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Recent advances in the genetic neuropathies

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Abstract

Purpose of review—Charcot-Marie-Tooth disease (CMT) is one of the commonest inherited neuromuscular diseases with a population prevalence of 1 in 2500. This review will cover recent advances in the genetics and pathomechanisms of CMT and how these are leading to the development of rational therapies.

Recent findings—Pathomechanistic and therapeutic target advances in CMT include the identification of the ErbB receptor signalling pathway as a therapeutic target in CMT1A and pharmacological modification of the unfolded protein response in CMT1B. In CMT2D, due to mutations in GARS, VEGF-mediated stimulation of the Nrp1 receptor has been identified as a therapeutic target. Preclinical advances have been accompanied by the publication of large natural history cohorts and the identification of a sensitive biomarker of disease (muscle MRI) that is able to detect disease progression in CMT1A over one year.

Summary—Advances in next generation sequencing technology, cell biology and animal models of CMT are paving the way for rational treatments. The combination of robust natural history data and the identification of sensitive biomarkers mean that we are now entering an exciting therapeutic era in the field of the genetic neuropathies.

Keywords

Charcot-Marie-Tooth disease; hereditary motor and sensory neuropathy; hereditary motor neuropathy; hereditary sensory neuropathy; treatment

Introduction

Genetic neuropathies are a heterogeneous group of diseases characterised by degeneration of peripheral nerves [1]. This review will focus on genetic diseases in which peripheral neuropathy is the sole or major feature of the disease as opposed to those in which neuropathy is only one aspect of a more complex multisystem disease, e.g. Friedreich's ataxia. The most common form of genetic neuropathy is Charcot-Marie-Tooth disease (CMT), also referred to as hereditary motor and sensory neuropathy (HMSN), in which both motor and sensory peripheral nerves are affected and which is divided into demyelinating

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Conflicts of interest

None

(CMT1, upper limb motor conduction velocity (MCV) < 38 m/s) and axonal forms (CMT2, MCV > 38 m/s). The terms Hereditary Sensory Neuropathy (HSN) and Hereditary Motor Neuropathy (HMN) refer to forms of CMT2 in which the burden of disease falls on sensory and motor nerves, respectively. This review will provide an update on the genetic causes and therapeutic advances in CMT.

Advances in the genetic diagnosis of CMT

Genetic diagnosis in CMT has evolved rapidly in recent years with the incorporation of next generation sequencing (NGS) into routine diagnostic practice [2]. NGS technology allows multiple parallel sequencing of either targeted genes (panels), only the protein coding sequences (whole exome sequencing (WES)) or the whole genome (whole genome sequencing (WGS)). A common conundrum is how best to employ NGS for routine clinical practice. In an attempt to answer this question for WES, Lupski et al. performed WES on 40 individuals with CMT and reported a diagnostic rate of 45%. Several of the mutations, however, were novel and their pathogenicity remains unclear [3*].

Disease-specific panels restricted to known CMT genes are currently the preferred method for employing NGS in clinical practice [4,5]. Whilst some groups have proposed disease-specific panels based on the phenotype (i.e. CMT1 and CMT2) [2], others have proposed a broader CMT panel incorporating all genes [4,5]. In two separate studies employing either a 56 or 70 gene CMT panel in patients negative for the common CMT mutations, diagnostic rates of 12 and 27% were reported [4,5]. To date, diagnostic algorithms for CMT1 have proposed using multiplex ligation probe amplification (MLPA) for the detection of duplications and deletions of the short arm of chromosome 17 before proceeding to disease-specific panels or WES [2]. In a small sample of three patients with CMT1A, Jo and colleagues were able to identify both duplications and deletions in chromosome 17p using WES suggesting that NGS may eventually supersede the need for MLPA for diagnosing CMT1A [6].

Recently discovered CMT genes

NGS technology continues to lead to the discovery of new CMT genes (Table 1). In addition, there has been an increase in the number of mutations in disease genes associated with complex multisystem diseases in which neuropathy is the initial manifestation of the disease.

