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Finding the Causes of Inherited Neuropathies

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The genetic causes of inherited neuropathies and their classification are the topics of this review. The large number of disorders as well as cumbersome and even inconsistent nomenclature make this a daunting task. Owing to limited space, I will not elaborate on the clinical features or diagnostic approaches of these disorders, and the primary literature is not referenced; these topics are more fully discussed elsewhere.[1-4] In addition, much information can be found in Online Mendelian Inheritance in Man (OMIM) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM; the 6-digit OMIM numbers of various disorders are given in the text and in the **Table**), the Mutation Database of Inherited Peripheral Neuropathies (http://www.molgen.ua.ac.be/CMTMutations), and the Neuromuscular Disease Center of Washington University (http://www.neuro.wustl.edu/neuromuscular).

WHAT IS CHARCOT-MARIE-TOOTH DISEASE?

More than a century ago, Charcot, Marie, and Tooth described patients who, as we now understand it, have a dominantly inherited, progressive neuropathy that affects myelinated motor and sensory axons in a length-dependent manner. This disorder is usually called Charcot-Marie-Tooth disease (CMT). Soon thereafter, recessive cases of more severely affected individuals (with Dejerine-Sottas neuropathy [DSN]) as well as kindreds with X-linked CMT type 1 (CMT1X) were described. Dyck and colleagues introduced the currently used classification scheme, although they used the term *hereditary motor and sensory neuropathy* rather than CMT. They demonstrated that most kindreds had CMT1, characterized by slowed motor conduction velocities (10-40 m/s) in the arms and histological evidence of segmental demyelination and remyelination in addition to axonal loss. The CMT2 kindreds tended to have a later age at onset, little if any slowing of nerve conductions, and loss of myelinated axons but without segmental demyelination or remyelination. These findings were extended by several groups, including Harding and Thomas,[5] who proposed that forearm motor conduction velocities of 38 m/s separated CMT1 from CMT2 (**Figure 1**A), a heuristic aid that can be misleading if applied too rigidly.

This classification underscored the idea that CMT1 might be caused by mutations in genes that are expressed by myelinating Schwann cells whereas CMT2 might be caused by mutations in genes expressed by neurons. This possibility was first formally demonstrated by Aguayo et al,[6] who grafted nerve segments from Trembler mice (which have a dominantly inherited demyelinating neuropathy) into the sciatic nerves of normal mice. The host axons that regenerated into the donor nerve grafts were abnormally myelinated by the donor Schwann cells, thereby demonstrating that the demyelination defect was intrinsic to the Schwann cells. This concept is supported by the demonstration that myelinating Schwann cells or neurons express the genes that cause demyelinating or axonal neuropathies, respectively.

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Table. Genetics of Nonsyndromic Inherited Neuropathies

