identified for demyelinating HNs, and the diagnostic yield is therefore higher in these patients.[5,7,8]

The increasing ease of genetic testing and the growing number of identified mutations has improved the accuracy of diagnosis of patients with HN, but has also expanded the complexity of the diagnostic process. It has become apparent that there is marked heterogeneity in the clinical phenotypes associated with individual genes, even within single families. Mutations in the *myelin protein zero* gene, for example, can result in a severe, childhood-onset, demyelinating neuropathy or a mild adult-onset axonal neuropathy.[10] Mutations in a single gene can also result in either dominantly or recessively inherited disease, as exemplified by the GDAP1 mutation.[11] Newly discovered genes have also shed light on the extensive overlap of disease categories previously thought to be distinct, particularly with regard to CMT and hereditary spastic paraparesis (HSP). Mutations in the KIF5A gene, for example, can manifest as CMT2 or HSP.[12]

Mutated proteins in HN appear to be involved in common molecular pathways including maintenance of Schwann cell cytoskeleton, myelin assembly, axonal transport, transcription and mRNA processing, maintenance of channel functions, mitochondrial function, and protein translation (►**Fig. 1**).[13,14] One way to classify HN in the future may be through the lens of specific pathophysiologic mechanisms that underlie the pathology of the Schwann cell or axon or both.[14] This will be particularly relevant if treatments can be developed that in some way target common pathophysiologic mechanisms that cause the disease phenotypes rather than by attempting to focus treatment all the way upstream on scores of mutations in the many individual genes associated with HN.

Here we will review the clinical presentations and pathogenesis of the most common forms of CMT and address the evolving diagnostic approaches to HN in the face of rapid genetic advances.

Clinical Diagnosis of Hereditary Neuropathy

The History

Making a diagnosis of HN is straightforward in a patient who presents with a slowly progressive polyneuropathy and a known family history of the disease. However, many patients present as adults without a known family history. This can be due to unrecognized cases in the family, de novo mutations or autosomal recessive cases. In the United States and north European populations, de novo mutations are a well-described cause of so-called sporadic cases in both CMT1 (e.g., some mutations in PMP22 and MPZ) and in CMT2 (e.g., CMT2A due to some MFN2 mutations), whereas in countries or ethnic groups with a high rate of consanguinity, such cases may be due to autosomal recessive inheritance. The clinical history in patients with suspected HN should include detailed questions regarding the first two decades of life, including timing of early milestones, ability to keep up with other children in races, history of ankle sprains or surgeries, and the need for special shoes or orthotics. Patients often recall having instability of the ankles and difficulty fitting shoes long before symptoms of muscle weakness or gait abnormality emerge. These early symptoms, while extremely common, are not universal, as some forms of HN (especially some axonal forms) remain asymptomatic until the sixth decade.

In contrast to acquired peripheral neuropathies, HN is generally associated with few "positive" sensory symptoms such as burning or paresthesias. Pain is common, but is usually related to musculoskeletal complications. Certain forms of HN, particularly those related to *SPTLC1*, *GJB1*, and *MPZ* genes, can be associated with significant neuropathic pain, and these symptoms should not dissuade one from considering a genetic etiology.

A careful family history, including at least three generations, should be obtained and the possibility of consanguinity assessed. It is also important to consider ethnicity and geography, as AD and de novo mutations are known to be more common in the United States and in northern Europe, whereas in regions with a high rate of consanguinity, AR disease accounts for up to 50% of HN.[15,16] The presence of male-to-male transmission excludes the possibility of X-linked disease, and pure maternal inheritance may point to one of the rare mitochondrial-encoded genes associated with HN.[17]

The Examination

Gait is almost always abnormal in CMT, and is most commonly the high stepping gait that results from bilateral foot drop. Cranial nerve examination is usually normal in CMT, but pupillary abnormalities are sometimes seen (most commonly with *MPZ* mutations). The presence of ptosis might suggest mitochondrial disease,[18] and deafness can be seen with specific mutations (e.g., *NDRG1*) or when CMT is severe. Hoarseness can be a clue to vocal cord involvement, and in severe forms of CMT (notably those related to *MTMR2* mutations) facial weakness and dysphagia can occur.[19] The motor examination involves a careful survey of the distribution of muscle weakness and atrophy. Although common forms of

Table 1 Causative genes and clinical features of hereditary neuropathy

Type (OMIM number)	Gene	Phenotype
Autosomal dominant CMT1		
CMT1A (118220)	17p dup. (*PMP22*) *PMP22* point mutation	Classic CMT1 Classic CMT1; DSD; CHN (rarely recessive)
CMT1B (118200)	*MPZ*	CMT1; DSD; CHN; CMT2 (rarely recessive)
CMT1C (601098)	*LITAF*	Classic CMT1
CMT1D (607678)	*EGR2*	Classic CMT1; DSD; CHN
CMT1F (607734)	*NEFL*	CMT2 but can have slow MCV in the CMT1 range (rarely recessive)
CMT1 plus (614434)	*FBLN5*	Macular degeneration; cutis laxa; HMN; slow NCV
SNCV / CMT1 (608236)	*ARHGEF10*	Asymptomatic slow conduction velocities
Hereditary neuropathy with liability to pressure palsies		
HNPP (162500)	17p del. (*PMP22*) *PMP22* point mutation	Typical HNPP Typical HNPP
Autosomal recessive CMT1		
CMT4A (214400)	*GDAP1*	CMT2, usually severe early onset Vocal cord and diaphragmatic paralysis described
CMT4B1 (601382)	*MTMR2*	Severe CMT1; facial; bulbar; focally folded myelin
CMT4B2 (604563)	*SBF2*	Severe CMT1; glaucoma; focally folded myelin
CMT4B3 (615284)	*SBF1*	CMT1; focally folded myelin
CMT4C (601596)	*SH3TC2*	Severe CMT1; scoliosis; cytoplasmic inclusions
CMT4D or HMSNL (601455)	*NDRG1*	Severe CMT1; gypsy; deafness; tongue atrophy
CMT4E (605253)	*EGR2*	CMT1; DSD; CHN phenotype
CMT4F (614895)	*PRX*	CMT1; predominantly sensory; focally folded myelin
CMT4G or HMSN Russe (605285)	*HK1*	Severe early-onset CMT1; gypsy
CMT4H (609311)	*FGD4* (Frabin)	Classic CMT1
CMT4J (611228)	*FIG4*	CMT1; predominantly motor; progressive
CCFDN (604168)	*CTDP1*	CMT1; gypsy; cataracts; dysmorphic features
CMT4	SURF-1	CMT1; encephalopathy; ataxia; reduced life span; Leigh syndrome
Autosomal dominant CMT2		
CMT2A (609260)	*MFN2*	CMT2; progressive; optic atrophy (rarely recessive)
CMT2B or HSAN1B (600882)	*RAB7*	CMT2 with sensory complications (ulcero mutilating)
CMT2C (606071)	*TRPV4*	CMT2; vocal cord paralysis
CMT2D (601472)	*GARS*	CMT2 with predominant hand wasting
CMT2E (607684)	*NEFL*	CMT2 but can have NCV in the CMT1 range (rarely recessive)

(*Continued*)

Table 1 (*Continued*)

Type (OMIM number)	Gene	Phenotype
CMT2F (606595)	*HSPB1*	Motor-predominant CMT2
CMT2I (607677)	*MPZ*	Late-onset CMT2
CMT2J (607736)	*MPZ*	CMT2 with hearing loss and pupillary abnormalities
CMT2K (607831)	*GDAP1*	Late-onset CMT2 (dominant); severe CMT2 (recessive)
CMT2L (608673)	*HSPB8*	Motor-predominant CMT2
CMTDIB or CMT2M (606482)	*DNM2*	Intermediate CMT or CMT2; cataracts; ophthalmoplegia; ptosis
CMT2N (613287)	*AARS*	Classic CMT2
CMT2P (614436)	*LRSAM1*	Mild sensory-predominant CMT2 (dominant and recessive)
CMT2Q (615025)	*DHTKD1*	CMT2
HMSNP (604484)	*TFG*	CMT2 with proximal involvement
CMT2	*MARS*	Late-onset CMT2
CMT2	*HARS*	CMT2
CMT2	*VCP*	CMT2
SPG10 (604187)	*KIF5A*	CMT; hereditary spastic paraplegia
CMT2	*MT-ATP6*	CMT2; pyramidal signs; relapsing
Autosomal recessive CMT2		
CMT2B1 (605588)	*LMNA*	CMT2 rapid progression
CMT2B2 (605589)	*MED25*	Classic CMT2
NMAN (137200)	*HINT1*	Neuromyotonia and axonal neuropathy; motor predominant
CMT2R (615490)	*TRIM2*	Infantile-onset CMT2
AR-CMT2	*IGHMBP2*	CMT2
AR-CMT2	*HSJ1*	CMT2
X-linked CMT		
CMTX1 (302800)	*GJB1*	Males CMT1 (patchy NCV); females CMT2
CMTX4 or Cowchock syndrome (310490)	*AIFM1*	CMT2; infantile onset; developmental delay; deafness; learning difficulties
CMTX5 (311070)	*PRPS1*	CMT2; deafness; optic atrophy
CMTX6 (300905)	*PDK3*	CMT2
Dominant intermediate CMT		
CMTDIB or CMT2M (606482)	*DNM2*	Intermediate CMT or CMT2; cataracts; ophthalmoplegia; ptosis
CMTDIC (608323)	*YARS*	Intermediate CMT
CMTDID (607791)	*MPZ*	Intermediate CMT
CMTDIE (614455)	*IFN2*	Intermediate CMT; focal segmental glomerulosclerosis; end-stage renal failure
CMTD1F (615185)	*GNB4*	Intermediate CMT
Recessive intermediate CMT		
CMTRIA (608340)	*GDAP1*	Intermediate CMT
CMTRIB (613641)	*KARS*	Intermediate CMT; learning difficulty; vestibular schwannoma

