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Inherited Peripheral Neuropathies

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ABSTRACT

Mutations in genes expressed in Schwann cells and the axons they ensheathe cause the hereditary motor and sensory neuropathies, also known as Charcot-Marie-Tooth disease (CMT). More than 40 different genes have been shown to cause inherited neuropathies; chromosomal localizations of many other distinct inherited neuropathies have been mapped, and new genetic causes for inherited neuropathies continue to be discovered. How to keep track of all of these disorders, when to pursue genetic testing, and what tests to order for specific patients are difficult challenges for any neurologist. This review addresses these issues and provides illustrative cases to help in dealing with them. CMT serves as a living system to identify molecules necessary for normal peripheral nervous system (PNS) function. Understanding how these various molecules interact will provide a better understanding of the pathogenesis of peripheral neuropathies in general as well as other neurodegenerative disorders involving the PNS.

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HISTORICAL BACKGROUND AND NOMENCLATURE

In the late 19th century, inherited neuropathies were described by Charcot and Marie in France and independently by Tooth in England, hence the name Charcot-Marie-Tooth disease (CMT) disorders. These investigators described the syndrome of weakness and atrophy of muscles innervated by the peroneal nerve, the characteristic foot abnormalities, and the familial nature of disease. They also began to recognize that these neuropathies were a heterogenous group. For example, Dejerine and Sottas described cases that were more severe and had an onset in infancy, and Roussy and Levy described cases associated with tremor, ataxia, areflexia, and pes cavus. Over the years it became apparent that clinicopathologic features were overlapping and precise diagnostic criteria for each of these entities were lacking. With the advent of nerve conduction velocity (NCV) testing, this confusion began to clear. Early studies suggested that most patients with CMT could be divided into one group with slow NCVs and pathologic evidence of a hypertrophic demyelinating neuropathy (CMT type 1 [CMT1]) and a second group with relatively normal NCVs and axonal degeneration (CMT type 2 [CMT2]). The clinical features of CMT1 and CMT2 were outlined in two publications in which Harding and Thomas[1,2] reported the genetic and clinical characteristics of over 200 patients. Patients with CMT1 were found to have median motor NCVs below 38 m/s whereas median motor NCVs were greater than 38 m/s in patients with CMT2.

Despite clinical similarities among patients with CMT1, the group is genetically heterogeneous. In 1991, two groups showed that CMT1A, the most common form of CMT1, was associated with a 1.4-megabase (Mb) duplication at chromosome 17p11.2.[3,4] CMT1B, linked to chromosome 1, is caused by mutations in the myelin protein zero (MPZ) glycoprotein, and X-linked neuropathy,

CMT1X, is caused by mutations in the gap junction protein, beta 1, 32kDa gene, *GJB1*, on the X chromosome encoding the gap junction protein, connexin 32. Deletion of the identical 1.4-Mb region responsible for CMT1A causes hereditary neuropathy with liability to pressure palsies (HNPPs). Dejerine-Sottas syndrome (DSS), a severe infantile neuropathy, is caused by mutations in multiple genes including *PMP22, MPZ*, *EGR2*, and several other dominantly and recessively inherited genes. At this writing, mutations in more than 40 genes that cause inherited neuropathies have been identified (**Table 5-1**).

CLASSIFICATION OF INHERITED NEUROPATHIES

It rapidly became apparent that not all patients could be simply classified as having CMT1 or CMT2. Detailed classification systems were therefore developed. In their landmark classification system, Dyck and Lambert used the term hereditary motor and sensory neuropathy (HMSN) to characterize many of these neuropathies (**Table 5-2**)[5,6] Currently the terms HMSN and CMT are loosely used interchangeably.

But classification systems are products of people, and the discovery of the causal genes led to the need to modify the classification system for several reasons. First of all, different mutations in the same gene, such as *MPZ* or *PMP22* (see below), can cause either typical CMT1 phenotypes or severe early-onset neuropathies. Many early-onset cases present sporadically with no family history and would previously have been diagnosed as HMSN type III (HMSN-III) (or DSS). Second, X-linked CMT does not fit easily into the original Dyck and Lambert classification scheme because of its X-linked inheritance and its intermediately slowed NCVs. Finally, different mutations in the same gene, such as *MPZ*, may cause slow NCVs characteristic of CMT1 or near-normal velocities more characteristic of CMT2. With this in mind, the classification scheme has been modified to one that is based on the genetic cause of the neuropathy and its inheritance pattern.

Autosomal dominant neuropathies caused by genes that result in slowed NCVs are generally classified as CMT1 or HMSN-I. Autosomal dominant neuropathies caused by mutations that result in normal or slightly decreased NCVs are termed CMT2 or HMSN-II. CMT4 or HMSN-IV is used to classify the demyelinating recessive forms of CMT or HMSN. The rare axonal recessive neuropathies are termed CMT2-AR.

Even this classification system has limitations. For example, a few mutations in the *PMP22* gene (eg, Thr118Met) cause autosomal recessively inherited neuropathies, whereas most other *PMP22* mutations cause autosomal dominantly inherited disease. Different mutations in the same gene, such as *NEFL* or *MPZ*, may cause CMT1 or CMT2. Moreover, some forms of inherited neuropathies are part of syndromes that affect other organs as well as peripheral nerves (**Table 5-3**). In the end, it may not be possible to ''perfectly'' classify the various types of CMT or HMSN because of the many different genetic causes and the phenotypic variability that can arise from different mutations within the same gene.

APPROACH TO PATIENTS WITH INHERITED NEUROPATHY

To diagnose a patient with an inherited neuropathy requires first establishing that the patient has a neuropathy and then identifying features that suggest the neuropathy is genetic. In some cases this process is straightforward. If the patient has symmetrical distal limb weakness and sensory loss, pes cavus, slow NCVs, and a strong family history of neuropathy, he or she likely has a

KEY POINTS

- Mutations in genes expressed in Schwann cells and the axons they ensheathe cause the hereditary motor and sensory neuropathies, also known as Charcot-Marie-Tooth disease (CMT).
- Early studies suggested that most patients with CMT could be divided into one group with slow nerve conduction velocities and pathologic evidence of a hypertrophic demyelinating neuropathy (CMT type 1) and a second group with relatively normal nerve conduction velocities and axonal degeneration (CMT type 2).

TABLE 5-1 Classification of Charcot-Marie-Tooth Disease

Type	Gene/Locus	Specific Phenotype
Autosomal dominant CMT1 (AD CMT1)		
CMT1A	Dup 17p (*PMP22*)	Classic CMT1
	PMP22 (point mutation)	Classic CMT1/DSS/CHN/HNPPs
CMT1B	*MPZ*	CMT1/DSS/CHN/intermediate/CMT2
CMT1C	*LITAF*	Classic CMT1
CMT1D	*EGR2*	Classic CMT1/DSS/CHN
CMT1E	*NEFL*	CMT2 but can have slow MCVs in CMT1 range +/- early-onset severe disease
Hereditary neuropathy with liability to pressure palsies (HNPPs)		
HNPPs	Del 17p (*PMP22*)	Typical HNPPs
	PMP22 (point mutation)	Typical HNPPs
X-linked CMT1 (CMT1X)		
CMT1X	*GJB1*	Intermediate +/- patchy MCVs/male MCVs less than female MCVs
Autosomal recessive demyelinating (CMT4)		
CMT4A	*GDAP1*	Demyelination or axonal, usually early onset and severe/ vocal cord and diaphragm paralysis described/rare AD CMT2 families described
CMT4B1	*MTMR2*	Severe CMT1/facial/bulbar/ focally folded myelin
CMT4B2	*SBF2*	Severe CMT1/glaucoma/focally folded myelin
CMT4C	*SH3TC2* (*KIAA1985*)	Severe CMT1/scoliosis/ cytoplasmic expansions
CMT4D (HMSNL)	*NDRG1*	Severe CMT1/gypsy/deafness/ tongue atrophy
CMT4E	*EGR2*	Classic CMT1/DSS/CHN
CMT4F	*PRX*	CMT1/more sensory/focally folded myelin

