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The Complex Clinical and Genetic Landscape of Hereditary Peripheral Neuropathy

Soumitra Ghosh and Warren G. Tourtellotte

Department of Pathology and Laboratory Medicine, Neurology, and Neurological Surgery, Cedars-Sinai Medical Center, Los Angeles, California 90048, USA;
email: warren.tourtellotte@cshs.org

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Abstract

Hereditary peripheral neuropathy (HPN) is a complex group of neurological disorders caused by mutations in genes expressed by neurons and Schwann cells. The inheritance of a single mutation or multiple mutations in several genes leads to disease phenotype. Patients exhibit symptoms during development, at an early age or later in adulthood. Most of the mechanistic understanding about these neuropathies comes from animal models and histopathological analyses of postmortem human tissues. Diagnosis is often very complex due to the heterogeneity and overlap in symptoms and the frequent overlap between various genes and different mutations they possess. Some symptoms in HPN are common through different subtypes such as axonal degeneration, demyelination, and loss of motor and sensory neurons, leading to similar physiologic abnormalities. Recent advances in gene-targeted therapies, genetic engineering, and next-generation sequencing have augmented our understanding of the underlying pathogenetic mechanisms of HPN.

INTRODUCTION

Hereditary peripheral neuropathy (HPN) is a complex group of neurological disorders that have wide-ranging symptoms, clinical severity, and causes. Clinical presentations of HPN are heterogeneous, and the gene mutations involved in the disorders often overlap. These disorders generally target the sensory, motor, and/or autonomic nervous systems, and disease-related symptomatology and physiologic deficits are secondary to effects on neurons, axons, and/or myelin produced by Schwann cells (1). In addition, there is a wide spectrum of morbidity and mortality for patients, depending on the cellular targets and underlying pathogenic abnormalities associated with the particular subtype of HPN. Historically, characterization of these disorders often depended on careful physical examination, neuromuscular and laboratory testing, and histopathological examination of muscles and nerves (2). In recent years, however, the emergence and widespread availability of modern genetic testing have helped to identify the root causes of these diseases and to better match therapies targeting the gene mutation that is driving the disease (3).

The most common form of HPN is Charcot-Marie-Tooth disease (CMT), also known as hereditary motor and sensory neuropathy (HMSN). Accordingly, the reader is referred to several comprehensive reviews on CMT for more in-depth discussion than is possible in this broad review on HPN (4–8). In this review, we briefly cover the major genes that are involved in the pathogenesis of CMT and other well-recognized subtypes of HPN, hereditary sensory and autonomic neuropathy (HSAN), hereditary motor neuropathy (HMN), and small fiber neuropathy (SFN) (1, 9). We also discuss the emergence of exaggerated symptoms in HPN patients who receive chemotherapy for cancer treatment. These symptoms are an emerging issue in HPN patients who are leading longer lives that are fraught with diseases that tend to occur later in life, such as cancer. Finally, while most current therapies focus on symptomatic treatment, we discuss the emergence of promising targeted molecular therapies that are under development for potential use in patients suffering from some of these devastating diseases.

CHARCOT-MARIE-TOOTH DISEASE (HEREDITARY MOTOR AND SENSORY NEUROPATHY)

HMSN, also collectively known as CMT, as mentioned above, is generally characterized by impairment in sensory and motor function. The overall prevalence of CMT is 1 in 2,500, and first symptoms typically start in the lower limbs and then gradually progress to other parts of the body (4, 10), with patients ultimately suffering from distal muscle wasting and generalized weakness (2). CMT has myelin- and axon-damaging forms that are distinguished primarily on the basis of nerve conduction velocity (NCV). Patients with the demyelinating form of the disease have NCVs that tend to be below 38 m/s, whereas with the axonal form, NCVs are typically above 38 m/s. Depending on the mode of inheritance and the specific underlying gene mutation, CMT is further classified into autosomal dominant, recessive, and X-linked subtypes (10, 11). More than 1,000 different mutations in 100 different genes have been associated with CMT (12, 13). To simplify the generalized classification scheme, the demyelinating forms are typically referred to as CMT1 and the axonal forms as CMT2. Some of the genes most frequently mutated in CMT patients are *Myelin Protein Zero* (*MPZ*), *Peripheral Myelin Protein 22* (*PMP22*), *Mitochondrially Encoded ATP Synthase Membrane Subunit 6* (*MT-ATP6A*), *Gap Junction Protein Beta 1* (*GJB1*), *Neurofilament Light* (*NEFL*), and *Gigaxonin* (*GAN*). The functional impact of many of these gene mutations on myelin and axons is summarized and referenced in **Table 1** and shown in **Figure 1** (14–16).

Table 1 Genes associated with different subtypes of Charcot-Marie-Tooth disease (CMT) and their roles in myelin pathology

CMT disease subtype (OMIM)	Associated gene (OMIM) and literature reference	Effect on myelin
HNPP (162500) CMT1A (118220) CMT1E (118300)	*PMP22* (601097) (134)	Disrupts myelin organization and disintegrates axonal structure; alters mRNA processing of myelin
CMT1B (11820)	*MPZ* (159440) (135)	Involved in myelin misfolding and translocation to endoplasmic reticulum for degradation
CMT1C (601098)	*LITAF/SIMPLE* (603795) (136, 137)	Involved in lysosomal-mediated protein degradation of myelin in endosomes
CMT1D (607678) CMT4E (605253)	*EGR2/Krox20* (129010) (138)	Required for myelin sheath formation; regulates downstream myelin genes such as *Connexin 32*, *Myelin Basic Protein*, *MPZ*, and *PMP22*
CMT1F (607734)	*NEFL* (162280) (139, 140)	Responsible for loss of large myelinated fibers and regenerating clusters
CMT1G (618279)	*PMP2* (170715) (141)	Responsible for abnormal myelin compaction with vacuoles, internal and external myelin folding, irregular myelin sheath, and pseudo-onion bulbs
CMT1X (302800)	*GJB1/connexin32* (304040) (142)	Affects the electrical communication through gap junctions in the myelin sheath
CMT4B1 (601382)	*MTMR2* (603557) (143)	Expressed mainly in neurons; alteration in axon-Schwann cell interaction due to reduced phosphatase activity is observed
CMT4B2 (604563)	*MTMR13/SBF2* (607697) (144)	Functions as a pseudophosphatase that acts as a scaffolding protein and causes myelin outfoldings
CMT4B3 (615284)	*SBF1* (603560) (145)	Responsible for loss of large myelinated fibers and focally folded myelin sheaths
CMT4C (601596)	*SH3TC2* (608206) (146)	Interacts with laminin receptor, Rab11; integrin-α_6 regulating the structural integrity of myelin is expressed late in myelination
CMT4D (601455)	*NDRG1* (605262) (147, 148)	Impairs splicing and leads to skipping of exon 9, Hirano bodies, and occasional intratubal macrophages
CMT4F (614895)	*PRX* (605725) (102)	Recruits proteins to abaxonal plasma membrane of the Schwann cell and thickening of the myelin sheath
CMT4H (609311)	*FGD4* (11104) (149)	Causes a decrease in the density of myelinated fibers, decrease in large fibers, irregular myelin thickness
CMT4J (611228)	*FIG4* (609390) (150)	Causes an increase of Schwann cell dedifferentiation due to influx of intracellular Ca^{2+} and causes macrophage infiltration in spinal roots with nerve-blood barriers

Abbreviations: MPZ, Myelin Protein Zero; OMIM, Online Mendelian Inheritance in Man® catalog; PMP22, Peripheral Myelin Protein 22.