Table 1 (*Continued*)

Type (OMIM number)	Gene	Phenotype
CMTRIC (615376)	*PLEKHG5*	Intermediate CMT; SMA
CMTRID (616039)	*COX6A1*	Intermediate CMT; onset 1st decade
Hereditary motor neuropathy		
HMN2A (158590)	*HSPB8*	Classical HMN; dominant
HMN2B (608634)	*HSPB1*	Classical HMN; dominant
HMN2C (613376)	*HSPB3*	Classical HMN; dominant
HMN2D (615575)	*FBXO38*	Classical HMN; dominant
HMN with pyramidal features or ALS4 (602433)	*SETX*	HMN with pyramidal signs; dominant
DSMA5 (614881)	*DNAJB2* (*HSJ1*)	Classical HMN; recessive
HMN5A (600794) or SPG17 (270685)	*BSCL2*	Predominant hand wasting; silver syndrome but can have sensory involvement as in CMT2D; dominant
HMN5A (600794)	*GARS*	Predominant hand wasting; dominant
HMN5B (614751) or SPG31 (610250)	*REEP1*	Predominant hand wasting; pyramidal signs; dominant
HMN6 or SMARD1 (604320)	*IGHMBP2*	Infantile onset; respiratory distress; recessive
SMARD2 or SMAX	*LAS1L*	Infantile onset; respiratory distress; X-linked recessive
HMN7A (158580)	*SLC5A7*	Classical HMN; vocal cord palsy; dominant
HMN7B (607641)	*DCTN1*	HMN; bulbar and facial weakness; dominant
SMAX3 (300489)	*ATP7A*	Classical HMN; X-linked
SMALED (158600)	*DYNC1H1*	Congenital; contractures; lower-limb predominant; pyramidal signs; cortical migration defects; learning difficulties; dominant
SMALED2 (615290)	*BICD2*	Congenital; contractures; lower-limb predominant; pyramidal signs; dominant
PNMHH (614369)	*MYH14*	Typical HMN; distal myopathy; hoarseness; hearing loss; dominant
SPSMA (181405)	*TRPV4*	HMN; scapular winging; vocal cord palsy; dominant
HMN	*AARS*	Typical HMN; dominant
HMN	HINT1	HMN with neuromyotonia; recessive
Hereditary sensory neuropathy (also called hereditary sensory and autonomic neuropathy [HSAN])		
HSAN1A (162400)	*SPTLC1*	HSN with sensory complications (ulceromutilating); dominant
HSAN1C (613640)	*SPTLC2*	HSN with sensory complications (ulceromutilating); dominant
CMT2B (600882)	*RAB7*	HSN with sensory complications (ulceromutilating); dominant
HSN1D (613708) or SPG3A (182600)	*ATL1*	HSN with sensory complications (ulceromutilating); spasticity; dominant
HSN1E (614116)	*DNMT1*	HSN; hearing loss; dementia; dominant
HSN1F (615632)	*ATL3*	HSN; bone destruction; dominant

(*Continued*)

Table 1 (*Continued*)

Type (OMIM number)	Gene	Phenotype
HSAN2A (201300)	*WNK1*	HSN with sensory complications (ulcero-mutilating); recessive
HSAN2B or HSAN1B (613115)	*FAM134B*	HSN with sensory complications (ulcero-mutilating); recessive
HSN2C (614213) or SPG30 (610357)	*KIF1A*	HSN with sensory complications (ulcero-mutilating); recessive
HSAN3, familial dysautonomia or Riley–Day (223900)	*IKBKAP*	Ashkenazi Jewish; autonomic dysfunction; HSN; absent fungiform papillae; recessive
Insensitivity to pain (24300), paroxysmal extreme pain disorder (167400), primary erythermalgia (133020), small-fiber neuropathy	*SCN9A*	Recessive: Insensitivity to pain Dominant: Paroxysmal extreme pain disorder; primary erythermalgia; small fiber neuropathy
CIPA or HSAN4 (256800)	*NTRK1*	Congenital insensitivity to pain with anhydrosis; recessive
HSAN5 (608654)	*NGF-B*	Insensitivity to pain; recessive
HSAN6 (614653)	*DST*	Ashkenazi Jewish; autonomic dysfunction; HSN; absent fungiform papillae; death by age 2; recessive
HSAN7 (615548)	*SCN11A*	Congenital insensitivity to pain with hyperhidrosis and gastrointestinal dysfunction; dominant
HSAN and dementia	*PRNP*	Autonomic dysfunction; sensory loss; dementia; dominant
Hereditary sensory neuropathy with spastic paraplegia (256840)	*CCT5*	HSN with sensory complications (ulcero-mutilating) and spastic paraplegia; recessive

Abbreviations: CHN, congenital hypomyelinating neuropathy; CMT, Charcot-Marie-Tooth disease; DSD, Dejerine-Sottas disease; HMN, hereditary motor neuropathy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; HSN, hereditary sensory neuropathy; NCV, nerve conduction velocity; SMA, spinal muscular atrophy; SNCV, slowed nerve conduction velocity.

HN manifest with wasting of the anterior compartment of the leg and foot dorsiflexion weakness, motor predominant forms can begin with posterior calf wasting, plantar flexion weakness and "knee bobbing."[20,21] Sensory examination will often uncover deficits of which the patient is unaware. Superficial sensory nerves such as the radial or great auricular nerve can be palpated to assess for nerve enlargement, a heralding feature of longstanding myelin breakdown and repair. Reflexes are generally absent or attenuated in HN; however, with certain axonal and motor-predominant forms (*MFN2* and *HSPB1* mutations), lower extremity reflexes can be preserved or even heightened. The presence of marked hyperreflexia, however, should lead one to consider alternative diagnoses such as HSP. The presence of cerebellar ataxia broadens the differential diagnosis to include spinocerebellar ataxia and related conditions (Friedreich ataxia and autosomal recessive spinocerebellar ataxia of Charlevoix-Saguenay [ARSACS]). Finally, evaluation should include a musculoskeletal examination with attention to foot deformities (pes cavus/planus, hammer toes, Achilles tendon tightness), scoliosis, and scapular winging, as well as a careful general medical examination for diagnostic clues (e.g., curly hair in giant axonal neuropathy).

Electrophysiology

Axonal and demyelinating forms of HN are indistinguishable on clinical grounds alone, making electrophysiology an essential part of the evaluation. In addition, nerve conduction studies (NCSs) allow the examiner to distinguish sensory motor neuropathies from pure sensory and pure motor forms of CMT. If demyelination is present, it is important to distinguish uniform findings from those with a patchy or asymmetric distribution and to assess for other features of "acquired" demyelination including partial conduction block and temporal dispersion. It is becoming increasingly recognized, however, that electrophysiological features previously associated with acquired neuropathies (i.e., chronic inflammatory demyelinating polyneuropathy [CIDP]) can also occur with certain forms of HN (►**Table 2**).[22–24] It is therefore important to consider these diagnoses, and Charcot-Marie-Tooth disease type X (CMTX) in particular given its prevalence, in patients with CIDP who show little improvement with immunotherapy.

The severity of clinical symptoms in HN correlates best with the degree of axonal loss rather than demyelination as seen on NCS. CMT1A patients with markedly slowed motor

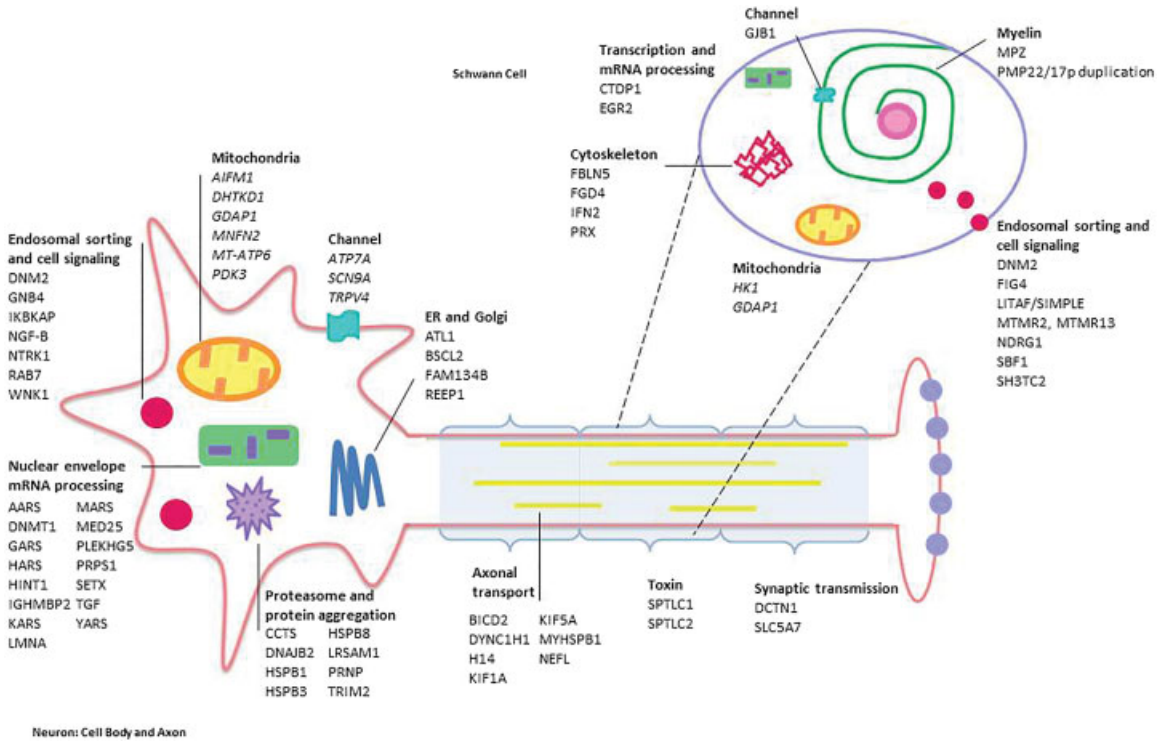

Fig. 1 Pathomechanisms in hereditary neuropathy.

conduction velocities can have little or no weakness, while significant motor amplitude reduction is associated with muscle weakness and atrophy. Electromyography (EMG) in HN most often demonstrates chronic neurogenic injury. Electromyography is especially helpful in distinguishing motor predominant neuropathies from distal myopathies, which can present with a similar clinical phenotype, as well as in detecting subtle abnormalities of early motor involvement before NCS changes are evident.