New disease genes

It is worth remembering when describing new and rare CMT genes that more than half of all CMT patients have one of five genetic mutations (PMP22 duplication 39.5%, PMP22 point mutation 1.4%, GJB1 10.8%, MFN2 2.8% and MPZ 3.1%). If one considers only autosomal dominant demyelinating CMT, almost all patients have mutations in one of the following genes; *GJB1*, *PMP22*, *MPZ*, *EGR2*, *LITAF* or *NEFL* [7,8]. Mutations in *PMP2* can now be added to this list following the identification of three mutations in four families with autosomal dominant CMT1 that was indistinguishable from CMT1A [3,9,10]. *PMP2* accounts for 5% of peripheral myelin proteins and both knockdown and overexpression of

wild type PMP2 cause nerve conduction velocity slowing suggesting that like PMP22, PMP2 gene dosage is critical to peripheral nerve conduction [3,9,11].

Unlike CMT1, the number of disease genes for CMT2 is large, many of which are rare and affect only a handful of families (Table 1). Recent novel genes of particular interest as they are reported to be mutated in multiple families are *MORC2* and *MME*. Autosomal dominant mutations in *MORC2* have been reported in eight families with severe axonal CMT [12*, 13*]. Disease onset was in the first decade and followed a progressive course with many patients requiring a wheelchair by middle age. Additional features included early proximal and asymmetric limb weakness, deafness and developmental delay.

Autosomal recessive mutations in the gene *MME* have been described as the commonest cause of autosomal recessive CMT2 in Japan, having been identified in 10 Japanese families with CMT2 with disease onset in the fifth decade [14*].

From a pathogenesis perspective, the discovery of frame-shift mutations in the final exon of *NEFH* in two autosomal dominant CMT2 families, while rare, is of interest as it has identified a novel pathomechanism for CMT2 in which loss of the terminating codon results in the translation of an extra 40 amino acid amyloidogenic motif resulting in protein aggregation [15**].

Further additions to the genetic milieu of CMT include mutations in the X-linked gene, *DRP2*, in one patient with intermediate CMT [16] and an autosomal dominant missense mutations in *DGAT2*, in two related patients with CMT2 presenting in the first decade with sensory ataxia and tremor [17].

Extending the phenotypic spectrum of genes previously described in complex diseases

With advances in NGS technology, an increasing number of mutations are being identified in patients with CMT in genes normally associated with complex childhood onset diseases. Recent additions to this list include mutations in *NAGLU*, *ALS5/SPG11/KIAA8140* and *VRK1*. Autosomal recessive mutations in *NAGLU* cause the severe childhood lysosomal storage disease, mucopolysaccharidosis type III, however, a heterozygous *NAGLU* mutation has now been described in a large Canadian pedigree with painful axonal sensory neuropathy [18]. Recessive mutations in *ALS5/SPG11/KIAA8140* typically cause recessive hereditary spastic paraplegia with thin corpus callosum and axonal neuropathy, but can now also cause recessive CMT2 [19]. Finally, recessive mutations in *VRK1*, a rare cause of the usually fatal condition ponto-cerebellar hypoplasia and spinal muscular atrophy may also cause HMN [20].

Therapeutic advances in CMT

Although there are currently no medical treatments for CMT, advances in our understanding of the pathomechanisms of CMT have led to the identification of therapeutic targets with trials of therapies in animal models of both CMT1 and CMT2 (Figure 1). There has also been a gene replacement trial in an animal model of CMTX1.

Therapeutic advances in CMT1

CMT1A is a slowly progressive, chronic disease. Identifying therapies for CMT1A that may need to be administered throughout life and have minimal side effects is a challenge. Initial efforts to treat CMT1A have focused on strategies that reduce PMP22 expression such as with vitamin C and progesterone antagonists. Unfortunately, these treatments have either been unsuitable for clinical trials (progesterone antagonists) or ineffective in clinical trials (vitamin C) [21,22]. A study of eight CMT1A patients demonstrated a mild positive effect of neurotrophin-3 (NT-3) on the sensory and reflex scores of the neuropathy impairment score [23], an effect replicated in a mouse model of CMT1A in which there was adeno-associated virus-mediated muscle overexpression of NT-3 [24].

The recent report by Fledrich et al. that treatment of CMT1A rats with neuregulin 1 (NRG1) between days 6 and 8 prevents axonal loss at days 18 and 90 is particularly encouraging, and suggests that if treated early enough, patients with CMT1A may not require life-long therapy [25**]. By examining the RNA profile of sciatic nerves from wild type and CMT1A rats, the authors demonstrated an increase in the expression of Schwann cell de-differentiation markers in CMT1A associated with decreased activation of the p13K-AKT signalling pathway and increased activation of MRKK/ERK signalling (NRG1 is an activator of P13K-AKT). Unfortunately, NRG1 is also an ErbB/HER receptor agonist (upregulated in several tumours) and may therefore have neoplastic potential. This is of particular concern if one intends to treat children for a disease that has no effect on lifespan [26]. ErbB receptor signalling, however appears to be of fundamental importance for many subtypes of CMT1 and is a pathway that can be targeted therapeutically [27*].