Gene copy number variation, chromosomal translocation, rearrangements, duplications, and inversions are some of the recognized mechanisms by which genotypic alternations occur in CMT patients (17). The gene most frequently mutated in CMT patients is *PMP22*, and this gene accounts for 60–70% of all CMT1 patients. Patients with *PMP22* mutations suffer from peripheral demyelinating disease. *PMP22* is located in a 1.5-Mb tandem duplication of chromosome 17p11.2-p12 (18). Patients with *GJB1* mutations account for 10–20% of CMT1 patients, and mutations in the *MPZ* gene account for <5% of all CMT1 cases. Advances in next-generation sequencing have led to the identification of several novel genes associated with CMT, such as *Myelin P2 protein* (*PMP2*), which is essential in axonal myelination; *Microrchidia 2* (*MORC2*), which is required

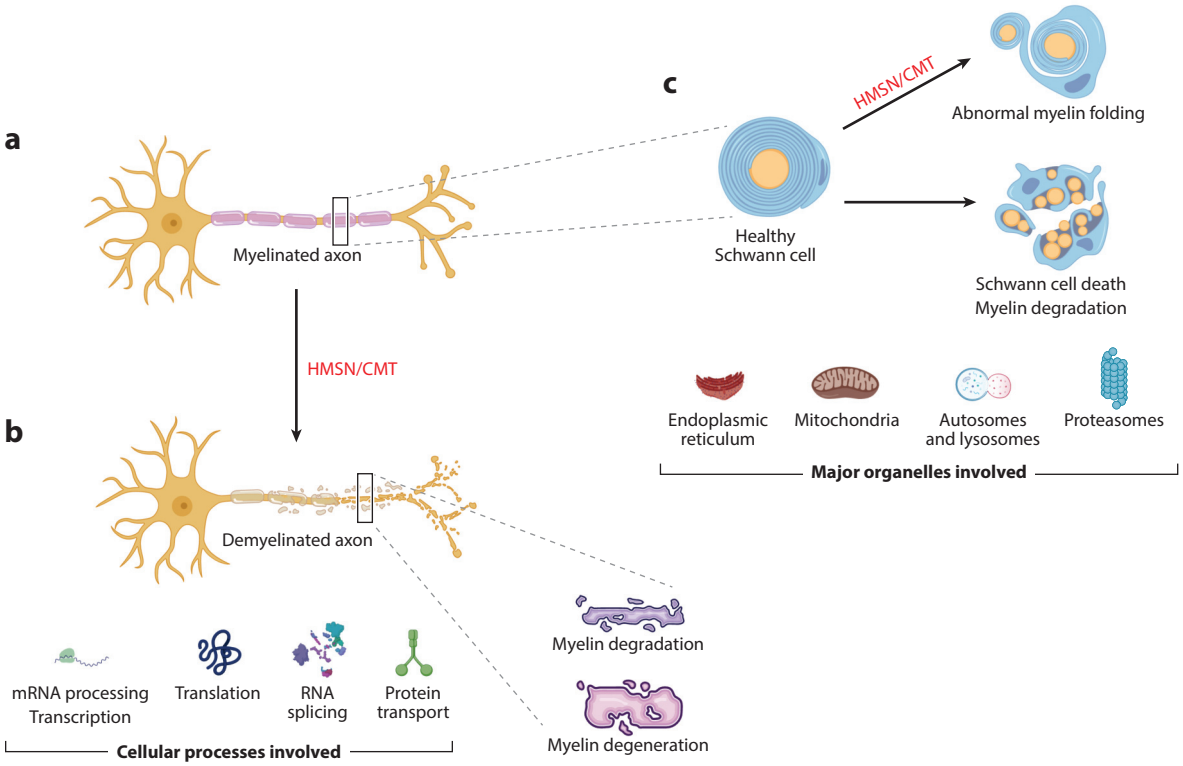

Figure 1

Many genes are involved in CMT pathogenesis. (*a*) Healthy myelinated axons maintain normal myelin sheath. (*b*) Specific gene mutations (**Table 1**) lead to disruption of cellular processes that results in myelin degradation and axon degeneration. (*c*) Gene mutations alter Schwann cell and neuron function and survival by targeting cellular organelle metabolism in CMT. Abbreviations: CMT, Charcot-Marie-Tooth disease; HMSN, hereditary motor and sensory neuropathy; mRNA, messenger RNA. Figure adapted from images created with BioRender.com.

for maintenance of the DNA damage response pathway; *Neurofilament heavy chain* (*NEFH*), which has a role in axon structure; *Membrane metalloendopeptidase* (*MME*), which encodes for the protein Neprilysin that is required for neuropeptide degradation; *Spatacsin* (*SPG11*), which maintains lipid homeostasis by preventing its lysosomal degradation; and *Diacylglycerol O-acyltransferase 2* (*DGAT2*), which catalyzes triglyceride biosynthesis (5). Advances in whole-genome, whole-exome, and panel-specific sequencing have made it easier to test CMT patients and to identify the precise gene mutations responsible for their disease. For example, in patients with autosomal dominant CMT, testing is often first done to identify whether there is 17p duplication, which is then typically followed by CMT-specific gene panel sequencing (19).

The lipid-rich myelin sheath on the peripheral axon is formed by tight concentric wrapping of Schwann cell membranes. Many different gene mutations in CMT can result in poor myelin formation (dysmyelination) or loss (demyelination) on axons, which leads to slowed axon conduction and often some degree of axon degeneration (3). The different genes and mutations in CMT subtypes that lead to demyelination and dysmyelination are listed in **Table 1**. Molecular studies have confirmed the genetic origin of CMT-associated pathology in Schwann cells, and detailed descriptions of how particular gene mutations lead to various CMT subtypes can be found in other detailed reviews (20–22).