Magnetic Resonance Imaging

Magnetic resonance imaging of the lower limbs (calf and thigh muscles) is increasingly used as a diagnostic tool in hereditary myopathies, and although not in routine use yet in HN patients, the patterns of muscle involvement in patients correspond both to the clinical examination and the EMG and may in the future be used as an early marker for disease and to monitor therapies.

CMT Neuropathy Score (CMTNS)

The CMT Neuropathy Score (CMTNS) is a 36-point composite score based on patients' symptoms, signs, and neurophysiology that was developed in an effort to standardize the evaluation of patients with HN. Based on the CMTNS, patients can be classified as having mild, moderate, or severe disease (CMTNS scores of <10, 11–20, or >20, respectively).[25–27]

Differential Diagnosis and the Need for Additional Diagnostic Studies

The most important alternative diagnosis to consider when evaluating a patient for HN is that of an immunomediated, and therefore treatable, neuropathy. In the appropriate clinical context (rapid symptom progression with "acquired" features on NCS, lack of clear childhood symptoms or family history), a cerebrospinal fluid (CSF) examination, lumbar spine MRI to evaluate for nerve root enhancement, and (in select cases) a nerve biopsy should be performed. The findings must be interpreted cautiously, however, as both modest elevations in CSF protein and nerve root thickening have been reported in patients with HN.[23,28,29] It is important to note that pes cavus can be seen in conditions other than HN, including acquired neuropathy, myelopathy, and in the absence of either peripheral or central nervous system pathology. In daily practice, the most useful tool in differentiating HN from acquired neuropathies is a careful history.

Genetic Testing

Genetic testing for CMT and many other neurologic conditions has traditionally involved sequential testing of individual genes using Sanger sequencing. This approach involves sequencing the most promising candidate gene after careful phenotyping, and if negative the next most likely candidate is tested. Using this approach, large studies from neuromuscular centers have shown that a genetic diagnosis is being achieved in 54% to 67% of patients.[5,7,8] Although there are over 80 potential causative genes, it is important to recognize that over 90% of identified mutations in HN have repeatedly been shown to involve one of only four genes: PMP-22, GJB1, MPZ, and MFN2, with mutations in PMP-22 being by far the most common.[5,7,8,30]

The advent of multiple parallel or next-generation sequencing (NGS) has transformed the approach to genetic

Table 2 Hereditary neuropathies with electrophysiology resembling acquired demyelination (chronic inflammatory demyelinating polyneuropathy)

GJB1
SH3TC2
FIG4
SPTLC1
MPZ
EGR2

testing in CMT.[24] The technology allows the mass sequencing of a selection of genes (panels), the exome (containing only the protein-encoding sequences), or the whole genome in a matter of days. There is a compromise, however, whereby for a given cost, either a select, usually disease-specific number of genes can be screened with good coverage (depth) or a large number of genes (e.g., a whole exome) can be screened but with less depth, so that the chance of missing a pathogenic mutation increases. Currently, the most common method employed is to screen for mutations in patients with CMT and related disorders using targeted panels, except in the case of CMT1 in which testing for the 17p duplication is done first as it is cheap and the hit rate is high. Furthermore, a current disadvantage of NGS is that it is currently unable to reliably detect large exonic duplications and deletions, such as the 17p duplication and deletion seen in CMT1A and HNPP, respectively. Next-generation sequencing is a rapidly advancing field, however, and it is likely that as the technology advances and the cost falls, whole exome (and eventually whole genome) sequencing will replace disease-specific panels.

The major challenge in diagnostic practice with the use of NGS techniques is determining if a mutation is pathogenic. It is estimated that the average individual carries 400 potentially pathogenic variants in their exome; using a CMT diagnostic panel encompassing up to 50 genes, it is usual to find several potentially pathogenic variants in more than one gene.[31] Determining which mutation is the causative one requires several approaches.

First, it is important to determine whether the patient's phenotype fits with what has already been described for the gene. If a mutation has previously been published for the patient's phenotype then this often (but not always) provides further evidence for the pathogenicity of a mutation. The caveat to this is that many published genes and mutations have only been described in single families and doubt therefore remains as to their true pathogenicity. With NGS, we are also seeing CMT caused by genes that traditionally cause a different phenotype, for example, Atlastin 1 causing HSN rather than hereditary spastic paraparesis, so the broadening phenotypes seen with different genes needs to be kept in mind.

Second, it is important to determine whether the mutation segregates with the disease. This requires that both affected and unaffected family members be examined with neurophysiology and DNA testing. As some forms of axonal neuropathy may manifest after the fifth decade, care must be taken in labeling a family member as unaffected.

Third, several useful predictive programs are freely available online (e.g., Sibyl, PON-P2, Predict SNP, META-SNP) that aim to predict the pathogenicity of a missense mutation. Although these programs can be helpful, it is worth remembering that for many known pathogenic mutations some of these programs have failed to predict pathogenicity. Other tools can be used to both investigate whether the substituted amino acid is conserved across species, as mutations in amino acids that are not conserved are less likely to be pathogenic, (http://genetics.bwh.harvard.edu/pph2/) and to search for novel mutations on public databases of single nucleotide polymorphisms (e.g., dbSNP and the exome variant server), which will reveal whether the novel variant is present in "healthy controls." The increasing information about polymorphisms in different ethnic groups being gained from NGS will greatly help in determining if a mutation is pathogenic in the future.

Neuropathies Related to *Peripheral Myelin Protein 22* (*PMP-22*) Gene Mutations

Duplications in PMP-22

CMT1A is the most common form of HN, accounting for 50% to 60% of all genetically confirmed HNs and 60% to 80% of all cases of CMT1.[5,7,8,13,30] It is an AD disease, so there is commonly a positive family history; however, de novo mutations are reported.[32] As demonstrated in Case 1 below, the disease manifests as the classic CMT phenotype of slowly progressive, length-dependent weakness and sensory loss, which is often but not always accompanied by pes cavus. Patients usually walk on time and become aware of symptoms in early childhood. They are likely to seek medical care between the first and third decade, when increasing ankle weakness, gait difficulty, and pain related to foot deformities set in.[33] Examination is notable for loss of muscle bulk and weakness of the anterior $>$ posterior compartment of the leg and the intrinsic hand muscles. Length-dependent sensory loss is usually present, starting with loss of pinprick and vibration, but ultimately involving all modalities.[33] Reflexes are attenuated or absent. Minor asymmetries on examination have been reported in up to 20% of patients with CMT1A.[34] Hip dysplasia is more common than with other forms of CMT, and X-rays should be obtained to screen for this.[35] Electrophysiology in CMT1A invariably reveals marked, uniform slowing of the motor CV ($<$38 m/s) and reduced motor and sensory amplitudes in a length-dependent pattern. Nerve biopsy, which is no longer employed for diagnosis, shows onion bulbs, the hallmark findings of chronic peripheral nerve demyelination (►**Fig. 2**).

On average, patients with CMT1A experience a mild-to-moderate degree of disability, often requiring ankle-foot orthotics and sometimes foot surgery, but rarely relying on a wheelchair.[6] Lifespan is usually not affected. Commensurate with this, CMTNS of 13.2 to 14.6 have been reported in large patient cohorts.[7,36] Rarely, the disease presents with a severe

phenotype, historically referred to as "Dejerine Sottas disease," with profound slowing of motor CVs (<10 m/s) and onset in infancy with delayed ambulation. Significant interfamilial phenotypic variability has been observed in CMT1A, suggesting that environmental factors and genetic modifiers may be influencing disease severity.

CMT1A results from a 1.4 million base pair duplication on chromosome 17p11.2 containing the *PMP-22* gene.[6] PMP-22 is a membrane glycoprotein that accounts for 5% of myelin sheath protein and plays an important role in the synthesis and assembly of myelin.[6,14] The functional role of the protein and mechanism by which abnormal copy numbers result in disease is not fully understood. Several potential mechanisms include the formation of abnormal aggregates by the mutated protein, abnormal interactions with myelin protein zero (another myelin protein) resulting in instability of the myelin sheath, and the blocking of wild type PMP-22 transport to the cell membrane by mutant protein.[14,37,38]

Given the prevalence of CMT1A, much of the therapeutic investigation in HN has been focused on reducing expression of PMP-22. The discovery that ascorbic acid (AA) lowers PMP-22 expression in transgenic mouse models and improves the phenotype motivated several large clinical trials evaluating varying doses of AA in CMT1A patients over a 2-year period. Unfortunately, the trials failed to demonstrate any clinical benefit.[36,39–41] Other potential therapies are under investigation in preclinical models at present.

Case 1

An 18-year-old woman presented to a neuromuscular clinic with gait difficulty and foot pain. As a child, she walked on time, but was always last in school races and had high arched feet. In adolescence, she experienced frequent ankle sprains and suffered from hip, knee, and foot pain. She was no longer able to run and noted that her hands fatigued during school examinations. The patient's sister, father, and grandfather had similar symptoms. Examination revealed a mildly unsteady, steppage gait and an inability to walk on the heels. She had wasting of the intrinsic hand muscles and from the midthigh down, pes cavus, tightness of the Achilles tendons, and mild scoliosis (►**Fig. 3**). Motor testing was notable for MRC grade ⅘ weakness of the intrinsic hand muscles, ⅖ foot dorsiflexion, and ⅘ foot eversion. Foot inversion was strong. Sensory examination revealed length dependent loss to all modalities. The patient was areflexic and plantar responses were flexor (►**Table 3**).