In mouse models of CMT1A, CMT1B and CMT1X, increased MEK/ERK signalling results in the upregulation of monocyte chemoattractant protein 1 (CCL2), which, in conjunction with Colony Stimulating Factor 1 (CSF-1), attracts macrophages resulting in phagocyte-mediated nerve injury and axonal degeneration [26]. In a mouse model of CMT1X (GJB1 null), treatment with a CSF-1 receptor antagonist was able to reduce the number of endoneurial macrophages leading to improved grip strength and compound muscle action potentials (CMAPs) of distal muscles [28**]. The same effect was demonstrated in a CMT1B, but not a CMT1A, mouse model (although a similar reduction in endoneurial macrophages was seen in the CMT1A model). Nevertheless, CSF-1 receptor antagonists appear to be effective in two mouse models of CMT1 and, if safe in humans, may be worthy of future trials.

PXT3003 is a combination drug containing baclofen, naltrexone and D-sorbitol designed to treat CMT1A [29*,30*]. The three composite drugs were selected based on their action on G-protein coupled receptor signalling pathways that are predicted to suppress *PMP22* transcription. In vitro, PXT3003 suppresses *PMP22* transcription and in vivo promotes myelination and ameliorates the phenotype of the CMT1A rat [30]. An exploratory, randomised and double-blind, placebo-controlled phase 2 safety study confirmed the safety and tolerability of PXT3003 [29]. Future phase 3 trials are ongoing.

The unfolded protein response (UPR) is an adaptive cellular response designed to manage increases of misfolded protein in the endoplasmic reticulum (ER) in response to cellular stress and has been implicated in the pathogenesis of several forms of CMT, including CMT1B [31]. The initial step in the UPR involves suppressing protein translation and recruiting chaperone proteins in an attempt to reduce the misfolded protein load. If this is ineffective, downstream signalling pathways are activated leading to apoptotic cell death. Under conditions of cellular stress only, the novel drug Sephin1 prolongs the initial phase of the UPR, inhibiting protein translation and preventing stimulation of apoptotic pathways [32**]. Treatment of a mouse model of CMT1B with sephin1 resulted in complete amelioration of the phenotype with no discernible side effects. Treatment of the SOD1G93A mouse model of amyotrophic lateral sclerosis (ALS) was similarly effective suggesting that Sephin1 may be effective in a broad range of axonopathies due to ER stress.

Therapeutic advances in CMT2

Therapeutic advances in CMT2 are less well developed than for CMT1 with the exception of CMT2 due to mutations in *MFN2*, *GARS* and *HSPB1*. It has previously been shown that in a primary sensory neuron model of CMT2A due to mutant *MFN2*, overexpression of the paralogue MFN1 and sodium channel blockade were able to rescue axonal degeneration [33]. *GARS* encodes the ubiquitously expressed enzyme glycyl-tRNA synthetase (GlyRS), which forms homodimers and attaches glycine to its cognate tRNA. To date, more than 15 pathogenic, CMT-associated mutations in *GARS* have been reported, all of which are located close to the GlyRS dimer interface and appear to result in a conformational opening of GlyRS leading to the exposure of new protein surfaces to solution [34]. These structural changes result in an increased interaction of mutant GlyRS with neuropilin 1, a receptor for the ligands VEGF and class 3 semaphorins. More importantly, lentiviral overexpression of VEGF in the hind limb muscles of mutant *GARS* mice was able to improve hind limb strength suggesting that pharmacological agonists of the Nrp1 receptor may be beneficial in CMT2D[35**]. In a separate study, pyridostigmine partially corrected neurotransmission defects in CMT2D mice leading to improvements in muscle function [36].