HEREDITARY MOTOR NEUROPATHY

HMN describes a spectrum of peripheral neuropathies with both clinical and genetic variation. As the name implies, impairment of motor control, most commonly in distal limbs, is the hallmark of these diseases. They are often caused by mutations in genes that encode ubiquitously expressed proteins; thus, deciphering how they have relatively specific roles in motor neuropathy is essential for understanding disease pathogenesis. Genes involved in protein folding that are mutated in HMN, such as *Heat Shock Protein B1* (*HSPB1*), *Heat Shock Protein B8* (*HSPB8*), and *Berardinelli-Seip Congenital Lipodystrophy 2* (*BSCL2*), when deregulated, form spheroids in axons and lead to axon degeneration. Other genes mutated in HMN have an important role in RNA metabolism. For example, *Immunoglobulin mu DNA binding protein 2* (*IGHMBP2*) is required for nonsense-mediated messenger RNA (mRNA) decay, *Senataxin* (*SETX*) is required for RNA transcriptome homeostasis, and *glycyl-tRNA synthetase* (*GARS*) couples glycine to its corresponding transfer ribonucleic acid (tRNA) during protein synthesis (21). More recently, mutations identified in *Copper-transporting ATPases* (*ATP7A* and *TRPV4*), which have an important role in copper metabolism and ionic concentration balance, have been identified (22, 23). HMN has also been classified into seven subtypes based on clinical signs and symptoms. HMN1 has a juvenile onset, whereas HMN2 has an adult onset. Both HMN1 and HMN2 patients suffer from muscular atrophy and distal weakness that arise as a consequence of motor neuron degeneration. Both heat shock proteins *HSPB1* and *HSPB8* are associated with HMN2 (23). HMN3 is a very rare disorder and gene mutations associated with this subtype are poorly defined. HMN4 is an autosomal recessive disorder that is caused by mutations in *PLEKHG5* (*pleckstrin homology domain-containing, family G member 5* gene). *PLEKHG5* activates the nuclear factor kappa B (NF-κB) signaling pathway in neurons and, when mutated, forms protein aggregates that lead to mislocalization and impaired NF-κB activation. HMN5, also known as Silver syndrome, is caused by mutations in the *BSCL2* gene, which encodes for Seipin protein. Mutations in *BSCL2* lead to spastic paraplegia with decreased Seipin expression, increased protein aggregation and increased ubiquitin-mediated Seipin degradation, and reduced cell viability (24). HMN6 is caused by mutations in *IGHMBP2*, and onset of the disease is typically detected three to four weeks after birth. The mechanism through which specific mutations in *IGHMBP2* lead to motor neuron death is still unknown. However, *IGHMBP2* is essential for RNA metabolism, which may have a role in disease pathogenesis. Mutation-driven functional studies using experimental model systems will continue to be essential to enhance mechanistic understanding of these diseases (25).

SMALL FIBER NEUROPATHY

Temperature and pain sensation are mediated primarily by myelinated and unmyelinated small-diameter axons. Approximately 50% of the patients suffering from SFN also suffer from impaired glucose tolerance and diabetes. The prevalence of SFN is approximately 52 people per 100,000. Although relatively poorly understood, mutations in voltage-dependent sodium channels are frequently found in patients with SFN. These channels are required to propagate action potentials in axons, and action potential abnormalities are observed in SFN patients. Specifically, three *Sodium Voltage-Gated Channel Alpha Subunit 9*, *10A*, and *11A* (*SCN9A*, *SCN10A*, and *SCN11A*) genes that encode for $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ sodium conduction channels have been closely studied and found to be mutated in SFN (26). Patients diagnosed with amyotrophic lateral sclerosis and Parkinson's disease have also been found to have SFN, but to date no definitive mechanistic correlations have been identified (27, 28). On the basis of pain perception and clinical symptoms, SFN is further characterized into small fiber sodium channel dysfunction (SFSCD), small fiber mediated painful neuropathy (SFMPN), and small fiber mediated widespread pain (SFMWP). SFSCD

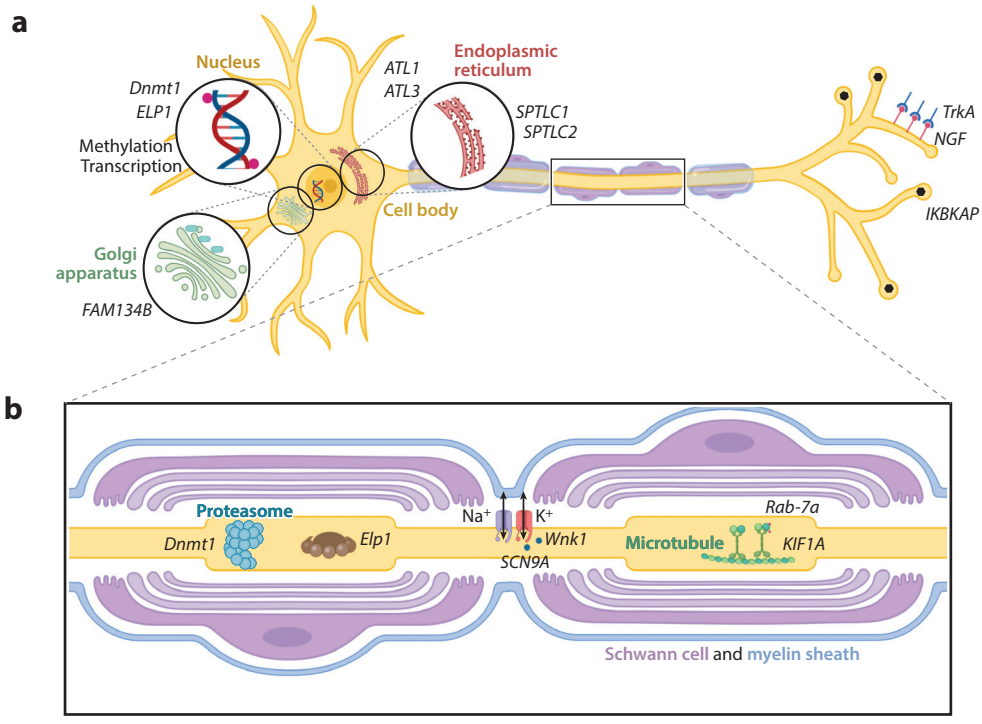

Figure 2

Gene mutations involved in HSAN pathogenesis lead to cellular dysfunction through a wide variety of mechanisms. (*a*) Many molecules are targeted by germ-line mutations in HSAN. They disrupt cell signaling in a wide variety of processes from growth factor signaling to epigenetic gene regulation to endoplasmic reticulum function. (*b*) Some genes also alter ion channel function required for dynamic membrane polarization (action potentials), growth factor signaling, and endosome intracellular trafficking. Abbreviations: Dnmt1, DNA methyltransferase 1; HSAN, hereditary sensory and autonomic neuropathy; NGF, nerve growth factor. Figure adapted from images created with BioRender.com.

patients suffer from peripheral pain in their lower extremities or hands due to blocked blood vessels, a condition known as erythromelalgia. They also experience paroxysmal pain, where nerve excitability is altered in the absence of nerve fiber density abnormalities (29).

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY

HSAN is a group of neurological disorders caused by mutations in genes associated with sensory and autonomic dysfunction. It was first classified by Dyck and Ohta into four subtypes: HSAN1–HSAN4 (30, 31). The initial classification was based on clinical phenotype, but gene mutations responsible for these diverse phenotypes were identified later (**Figure 2**). With the advancement of genetic testing, new subtypes such as HSAN5, HSAN6, and HSAN7 have been included. Major sensory dysfunction symptoms include depressed reflexes and inability to sense pain and temperature. Autonomic dysfunction can range from postural hypotension, gastroesophageal reflux, and cardiac arrhythmia to anhidrosis. Anatomically, loss of myelinated axons, loss of some dorsal root ganglion sensory neurons, and loss of sympathetic neurons have been described (32). Since the patients affected with HSAN4, HSAN5, HSAN6, and HSAN7 are very rare, less is known about the

pathophysiology of these subtypes (33, 34). In this review, we discuss more commonly recognized HSAN subtypes and the gene mutations and biology associated with them.

