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INHERITED NEUROPATHIES: CLINICAL OVERVIEW AND UPDATE

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Abstract

Inherited neuropathy is a group of common neurologic disorders with heterogeneous clinical presentations and genetic causes. Detailed neuromuscular evaluations, including nerve conduction studies, laboratory testing, and histopathologic examination, can assist in identification of the inherited component beyond family history. Genetic testing increasingly enables definitive diagnosis of specific inherited neuropathies. Diagnosis, however, is often complex, and neurologic disability may have both genetic and acquired components in individual patients. The decision of which genetic test to order or whether to order genetic tests is often complicated, and the strategies to maximize the value of testing are evolving. Apart from rare inherited metabolic neuropathies, treatment approaches remain largely supportive. We provide a clinical update of the various types of inherited neuropathies, their differential diagnoses, and distinguishing clinical features (where available). A framework is provided for clinical evaluations, including the inheritance assessment, electrophysiologic examinations, and specific genetic tests.

Keywords

ataxia; neuropathy; spinocerebellar; cerebellum; triplet repeats

Inherited neuropathies are diverse in both genetic causes and clinical phenotypes. They are frequently underdiagnosed or misdiagnosed. A large prospective study found that approximately half of patients referred to peripheral neuropathy clinics have an unrecognized inherited cause.¹ Family history is the foremost factor in considering an inherited neuropathy, but it is often difficult to obtain. Because the initial presentation of chronic symmetric progression of motor and/or sensory deficits in the distal lower extremities is nonspecific, reviewing the clinical details, such as ascertaining the specific anatomic localization and the part of the nerve fibers affected (axon or myelin), is often helpful in genetic diagnosis. The affected neurologic tissues have been incorporated into the current classifications. Specifically, whether the neuropathy involves motor, sensory, or autonomic nerve fibers, or has superimposed spinal or cerebellar involvement, has been integrated into the current nomenclature system. By appreciating these specific anatomic localizations combined with the temporal course, it is often possible to predict inherited

cause without a known family history. This is especially useful in patients who have *de novo* mutations, complex family dynamics, small family size, or are adopted.

The Mendelian inherited (autosomal dominant, recessive, or X-linked) neuropathies can be divided into 3 disparate groups: (1) isolated neuropathy involving peripheral nervous system exclusively; (2) multisystem neuropathy involving both central (brain or spinal cord) and peripheral nervous systems; and (3) neuropathy with multiorgan involvement affecting non-neurologic organs such as skin, kidney, heart, and liver (Table 1). With the increasing rate of genetic discoveries and emerging treatment potentials, it is important for physicians to be familiar with the evolving genetic information for a wide range of inherited neuropathies. One web-based medical genetics information resource (<http://www.geneclinics.org/>) is continually updated, NIH-supported, and provides comprehensive data. It also provides laboratory contact information, clinically relevant reviews for physicians and patients, and information regarding clinical trial opportunities for patients.

IDENTIFICATION OF INHERITED NEUROPATHIES

Acquired vs. Inherited

Among both adult- and juvenile-onset neuropathy patients, distinguishing inherited from acquired etiologies is often difficult, especially in the absence of a recognized family history. An acquired etiology of neuropathy may compound an inherited neurologic defect, and the acquired etiology can be mistakenly diagnosed to be the primary cause. Rapid or accelerated neurologic declines generally suggest superimposed acquired etiologies. An illustrative case comes from an adult patient with demyelinating neuropathy who was confirmed to have a peripheral myelin protein 22 (*PMP22*) duplication. He had marked progression of demyelinating neuropathy and was found to have an M-spike monoclonal protein, which led to the diagnosis of POEMS syndrome (*polyneuropathy, organomegaly, endocrinology, M-spike, skin changes*). His nerve biopsy showed marked interstitial inflammation and supported the conclusion that an acquired process compounded his inherited demyelinating neuropathy.² Through autologous peripheral blood stem cell transplantation, he went from wheelchair dependency to walking independently and returned to his prior deficit baseline from demyelinating neuropathy.

It is important to realize that inherited neuropathy patients may be more susceptible to injury from metabolic, toxic, and other nervous system insults, such as side effects from chemotherapy.³ A genetic cause should be considered when major deficits occur with only limited toxic or metabolic exposure. Inherited neuropathy patients are frequently misdiagnosed as having primary diabetic neuropathy, because diabetes is common and can cause neuropathy. However, in the absence of retinopathy or nephropathy, it is unlikely that diabetes is the cause of neurologic deficits that exhibit characteristics of many inherited neuropathies.⁴ Specifically, diabetic patients rarely have the extent of symmetric motor weaknesses seen in many varieties of inherited neuropathies.

Temporal Course in Genetic Varieties of Inherited Neuropathies

Some inherited neuropathy patients describe subacute or even acute onset when the long-existing and progressive deficits finally reach a threshold to cause clear neuropathic symptoms, such as difficulties in walking, climbing stairs, and ulceration of the extremities from profound sensory loss. Much of this relates to the fact that positive sensory symptoms (paresthesias, burning, lancinating pain) are often absent in many motor and sensory inherited neuropathies, thus preventing earlier appreciation of the problem.¹ Some inherited neuropathies or neuronopathies can have acute or subacute onset and rapid worsening, such as those caused by the mutations of: (1) myelin protein zero (*MPZ*), sometimes accompanied

by an Adie pupil or bulbar involvement⁵⁻⁹; (2) *PMP22* deletion, leading to hereditary neuropathy with tendency to pressure palsies (HNPP); (3) septin 9 (*SEPT9*), presenting with attacks of brachial plexus neuropathy^{10,11}; (4) androgen receptors (*AR*), causing spinobulbar muscular atrophy (Kennedy disease)^{12,13}; and (5) mitofusin 2 (*MFN2*), presenting with sudden-onset optic neuropathy.

Many inherited neuropathies present late in life, which may obscure their inherited cause.¹⁴ Specifically, genetic discoveries among these varieties have been less forthcoming due to the difficulties in gene discovery by conventional kindred evaluations combined with linkage studies. Among the inherited neuropathies with multisystem involvement, adult onset is most common, as illustrated by inherited amyloidosis (transthyretin, gelsolin) and adult-onset polyglucosan disease. For DNA repeat expansion diseases, such as spinal bulbar muscular atrophy (Kennedy disease),^{12,13} Friedreich ataxia,¹⁵ and dominantly inherited varieties of spinocerebellar degeneration,¹⁶ the smaller the repeat length, the later in life patients tend to present with symptoms.

Historical and Examination Clues of Inherited Neuro-pathy

When taking the history from neuropathy patients, the clues for an inherited cause include: (1) frequent childhood ankle sprains and toe-catching falls, often with children being labeled “clumsy”; (2) recurrent foot and ankle fractures; (3) regularly being the slowest child in foot races; and (4) recurrent acral paronychia, calluses, and ulcers in sensory predominant forms. Clues and signs from physical examination may include the following: (1) foot drop identified by a doctor but not appreciated by the patient; (2) high arches and hammer toes with a history of early or frequent podiatric surgery; (3) inverted champagne bottle appearance of the legs from anterior and posterior compartment leg muscle atrophy with preserved thigh musculature; (4) exuberant lateral or medial foot plantar callus from ankle valgus or varus deformity with ankle-foot weakness; (5) recurrent painless foot ulcers; (6) palpable large nerves in hypertrophic demyelinating varieties; (7) refractory response to the treatment of acquired disease; and (8) major sensory loss without positive sensory symptoms (e.g., paresthesia, burning, or lancinating pain).

Kindred Evaluation in Diagnosing Inherited Neuropathies

Establishing a family history of neuropathy remains the foremost tool for diagnosis of most inherited neuropathies. Because many patients are unaware of neuropathy in their family, additional work is often required.¹ After conversation with the patient about the family medical history, further investigation of possibly affected or at-risk persons can be quite helpful. Specific confirmatory investigations include asking family members to walk on heels and toes to ascertain ankle dorsiflexion weakness, and applying a cotton swab across the feet to assess any sensory loss. For families interested in participating, a personal visit can be extremely helpful in accurately establishing affected status. In such family studies, clinical examination and nerve conduction studies by the specialist are often required to better determine the familial occurrence.^{1,17,18}

Molecular Targets in Inherited Neuropathies

The fact that a single neuron and its axon are often >1 meter in length contributes to a susceptibility to diverse genetic pathologic insults (Fig. 1). The precisely regulated interactions of many synthesized proteins, organelles, and cargo molecules in nerves are necessary for proper maintenance and function of axons. The energy requirements of transporting processes in neurons exceed those of many other cell types. Disruption of this complicated maintenance system can lead to axonal degeneration and resultant neurologic handicaps. Not surprisingly, major pathogenic targets of this complex supportive axonal network include the essential proteins produced by Schwann cells within the myelin

architecture (*PMP22*, *MPZ*, *CX32*), axonal transport (*DCTN1*, *DYNC1H*, *NFL*), cytoskeletal formation (*FGD4*), endosomal vesicular transport (*RAB7*, *NDRG1*, *SH3TC2*), and microtubule interaction (*SPG20*).

Previously, only the metabolic neuropathies with multiorgan (neurologic and non-neurologic) involvement were thought to have mutations in fundamental cell metabolism genes. However, it is increasingly recognized that many inherited neuropathies with exclusive involvement of the nervous system also have mutations in fundamental metabolic genes such as those involved in the cellular functions of transcription (*EGR2*), translation (*GARS*, *YARS*, *BSCL2*), DNA maintenance (*TDPI*), DNA methylation (*DNMT1*), divalent cation metabolism (*TRPV4*), mitochondrial fusion or fission (*MFN2*, *GDAP1*), endoplasmic reticulum formation (*ATL1*), sphingolipid metabolism (*SPTLC1*, *SPTLC2*), Golgi body structure (*FAM134B*), protein degradation chaperones and stress regulation (*LITAF*, *HSPs*, *BAG3*), neurofilament organization (*GAN*), and others. These observations further support the high fidelity of nerve and its relative sensitivity to various insults that are tolerated by other cell types.

UTILITY OF NEUROPHYSIOLOGIC TESTING IN THE INHERITED NEUROPATHIES

Distinction of Inherited vs. Acquired Neuropathies

Neurophysiologic studies, including needle electro-myography (EMG), are very useful in the distinction of acquired vs. inherited mechanisms. Chronic motor unit potential changes on needle EMG, characterized by amplitude >2 mV and duration >15–20 ms, can help establish the chronic nature of the inherited neuropathy. Through nerve conduction studies among patients with demyelinating neuropathy, notable observational discoveries have been made. In 1982, Lewis and Sumner made the important observation that temporal dispersion and conduction blocks are often absent in inherited, yet they are common in acquired demyelinating neuropathies.¹⁹ Exceptions have subsequently been observed; for example, among patients with *CX32* mutations, temporal dispersion can occur.^{20,21} Nonetheless, the lack of dispersion and conduction blocks is very suggestive of an inherited demyelinating process, especially when conduction velocities are in the 20–30-m/s range. The explanation for these electrophysiologic findings can be found in the pattern of pathologic observations. Specifically, in acquired chronic immune demyelinating polyradiculoneuropathy (CIDP), there are multifocal myelin lamellar collagen thickenings (onion bulbs) at different stages, resulting in conduction block and temporal dispersion. In contrast, patients with *PMP22* duplications have diffuse onion bulbs with the same extent of laminated processes; therefore, there is no temporal dispersion on motor nerve conduction studies (Fig. 2). In patients with *CX32* (also known as *GJB1*) mutations, pseudo- or rudimentary onion bulbs (minimal varied laminated collagen layers around axons) are present and may lead to mild temporal dispersion and intermediate nerve conduction velocities (38–45 m/s).