Disease (OMIM No.)	Linkage or Gene
CMT1, autosomal or X-linked dominant demyelinating	
HNPP (162500)	*PMP22*
CMT1A (118220)	*PMP22*
CMT1B (118200)	*MPZ*
CMT1C (601098)	*LITAF/SIMPLE*
CMT1D (607687)	*EGR2*
CMT1X (302800)	*GJB1*
DI-CMT	
DI-CMTA (606483)	10q24.1-25.1
DI-CMTB (696482)	*DNM2*
DI-CMTC (608323)	*YARS*
CMT2, autosomal dominant axonal or neuronal	
CMT2A1 (118210)	*KIF1B*
CMT2A2 (609260)	*MFS2*
CMT2B (600882)	*RAB7*
CMT2C (606071)	12q23-24
CMT2D (601472)	*GARS*
CMT2E (162280)	*NEFL*
CMT2F (606595)	*HSPB1*
CMT2G (608591)	12q12-q13.3
CMT2 (604484)	3q13.1
CMT2-P0 (118200)	*MPZ*
CMT2L (608673)	*HSPB8*
CMT4, AR demyelinating neuropathy	
CMT4A (214400)	*GDAP1*
CMT4B-1 (601382)	*MTMR2*
CMT4B-2 (604563)	*MTMR13*
CMT4C (601596)	*KIAA1985*
CMT4D (601455)	*NDRG1*
CMT4F (605260)	*PRX*
HMSN-R (605285)	10q23.2
CMT4H (609311)	12p11.21-q13.11
CMT4 (605253)	*EGR2*
AR-CMT2, AR axonal neuropathy or CMT2B	
AR-CMT2A (605588)	*LMNA*
AR-CMT2B (605589)	19q13.1-13.3
CMT2K (607831)	*GDAP1*
Congenital AR axonal neuropathy	5q deletion
HSAN	
HSAN1 (162400)	*SPTLC1;* dominant
HSAN1B (608088)	3p22-24; dominant
HSAN2 (201300)	*HSN2;* recessive
HSAN3 (223900)	*IKBKAP;* recessive
HSAN4 (256800)	*TRKA;* recessive
HSAN5 (162030)	*NGFB;* recessive
Primary erythermalgia (133020)	*SCN9A;* dominant
Cold-induced sweating (272430)	*CRLF1;* recessive
HMN	
HMN I (606595)	Dominant
HMN II (158590)	*HSPB8;* dominant
HMN II (608634)	*HSPB1;* dominant
HMN III (607088)	11q13; recessive
HMN IV	Recessive
HMN V (600794)	*GARS*, dominant; *BSCL2*, dominant
HMN VI/SMARD1 (604320)	*IGHMBP2;* recessive
HMN VII (158580)	*DCTN1*
HMN/ALS4 (602433)	*SETX;* dominant
Congenital distal SMA (600175)	12q23-q24; dominant
HMN Jerash (605726)	9p21.1-p12; recessive

Abbreviations: ALS4, amyotrophic lateral sclerosis type 4; AR, autosomal recessive; CMT, Charcot-Marie-Tooth disease; DI, dominant intermediate; HMN, hereditary motor neuropathy; HMSN, hereditary motor and sensory neuropathy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; OMIM, Online Mendelian Inheritance in Man; SMA, spinal muscular atrophy; SMARD1, spinal muscular atrophy with respiratory distress type 1.