HSAN1 Subtype

Hereditary sensory and autonomic neuropathy type 1 (HSAN1) is caused by several missense mutations in the genes encoding subunits of serine palmitoyltransferase (SPT). SPT catalyzes the first step in sphingolipid biosynthesis, and the haloenzyme has three heteromeric subunits encoded by the *SPTLC1*, *SPTLC2*, and *SPTLC3* genes, with a majority of HSAN1 patients having mutations in *SPTLC1* or *SPTLC2*. The missense mutations lead to a shift in substrate preference for SPT from L-serine to L-alanine, which induces formation of neurotoxic deoxysphingolipids (dSLs) (35). The two most widely studied *SPTLC1* mutations are in exon 5 (C133Y and C133W) and exon 6 (V144D), and while all are involved in late-onset HSAN1 (33, 36), a novel missense mutation (S331F) has been associated with early onset disease (37). *SPTLC1* is required for de novo glucosyl ceramide synthesis, and the mutations seem to trigger neuronal apoptosis through the generation of dSLs (37). An interesting study using *SPTLC1*-mutant mice expressing the pathogenic C133W mutation showed clear differences when the mice were fed either a 10% L-alanine-enriched diet or a 10% L-serine-enriched diet. The L-alanine-enriched diet induced peripheral neuropathy and increased dSL levels. Interestingly, when the mutant mice were fed the L-serine-enriched diet, neuropathology was reduced, with recovery in axon diameter and myelination and with improved motor and sensory performance. On the basis of these promising animal data, a small pilot study was extended to 14 HSAN1 patients with the C133W mutation. The patients were supplemented with L-serine, which showed some transient disease improvement that was limited to the duration of dietary supplementation. Moreover, with L-serine supplementation, sphinganine and sphingosine levels increased, and deoxysphingosine and deoxymethylsphinganine levels decreased (38). A follow-up year-long study of L-serine supplementation in humans later showed slower disease progression, a change in plasma levels of canonical sphingolipids, and changes in epidermal nerve fiber density (39).

Three heterozygous mutations (V359M, G382V, and I504F) were the first to be identified in *SPTLC2* in patients with HSAN1. Similar to *SPTLC1*, the mutant proteins also cause the accumulation of neurotoxic sphingoid metabolite 1-deoxy-sphinganine (35). Several additional mutations in *SPTLC2* were identified (A182P) with similar HSAN1 phenotypes (40), and additional in vitro studies showed that expression of the *SPTLC2* mutants (G382V or I504F) resulted in 20-fold higher levels of 1-deoxy-sphinganine when compared with control cells (41). Interestingly, a new variant of *SPTLC2* (R183W) has been associated with late-onset HSAN1C, further emphasizing the role of *SPTLC2* mutations in HSAN1 pathophysiology. A novel *SPTLC2* mutation (N177D) was found to elevate canonical SPT activity and increased C20 sphingoid base production (42). Still other studies have shown that HSAN1-associated *SPTLC2* mutations dampen the protective role of $CD8^+$ T cells. This leads to suppression of protective immunity, making HSAN1 patients vulnerable to infections. In mouse models, murine T cell–specific ablation of *Sptlc2* resulted in impaired antiviral–T cell expansion and effector function, identifying a novel role of *SPTLC2* in external stimuli response and endoplasmic reticulum (ER) stress (43).

Additional genes mutated in HSAN1 have been identified. For example, *ATL1* codes for the large dynamin-related GTPase atlastin-1, and a missense mutation (N355K) and two dominant mutations (E66Q, V326W) have been identified. In cells, the mutant protein reduces the GTPase activity and disrupts the ER network and morphology (44). Nerve biopsy from mutant carrier patients showed severe, chronic axonal dystrophy with moderate demyelination and significant distal sensory abnormalities. *ATL1* mutations are also observed in spastic paraplegia (SPG3A), a

hereditary disorder characterized by progressive weakness and stiffness of the legs (44). How these mutations relate to different phenotypic expression in HSAN1 is not understood. A closely related gene, *ATL3*, is an ER-shaping GTPase that contains a membrane-binding reticulon domain that localizes to branch points of the ER. An autosomal dominant mutation (Y192C) within *ATL3* encodes for protein that fails to localize to ER branch points and disrupts its structure (45).

DNA methyltransferase 1 (Dnmt1) is an enzyme responsible for conversion of unmethylated DNA into hemimethylated DNA and has been implicated in a subtype of HSN known as HSN1E/HSAN1E. Mutations in *DNMT1* are known to cause HSAN1E, with the Y495C mutation identified in two American patients and one Japanese patient. A triple nucleotide change resulting in two amino acid substitutions (D490E and P491Y) was identified in a separate cohort. These mutations, when expressed in cells, lead to protein instability, impaired heterochromatin binding, global methylation, site-specific hypermethylation, and reduced methyltransferase activity (46). Additional mutations in exon 20 and 21 of *DNMT1* cause both HSN1E and autosomal dominant cerebellar ataxia, and, again, how the specific mutations lead to distinct phenotypes is not well understood. In HSN1E, the predominant clinical symptoms result from optic neuropathy, large- and small-diameter axon neuropathy, short sleep latencies, multiple sleep-onset REM periods, deafness, and narcolepsy (47). Another missense mutation (H569R) that was identified in exon 21 encodes the replication focus targeting sequence domain of *DNMT1* and is considered a mutation hot spot (48). Genome-wide analysis of DNA methylation in HSAN1E patients carrying the hot-spot mutation Y495C showed differential methylation in CpG islands of genes associated with mitochondrial function (49). Another domain of *DNMT1* that plays an important role in HSAN1 is the target-sequence domain. Mutations T481P, Y524D, and I531N on the target-sequence domain of the *DNMT1* gene have been identified in HSAN1 patients. Expression of these mutant proteins in cells resulted in mislocalization of *DNMT1* and its associated DNA replication foci proteins such as *Proliferating cell nuclear antigen* (*PCNA*) and *Ubiquitin Like With PHD And Ring Finger Domains 1* (*UHRF1*) to the cytoplasm. DNMT1 is then transported to aggresomes and directed to an early degradation through autophagy (50).

HSAN2 Subtype

Mutations in *Hereditary Sensory Neuropathy 2* (*HSN2*) are most commonly observed in HSAN2 patients (51). *HSN2* is an alternatively spliced exon of *WNK1* that is expressed in sympathetic neurons, dorsal root ganglion satellite cells, and Schwann cells. Most of the mutations in *HSN2* lead to autosomal recessive disease. The two mutations initially identified in *HSN2* exons are a heterozygous 1-bp deletion (639delA, R214fsX215) and a 2-bp deletion (1584_1585delAG, D531fsX547) (52, 53). These mutations have been confirmed in various populations such as Lebanese, French Canadian, Japanese, Korean, Mexican, and Belgian populations (54–57). Mice lacking the *HSN2* exon of *WNK1* showed reduced hypersensitivity to cold and mechanical stimuli after peripheral nerve injury. *Potassium-chloride transporter member 5* (*KCC2*) downstream of WNK1 is directly regulated by *HSN2* mutations. A reduction in KCC2 T906/T1007 phosphorylation and increase in KCC2-channel-mediated cellular chloride extrusion were also observed in this transgenic mouse. Overall, WNK1 inhibition leads to hyperpolarization and abnormal GABAergic activity in sensory neurons (58). A separate study in zebrafish showed that *WNK1/HSN2* isoform knockdown leads to impairment of the peripheral lateral line system (similar to the peripheral nervous system in mammals) and interacts with KCC2 in the peripheral lateral line. Interaction between WNK1 and KCC2 is mediated by C568 on KCC2. A mutant zebrafish expressing KCC2-C568A (inactivating mutation of KCC2) lacks interaction between WNK1/HSN2 and KCC2. This study also showed that WNK1/HSN2 isoform can regulate transcription of KCC2, independent of its

activity (59). All these results collectively emphasize the role of WNK1 in maintaining ionic balance in sensory neurons.

