This chapter reviews current ideas regarding clinical evaluation, genetics, and molecular pathogenesis of hereditary neuropathies. Acquired neuropathies (mostly immune mediated), neuropathies secondary to systemic disease (diabetes and vasculitides), primary motor neuron degenerations (spinal muscular atrophies), and disorders in which neuropathy is part of a more widespread neurologic disorder (leukodystrophies, mitochondrial disorders, lipoprotein deficiencies, Fabry’s disease, porphyrias, and hereditary ataxias) are considered elsewhere. The genetic defects underlying many of the hereditary neuropathies have been determined and others are under investigation, accounting for the continually changing classification of the inherited neuropathies.

Early classification schemes were based on clinical features (age of onset, inheritance pattern, and presence of hypertrophic nerves), results of electrodiagnostic tests (separating demyelinating from axonal processes), and pathological features on nerve biopsy. This led to a classification into clinical subtypes: hereditary motor and sensory neuropathies (HMSNs), hereditary motor neuropathies (HMNs), and hereditary sensory and autonomic neuropathies (HSANs). The best-recognized clinical HMSN syndromes are Charcot-Marie-Tooth (CMT) disease (demyelinating and axonal types), Dejerine-Sottas disease (DSD), hereditary neuropathy with susceptibility to pressure palsies (HNPP), and congenital hypomyelinating neuropathy. There is a more-or-less parallel genetic classification into CMT subtypes (Table 61-1), but one needs a fairly complex table to see the correspondence between the clinical and genetic classification schemes. Clinical and genetic heterogeneity confound the classification problem. For instance, several genes (PMP22, MPZ, EGR) can result in the demyelinating HMSN I phenotype, and different mutations in a given gene can cause distinct clinical syndromes (either HMSN I, DSD, or HNPP). Ultimately, the classification scheme will be based entirely on the underlying genetic defect, which attempts to correlate genotype with phenotype, and relates the gene defect to pathogenesis. Because of the multitude of genes that have been discovered, it has become even more important for the clinician to formulate an optimal and cost-effective diagnostic plan on the basis of clinical features.

Clinical Syndromes

CMT is the most common inherited peripheral neuropathy, with a prevalence of 1/10,000 to 4/10,000. Clinical symptoms appear in the first or second decade, with slowly progressive distal weakness and atrophy, particularly of the small muscles of the foot and peroneal muscles. This is responsible for the typical foot drop and the high-step gait characteristic of these patients. Atrophy due to wasting of the peroneal muscles results in the inverted “champagne bottle” appearance of the leg. Progression can lead to hand and forearm atrophy, often with a “claw-hand” deformity. These features are accompanied by distal sensory deficits and loss of deep tendon reflexes.

The autosomal dominant forms of CMT can be divided into two groups on the basis of results from
The Office Visit: Other Neurologic Complaints and Conditions

Electrophysiologic studies: (1) CMT1, with features suggesting demyelination as the primary pathology and symptom onset in the first or second decade, and (2) CMT2, with features suggesting a primary axonal process and later onset of symptoms. An X-linked form also exists, CMTX, in which affected males exhibit a more severe phenotype and slower motor nerve conduction than female carriers.

DSD can be viewed as a more severe form of demyelinating neuropathy, with onset in infancy. The term “DSD-like neuropathy” is used to describe such patients with severe and early onset symptoms but without signs of demyelination on electrophysiologic studies.

Congenital hypomyelinating neuropathy (CHN) implies onset at birth. It is characterized by infantile hypotonia, distal weakness, and areflexia, with very slow motor nerve conduction velocity.