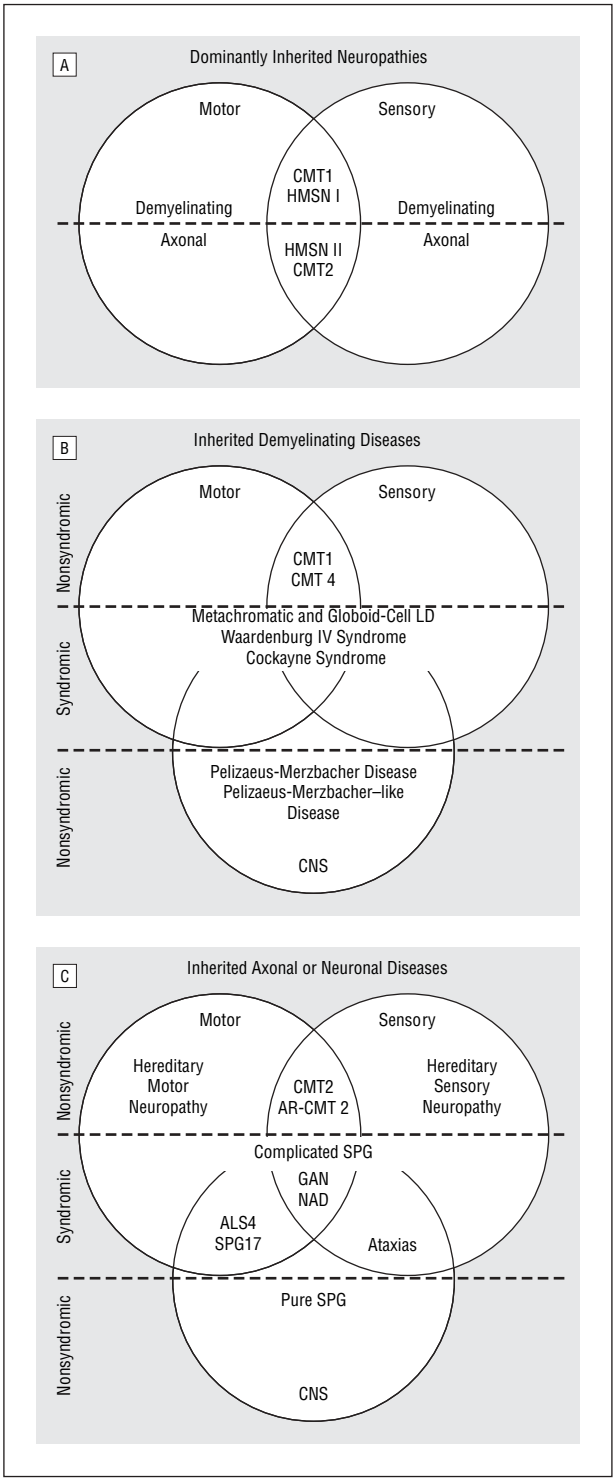

Figure 1. The relationships of inherited neuropathies to each other and other syndromes. These Venn diagrams depict that dominantly inherited neuropathies can be separated into demyelinating and axonal forms (A); that inherited demyelinating diseases can be separated into those that cause peripheral nervous system and/or central nervous system (CNS) dysmyelination or demyelination (B); and that inherited axonal diseases can be separated into those that cause combinations of a motor neuropathy, sensory neuropathy, or both sensory and motor neuropathy, each of which may also involve CNS axons. CMT indicates Charcot-Marie-Tooth disease; HMSN, hereditary motor and sensory neuropathy; LD, leukodystrophy; AR, autosomal recessive; SPG, spastic paraplegia; GAN, giant axonal neuropathy; ALS, amyotrophic lateral sclerosis; and NAD, neuroaxonal dystrophy.

DOMINANT KINDS OF CMT

Mapping the genetic loci of different kindreds led to the identification of the causative genetic defects and the realization that multiple genes cause CMT1, CMT2, and DSN. This began with the discovery that the *PMP22* gene (which encodes an intrinsic membrane protein of compact myelin, peripheral myelin protein 22) is duplicated in CMT1A and deleted in hereditary neuropathy with liability to pressure palsies. Mutations in genes already known to be expressed by myelinating Schwann cells were found to cause other kinds of dominantly inherited demyelinating neuropathies—myelin protein zero (*MPZ*), which encodes the major adhesive protein of compact myelin, and *EGR2*, which encodes a transcription factor. Charcot-Marie-Tooth disease type 1 was also found to be caused by mutations in genes not previously known to be expressed by myelinating Schwann cells—*GJB1*, which encodes the gap junction protein connexin32, and *LITAF/SIMPLE*, which encodes a protein that may be involved in the degradation of intracellular proteins.