Mutations in *HSPB1* encoding the small heat shock protein HSP27 are a rare cause of motor predominant CMT2 [2]. Mutations in *HSPB1* cause a reduction in peripheral nerve acetylated alpha tubulin leading to deficits in mitochondrial axonal transport, an effect that was reversed by treatment with an HDAC6 inhibitor [37]. Unlike other members of the Histone Deacetylase (HDAC) family, HDAC6 is not involved in the post-translational modification of histone proteins, but instead regulates the acetylation status of target proteins. HDAC6 inhibitors have emerged as a promising therapeutic approach in CMT2 in which defective axonal transport may be a final common disease pathway. Unfortunately, current HDAC6 inhibitors have limited specificity and this is important as non HDAC6 inhibitors modify epigenetic proteins resulting in changes in gene transcription and protein expression. Recent advances in HDAC6 pharmacology have identified several highly selective HDAC6 inhibitors that have also been shown to reverse mitochondrial axonal transport defects in an in vitro model of CMT2F [38].

Gene replacement therapy in CMT

CMTX1 is due to loss-of-function mutations in *GJB1* encoding the gap junction protein connexin 32 and therefore should be amenable to gene replacement therapy. Intrathecal injection of a lentivirus expressing *GJB1* using a Schwann cell-specific promoter resulted in connexin 32 expression throughout the length of the sciatic nerve and improvement in the neurophysiological, neuropathological and motor phenotype of *GJB1* null mice [39**]. Local injection of the same lentivirus into the sciatic nerve of *GJB1* null mice also resulted in sustained and stable expression of connexin 32 in Schwann cells along the length of the sciatic nerve [40*]. Humans, however, are considerably larger than mice and it is unclear whether such diffuse and sustained expression in the peripheral nerves would be possible. Although viral mediated therapies are promising, the demonstration that AAV1 integration into the host genome may promote tumorigenesis in mice prompts caution if one is to consider translating these therapies to humans for a disease that, although disabling, does not shorten life span [41].

Trial design and outcome measures

The translation of preclinical studies into therapies for patients requires well designed trials with sufficiently responsive outcome measures to identify a clinically relevant effect. This requires knowledge of the natural history of the disease and sensitive outcome measures. In a baseline study of 520 children and adolescents with CMT, disease severity tended to worsen in childhood (3-10 years) in CMT1X and CMT4C, whereas for CMT2A and CMT1B it worsened during adolescence (11-20 years). CMT1A, however, progressed consistently throughout childhood and adolescence [42*]. This is an important observation that has implications for the timing of future trials especially if the findings are confirmed in the ongoing longitudinal natural history study. A large and recent study of the baseline characteristics of 107 patients with CMT1B confirmed previous genotype phenotype correlations whereby some MPZ mutations cause an early onset, severe demyelinating neuropathy and others a late onset, axonal neuropathy [43]. This has clear implications for patient inclusion criteria in CMT1B trials, which may need to be limited to a specific phenotype.

The CMT neuropathy score and CMTpaeds are disease severity scales based on symptoms, clinical examination and tasks, and for the CMTNS, neurophysiology [42,44]. In the recent vitamin C trials for CMT1A, the original version of the CMTNS was unable to detect disease progression over two years highlighting the need for new outcome measures [45]. Longitudinal studies using a Rasch modified version of the CMTNS are underway [44]. The recent report by Morrow and colleagues that quantification of calf muscle fat fraction using lower limb MRI is able to detect disease progression over 12 months in CMT1A represents a significant advance in the development of responsive outcome measures for CMT [46**]. As almost all forms of CMT result in disability through axonal loss and denervation, it is probable that lower limb muscle MRI may be a suitable outcome measure for other forms of CMT.

Conclusion

Over the last year there have been significant advances in deciphering the genetic causes of CMT. It is now 25 years since the 17p duplication was discovered to cause CMT1A and although no treatments exist, basic advances into our understanding of the pathomechanisms of CMT are now starting to translate into treatment trials. That this is occurring at the same time as advances in CMT trial design and outcome measure development means that we are now entering an exciting time in the field of CMT research and one that will hopefully lead to meaningful treatments for patients.

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Key-points

1. Next generation sequencing is now firmly embedded in clinical diagnostic practice in CMT and has resulted in the discovery of several new disease genes including *PMP2*, *MORC2*, *MME* and *NEFH*.
2. Advances in our understanding of the pathogenesis of CMT have led to successful preclinical therapies in CMT1A, CMT1X, CMT1B and CMT2D.
3. Clinical trial design in CMT has been significantly advanced by the discovery that quantification of lower limb muscle fat fraction on MRI can detect disease progression in CMT1A over one year.