The *FAM134B* gene, also known as *RETREG1*, encodes a *cis*-Golgi protein that has been associated with HSAN2B. Mild dysautonomia along with ulcerations in feet and hands, osteomyelitis, and osteonecrosis has been observed in patients with HSAN2B. The first mutation identified in *FAM134B* was a loss-of-function nonsense mutation (60, 61). In another study, an HSAN2 patient carrying the *FAM134B* mutation showed diverse pathological symptoms such as axonal, sensory, and large fiber neuropathy. Sural nerve biopsy showed reduced myelinated axons and regenerating axon clusters (62). In an Eastern European cohort, affected sisters carrying mutations for *FAM134B* also showed symptoms of progressive distal sensory loss, recurrent ulceration of hands and feet, soft tissue infections, and osteomyelitis (63). A whole-exome sequencing–based gene analysis study identified a novel nonsense mutation (c.926C>G; p.S309*), and two patients with the mutation who were unrelated showed early onset mild spasticity and lower limb weakness. *FAM134B* has a significant role in selective autophagy of ER receptors, as shown by expression of *FAM134B* mutants leading to disruption of selective autophagy of ER proteins and death of sensory and autonomic neurons by incompletely understood mechanisms (64). Calcium/calmodulin-dependent protein kinase type II beta chain (CAMK2B) can activate *FAM134B* through direct phosphorylation. Activation of *FAM134B* promotes its oligomerization through reticulon domains in the protein, which also promotes ER membrane fragmentation and ER-specific autophagy. In some HSAN2 patients, the presence of a *FAM134B* G216R mutation enhances its oligomerization and accelerates the rate of ER autophagy, ultimately leading to death of sensory neurons (65).

Mutations in the *SCN9A* gene cause a subtype of HSAN2 known as HSAN2D. Voltage-gated sodium channels are required in development and for propagation of action potentials in neurons and muscle cells. One of the symptoms specifically observed in HSAN2D patients is insensitivity to pain. Two loss-of-function mutations identified in *SCN9A* that are associated with HSAN2 are a nonconservative missense mutation (C1719R) in exon 26 and a 1-bp splice donor deletion in intron 17. The mutation leads to insensitivity to both pain and mechanical nociception. Detailed investigations showed loss of function of $Na_v1.7$, resulting in lower sodium activation currents in axons (66). Another study in a Japanese patient cohort identified a homozygous mutation in exon 22 (c.3993delGinsTT) of *SCN9A*. The clinical phenotype included loss of pain and temperature sensation, autonomic nervous system dysfunction, hearing loss, and hyposmia with loss of large myelinated axons (67).

The *KIF1A* gene has also been identified to be mutated in some HSAN2 patients. It encodes a motor protein required for anterograde transport of synaptic-vesicle precursors along axons (68). Homozygosity mapping and yeast two-hybrid-based studies revealed mutations in *KIF1A* in HSAN2 patients. All patients showed mutations in an alternatively spliced exon, predominantly in a heterozygous state. The binding assay further showed direct interaction between KIF1A and WNK1/HSN2 proteins. Colocalization of KIF1A proteins and WNK1/HSN2 was observed along axons of DRG sensory neurons. The patients developed sensory loss, severe peripheral appendage mutilation, and distal muscle weakness. Localization of KIF1A at the axonal tip of neurons further emphasizes its role in cargo transport in axons. A 1-bp deletion in the alternatively spliced exon 25b and another 1-bp insertion in exon 46 of *KIF1A* lead to frameshift mutation in these patients. These mutations are located downstream of Forkhead-associated domains of *KIF1A*. This domain binds to the C-terminal lipid binding pleckstrin domain and is essential in vesicular transport (69). Apart from HSAN2, *KIF1A* mutations have been associated with hereditary spastic paraplegia (HSP), another inherited neurological disorder that features symptoms similar to those seen in HSAN patients. In an HSP patient cohort, next-generation sequencing of the spastic paraplegia 30 (SPG30) chromosomal region on chromosome 2q37.3 revealed two autosomal

recessive mutations on the *KIF1A* gene (70). One hypomorphic mutation (R561H) in *KIF1A* was identified in both HSP and HSAN patients. Expression of the R561H mutated protein restricts neuromuscular junction growth, synaptic vesicle formation, and postsynaptic domain apposition. Interaction between KIF1A and Bruchpilot protein is essential for these functions, and the R561H mutation impairs its interaction with Bruchpilot (71). Exome analysis–based studies are identifying novel mutations in *KIF1A* (such as A85D), but their role in neuropathy pathogenesis is yet to be discovered (72).

HSAN3 Subtype

HSAN3, also known as familial dysautonomia (FD) or Riley-Day syndrome, is associated with severe sensory and variable autonomic dysfunction (73). Most of the patients have Ashkenazi Jewish heritage, and the ethnic bias arises due to a founder effect, with >99.5% of disease alleles sharing a common ancestral haplotype. Progressive loss of small-diameter sensory and autonomic neurons in FD leads to diverse symptoms such as gastrointestinal dysfunction, abnormal respiratory responses to hypoxic and hypercarbic states, scoliosis, gastroesophageal reflux, vomiting crises, lack of overflow tears, inappropriate sweating, and postural hypotension. FD is a fatal disease with very little effective therapy available, and the average age of death is 24 years. The loss of sympathetic and nociceptive sensory neurons occurs during development, which significantly decreases the numbers of neurons and reduces the size of sympathetic and dorsal root ganglia (74–77).

In 2001, DNA analysis of FD patients identified the founder mutation in the *ELP1* gene (c.2204 + 6T > C). The founder mutation accounts for >99.5% of the patients with disease and consists of a single T-to-C nucleotide change in base pair 6 of intron 20. Detailed studies revealed that the mutation causes skipping of exon 20 during splicing due to weakened intron-exon boundary recognition. Mis-splicing occurs more frequently in some cells, and it introduces a nonsense mutation leading to truncation of the translated ELP1 protein, which is highly unstable and rapidly degraded. For example, in lymphoblastoid cells from FD patients, properly spliced mRNA is generated; however, in neurons, exon 20 is preferentially skipped, leading to loss of the ELP1 protein preferentially in sympathetic neurons and some sensory neurons, which leads to their death (78). Two additional very rare mutations in *ELP1* have been identified: one that impairs phosphorylation of the ELP1 protein and another that introduces a proline to leucine missense mutation in exon 26 of Elp1 (79).