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**TABLE 61-1. Gene Mutations and Clinical Syndromes in Hereditary Neuropathies**

<table>
<thead>
<tr>
<th>Clinical Subtype</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Locus</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demyelinating Neuropathies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT1A</td>
<td>AD</td>
<td>PMP22</td>
<td>17p11</td>
<td>Onset in 1st to 2nd decade; distal weakness, atrophy, and sensory loss; gene duplication</td>
</tr>
<tr>
<td>HNPPAD</td>
<td></td>
<td>PMP22</td>
<td>17p11</td>
<td>Focal neuropathies, entrapment syndromes, tomacula, and gene deletion</td>
</tr>
<tr>
<td>CMT1B</td>
<td>AD</td>
<td>MPZ</td>
<td>1q22</td>
<td>More severe than CMT1A; 30% primary axonal pathology</td>
</tr>
<tr>
<td>CMT1C</td>
<td>AD</td>
<td>LITAF (SIMPLE)</td>
<td>16p13</td>
<td>Marked reduction in mNCV, temporal dispersion, and conduction block</td>
</tr>
<tr>
<td>CMT1D</td>
<td>AD</td>
<td>EGR2</td>
<td>10q21</td>
<td>Variable severity</td>
</tr>
<tr>
<td>CMT-X</td>
<td>XR/XD</td>
<td>GJB1 (Cx32)</td>
<td>Xq</td>
<td>Distal atrophy; males more severe than females</td>
</tr>
<tr>
<td>CMT3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSD</td>
<td>AD</td>
<td>PMP22, MPZ, GJB1, EGR2, NEFL</td>
<td></td>
<td>Delayed motor development by age 3 years; severe distal motor disease with severe large fiber sensory loss</td>
</tr>
<tr>
<td>AR</td>
<td>MTMR2, PRX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHN</td>
<td>AD</td>
<td>PMP22, MPZ, EGR2</td>
<td></td>
<td>Hypotonia at birth; delayed motor development</td>
</tr>
<tr>
<td>AR</td>
<td>EGR2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT4A</td>
<td>AR</td>
<td>GDAP1</td>
<td>8q21.1</td>
<td>Early childhood onset, loss of mobility over time</td>
</tr>
<tr>
<td>CMT4B</td>
<td>AR</td>
<td>MTMR2</td>
<td>11q23</td>
<td>Milder than CMT4A; focally folded myelin</td>
</tr>
<tr>
<td>CMT4B2</td>
<td></td>
<td>(MTMR13, SBF2)</td>
<td>11p15</td>
<td>Childhood onset; glaucoma; focally folded myelin</td>
</tr>
<tr>
<td>CMT4C</td>
<td>AR</td>
<td>KIAA1985</td>
<td>5q23-q33</td>
<td></td>
</tr>
<tr>
<td>CMT4C4</td>
<td></td>
<td>MPZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT4D</td>
<td>AR</td>
<td>NEFL</td>
<td>8q21.1</td>
<td></td>
</tr>
<tr>
<td>CMT4F</td>
<td>AR</td>
<td>EGR2</td>
<td>10q21</td>
<td>Infantile onset, early loss of mobility</td>
</tr>
<tr>
<td>CMT4R</td>
<td></td>
<td>?</td>
<td>10q23</td>
<td>Infantile onset, progression to wheelchair dependency</td>
</tr>
<tr>
<td>Axonal Neuropathies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT2A</td>
<td>AD</td>
<td>KIF1B</td>
<td>1p35-p36</td>
<td>Onset by age 10 years; motor greater than sensory; feet</td>
</tr>
<tr>
<td>CMT2B</td>
<td>AD</td>
<td>RAB7</td>
<td>3q13-q22</td>
<td>Onset in 2nd to 3rd decade; severe sensory symptoms with ulcers</td>
</tr>
<tr>
<td>CMT2C</td>
<td></td>
<td>?</td>
<td>12q23</td>
<td></td>
</tr>
<tr>
<td>CMT2D</td>
<td>AD</td>
<td>GARS</td>
<td>7p15</td>
<td>Onset in 2nd decade; atrophy and weakness in hands, with sensory and leg symptoms occasionally</td>
</tr>
<tr>
<td>CMT2E</td>
<td>AD</td>
<td>NEFL</td>
<td>8q21</td>
<td>Variable onset and severity</td>
</tr>
<tr>
<td>CMT2-P0</td>
<td>AR</td>
<td>MPZ</td>
<td>1q22</td>
<td>Onset in 3rd decade; pain, hearing loss, and abnormal pupil reaction</td>
</tr>
<tr>
<td>AR-CMT2A</td>
<td>AR</td>
<td>LMNA</td>
<td>1q21</td>
<td>Onset in 2nd decade; eventual severe distal weakness</td>
</tr>
<tr>
<td>GAN</td>
<td></td>
<td>Gigaxonin</td>
<td>16q24</td>
<td>Onset in 1st decade, giant axons with neurofilament CNS involvement</td>
</tr>
<tr>
<td>Sensory and Autonomic Neuropathies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSAN 1</td>
<td>AD</td>
<td>SPTLC-1</td>
<td>9q22</td>
<td>Onset in 2nd to 3rd decade, ulceration distally, lancinating pain, sensory loss, and distal weakness</td>
</tr>
<tr>
<td>HSAN 3</td>
<td>AR</td>
<td>IKBKAP</td>
<td>9q31</td>
<td>Riley-Day syndrome, neonatal onset, autonomic</td>
</tr>
<tr>
<td>HSAN 4</td>
<td>AR</td>
<td>NTRK-1</td>
<td>1q22-q23</td>
<td>Congenital insensitivity to pain; anhidrosis and mental retardation</td>
</tr>
</tbody>
</table>