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Type	Gene/Locus	Specific Phenotype
CMT4H	*FGD4*	CMT1
CMT4J	*FIG4*	CMT1
CCFDN	*CTDP1*	CMT1/gypsy/cataracts/ dysmorphic features
HMSN-Russe	10q22–q23	CMT1
CMT1	*PMP22* (point mutation)	Classic CMT1/DSS/CHN/ HNPPs
CMT1	*MPZ*	CMT1/DSS/CHN/ intermediate/CMT2
Autosomal dominant CMT2 (AD CMT2)		
CMT2A	*MFN2*	CMT2/usually severe/ optic atrophy
CMT2B	*RAB7*	CMT2 with predominant sensory involvement and sensory complications
CMT2C	12q23–q24	CMT2 with vocal cord and respiratory involvement
CMT2D	*GARS*	CMT2 with predominant hand wasting/weakness or dHMN-V
CMT2E	*NEFL*	CMT2 but can have slow MCVs in CMT1 range +/- early-onset severe disease
CMT2F	*HSPB1* (*HSP27*)	Classic CMT2 or dHMN-II
CMT2G	12q12–q13.3	Classic CMT2
CMT2L	*HSPB8* (*HSP22*)	Classic CMT2 or dHMN-II
CMT2	*MPZ*	CMT1/DSS/CHN/ intermediate/CMT2
CMT2 (HMSNP)	3q13.1	CMT2 with proximal involvement
Autosomal recessive CMT2 (also called AR CMT4)		
AR CMT2A	*LMNA*	CMT2 proximal involvement and rapid progression described/also causes muscular dystrophy/ cardiomyopathy/ lipodystrophy

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KEY POINT

■ Phenotypic variability occurs within given genotypes, and natural history studies of many types of CMT are lacking.

Continued

Type	Gene/Locus	Specific Phenotype
AR CMT2B	19q13.1–13.3	Typical CMT2
AR CMT2	*GDAP1*	CMT1 or CMT2 usually early onset and severe/vocal cord and diaphragm paralysis described/rare AD CMT2 families described
Dominant intermediate CMT (DI-CMT)		
DI-CMTA	10q24.1–25.1	Typical CMT
DI-CMTB	*DNM2*	Typical CMT
DI-CMTC	*YARS*	Typical CMT
Hereditary neuralgic amyotrophy (HNA)		
HNA	*SEPT9*	Recurrent neuralgic amyotrophy

CMT = Charcot-Marie-Tooth disease; AD = autosomal dominant; Dup = duplication; *PMP22* = peripheral myelin protein 22kD; DSS = Dejerine-Sottas syndrome; CHN = congenital hypomyelinating neuropathy; HNPPs = hereditary neuropathy with liability to pressure palsies; *MPZ* = myelin protein zero; *LITAF* = lipopolysaccharide-induced TNF; *EGR2* = early growth response 2; *NEFL* = neurofilament, light polypeptide; MCVs = motor conduction velocities; Del = deletion; *GJB1* = gap junction protein beta 1, 32kDa; *GDAP1* = ganglioside-induced differentiation-associated protein 1; *MTMR*2= myotubularin related protein 2; *SBF2* = SET binding factor 2; *SH3TC2* = SH3 domain and tetratricopeptide repeats 2; HMSNL = hereditary motor and sensory neuropathy-LOM; *NDRG1* = N-myc downstream regulated 1; *PRX* = periaxin; *FGD4* = FYVE, RhoGEF and PH domain containing 4; *FIG4* = FIG4 homolog, SAC1 lipid phosphatase domain containing (S. cerevisiae); CCFDN = congenital cataract, facial dysmorphism, and neuropathy syndrome; *CTDP1* = CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) phosphatase, subunit 1; HMSN-Russe = hereditary motor and sensory neuropathy-Russe; *MFN2* = mitofusin 2; *RAB7* = RAS-oncogene family-like 1; *GARS* = glycyl-tRNA synthetase; dHMN-V = distal hereditary motor neuropathy type V; *HSPB1* = heat shock 27kDa protein 1; dHMN-II = distal hereditary motor neuropathy type II; *HSPB8* = heat shock 22kDa protein 8; AR = autosomal recessive; *LMNA* = lamin A/C; DI = dominant intermediate; *DNM2* = dynamin 2; *YARS* = tyrosyl-tRNA synthetase; HNA = hereditary neuralgic amyotrophy; *SEPT9* = septin 9.

form of CMT. In other cases, however, the process can be more difficult because inherited neuropathies can present de novo and some inherited neuropathies present in adulthood. Moreover, simply determining on clinical grounds that a patient has an inherited neuropathy is rarely adequate for patient management. Many different genetically based neuropathies are inherited in different patterns, place different family members at risk, and progress at different rates. This article provides a framework for how to approach and manage these patients.

CLINICAL FEATURES OF AN INHERITED NEUROPATHY

Phenotypic variability occurs within given genotypes, and natural history studies of many types of CMT are lacking. Nevertheless, generalizations can be made about the course of many forms of CMT. In the classic CMT phenotype, symptoms of neuropathy develop gradually within the

TABLE 5-2 Dyck and Lambert Classification of Hereditary Motor and Sensory Neuropathies

Type	Features
HMSN type I A and B (dominantly inherited hypertrophic neuropathy)	Slow nerve conduction velocities
	Distal weakness
	Mild sensory loss
	Palpable nerves
	Decreased reflexes
	Pathology demonstrating segmental demyelination, remyelination, onion bulb formation, and axonal loss
	Autosomal dominant
HMSN type II (neuronal type of peroneal muscular atrophy)	Normal nerve conduction velocities
	Distal weakness
	Mild sensory loss
	Nonpalpable nerves
	Pathology demonstrating degeneration of motor and sensory nerves
	Autosomal dominant
HMSN type III hypertrophic neuropathy of infancy (Dejerine-Sottas)	Delayed motor development
	Severe motor-sensory loss
	Slow nerve conduction velocities
	Autosomal recessive
HMSN type IV hypertrophic neuropathy (Refsum) associated with phytanic acid excess	Refsum disease
HMSN type V associated with spastic paraplegia	Spastic paraplegia
HMSN type VI (with optic atrophy)	Optic atrophy
HMSN type VII	Retinitis pigmentosa

HSMN = hereditary motor and sensory neuropathy.