The ELP1 protein is a scaffold protein of the six-subunit halo elongator complex with no known catalytic activity. It is highly conserved and expressed in all eukaryotic cells (80–82). The elongator protein complex has been shown to bind to RNA polymerase II and orchestrate transcriptional elongation, which requires histone acetylation. ELP3 is the major subunit of the elongator complex, which functions as a histone acetyltransferase and mediates histone modification (83). Another important role mediated by the elongator complex is to synthesize 5-methoxycarbonylmethyl and 5-carbamoylmethyl groups present on uridines at the wobble position in tRNA. This is a necessary step in translation of some proteins (84). Cytosolic ELP1 also mediates actin cytoskeleton acetylation, organization, and cell migration. Studies in ELP1 conditional knockout (KO) mice from our laboratory showed that ELP1 has a neuron-autonomous role in target tissue innervation and in maintaining innervation homeostasis (85). More recently, work from our laboratory showed that cytosolic ELP1 plays an essential role in retrograde nerve growth factor (NGF) signaling. For example, ELP1 protein binds to TRKA receptors on axons in target tissues, where it regulates TRKA phosphorylation by inhibiting SHP1 phosphatase. In HSAN3, where ELP1 protein is lacking, elevated SHP1 phosphatase activity inhibits TRKA phosphorylation, thereby impairing NGF signaling and its downstream transcriptional mediators (**Figure 3**).

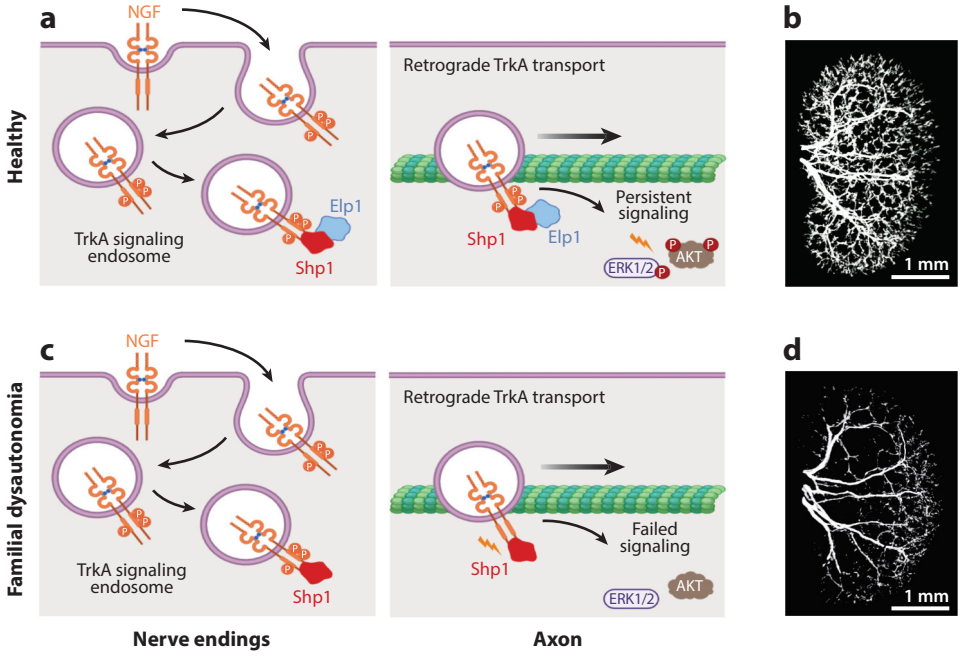

Figure 3

Impaired NGF signaling in HSAN3 (also known as familial dysautonomia): (*a*) Retrograde NGF signaling involves NGF ligation to the TrkA receptor at axon terminals, receptor internalization and phosphorylation, and retrograde transport of the phosphorylated NGF/TrkA receptor complex to the cell body to engage transcriptional pathways involved in neuron differentiation and survival. Elp1, the protein lost in HSAN3, binds to the NGF/TrkA receptor complex and regulates retrograde signaling by inhibiting Shp1 phosphatase activity. (*b*) Normal retrograde NGF signaling in sympathetic neurons that have normal levels of Elp1 leads to robust target tissue innervation. Tyrosine hydroxylase staining in optically cleared kidney from normal mice is shown here. (*c*) In the absence of Elp1 in HSAN3, Shp1 phosphatase is precociously activated, leading to premature TrkA dephosphorylation, retrograde signaling failure, neuron death, and target tissue innervation abnormalities. (*d*) In the absence of Elp1 in HSAN3, there are profound sympathetic neuron death and target tissue innervation abnormalities. Tyrosine hydroxylases staining in optically cleared kidney from a mouse lacking Elp1 in sympathetic neurons is shown here. Sympathetic innervation to the kidney is markedly reduced compared with kidney from a normal mouse shown in panel *b*. Abbreviations: ERK, extracellular signal-regulated kinase; NGF, nerve growth factor. Panels *a* and *c* adapted from images created with BioRender.com. Entire figure adapted with permission from Li et al. 2020 (86).

Defective retrograde NGF signaling results in sympathetic and sensory neuron loss that explains the developmental neurological deficits in patients with FD (86).

Patients with FD have a variety of physiologic abnormalities. Abnormalities in cardiovascular function are common and due primarily to defective glossopharyngeal and vagus nerve function. Additionally, inability to distinguish smell and progressive optic atrophy are observed in these patients (87). Another common observation is a decrease in the number of nociceptive C-fiber afferents, which results in lack of pain sensation and development of neuropathic joints. The proprioceptive gait ataxia observed in FD patients arises from lack of sensory signaling from skeletal muscle stretch receptors (88, 89). Although many sensory and sympathetic neurons are lost early in development, there is evidence of continued postnatal neuron degeneration. If accurate, this could indicate that rational therapy to halt or slow disease progression could be devised to treat patients with FD to ameliorate their suffering.

HSAN4, HSAN5, and HSAN6

HSAN4 is a rare autosomal recessive disease caused by mutations in the *NTRK1/TrkA* gene (90). *NTRK1* encodes the tropomyosin kinase receptor type 1. Sympathetic neurons and some sensory neurons require signaling through NTRK1 in response to their cognate ligand NGF for survival. Mutations in HSAN4 prevent NTRK1 activation and cause loss of NGF-dependent sympathetic and sensory (nociceptive) neurons. HSAN4 patients suffer from inability to sense temperature, pain, and anhidrosis (inability to sweat). Loss of myelinated and nonmyelinated small-diameter axons is observed following nerve biopsy, and skin biopsy shows loss of innervation in sweat glands, which leads to anhidrosis (91, 92). HSAN5 is an extremely rare genetic disorder caused by mutations in the *NGFβ* gene. The NGFβ protein is the ligand for the NTRK1/TrkA tyrosine kinase receptor protein. Mutations in *NGFβ* reduce levels of the NGFβ protein and prevent the NTRK1 activation that is required for the survival of sympathetic and some sensory neurons. HSAN5 patients also suffer from loss of pain and temperature sensation as with HSAN4 (92). HSAN6 is a recessive genetic disorder that is caused by mutations in the *DYSTONIN* (*DST*) gene. Loss of neuronal isoform dystonin-a2 is frequently observed in HSAN6 patients (93). The patients can have mild symptoms associated with skin blisters or headaches, or they can have severe symptoms including motor and intellectual disabilities. Depending on the mutated isoform or single-point mutations of *DYSTONIN*, the symptoms of the disease can be variable (94).