AD = autosomal dominant; AR = autosomal recessive; CMT = Charcot-Marie-Tooth; CNS = central nervous system; GAN = giant axonal neuropathy; HSAN = hereditary sensory and autonomic neuropathy; HNPP = hereditary neuropathy with susceptibility to pressure palsies; HSAN = hereditary sensory and autonomic neuropathy; mNCV = motor nerve conduction velocity.

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Heredity Neuropathy  
Pages 391–398
Clinical Approach

As with any other neurologic problem, a careful history and physical examination are essential in evaluating patients with suspected peripheral neuropathy. In children, this should be considered in the differential diagnosis when the complaint is weakness or muscle wasting, delay in achieving motor milestones, clumsiness or ataxia, gait disorder, foot or wrist drop, tingling or numbness, foot deformity, toe walking, or hypotonia and feeding or breathing difficulties in the neonate. It is absolutely essential to obtain a detailed family history, including questions about the presence of foot deformity, use of a cane or other aid for walking, orthopedic surgical procedures, and use of splints or supports as a child. When possible, family members should also be examined and studied. History and physical examination alone frequently allow exclusion of brain or spinal cord lesions from the differential diagnosis. However, clearly distinguishing between muscle disease, disorders of the neuromuscular junction, and demyelinating versus axonal neuropathy might not be possible on the basis of clinical examination alone. One example where such difficulty arises is in a child with distal muscle weakness and atrophy. Electrodiagnostic testing (nerve conduction studies and electromyography [EMG]) plays a crucial role in the evaluation of these patients.

In most cases, the history alone is sufficient to decide if one is dealing with an acquired disease rather than an inherited neuropathy. The classic exceptions are the rare indolent course of chronic inflammatory demyelinating neuropathy (CIDP) and acute focal neuropathy due to HNPP. Electrodiagnostic testing is also useful in distinguishing acquired from inherited neuropathies. Nerve biopsy is reserved for sporadic cases when electrophysiologic studies are not helpful. The nerve biopsy may exclude acquired disorders (inflammatory disorders or focal tumors) and provide clues to the primary pathology involved, when electrophysiologic studies are not diagnostic.

Electrodiagnostic Testing

To minimize discomfort to the patient, electrophysiologic studies are planned as an extension to and in the context of the clinical examination. Electrophysiologic studies should not only confirm a peripheral disorder, but also localize it to the peripheral nerve, to the spinal motor neuron or motor nerves, to the neuromuscular junction, or to the skeletal muscle. In addition, electrophysiologic studies should categorize the primary pathological process as a demyelinating or an axonal process and help to exclude the rare acquired treatable neuropathies, such as CIDP. The primary pathology identified then may direct the search for genetic cause.