KEY POINT

- Most patients with CMT remain ambulatory throughout their life, which is not shortened by their neuropathy.

first 2 decades of life. Early milestones, such as the onset of walking by 1 year of age, are normal. Parents may report that children have ankle weakness, stumble, run abnormally, or do not pick up their feet. Balance is often a problem. Patients are often slow runners in childhood, develop foot problems in their teenage years, and may require orthotics to support their ankles as adults. Variable degrees of hand weakness occur, typically lagging about 10 years behind the development of foot weakness. Sensory loss, also variable, occurs in both large (vibration and proprioception) and small (pain and temperature) modalities. Most patients remain ambulatory

TABLE 5-3 Classification of the Genetic Neuropathies

▶ **Neuropathies in Which the Neuropathy is the Sole or Primary Part of the Disorder**
Charcot-Marie-Tooth disease
Hereditary neuropathy with liability to pressure palsies
Hereditary sensory and autonomic neuropathies/hereditary sensory neuropathies
Distal hereditary motor neuropathies
Hereditary neuralgic amyotrophy
▶ **Neuropathies in Which the Neuropathy is Part of a More Widespread Neurologic or Multisystem Disorder**
Familial amyloid polyneuropathy
Disturbances of lipid metabolism
Porphyrias
Disorders with defective DNA
Neuropathies associated with mitochondrial diseases
Neuropathies associated with hereditary ataxias
Miscellaneous

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throughout their life, which is not shortened by their neuropathy. Some of the typical features of patients with CMT are illustrated in **Figure 5-1**. One may be able to palpate the enlarged nerve trunks in subcutaneous tissue, although this is not common. Additional features, including postural tremor (once referred to as Roussy-Lévy syndrome but known to be a phenotypic subset of CMT and not a separate disorder) and muscle cramps, may also occur. Reflexes are often diffusely absent in patients with CMT1, whereas patients with CMT2 may have normal patellar reflexes although Achilles reflexes are usually absent. Although this phenotype is typical for patients with CMT, it is not invariable. Some patients have delayed motor development in infancy, and motor development remains abnormal. Similarly, some patients present with severe sensory loss in infancy, whereas others, even with severe weakness, may have normal sensation. Finally, patients with inherited

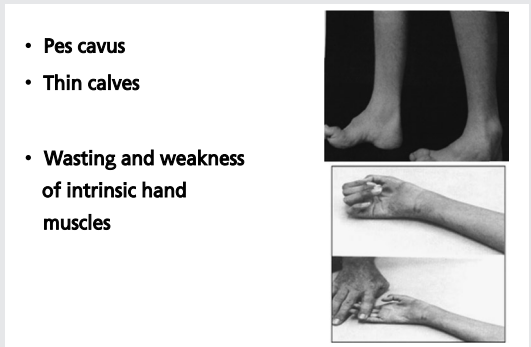

FIGURE 5-1 Characteristic features of Charcot-Marie-Tooth disease. Typical examples of pes cavus and wasting of both calf and intrinsic hand muscles are shown. Although these findings are typical, they are not invariable.

neuropathies may first present in adulthood, resembling individuals with acquired neuropathies such as chronic inflammatory demyelinating neuropathy or diabetic neuropathies. Some of the abnormalities found in patients are reviewed in more detail below.

Muscle Weakness

Muscle weakness is usually distal and often manifests as gait abnormality or clumsiness in running. Typically, increased instability at the ankle and a tendency toward varus deformity of the foot are present, and patients will have a steppage gait. In steppage gaits, the knees have to be raised higher than normal to lift the feet off the ground (**Figure 5-2**). Muscle weakness and atrophy typically begin insidiously in the foot and leg muscles and especially affect intrinsic foot and peroneal muscles. Patients often have extreme difficulty walking on their heels because of dorsiflexion weakness, which causes them to catch their toes on the curb or carpet. Difficulty with toe walking is also common. However, idiopathic toe walking of childhood can be an early presentation of inherited neuropathy. Later, calf and intrinsic hand muscles become affected. Occasionally, in more severe cases, proximal thigh muscles may become affected. The atrophy tends to affect the distal part of the gastrocnemius, soleus, and quadriceps muscles, leaving only a small mass of muscle at the proximal end.

Sensory Dysfunction

Sensory symptoms can be separated into those that affect large myelinated fibers subserving position sense and those that involve small, thinly myelinated or nonmyelinated fibers subserving pain and temperature modalities. Large fiber sensory loss is more common in most forms of CMT and usually presents with difficulties in balance. Children may be unable to walk on a balance beam or log. In patients of any age, difficulties with balance are usually worse in a crowd at night, when vision cannot overcome proprioceptive loss. Because loss of proprioception is usually length dependent, patients may be able to stabilize themselves by simply lightly touching a wall with their hand or elbow because nerves from the arm can then provide proprioceptive input to the brain. Common concerns with small fiber sensory neuropathy include, ''I feel like my feet are walking on pebbles''; ''My feet feel like ice all the time''; or ''I can't tell with my feet whether bath water is hot or cold.'' Painful dysesthesias such as feeling like one's feet are on fire or stuck with pins may occasionally occur but are not the common presentation. Sensory symptoms in the hands occur less frequently, probably because most inherited neuropathies are length dependent. A general rule of thumb is that sensory symptoms in the hands begin about the time sensory symptoms in the lower extremities have progressed to the knee. An exception to this rule is the development of carpal tunnel syndrome, in which case dysesthesias in the hands can be prominent and may wake the

KEY POINTS

- In CMT, muscle weakness and atrophy typically begin insidiously in the foot and leg muscles and especially affect intrinsic foot and peroneal muscles.
- Large fiber sensory loss is more common in most forms of CMT and usually presents with difficulties in balance.

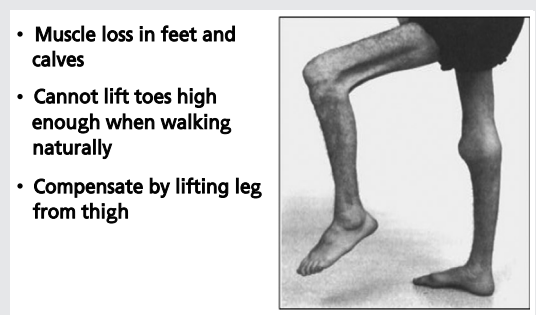

FIGURE 5-2 An example of steppage gait is shown in a patient with an unusual amount of leg wasting.

Reprinted from Charcot J, Marie P. Sur une forme particulière d'atrophie musculaire progressive, souvent familiale, débutant par les pieds et les jambes et atteignant plus tard les mains. Rev Med Paris 1886;6:97–138.

KEY POINTS

- Pes cavus and high arches are not specific to inherited neuropathies and may also occur in developmental disorders of the CNS.
- Dejerine-Sottas syndrome refers to severe genetic neuropathies that begin in infancy.
- In the early 1980s, most cases of inherited demyelinating neuropathies were demonstrated to have uniformly slow nerve conduction velocities, whereas acquired demyelinating neuropathies, such as chronic inflammatory demyelinating neuropathy, have asymmetric slowing.

patient from sleep. On neurologic examination, sensory loss is usually found in a stocking-glove distribution for both large fiber and small fiber modalities. Cold, erythematous, or bluish discolored feet suggest a loss of small fiber function. Large fiber sensory loss or sensory ataxia in the upper limbs can be detected when patients, with eyes closed, cannot accurately locate their thumb with the opposite index finger or display characteristic irregular movement (pseudoathetosis) of the fingers. The sensory examination should include tests of vibration, position, light touch, pain, and temperature. Determining the degree and extent of sensory loss, as well as the pattern of the deficits (symmetric or asymmetric; distal or generalized; focal, multifocal, or diffuse), is important because some forms of inherited neuropathy are more likely than others to present asymmetrically.

Foot Deformities

Because the neuropathy is often asymmetric around joints, muscle imbalances develop between agonist and antagonist muscle groups (eg, ankle dorsiflexors versus plantar flexors, ankle invertors versus evertors), often leading to pes cavus and hammer toes (**Figure 5-1**). In the Mayo Clinic experience, only one-fourth of affected persons in the first decade of life had high arches, whereas two-thirds had high arches in later decades. Pes cavus and high arches are not specific to inherited neuropathies and may also occur in developmental disorders of the CNS.