Figure 1.

This figure illustrates the genes involved in CMT. * Those genes for which clinical trials in man have either been performed or are in progress. ** Those genes for which there have been successful therapeutic trials in animal models of the disease.

Table 1

A summary of the genes known to cause inherited peripheral neuropathy according to the phenotype.

Type (OMIM number)	Gene	Phenotype	Published Cases
Autosomal dominant CMT1			
CMT1A (118220)	17p dup. (<i>PMP22</i>) <i>PMP22</i> point mutation	Classic CMT1 Classic CMT1; DSD; CHN (rarely recessive)	Multiple families
CMT1B (118200)	<i>MPZ</i>	CMT1; DSD; CHN; CMT2 (rarely recessive)	Multiple families
CMT1C (601098)	<i>LITAF</i>	Classic CMT1	Multiple families
CMT1D (607678)	<i>EGR2</i>	Classic CMT1; DSD; CHN	Multiple families
CMT1F (607734)	<i>NEFL</i>	CMT2 but can have slow MCV in the CMT1 range (rarely recessive)	Multiple families
CMT1 plus (614434)	<i>FBLN5</i>	Macular degeneration; cutis laxa; HMN; slow NCV	Two families
CMT1	<i>PMP2</i>	Classic CMT1	Multiple families
SNCV / CMT1 (608236)	<i>ARHGEF10</i>	Asymptomatic slow conduction velocities	One family and one sporadic case
Hereditary neuropathy with liability to pressure palsies			
HNPP (162500)	17p del. (<i>PMP22</i>) <i>PMP22</i> point mutation	Typical HNPP Typical HNPP	Multiple families
Autosomal recessive CMT1			
CMT4A (214400)	<i>GDAP1</i>	CMT1 or CMT2, usually severe early onset (dominant and recessive). Vocal cord and diaphragmatic paralysis described	Multiple families
CMT4B1 (601382)	<i>MTNR2</i>	Severe CMT1; facial; bulbar; focally folded myelin	Multiple families
CMT4B2 (604563)	<i>SBF2 (MTMR13)</i>	Severe CMT1; glaucoma; focally folded myelin	Multiple families
CMT4B3 (615284)	<i>SBF1 (MTMR5)</i>	CMT1; focally folded myelin	Two families
CMT4C (601596)	<i>SH3TC2</i>	Severe CMT1; scoliosis; cytoplasmic inclusions	Multiple families
CMT4D or HMSNL (601455)	<i>NDRG1</i>	Severe CMT1; gypsy; deafness; tongue atrophy	Multiple families
CMT4E (605253)	<i>EGR2</i>	CMT1; DSD; CHN phenotype	Multiple families
CMT4F (614895)	<i>PRX</i>	CMT1; predominantly sensory; focally folded myelin	Multiple families
CMT4G or HMSN Russe (605285)	<i>HK1</i>	Severe early-onset CMT1; gypsy	Multiple families
CMT4H (609311)	<i>FGD4</i>	Classic CMT1	Multiple families
CMT4J (611228)	<i>FIG4</i>	CMT1; predominantly motor; progressive, complex syndromes including the Yunis-Varon syndrome	Multiple families
CMT4K (616684)	<i>SURF-1</i>	CMT1; encephalopathy; ataxia; reduced life span; Leigh syndrome	Multiple families