Unlike CIDP, IgM monoclonal gammopathy-associated neuropathy is more difficult to distinguish from inherited demyelinating neuropathy. The distal foot and ankle involvement in IgM-monoclonal gammopathy of undetermined significance (MGUS), the insidious onset, and common incidental occurrence of IgM monoclonal proteins in adult populations all make the distinction problematic. Population-based studies showed that 3.2% of individuals 50 years of age and 5.3% of those 70 years of age had MGUS, and 17.2% of these patients had IgM-MGUS.²² The presence of antibodies to myelin-associated glycoprotein (MAG) may be found in IgM-MGUS neuropathy, but unfortunately MAG antibodies can also be found incidentally in IgM-MGUS patients without neuropathy, as demonstrated by Western blot analysis.²³ Nerve conduction studies may allow distinction of IgM-MGUS

demyelinating neuropathy, which has preferential distal slowing in conduction velocities, from inherited demyelinating neuropathies, where proximal and distal slowing are relatively equal. By calculating a ratio of proximal-to-distal conduction slowing by the terminal latency index [TLI= (1/distal motor latency) $\times$ (distance_(wrist to thenar)/conduction velocity)] the distinction is generally possible.²⁴ A median TLI <0.26 is more common in IgM-MGUS with associated neuropathy, whereas hereditary demyelinating neuropathies generally have a TLI >0.26. Obviously, severe carpal tunnel syndrome needs to be excluded, but overall this approach can be helpful.

Nerve Conduction Studies in Genetic Classification

Since the first modern electrophysiologic classification schemes of hereditary motor and sensory neuropathies (HMSNs) were proposed by Dyck and Lambert in 1968,²⁵ nerve conduction studies have continued to be an important component in the classification and determination of specific genetic forms (Fig. 3). Factors that influence the details of nerve conduction studies are obviously complex. The patient's age, duration of disease, and severity of symptoms all influence the ascertainable features. During nerve myelination, nerve conduction velocity changes with age. It increases through early childhood, plateaus, and then slows as a part of normal aging. Superimposed illness on this natural physiologic process makes the determination of demyelination less straightforward. By convention, the ulnar motor nerve in the forearm has been chosen as the standard nerve for demarcation of axonal vs. demyelinating pathogenesis. If the ulnar compound motor action potential amplitude is >0.5 mV, a conduction velocity <38 m/s is considered demyelinating, and 38–45 m/s is intermediate. When there is loss of compound motor action potential amplitude and/or needle EMG denervation, a conduction velocity >45 m/s is considered to indicate a primary axonal process. If patients present with symptoms late in the course of their disease, it may be more difficult to distinguish primary axonal from demyelinating forms. For these patients, studies of proximal nerves (musculocutaneous or radial motor studies) may be helpful. With careful measurements, these conduction studies can have cut-off values similar to those in the ulnar forearm.

Recently, forearm nerve conduction has been further categorized into: (1) very slow (<15 m/s); (2) slow (15–35 m/s); (3) intermediate (35–45 m/s); and (4) normal (>45 m/s). This subdivision has proven to be helpful in selecting genetic testing for patients with inherited neuropathies.²⁶

Nerve Conduction Studies in Prognosis of Inherited Neuropathies

Nerve conduction studies have also been found useful in establishing prognosis of inherited neuropathies as indicated by previous longitudinal studies (15 years).²⁷ Patients with the *PMP22* duplication and extremely slow motor nerve conduction velocities often exhibit earlier distal motor amplitude declines. They also tend to have more severe neurologic impairment and deficits compared with other affected persons in the same family.²⁷

Special Neurophysiologic Testing in Inherited Neuropathies

Electrophysiologic examination other than nerve conduction study or needle EMG can also be helpful in diagnosing and prognosticating some inherited neuropathies. Detailed autonomic testing is available to examine cardiovascular (orthostatic hypotension), sudomotor (sweat impairment), and adrenergic (heart rate variability) function.²⁸ Among the majority of patients with hereditary motor and sensory neuropathy [HMSN, also called Charcot–Marie–Tooth (CMT) disease], sudomotor loss is often absent, whereas, in hereditary sensory and autonomic neuropathies (HSAN), sudomotor loss is typical, consistent with prominent small nerve fiber involvement.²⁹

Quantitative sensory testing by validated approaches, such as using sensory references, provides an additional tool for addressing the extent and specifics of sensory involvement for diagnosis and prognosis of neuropathies.³⁰ Importantly, this testing quantifies the small-fiber sensory function of A- and C-fibers, which is not possible by conventional electrodiagnostic examination. Patients found to have dramatic early C-fiber nociceptive sensory small-fiber involvement (heat pain thresholds) are at greater risk for foot ulcers and amputations, typical of HSAN but not HMSN. These HSAN patients require aggressive early instruction in foot care. If weakness coexists, ankle-foot orthotics with special attention to custom fitting or external metal bracing of the shoe is important for avoiding skin breakdown and ulceration.

Among inherited neuropathy patients with spinal cord involvement, somatosensory evoked potential studies assess large-fiber somatic sensory myelopathy, because it can occur in hereditary spastic paraparesis,³¹ spinocerebellar ataxias,³² and rare hereditary motor and sensory neuropathies with myelopathy, such as HMSN 2A2 with mitofusin 2 (*MFN2*) mutations.³³ It also can be useful for studying degeneration of the centripetal large-fiber projections of dorsal root ganglion neurons when they are the target of diseases such as Friedreich ataxia, spinocerebellar ataxias, and *POLG1*-related sensory ataxic neuropathies.

Histopathologic Testing in Inherited Neuropathies

Nerve biopsies for inherited neuropathies should be limited to cases in which a hereditary etiology is unclear or acquired etiologies are considered to be superimposed on a primary inherited mechanism. Such situations are frequently seen in varieties of demyelinating neuropathies, particularly in children, when the temporal course is unclear and family history of neuropathy is absent. The presence of interstitial inflammatory collections within the endoneurium, epineurium, and perineurium would be uncharacteristic of hypertrophic inherited demyelinating neuropathy and should raise strong consideration of treatable CIDP.

In our experience, nerve biopsy has been most instructive when an inherited mechanism was not suspected. Specifically, the discovery of various types of infiltrative inclusions of inherited neuropathies can lead to the diagnosis of a genetic systemic metabolic disorder. Transthyretin amyloidosis is a disorder in which this scenario occurs commonly (Fig. 4). Patients are often unaware of their family history. Mass spectrometric evaluation to analyze nerve infiltration with amyloid can further assist in rapid diagnosis of the specific amyloid type.³⁴ Mutant transthyretin amyloid protein, including the predicted amino acid alteration can be determined directly from the tissue without ambiguity. This is especially useful among those amyloid transthyretin patients who have incidental circulating serum monoclonal proteins that can lead to consideration of primary AL amyloidosis, where treatment and prognosis is quite different.

Some patients with metabolic storage diseases and neuropathy have intraneuronal and Schwann cell inclusions that may be very characteristic of a specific genetic diagnosis, such as giant axonal neuropathy (Fig. 5) or adult-onset polyglucosan disease (Fig. 6). Other metabolic disorders that have less distinct inclusions in various portions of nerve, including organelles are Krabbe disease (prismatic inclusions in endoneurial macrophages), Fabry disease (dispersed perivascular osmophilic granules), metachromatic leukodystrophy (Schwann cell methachromatic granules), ceroid lipofuscinosis (curvilinear granular inclusions in Schwann cells), and cerebrotendinous xanthomatosis (minor Schwann cell lipids). These histopathologic features can suggest a narrowed differential diagnosis that can lead to confirmatory metabolic or genetic testing, and revisiting the clinical picture for additional clues can be helpful. Nerve biopsy may remain useful, especially in those patients with atypical presentations and therefore an unanticipated diagnosis.

Skin biopsies can quantify C-fiber sensory loss by PGP9.5 autoantibody staining of paraffin-embedded nerve. This may be useful for distinction of certain inherited neuropathies, where small-fiber loss is prominent. For motor predominant inherited neuropathy such as HMSN, large-fiber sensory loss is predominant. In contrast, among those with inherited sensory neuropathy, a significant reduction in fiber density on skin biopsy is predicted.³⁵ Skin biopsies are seldom required if autonomic or quantitative sensory testing fails to identify small-fiber involvement. Skin biopsy studies have been most useful for research instead of diagnostic purposes in the inherited neuropathies.³⁶ For example, dermal biopsies from glabrous skin have demonstrated elevated PMP22 protein levels,³⁷ shortened internodes, and abnormalities of paranodes in patients with HMSN 1A.³⁸

INHERITED NEUROPATHIES INVOLVING ONLY PERIPHERAL NERVOUS SYSTEM

The names of the inherited neuropathies with isolated neuronal involvement emphasize anatomic localization: (1) HMSN, affecting mainly lower extremity motor and primary sensory neurons; (2) HSAN, affecting primary sensory and autonomic neurons and, when the autonomic system is not involved, referred to as hereditary sensory neuropathy (HSN); (3) distal hereditary motor neuropathy (dHMN), affecting distal lower motor neurons; (4) hereditary brachial plexus neuropathy (HBPN), affecting the brachial plexus and upper extremity nerves; and (5) hereditary neuropathy with liability to pressure palsies (HNPP), presenting as focal symptoms of weakness or sensory loss after compression of individual nerves. As the genetic discoveries and the spectrum of phenotypes have expanded in each of these categories, a wider range of neuronal involvement has become recognized. For example, some genetic varieties within HSAN have clear motor involvement that is variable among affected patients. Nevertheless, the classifications remain useful in phenotypic descriptions, which is important for prognosis and prediction of future progressive disabilities.

Hereditary Motor and Sensory Neuropathies

HMSN is composed of many types of neuropathy and has been estimated to have a prevalence rate between 17 and 40 per 10,000 persons.^{39,40} Patients generally present with length-dependent neuropathy of large-diameter motor and sensory nerves. Current application of electrophysiology, prior pathologic descriptions,⁴¹ and genetic findings provide the framework for detailed classification. The patterns of inheritance and the details of the primary neuronal localization are complemented by combining both genetic and modern electrophysiologic studies.^{19,21,26}

HMSN is classified into 5 groups: (1) HMSN 1 (Table 2) is a dominantly inherited demyelinating form with slow nerve conduction velocity (< 38 m/s in ulnar forearm), showing gross nerve hypertrophy and diffuse myelin lamellae separated by longitudinally directed collagen fibrils (onion bulbs) on nerve biopsy. (2) HMSN 2 (Table 3) is a dominantly inherited axonal predominant neuropathy showing normal to borderline slow nerve conduction velocities (>38 m/s in ulnar forearm) with axonal atrophy on nerve biopsy. (3) HMSN 3 (also called Dejerine–Sottas disease) usually has onset in infancy or childhood with loss of ambulatory milestones and more generalized neurologic deficit. It is often inherited dominantly and has extremely slow nerve conduction velocities (typically in the single digits to low teens in the ulnar motor nerve) (Table 2). The HMSN 3 category, however, has been overshadowed by the genetic classification, as many patients with HMSN 3 have mutations that also occur with HMSN 1. This HMSN 3 category refines the spectrum of clinical severity and does not expand the genetic causes. (4) HMSN 4 has autosomal recessive inheritance, usually with childhood onset and demyelinating nerve

conduction velocities (Table 2). Many patients in this group have consanguineous parents; they may also have extraneural features, including facial dysmorphism and scoliosis, particularly those with HMSN 4C, the most frequent form of HMSN 4.⁴² Those familiar with the earliest classifications will recall that HMSN 4 was initially used to describe patients with phytanic acid metabolic disorder (i.e., Refsum disease); that earlier formulation has been abandoned, as these neuropathy patients are recognized to have systemic multiorgan involvement, including skin (ichthyosis), retina (retinitis pigmentosa), and cerebellum (ataxia). (5) HMSN 5 was initially described with spasticity. It has been recognized as “complex HSP” by having both spasticity and neuropathy (Table 4).⁴³ Within each of these 5 categories of HMSN, each group has additional subclassifications based on the specific genetic cause.

Two additional HMSN categories were initially described: HMSN 6 with optic nerve atrophy and HMSN type 7 with retinitis pigmentosa. Mutations in the *MFN2* gene have been found in many patients with HMSN 6, which is now commonly referred as HMSN 2A2.⁴⁴ The optic nerve findings among patients with *MFN2* mutations may lead to a diagnosis of optic neuritis and misdiagnosis of multiple sclerosis.³³ This is especially true if the neuropathy is very mild or the diagnosis is missed. Adding to the risk of potential misdiagnosis with *MFN2* mutations is that periventricular white-matter changes may also occur.⁴⁵ Last, based on the neurophysiologic criteria, patients with ulnar motor conduction velocities between 25 and 45 m/s are sometimes referred to as having intermediate HMSN. Recent genetic discoveries combined with increasingly expanded clinical phenotypes continue to refine the classifications of HMSN.