Dejerine-Sottas Syndrome and Congenital Hypomyelination

DSS refers to severe genetic neuropathies that begin in infancy. Early motor milestones, such as walking, are often delayed, and the course of disease is more severe than described above, but patients may continue to ambulate as adults with appropriate aids. Occasionally, however, patients with DSS die from their neuropathy, particularly when pulmonary sequelae arise. Clinical criteria for DSS have included the following: (1) onset by age 2 years with delayed motor milestones; (2) severe motor, sensory, and skeletal deficits with frequent extension to proximal muscles, sensory ataxia, and scoliosis; (3) markedly abnormal NCVs with either slowing in the range of 10 m/s or severe reductions in motor and sensory amplitudes; and (4) evidence of severe demyelination or axonal loss on nerve biopsy.

Congenital hypomyelination (CH) is a pathologic term originally used to describe peripheral nerves so markedly abnormal that they suggest a developmental failure of peripheral nervous system (PNS) myelination. Patients with CH are usually hypotonic in the first year of life, have developmental delays in walking, and, in some cases, have swallowing or respiratory difficulties. Patients with CH often appear as ''floppy'' infants. Patients classified as having either CH or DSS have shown the same severe pathologic changes on sural nerve biopsies, and both diseases are associated with very slow NCVs (less than 10 m/s). Taken together, these data suggest that it can be difficult to distinguish DSS from CH.

ELECTROPHYSIOLOGY

Because NCV testing is easily performed and provides important information about whether neuropathies are primarily demyelinating or axonal processes, this measure is frequently used alone to classify CMT, particularly because sural nerve biopsies are invasive procedures. In the early 1980s, Lewis and Sumner demonstrated that most cases of inherited demyelinating neuropathies have uniformly slow NCVs, whereas acquired demyelinating neuropathies, such as chronic inflammatory demyelinating neuropathy, have asymmetric slowing.

Thus, NCVs may be used, along with a patient's pedigree, to help distinguish inherited and acquired neuropathies. In the past decade, however, this approach has had to be qualified. Most patients with CMT1, particularly those with CMT1A, do have uniformly slow NCVs of about 20 m/s, and values above 30 m/s are unusual. However, asymmetric slowing is characteristic of HNPP and may also be found in patients with missense mutations in *PMP22*, *MPZ*, *EGR2*, and *GJB1*. Because all of these disorders may appear without a clear family history of neuropathy, one must exercise caution in using NCVs to distinguish acquired from inherited demyelinating neuropathies.

The use of NCVs to distinguish between demyelinating and axonal neuropathies is important. Virtually all forms of CMT1 show both axonal loss and demyelination, and it is likely that of the two, axonal loss correlates better with a patient's actual disability. Reductions in compound motor action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes are found in most patients with CMT1. In one series of 43 patients with CMT1A, 34 had unobtainable peroneal CMAPs, and 41 had unobtainable sural SNAPs. The distinction between demyelinating and axonal features of NCVs can be particularly confusing in CMT1X and CMT1B. NCVs in patients with CMT1X are ''intermediately'' slow and therefore faster than in most patients with CMT1. These patients often also have prominent reductions in CMAP and SNAP amplitudes. CMT1X has even been described by some as an ''axonal'' neuropathy, but careful analysis of conductions will reveal the primary demyelinating features of the neuropathy. The conduction velocities are usually not normal: 30 m/s to 40 m/s, or intermediate between CMT1 and CMT2. Moreover, distal motor latencies and F wave latencies are usually prolonged. In distinguishing between the demyelinating and axonal features of CMT1X, it is important to remember that the disease is caused by mutations in the Cx32 protein, which is expressed in the myelinating Schwann cell. Similar issues occur in some patients with mutations in the *MPZ* gene. For example, the Thr124Met mutation often has NCVs suggestive of an axonal neuropathy, and only through careful evaluation of the studies can evidence of the primary demyelinating features be detected. Finally, some forms of CMT are now defined by intermediately slowed NCVs in the upper extremities. Whether these dominant intermediate forms of CMT are primarily demyelinating or axonal is at present unclear.

KEY POINT

- Nerve conduction velocities in patients with CMT1X are ''intermediately'' slow and therefore faster than in most patients with CMT1.

GENETIC EVALUATION OF INHERITED NEUROPATHIES

Inheritance Patterns in Charcot-Marie-Tooth Disease

Most cases of CMT (eg, CMT1, HNPP, CMT2) are inherited in an autosomal

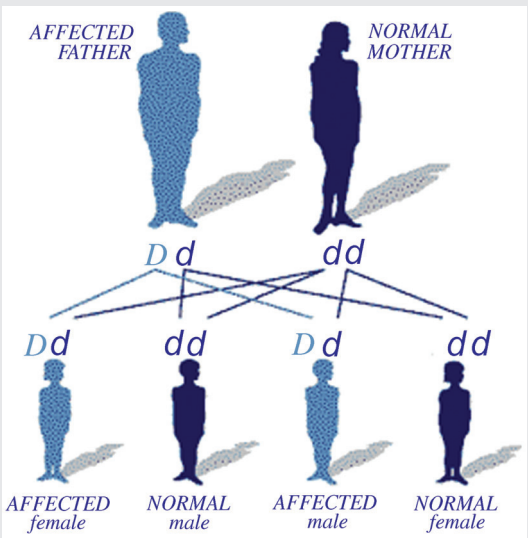

FIGURE 5-3 Autosomal dominant inheritance. Each child of an affected individual has a 50% chance of inheriting the disease-causing gene. Unaffected people cannot pass CMT on to their children. Both males and females can be equally affected with autosomal dominant CMT.

KEY POINT

■ An autosomal dominant mutation can occur de novo in a patient.

dominant pattern (**Figure 5-3**). *Autosomal* refers to nonsex chromosomes, meaning that the condition equally affects males and females, and *dominant* indicates that only one mutant copy of the gene is needed for the condition to be present. Each child of a parent with autosomal dominant neuropathy has a 50% chance of inheriting the disease gene. *Variable expression* of the phenotype among members of the family is often seen in CMT. An autosomal dominant mutation can occur de novo in a patient. In such sporadic disease, the parents of the patient will be unaffected (**Case 5-1**).

The gene causing the major X-linked form of CMT, CMT1X, is located on the X chromosome and is called the gap

Case 5-1

A 35-year-old woman presented with increasing ankle sprains from tripping over carpets and curbs. She was the product of a normal pregnancy and delivery, and early milestones such as sitting up, walking, and talking were met on time. Activities such as riding a bicycle were not difficult for her, but she was a slow runner and had trouble with activities such as walking on the balance beam in high school. An extensive examination of her family history revealed no other individuals with similar problems.

On examination she had normal strength in her upper extremities. Her hands had mild atrophy of her first dorsal interossei bilaterally. She also had mild atrophy in her feet and calves. Bilateral anterior tibialis and posterior longus/brevis muscles were 4+/5, and both extensor hallucis longus muscles were 4/5. All other lower extremity muscles were full strength. Very mild pes cavus and hammer toes were present. Deep tendon reflexes were diffusely absent. Pinprick and vibratory sensations were decreased in her big toes but normal elsewhere. Cerebellar testing was normal. Her gait was normal. She was able to walk on her toes but not on her heels. She had some difficulty with tandem walking, but Romberg sign was absent. NCVs were uniformly slow (about 25 m/s in the ulnar and median nerves) with prolonged distal motor and F wave latencies. Motor and sensory potentials were unobtainable in the lower extremities.