Given the presence of a likely AD pattern of inheritance (male-to-male transmission excludes the possibility of X-linked disease in this case) and uniform CV slowing on NCS, genetic testing for the *PMP-22* duplication was obtained and was positive.

Deletions in PMP-22

Interestingly, deletions of the same 1.4 million base pair on chromosome 17p11.2, which is duplicated in CMT1A, result in a different clinical phenotype referred to as hereditary neuropathy with liability to pressure palsy (HNPP).[42] Patients with HNPP develop recurrent mononeuropathies at common sites of compression following minimal injury. Often, there is a spontaneous recovery; however, over time the deficits can accumulate, and a length-dependent neuropathy can develop. Cranial neuropathies and brachial plexopathy also occur, but are infrequent.

Electrophysiology is extremely helpful in the diagnosis of HNPP and reveals classic findings of CV slowing and conduction block at multiple entrapment sites, which may be largely asymptomatic to the patient. Reduced sensory amplitudes may reveal the presence of a mild generalized sensory

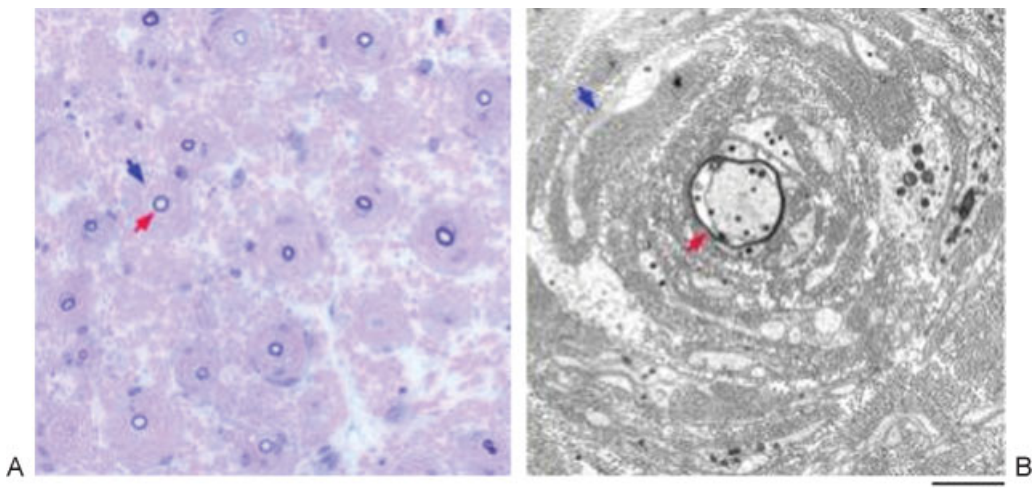

Fig. 2 Morphological appearances of sural nerve biopsy in a patient with Charcot-Marie-Tooth disease 1A (CMT1A). Semithin resin preparation (**A**) stained with methylene blue azure-basic fuchsin (MBA-BF) shows a transverse section of a nerve fascicle in which there is reduced density of myelinated fibers. All the remaining fibers are thinly myelinated (*red arrow*) and surrounded by multiple layers of Schwann cell processes forming so-called onion bulbs (*blue arrow*) indicative of chronic demyelinating/remyelinating process. Ultrastructural examination (**B**) highlights an onion bulb formation with centrally located axon surrounded by thin myelin sheath (*red arrow*) and several concentric layers of Schwann cell profiles (*blue arrow*). Scale bar: 20 μm in (**A**) and 3 μm in (**B**).

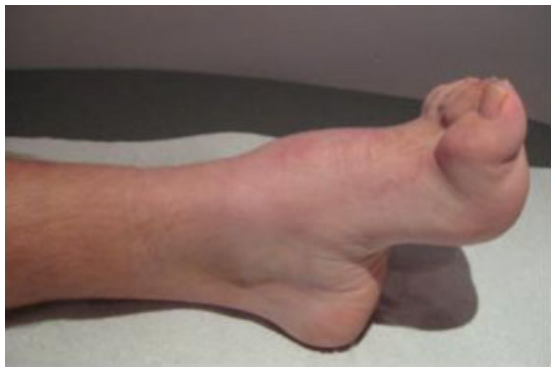

Fig. 3 Pes cavus in a patient with Charcot-Marie-Tooth disease 1A (CMT1A).

polyneuropathy. Commonly involved are the median, peroneal, ulnar, and radial nerves, and prolongation of the peroneal and median distal motor latencies is almost universal.[43–45] Nerve biopsy in HNPP demonstrates focal areas of folded myelin sheath, referred to as tomacula. These structures are unstable and are thought to contribute to the pathogenesis of HNPP.[14]

It is important to counsel patients with HNPP on ways to avoid nerve compression. Patients are particularly at risk during times of decreased awareness, such as while intoxicated or undergoing general anesthesia. The role of surgery for compressive neuropathies in HNPP remains unclear, and emphasis should be placed on preventing injury.[46]

Point Mutations in PMP-22

Point mutations in *PMP-22* also give rise to neuropathy (CMT1E), which can result in variable phenotypes including "classic" CMT, severe CMT with onset in infancy, and (in rare cases) a phenotype resembling HNPP (when the mutation causes a loss of function). Deafness has also been associated with select mutations. Overall, point mutations in the gene are far less common than either the PMP-22 duplication or deletion, accounting for less than 5% of *PMP-22*-related neuropathies.[47]

Neuropathies Related to *Myelin Protein Zero* (*MPZ*) Gene Mutations

Mutations in the *MPZ* gene (chromosome 1.q22–23) account for approximately 5% of all HNs. Patients can present with one of three clinical phenotypes: a severe, early-onset demyelinating neuropathy, the classic CMT phenotype resembling CMT1A (least common), and a milder adult-onset neuropathy with axonal or intermediate conduction velocities.[10,48] Other clinical features include tonic pupils, associated specifically with mutations resulting in axonal neuropathy, and tremor, though the latter is a relatively common feature in many forms of CMT.[49] On average, MPZ-associated neuropathies cause a moderate degree of disability (CMTNS of 13.4 in a recent multicenter analysis of 42 patients).[7]

The MPZ protein is a member of the immunoglobulin supergene family and makes up to 50% of the myelin found in the peripheral nervous system. It functions as an adhesion molecule, holding together the myelin membrane and allowing for myelin compaction.[6,48,50] Nearly all mutations that alter the coding sequence of *MPZ* result in neuropathy, with more than 200 different disease-causing mutations identified to date.[6,14,48,50,51] Although a genotype–phenotype correlation has been demonstrated, the biological basis for why specific mutations give rise to one phenotype versus another remains unknown.[10]

One of the main mechanisms by which mutations in *MPZ* are thought to cause disease involves the retention of mutated protein in the endoplasmic reticulum (ER) of Schwann cells. The retention of misfolded protein results in ER stress and activates the unfolded protein response

Table 3 Case 1 electrophysiology

	SNAP (μV)	CV (m/s)	
R. Median	Absent	–	–
R. Ulnar	Absent	–	–
R. Radial	Absent	–	–
R. Sural	Absent	–	–
	DML (ms)	**CMAP (mV)**	**CV (m/s)**
R. Median	14.2	1.5 (wrist) 1.0 (elbow)	19
R. Ulnar	7.8	2.2 (wrist) 2.0 (below elbow) 2.0 (above elbow)	17 17
R. Peroneal	–	Absent	–
R. Tibial	–	Absent	–

Abbreviations: CMAP, compound muscle action potential; DML, distal motor latency; SNAP, sensory nerve action potential.

(UPR). Unfolded protein response activation in turn causes the downregulation of protein synthesis with reduced myelination, and in more extreme cases, Schwann cell apoptosis.[14,52] Importantly, retention of mutated protein in the ER is not specific to *MPZ,* but has also been demonstrated with many point mutations in *PMP22* (CMT1E) and *GJB1* (CMTX).[53,54] Defining the role of UPR activation in CMT has led to a therapeutic strategy using Sarcoplasmic/endoplasmic reticulum calcium pump (SERCA) inhibitors, which are known to facilitate the release of misfolded protein from the ER.[55,56] A study of curcumin (a low affinity SERCA inhibitor) in mouse models of CMT1B, has demonstrated clinical, electrophysiological, and pathological improvement of neuropathy.[57] This work has motivated the clinical investigation of curcumin as a potential treatment for select forms of CMT in humans.

Case 2

A 5-year-old girl was evaluated at a neuromuscular center for gait difficulty and falls. She did not walk until age 2 and was never able to run. She had high arched feet, requiring special shoes. No family history of neuropathy was reported. Examination revealed a wide-based, steppage gait, with a tendency to invert the right foot. The patient could not rise on the heels or walk on the toes. There was wasting of the intrinsic hand muscles and the muscles of the anterior and posterior compartments of the legs. She had pes cavus, hammer toes, and notable tightness of the Achilles tendons. Motor testing revealed weakness of thumb and finger abduction and adduction, (MRC grade 4/5 APB and FDI), and of ankle dorsiflexion > plantarflexion (MRC grade 3/5 tibialis anterior and 4/5 gastrocnemius, respectively). Pin and vibration perception were reduced distal to the knees and wrists and proprioception was reduced at the toes and ankles. The patient was areflexic (►**Table 4**).

Based on the history of delayed walking, and the presence of severe demyelinating sensory motor polyneuropathy, genetic testing for *MPZ* was obtained and was positive.