Hereditary Neuropathy With Liability to Pressure Palsies

HNPP is a dominantly inherited neuropathy characterized by recurrent episodic focal numbness, tingling, and weakness in response to nerve injury from pressure or stretching.⁴⁶ These often dramatic individual mononeuropathies (characteristically painless) are superimposed on preexisting diffuse, length-dependent, sensory-predominant neuropathy of large fibers sparing small-fiber heat pain modalities. Macrodeletions of 17p11.2, which includes the entire *PMP22* gene, are the most common cause of HNPP. Microinsertions, microdeletions, and point mutations in *PMP22* leading to frameshift and nonsense mutations (stop codons) are also responsible for HNPP. The same *PMP22* gene, when duplicated or having missense mutations, causes HSMN 1A. HNPP is less common than HSMN 1A. Nerve conduction studies within families support clinical heterogeneity with varied degrees of generalized sensory neuropathy, motor distal latency prolongation, and conduction blocks at sites of compression. Attacks of focal weakness and sensory loss improve with time, but the underlying generalized neuropathy generally worsens. On sural nerve biopsy, there are folded loops of myelin, which produce the characteristic tomaculae (sausage-like) nerve thickenings (Fig. 7). These are distinct from onion bulbs, where folded loops of myelin are not observed. In addition to tomaculae, there is general thinness of myelin throughout the other myelinated nerve fibers.

Genetic Testing in HMSN (CMT)

More than 30 genes have been linked to various types of HMSN, and gene defects can have divergent electrophysiologic and clinical presentations. Among these disorders, the clinical utility of genetic testing is supported by consensus statements in cryptogenic distal symmetric polyneuropathy having hereditary neuropathy phenotypes.⁴⁷ A recent, large, retrospective genotype–phenotype correlative study by Saporta *et al.* demonstrated the utility of combining clinical and electrophysiologic features to determine which specific genetic test to order.²⁶ Their report indicated that a reasonably high yield from specific genetic testing can be expected based on neurophysiologic studies. In their CMT

subspecialty clinic, 67% (527 of 787) of CMT patients undergoing clinically directed genetic testing had identified mutations. Only 1.8% of dominantly inherited demyelinating neuropathies lacked a genetic diagnosis. Mutations in *PMP22* (duplication and missense 55%, deletion 9.1%), *GJB1* (15%), or *MPZ* (8.5%) were found to be most common. These findings led to the recommendation for patients with a classical phenotype (e.g., those with motor conduction velocities of 15–35 m/s and walking before age 15 months) that *PMP22* duplication analysis should be the initial screen, accounting for 89% of positive cases. For patients with conduction velocities of <15 m/s and delayed walking (previously Dejerine–Sottas, or HMSN 3), *PMP22* duplication combined with *MPZ* sequence testing had the highest yield, followed by *PMP22*, *SIMPLE*, or *EGR2* sequencing analysis. If consanguinity is excluded in the family history, *de novo* duplications of *PMP22* are most likely to account for most sporadic demyelinating inherited neuropathies. This relates to the high rate of unequal sister chromatid exchange at position 17p11.2, where the flanking large repeat regions promote the mutation. One study of a cohort of 118 HMSN 1A patients indicated that approximately 11% of the *PMP22* duplications were due to a *de novo* mutation,⁴⁸ thus the absence of a family history of neuropathy should not dissuade clinicians from considering the *PMP22* duplication.

Among patients with axonal dominantly inherited neuropathy, genetic testing is less likely to be positive. At most, 35% of those with axonal dominantly inherited forms (defined by corrected normal or unobtainable nerve conduction velocities) had a genetic diagnosis; mutations in *MFN2*, *MPZ*, and *GJB1* were most common.²⁶ Among children with axonal neuropathies with loss of ambulation, *MFN2* is the most likely mutation.⁴⁹ There is a great need for further discovery of genetic causes among inherited axonal forms.

A study from the USA²⁶ and studies from the UK⁵⁰ and France⁵¹ suggested that >90% of cases in which a genetic diagnosis is made will have a mutation in 1 of just 4 genes—*PMP22*, *MPZ*, *GJB1*, or *MFN2*. These findings should be kept in mind when considering genetic testing in these countries.

It is also important to be aware of the specific mutation frequencies occurring in certain populations where consanguinity is more common. The occurrence of causal homozygous mutations through consanguinity (homozygous mutations) in European origin families is thought to be rare (4%). In Mediterranean and Middle Eastern populations, however, it accounts for approximately 50% of demyelinating neuropathies caused by homozygous mutations, most of which are not tested by commercial laboratories.⁵² Tables 2 and 3 provide additional clinical and electrophysiologic characteristics as well as gene descriptions in consideration of those rarer forms related to consanguinity.

Hereditary Sensory and Autonomic Neuropathies

HSAN is a group of severe disorders affecting peripheral sensory and autonomic neurons with considerable clinical and genetic heterogeneity.⁵³ A prominent hallmark of virtually all patients is the presence of prominent small-fiber sensory loss (A-delta and/or C-fibers). As a group, these patients tend to have more devastating handicaps compared with HMSN, due to the frequent occurrence of ulcers, amputations, and variably severe autonomic dysfunction, including central dysautonomia; some patients have severe complications that can lead to death. It is important to realize that extremity weakness need not be excluded in consideration of these genetic disorders, as variable expression has been described. Generally, the sensory features are prominent. This is best illustrated in some HSAN 1 patients with *RAB7* and *SPTLC* mutations. Unlike with HMSN, there is a much smaller set of known genes for HSAN, currently 14 (Table 5).^{54,55} Commercially available testing is searchable through GeneTests (<http://www.geneclinics.org/>).

Classification within HSAN is based on the mode of inheritance and clinical features, including the initial histopathologic descriptions, and the genetic causes (Table 5).⁵³ HSAN is currently divided into 5 groups.⁵⁶ HSAN 1 varieties (HSAN 1A–E) are dominantly inherited and have a juvenile or adult onset characterized by prominent sensory loss as well as autonomic disturbance. Mutations in *SPTLC1*, *RAB7*, *SPTLC2*, *ATL1*, and *DNMT1* have all been described. In type 1A, caused by mutations of *SPTLC1*, *SPTLC2*, and *RAB7*, patients typically have lancinating leg pains, early-onset insensate foot ulcers, and variable ankle and toe dorsiflexion weakness with large A-alpha fiber loss (documented on neurophysiologic studies). Nerve biopsies among these patients show pansenory fiber loss, including A α (vibration, touch), A δ (cooling), drC (dorsal nociceptive heat pain), and sC (sudomotor sweat). Patients with type 1E (*DNMT1* mutations) have pansenory fiber loss, early-onset dementia with deafness, and insensate extremity ulcers in approximately half.⁵⁷ The recently expanded clinical features of patients with *DNMT1* mutations also includes optic atrophy and narcolepsy in addition to sensory neuropathy and cerebellar features.⁵⁸

HSAN types 2–5 all have autosomal recessive inheritance and usually congenital onset. Mutations in each of these varieties are commonly seen in consanguineous families from founder mutations. HSAN 2A (*WNK1* gene) has infant onset with diffuse sensory loss, distal numbness, early finger and toe ulcers, and need for amputation. Although many ethnicities have been described with *WNK1* mutations, French-Canadian cases account for the majority of those reported from 2 founder mutations.⁵⁹ Homozygous missense mutations in *FAM134B*⁶⁰ and frameshift mutation of *KIF1A*⁶¹ have been described in families with HSAN 2. HSAN 3 occurs in Ashkenazi Jews, with prominent autonomic and small-fiber sensory involvement; this variety is also known as familial dysautonomia, or Riley–Day syndrome.⁶² HSAN 4 (*NTRK1*)⁶³ and HSAN 5 (*NGFB*)^{64,65} have congenital onset and sensory neuropathy with insensitivity to pain, widespread autonomic disturbance, and mental retardation. The latter is commonly observed in type 4 only.⁶⁶ The diagnosis of these disorders can be assisted by specialized studies, including autonomic testing of postganglionic small nerve fiber function and nerve biopsy morphometrics to define the specific sensory fiber involvement, including C- or A-delta fibers. In HSAN 5 patients, there has been selective loss of small myelinated (A-delta) fibers.⁶⁷ In HSAN 4, widespread loss of sweating is common, and C-fiber loss is detectable by skin biopsy or autonomic sweat testing.⁶⁶

Recently, divergent phenotypes, including insensitivity to pain, familial erythromelalgia, and paroxysmal extreme pain disorder, have all been linked to mutations in the Nav1.7 subunit gene *SCN9A*.⁶⁸ *SCN9A* is highly expressed in dorsal ganglia cells, but central nervous system channel dysfunction also remains possible, given its ubiquitous nervous system expression. In familial erythromelalgia, distal localized skin redness and warmth combined with abnormalities in the distal extremities from laser Doppler flow studies support the peripheral nervous system component.^{69,70} A recent study found 8 of 28 patients with idiopathic small-fiber loss have variants of *SCN9A*.⁷¹ However, some variants have been reported in normal DNA databases (dbSNP and IK_Genome). It remains unclear whether other unrecognized modifying factors are involved. Detailed kindred evaluations tracking with DNA alterations will be helpful in establishing the exact functions of these variants in susceptibility to inherited small-fiber sensory neuropathy.

Last, it is important to recognize that, among some varieties of HSAN, spinal cord involvement is suggested by the presence of brisk reflexes in patients with the *RAB7*⁷² mutation, spinal cord pathology in patients with the *DNMT1* mutation,⁵⁷ or mutations in genes previously recognized in varieties of spastic paraparesis (*CCT5*⁷³ and *ATL1*⁷⁴).

Distal Hereditary Motor Neuropathies

Distal HMNs (dHMNs) are a group of disorders characterized by length-dependent, slowly progressive motor neuropathies. The nerve conduction velocities are variable. The slowing of conduction velocity may relate to extensive primary axonal injury, as myelin defects are not recognized within this group of disorders. For the clinical diagnosis, sensory loss should be absent but can occur by variable expression in some dHMN genes. Therefore, it is possible that the same gene abnormality can be found in both HMSN and dHMN with and without sensory involvement. Such examples are noted in mutations of heat shock protein genes (*HSPB1*, *HSPB8*),^{75,76} the divalent cation channel gene (*TRPV4*),^{77–80} and the tRNA synthetase gene (*GARS*).⁸¹

Currently, dHMN is divided into 11 different subtypes, which are distinguished by their clinical features, pattern of inheritance, and genetic details alone in some cases (Table 6). Genetic discoveries in this group remain problematic, and there was a report showing that 80% of tested dHMN patients with dominant inheritance had no positive genetic test.⁸² Therefore, similar to the axonal varieties of HMSN, genetic testing may be less informative. However, some dHMN disorders have signature clinical features that suggest specific genetic testing. For example, infants with respiratory distress, low birth weight, and slowed conduction velocities with prominent distal weakness are very likely to have dHMN type 7 by *IGHMBP2* mutation.⁸³ This mutated *IGHMBP2* was reported to potentially reduce neuronal protein formation by altering RNA secondary and tertiary structure.⁸⁴ Other clinical features may help in the selection of genetic testing in patients. Pyramidal tract signs of hyperreflexia and spasticity with distal motor weakness are likely associated with mutations in *SETX* or *BSCL2*. *SETX* mutations are also linked to the phenotypes diagnosed as juvenile amyotrophic lateral sclerosis (ALS4)^{85,86} and ataxia–oculomotor apraxia.⁸⁷ Among patients with *BSCL2* mutations, the upper limbs may be the first involved with a variable degree of spastic paraplegia, that is, Silver syndrome.⁸⁸ The upper extremity onset without spasticity could also suggest mutations in *GARS*.⁸¹ Vocal cord involvement with scoliosis and skeletal dysplasias may suggest *TRPV4* mutations, which can present with phenotypes of scapuloperoneal spinal muscular atrophy, HMSN 2C, or dHMN.^{77–80,89}

Hereditary Brachial Plexus Neuropathy

HBPN (also called hereditary neuralgic amyotrophy) is an autosomal dominant disorder exhibiting incomplete but high penetrance with genetic heterogeneity.^{90,91} The presenting attacks can occur as isolated upper extremity mononeuropathies (long thoracic, anterior interosseous, radial, suprascapular, or axillary nerves) or more commonly brachial plexus involvement of the C5–C6 myotomes of the shoulder and arm. Attacks typically present with severe debilitating pain and characteristic early muscle atrophy. Weakness may be abrupt but more commonly occurs within 1 week of onset of pain. The extent of early atrophy is often dramatic and beyond what is typically seen, even with traumatic nerve transection. This atrophy is a useful clinical finding, especially in postsurgical attacks, where iatrogenic injury is often questioned. HBPN attacks have been shown to be associated with perivascular nerve inflammation characteristic of autoimmunity.¹¹ Surgery, childbirth, immunization, trauma, and even psychological distress have all been documented to trigger attacks, but a clear trigger is not found in many patients. Pain may be persistent, and recovery is often slow and incomplete. Mild neurologic injury can result in major clinical handicaps, especially when the phrenic nerves, dominant hand, or shoulder are involved.