Because of her normal early milestones, slow NCVs, and gradual onset, blood was drawn and genetic testing for the duplication of the *PMP22* gene located on chromosome 17 was performed. The diagnosis of CMT1A was made. After her diagnosis, NCVs were performed on her parents, who were both in their midsixties. Both were completely normal. Paternity was not in question. Therefore, the patient has a new mutation that arose spontaneously around the time of her conception.

Comment. Although the patient will have a 50% chance of passing on the condition to any future children, other family members are not at risk for developing the disease or passing it on to their children. The *PMP22* gene has a relatively high rate of new mutation, and it is common for individuals with no family history of the condition to have this mutation. Patients with CMT1A may have a range of disease severity, and it is entirely possible to have a patient with such mild symptoms.

The patient subsequently brought in her 8-year-old son and 6-year-old daughter for evaluation. Her son had no symptoms of neuropathy, but the daughter was spraining her ankles frequently and falling often when running. She asked for advice about genetic testing for her children.

Because no medications are available to treat CMT, no benefit from offering therapy of any form to presymptomatic patients is known, and because a risk of psychological harm to children carrying the diagnosis of a genetic disease exists, this author does not recommend testing asymptomatic children. Because slow NCVs would also diagnose a child, we at the CMT clinic at Wayne State University would suggest to the mother that the asymptomatic son not obtain genetic testing or NCV testing for CMT. Because the 6-year-old daughter has symptoms of CMT, we would suggest performing a limited NCV of her median or ulnar motor nerves. If it demonstrates slowing in the range of 20 m/s, we would accept this as confirmation of her diagnosis of CMT1A and would not pursue further diagnostic testing.

junction protein, beta 1, 32kDa gene, *GJB1*. *GJB1* encodes the gap junction channel known as connexin 32 (Cx32). Because of its location on the X chromosome, CMT1X is inherited in a different pattern than CMT1 or CMT2 (**Figure 5-4**). Females have two X chromosomes, and males have only one. In families with CMT1X, the affected males usually have more symptoms than affected females. In fact, some gene-positive women have symptoms so mild that they go unnoticed. Females pass either of their X chromosomes on to daughters and sons, whereas males pass on their X chromosome to their daughters and their Y chromosome to their sons. Thus, in a family with CMT1X, an affected mother has a 50% chance of transmitting the mutation to each son or daughter and a 50% chance of not transmitting the mutation to each child. Alternatively, an affected father will never transmit the CMT1X mutation to his sons but will always transmit it to his daughters (**Case 5-2**).

In some patients with CMT, the pattern of inheritance is autosomal recessive. These patients can have either axonal or demyelinating disorders.

Reasons to Pursue Genetic Testing

Clearly, not all patients with a genetic neuropathy want or need testing to identify the genetic cause of their disease. The ultimate decision to undergo genetic testing rests with the patient or the patient's parents if a symptomatic child is younger than 18 years. Reasons that patients give for obtaining testing include identifying the inheritance pattern of their CMT, making family planning decisions, and obtaining knowledge about the cause and natural history of their form of CMT. Natural history data are available for some forms of CMT, such as CMT1A and CMT1X, and can provide guidance for prognosis, although phenotypic variability can occur in these subtypes. Reasons patients do not want genetic testing include the high costs of commercial testing and fears of discrimination in the workplace or in obtaining health insurance. Federal laws (Genetic Information Nondiscrimination Act [GINA]) that should alleviate most of these concerns are now in place. GINA is discussed in the article "Primer on Genetic Counseling." Because no medications are available to reverse any form of CMT, many patients decide against testing because their therapies will not depend on the results. The article "Primer on Genetics Counseling" includes an excellent guideline to help the physician and patient make decisions on genetic testing.

At my clinic, patients are not typically tested for multiple genetic causes of CMT simultaneously, although we have identified 11 patients with multiple genetic causes of CMT. It is our current policy to consider genetic testing in clinically affected family members of the proband only if their phenotype is atypical for the type of CMT in the family. In addition, we do not test asymptomatic minors (younger than 18 years) with a family history of CMT, either by electrophysiology or

KEY POINTS

- An affected father will never transmit the CMT1X mutation to his sons but will always transmit it to his daughters.
- Reasons patients with CMT give for obtaining testing include identifying the inheritance pattern of their neuropathy, making family planning decisions, and obtaining knowledge about the cause and natural history of their form of CMT.
- Reasons patients do not want genetic testing include the high costs of commercial testing and fears of discrimination in the workplace or in obtaining health insurance.

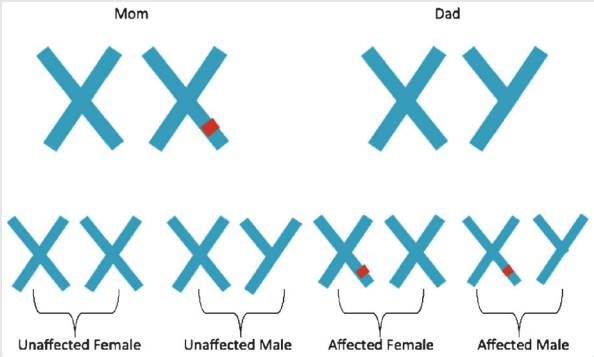

FIGURE 5-4 X-linked dominant inheritance. Although this type of inheritance is called dominant, affected females may have very mild symptoms that can go unnoticed.

Case 5-2

Approximately 1 year ago, a 32-year-old woman began to have tingling in her hands and feet while running in very warm weather. Around this time she also noted minor problems with fine motor skills. The tingling sensation later resolved, but she noticed that she was tripping and falling on occasion. She had no other pain or abnormal sensations.

She was the product of a normal pregnancy and delivery, did not have any physical difficulties as a child, and easily kept up with her peers. At the age of 30 she ran a marathon and was able to finish.

Her father died at a young age in a car accident but had no neurologic problems. Little information was available about his side of the family. Her mother had had high arches and weak ankles for many years, but her situation was complicated by other neurologic problems stemming from a car accident. The patient's maternal grandfather died at age 60 from a stroke but had been in a wheelchair for many years, although the reason that he was unable to walk was unknown. The patient's maternal grandmother had a niece who was diagnosed with a neuropathy, although little was known about her diagnosis.

On examination, the patient's mental status and cranial nerves were normal. She had slight wasting in her intrinsic hand muscles. Her ankles were somewhat thin, and she had pes cavus. First dorsal interosseus and adductor digiti minimi muscles were 4+/5, and all other upper extremity muscles were normal. Anterior tibialis was 4-/5, foot eversion was 4/5, extensor hallucis longus was 3/5, and all other lower extremity muscles were normal. She had a stocking-glove loss of sensation to vibration and temperature in her hands and feet. Patellar, Achilles, and biceps reflexes were absent; brachioradialis and triceps were normal. Her gait was mildly abnormal, and she was not able to walk on her heels.

Her NCVs were intermediately slowed in both motor and sensory nerves, with most values being in the 30-m/s to 40-m/s range.