Neuropathies Related to *GJB1* Gene Mutations

Mutations in *GJB1* (chromosome X13.1) give rise to CMTX1, the second most common form of HN, affecting 15% of patients with CMT.[14] Male patients have a more severe form of the disease; however, females are also usually affected and the disease is therefore considered to be X-linked dominant. Men with CMTX1 commonly present in the beginning of the second decade with progressive muscle weakness, varying degrees of sensory involvement and areflexia.[58] Up to 20% of patients have a later disease onset.[59,60] Disability tends to be in the moderate range, with reported CMTNS ranging from 11 to 16.[7,61]

A distinguishing clinical feature of CMTX1 is the often disproportionate involvement of the APB as compared with the FDI muscle, a finding referred to as "split hand syndrome." Neuropathic pain in CMTX1 is also common,[58,62] and CNS symptoms including mild hearing loss,[63] transient encephalopathy provoked by high altitude or intensive physical activity,[58] and white matter lesions on brain MRI[64,65] have been described. Women with CMTX1 develop symptoms later in life and show variable disease severity as a result of X-inactivation.[61,66,67] As demonstrated in Case 3 below, electrophysiology tends to demonstrate nonuniform, intermediate range motor CV slowing (30–40 m/s in the upper extremities).[58,68] Conduction velocities in the axonal range can also be seen, particularly in female patients.[62]

The GJB1 protein (or connexin 32) is a myelin protein that forms functional gap junctions allowing for the passage of ions and small molecules between cells.[69] Mutations in the gene usually result in abnormal gap junctions, disrupting communication between Schwann cells and neurons. In addition, mutations in *GJB1* have been shown to impair intracellular trafficking of the protein.[14,58,70] More than 400 mutations have been identified, and interestingly only one of the reported amino acid changes resulted in a polymorphism.[66] Identified mutations in CMTX1 are therefore very likely to be disease-causing as opposed to benign variants.

Similarly to *PMP-22* and *MPZ*, select mutations in the *GJB1* are known to result in abnormal accumulations of misfolded protein in the ER with subsequent activation of the (UPR). Although both Schwann cells and oligodendrocytes express GJB1, peripheral neuropathy is most often the sole manifestation of the disease, an outcome that is thought to stem from the protective role of other connexins found in oligodendrocytes.[58,71]

Case 3

An 18-year-old man presented to neuromuscular clinic with hand clumsiness and difficulty writing. An as an infant he met his milestones on time. He was always a slow runner, however, fell frequently and required insoles for his shoes at age 7. In his teenage years he developed pain in both feet and cramping in the leg muscles. He denied sensory symptoms. Family history was notable for neuropathy in the patient's sister, mother, maternal grandfather, and maternal aunt. On examination, he had a steppage gait and could not stand on his heels. There was prominent wasting of the intrinsic hand muscles and of the legs below the level of the knees (►**Fig. 4**). He had pes cavus and hammer toes, and foot calluses were noted bilaterally. The intrinsic hand muscles, and abductor pollicis brevis muscle in particular, were weak (MRC grade 3/5 at APB, 4/5 at FDI and ADM), as was foot dorsiflexion (4/5). Sensory examination revealed loss of pin perception distal to the midfoot bilaterally as well as absent vibratory perception below the ankles. Proprioception was spared. The patient was areflexic and plantar responses were flexor (►**Table 5**).

The pronounced hand weakness with disproportionate involvement of the APB muscle, patchy CV slowing in the intermediate range, and the absence of male-to-male transmission, all suggested the presence of a *GJB1* mutation, which was confirmed. (The majority of patients with intermediate CV are known to harbor mutations in either the *GJB1* or *MPZ* gene (53% and 28% in one series).[4,72]

Table 4 Case 2 electrophysiology

	SNAP (μV)	CV (m/s)	–
R. Median	NR	–	–
R. Ulnar	NR	–	–
R. Radial	NR	–	–
	DML (ms)	**CMAP mV**	**CV (m/s)**
R. Median	6.6	1.5 (wrist) 1.2 (elbow)	8
R. Ulnar	5.0	1.4 (wrist) 1.0 (below elbow) 1.0 (above elbow)	9
L. Ulnar	6.2	2.3 (wrist)	7
R. Tibial	–	0.5 (ankle) 0.2 (popliteal fossa)	8

Abbreviations: CMAP, compound muscle action potential; DML, distal motor latency; NR, no response; SNAP, sensory nerve action potential.

Neuropathies Related to *MFN2* Gene Mutations

Mutations in the *MFN2* gene (chromosome 1p36) give rise to CMT2A, the most common form of AD axonal CMT, and account for 30% of all CMT2 cases.[5,7,8,13] Twenty percent of mutations in MFN2 are de novo.[13] Patients usually present in the first decade of life with a classical CMT phenotype. Progression tends to be more rapid than that seen in other forms of CMT, however, with up to one-third of patients developing proximal weakness, and many patients requiring a wheelchair by young adulthood.[73,74] Average CMTNS of 13 to 20 have been reported, with significantly higher scores in patients presenting by 10 years of age.[7,73,74] Like many of the HNs, *MFN2*-related neuropathy is clinically heterogeneous and milder forms do exist.

In contrast to CMT1A, some patients with *MFN2* mutations experience a marked loss of proprioception early in the disease course.[74] Asymmetrical presentations, while infrequent, have also been described.[73] In addition to the sensory and motor form of HN, mutations in *MFN2* can give rise to a pure motor neuropathy (HMN). Both the CMT2 and HMN presentations can occur in the same family, and genotype-phenotype correlations do not appear clear cut, as the same mutations are known to cause both the pure motor and sensory motor forms of the disease.[73,74]

Additional clinical features in CMT2A can include optic atrophy, hearing loss, vocal cord paralysis, and diaphragmatic weakness (particularly with advanced disease). Although most patients with optic atrophy develop this finding early in life, late-onset optic neuropathy (up to the sixth decade) has also been reported. Similarly, auditory involvement is not clearly correlated with disease severity.[73–75] Central nervous system involvement can occur in CMT2A, as evidenced by preserved or paradoxically heightened deep tendon reflexes on examination. Atrophy of the spinal cord with or without hydromyelia, as well as periventricular, brainstem, and cerebellar white matter changes have also been reported on MRI.[73,75–78]

MFN2 is a nuclear-encoded mitochondrial GTPase located on the outer membrane of mitochondria.[14,79] The protein is necessary for effective mitochondrial fusion, which is a prerequisite for mitochondrial transport.[52,79–81] In addition to disrupting fusion, mutations in *MFN2* are believed to interfere with axonal transport, which is critical to the maintenance of peripheral sensory and motor neurons with their long axon extensions.[14,82] Interestingly, there is another mitofusin (MFN1), which is also located on the outer mitochondrial membrane. Upregulation of MFN1 expression in

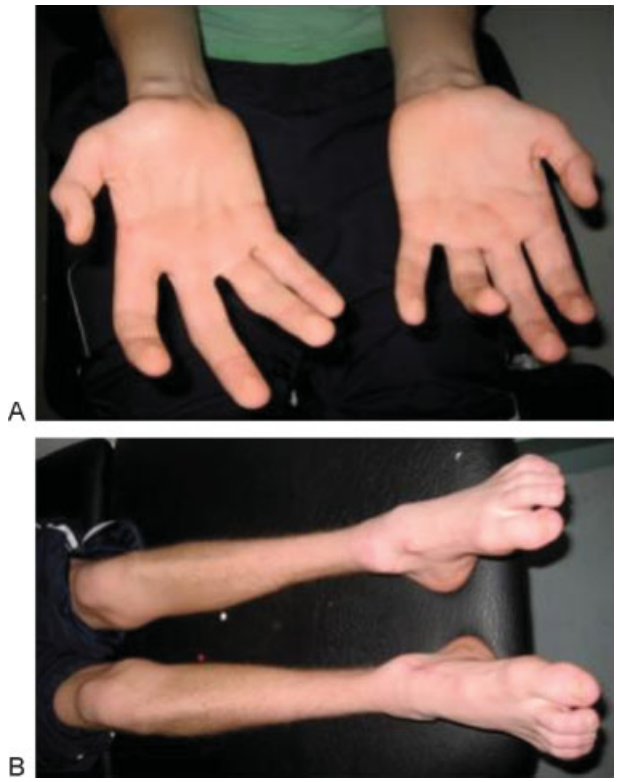

Fig. 4 Marked muscle atrophy of the hands (**A**) and legs (**B**) in patient with Charcot-Marie-Tooth disease (CMTX).

Table 5 Case 3 electrophysiology

	SNAP (μV)	CV (m/s)	–
R. Median	NR	–	–
R. Ulnar	NR	–	–
R. Radial	NR	–	–
	DML (ms)	**CMAP mV**	**CV (m/s)**
R. Median	5.1	1.9 (wrist) 1.4 (elbow)	34
L. Median	4.7	4.3 (wrist) 3.6 (elbow)	44
R. Ulnar	4.2	1.4 (wrist) 1.0 (below elbow) 1.0 (above elbow)	39 41
L. Ulnar	3.1	3.6 (wrist) 3.2 (below elbow) 3.2 (above elbow)	32 29
R. Tibial	4.1	1.0 (ankle) 0.6 (popliteal fossa)	40

Abbreviations: CMAP, compound muscle action potential; DML, distal motor latency; NR, no response; SNAP, sensory nerve action potential.

animal models has successfully promoted mitochondrial fusion, suggesting that this protein may be a therapeutic target in CMT2A.[83]

The interpretation of genetic testing results in patients with suspected CMT2A can be particularly challenging due to a large number of polymorphisms. It should be considered that the majority of pathogenic mutations are found in the region of the molecule responsible for inducing fusion, as well as in domains required to make connections between the mitochondria and the ER. These regions include the GTPase, coiled-coil, and R3 portion domains of the gene.[74]

Autosomal Recessive Forms of CMT

The AR forms of hereditary neuropathy are rare, comprising less than 10% of all CMT cases, but are more prevalent in communities with high rates of consanguinity.[13,84] Patients with these conditions usually present in childhood and may experience a more rapid progression of symptoms, with loss of ambulation occurring by the third decade of life in many patients.[13] The neuropathies also tend to be phenotypically complex with more bulbar weakness, respiratory involvement, and severe musculoskeletal deformities than is seen in the dominant forms.