Family occurrence distinguishes HBPN from Parsonage–Turner syndrome (idiopathic neuralgic amyotrophy), but exceptions have been noted.¹¹ Genetic testing can be helpful, but the results are usually negative even for those with a clear family history.^{10,92} Recurrent attacks are more suggestive of HBPN but can occur in persons without established

inheritance.⁹³ The only genetic causes found to date are missense mutations and copy-number duplications of the septin 9 gene (*SEPT9*).^{94,95} Treatment with steroids after attacks, including high-dose intravenous steroids, may help reduce pain, but neurologic deficits can still progress.¹¹ Physical therapy, pain management, and time are likely the best treatments. Because recurrent HBPN attacks are often predictable after surgery and child delivery, the potential role of prophylactic steroids is being investigated with promising early results.⁹⁶

INHERITED NEUROPATHIES INVOLVING BOTH CENTRAL AND PERIPHERAL NERVOUS SYSTEMS

Spinocerebellar Ataxias with Neuropathy

Over 40 genes have now been identified to cause spinocerebellar ataxia (SCA) syndromes in both dominant and recessive forms, but a detailed description is beyond the scope of this review.⁹⁷ However, it is important to recognize this group in the potential differential diagnosis of unexplained inherited neuropathy. These syndromes are characterized by slowly progressive cerebellar and spinal degeneration with ataxia of speech, hands, gait, and eye movements. Many have areflexia and paradoxical Babinski or other upper motor neuron signs with peripheral neuropathy. Patients do not have mutilating extremity or painful extremity symptoms (A-delta, and C-fiber features), but rather they have large-fiber A-alpha-predominant involvement (proprioceptive and vibratory loss). In some varieties, such as Machado–Joseph disease (SCA3), neuropathy may be a major presenting feature,⁹⁸ and SCA3 patients with prominent neuropathy may have smaller CAG repeat lengths in the *ATXN3* gene. Axonal sensory nerve conduction abnormalities are characteristic, and SCA should be considered if the ataxia is much more prominent in comparison with the sensory loss by clinical and electrophysiologic examinations.

Dominantly inherited forms make up most of the hereditary ataxia varieties, but autosomal recessive Friedreich ataxia is the most common cause of hereditary ataxia. It occurs in approximately 1 in 100,000 persons. This frequency relates to the high rate of carrier frequency expansions in the general population (1:60–1:100 persons). It is caused by the expansion of an intronic GAA triplet repeat located within the first intron of the frataxin gene, resulting in reduced levels of frataxin in some tissues.⁹⁹ As with other spinocerebellar ataxias, there is an inverse relationship between the size of the repeat expansion and the age for onset of symptoms. Patients have sensory onset neuropathy with progressive motor and sensory involvement. Some may be miscategorized as HMSN 2 if the ocular and other ataxic features are missed. The high incidence of diabetes in Friedreich ataxia can mistakenly lead to a diagnosis of diabetic neuropathy.

Hereditary Spastic Paraplegias with Neuropathy

Hereditary spastic paraplegias exhibit a high degree of clinical and genetic heterogeneity with the primary manifestation being progressive spasticity and weakness of the lower limbs. If the spastic paraplegia occurs in isolation, it is considered to be a pure form; if another neurologic abnormality is present, it is considered to be a complicated form. Hereditary spastic paraplegia with neuropathy is one of the complicated varieties. Similar to spinocerebellar syndromes, the lower motor neuron involvement of hereditary spastic paraplegia with neuropathy may be mild and overlooked; therefore, it has not generally been the focus of most clinical investigations. There are over 40 genetically characterized forms of spastic paraplegia.¹⁰⁰ Variable extremity weakness and atrophy have been noted among some patients (Table 4). The conduction velocities of nerves are typically normal in the upper extremities, but in the lower extremity the compound motor action potential amplitudes may be reduced. Fibrillation and fasciculation potentials are often seen distally with increased size of motor unit potentials on needle examination.

INHERITED NEUROPATHIES WITH MULTIORGAN INVOLVEMENT

The inherited neuropathies with multiorgan involvement often have genetic defects in circulating proteins and common enzymes important in metabolic pathways of cell maintenance. The causal genes in these disorders are often ubiquitously expressed in many tissues, and patients often have other organ system involvement beyond the nervous system. For some varieties, there are rational treatments or prophylactic strategies (Table 7).¹⁰¹ GeneTests (<http://www.geneclinics.org/>) provides the contact information of available investigational treatments and is useful for affected families when considering the listed treatments. Recognizing the non-neurologic organ systems involvement is essential in making the diagnosis, and nerve biopsy is often useful in identifying these disorders (Table 7).

Clinical Clues to Specific Genetic Causes

Most inherited neuropathies do not have pathognomonic clinical findings linked with genetic causes. However, some may have distinguishing clinical features (Table 1). Among the inherited neuropathies with multiorgan involvement, identifying the affected non-neurologic organ provides the clue for a probable diagnosis. As an example, familial amyloidosis caused by mutations of transthyretin (*TTR*) is commonly associated with cardiac conduction and pumping defects as well as nephropathy from amyloid infiltration of the organs. Some findings may be quite specific, such as in gelsolin (*GEL*) amyloidosis, characterized by corneal lattice dystrophy and facial diplegia. In X-linked Fabry disease, boys commonly have thigh and scrotal angiokeratomas in combination with painful small-fiber neuropathy.

Among the inherited neuropathies affecting isolated neural tissues, the patterns of neural involvement can sometimes suggest the diagnosis. However, as more causal mutations are discovered, the range of clinical involvement also expands and makes the diagnosis of the specific genetic cause more complex (i.e., diverse phenotype–genotype correlations). For example, mutation in transient receptor vanilloid protein 4 (*TRPV4*) gene is now recognized to have diverse involvement beyond HMSN 2, including vocal cord and diaphragmatic paralysis, scapuloperoneal spinal muscular atrophy, distal spinal muscular atrophy, isolated arthropathy with brachyolmia (small hands), and scoliosis, all of which are linked to mutations in *TRPV4*.⁸⁰

PRACTICAL CONCERNS IN GENETIC TESTING

Family history, temporal course, and electrodiagnostic testing combined with neurologic examination are often adequate to determine whether a disorder is inherited. For many patients, genetic testing is not required if the phenotype suggests an untreatable variety. In contrast, genetic testing for metabolic multisystem disorders is often essential (Table 7). Regardless, prior to genetic testing, clinicians should have a conversation with patients that addresses: (1) variable clinical severity or expressivity of the tested genetic disease; (2) potential job-related and insurance discrimination; (3) risk for emotional upset; (4) implications for family planning; and (5) risk for discovery of an individual's illegitimate or adopted status. Often the testing delivers a result with ambiguous significance and needs to be interpreted with caution. If the DNA base alteration does not change the amino acid, it is unlikely to have clinical significance. If a non-synonymous rare variant of a known gene is found in an affected family, further investigation is needed to determine the likelihood of its causative nature. Generally, the family should be referred to a clinical research center for kindred evaluation and additional functional analysis of the alteration.

THERAPEUTIC OPTIONS AND TREATMENT POTENTIALS

Treatment still remains supportive for most inherited neuropathies. We have reviewed those approaches previously with special attention to: (1) anticipating specific impairment relevant to injury and providing early supportive interventions; (2) taking care of acral appendages, especially in the varieties of HSAN in which mutilating injuries and amputations are preventable; (3) arranging proper bracing and supportive devices; (4) emphasizing routine health maintenance, such as weight control, screening for early diabetes, thyroid disease, and limiting alcohol consumption; (5) considering the increased risk for worsened neuropathy associated with certain chemotherapeutic agents, including platinum-based agents, vinca alkaloids, and probably paclitaxel, thalidomide, and bortezomib products; and (6) providing reassurance that these disorders are often compatible with productive lives.¹⁰²

There have been significant advances in potential therapeutic interventions for the inherited neuropathies with multiorgan involvement (Table 7). Many of the defective gene products in these conditions have replaceable or modifiable blood circulating defects.¹⁰¹ These rare disorders have devastating morbidity and mortality compared with the neuropathies associated with selective neuronal involvement (e.g., HMSN, HSAN, etc). However, the latter group frequently demonstrates complex structural defects within the nerve and is more problematic when seeking rational treatment. The negative result in a large treatment trial of ascorbic acid for HMSN with *PMP22* duplications has highlighted the difficulties.¹⁰³

Among some metabolic mitochondrial disorders, although no treatment is available, certain risks associated with hepatic metabolizing drugs such as valproic acid are important to recognize—for example, sensory ataxic neuropathy, dysarthria, and ophthalmoplegia (SANDO; *POLG1* mutations) or neuropathy, ataxia, and retinitis pigmentosa (NARP; *MTATP6* mutations). Future discoveries are more likely to occur first in specific types with defective genes that are ubiquitously expressed and circulated and are therefore relatively easier to access and regulate. One such example is reported for hereditary sensory and autonomic neuropathy (HSAN 1). It is caused by mutations of *SPTLC1*, where the neurotoxic byproduct of the defective gene (deoxysphingolipids) circulates within the blood and can be reduced by oral supplementation with L-serine.¹⁰⁴ Both patients and transgenic mutant mice showed a dramatic reduction in neurotoxic deoxysphingolipids, but demonstrable neurologic improvement was only seen in the mice. Longitudinal clinical trials for patients are still needed.¹⁰⁵ It is predicted that individualized treatment strategies will be required for each genetic defect. Therapeutic interventions prior to the destruction of the neuronal cell body, nerve basement membrane, and supportive structures will provide the greatest chance for an effective treatment response.