Motor conduction studies and EMG are best done after sensory nerve conduction studies. One could study sensory nerve action potentials (SNAP) by stimulating a mixed nerve and recording distally over a cutaneous branch or vice versa. A pure sensory nerve also could be studied this way. The SNAP recorded represents the summated action potentials of individual fibers. A reduction in SNAP amplitude or slowing of conduction, confirmed in more than one nerve, would localize the process to the peripheral sensory nerve or sensory ganglion. This alone is sufficient to confirm a polyneuropathy, in the appropriate clinical context.

The compound motor action potential (CMAP) is the summated electrical activity recorded from synchronously activated muscle fibers by stimulating the motor axons innervating that muscle (motor nerve conduction studies). By performing distal and proximal supramaximal stimulation on a motor nerve while recording from an innervated muscle, one may determine the distal latency and conduction velocity proximally. More proximal motor conduction velocity in the proximal nerves and roots can be measured by the recording F-wave. The CMAP amplitude provides a physiologic assessment of the motor axon, neuromuscular junction, and muscle fiber activated by the stimuli, and thus is affected by disease at any one of these sites. Significant slowing of conduction (prolonged distal latency, slowing of proximal conduction velocity, or delayed F-wave latencies) and the phenomenon of dispersion and conduction block suggests a demyelinating process and localizes the pathology to the motor components of the peripheral nerves. Studies in two motor nerves are often sufficient to determine these features. Because motor conduction velocity may be normal in axonal neuropathies, the lack of features of demyelination does not exclude a peripheral nerve process. Thus, abnormal motor nerve conduction also
helps to determine the underlying pathological process in a patient with peripheral neuropathy.

EMG becomes necessary only when abnormalities of the SNAP or motor nerve conduction have not been seen, essentially to distinguish myopathies from pathological processes that affect the motor neuron or axon. For this purpose, we sample a proximal and distal muscle in an upper and lower extremity. The electrical activity of motor units recorded with a needle electrode in a muscle is derived from action potentials of the muscle fibers that are firing singly or in groups near the electrode. Fibrillation and positive sharp waves are spontaneous pathological discharges from individual muscle fibers. Although their presence can easily confirm a peripheral nervous system disorder, they are not useful in distinguishing a primary myopathy from a neurogenic process affecting the muscle. This is achieved by an assessment of the voluntary motor units and their activity, to identify myopathic or neurogenic potentials. In general, short, low-amplitude motor unit potentials that are rapidly recruited to produce a given force resulting in a full interference pattern on the screen suggest a myopathic process. In contrast, reduced recruitment where fewer motor units have to fire more rapidly to generate a given force is suggestive of a neurogenic process, especially when the motor units show features of reinnervation, such as long duration and high amplitude.

**Demyelinating or Axonal Neuropathy**

The primary function of myelin is to increase axonal conduction velocity without a significant increase in axonal diameter. This function is achieved by the process of saltatory conduction, in which nerve impulses jump between electrically excitable regions of the axon, called nodes of Ranvier, located between the electrically insulated areas ensheathed by myelinating Schwann cells. A demyelinating process results in local or ephaptic nerve conduction that is slow. It is often accompanied by remyelination, resulting in reduced internodal length, also slowing saltatory conduction. Sensory responses are often too small or absent in polyneuropathies to reliably suggest a demyelinating process. The electrophysiologic abnormalities of a primary demyelinating process—slowing of nerve conduction, dispersion, and conduction block—are best seen in motor nerves. If slowing of greater than 25% is seen in the various measures of motor nerve conduction in two nerves, a primary demyelinating process can be diagnosed. In the absence of such slowed conduction, when a peripheral nerve process has been confirmed by sensory nerve studies, an axonal polyneuropathy is diagnosed.

Most demyelinating neuropathies eventually show secondary axonal loss, resulting in a very small or absent CMAP, where conduction velocities cannot be measured. Conversely, severe axonal neuropathies, with very low CMAPs, may show conduction slowing greater than 25%, making the determination of the primary process and classification difficult. In chronic inherited neuropathies, the last distal muscle to atrophy is the abductor digiti minimi. Thus, ulnar nerve conduction studies may be the only ones with velocities that permit appropriate classification of the disease. The ulnar nerve is also the initial motor nerve studied in the context of an inherited polyneuropathy. EMG is usually not necessary in the diagnostic evaluation of a patient with an inherited neuropathy. However, fibrillation and positive sharp waves are usually seen in either the axonal neuropathies or in the late stages of demyelinating neuropathies. This may also be of some help in classifying the disorder.