The most common AR neuropathies in northern Europe and North America are those resulting from mutations in the *SH3TC2* gene (chromosome 5q32, CMT4C). Patients present with a severe, early-onset, demyelinating sensory motor neuropathy, which is often associated with severe kyphoscoliosis, a distinguishing feature of the disease. The SH3TC2 protein is involved in the trafficking of membrane components believed important for normal myelination; however, the exact mechanism of the neuropathy is unknown.[6,85]

The majority of mutations in the *GDAP1* gene also result in AR disease, though rare AD forms also exist. Motor CVs can be in the demyelinating, axonal, or intermediate range. The demyelinating form is severe and can be associated with diaphragmatic weakness and vocal cord involvement. In contrast, the rare axonal forms tend to result in milder severity and later-onset disease.[86] GDAP1 is a nuclear-encoded protein that is expressed in the mitochondria of both neurons and Schwann cells, perhaps explaining its role in both axonal and demyelinating neuropathy.[86] Like the MFN2 protein, it is located on the outer membrane of mitochondria; however, in contrast to MFN2, the protein is thought to promote fission rather than fusion of mitochondria.[6]

Sensory Predominant Forms of Hereditary Neuropathy

Hereditary sensory neuropathy (also referred to as hereditary sensory and autonomic neuropathy) comprises a rare set of heterogeneous diseases in which sensory loss is a prominent feature. The most common of these disorders is hereditary sensory and autonomic neuropathy type I (HSAN1), which results from mutations in the *SPTLC1* and *SPTLC2* genes.[22,87,88] Patients commonly present in the second or third decade, though symptom onset is highly variable. The neuropathy is characterized by dissociated sensory loss with pain and temperature affected more so than vibration and joint position sense.[22,89,90] Despite its name, HSAN1 has little autonomic involvement, but often has significant motor weakness especially later in the disease course and particularly in male patients.[22,89,90] Positive sensory symptoms such as lancinating pains are also common. The most striking feature of the disease is the propensity toward severe skin ulceration (►**Fig. 5**), which may result in the need for limb

amputation.[22,90,91] Electrophysiology in HSAN1 most often discloses an axonal sensory motor neuropathy; however, demyelinating features have also been described.[22]

The *SPLTC1* and *SPTLC2* genes (chromosome 9q22.1–22.3), encode two of the three subunits of the enzyme serine palmitoyltransferase (SPT). SPT catalyzes the condensation of L-serine and palmitoyl-CoA, in the first step toward sphingolipid formation. Mutations in SPT alter the selectivity of the enzyme, giving rise to two atypical (and potentially toxic) deoxysphingoid lipids.[92,93] It has been shown that supplementation with high doses of the enzyme's normal substrate, L-serine, shifts the pathway away from the formation of the atypical sphingolipids,[94] and improves both sensory and motor function in a mouse model of HSAN1.[94] Interestingly, the increased level of atypical sphingolipids has also been observed in diabetes, potentially implicating this pathway in diabetic neuropathy, which closely resembles HSAN1.[95,96]

Motor Predominant Forms of Hereditary Neuropathy

The distal hereditary motor neuropathies (dHMN) encompass a heterogeneous set of disorders, which manifest with slowly progressive, length-dependent motor weakness and atrophy. Upper motor neuron signs and mild sensory involvement can also be seen, and there is notable overlap between these conditions and axonal forms of CMT (CMT2), spinal muscular atrophy (SMA), and HSP.[20] The yield of genetic testing in dHMN is currently low, as 80% of patients have mutations in genes that have not yet been identified.[20] Causative genes in dHMN include *HSPB1* and *HSPB8*. Patients harboring mutations in these genes most commonly present in the 3rd to 6th decades with slowly progressive leg weakness. Foot plantarflexion is often disproportionately affected, and examination can also reveal upper motor neuron signs. Neuromuscular MRI often reveals a distinct pattern, with atrophy of the posterior compartment of the leg and relative preservation of the anterolateral musculature.[20]

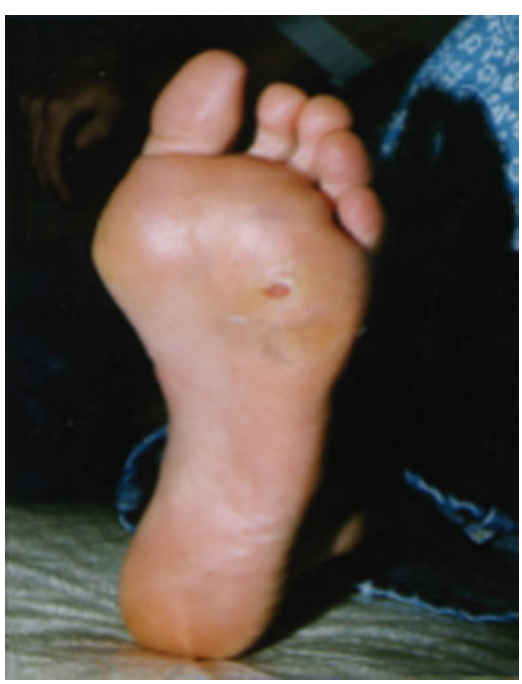

Fig. 5 Foot deformity and ulceration in patient with hereditary sensory and autonomic neuropathy type I (HSAN1).

HSPB1 and *HSPB8* encode the HSP27 and HSP22 proteins, respectively. The proteins are members of the heat shock protein superfamily and are important in maintaining the integrity of the cytoskeleton and of microtubules.[14,20] If mutated, the proteins form aggregates, which can disrupt axonal function.

Treatment Updates in Hereditary Neuropathy

No effective pharmacological treatments for hereditary neuropathy have been identified to date. Successful preclinical trials in animal models have included those of HDAC6 inhibitors in HSPB1,[97] serine in HSAN1,[94] curcumin in CMT1B,[57] and ascorbic acid,[41] progesterone antagonists (particularly Lonaprisan),[98] and neurotrophin-3[14] in CMT1A. As discussed previously, large clinical trials of ascorbic acid in CMT1A were performed and showed no clinical benefit. One of the major problems encountered in these trials was the limited capability of currently available outcome measures to capture disease progression and likewise treatment response in CMT. The CMTNS, which was the primary outcome measure, was not able to detect significant progression in the placebo group over the 2-year trial period.[36] It is clear that new quantitative outcome measures are needed to effectively capture the slow progression of these conditions.

Even in the absence of pharmacological treatment, much can be done to optimize the quality of life of patients with CMT. It is important that patients with muscle weakness or skeletal deformities work with a physical therapist, occupational therapist, and orthotist familiar with the disease. Simple devices such as ankle–foot orthotics can significantly impact a patient's ability to perform daily activities by improving ambulation and reducing pain. It is important to encourage patients to exercise.[99,100] Finally, both neuropathic and musculoskeletal pain should be assessed and treated, including using medications for neuropathic pain when indicated.

Early detection of the known complications of HN is critical. Patients with hip pain and back pain should be screened for hip dysplasia and scoliosis. In the context of certain specific mutations or in patients with severe disease, pulmonary function tests and swallowing studies should also be obtained. Sleep disorders are reported with a higher incidence in patients with CMT, and polysomnography should be considered if the history is suggestive of sleep apnea.[101] Hearing loss should be evaluated with audiology, and appropriate visual symptoms require a dilated funduscopic examination to look for optic atrophy. Regular podiatry evaluations are important for all patients with sensory nerve involvement or foot deformity. For foot and ankle deformities that are not easily corrected with bracing and other conservative measures, a prompt specialized orthopedic evaluation

should be sought. In addition to pes cavus, patients with HN frequently develop inversion of the ankle (hindfoot varus), which can cause significant damage to the joint. The timing and nature of surgical intervention in such cases has not been standardized, and studies are ongoing to address this.

Summary

Hereditary neuropathies comprise a heterogeneous set of progressive conditions resulting in the degeneration of peripheral nerves. In recent years, the number of known causative mutations of HN has rapidly increased, and the phenotypic spectrum of individual mutations has broadened. It is noteworthy, however, that over 90% of identified pathogenic mutations of HN involve one of only four genes. Unifying biological mechanisms appear to underlie many forms of HN, and are the basis for ongoing studies aimed at identifying treatments. Through the increasing use of NGS, it has also become apparent that many forms of HN fall within a spectrum of diseases and overlap with other clinical entities including HSP, mitochondrial disease, and SMA. The flood of genetic information has made the diagnostic evaluation of HN more complex and has forced clinicians to reconsider traditional classification schemes. What remains essential is that genetic information be interpreted within the context of the patient's clinical history, examination, and electrophysiology. Despite the absence of a definitive treatment at this time, patients benefit tremendously from thoughtful multidisciplinary care.