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Abbreviations

AL	amyloid light chain
ALS	amyotrophic lateral sclerosis
<i>ATL1</i>	atlastin 1

<i>ATXN3</i>	ataxin 3
<i>BAG3</i>	BSCL2-associated athano-gene 3
<i>BSCL2</i>	Berardinelli–Seip congenital lipodystrophy 2 (seipin)
<i>CCT5</i>	chaperonin-containing TCP1, subunit 5
<i>CX32</i>	connexin32
<i>DCTN1</i>	dynactin 1
<i>DNMT1</i>	DNA methyltransferase 1
<i>DYNC1H1</i>	dynein, cytoplasmic 1, heavy chain 1
<i>EGR2</i>	early growth response 2
<i>FGD4 FYVE</i>	RhoGEF and PH domain containing 4
<i>FAM134B</i>	family with sequence similarity 134, member B
<i>GAN</i>	gigaxonin
<i>GARS</i>	glycyl-tRNA synthetase
<i>GDAP1</i>	ganglioside-induced; differentiation associated protein
<i>HSPB1</i>	heat shock 27-kDa protein 1
<i>HSPB8</i>	heat shock 22-kDa protein 8
<i>IGHMBP2</i>	immunoglobulin mu binding protein 2
<i>KIF1A</i>	kinesin family member 1A
<i>LITAF</i>	lipopolysaccharide-induced tumor necrosis factor-alpha
<i>MFN2</i>	mitofusin 2
<i>MGUS</i>	monoclonal gammopathy of undetermined significance
<i>MPZ</i>	myelin protein zero
<i>MTATP6</i>	mitochondrial-encoded ATP synthase 6
<i>NDRG1</i>	N-myc downstream-regulated 1
<i>NFL</i>	neurofilament light
<i>NGFB</i>	nerve growth factor (beta-polypeptide)
<i>NTRK1</i>	neurotrophic tyrosine kinase, receptor type 1
<i>PGP9.5</i>	protein gene product 9.5
<i>PMP22</i>	peripheral myelin protein 22
<i>POLG</i>	polymerase (DNA-directed), gamma
<i>RAB7</i>	Ras oncogene family member 7A
<i>SCN9A</i>	sodium channel type IX subunit-alpha
<i>SEPT9</i>	septin 9
<i>SETX</i>	senataxin
<i>SH3TC2</i>	SH3 domain and tetratricopeptide repeats 2
<i>SPG20</i>	spastic paraplegia 20

SPTLC1 and 2	serine palmitoyltransferase, long-chain base subunit 1 and 2
TDP	1 tyrosyl-DNA phosphodiesterase 1
TRPV4	transient receptor potential cation channel subfamily V, member 4
WNK1	WNK lysine-deficient protein kinase 1
YARS	tyrosyl tRNA synthetase

References

1. Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of unclassified neuropathies yields improved diagnosis. *Ann Neurol*. 1981; 10:222–226. [PubMed: 7294727]
2. Chahin N, Zeldenrust SR, Amrami KK, Engelstad JK, Dyck PJ. Two causes of demyelinating neuropathy in one patient: CMT1A and POEMS syndrome. *Can J Neurol Sci*. 2007; 34:380–385. [PubMed: 17803044]
3. Chaudhry V, Chaudhry M, Crawford TO, Simmons-O'Brien E, Griffin JW. Toxic neuropathy in patients with pre-existing neuropathy. *Neurology*. 2003; 60:337–340. [PubMed: 12552058]
4. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology*. 1993; 43:817–824. [PubMed: 8469345]
5. Triggs WJ, Brown RH Jr, Menkes DL. Case records of the Massachusetts General Hospital. Case 18-2006. A 57-year-old woman with numbness and weakness of the feet and legs. *N Engl J Med*. 2006; 354:2584–2592. [PubMed: 16775239]
6. Kilfoyle DH, Dyck PJ, Wu Y, Litchy WJ, Klein DM, Kumar N, et al. Myelin protein zero mutation His39Pro: hereditary motor and sensory neuropathy with variable onset, hearing loss, restless legs and multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2006; 77:963–966. [PubMed: 16844954]
7. Laura M, Milani M, Morbin M, Moggio M, Ripolone M, Jann S, et al. Rapid progression of late onset axonal Charcot-Marie-Tooth disease associated with a novel MPZ mutation in the extracellular domain. *J Neurol Neurosurg Psychiatry*. 2007; 78:1263–1266. [PubMed: 17940173]
8. Burns TM, Phillips LH II, Dimberg EL, Vaught BK, Klein CJ. Novel myelin protein zero mutation (Arg36Trp) in a patient with acute onset painful neuropathy. *Neuromuscul Disord*. 2006; 16:308–310. [PubMed: 16616847]
9. Auer-Grumbach M, Strasser-Fuchs S, Robl T, Windpassinger C, Wagner K. Late onset Charcot-Marie-Tooth 2 syndrome caused by two novel mutations in the MPZ gene. *Neurology*. 2003; 61:1435–1437. [PubMed: 14638973]
10. Klein CJ, Wu Y, Cunningham JM, Windebank AJ, Dyck PJB, Friedenberg SM, et al. SEPT9 mutations and a conserved 17q25 sequence in sporadic and hereditary brachial plexus neuropathy. *Arch Neurol*. 2009; 66:238–243. [PubMed: 19204161]
11. Klein CJ, Dyck PJ, Friedenberg SM, Burns TM, Windebank AJ. Inflammation and neuropathic attacks in hereditary brachial plexus neuropathy. *J Neurol Neurosurg Psychiatry*. 2002; 73:45–50. [PubMed: 12082044]
12. Sinnreich M, Sorenson EJ, Klein CJ. Neurologic course, endocrine dysfunction and triplet repeat size in spinal bulbar muscular atrophy. *Can J Neurol Sci*. 2004; 31:378–382. [PubMed: 15376484]
13. Amato AA, Prior TW, Barohn RJ, Snyder P, Papp A, Mendell JR. Kennedy's disease: a clinicopathologic correlation with mutations in the androgen receptor gene. *Neurology*. 1993; 43:791–794. [PubMed: 8469342]
14. Bennett CL, Lawson VH, Brickell KL, Isaacs K, Seltzer W, Lipe HP, et al. Late-onset hereditary axonal neuropathies. *Neurology*. 2008; 71:14–20. [PubMed: 18495953]
15. La Pean A, Jeffries N, Grow C, Ravina B, Di Prospero NA. Predictors of progression in patients with Friedreich ataxia. *Mov Disord*. 2008; 23:2026–2032. [PubMed: 18759347]

16. Schmitz-Hubsch T, Coudert M, Bauer P, Giunti P, Globas C, Baliko L, et al. Spinocerebellar ataxia types 1, 2, 3, and 6: disease severity and nonataxia symptoms. *Neurology*. 2008; 71:982–989. [PubMed: 18685131]
17. Klein CJ, Cunningham JM, Atkinson EJ, Schaid DJ, Hebring SJ, Anderson SA, et al. The gene for HMSN2C maps to 12q23–24: a region of neuromuscular disorders. *Neurology*. 2003; 60:1151–1156. [PubMed: 12682323]
18. Dyck PJ, O'Brien PC, Litchy WJ, Harper CM, Daube JR. Use of percentiles and normal deviates to express nerve conduction and other test abnormalities. *Muscle Nerve*. 2001; 24:307–310. [PubMed: 11353414]
19. Lewis RA, Sumner AJ. The electrodiagnostic distinctions between chronic familial and acquired demyelinating neuropathies. *Neurology*. 1982; 32:592–596. [PubMed: 6283420]
20. Gutierrez A, England JD, Sumner AJ, Ferer S, Warner LE, Lupski JR, et al. Unusual electrophysiological findings in X-linked dominant Charcot–Marie–Tooth disease. *Muscle Nerve*. 2000; 23:182–188. [PubMed: 10639608]
21. Lewis RA, Sumner AJ. Electrophysiologic features of inherited demyelinating neuropathies: a reappraisal. *Ann NY Acad Sci*. 1999; 883:321–335. [PubMed: 10586257]
22. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2006; 354:1362–1369. [PubMed: 16571879]
23. Garces-Sanchez M, Dyck PJ, Kyle RA, Zeldenrust S, Wu Y, Ladha SS, et al. Antibodies to myelin-associated glycoprotein (anti-Mag) in IgM amyloidosis may influence expression of neuropathy in rare patients. *Muscle Nerve*. 2008; 37:490–495. [PubMed: 18236455]
24. Lupu VD, Mora CA, Dambrosia J, Meer J, Dalakas M, Floeter MK. Terminal latency index in neuropathy with antibodies against myelin-associated glycoproteins. *Muscle Nerve*. 2007; 35:196–202. [PubMed: 17068765]
25. Dyck PJ, Lambert EH. Lower motor and primary sensory neuron diseases with peroneal muscular atrophy: I. Neurologic, genetic, and electrophysiologic findings in hereditary polyneuropathies. *Arch Neurol*. 1968; 18:603–618. [PubMed: 4297451]
26. Saporta AS, Sottile SL, Miller LJ, Feely SM, Siskind CE, Shy ME. Charcot–Marie–Tooth disease subtypes and genetic testing strategies. *Ann Neurol*. 2011; 69:22–33. [PubMed: 21280073]
27. Dyck PJ, Karnes JL, Lambert EH. Longitudinal study of neuropathic deficits and nerve conduction abnormalities in hereditary motor and sensory neuropathy type 1. *Neurology*. 1989; 39:1302–1308. [PubMed: 2797453]
28. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. *Mayo Clin Proc*. 1993; 68:748–752. [PubMed: 8392653]
29. Mauermann, M.; Klein, C. Hereditary sensory and autonomic neuropathies and miscellaneous inherited neuropathies with autonomic involvement. In: Bennaroch, EE.; Low, PA., editors. *Clinical autonomic disorders*. 3. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008. p. 468–481.
30. Dyck, P.; O'Brien, P.; Johnson, D.; Klein, C.; Dyck, P. Quantitative sensation testing. In: Dyck, PT., editor. *Peripheral neuropathy*. 4. Vol. 1. Philadelphia: Elsevier Saunders; 2005. p. 1063–1093.
31. Pelosi L, Lanzillo B, Perretti A, Santoro L, Blumhardt L, Caruso G. Motor and somatosensory evoked potentials in hereditary spastic paraplegia. *J Neurol Neurosurg Psychiatry*. 1991; 54:1099–1102. [PubMed: 1783925]
32. Abele M, Burk K, Andres F, Topka H, Laccone F, Bosch S, et al. Autosomal dominant cerebellar ataxia type I. Nerve conduction and evoked potential studies in families with SCA1, SCA2 and SCA3. *Brain*. 1997; 120:2141–2148. [PubMed: 9448569]
33. Klein CJ, Kimmel GW, Pittock SJ, Engelstad JE, Cunningham JM, Wu Y, et al. Large kindred evaluation of mitofusin 2 novel mutation, extremes of neurologic presentations, and preserved nerve mitochondria. *Arch Neurol*. 2011; 68:1295–1302. [PubMed: 21987543]
34. Klein CJ, Vrana JA, Theis JD, Dyck PJ, Spinner RJ, Mauermann ML, et al. Mass spectrometric-based proteomic analysis of amyloid neuropathy type in nerve tissue. *Arch Neurol*. 2011; 68:195–199. [PubMed: 20937937]

35. Verze L, Viglietti-Panzica C, Plumari L, Calcagni M, Stella M, Schrama LH, et al. Cutaneous innervation in hereditary sensory and autonomic neuropathy type IV. *Neurology*. 2000; 55:126–128. [PubMed: 10891921]
36. Li J, Bai Y, Ghandour K, Qin P, Grandis M, Trostinskaia A, et al. Skin biopsies in myelin-related neuropathies: bringing molecular pathology to the bedside. *Brain*. 2005; 128:1168–1177. [PubMed: 15774502]
37. Katona I, Wu X, Feely SM, Sottile S, Siskind CE, Miller LJ, et al. PMP22 expression in dermal nerve myelin from patients with CMT1A. *Brain*. 2009; 132:1734–1740. [PubMed: 19447823]
38. Saporta MA, Katona I, Lewis RA, Masse S, Shy ME, Li J. Shortened internodal length of dermal myelinated nerve fibres in Charcot–Marie–Tooth disease type 1A. *Brain*. 2009; 132:3263–3273. [PubMed: 19923170]
39. Skre H. Genetic and clinical aspects of Charcot–Marie–Tooth’s disease. *Clin Genet*. 1974; 6:98–118. [PubMed: 4430158]
40. Martyn CN, Hughes RA. Epidemiology of peripheral neuropathy. *J Neurol Neurosurg Psychiatry*. 1997; 62:310–318. [PubMed: 9120441]
41. Dyck PJ. Changing concepts, differential diagnosis, and classification. *Med Clin N Am*. 1968; 42:895–908. [PubMed: 4192680]
42. Houlden H, Laura M, Ginsberg L, Jungbluth H, Robb SA, Blake J, et al. The phenotype of Charcot–Marie–Tooth disease type 4C due to SH3TC2 mutations and possible predisposition to an inflammatory neuropathy. *Neuromuscul Disord*. 2009; 19:264–269. [PubMed: 19272779]
43. Fink JK. The hereditary spastic paraplegias: nine genes and counting. *Arch Neurol*. 2003; 60:1045–1049. [PubMed: 12925358]
44. Zuchner S, de Jonghe P, Jordanova A, Claeys KG, Guergueltcheva V, Cherninkova S, et al. Axonal neuropathy with optic atrophy is caused by mutations in mitofusin 2. *Ann Neurol*. 2006; 59:276–281. [PubMed: 16437557]
45. Chung KW, Kim SB, Park KD, Choi KG, Lee JH, Eun HW, et al. Early onset severe and late-onset mild Charcot–Marie–Tooth disease with mitofusin 2 (MFN2) mutations. *Brain*. 2006; 129:2103–2118. [PubMed: 16835246]
46. Windebank, A. Inherited recurrent focal neuropathies. In: Dyck, PJ.; Low, PA.; Poduslo, JF., editors. *Peripheral neuropathy*. 3. Vol. 2. Philadelphia: Saunders; 1993. p. 1137–1160.
47. England JD, Gronseth GS, Franklin G, Carter GT, Kinsella LJ, Cohen JA, et al. Evaluation of distal symmetric polyneuropathy: the role of laboratory and genetic testing (an evidence-based review). *Muscle Nerve*. 2009; 39:116–125. [PubMed: 19086068]
48. Blair IP, Nash J, Gordon MJ, Nicholson GA. Prevalence and origin of de novo duplications in Charcot–Marie–Tooth disease type 1A: first report of a de novo duplication with a maternal origin. *Am J Hum Gen*. 1996; 58:472–476.
49. Feely SM, Laura M, Siskind CE, Sottile S, Davis M, Gibbons VS, et al. MFN2 mutations cause severe phenotypes in most patients with CMT2A. *Neurology*. 2011; 76:1690–1696. [PubMed: 21508331]
50. Murphy SM, Laura M, Fawcett K, Pandraud A, Liu YT, Davidson GL, et al. Charcot–Marie–Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. *J Neurol Neurosurg Psychiatry*. 2012; 83:706–710. [PubMed: 22577229]
51. Latour P, Vial C. Molecular diagnosis of axonal forms of Charcot–Marie–Tooth disease [in French]. *Rev Neurol (Paris)*. 2009; 165:1122–1126. [PubMed: 19942244]
52. Dubourg O, Azzedine H, Verny C, Durosier G, Birouk N, Gouider R, et al. Autosomal-recessive forms of demyelinating Charcot–Marie–Tooth disease. *Neuromol Med*. 2006; 8:75–86.
53. Klein, CJ.; Dyck, P. Hereditary sensory and autonomic neuropathies (HSAN): clinical features pathologic classification, and molecular genetics. In: Dyck, PJ., editor. *Peripheral neuropathy*. 4. Vol. 2. Elsevier; 2005. p. 1809–1845.
54. Roththier A, Penno A, Rautenstrauss B, Auer-Grumbach M, Stettner GM, Asselbergh B, et al. Characterization of two mutations in the SPTLC1 subunit of serine palmitoyltransferase associated with hereditary sensory and autonomic neuropathy type I. *Hum Mut*. 2011; 32:E2211–2225. [PubMed: 21618344]