Comment. Although the family history was not conclusive, the patient's examination and intermediate NCVs were consistent with an inherited form of peripheral neuropathy. The two common forms of CMT that typically exhibit intermediate NCVs are CMT1B and CMT1X. The patient is tested simultaneously for mutations in both the *MPZ* gene located on chromosome 1, which is responsible for CMT1B, and *GJB1* located on the X chromosome, which is responsible for CMT1X. Test results reveal known disease-causing mutations in both of these genes. Further testing on other family members is necessary to determine where in the family these mutations came from and the chances for other family members to be at risk of developing CMT. Genetic counseling for the patient regarding her chances of passing CMT on to future children is complicated. One needs not only to take into account the mendelian odds of passing on each of the mutations but also the effect of gender on a child who receives the *GJB1* mutation. The patient is not more severely affected because having mutations in more than one CMT gene does not necessarily mean that the CMT will be more severe than either form because the disability may not be additive in all cases. In this case, it is possible that she is relatively asymptomatic from the *GJB1* mutation because of random or skewed X inactivation.

genetic testing, because of the chance for increased psychological harm to the child. We do routinely perform limited nerve conduction studies, although not needle EMG, on symptomatic children with CMT. Because nerve conduction changes, including slowing, are often uniform and detectable in early childhood in CMT, testing of a single nerve is often adequate to guide genetic testing or determine whether a symptomatic child is affected in a family with CMT.

SPECIFIC GENETIC TYPES OF CHARCOT-MARIE-TOOTH DISEASE

Charcot-Marie-Tooth Disease Type 1

A 1.4-Mb duplication at chromosome 17p11.2 causes CMT1A, the most

common form of CMT. A few rare patients have been reported with single base pair changes in the *PMP22* gene as well. The duplication is thought to arise from homologous recombination occurring within a repeated sequence that flanks the duplicated region. The 1.4-Mb genomic segment is flanked by two nearly identical sequence elements, known as CMT1A-REPs. The two repeats are thought to contain a ''hot spot'' for recombination that results in duplication of the intervening genomic segment. Approximately 10% of all CMT1A duplications in patients are de novo mutations. Deletion of exactly the same 1.4-Mb region, containing *PMP22,* was subsequently shown to cause most cases of HNPP, an entirely different disorder characterized by episodes of focal weakness or sensory loss rather than a length-dependent neuropathy.

CMT1B, caused by mutation in *MPZ*, comprises about 10% of CMT1. Patients can present with the classic CMT1 phenotype but are more likely to have either a more severe early-onset form of CMT with motor conduction velocity (MCV) less than 10 m/s or a late-onset form of CMT with median MCVs in the axonal range.

EGR protein and *LITAF* mutations cause rare (less than 1%) cases of CMT1. Patients with *EGR2* mutations usually present with DSS, and patients with *LITAF* mutations frequently resemble those with CMT1A. Mutations in the neurofilament, light polypeptide gene, *NEFL*, were originally described as a cause of CMT2; however, some patients have MCVs in the demyelinating range although the gene is expressed in neurons but not Schwann cells.[7] This is another example of how the electrophysiologic and the genetic classifications do not always concur.

Charcot-Marie-Tooth Disease Type X

CMT1X is sometimes included with CMT1 because it is a dominantly inherited demyelinating neuropathy; although, as discussed above, it is X-linked, which leads to a different inheritance pattern than autosomal dominant disorders. CMT1X is the second most frequent form of CMT1, accounting for 10% to 20% of all patients with CMT. CMT1X is caused by point mutations in the *GJB1* gene on the X chromosome at locus Xq13.1.[8]

Charcot-Marie-Tooth Disease Type 2

CMT2 can be difficult to distinguish from idiopathic axonal neuropathies when no family history is present. At least eight causative genes have been identified, accounting for about one-third of all CMT2 cases. Most patients with CMT2 present with length-dependent weakness and sensory loss that is clinically similar to patients with CMT1. However, occasional forms present with prominent upper extremity weakness that precedes lower extremity involvement (CMT2D). Mitofusin 2 mutations (CMT2A) are the most common form of CMT2 (**Case 5-3**).[9] Although one series has reported finding mutations of the mitofusin 2 gene, *MFN2*, in up to 33% of cases of CMT2,[10] in most series this number is about 20% of cases with clinically defined CMT2. These patients also tend to have a more severe phenotype. In fact, in one study, up to 28% of patients with CMT2A were found to require wheelchairs,[10] which is not common in other forms of CMT. Occasional patients with CMT2A also have optic atrophy and severe axonal neuropathy (HMSN-VI in previous classifications), brisk reflexes, and minor white matter changes on brain MRI.[11] Small heat shock protein genes *HSPB1*

KEY POINTS

- An 1.4-Mb duplication at chromosome 17p11.2 causes CMT1A, the most common form of CMT. A few rare patients have been reported with single base pair changes in the *PMP22* gene as well.
- CMT1B, caused by mutation in myelin protein zero, *MPZ*, comprises about 10% of CMT1.
- Mitofusin 2 mutations (CMT2A) are the most common form of CMT2.
- Occasional patients with CMT2A also have optic atrophy and severe axonal neuropathy (hereditary motor and sensory neuropathy type VI in previous classifications), brisk reflexes, and minor white matter changes on brain MRI.

Case 5-3

An 11-year-old girl with significant neurologic problems needed a wheelchair full time since the age of 8. Her mother's pregnancy and delivery were uncomplicated, but she began showing signs of respiratory distress at 12 hours of age. She began walking around the age of 2 and was able to walk independently until the age of 6. During this time, her gait was unstable and she was never able to run. She was able to walk with a walker until the age of 8. Cognitively she was normal and did very well in school. She had no problems with bowel or bladder function.

Extensive inquiry into the family history revealed no individuals with a similar condition.

On examination, she had significant muscle atrophy in both her upper and lower extremities, and her hands were clawed. She had slight movement in her triceps and wrist flexors but no other movement in her upper or lower extremities. She had no obvious sensory loss to large or small fiber modalities. She was areflexic. Mental status and cranial nerve examination were normal.

Nerve conduction velocities performed at 6 years of age were unobtainable from the usual distal sites in the leg or arm. Recording from proximal muscles in the forearm revealed normal velocities but reduced CMAP amplitudes. Genetic testing identified an arginine94tryptophan missense mutation in the coiled coil domain of the *MFN2* gene.

Comment. Heterozygous mutations in the *MFN2* gene cause CMT2A. This is the most common form of CMT2. Phenotypes are often severe in childhood and may present as pure motor neuropathies. Both parents were tested and were negative for this mutation. De novo cases occur in about 20% of patients with CMT2A. Some cases also present with optic atrophy (CMT6) or pyramidal signs (CMT5).

(*HSP27*) and *HSPB8* (*HSP22*) are rare causes of CMT2 but usually are associated with minimal sensory involvement (these two genes also cause a purely motor phenotype, distal hereditary motor neuropathy [dHMN] type II).[12] A homozygous mutation in *HSPB1* has also recently been shown to cause the autosomal recessive type of CMT.[13] Mutations in *MPZ* and *NEFL* can also cause CMT2 phenotypes.

Profound sensory impairment, often including ''ulceromutilations,'' characterizes another CMT2 phenotype. The causative gene is a member of the RAS oncogene family, *RAB7*, and patients are classified as having CMT2B.[14] Patients with CMT2B are difficult to distinguish from those with hereditary sensory and autonomic neuropathy (HSAN) type I (see below), caused by mutations in the serine palmitoyltransferase, long chain base subunit 1 gene, *SPTLC1*.[15,16] If patients present with prominent sensory features, both the *RAB7* and *SPTLC1* genes should be initially considered.