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References

1 Skre H. Genetic and clinical aspects of Charcot-Marie-Tooth's disease. Clin Genet 1974;6(2):98–118
2 Harding AE, Thomas PK. The clinical features of hereditary motor and sensory neuropathy types I and II. Brain 1980;103(2): 259–280
3 Davis CJ, Bradley WG, Madrid R. The peroneal muscular atrophy syndrome: clinical, genetic, electrophysiological and nerve biopsy studies. I. Clinical, genetic and electrophysiological findings and classification. J Genet Hum 1978;26(4):311–349
4 Liu L, Zhang R. Intermediate Charcot-Marie-Tooth disease. Neurosci Bull 2014;30(6):999–1009
5 Saporta AS, Sottile SL, Miller LJ, Feely SM, Siskind CE, Shy ME. Charcot-Marie-Tooth disease subtypes and genetic testing strategies. Ann Neurol 2011;69(1):22–33
6 Brennan KM, Bai Y, Shy ME. Demyelinating CMT-what's known, what's new and what's in store? Neurosci Lett 2015;596:14–26
7 Fridman V, Bundy B, Reilly MM, et al; on behalf of the Inherited Neuropathies Consortium. CMT subtypes and disease burden in patients enrolled in the Inherited Neuropathies Consortium natural history study: a cross-sectional analysis. J Neurol Neurosurg Psychiatry 2014
8 Murphy SM, Laura M, Fawcett K, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. J Neurol Neurosurg Psychiatry 2012;83(7):706–710
9 England JD, Gronseth GS, Franklin G, et al; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evaluation of distal symmetric polyneuropathy: the role of laboratory and genetic testing (an evidence-based review). Muscle Nerve 2009;39(1):116–125
10 Shy ME, Jáni A, Krajewski K, et al. Phenotypic clustering in MPZ mutations. Brain 2004;127(Pt 2):371–384
11 Niemann A, Wagner KM, Ruegg M, Suter U. GDAP1 mutations differ in their effects on mitochondrial dynamics and apoptosis depending on the mode of inheritance. Neurobiol Dis 2009; 36(3):509–520
12 Liu YT, Laurá M, Hersheson J, et al. Extended phenotypic spectrum of KIF5A mutations: from spastic paraplegia to axonal neuropathy. Neurology 2014;83(7):612–619
13 Bassam BA. Charcot-Marie-Tooth disease variants-classification, clinical, and genetic features and rational diagnostic evaluation. J Clin Neuromuscul Dis 2014;15(3):117–128
14 Jerath NU, Shy ME. Hereditary motor and sensory neuropathies: understanding molecular pathogenesis could lead to future treatment strategies. Biochim Biophys Acta 2015;1852(4): 667–678
15 Szigeti K, Nelis E, Lupski JR. Molecular diagnostics of Charcot-Marie-Tooth disease and related peripheral neuropathies. Neuromolecular Med 2006;8(1-2):243–254
16 Tazir M, Hamadouche T, Nouioua S, Mathis S, Vallat JM. Hereditary motor and sensory neuropathies or Charcot-Marie-Tooth diseases: an update. J Neurol Sci 2014;347(1-2):14–22
17 Pitceathly RD, Murphy SM, Cottenie E, et al. Genetic dysfunction of MT-ATP6 causes axonal Charcot-Marie-Tooth disease. Neurology 2012;79(11):1145–1154
18 Houlden H, Reilly MM, Smith S. Pupil abnormalities in 131 cases of genetically defined inherited peripheral neuropathy. Eye (Lond) 2009;23(4):966–974
19 Houlden H, King RH, Wood NW, Thomas PK, Reilly MM. Mutations in the 5′ region of the myotubularin-related protein 2 (MTMR2) gene in autosomal recessive hereditary neuropathy with focally folded myelin. Brain 2001;124(Pt 5):907–915
20 Rossor AM, Kalmar B, Greensmith L, Reilly MM. The distal hereditary motor neuropathies. J Neurol Neurosurg Psychiatry 2012;83(1):6–14
21 Rossor AM, Murphy S, Reilly MM. Knee bobbing in Charcot-Marie-Tooth disease. Pract Neurol 2012;12(3):182–183
22 Houlden H, King R, Blake J, et al. Clinical, pathological and genetic characterization of hereditary sensory and autonomic neuropathy type 1 (HSAN I). Brain 2006;129(Pt 2):411–425
23 Michell AW, Laura M, Blake J, et al. GJB1 gene mutations in suspected inflammatory demyelinating neuropathies not responding to treatment. J Neurol Neurosurg Psychiatry 2009; 80(6):699–700
24 Rossor AM, Polke JM, Houlden H, Reilly MM. Clinical implications of genetic advances in Charcot-Marie-Tooth disease. Nat Rev Neurol 2013;9(10):562–571
25 Burns J, Ouvrier R, Estilow T, et al. Validation of the Charcot-Marie-Tooth disease pediatric scale as an outcome measure of disability. Ann Neurol 2012;71(5):642–652
26 Murphy SM, Herrmann DN, McDermott MP, et al. Reliability of the CMT neuropathy score (second version) in Charcot-Marie-Tooth disease. J Peripher Nerv Syst 2011;16(3):191–198
27 Shy ME, Blake J, Krajewski K, et al. Reliability and validity of the CMT neuropathy score as a measure of disability. Neurology 2005;64(7):1209–1214
28 Ishigami N, Kondo M, Nakagawa M. [Case of Charcot-Marie-Tooth disease type 1A with increased cerebrospinal fluid proteins and nerve root hypertrophy]. Rinsho Shinkeigaku 2008;48(6): 419–421

29 Liao JP, Waclawik AJ. Nerve root hypertrophy in CMT type 1A. Neurology 2004;62(5):783
30 Latour P, Gonnaud PM, Ollagnon E, et al. SIMPLE mutation analysis in dominant demyelinating Charcot-Marie-Tooth disease: three novel mutations. J Peripher Nerv Syst 2006;11(2): 148–155
31 Wright CF, Middleton A, Burton H, et al. Policy challenges of clinical genome sequencing. BMJ 2013;347:f6845
32 Blair IP, Nash J, Gordon MJ, Nicholson GA. Prevalence and origin of de novo duplications in Charcot-Marie-Tooth disease type 1A: first report of a de novo duplication with a maternal origin. Am J Hum Genet 1996;58(3):472–476
33 Thomas PK, Marques W Jr, Davis MB, et al. The phenotypic manifestations of chromosome 17p11.2 duplication. Brain 1997;120(Pt 3):465–478
34 Pelayo-Negro AL, Carr AS, Laura M, Skorupinska M, Reilly MM. An observational study of asymmetry in CMT1A. J Neurol Neurosurg Psychiatry 2015;86(5):589–590
35 Bamford NS, White KK, Robinett SA, Otto RK, Gospe SM Jr. Neuromuscular hip dysplasia in Charcot-Marie-Tooth disease type 1A. Dev Med Child Neurol 2009;51(5):408–411
36 Pareyson D, Reilly MM, Schenone A, et al; CMT-TRIAAL; CMT-TRAUK groups. Ascorbic acid in Charcot-Marie-Tooth disease type 1A (CMT-TRIAAL and CMT-TRAUK): a double-blind randomised trial. Lancet Neurol 2011;10(4):320–328
37 Adlkofer K, Frei R, Neuberg DH, Zielasek J, Toyka KV, Suter U. Heterozygous peripheral myelin protein 22-deficient mice are affected by a progressive demyelinating tomaculous neuropathy. J Neurosci 1997;17(12):4662–4671
38 Fortun J, Verrier JD, Go JC, Madorsky I, Dunn WA, Notterpek L. The formation of peripheral myelin protein 22 aggregates is hindered by the enhancement of autophagy and expression of cytoplasmic chaperones. Neurobiol Dis 2007;25(2):252–265
39 Burns J, Ouvrier RA, Yiu EM, et al. Ascorbic acid for Charcot-Marie-Tooth disease type 1A in children: a randomised, double-blind, placebo-controlled, safety and efficacy trial. Lancet Neurol 2009;8(6):537–544
40 Lewis RA, McDermott MP, Herrmann DN, et al; Muscle Study Group. High-dosage ascorbic acid treatment in Charcot-Marie-Tooth disease type 1A: results of a randomized, double-masked, controlled trial. JAMA Neurol 2013;70(8):981–987
41 Passage E, Norreel JC, Noack-Fraissignes P, et al. Ascorbic acid treatment corrects the phenotype of a mouse model of Charcot-Marie-Tooth disease. Nat Med 2004;10(4):396–401
42 Chance PF, Alderson MK, Leppig KA, et al. DNA deletion associated with hereditary neuropathy with liability to pressure palsies. Cell 1993;72(1):143–151
43 Andersson PB, Yuen E, Parko K, So YT. Electrodiagnostic features of hereditary neuropathy with liability to pressure palsies. Neurology 2000;54(1):40–44
44 Chance PF. Inherited focal, episodic neuropathies: hereditary neuropathy with liability to pressure palsies and hereditary neuralgic amyotrophy. Neuromolecular Med 2006;8(1-2): 159–174
45 Li J, Krajewski K, Shy ME, Lewis RA. Hereditary neuropathy with liability to pressure palsy: the electrophysiology fits the name. Neurology 2002;58(12):1769–1773
46 Earle N, Zochodne DW. Is carpal tunnel decompression warranted for HNPP? J Peripher Nerv Syst 2013;18(4):331–335
47 Russo M, Laurá M, Polke JM, et al. Variable phenotypes are associated with PMP22 missense mutations. Neuromuscul Disord 2011;21(2):106–114
48 Shy ME. Peripheral neuropathies caused by mutations in the myelin protein zero. J Neurol Sci 2006;242(1-2):55–66
49 Saifee TA, Pareés I, Kassavetis P, et al. Tremor in Charcot-Marie-Tooth disease: No evidence of cerebellar dysfunction. Clin Neurophysiol 2015
50 Filbin MT, Walsh FS, Trapp BD, Pizzey JA, Tennekoon GI. Role of myelin P0 protein as a homophilic adhesion molecule. Nature 1990;344(6269):871–872
51 Suter U, Scherer SS. Disease mechanisms in inherited neuropathies. Nat Rev Neurosci 2003;4(9):714–726
52 Shy ME. Therapeutic strategies for the inherited neuropathies. Neuromolecular Med 2006;8(1-2):255–278
53 Colby J, Nicholson R, Dickson KM, et al. PMP22 carrying the trembler or trembler-J mutation is intracellularly retained in myelinating Schwann cells. Neurobiol Dis 2000;7(6 Pt B):561–573
54 Yum SW, Kleopa KA, Shumas S, Scherer SS. Diverse trafficking abnormalities of connexin32 mutants causing CMTX. Neurobiol Dis 2002;11(1):43–52
55 Egan ME, Pearson M, Weiner SA, et al. Curcumin, a major constituent of turmeric, corrects cystic fibrosis defects. Science 2004;304(5670):600–602
56 Khajavi M, Inoue K, Wiszniewski W, Ohyama T, Snipes GJ, Lupski JR. Curcumin treatment abrogates endoplasmic reticulum retention and aggregation-induced apoptosis associated with neuropathy-causing myelin protein zero-truncating mutants. Am J Hum Genet 2005;77(5):841–850
57 Patzkó A, Bai Y, Saporta MA, et al. Curcumin derivatives promote Schwann cell differentiation and improve neuropathy in R98C CMT1B mice. Brain 2012;135(Pt 12):3551–3566
58 Scherer SS, Kleopa KA. X-linked Charcot-Marie-Tooth disease. J Peripher Nerv Syst 2012;17(Suppl 3):9–13
59 Shy ME, Siskind C, Swan ER, et al. CMT1X phenotypes represent loss of GJB1 gene function. Neurology 2007;68(11):849–855
60 Bergoffen J, Scherer SS, Wang S, et al. Connexin mutations in X-linked Charcot-Marie-Tooth disease. Science 1993;262(5142): 2039–2042
61 Siskind CE, Murphy SM, Ovens R, Polke J, Reilly MM, Shy ME. Phenotype expression in women with CMT1X. J Peripher Nerv Syst 2011;16(2):102–107
62 Kleopa KA, Scherer SS. Molecular genetics of X-linked Charcot-Marie-Tooth disease. Neuromolecular Med 2006;8(1-2):107–122
63 Hahn AF, Brown WF, Koopman WJ, Feasby TE. X-linked dominant hereditary motor and sensory neuropathy. Brain 1990;113(Pt 5):1511–1525
64 Lee MJ, Nelson I, Houlden H, et al. Six novel connexin32 (GJB1) mutations in X-linked Charcot-Marie-Tooth disease. J Neurol Neurosurg Psychiatry 2002;73(3):304–306
65 Sato K, Kubo S, Fujii H, et al. Diffusion tensor imaging and magnetic resonance spectroscopy of transient cerebral white matter lesions in X-linked Charcot-Marie-Tooth disease. J Neurol Sci 2012;316(1-2):178–180
66 Bondurand N, Girard M, Pingault V, Lemort N, Dubourg O, Goossens M. Human Connexin 32, a gap junction protein altered in the X-linked form of Charcot-Marie-Tooth disease, is directly regulated by the transcription factor SOX10. Hum Mol Genet 2001;10(24):2783–2795
67 Murphy SM, Ovens R, Polke J, et al. X inactivation in females with X-linked Charcot-Marie-Tooth disease. Neuromuscul Disord 2012;22(7):617–621
68 Nicholson G, Nash J. Intermediate nerve conduction velocities define X-linked Charcot-Marie-Tooth neuropathy families. Neurology 1993;43(12):2558–2564
69 Scherer SS, Deschênes SM, Xu YT, Grinspan JB, Fischbeck KH, Paul DL. Connexin32 is a myelin-related protein in the PNS and CNS. J Neurosci 1995;15(12):8281–8294
70 Kleopa KA, Abrams CK, Scherer SS. How do mutations in GJB1 cause X-linked Charcot-Marie-Tooth disease? Brain Res 2012; 1487:198–205
71 Menichella DM, Goodenough DA, Sirkowski E, Scherer SS, Paul DL. Connexins are critical for normal myelination in the CNS. J Neurosci 2003;23(13):5963–5973