Type (OMIM number)	Gene	Phenotype	Published Cases
CCFDN (604168)	<i>CTDPI</i>	CMT1; gypsy; cataracts; dysmorphic features	Multiple families
<i>Autosomal dominant CMT2</i>			
CMT2A (609260)	<i>MFN2</i>	CMT2; progressive; optic atrophy (rarely recessive / semi-dominant)	Multiple families
CMT2B (600882)	<i>RAB7</i>	CMT2 with sensory complications (ulcero mutilating) / HSN	Multiple families
CMT2C (606071)	<i>TRPV4</i>	CMT2; vocal cord paralysis also SPSMA	Multiple families
CMT2D (601472)	<i>GARS</i>	CMT2 with predominant hand wasting / HMN5A	Multiple families
CMT2	<i>BSC12</i>	CMT2 with predominant hand wasting / HMN5A / SPG17	Multiple families
CMT2E (607684)	<i>NEFL</i>	CMT2 but can have NCV in the CMT1 range (rarely recessive)	Multiple families
CMT2F (606595)	<i>HSPB1</i>	Motor-predominant CMT2 / HMN2B	Multiple families
CMT2I (607677)	<i>MPZ</i>	Late-onset CMT2; CMT1B	Multiple families
CMT2J (607736)	<i>MPZ</i>	CMT2 with hearing loss and pupillary abnormalities; CMT1B	Multiple families
CMT2K (607831)	<i>GDAP1</i>	Late-onset CMT2 (dominant); severe CMT2 (recessive); CMT4A	Multiple families
CMT2L (608673)	<i>HSPB8</i>	Motor-predominant CMT2; HMN2A	Multiple families
CMTDIB or CMT2M (606482)	<i>DNM2</i>	Intermediate CMT or CMT2; cataracts; ophthalmoplegia; ptosis	Multiple families
CMT2N (613287)	<i>AARS</i>	Classic CMT2 / HMN	Multiple families
CMT2P (614436)	<i>LRSAMI</i>	Mild sensory-predominant CMT2 (dominant and recessive)	Multiple families
CMT2Q (615025)	<i>DHTKDI</i>	CMT2	One family
HMSNP (604484)	<i>TFG</i>	CMT2 with proximal involvement	Multiple families
CMT2U (616280)	<i>MARS</i>	Late-onset CMT2	One family and one sporadic case
CMT2V (616491)	<i>NAGLU</i>	Late onset painful sensory predominant CMT2	One family
CMT2W (616625)	<i>HARS</i>	CMT2; HMN	Multiple families
CMT2Y (616687)	<i>VCP</i>	CMT2	One family and one sporadic case
CMT2Z (616688)	<i>MORC2</i>	CMT2 with pyramidal signs	Multiple families
SPG10 (604187)	<i>KIF5A</i>	CMT2 hereditary spastic paraplegia	Multiple families
CMT2	<i>MT-ATP6</i>	CMT2; pyramidal signs; relapsing	Multiple families
CMT2 with giant axons (GAN2 / 610100)	<i>DCAF8</i>	CMT2 with childhood onset, NEFL accumulations on nerve biopsy	One family
CMT2 (600638)	<i>TUBB3</i>	CMT2; CFEOM3	One family
CMT2	DGAT2	Early onset axonal neuropathy with sensory ataxia	One family

Type (OMIM number)	Gene	Phenotype	Published Cases
Autosomal recessive CMT2			
CMT2B1 (605588)	<i>LMNA</i>	CMT2 rapid progression	Two families
CMT2B2 (605589)	<i>MED25</i>	Classic CMT2	One family
NMAN (137200)	<i>HINT1</i>	Neuromyotonia and axonal neuropathy; motor predominant	Multiple families
CMT2R (615490)	<i>TRIM2</i>	Infantile-onset CMT2	Two families
CMT2S (616155)	<i>IGHMBP2</i>	CMT2; SMARD1	Multiple families
CMT2T (616233)	<i>HSJ1</i>	CMT2, motor predominant; DSMA5	Multiple families
CMT2X (616668)	<i>ALS5/SPG11/KIAA8140</i>	Onset in the second decade, CMT2 with UMN signs	Multiple families
AR-CMT2	<i>MME</i>	Late onset CMT2	Multiple families.
AR-CMT2 (607706)	<i>GDAP</i>	Severe CMT2 with vocal cord involvement; CMT4A; CMT2K; CMTR1A	
AR-CMT6	<i>C12orf65</i>	CMT2 and optic atrophy	One family.
X-linked CMT			
CMTX1 (302800)	<i>GJB1</i>	Males CMT1 (patchy MCV); females CMT2	Multiple families
CMTX4 or Cowchock syndrome (310490)	<i>AIFM1</i>	CMT2; infantile onset; developmental delay; deafness; learning difficulties	One family and one sporadic case
CMTX5 (311070)	<i>PRPS1</i>	CMT2; deafness; optic atrophy	Multiple families
CMTX6 (300905)	<i>PDK3</i>	CMT2	One family
CMTX	<i>DRP2</i>	Intermediate MCV	Multiple families
Dominant intermediate CMT			
CMTDIB or CMT2M (606482)	<i>DNM2</i>	Intermediate CMT or CMT2; cataracts; ophthalmoplegia; ptosis	Multiple families
CMTDIC (608323)	<i>YARS</i>	Intermediate CMT	Multiple families
CMTDID (607791)	<i>MPZ</i>	Intermediate CMT	Multiple families
CMTDIE (614455)	<i>IFN2</i>	Intermediate CMT; focal segmental glomerulosclerosis; end-stage renal failure	Multiple families
CMTDIF (615185)	<i>GNB4</i>	Intermediate CMT	One family and one sporadic case
Recessive intermediate CMT			
CMTRIA (608340)	<i>GDAP1</i>	Intermediate CMT; recessive CMT2, CMT2K and CMT4A	Multiple families
CMTRIB (613641)	<i>KARS</i>	Intermediate CMT; learning difficulty; vestibular schwannoma	One sporadic case
CMTRIC (615376)	<i>PLEKHG5</i>	Intermediate CMT; SMA	Multiple families
CMTRID (616039)	<i>COX6A1</i>	Intermediate CMT; onset 1 st decade	Two families