CHEMOTHERAPY IN THE CONTEXT OF HEREDITARY NEUROPATHY

Cancer patients often suffer from peripheral neuropathies because of neurotoxic chemotherapeutic agents used in their treatment. Chemotherapy-induced neuropathy (CIPN) is a dose-limiting side effect of cancer treatment, and with the advancement of cancer treatment and patient survival, the incidence of CIPN has increased in recent years (95). Chemotherapeutic neurotoxic agents, such as platinum, vinca alkaloids, taxanes, epothilones, thalidomide, and bortezomib, are established to cause CIPN. More than half of patients on chemotherapy develop peripheral neuropathy, and they often suffer from chemotherapy-induced pain and other sensory abnormalities. These agents affect the neurons through different mechanisms by causing microtubular damage/instability, mitochondrial dysfunction, neuronal apoptosis, impaired axonal transmission, and/or Ca^{2+} deregulation (96–98).

Recent studies have shown that CIPN is more severe in cancer patients who are already suffering from a hereditary neuropathy such as CMT. Some of the chemotherapeutic agents such as Vincristine have severe toxicity on neurons, and many cancer patients are treated with agents such as Vincristine before they have been tested for an underlying inherited neuropathy. As a result, some patients develop severe neuropathy, and, in rare cases, CIPN accelerates the neuropathy symptoms. This has become a serious challenge in cancer treatment, and new treatment methods are being devised (99). A majority of cancer patients with CMT-associated mutations had acute lymphocytic leukemia, and most were treated with CIPN-inducers, such as Vincristine followed by paclitaxel and cisplatin, and then later showed positive screening for CMT1 or CMT1X subtype (100, 101). A next-generation sequencing study on allelic variability of CMT genes in CIPN patients treated with paclitaxel showed mutations in two CMT-associated genes, *PRX* and *ARHGEF10*. *PRX* is a recessive CMT gene with a loss of function affecting myelin stabilization (102), and ARHGEF10 is essential for actin cytoskeleton maintenance, microtubule dynamics, cell migration, and axonal growth/guidance (103). Three single-nucleotide variants of *ARHGEF10* were tested (rs9657362, rs2294039, and rs17683288), and, of these, rs9657362 had the strongest effect with the highest susceptibility to polyneuropathy or CIPN. The mechanism behind these

observations is not yet known, but new studies are finding novel mutations in genes associated with CIPN and inherited neuropathies (104, 105). In one interesting study, a 55-year-old woman developed CMT1A-associated neurological symptoms after being treated with docetaxel in combination with anti-HER2 antibodies for metastatic breast cancer. Although her family had a history of hereditary neuropathy, she did not show symptoms of CMT1A until after she was treated with docetaxel (106). This further emphasizes the importance of testing for HPN before administering chemotherapeutic agents for cancer treatment and choosing agents that may have a lower chance of exacerbating existing neuropathy and inducing severe CIPN (107).

Taxane-induced peripheral neuropathy (TIPN) is a serious condition reported in cancer survivors. African Americans specifically have higher susceptibility to TIPN toxicity, and paclitaxel-based cancer treatment appears to have the most risk for causing TIPN. Whole-exome sequencing studies identified a mutation in the *SBF2* gene associated with increased risk of developing TIPN. SBF2 is a member of the myotubularin-related proteins and, when mutated, leads to CMT. This mutation has a recessive pattern of inheritance, and patients suffer from axon degeneration and myelin abnormalities (108). A separate genome-wide association study in approximately 1,000 patients treated with paclitaxel showed a single-nucleotide polymorphism in the *FDG4* gene (rs10771973) that appears to increase susceptibility to TIPN. Accordingly, point mutations in *FDG4* have been identified to cause CMT4H (109, 110). Although most of the CIPN- and TIPN-based studies have been limited to CMT hereditary neuropathy, there appears to be some evidence that chemotherapeutic agents can exacerbate the symptoms of HSAN1. For example, paclitaxel treatment in breast cancer patients elevates the level of neurotoxic 1-dSLs, which is an important driver of HSAN1 (111).

These studies clearly show the importance of screening for neuropathy mutations in cancer patients before subjecting them to neurotoxic chemotherapeutic agents. Newer treatment approaches are taking hereditary neuropathies into consideration and successfully treating cancer patients without triggering CIPN (112). With the advent of affordable sequencing technology and sophisticated genetic screening, it is possible to devise safer approaches to treat cancer patients and improve long-term outcome and morbidity.

TARGETED EXPERIMENTAL THERAPIES IN INHERITED NEUROPATHY

Treatment currently available for HPN patients is limited to symptomatic relief, and most of these therapies are directed toward CMT patients. Over the last couple of years, some therapies have focused on reducing expression of mutant proteins with known dominant function. For example, a combination therapy using a CMT1A transgenic mouse was devised using baclofen, sorbitol, and naltrexone to reduce the PMP22 mRNA expression. The treated mice showed improved myelination and Schwann cell differentiation. Additionally, short-term drug administration during development had a long-term effect on reducing symptoms (113, 114). On the basis of the success of these preclinical studies, a clinical trial (ClinicalTrials.gov number NCT03023540) for treating CMT1A patients is in phase III testing (115).

Antisense oligonucleotide (ASO)–based therapy has also shown significant promise in treating genetic disorders. It is effective in reducing expression of specific isoforms of a gene and appears safe for use in humans. ASOs bind to the target mRNA via Watson-Crick base pairing and degrade the targeted mRNA by an RNAaseH-dependent mechanism. Recent clinical successes of nusinersen and inotersen for spinal muscular atrophy and familial amyloid polyneuropathy, respectively (ClinicalTrials.gov numbers NCT02292537 and NCT01737398), have provided hope that successful ASO-based therapies may be developed for HPN patients. An ASO-based therapy in two

different transgenic mouse models of CMT1A has been developed. The ASOs targeted PMP22 mRNA, which restored myelination, nerve conduction velocity, and action potentials (116). On the basis of these results, a clinical trial targeting PMP22 mRNA with ASO therapy could be promising in CMT1A patients. A similar therapeutic approach that is being considered to treat genetic disorders in humans is the use of allele-specific small interfering RNA (siRNA). siRNA targeting PMP22 in a CMT1A mouse model showed significant recovery with improved motor function, muscle volume, nerve conduction velocity, and Schwann cell survival (117). Selective suppression of mutant alleles in CMT with siRNA could be a potential therapeutic approach that needs to be evaluated further in humans.