Charcot-Marie-Tooth disease type 2 is less common than CMT1, and it also results from diverse genetic causes. A dominant mutation in *KIF1B*, which encodes a kinesin, was reported to cause CMT2A, but most CMT2A kindreds appear to have dominant mutations in *MFS2*, which encodes mitofusin 2, an intrinsic membrane protein of mitochondria. Mutations in *MFN2* appear to account for about one fourth of CMT2 cases, and optic atrophy and myelopathy may be found in affected patients. Dominant mutations of *RAB7* (which encodes a guanosine triphosphatase), *GARS* (which encodes a glycyl transfer RNA synthase), *NEFL* (which encodes the light subunit of neurofilaments), and *HSPB1* and *HSPB8* (which encode heat shock proteins 27 and 22, respectively) cause other kinds of CMT2 (Table). These 2 heat shock proteins interact, so it is likely that disrupted interactions caused by either heat shock protein 22 or heat shock protein 27 mutants disrupt the complex and result in an axonopathy. Mutations in *GARS*, *HSPB1*, or *HSPB8* also cause hereditary motor neuropathy (HMN) rather than CMT2; in patients with HMN, one presumes that the mutations chiefly affect myelinated motor axons and not myelinated sensory axons. On a related note, because myelinated motor axons are affected in hereditary sensory and autonomic neuropathy type 1 (HSAN1), this could be considered a form of CMT2. Finally, some *NEFL* mutations cause marked conduction slowing well into the demyelinating range; perhaps these mutations cause secondary demyelination because they profoundly affect axonal calibers, akin to the effects of recessive *Gigaxonin* mutations that cause giant axonal neuropathy.

A third group of dominantly inherited neuropathies has been proposed, dominant intermediate CMT, so named owing to their intermediate conduction velocities and thus an uncertainty regarding whether the neuropathy is primarily axonal or demyelinating. Dominant intermediate CMT type B is caused by mutations in *DNM2*, which encodes dynamin 2, a cell membrane–associated protein that pinches off newly formed clathrin-coated vesicles. Because dynamin 2 is ubiquitously expressed, it remains to be determined whether the fundamental disturbance caused by *DNM2* mutations affects neurons or axons, Schwann cells, or both.

RECESSIVE KINDS OF CMT

Recessive types of CMT are less common than dominantly inherited neuropathies and are mainly caused by mutations in a different group of genes (Table). The demyelinating forms (CMT4) are caused by mutations in *MTMR2* or *MTMR13* (which likely interact to form a phosphatase), *EGR2*, *PRX* (which encodes periaxin, part of a dystroglycan complex), and *NDRG1* or *KIAA1985* (which encode proteins of unknown function). Myelinating Schwann cells express all of these genes, and the available data indicate that each of the corresponding proteins likely has an essential role in Schwann cells so that recessive mutations result in demyelination. Although recessive *GDAP1* mutations cause a neuropathy with some demyelinating features, the neuropathy appears to be axonal in other kindreds. The basis of this discrepancy remains to be determined.

Besides *GDAP1*, pure recessively inherited axonal neuropathies are rare.[7] Recessive mutations in *LMNA* (which encodes lamin A/C) cause a severe axonal neuropathy. Homozygous deletion or conversions of the region of chromosome 5q that contains the *SMN1* gene (the genetic basis of spinal muscular atrophy) cause a severe neuropathy. In 1 family, the gene has been mapped to chromosome 19q13.1-13.3. At least 2 forms, early-onset autosomal recessive CMT2 and lethal neonatal autosomal recessive axonal neuropathy (OMIM 604431), have yet to be mapped. It is inferred that the proteins encoded by these genes have essential functions in neurons or axons.

CONGENITAL HYPOMYELINATING NEUROPATHY AND DSN

The terms *congenital hypomyelinating neuropathy* (OMIM 605253) and *DSN* (also known as CMT3; OMIM 145900) are used to describe individuals who have a severe neuropathy with a clinically recognized onset in infancy or before age 3 years, respectively. These 2 syndromes can be difficult to separate, and both can be caused by dominant mutations in *MPZ*, *PMP22*, and *EGR2*, resulting in severe dysmyelination. One mutation in *GJB1* as well as recessive mutations in *PRX*, *GDAP1*, and *MTMR2* can also cause a DSN phenotype. Furthermore, many cases of CMT, sometimes referred to as severe CMT, could just as well have been labeled DSN. The genetic heterogeneity of both congenital hypomyelinating neuropathy and DSN has led to the proposal that these terms be abandoned from genetic classifications.[7]