**Clues to an Acquired Neuropathy**

In an isolated, sporadic patient, it is important to exclude a treatable process. Scattered demyelination, rather than uniform demyelination, favors an acquired disease process, such as CIDP. Scattered demyelination results in variable slowing in different nerves, different segments of the nerves (preserved distal latency, with slowing of the proximal conduction velocity and F-wave latency), and only in some of the nerve fibers in a given segment of the nerve resulting in dispersion or conduction block. In inherited demyelinating neuropathies, the degree of slowing would be nearly identical in distal latency, conduction velocity, and F-wave latency in all the nerves with a lack of dispersion or conduction block, reflecting a uniform pathology (see Table 61-1 for exceptions). It is nearly impossible to distinguish an inherited from an acquired process in patients with an axonal neuropathy on the basis of electrophysiologic criteria. However, multifocal abnormalities recorded in nerve conduction studies usually points toward an acquired process, with the exception of HNPP.

**Genetic Lesions**

The genetic basis of many forms of inherited neuropathy has been determined (see Table 61-1). The corresponding genes and proteins have been implicated in Schwann cell function (myelination and axon trophic function) or in axonal function (structure of axonal components and axon transport). This has led to an improved understanding of the pathogenesis of the various polyneuropathies. A comprehensive and constantly updated database of mutations in inherited peripheral neuropathies, the Inherited Peripheral Neuropathy Mutation Database (IPNMDDB), is maintained by Nelis and colleagues <http://molgen-www.uia.ac.be/CMTmutations>.
**PMP22**

In 1991, genetic linkage studies in autosomal dominant demyelinating neuropathy (CMT1) located a causative gene at chromosome 17p11.2-p12. The defect was an intrachromosomal duplication of a 1.5 Mb segment of 17p11.2. Analysis of two murine mutant models of CMT, Trembler (Tr) and Trembler-J (Tr-J), led to the identification of the peripheral myelin protein 22 (PMP22) gene. This gene was then shown to be contained within the chromosomal segment duplicated in CMT1. Different types of mutations of PMP22 result in different clinical syndromes, including CMT1, HNPP, and DSD.

The most common mutation in autosomal dominant CMT1, occurring in about 70% of these cases, is the heterozygous 1.5 Mb tandem duplication that includes PMP22. This results in increased PMP dosage (three copies of the gene) and is associated with the CMT1 phenotype. Homozygosity for the duplication (four copies of the gene) causes a very severe, early-onset phenotype (DSD-phenotype).

The 1.5 Mb segment is flanked by highly homologous proximal and distal tandem repeat sequences. As a result of unequal crossing over during gametogenesis, one haploid gamete contains a duplication, while the other contains a deletion. This reciprocal deletion of the same 1.5 Mb segment causes a different phenotype, HNPP. This deletion is detected in about 85% of patients with HNPP. These patients are haploinsufficient and have reduced PMP22 dosage (single copy). Smaller deletions, but still including the coding region of PMP22, have also been associated with the HNPP phenotype.

A total of 44 other mutations have been cataloged in the IPNMDB, and most of these are missense point mutations. Of these, 18 result in the CMT1 phenotype (with or without hearing impairment), 16 in the DSD phenotype, and 1 in the HNPP phenotype. The remaining eight mutations that cause the HNPP phenotype are either small deletions that result in a frame shift, nonsense mutations, or splice site mutations. This is consistent with the idea that mutations that result in a single functional allele cause HNPP. The other point mutations must result in a gain-of-function that mimics the increased gene dosage of the gene duplication.

Naturally occurring murine mutants recapitulate the pathology seen in human patients. The Trembler (G150D) acts via a gain-of-function or dominant negative mechanism and causes a severe hypomyelination with onion bulb formation, similar to DSD patients with the same G150D mutation. The Trembler-J (L16P) has been identified in CMT1 patients, and the pathology in the Trembler-J mice is similar to that seen in human CMT1 patients.