In the last decade, the clinical success of gene therapy–based drugs has demonstrated their potential for treating genetic disorders (118). The recent approval of Luxturna® to treat inherited retinal dystrophy further supports the possibility of using gene therapy for other genetic disorders. In inherited retinal dystrophy, adeno-associated virus 2–mediated gene replacement corrects the retinal pigment epithelium-specific 65 kDa protein (RPE65) mutation (ClinicalTrials.gov number NCT00999609) (119). Several CMT-associated genes have also been targeted by gene therapy. One of the genes that was initially targeted with adenovirus in a CMT1A transgenic mouse model (Tr-J) was *NEUROTROPHIN-3* (*NT-3*). NT-3 is expressed by Schwann cells, which stimulate neurite outgrowth and myelination. Tr-J mice, when treated with NT-3 peptide, showed improved axonal regeneration and associated myelination. A pilot study on CMT1A human patients with recombinant NT-3 showed improved axonal regeneration and enhanced myelination (120). In the gene therapy study with NT-3, Tr-J mice were injected with recombinant adeno-associated virus type 1 expressing NT-3 into muscle fibers, and this injection produced some recovery based on histopathological and electrophysiological measures (121). A second gene that has been targeted through gene therapy is *GJB1*. Mutations in *GJB1* lead to the X-linked subtype of CMT, CMT1X. GJB1 encodes the gap junction protein CONNEXIN32 (Cx32). Cx32 KO mice have been used to study CMT1X due to the phenotypical resemblance between these mice and CMT1X-mutant mice. The study was conducted by injecting a lentiviral vector carrying the *GJB1* gene expressed by the Schwann cell–specific MPZ promoter into the sciatic nerve of Cx32 KO mice. A single viral injection produced Cx32 expression and proper localization of Cx32 protein, and it inhibited demyelination (122). In another study, GJB1-expressing adeno-associated virus was intrathecally delivered in Cx32 KO mice expressing various CMT1X mutations (R75W, N175D, and T55I). In R75W mutant–expressing Cx32 KO mice, the results were promising, but in the other two mutant-expressing Cx32 KO mice, there was no effect. Although this study shows the therapeutic potential of gene therapy to treat HPNs such as CMT1X, it also demonstrates the necessity of designing treatments in patients based on specific mutations (123).

CMT4C is the third CMT subtype where gene therapy–based approaches have been developed using transgenic animal models. CMT4C is caused primarily by loss-of-function mutations in the *SH3TC2* gene. Demyelination, slowed nerve conduction velocity, and disturbed node of Ranvier architecture in myelin are common features of the disease, which are recapitulated in SH3TC2 KO mice. A gene-replacement strategy was used to deliver a viral vector intrathecally to express SH3TC2 in SH3TC2 KO mice. The virus was delivered at 3 weeks of age, and the mice were analyzed for morphological improvements at 11 weeks of age. Partial improvements were observed in myelination and myelin morphology. Potentially, administration of the treatment at a more optimal developmental time point may lead to long-term and more effective therapy for CMT4C (124).

There are a couple of alternative approaches that have been examined by other groups to find a therapeutic intervention in CMT1B, CMT2A, CMT2D, and CMT2F. For example, stress-induced *protein phosphatase 1 regulatory subunit 15A (PPP1R15A)* encodes the growth arrest and

DNA damage-inducible protein GADD34. In CMT1B, demyelination is attributed to ER stress mediated by a mutation in *MPZ* (deletion of serine 63). This *MPZ* mutant causes PPP1R15A-mediated activation of ER stress, which leads to accumulation of misfolded proteins in the ER, resulting in demyelination (125, 126). SEPHIN1, a small-molecule inhibitor of *PPP1R15A*, was used to reduce ER stress, which resulted in maintained myelin thickness around axons and restored myelination without any noticeable side effects (127). SEPHIN1 was also able to rescue the pathological phenotype in an amyotrophic lateral sclerosis mouse model, where protein misfolding is the major cause behind the associated pathology (127). This therapeutic approach of inhibiting phosphatase activity with SEPHIN1 could potentially be administered to a broad range of diseases caused by accumulation of misfolded proteins.

Another approach to treating CMT has been to target MITOFUSINS (MFN), which promote fusion-mediated mitochondrial exchange and subcellular trafficking. Mutations in *MFN2* cause CMT2A. Transgenic mice expressing the CMT2A causative mutant MFN2 (T105M) show phenotypical impairments similar to those seen in CMT2A patients. When the mutant mice were treated with a selective MITOFUSIN agonist, mitochondrial dysmorphic changes significantly reversed and mitochondrial mobility was returned to normal in neurons. Although this study focused on therapeutic intervention in CMT2A, the approach can be tested in other diseases where mitochondrial trafficking and dynamics are impaired (128). Histone deacetylase 6 (HDAC6) inhibitors in mouse models of CMT2F and CMT2D have also been used. The inhibitors increased the acetylation of tubulin, thereby maintaining axonal transport and preventing axonal degeneration. Mutations in *HSPB1*, such as S135F, can lead to both CMT2F and distal HMN2B. Use of HDAC6 inhibitors in HSPB1-mutant mice blocked deacetylation of tubulin, thereby rescuing neurofilament network abnormalities (129). The investigators expanded this therapeutic approach to another mouse model of CMT2D using a transgenic mouse that carries mutation C201R in the *GARS* gene, which leads to motor and sensory axonal degeneration. HDAC6 inhibition with a selective inhibitor, tubastatin A, significantly rescued target tissue innervation, axonal diameter, and axonal degeneration. Additionally, increase in α-tubulin acetylation was observed after HDAC6 inhibition, which was otherwise low in *GARS*-mutant mice (130, 131). Both studies suggest that some of the subtypes of CMT might share a common mechanism of pathogenesis that could be targeted using HDAC inhibition to prevent tubulin deacetylation and axonal degeneration.

As reviewed here, a variety of approaches have been used to treat HPN, and most are focused on CMT therapy. Some approaches have used selective antagonist or agonist drug therapy, some have used diet to manipulate metabolism, and still others have used viral-mediated ASO or siRNA strategies to manipulate relevant protein expression. Additional therapies to treat FD (HSAN3) have targeted the intronic splice mutation in the *ELP1* gene. This mutation leads to partial skipping of exon 20, resulting in tissue-specific loss of IKAP/ELP1 protein. Kinetin (6-furfurylaminopurine) has been found to modulate splicing in cells from patients with FD, thereby rescuing the loss of ELP1 protein in neurons. Kinetin was administered as a drug in a pilot study to eight FD patients, and increased ELP1 protein levels were observed in leukocytes in six of eight patients. Since patients were administered Kinetin for only 28 days, long-term efficacy was not evaluated, but safety and tolerability were favorable (132). In the FD mouse model (TgFD9;Ikbkap$^{\Delta 20/flox}$) that emulates the Elp1 mutation and the pathophysiology of disease, Kinetin administration starting at birth prevented loss of Elp1 protein and rescued scoliosis, which is characteristic of the disease. Additionally, it prevented loss of proprioceptive peripheral neurons and maintained sensory-motor coordination (133). Collectively, all the above studies emphasize the potential of Kinetin as a therapeutic drug in FD patients.

CONCLUSIONS AND PERSPECTIVES

Hereditary neuropathies give rise to a broad range of symptoms, and new genes associated with the diseases are frequently being discovered. Advancements in genomic testing and translational studies have shed new light into the mechanisms of disease, but there is still much work to be done to cure these disorders. The shift from relying on symptoms alone for therapeutic intervention to identifying the gene mutations leading to disease pathogenesis is making it possible to formulate rational gene therapies to restore function. Since many genes lead to disease with overlapping phenotypes, as more is learned about gene function, it may be possible to find common pathways among the varying diseases that can be targeted for therapy. The rise in cancer patients treated with effective new cytotoxic agents underscores the need to establish new protocols for early detection of mutations that may lead to exacerbation of symptoms following chemotherapy. Many efforts are underway to prevent chemotherapy-triggered neuropathy-based side effects, but with the wide variation in disease gene mutations, improved screening protocols will be beneficial. In the last decade, there has been tremendous progress in correcting the underlying gene mutations that give rise to these devastating disorders. New therapies using stem cell–based and gene-editing technologies hold promise for eventual cures where single-gene mutations underlie disease pathogenesis.

DISCLOSURE STATEMENT

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