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES

In HSAN, sensory (and variably autonomic) neurons or axons are affected, with relative or complete sparing of motor neurons or axons. Dominant mutations in *SPLTC1* cause HSAN1, likely because the mutant protein has dominant interactions with its wild-type counterpart. Recessive mutations in *IKBKAP* cause HSAN3 (also known as

familial dysautonomia or Riley-Day syndrome); the most common allele causes aberrant splicing of neuronal transcripts, resulting in defective protein. Recessive mutations in *NGFB*, which encodes nerve growth factor, and *TRKA*, which encodes a receptor for nerve growth factor, cause HSAN5 and HSAN4 (also known as congenital insensitivity to pain and anhydrosis syndrome), respectively. The profound loss of many sensory and autonomic axons in affected individuals is in keeping with the developmental loss of the corresponding neurons in mouse models.[8] Recessive mutations in another growth factor receptor cause cold-induced sweating, likely owing to a loss of peripheral sensory and autonomic neurons. Hereditary sensory and autonomic neuropathy type 2 is caused by recessive mutations in a gene that encodes a protein of unknown function. Dominant mutations in *SCNA9*, which encodes the voltage-gated sodium channel Nav1.7, cause primary erythermalgia characterized by a painful small-fiber neuropathy with dysfunction of distal sensory and autonomic axons. The mutant channels appear to remain open too long, which may cause the overactivity of nociceptive neurons that express Nav1.7, resulting in pain.

HEREDITARY MOTOR NEUROPATHIES

The current classification is based on the 7 types of distal hereditary motor neuronopathies described by Harding,[9] who separated them by their clinical features and patterns of inheritance. These are now known as HMN types I through VII[10] and can be conceptualized as length-dependent neuropathies of only motor axons. Sensory axon involvement, however, is reported for at least some mutations in a subset of these genes (*GARS*, *HSPB8*, and *HSPB1*) and may be overlooked in cases of HMN VI or spinal muscular atrophy with respiratory distress type 1 (raising the possibility that this is really a severe axonal neuropathy). Hereditary motor neuropathy type V and HMN VII are distinguished by denervation in distal arm muscles that is disproportionate to the involvement of distal leg muscles, and HMN VII also has prominent involvement of the laryngeal muscles. How mutations in these genes, which are not known to serve a common function, cause a similar phenotype is unknown. Mutations in *DCTN1*, which encodes the p150^{Glued} subunit of dynactin (the largest subunit of dynactin), may disrupt retrograde axonal transport.

INHERITED NEUROPATHY AS PART OF A SYNDROME

When peripheral neuropathy is part of an inherited syndrome (Figure 1B and C), it is typically overshadowed by the other manifestations. Nevertheless, demyelination or dysmyelination of peripheral axons is a feature of metachromatic (OMIM 250100) and globoid-cell (OMIM 245200) leukodystrophy as well as Cockayne syndrome (OMIM 216400), syndromes associated with *SOX10* mutations (OMIM 602229 and OMIM 609136), congenital disorder of glycosylation type Ia (OMIM 212065), Refsum disease (OMIM 266500), congenital cataracts, facial dysmorphism, and neuropathy (OMIM 604168), and minifascicular neuropathy (OMIM 605423). Syndromes associated with axonal neuropathies are even more common. Several types of hereditary spastic paraparesis or paraplegia (SPG) have an axonal neuropathy involving both motor and sensory axons (SPG types 7, 11, 20, and 23) or just motor axons (SPG17, or Silver syndrome). An axonal neuropathy is a feature of many hereditary ataxias, including Friedrich ataxia (OMIM 229300), ataxia-oculomotor apraxia type 2 (OMIM 606002), spinocerebellar syndrome with axonal neuropathy (OMIM 607250), and spinocerebellar ataxia types 1, 2, 3, 4, 6, 7, and 25.[11] The clinical phenotypes of giant axonal neuropathy, neuraxonal dystrophy, and SPG associated with peripheral axonal neuropathy are consistent with the idea that these diseases are length-dependent axonopathies of both central and peripheral nervous system neurons.