**Myelin Protein Zero**

Myelin protein zero (MPZ) is the most abundant protein of peripheral myelin and is a transmembrane protein with a single extracellular immunoglobulin domain. It functions as a homophilic adhesion molecule in the formation of compact myelin. The extracellular domain is important in formation of the minor dense line of myelin, and the cytoplasmic domain is important in formation of the major dense line. The human MPZ gene is located at chromosome 1q22-q23.

One form of CMT1 (designated CMT1B) was linked to the Duffy blood group antigens on chromosome 1q22-q23 in 1982, but it took another 11 years to demonstrate mutations in MPZ in both CMT1 and Dejerine-Sottas families. Just as was the case with PMP22 mutations, several phenotypes have been associated with MPZ mutations, including autosomal dominant demyelinating neuropathy (CMT1B, DSD, or CHN), and autosomal dominant axonal neuropathy (CMT2). About 100 different point mutations (missense, nonsense, and frameshift) in MPZ have been described, with the majority resulting in either the CMT1 phenotype (55 mutations) or the more severe DSD phenotype (20 mutations). Two are associated with CHN, and 9 with the CMT2 (axonal neuropathy) or an intermediate phenotype. The question of why certain point mutations cause demyelination and others primarily axonal dysfunction is not understood.

**EGR2**

Early growth response gene (EGR2, chromosome 10q21-q22) is a zinc finger transcription factor. Transgenic mice in which the murine orthologue Krox20 is knocked out show abnormalities of hindbrain development and peripheral myelination. In these knockout mice, Schwann cells are arrested at an early stage of differentiation and do not express many of the late myelin protein genes, including PMP22, MPZ, connexin 32, and periaxin. This results in a severe hypomyelination. Mutations in EGR2 were found in patients with a severe demyelinating neuropathy phenotype (CMT1, DSD, or CHN). Familial cases with dominant inheritance, de novo mutations in sporadic cases, and recessive (homozygous) mutations have been described. Mutations in the zinc-finger deoxyribonucleic acid (DNA) binding domains cause a loss of transcription factor activity but act in a dominant fashion (ie, heterozygous state), suggesting a dominant negative effect. A recessive mutation presenting as CHN has also been described. This mutation (Ile268Asn) causes an increase in transcriptional activity of EGR2, perhaps affecting levels of myelin protein messenger ribonucleic acids (mRNAs) by a gene dosage effect.
GJB1 and Connexin 32

Gap junction protein, beta one (GJB1) gene, encoding the connexin 32 protein, is currently the only identified X-chromosome gene implicated in peripheral neuropathies. Connexin 32 is expressed in myelinating Schwann cells, and is localized to the paranodal loops and Schmidt-Lanterman incisures. Connexins oligomerize to form connexons, which then form channels allowing transport of small molecules between the Schwann cell body and the periaxonal region of the myelin sheath. Connexins may thus play a role in maintenance of the myelin sheath, or may permit transport of molecules that are important in axon–Schwann cell interaction.

Mutations in GJB1 cause CMTX, which can be either X-linked dominant or recessive, and have a demyelinating or axonal phenotype. In some families, the distinction between autosomal and X-linked inheritance may be difficult—female carriers may have a subclinical neuropathy, leading to the conclusion of X-linked recessive instead of dominant inheritance. Male-to-male transmission within a family would exclude X-linked inheritance. CMTX is the second most common form of CMT, after the dominant form caused by PMP22 gene duplication. In most cases, males are more severely affected than females, with motor nerve conduction velocities (mNCVs) in the 25 to 40 m/s range, whereas female carriers have mNCVs between 25 and 50 m/s. About 265 different mutations in GJB1 have been reported to date and include missense, frameshift, and nonsense mutations, small and large deletions, and noncoding region mutations. Some mutations result in a loss-of-function (severe phenotype), whereas others result in functionally altered channels (milder phenotype).

LITAF

A rare form of autosomal dominant demyelinating neuropathy, CMT1C, was localized to chromosome 16p13.1-p12.3. The responsible gene has been identified as LITAF (lipopolysaccharide-induced tumor necrosis factor-α, also known as SIMPLE), a protein component of lysosomes and endosomes. The mechanism by which this mutation causes demyelination is not clear.