Type (OMIM number)	Gene	Phenotype	Published Cases
Hereditary motor neuropathy			
HMN2A (158590)	<i>HSPB8</i>	Classical HMN; dominant; CMT2L	Multiple families
HMN2B (608634)	<i>HSPB1</i>	Classical HMN; dominant; CMT2F	Multiple families
HMN2C (613376)	<i>HSPB3</i>	Classical HMN; dominant	Two siblings
HMN2D (615575)	<i>FBXO38</i>	Classical HMN; dominant	Two families
HMN5A (600794) or SPG17 (270685)	<i>BSCL2</i>	Predominant hand wasting; Silver syndrome but can have sensory involvement as in CMT2D; dominant	Multiple families
HMN5A (600794)	<i>GARS</i>	Predominant hand wasting; dominant; CMT2D	Multiple families
HMN5B (614751) or SPG31 (610250)	<i>REEP1</i>	Predominant hand wasting; pyramidal signs; dominant	Multiple families
HMN6 or SMARD1 (604320)	<i>IGHMBP2</i>	Infantile onset; respiratory distress; recessive; CMT2S	Multiple families
HMN7A (158580)	<i>SLC5A7</i>	Classical HMN; vocal cord palsy; dominant	Multiple families
HMN7B (607641)	<i>DCTN1</i>	HMN; bulbar and facial weakness; dominant	One family
DSMA2 (605726)	<i>SIGMAR1</i>	HMN with pyramidal signs; recessive Juvenile ALS	Multiple families
DSMA4 (611067)	<i>PLEKHG5</i>	SMA; CMTRIC	Multiple families
DSMA5 (614881)	<i>DNAJB2 (HSJ1)</i>	Classical HMN; recessive; CMT2T	Multiple families
SMARD2 or SMA X	<i>LAS1L</i>	Infantile onset; respiratory distress; X-linked recessive	One sporadic case
SMA X3 (300489)	<i>ATP7A</i>	Classical HMN; X-linked	Two families
SMALED (158600)	<i>DYNC1H1</i>	Congenital; contractures; lower-limb predominant; pyramidal signs; cortical migration defects; learning difficulties; dominant	Multiple families
SMALED2 (615290)	<i>BICD2</i>	Congenital; contractures; lower-limb predominant; pyramidal signs; dominant	Multiple families
PNNMH (614369)	<i>MYH14</i>	Typical HMN; distal myopathy; hoarseness; hearing loss; dominant	One family
SPSMA (181405)	<i>TRPV4</i>	HMN; scapular winging; vocal cord palsy; dominant; CMT2C	Multiple families
HMN	<i>AARS</i>	Typical HMN; dominant; CMT2N	Multiple families
HMN	<i>HARS</i>	Typical HMN; dominant; CMT2W	Multiple families
HMN	<i>HINT1</i>	HMN with neuromyotonia; recessive also CMT2 with neuromyotonia	Multiple families
HMN with UMN signs	<i>VRK1</i>	SMA with PCH; HMN; recessive	One sporadic case
HMN with pyramidal features or ALS4 (602433)	<i>SETX</i>	HMN with pyramidal signs; dominant	Multiple families
SMAJ (615048)	<i>CHCHD10</i>	HMN; CMT2; Late onset; Finnish; dominant	Multiple families
Hereditary sensory neuropathy (also called Hereditary sensory and autonomic neuropathy (HSAN))			
HSAN1A (162400)	<i>SPTLC1</i>	HSN with sensory complications (ulcero mutilating); dominant	Multiple families