55. Rotthier A, Baets J, de Vriendt E, Jacobs A, Auer-Grumbach M, Levy N, et al. Genes for hereditary sensory and autonomic neuropathies: a genotype-phenotype correlation. *Brain*. 2009; 132:2699–2711. [PubMed: 19651702]
56. Rotthier A, Baets J, Timmerman V, Janssens K. Mechanisms of disease in hereditary sensory and autonomic neuropathies. *Nat Rev Neurol*. 2012; 8:73–85. [PubMed: 22270030]
57. Klein CJ, Botuyan M-V, Wu Y, Ward CJ, Nicholson GA, Hammans S, et al. Mutations in DNMT1 cause hereditary sensory neuropathy with dementia and hearing loss. *Nat Genet*. 2011; 43:595–600. [PubMed: 21532572]
58. Winkelmann J, Lin L, Schormair B, Kornum BR, Faraco J, Plazzi G, et al. Mutations in DNMT1 cause autosomal dominant cerebellar ataxia, deafness and narcolepsy. *Hum Mol Genet*. 2012; 21:2205–2210. [PubMed: 22328086]
59. Roddier K, Thomas T, Marleau G, Gagnon AM, Dicaire MJ, et al. Two mutations in the HSN2 gene explain the high prevalence of HSN2 in French Canadians. *Neurology*. 2005; 64:1762–1767. [PubMed: 15911806]
60. Kurth I, Pamminger T, Hennings JC, Soehendra D, Huebner AK, Rotthier A, et al. Mutations in FAM134B, encoding a newly identified Golgi protein, cause severe sensory and autonomic neuropathy. *Nat Genet*. 2009; 41:1179–1181. [PubMed: 19838196]
61. Riviere JB, Ramalingam S, Lavastre V, Shekarabi M, Holbert S, Lafontaine J, et al. KIF1A, an axonal transporter of synaptic vesicles, is mutated in hereditary sensory and autonomic neuropathy type 2. *Am J Hum Genet*. 2011; 89:219–230. [PubMed: 21820098]
62. Gold-von Simson G, Axelrod FB. Familial dysautonomia: update and recent advances. *Curr Probl Pediatr Adolesc Health Care*. 2006; 36:218–237. [PubMed: 16777588]
63. Indo Y, Tsuruta M, Hayashida Y, Karim MA, Ohta K, Kawano T, et al. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. *Nat Genet*. 1996; 13:485–488. [PubMed: 8696348]
64. Einarsdottir E, Carlsson A, Minde J, Toolanen G, Svensson O, Solders G, et al. A mutation in the nerve growth factor beta gene (NGFB) causes loss of pain perception. *Hum Mol Genet*. 2004; 13:799–805. [PubMed: 14976160]
65. Carvalho OP, Thornton GK, Hertecant J, Houlden H, Nicholas AK, Cox JJ, et al. A novel NGF mutation clarifies the molecular mechanism and extends the phenotypic spectrum of the HSAN5 neuropathy. *J Med Genet*. 2011; 48:131–135. [PubMed: 20978020]
66. Indo Y. Genetics of congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV. Clinical, biological and molecular aspects of mutations in TRKA(NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor. *Clin Auton Res*. 2002; 12(suppl 1):I20–32. [PubMed: 12102460]
67. Dyck PJ, Mellinger JF, Reagan TJ, Horowitz SJ, McDonald JW, Litchy WJ, et al. Not 'indifference to pain' but varieties of hereditary sensory and autonomic neuropathy. *Brain*. 1983; 106:373–390. [PubMed: 6189547]
68. Waxman SG. Neuroscience: channelopathies have many faces. *Nature*. 2011; 472:173–174. [PubMed: 21490662]
69. Davis MD, Weenig RH, Genebriera J, Wendelschafer-Crabb G, Kennedy WR, Sandroni P. Histopathologic findings in primary erythromelalgia are nonspecific: special studies show a decrease in small nerve fiber density. *J Am Acad Dermatol*. 2006; 55:519–522. [PubMed: 16908366]
70. Davis MD, Sandroni P, Rooke TW, Low PA. Erythromelalgia: vasculopathy, neuropathy, or both? A prospective study of vascular and neurophysiologic studies in erythromelalgia. *Arch Dermatol*. 2003; 139:1337–1343. [PubMed: 14568838]
71. Faber CG, Hoeijmakers JG, Ahn HS, Cheng X, Han C, Choi JS, et al. Gain of function Na(V) 1.7 mutations in idiopathic small fiber neuropathy. *Ann Neurol*. 2012; 71:26–39. [PubMed: 21698661]
72. Auer-Grumbach M, de Jonghe P, Wagner K, Verhoeven K, Hartung HP, Timmerman V. Phenotype-genotype correlations in a CMT2B family with refined 3q13–q22 locus. *Neurology*. 2000; 55:1552–1557. [PubMed: 11094113]
73. Bouhouche A, Benomar A, Bouslam N, Chkili T, Yahyaoui M. Mutation in the epsilon subunit of the cytosolic chaperonin-containing t-complex peptide-1 (Cct5) gene causes autosomal recessive

- mutilating sensory neuropathy with spastic paraplegia. *J Med Genet.* 2006; 43:441–443. [PubMed: 16399879]
74. Guelly C, Zhu PP, Leonardis L, Papic L, Zidar J, Schabhuhtl M, et al. Targeted high-throughput sequencing identifies mutations in atlastin-1 as a cause of hereditary sensory neuropathy type I. *Am J Hum Genet.* 2011; 88:99–105. [PubMed: 21194679]
 75. Irobi J, van Impe K, Seeman P, Jordanova A, Dierick I, Verpoorten N, et al. Hot-spot residue in small heat-shock protein 22 causes distal motor neuropathy. *Nat Genet.* 2004; 36:597–601. [PubMed: 15122253]
 76. Tang BS, Zhao GH, Luo W, Xia K, Cai F, Pan Q, et al. Small heat-shock protein 22 mutated in autosomal dominant Charcot–Marie–Tooth disease type 2L. *Hum Genet.* 2005; 116:222–224. [PubMed: 15565283]
 77. Deng HX, Klein CJ, Yan J, Shi Y, Wu Y, Fecto F, et al. Scapuloperoneal spinal muscular atrophy and CMT2C are allelic disorders caused by alterations in TRPV4. *Nat Genet.* 2010; 42:165–169. [PubMed: 20037587]
 78. Landouere G, Zdebek AA, Martinez TL, Burnett BG, Stanescu HC, Inada H, et al. Mutations in TRPV4 cause Charcot–Marie–Tooth disease type 2C. *Nat Genet.* 2010; 42:170–174. [PubMed: 20037586]
 79. Auer-Grumbach M, Olschewski A, Papic L, Kremer H, McEntagart ME, Uhrig S, et al. Alterations in the ankyrin domain of TRPV4 cause congenital distal SMA, scapuloperoneal SMA and HMSN2C. *Nat Genet.* 2010; 42:160–164. [PubMed: 20037588]
 80. Zimon M, Baets J, Auer-Grumbach M, Berciano J, Garcia A, Lopez-Laso E, et al. Dominant mutations in the cation channel gene transient receptor potential vanilloid 4 cause an unusual spectrum of neuropathies. *Brain.* 2010; 133:1798–1809. [PubMed: 20460441]
 81. Antonellis A, Ellsworth RE, Sambuughin N, Puls I, Abel A, Lee-Lin SQ, et al. Glycyl tRNA synthetase mutations in Charcot–Marie–Tooth disease type 2D and distal spinal muscular atrophy type V. *Am J Hum Genet.* 2003; 72:1293–1299. [PubMed: 12690580]
 82. Dierick I, Baets J, Irobi J, Jacobs A, De Vriendt E, Deconinck T, et al. Relative contribution of mutations in genes for autosomal dominant distal hereditary motor neuropathies: a genotype–phenotype correlation study. *Brain.* 2008; 131:1217–1227. [PubMed: 18325928]
 83. Pitt M, Houlden H, Jacobs J, Mok Q, Harding B, Reilly M, et al. Severe infantile neuropathy with diaphragmatic weakness and its relationship to SMARD1. *Brain.* 2003; 126:2682–2692. [PubMed: 14506069]
 84. Guenther UP, Handoko L, Lagerbauer B, Jablonka S, Chari A, Alzheimer M, et al. IGHMBP2 is a ribosome-associated helicase inactive in the neuromuscular disorder distal SMA type 1 (DSMA1). *Hum Mol Genet.* 2009; 18:1288–1300. [PubMed: 19158098]
 85. Zhao ZH, Chen WZ, Wu ZY, Wang N, Zhao GX, Chen WJ, et al. A novel mutation in the senataxin gene identified in a Chinese patient with sporadic amyotrophic lateral sclerosis. *Amyotroph Lateral Scler.* 2009; 10:118–122. [PubMed: 19058054]
 86. de Jonghe P, Auer-Grumbach M, Irobi J, Wagner K, Plecko B, Kennerson M, et al. Autosomal dominant juvenile amyotrophic lateral sclerosis and distal hereditary motor neuronopathy with pyramidal tract signs: synonyms for the same disorder? *Brain.* 2002; 125:1320–1325. [PubMed: 12023320]
 87. Moreira MC, Klur S, Watanabe M, Nemeth AH, Le Ber I, Moniz JC, et al. Senataxin, the ortholog of a yeast RNA helicase, is mutant in ataxia-ocular apraxia 2. *Nat Genet.* 2004; 36:225–227. [PubMed: 14770181]
 88. Windpassinger C, Auer-Grumbach M, Irobi J, Patel H, Petek E, Horl G, et al. Heterozygous missense mutations in BSCL2 are associated with distal hereditary motor neuropathy and Silver syndrome. *Nat Genet.* 2004; 36:271–276. [PubMed: 14981520]
 89. Klein CJ, Shi Y, Fecto F, Donaghy M, Nicholson G, McEntagart ME, et al. TRPV4 mutations and cytotoxic hypercalcemia in axonal Charcot–Marie–Tooth neuropathies. *Neurology.* 2011; 76:887–894. [PubMed: 21288981]
 90. van Alfen N. Clinical and pathophysiological concepts of neuralgic amyotrophy. *Nat Rev Neurol.* 2011; 7:315–322. [PubMed: 21556032]