Autosomal Recessive Forms of CMT: Mutations in GDAP1, MTMR2, NDRG1, and Periaxin

Autosomal recessive forms of demyelinating peripheral neuropathy, classified as subtypes of CMT4, are rare. Genetic studies in a few families (often in isolated populations) have led to identification of mutations in several genes. These include GDAP1 (ganglioside-induced differentiation-associated protein 1) located at 8q13–q21; MTMR2 (myotubularin-related protein 2) located at 11q23; NDRG1 (N-myc downstream-regulated gene 1); and PRX (periaxin) located at 19q13. The onset of symptoms in these recessive forms is typically in early childhood, with progression to wheelchair-dependence. Nerve biopsies typically show demyelination and onion-bulb formation, except in MTMR2 defects, which show focal infolding and redundant loops of the myelin sheath. The precise function of these genes in myelination is unknown.

Inherited Axonal (CMT2)

Neuropathies: KIF1B, NEFL, RAB7, and LMNA

The axonal neuropathies can be inherited in an autosomal dominant or a recessive fashion and are characterized by normal or near normal mNCVs. They are about one-half as prevalent as the demyelinating form of CMT. Mutations have been described in KIF1B (kinesin family member 1B), NEFL (neurofilament light chain), RAB7 (an RAS-related GTPase), and LMNA (lamin A/C). Initial reports of NEFL mutations were associated with an axonal neuropathy, but subsequent reports suggest a demyelinating form as well. KIF1B, like other kinesins, plays an important role in axonal transport, and neurofilament is a major component of the neuronal cytoskeleton. Mutations in these genes might, thus, disrupt normal axonal function. The exact function of RAB7 and LMNA in neurons is unknown.

Sensory and Autonomic Neuropathies: SPTLC1, IKBKAP, and NTRK1

The most prevalent form of hereditary sensory neuropathy is caused by mutations in SPTLC1 (serine palmitoyltransferase, long chain base subunit 1) located on 9q22. It is characterized by distal lancinating pain, ulcerations, and a severe distal sensory deficit in pain and temperature sense. SPTLC1 codes for an enzyme involved in sphingolipid synthesis.

Familial dysautonomia or Riley-Day syndrome, an autosomal recessive disorder mapped to 9q31, is caused by mutation in the IKBKAP gene (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein). This disorder is characterized by neonatal feeding difficulty and autonomic problems (temperature, sweating, blood pressure).

Congenital insensitivity to pain and anhidrosis (CIPA) is also an autosomal recessive disorder, characterized by unexplained fever, anhidrosis, and absence of reaction to pain. This disorder is caused by mutations in NTRK1 (neurotrophin tyrosine kinase, receptor, type 1), a receptor...
nerve growth factor. Around 30 different point mutations (missense, nonsense, and splice site) of the NTRK1 gene have been described in CIPA. Mice with the NTRK1 gene knocked out have a similar phenotype.

An Approach to Genetic Testing

There are several reasons for pursuing an accurate genetic diagnosis. Genotype–phenotype correlations: (1) allow for anticipation of the clinical course of the disease, (2) permit (noninvasive) testing and counseling of at-risk individuals in families, and (3) allow for preimplantation or in utero diagnosis and appropriate genetic counseling. Currently, mutation analysis of seven hereditary neuropathy genes is available commercially but at a cost that is significantly higher than the cost of a discerning electrophysiologic study. There are few clinical clues in nonsyndromic neuropathies that allow one to restrict the number of genes to be tested. Soon, the number of genes related to HMSN will be so numerous that an economical, efficient, DNA chip–based method for mutation identification will become available.