Type (OMIM number)	Gene	Phenotype	Published Cases
HSAN1C (613640)	<i>SPTLC2</i>	HSN with sensory complications (ulcero mutilating); dominant	Multiple families
CMT2B (600882)	<i>RAB7</i>	HSN with sensory complications (ulcero mutilating); dominant	Multiple families
HSN1D (613708) or SPG3A (182600)	<i>ATL1</i>	HSN with sensory complications (ulcero mutilating); spasticity; dominant	Multiple families
HSN1E (614116)	<i>DNMT1</i>	HSN; hearing loss; dementia; dominant	Multiple families
HSN1F (615632)	<i>ATL3</i>	HSN; bone destruction; dominant	Multiple families
HSAN2A (201300)	<i>WNK1</i>	HSN with sensory complications (ulcero mutilating); recessive	Multiple families
HSAN2B (613115)	<i>FAM134B</i>	HSN with sensory complications (ulcero mutilating); recessive	Multiple families
HSN2C (614213) or SPG30 (610357)	<i>KIF1A</i>	HSN with sensory complications (ulcero mutilating); recessive	Multiple families
HSAN3, familial dysautonomia or Riley-Day (223900)	<i>IKBKAP</i>	Ashkenazi Jewish; autonomic dysfunction; HSN; absent fungiform papillae; recessive	Multiple families
CIPA or HSAN4 (256800)	<i>NTRK1</i>	Congenital insensitivity to pain with anhidrosis; recessive	Multiple families
HSAN5 (608654)	<i>NGF-B</i>	Insensitivity to pain; recessive	Multiple families
HSAN6 (614653)	<i>DST</i>	Ashkenazi Jewish; autonomic dysfunction; HSN; absent fungiform papillae; death by age 2; recessive	One family
HSAN7 (615548)	<i>SCN11A</i>	Congenital insensitivity to pain with hyperhidrosis and gastrointestinal dysfunction; painful peripheral neuropathy; dominant	Multiple families
HSAN8 (616488)	<i>PRDM12</i>	Congenital insensitivity to pain; recessive	Multiple families
Insensitivity to pain (24300), paroxysmal extreme pain disorder (167400), primary erythralgia (133020)	<i>SCN9A</i>	Recessive; insensitivity to pain Dominant: paroxysmal extreme pain disorder; primary erythralgia; small fibre neuropathy	Multiple families
CIP	<i>CLTCL1</i>	Congenital insensitivity to pain and severe global developmental delay; dysmorphic, delayed myelination on brain MRI; Iranian; recessive	One family
HSAN and dementia	<i>PRNP</i>	Autonomic dysfunction; sensory loss; dementia; dominant	Two families
Hereditary sensory neuropathy with spastic paraplegia (256840)	<i>CCT5</i>	HSN with sensory complications (ulcero mutilating) and spastic paraplegia; recessive	One family
Posterior column ataxia & Retinitis pigmentosa (PCARP / 609033)	<i>FLVCR1</i>	Retinitis pigmentosa, sensory ganglionopathy and abnormal posterior columns on MRI; recessive.	Multiple families

The number in parenthesis is the phenotype number according to OMIM. CMT = Charcot-Marie-Tooth Disease, HNPP = Hereditary Neuropathy with Liability to Pressure Palsies, CMT1 = Demyelinating CMT, CMT2 = Axonal CMT, SNCV = Slow Nerve Conduction Velocity, MCV = Motor Conduction Velocity, CHN = Congenital Hypomyelinating Neuropathy, DSD = Dejerine-Sottas Disease, HMSN = Hereditary Motor and Sensory Neuropathy, CFEMO3 = Congenital Fibrosis of Extraocular Muscles, HMN = Hereditary Motor Neuropathy, NMAN = Neuromyotonia and axonal neuropathy, SMA = Spinal Muscular Atrophy, SPG = Spastic Paraplegia, PNMMH = Peripheral Neuropathy, Myopathy, Hoarseness and Hearing Loss, SPSMA = Scapuloperoneal SMA, UMN = Upper Motor Neuron, SMALED = SMA Lower Extremity Predominant, DSMA = Distal SMA, SMARD = SMA with Respiratory Distress, PCH = Ponto Cerebellar Hypoplasia, HSN = Hereditary Sensory Neuropathy, HSAN = Hereditary Sensory and Autonomic Neuropathy, . CIP= Congenital Insensitivity to Pain.