72 Miller LJ, Saporta AS, Sottile SL, Siskind CE, Feely SM, Shy ME. Strategy for genetic testing in Charcot-Marie-disease. Acta Myologica: Myopathies and Cardiomyopathies 2011;30(2):109–116
73 Bombelli F, Stojkovic T, Dubourg O, et al. Charcot-Marie-Tooth disease type 2A: from typical to rare phenotypic and genotypic features. JAMA Neurol 2014;71(8):1036–1042
74 Feely SM, Laura M, Siskind CE, et al. MFN2 mutations cause severe phenotypes in most patients with CMT2A. Neurology 2011; 76(20):1690–1696
75 Rojo M, Legros F, Chateau D, Lombès A. Membrane topology and mitochondrial targeting of mitofusins, ubiquitous mammalian homologs of the transmembrane GTPase Fzo. J Cell Sci 2002;115 (Pt 8):1663–1674
76 Boaretto F, Vettori A, Casarin A, et al. Severe CMT type 2 with fatal encephalopathy associated with a novel MFN2 splicing mutation. Neurology 2010;74(23):1919–1921
77 Brockmann K, Dreha-Kulaczewski S, Dechent P, et al. Cerebral involvement in axonal Charcot-Marie-Tooth neuropathy caused by mitofusin2 mutations. J Neurol 2008;255(7): 1049–1058
78 Chung KW, Kim SB, Park KD, et al. Early onset severe and late-onset mild Charcot-Marie-Tooth disease with mitofusin 2 (MFN2) mutations. Brain 2006;129(Pt 8):2103–2118
79 Züchner S, Vance JM. Molecular genetics of autosomal-dominant axonal Charcot-Marie-Tooth disease. Neuromolecular Med 2006; 8(1-2):63–74
80 Calvo J, Funalot B, Ouvrier RA, et al. Genotype-phenotype correlations in Charcot-Marie-Tooth disease type 2 caused by mitofusin 2 mutations. Arch Neurol 2009;66(12):1511–1516
81 de Brito OM, Scorrano L. Mitofusin 2 tethers endoplasmic reticulum to mitochondria. Nature 2008;456(7222):605–610
82 Baloh RH, Schmidt RE, Pestronk A, Milbrandt J. Altered axonal mitochondrial transport in the pathogenesis of Charcot-Marie-Tooth disease from mitofusin 2 mutations. J Neurosci 2007;27(2): 422–430
83 Detmer SA, Chan DC. Complementation between mouse Mfn1 and Mfn2 protects mitochondrial fusion defects caused by CMT2A disease mutations. J Cell Biol 2007;176(4):405–414
84 Tazir M, Bellatache M, Nouioua S, Vallat JM. Autosomal recessive Charcot-Marie-Tooth disease: from genes to phenotypes. J Peripher Nerv Syst 2013;18(2):113–129
85 Roberts RC, Peden AA, Buss F, et al. Mistargeting of SH3TC2 away from the recycling endosome causes Charcot-Marie-Tooth disease type 4C. Hum Mol Genet 2010;19(6):1009–1018
86 Nicholson G, Ouvrier R. GDAP1 mutations in CMT4: axonal and demyelinating phenotypes?: The exception "proves the rule" Neurology 2002;59(12):1835–1836
87 Rotthier A, Baets J, De Vriendt E, et al. Genes for hereditary sensory and autonomic neuropathies: a genotype-phenotype correlation. Brain 2009;132(Pt 10):2699–2711
88 Rotthier A, Penno A, Rautenstrauss B, et al. Characterization of two mutations in the SPTLC1 subunit of serine palmitoyltransferase associated with hereditary sensory and autonomic neuropathy type I. Hum Mutat 2011;32(6):E2211–E2225
89 Denny-Brown D. Hereditary sensory radicular neuropathy. J Neurol Neurosurg Psychiatry 1951;14(4):237–252
90 Fridman V, Oaklander AL, David WS, et al. Natural history and biomarkers in hereditary sensory neuropathy type 1. Muscle Nerve 2015;51(4):489–495
91 Auer-Grumbach M. Hereditary sensory neuropathy type I. Orphanet J Rare Dis 2008;3:7
92 Eichler FS, Hornemann T, McCampbell A, et al. Overexpression of the wild-type SPT1 subunit lowers desoxysphingolipid levels and rescues the phenotype of HSAN1. J Neurosci 2009;29(46): 14646–14651
93 Penno A, Reilly MM, Houlden H, et al. Hereditary sensory neuropathy type 1 is caused by the accumulation of two neurotoxic sphingolipids. J Biol Chem 2010;285(15):11178–11187
94 Garofalo K, Penno A, Schmidt BP, et al. Oral L-serine supplementation reduces production of neurotoxic deoxysphingolipids in mice and humans with hereditary sensory autonomic neuropathy type 1. J Clin Invest 2011;121(12):4735–4745
95 Bertea M, Rütti MF, Othman A, et al. Deoxysphingoid bases as plasma markers in diabetes mellitus. Lipids Health Dis 2010;9:84
96 Othman A, Bianchi R, Alecu I, et al. Lowering plasma 1-deoxysphingolipids improves neuropathy in diabetic rats. Diabetes 2015;64(3):1035–1045
97 d'Ydewalle C, Krishnan J, Chiheb DM, et al. HDAC6 inhibitors reverse axonal loss in a mouse model of mutant HSPB1-induced Charcot-Marie-Tooth disease. Nat Med 2011;17(8):968–974
98 Sereda MW, Meyer zu Hörste G, Suter U, Uzma N, Nave KA. Therapeutic administration of progesterone antagonist in a model of Charcot-Marie-Tooth disease (CMT-1A). Nat Med 2003;9(12):1533–1537
99 Piscosquito G, Reilly MM, Schenone A, et al; CMT-TRIAAL & CMT-TRAUK Group. Is overwork weakness relevant in Charcot-Marie-Tooth disease? J Neurol Neurosurg Psychiatry 2014;85(12): 1354–1358
100 Ramdharry GM, Day BL, Reilly MM, Marsden JF. Hip flexor fatigue limits walking in Charcot-Marie-Tooth disease. Muscle Nerve 2009;40(1):103–111
101 Boentert M, Knop K, Schuhmacher C, Gess B, Okegwo A, Young P. Sleep disorders in Charcot-Marie-Tooth disease type 1. J Neurol Neurosurg Psychiatry 2014;85(3):319–325