One possible approach to molecular diagnosis of hereditary neuropathy is presented in Figure 61-1. We incorporate clinical, electrophysiologic, histopathologic, and genetic tests in our approach:

- If the neuropathy is part of a systemic disorder or is associated with central nervous system involvement, other investigations are necessary.
- Does electrodiagnostic testing confirm a neuropathy and suggest a pathogenic mechanism (demyelination or axonal)?
- Are there clinical or electrophysiologic features to suggest an acquired, treatable disorder?
- What is the likely mode of inheritance?
- Specific gene testing (commercial or clinical lab):
  - Commercial genetic testing has the highest yield when electrophysiologic studies identify a demyelinating neuropathy.
  - Electrical features of an axonal neuropathy may be seen as a result of mutations in the genes more commonly associated with demyelinating neuropathy (GJB1, P0, and GDAP).
  - If the inheritance pattern were known with certainty, genetic testing after electrophysiologic studies could be more selective. Sequential evaluation of these genes based on the frequency of that particular gene abnormality for the type of pathology in the ethnic group being studied would be the ideal approach, rather than the “shotgun” approach offered commercially.
  - If the electrophysiologic studies are unable to characterize the pathology in a sporadic case, genetic tests are unlikely to yield a diagnosis.
- Evaluating the other genes in research laboratories as part of a research study may yield results, if there are additional clinical or histopathologic clues that implicate a specific gene (see Figure 61-1). A good example of this would be CMT2D.

Management

During the past 15 years, the genetic basis of many hereditary neuropathies has been identified or mapped. The process of mutation detection should become even faster with the improvements in genomic technology. The information relating gene mutations to clinical phenotype has already provided insights into the molecular mechanisms of disease pathogenesis, but much work remains to be done.

Treatment of patients with such hereditary neuropathies is limited to physical therapy and prevention or delay of complications. Physical therapy and exercise are aimed at minimizing the weakness and atrophy of affected muscles and at preserving range of motion and preventing joint contractures. Orthotic devices are useful in correcting the foot drop and in optimizing hand use. Selected patients benefit from arthrodesis in the feet, by tendon transfer surgery, and release of contractures to reduce deformity and to improve mobility and dexterity.

Summary

Inherited peripheral neuropathies are quite prevalent (about 1:2,500) and are clinically and genetically heterogeneous. Clinical history and physical examination lead to the suspicion of a peripheral neuropathy. Family history is crucial not only in suggesting a genetic cause, but also in distinguishing autosomal dominant from recessive and X-linked patterns of inheritance. Electrodiagnostic testing plays a vital role in differentiating a hereditary neuropathy from rare acquired (treatable) neuropathies and also allows differentiation between a demyelinating process and an axonal process. The most common genetic lesions are duplication or reciprocal deletion of a 1.5 Mb segment of chromosome 17p11.2 containing the PMP22 gene, causing the CMT1 phenotype or the HNPP phenotype, respectively. Mutations of GJB1 causing an X-linked dominant or recessive neuropathy and mutations of MPZ and EGR2, are all associated with a demyelinating neuropathy. Genes responsible for several of the recessive demyelinating neuropathies, dominant and recessive axonal neuropathies, and the sensory or autonomic neuropathies have been identified (see Table 61-1). Testing for mutation detection in many of these genes is available from several laboratories (see <http://www.genetests.org>) for laboratories that test on a clinical or research basis). However, when the more common mutations are not discovered (eg, PMP22,
One has to contact individual research labs that are studying particular forms of neuropathies. Many more genes responsible for inherited neuropathy have been mapped. Such progress in the molecular pathology of hereditary neuropathy will lead to a better understanding of pathogenesis, a better ability to predict the course of disease based on genetic testing, and, eventually, to specific cellular or genetic therapies.

**Suggested Readings**


**Practitioner and Patient Resources**

**International Peripheral Neuropathy Mutation Database (IPN MDB)**
http://molgen-www.uia.ac.be/CMTmutations

The IPN MDB aims to offer the scientific community useful and relevant information on IPN mutations in a comprehensive manner.

**Online Mendelian Inheritance in Man**

This database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by National Center for Biotechnology Information (NCBI). The database contains textual information and references. It also contains copious links to Medline and sequence records in the Entrez system, as well as links to additional related resources at NCBI and elsewhere.

**Neuromuscular Disease Center**
Washington University, St. Louis, MO
http://www.neuro.wustl.edu/neuromuscular/

This informational Web site is geared toward physicians.