Patients with mutations in the glycyl-tRNA synthetase gene, *GARS*, develop CMT2D, one of the more surprising findings in CMT. This enzyme is responsible for charging the transfer RNA (tRNA) molecule with glycine, and as such is ubiquitous. The existence of this specific phenotype suggests a unique role for the enzyme in axons or that axons lack some compensating mechanism found elsewhere. Since this discovery, mutations in at least two other aminoacyl synthetase genes have been found,[17,18] which suggests that this unique role may involve multiple tRNA synthetase genes. A second surprise was that same mutation in the *GARS* gene causes spinal muscular atrophy type V, with both phenotypes found in the same family. Such patients present with atrophy and weakness of the small muscles of the hand (this can be unilateral and misdiagnosed as thoracic outlet syndrome) and much later involvement of the distal lower limb muscles. CMT2D is caused by mutations in *GARS*.[19] The dHMN-V/CMT2D

phenotype has subsequently been shown to be more commonly due to mutations in the Berardinelli-Seip congenital lipodystrophy 2 (seipin) gene, *BSCL2*, which usually causes Silver syndrome (spastic legs and distal amyotrophy of the upper limbs) but can present (33% of cases) with just amyotrophy of the upper limbs.[20]

Charcot-Marie-Tooth Disease Type 4: Autosomal Recessive

Thirteen genes have been identified that cause autosomal recessive CMT4 (including three genes—*PMP22, MPZ*, and *EGR2*—that more commonly cause CMT1). All but two of these genes cause demyelinating CMT. Usually CMT4 patients have early, infantile onset and severe weakness. Weakness often progresses to involve proximal muscles and results in early loss of ambulation. Recent comprehensive reviews of demyelinating[21] and axonal CMT4 are available.[22] *GDAP1* mutations, which cause CMT4A, are interesting in that mutations of the same gene have been described as causing both axonal and demyelinating CMT.[23,24] *GDAP1* is expressed in both Schwann cells and the axon, which may explain its dual phenotypes in different families. CMT4 does exist in outbred societies such as the United States. Allen, in his famous 1939 manuscript describing how autosomal recessive disorders were more severe than autosomal dominant diseases, used CMT4 families in North Carolina as an example. Thus, patients with early-onset CMT and no family history should be considered for CMT4. In most European or North American populations, however, such patients most likely have de novo mutations in CMT1 genes.

Particular points to consider include the following:

- Autosomal recessive neuropathies can be difficult to identify because few cases have been identified, polymorphisms are frequent, and compound heterozygous mutations can be disease causing. Often multiple family members must be screened to ensure mutations are disease causing.
- Identification of demyelination by MCV can be difficult in CMT4 because motor and sensory amplitudes are often unobtainable at routine recording sites in these severely affected patients. Conduction studies of nerves innervating proximal muscles may be necessary to identify slow MCV.
- Nerve biopsies showing focally folded myelin are characteristic of CMT4B1 (*MTMR2* mutations)[25] (**Case 5-4**) and CMT4B2 (*SBF2* mutations)[26] but can also be seen with *MPZ* mutations and in CMT4F secondary to periaxin mutations.
- Severe and early scoliosis may be seen with CMT4C due to mutations in the *SH3TC2* gene (**Case 5-5**). Several patients have had characteristic nerve biopsy features, including basal membrane onion bulbs and multiple cytoplasmic processes of the Schwann cells ensheathing unmyelinated axons.[27] Two forms of CMT4 are largely confined to patients of Balkan gypsy origin. CMT4D secondary to *NDRG1* mutations is characterized by a demyelinating neuropathy with a high prevalence of deafness. Tongue atrophy has also been described. Congenital cataract, facial dysmorphism, and neuropathy syndrome secondary to *CTDP1* mutations is also found in gypsies.
- Predominant sensory involvement and variable phenotypes are characteristic of CMT4F (*PRX* mutations).[28]

KEY POINT

■ Patients with early-onset CMT and no family history should be considered for CMT4. However, in most European or North American populations such patients are most likely to have de novo mutations in CMT1 genes.

Case 5-4

A 9-year-old boy was brought by his parents for evaluation of bilateral footdrop without sensory loss. He had begun walking by 13 months of age. He wore ankle-foot orthoses that extended above the ankle whenever he was out of the house. He played on a local football team. The patient had difficulty buttoning his pants although he could button his shirt. He needed assistance cutting meat. Motor and sensory NCVs were around 20 m/s in all extremities. Before arriving in clinic he had had genetic testing that was negative for mutations in *PMP22* (duplicate/deletion and point mutations), *GJB1*, *MPZ*, *EGR2*, *NEFL*, *PRX*, *GDAP1*, *LITAF*, and *MFN2*. A sural nerve biopsy was performed.

Electron microscopy revealed a characteristic outfolding of myelin known to be associated with autosomal recessive forms of CMT, CMT4B1, and CMT4B2. Testing in an appropriate research laboratory revealed a known disease-causing mutation in the myotubularin related protein 2 gene, *MTMR2*, causing CMT4B1. Each parent was heterozygous for the mutation.

Comment. Autosomal recessive forms of CMT can be very difficult to diagnose. This situation is one of the few indications for sural nerve biopsy in inherited neuropathies because the specific findings from the biopsy targeted the gene to look for after the more common forms of demyelinating CMT had been excluded.

Case 5-5

A 10-year-old girl with no family history of neuropathy presented with hand and foot weakness. She was the product of a normal pregnancy and delivery. Her feet were reported to be turned in at birth such that serial casting was required to straighten them out in the first 14 weeks of life. She began walking by 12 months of age, although she was a toe walker at that time. At 2 years of age she started physical therapy because of leg stiffness. At the age of 10 she was able to keep up with her peers, ride a bicycle, roller-skate, and ice-skate. She was the slowest runner of her friends and teammates, had occasional foot cramps, and had mild problems with balance. She had difficulty cutting her food and avoided clothes with buttons.

On neurologic examination, strength was 5/5 throughout except for mild (4+) weakness of her adductor digiti minimi and toe dorsiflexors. Vibratory sensation was decreased at her left toe. Deep tendon reflexes were absent. Median and ulnar motor NCVs were 32 m/s and 38 m/s. Median and ulnar sensory NCVs were around 40 m/s. Both CMAP and SNAP amplitudes were normal. No scoliosis was noted. When she returned to the office at the age of 12, however, pronounced scoliosis had developed over the preceding 3 months.

At this time genetic testing was performed and identified an asparagine>serine substitution at codon 881 of the SH3 domain and tetratricopeptide repeats 2 gene, *SH3TC2*, that has been previously reported to cause CMT4C.

Comment. CMT4C is the most common form of CMT4,[36] at least in countries with predominantly European populations and with low levels of consanguinity. CMT4C often causes pronounced scoliosis with mild weakness or sensory loss, and NCVs may be mildly slowed. An unusual feature of this case is the absence of scoliosis on initial evaluation and its rapid development over a few-month period before the second evaluation.

- Only two known causative genes have been identified for autosomal recessive axonal CMT4, *LMNA* and *GDAP1*. Most patients with mutations in the lamin A/C gene, *LMNA*, present in the second decade with a severe CMT phenotype including proximal muscle involvement, although some have a milder phenotype. Lamin A/C mutations have been associated with a wide spectrum of other phenotypes, including Emery-Dreifuss muscular dystrophy, cardiomyopathy, and Dunnigan-type familial partial lipodystrophy.

Intermediate Charcot-Marie-Tooth Disease

Certain forms of CMT characteristically present with MCVs in the intermediate range (25 m/s to 45 m/s). These include dominant intermediate (DI)-CMTB caused by *DNM2* mutations,[29] DI-CMTC caused by *YARS* mutations,[17] and DI-CMTA in which only linkage has been identified at 10q24.1–25.1. In addition, patients with CMT1X, CMT2E, late-onset CMT1B, and CMT4A often present with intermediate MCVs.