91. Klein, CJ.; Windebank, AJ. Hereditary brachial plexus neuropathy. In: Dyck, PJ.; Thomas, PK., editors. *Peripheral neuropathy*. 4. Philadelphia: Elsevier; 2005. p. 1753-1767.
92. Hannibal MC, Ruzzo EK, Miller LR, Betz B, Buchan JG, Knutzen DM, et al. SEPT9 gene sequencing analysis reveals recurrent mutations in hereditary neuralgic amyotrophy. *Neurology*. 2009; 72:1755-1759. [PubMed: 19451530]
93. van Alfen N, van Engelen BG. The clinical spectrum of neuralgic amyotrophy in 246 cases. *Brain*. 2006; 129:438-450. [PubMed: 16371410]
94. Landsverk ML, Ruzzo EK, Mefford HC, Buysse K, Buchan JG, Eichler EE, et al. Duplication within the SEPT9 gene associated with a founder effect in North American families with hereditary neuralgic amyotrophy. *Hum Mol Genet*. 2009; 18:1200-1208. [PubMed: 19139049]
95. Kühlenbaumer G, Hannibal MC, Nelis E, Schirmacher A, Verpoorten N, Meuleman J, et al. Mutations in SEPT9 cause hereditary neuralgic amyotrophy. *Nat Genet*. 2005; 37:1044-1046. [PubMed: 16186812]
96. Klein CJ, Barbara DW, Sprung J, Dyck PJ, Weingarten TN. Surgical and postpartum hereditary brachial plexus attacks and prophylactic immunotherapy. *Muscle Nerve*. 2013; 47:23-27. [PubMed: 23042485]
97. Bird, TD. The hereditary ataxias. *GeneReviews*. 2012. <http://www.ncbi.nlm.nih.gov/sites/GeneTests/review>
98. Graves TD, Guilloff RJ. SCA3 presenting as an isolated axonal polyneuropathy. *Arch Neurol*. 2011; 68:653-655. [PubMed: 21555642]
99. Alper G, Narayanan V. Friedreich's ataxia. *Pediatr Neurol*. 2003; 28:335-341. [PubMed: 12878293]
100. Blackstone C. Cellular pathways of hereditary spastic paraplegia. *Annu Rev Neurosci*. 2012; 35:25-47. [PubMed: 22540978]
101. Burns TM, Ryan MM, Darras B, Jones HR Jr. Current therapeutic strategies for patients with polyneuropathies secondary to inherited metabolic disorders. *Mayo Clin Proc*. 2003; 78:858-868. [PubMed: 12839082]
102. Klein CJ. The inherited neuropathies. *Neurol Clin*. 2007; 25:173-207. [PubMed: 17324725]
103. Pareyson D, Reilly MM, Schenone A, Fabrizi GM, Cavallaro T, Santoro L, et al. Ascorbic acid in Charcot-Marie-Tooth disease type 1A (CMT-TRIAAL and CMT-TRAUK): a double-blind randomised trial. *Lancet Neurol*. 2011; 10:320-328. [PubMed: 21393063]
104. Garofalo K, Penno A, Schmidt BP, Lee HJ, Frosch MP, von Eckardstein A, et al. Oral l-serine supplementation reduces production of neurotoxic deoxysphingolipids in mice and humans with hereditary sensory autonomic neuropathy type 1. *J Clin Invest*. 2011; 121:4735-4745. [PubMed: 22045570]
105. Scherer SS. The debut of a rational treatment for an inherited neuropathy? *J Clin Invest*. 2011; 121:4624-4627. [PubMed: 22045569]
106. Edvardson S, Cinnamon Y, J alas C, Shaag A, Maayan C, Axelrod FB, et al. Hereditary sensory autonomic neuropathy caused by a mutation in dystonin. *Ann Neurol*. 2012; 71:569-572. [PubMed: 22522446]
107. Leonardis L, Auer-Grumbach M, Papic L, Zidar J. The N355K atlastin 1 mutation is associated with hereditary sensory neuropathy and pyramidal tract features. *Eur J Neurol*. 2012; 19:992-998. [PubMed: 22340599]
108. Rothhler A, Baets J, De Vriendt E, Jacobs A, Auer-Grumbach M, Levy N, et al. Genes for hereditary sensory and autonomic neuropathies: a genotype-phenotype correlation. *Brain*. 2009; 132:2699-2711. [PubMed: 19651702]

FIGURE 1.
Molecular targets of inherited neuropathy illustrate the diverse pathogenesis of inherited neuropathies.

FIGURE 2. Demyelinating neuropathy in the absence of dispersion and conduction block favors an inherited *PMP22* duplication over acquired chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The electrophysiologic differences relate to the observed pathologic findings in each case where uniform myelin lamella collagen thickening (onion bulbs) with *PMP22* duplications differs from the mixed onion bulbs of CIDP; the latter produces variable conduction velocities between fibers with observed dispersion and potential conduction blocks.

Varieties of Hereditary Motor and Sensory Neuropathies

HMSN (CMT)						HMSN V (spinal cord)	HMSN VI (optic)	HSAN		dHMN
AD	AR	AD	X-linked D	AD	AR	AD	AD	AD	AR	AD
PMP22	GDAP1	MPZ	GJB1	MFN2	GDAP1	MFN2	MFN2	SPTLC1	IKBKAP	HSPB8
MPZ	MTMR2, 13	DNM2	PRPS1	MPZ	HINT1	BSCL2	AR	RAB7	TRKA	HSPB1
<i>SIMPLE/LITAF</i>	<i>SBF2</i>	<i>YARS</i>		<i>GARS</i>	<i>LMNA</i>	<i>GJB1</i>		<i>SPTLC2</i>	HSN2	GARS
<i>EGR2</i>	<i>FDG4</i>	<i>INF2</i>		<i>NEFL</i>	<i>MED25</i>		<i>PRPS1</i>	<i>DNMT1</i>	<i>WNK1</i>	DCTN1
<i>NEFL</i>	<i>SH3TC2</i>			<i>BSCL2</i>				<i>ATL1</i>	<i>NGFβ</i>	BSCL2
<i>GDAP1</i>	<i>NDRG1</i>			<i>GPAP1</i>					<i>FAM134B</i>	TRPV4
<i>INF2</i>	<i>EGR2</i>			<i>HSPB1</i>					<i>KIF1A</i>	DYNC1H1
	<i>CTDP1</i>			<i>HSPB8</i>					<i>CCT5</i>	SETX
	<i>PRX</i>			<i>TRPV4</i>					<i>DST</i>	AR
				<i>RAB7</i>					<i>NTRK1</i>	IGHMBP2
				<i>KIF1B</i>						X-linked
				<i>AARS</i>						<i>ATP7A</i>
				<i>DYNC1H1</i>						
				<i>LRSAM1</i>						
				<i>TFG</i>						
Demyelinating		Intermediate		Axonal						
Ulnar MNCV <38m/s		Ulnar MNCV 38-45m/s		Ulnar MNCV >45m/s						

FIGURE 3.

The pattern of inheritance and nerve conduction details are useful in limiting the candidate genes in genetic testing of varieties of motor and sensory neuropathies. Retrospective cohort studies with comprehensive gene sequencing support the utility of some genetic tests (bold) as having the highest probability of positive testing.^{26,83,108}

FIGURE 4.

Nerve biopsy assists diagnosis of familial amyloid polyneuropathy. Paraffin-embedded sural nerve stained with (A) methyl violet with characteristic metachromatic staining of amyloid, (B) Congo red with amyloid congophilia, and (C) apple-green birefringence shown under polarized light, later determined by laser dissection³⁴ of the infiltrate and mass spectrophotometric analysis to be transthyretin amyloidosis due to the Val30Met mutation.

FIGURE 5.

A sural nerve biopsy in a child that led to genetic testing and discovery of the gigaxonin mutation in giant axonal neuropathy, which had not been considered previously. (A) Osmium-stained teased nerve fiber preparation demonstrates neurofilament accumulations characteristic of the disorder with (B) light microscopy epoxy-embedded methyl blue-stained nerve showing the characteristic axonal enlargements (C) confirmed on electron micrographs to be localized to intermediate filament inclusions and myelin lamella thickening.

FIGURE 6.

Histopathologic evaluation of sural nerve in a patient with an unexplained axonal polyradiculoneuropathy where frequent polyglucosan bodies led to enzymatic and DNA confirmation of autosomal recessive adult-onset polyglucosan-body disease (APBD). **(A)** Teased-fiber nerve preparation stained by osmium showing the characteristic homogeneous axonal glycogen deposits of APBD. **(B)** Basophilic staining of polyglucosan by hematoxylin and eosin. **(C)** Epoxy-embedded nerve having the characteristic targetoid features of APBD.

FIGURE 7.

Myelin abnormalities are distinct between patients with HMSN 1A caused by duplications of *PMP22* [onion bulbs (A) teased fibers and (B) high-power electron micrograph] and those found in HNPP [tomaculae (C) teased fibers and (D) high-power electron micrograph] caused by deletions in *PMP22*. In (A) and (C), the top teased fiber shown is a normal control. Onion bulbs have characteristic generalized nerve fiber thickening from exuberant collagen lamellae with loss of nodal definition. In contrast, tomaculae have focal myelin thickening caused by localized redundant loops of myelin, creating the typical tomaculous swellings.

Table 1**Inherited neuropathies in broad categories.**

Neuropathy with isolated nerve involvement
Hereditary motor and sensory neuropathy (HMSN, or Charcot–Marie–Tooth)
Hereditary sensory and autonomic neuropathy (HSAN)
Hereditary sensory neuropathy (HSN)
Distal hereditary motor neuropathy (dHMN)
Hereditary brachial plexus neuropathy (HBPN)
Hereditary neuropathy with liability to pressure palsies (HNPP)
Neuropathy with brain and/or spinal cord involvements
Spinocerebellar atrophy (SCA)
Friedreich ataxia (FA)
Hereditary spastic paraplegia neuropathy (i.e., complicated HSP, HMSN 5)
Neuropathy with non-neurologic organ involvement
Familial amyloid (transthyretin, gelsolin, ApoA1)
Leukodystrophy
Peroxisomal
Lipoprotein deficiency
Porphyrias
Defective DNA maintenance
Mitochondrial defects
Miscellaneous
Giant axonal neuropathy
Neurofibromatosis type 1
Neurofibromatosis type 2
Others

Table 2

Demyelinating hereditary motor sensory neuropathy (HMSN1).

Disease	Gene	Clinical variability and comments
Autosomal dominant (CMT1)		
1A	<i>PMP22</i> duplication	Most common cause of HMSN, allelic with HNPP
1B	<i>MPZ</i>	Rare occurrence late onset rapid onset
1C	<i>LITAF</i> (<i>SIMPLE</i>)	Uncommon cause
1D	<i>EGR2</i>	Uncommon cause
1E	<i>PMP</i> missense mutation	Clinically similar to HMSN 1A
1F	<i>NEFL</i>	Uncommon cause
1G	<i>INF2</i>	Glomerulopathy, uncommon
HNPP		
HNPP	Del17p(<i>PMP22</i>)	Generalized neuropathy plus at sites of compression
X-linked dominant (CMTX)		
X1-linked	<i>GJB1</i>	CNS, hearing loss, thenar atrophy (axonal or intermediate conduction)
Autosomal dominant HMSN-3 ^a		
3A	<i>PMP22</i>	Prominent hypertrophic nerves
3B	<i>MPZ</i>	Prominent hypertrophic nerves
3C	<i>EGR2</i>	Prominent hypertrophic nerves
Autosomal recessive (CMT4)		
4A	<i>GDAP1</i>	Vocal cord paresis
4B1	<i>MTMR2</i>	Focally folded myelin
4B2	<i>MTMR13</i>	Early onset glaucoma
4C	<i>SH3TC2</i>	Prominent scoliosis, facial involvement
4D	<i>NDRG1</i>	Deafness
4E	<i>EGR2</i>	Allelic to HMSN 1 and 3
4F	<i>PRX</i>	Prominent hypertrophic nerves
4H	<i>FGD4</i>	Variable scoliosis and severity
4J	<i>FIG4</i>	Profound axonal loss, early onset

CMT, Charcot-Marie-Tooth; HNPP, hereditary neuropathy with pressure palsy from *PMP22* deletions; *PMP*, peripheral myelin protein; *MPZ*, myelin protein zero; *LITAF*, lipopolysaccharide-induced tumor necrosis factor- α ; *SIMPLE*, small integral protein of lysosome; *EGR2*, early growth response 2; *NFL*, neurofilament light; *GJB1*, encodes connexin32, *GDAP1*, ganglioside-induced differentiation-associated protein 1; *MTMR2*, myotubularin-related protein 2; *SBF2*, set binding factor 2; *SH3TC2*, SH3 domain and tetratricopeptide repeats 2; *NDRG1*, N-myc downstream regulation gene 1; *PRX*, periaxin; *FGD4*, FYVE, RhoGEF and PH domain containing 4.