If CMT, HSAN, and HMN should be restricted to nonsyndromic inherited neuropathies, then CMT4D, HSAN4, HMN Jerash, and HMN caused by *BSCL2* or *SETX* mutations seem to be misclassified, as many patients have other manifestations, particularly of central nervous system involvement. Some patients appear to have been misclassified owing to an insufficient clinical examination, electrophysiological analysis, or ancillary imaging studies, but even a thorough evaluation may not suffice to characterize the phenotype of an individual mutation. For example, in large kindreds with a dominant *BSCL2* mutation, some individuals had a clinical picture of HMN V with prominent weakness of intrinsic hand muscles, others also had a spastic paraparesis producing the clinical picture of Silver syndrome/SPG17, and others had a spastic paraparesis without hand weakness.[12]

FINDING THE CAUSES

The discovery of the genetic causes of neuropathy is an unprecedented accomplishment and has enabled patients with CMT to find out exactly which mutation causes their neuropathy. Helping patients discover the cause of their neuropathy, however, can be difficult, and an efficient approach benefits from the expertise of a neuromuscular specialist. **Figure 2** is an outline of a logical approach that takes into account that *PMP22* duplications are by far the most common cause of CMT1. It may become crucial for patients to know their molecular diagnosis, as some treatments may only help certain kinds of neuropathy and may even worsen other kinds. For example, a drug that decreases the expression of *PMP22* may improve the neuropathy in patients with a *PMP22* duplication but worsen the neuropathy in patients with a *PMP22* deletion.

Inherited neuropathies are common, affecting about 1 in 2500 people, and are thus one of the most prevalent inherited neurologic diseases. Neuropathy diminishes the quality of life in small and large ways and can result in disabilities. Thus, patients are not content with knowing the cause of their neuropathy—they want treatments that work. Their hope can only be realized by acquiring new insights into how mutations in these genes cause neuropathies. Substantial progress has been made, especially through the study of genetically authentic animal models. To date, this work has underscored the

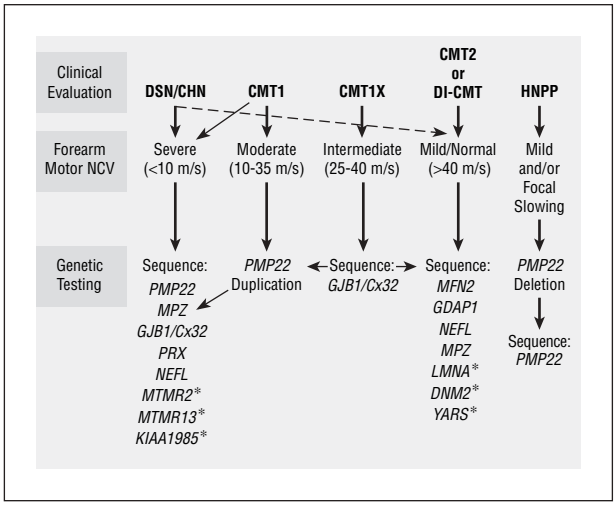

Figure 2. Ordering the appropriate genetic test for inherited neuropathies (updated information on the availability of new genetic testing can be found on the Web site http://www.genetests.org). DSN indicates Dejerine-Sottas neuropathy; CHN, congenital hypomyelinating neuropathy; CMT1X, X-linked Charcot-Marie-Tooth disease type 1; DI, dominant intermediate; HNPP, hereditary neuropathy with liability to pressure palsies; NCV, nerve conduction velocity; and asterisks, not commercially available.

unique specializations of myelinating glial cells, the selective vulnerability of axons owing to their precarious length, and the importance of axonal transport. The lessons learned in the molecular pathogenesis of neuropathies may illuminate the causes of more complex neurological diseases.[13]

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