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY

The HSANs are rare, but many of the genes have been identified (**Table 5-4**). Autonomic abnormalities are often minimal, and motor involvement can be present. The sensory loss can lead to severe complications, including recurrent injuries, ulcerations, osteomyelitis, and amputations. The most common autosomal dominant form is HSAN type I (HSAN-I) (or hereditary sensory neuropathy [HSN]) type I caused by *SPTLC1* mutations. Patients usually present in the second decade with distal lower limb sensory loss, and many have neuropathic pain. Motor involvement can be significant, especially later in the disease course. MCVs can be in the demyelinating range, with males being more severely affected than females.[30] This disease is very difficult to differentiate from CMT2B secondary to *RAB7* mutations, although the lancinating pain in patients with *SPTLC1* mutations can be a useful guide to this diagnosis.

HSAN-II is an early-onset autosomal recessive severe sensory neuropathy with prominent sensory complications caused by mutations in the *WNK1* gene.[31]

HSAN-III (Riley-Day syndrome) is an autosomal recessive neuropathy seen in Ashkenazi Jews and characterized by mainly autonomic involvement, but it also involves the PNS, particularly the sensory nerves. The causative gene is *IKBKAP*.[32]

HSAN-IV and HSAN-V are both autosomal recessive neuropathies characterized by congenital insensitivity to pain. HSAN-IV (also called congenital insensitivity to pain with anhidrosis) presents with a severe sensory neuropathy, anhidrosis, and mental retardation and is caused by mutations in the *NTRK1* gene. HSAN-V is similar but without the mental retardation or significant anhidrosis, described with both *NTRK1* and *NGF* mutations.

Recently the identification of homozygous mutations in the *SCN9A* gene as a rare cause of congenital insensitivity to pain[33] has been of great interest because heterozygous mutations in the same gene cause hereditary erythermalgia[34] and paroxysmal extreme pain disorders.[35]

DISTAL HEREDITARY MOTOR NEUROPATHIES

The dHMNs are a complex group of disorders that typically present with length-dependent weakness and no sensory loss (**Table 5-5**). dHMN-II is the classic form of autosomal dominant dHMN and is caused by mutations in the *HSPB1* and *HSPB8* genes, which also cause CMT2F and CMT2L. Many other

forms exist, but the genes are only known for the following:

- Mutations in *GARS* and *BSCL2* cause dHMN type V (also CMT2D).
- dHMN type VI, an unusual severe autosomal recessive form of dHMN, presents in infancy with respiratory and distal limb involvement (called spinal muscle atrophy with respiratory distress type I). This is caused by mutations in *IGHMBP2*.

TABLE 5-4 Classification of the Hereditary Sensory and Autonomic Neuropathies

Type	Inheritance	Gene/Locus	Specific Phenotype
HSAN-I	AD	*SPTLC1*	Mainly sensory, sensory complications, motor involvement variable, males may be more severe
CMT2B	AD	*RAB7*	Sensorimotor, sensory complications, no pain
HSAN-1B	AD	3p22–p24	Sensory, cough, gastroesophageal reflux
HSAN-II	AR	*WNK1*	Severe sensory complications, mutilations, onset first 2 decades
HSAN-III	AR	*IKBKAP*	Familial dysautonomia or Riley-Day syndrome, prominent autonomic, absence fungiform papillae of the tongue
HSAN-IV	AR	*NTRK1*	Congenital insensitivity to pain with anhydrosis (CIPA), severe sensory, anhydrosis, mental retardation, unmyelinated fibers mainly affected
HSAN-V	AR	*NTRK1*	Congenital insensitivity to pain with mild anhydrosis, no mental retardation, small myelinated fibers mainly affected
HSAN-V	AR	*NGF*	Congenital insensitivity to pain, minimal autonomic, no mental retardation, mainly unmyelinated fibers affected
Channelopathy	AR	*SCN9A*	Congenital insensitivity to pain, associated insensitivity to pain

HSAN-I = hereditary sensory and autonomic neuropathy type I; AD = autosomal dominant; *SPTLC1* = serine palmitoyltransferase, long chain base subunit 1; CMT2B = Charcot-Marie-Tooth neuropathy type 2B; *RAB7* = RAS-oncogene family-like 1; HSAN-1B = hereditary sensory and autonomic neuropathy type 1B; HSAN-II = hereditary sensory and autonomic neuropathy type II; *WNK1* = WNK lysine deficient protein kinase 1; HSAN-III = hereditary sensory and autonomic neuropathy type III; AR = autosomal recessive; *IKBKAP* = inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein; HSAN-IV = hereditary sensory and autonomic neuropathy type IV; *NTRK1* = neurotrophic tyrosine kinase receptor, type 1; HSAN-V = hereditary sensory and autonomic neuropathy type V; *NGF* = nerve growth factor (beta polypeptide); *SCN9A* = sodium channel, voltage-gated, type IX, alpha subunit.

TABLE 5-5 Classification of the Distal Hereditary Motor Neuropathies

Type	Inheritance	Gene/Locus	Specific Phenotype
dHMN-I	AD	unknown	Juvenile-onset dHMN
dHMN-II	AD	*HSPB1* (*HSP27*)	Adult-onset typical dHMN/CMT2F
dHMN-II	AD	*HSPB8* (*HSP22*)	Adult-onset typical dHMN/CMT2L
dHMN-III	AR	11q13	Early onset, slowly progressive
dHMN-IV	AR	11q13	Juvenile onset, diaphragmatic involvement
dHMN-V	AD	*GARS*	Upper limb onset, slowly progressive/CMT2D
dHMN-V	AD	*BSCL2*	Upper limb onset, +/-spasticity lower limbs/Silver-Russell syndrome
dHMN-VI	AR	*IGHMBP2*	Spinal muscle atrophy with respiratory distress (SMARD1), infantile-onset respiratory distress
dHMN-VIIA	AD	2q14	Adult onset, vocal cord paralysis
dHMN-VIIB	AD	*DCTN1*	Adult onset/vocal cord paralysis/facial weakness
dHMN/ALS4	AD	*SETX*	Early onset, pyramidal signs
dHMN-J	AR	9p21.1–p12	Juvenile onset, pyramidal features, Jerash congenital distal
SMA	AD	12q23–12q24	Antenatal onset, arthrogryposis

dHMN-I = distal hereditary motor neuropathy type I; AD = autosomal dominant; dHMN = distal hereditary motor neuropathy; dHMN-II = distal hereditary motor neuropathy type II; *HSPB1* = heat shock 27kDa protein 1; CMT2F = Charcot-Marie-Tooth type 2F; *HSPB8* = heat shock 22kDa protein 8; CMT2L = Charcot-Marie-Tooth type 2L; dHMN-III = distal hereditary motor neuropathy type III; AR = autosomal recessive; dHMN-IV = distal hereditary motor neuropathy type IV; dHMN-V = distal hereditary motor neuropathy type V; *GARS* = glycyl-tRNA synthetase; CMT2D = Charcot-Marie-Tooth type 2D; *BSCL2* = Berardinelli-Seip congenital lipodystrophy 2 (seipin); *IGHMBP2* = immunoglobulin mu binding protein 2; dHMN-VIIA = distal hereditary motor neuropathy type VIIA; dHMN-VIIB = distal hereditary motor neuropathy type VIIB; *DCTN1* = dynactin1; *SETX* = senataxin.

- Mutations in the dynactin gene, *DCTN1*, cause one form of dHMN type VII, which is characterized by vocal cord paralysis and progressive weakness and atrophy of the face, hands, and legs.
- Missense mutations in the senataxin gene, *SETX*, can cause a form of dHMN with pyramidal features, whereas nonsense mutations in the same gene cause autosomal recessive ataxia with oculomotor apraxia type 2.

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