* Symptomatic onset in infancy with delayed ambulation. This group eliminated in some classification schemes rather considered severe expression of HMSN 1 genes.

Table 3

Axonal and intermediate hereditary motor sensory neuropathy (HMSN 2).

Disease	Gene or locus	Clinical comments
Autosomal dominant (HMSN2, CMT2)		
2A	<i>KIF1B</i>	1 Japanese family
2A2	<i>MFN2</i>	Some with optic atrophy, spasticity, i.e., HMSN 5
2B	<i>RAB7</i>	Allelic to HSAN 1B with foot ulcers
2C	<i>TRPV4</i>	Diaphragm & vocal cord paresis, several with infant onset, allelic to dHMN, SPSMA
2D	<i>GARS</i>	Allelic to dSMAV
2E and 1F	<i>NEFL</i>	Foot hyperkeratosis
2F	<i>HSPB1</i>	Variable sensory, allelic dHMN
2G	–12q12	Young adults
2H and K	<i>GDAP1</i>	GDAP1 mutation is also linked with recessive intermediate conduction slowing HMSN
2I and J	<i>MPZ</i>	Allelic to HMSN 1B; J=pupillary involvement±deafness
2L	<i>HSPB8</i>	Proximal and distal involvement
2N	<i>AARS</i>	–
2O	<i>DYNC1H1</i>	Variable sensory involvement, allelic dHMN, SMA, SPSMA
2P	<i>LRSAM1</i>	–
2P-Okinawa	<i>TFG</i>	Proximal involvement, fasciculations, high CK, Okinawa founder
Autosomal dominant [HMSN DI (intermediate slowed conduction)]		
DI-A	<i>10q24</i>	–
DI-B	<i>DNM2</i>	Neutropenia, primary axonal or demyelinating
DI-C	<i>YARS</i>	Primary axonal or demyelinating
DI-D	<i>MPZ</i>	Similar to HMSN I and J
Autosomal recessive and X-linked (CMT2)		
2G and K	<i>GDAP1</i>	Vocal cord involvement
2H	–8q21	Pyramidal features
X1-linked	<i>GJB1</i>	CNS, hearing loss, thenar atrophy
X2-linked	–Xp22.2	Infantile onset, ±mental retardation
X3-linked	–Xq26	Spasticity
X5-linked	<i>PRPS1</i>	Hearing loss and optic atrophy
2B1	<i>LMNA</i>	Moroccan family
2B2	<i>MED25</i>	Costa Rican family
2	<i>HINT1</i>	Neuromyotonia variable hyperCKemia

KIF1B, kinesin family member; MFN2, mitofusin; RAB7, ras-associated protein; TRPV4, transient receptor potential cation channel subfamily V, member 4; SPSMA, scapuloperoneal spinal muscular atrophy; GARS, glycyl-tRNA synthetase; NFL, neurofilament light; HSPB1, heat shock 27kDa protein 1; GDAP1, ganglioside-induced differentiation-associated protein; MPZ, myelin protein zero; HSPB1, heat shock 22kDa protein 8; AARS, alanyl-tRNA synthetase; SMA, spinal muscular atrophy; DYNC1H1, cytoplasmic dynein 1 heavy chain 1; LRSAM1, E3 ubiquitin-protein ligase; DNM2, dynamin 2; YARS, tyrosyl tRNA synthetase; GJB1, gap junction protein beta 1; PRPS1, phosphoribosyl pyrophosphate synthetase 1; LMNA, lamin A/C; MED25, mediator complex subunit.

Table 4

Hereditary spastic paraplegias with neuropathy (complicated^a hereditary spastic paraplegia or HMSN 5).

Disease	Gene or locus, protein	Clinical comments
Autosomal dominant		
3A	<i>ATL1</i> , atlastin	One family with sensory neuropathy, minimal spasticity ¹⁰⁷
9	10q23, unknown	Motor neuronopathy, cataracts, GERD
10	<i>KIF5A</i> , KIF5A	Distal amyotrophy
17	<i>BSCL2</i> , seipen	Hand atrophy, Silver syndrome
Autosomal recessive		
7	<i>SPG7</i> , paraplegin	Neuropathy, dysarthria, dysphagia, optic disk pallor
11	<i>SPG11</i> , spatacsin	Corpus callosum atrophy, mental retardation, extremity weakness, nystagmus
15	<i>ZFYVE26</i> , spastizin	Motor neuronopathy, pigmented macula, mental retardation, dysarthria
20	<i>SPG20</i> , spartin	Distal wasting, Troyer syndrome
39	<i>NTE</i>	Prominent extremity amyotrophy
X-linked		
2	<i>PLP</i>	CNS white matter disease, neuropathy
16	Xq11	motor aphasia, mental retardation, gastrointestinal

GERD, gastrointestinal reflux; KIF5A, kinesin family; BSCL2, Berardinelli-Seip congenital lipodystrophy 2 (seipin); P, proteolipid protein; NTE, neuropathy target esterase.

* Complicated refers to those cases with more than spasticity, and when neuropathy is prominent may also be referred to as HMSN 5.

Table 5

Hereditary sensory and autonomic neuropathies (HSAN).

Disease	Onset	Gene or locus	Clinical comments
Autosomal dominant			
1A	2nd+ decade	<i>SPTLC1</i>	Lancinating leg pains, variable distal weakness, distal sweat loss
1B	2nd+ decade	<i>3p24-p22</i>	Cough and gastroesophageal reflux
1B	2nd+ decade	<i>RAB7</i>	Allelic with HMSN 2B, prominent distal weakness
1C	2nd+ decade	<i>SPTLC2</i>	Lancinating leg pains, variable distal weakness
1D	2nd+ decade	<i>ATL1</i>	One family, increased leg tone
1E	2nd+ decade	<i>DNMT1</i>	Early hearing loss and dementia
Autosomal recessive			
2A	Congenital	<i>WNK1</i>	French-Canadian and other races, common early digit autoamputations
2B	Congenital	<i>FAM134B</i>	Digit auto-amputations
2C	Congenital	<i>KIF1A</i>	Mild distal weakness ulcers
3 aka Riley–Day syndrome	Congenital	<i>IKBKAP</i>	Ashkenazi Jewish families, cognitive involvement, pandysautonomia, systemic features
4	Congenital	<i>NTRK1</i>	Cognitive disorder, infections, bladder, and other dysautonomias
5	Congenital	<i>NGFβ</i>	Spared cognition, common Charcot joints
HSAN+spastic paraparesis	Congenital	<i>CCT5</i>	Moroccan family
HSAN+myopathic facies	Congenital	<i>DST</i>	Ashkenazi Jewish families, feeding difficulty, early death ¹⁰⁶

SPTLC, serine palmitoyltransferase subunit; RAB7, ras-associated protein; ATL, atlastin; DNMT1, DNA methyltransferase 1; WNK1, WNK lysine deficient protein kinase 1; FAM134B, family with sequence similarity 134, member B; KIF1A, kinesin family 1A; IKBKAP, inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein; NTRK1, neurotrophic tyrosine kinase; NGFβ, nerve growth factor-beta; CCT5, chaperone containing CPT1; DYS, dystonin.

Table 6

Distal hereditary motor neuropathies (dHMN).

Disease	Inheritance	Gene(s) or locus	Clinical comments
Type 1	AD	<i>HSPB1</i> <i>HSPB8</i> <i>DYNC1H1</i> <i>GARS</i>	Childhood-onset distal weakness and atrophy
Type 2	AD	<i>HSPB1</i> <i>HSPB8</i> <i>BSCL2</i>	Adult-onset distal weakness and atrophy
Type 3	AR	11q13	Insidious progressive distal weakness and atrophy
Type 4	AR	11q13	Diaphragm paralysis plus distal weakness and atrophy
Type 5	AD	<i>GARS</i> <i>BSCL2</i>	Upper limb predominant distal weakness and atrophy
Type 6	AR	<i>IGHMBP2</i>	Low birth-weight, slowed conduction, respiratory distress
Type 7	AD	<i>DCTN1</i> <i>TRPV4</i> 2q14	Adult onset with vocal cord involvement
dHMN plus pyramidal signs	AD	<i>SETX</i> <i>BSCL2</i> 4q34 7q34	Distal involvement plus pyramidal signs
X-linked	X-linked	<i>ATP7A</i>	Allelic to Menke disease
Congenital distal SMA	AD	<i>TRPV4</i>	Bony changes including scoliosis, small hands, arthrogryposis
Jerash type	AR	9p21	Pyramidal signs, childhood

AD, autosomal dominant; AR, autosomal recessive; HSP, heat shock protein; DYNC1H1, dynein cytoplasmic 1, heavy chain 1; GARS, glycyl-tRNA synthetase; BSCL2, Berardinelli-Seip congenital lipodystrophy 2 (seipin); IGHMBP2, immunoglobulin mu binding protein 2; DCTN1, dynactin subunit 1; TRPV4, transient receptor potential cation channel, subfamily V, member 4; SETX, sentaxin.

Table 7

Metabolic neuropathies with potential treatment.

Disease	Inherited	Gene	Clinical comments	Possible interventions
Familial amyloid				
Transthyretin amyloidosis	AD	<i>TTR</i>	Frequent autonomic	Liver transplant, possible oral medications
Leukodystrophy				
Metachromatic	AR	<i>ARSA</i>	Schwann cell metachromatic granules	Bone marrow or hematopoietic transplant
Krabbe	AR	<i>GALC</i>	Prismatic inclusions in endoneurial macrophages	Bone marrow or hematopoietic transplant
Adrenoleukodystrophy	XR	<i>ABCD1</i>	Myeloneuropathy	Bone marrow transplant, "Lorenzo's oil"
Peroxisomal				
Refsum disease	AR	<i>PHYH</i>	Varied onion bulbs	Low phytanic acid diet
Fabry	XR	<i>GLA</i>	Varied osmophilic granules	Alpha galactosidase-A infrared
Lipoprotein deficiency				
Cerebrotendinous xanthomatosis	AR	<i>CYP27A1</i>	Minor Schwann cell lipids	Chenodeoxycholic acid plus statin
Porphyrrias				
Acute intermittent	AD	<i>PBGD</i>	Axonal greater than demyelinating	Avoid precipitant factors
Defective DNA maintenance				
Xeroderma pigmentosa	AR	<i>XPC</i>	Axonal degeneration	Avoidance of sun
Ataxia telangiectasia	AR	<i>ATM</i>	Sensory greater than motor	Early cancer screening
Mitochondrial (Mt) defects				
Kearns–Sayre	Varied	<i>MT gene</i> deletions	Demyelinating radiculopathy	Superoxide scavengers
MNGIE	AR	<i>TYMP</i>	Mitochondrial neuro-gastrointestinal encephalomyopathy	Caution with liver primary metabolizing drugs (e.g., valproic acid), peritoneal dialysis, bone marrow transplant

AD, autosomal dominant; AR, autosomal recessive; TTR, transthyretin; ARSA, arylsulfatase A; GALC, galactocerebrosidase; ABCD1, ATP-binding cassette domain 1; PHYH, phytanic acid oxidase; GLA, galactosidase alpha; CYP27A1, steroid 27-hydroxylase; PBGD, porphobilinogen deaminase; XPC, xero-derma complex; ATM, ataxia telangiectasias mutated; Mt, mitochondria; TYMP, thymidine phosphorylase.