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REVIEW ARTICLE

Molecular Genetics of Autosomal-Dominant Demyelinating Charcot-Marie-Tooth Disease

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Abstract

Charcot-Marie-Tooth disease (CMT) is a clinically and genetically heterogeneous group of disorders and is the most common inherited neuromuscular disorder, with an estimated overall prevalence of 17–40/10,000. Although there has been major advances in the understanding of the genetic basis of CMT in recent years, the most useful classification is still a neurophysiological classification that divides CMT into type 1 (demyelinating; median motor conduction velocity < 38 m/s) and type 2 (axonal; median motor conduction velocity > 38 m/s). An intermediate type is also increasingly being described. Inheritance can be autosomal-dominant (AD), X-linked, or autosomal-recessive (AR). AD CMT1 is the most common type of CMT and was the first form of CMT in which a causative gene was described. This review provides an up-to-date overview of AD CMT1 concentrating on the molecular genetics as the clinical, neurophysiological, and pathological features have been covered elsewhere. Four genes (*PMP22*, *MPZ*, *LITAF*, and *EGR2*) have been described in the last 15 yr associated with AD CMTI and a further gene (*NEFL*), originally described as causing AD CMT2 can also cause AD CMT1 (by neurophysiological criteria) (Table 1, Figs. 1 and 2). Studies have shown many of these genes, when mutated, can cause a wide range of CMT phenotypes from the relatively mild CMT1 to the more severe Dejerine–Sottas disease and congenital hypomyelinating neuropathy, and even in some cases axonal CMT2 (Table 1). This review discusses what is known about these genes and in particular how they cause a peripheral neuropathy, when mutated.

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Index Entries: CMT; demyelinating neuropathy; hereditary; HMSN; mutation.

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Table 1
Classification of AD Demyelinating CMT1

	Classification	Inheritance	Clinical phenotype
Genes associated with AD CMT1			
Duplication of 17p11.2-12	CMT1A	AD or *de novo*	Demyelinating CMT
PMP22 mutations	CMT1A	AD or *de novo*	Demyelinating CMT
		AD or *de novo*	DSD/CHN
		AR	Demyelinating CMT
MPZ mutations	CMT1B	AD or *de novo*	Demyelinating CMT
		AD or *de novo*	DSD/CHN
		AD	Axonal CMT
LITAF mutations	CMT1C	AD or *de novo*	Demyelinating CMT
		AD	Axonal CMT
EGR2 mutations	CMT1D	AD or *de novo*	Demyelinating CMT
		AD or *de novo*	DSD/CHN
Genes associated with AD CMT2 and AD CMT1			
NEFL mutations	CMT2E	AD	Axonal CMT
		AD	Demyelinating CMT

AD, autosomal-dominant; AR, autosomal-recessive; CMT, Charcot-Marie-Tooth disease; *PMP22*, peripheral myelin protein 22 gene; *MPZ*, myelin protein zero gene; *EGR2*, early growth response 2 gene; *LITAF*, lipopolysaccharide-induced TNF factor gene; *NEFL*, neurofilament protein light polypeptide gene; DSD, Dejerine–Sottas disease; CHN, congenital hypomyelinating neuropathy.

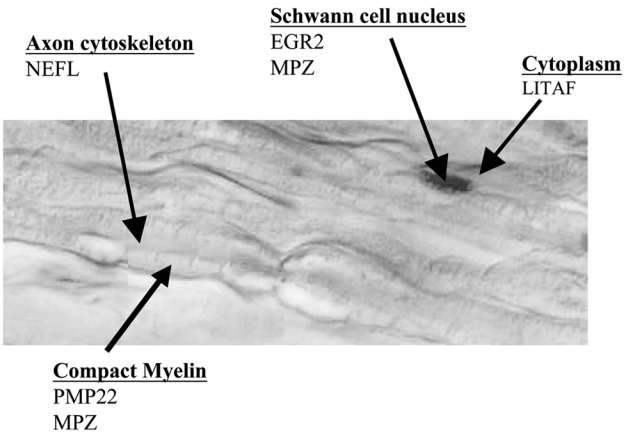

Fig. 1. Structural organization of myelinated axons highlighting the proteins that are mainly affected in autosomal-dominant demyelinating CMT disease.

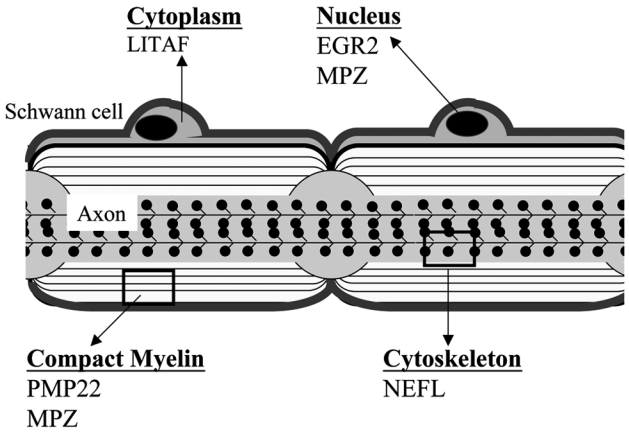

Fig. 2. Structural organization of myelinated axons highlighting the proteins that are mainly affected in autosomal-dominant demyelinating CMT disease.

Introduction

CMT1 is the demyelinating form of Charcot-Marie-Tooth disease (CMT) and as such is characterized by median motor conduction velocities (MCV) below 38 m/s and pathologically by demyelination. AD CMT1 is the most common form of CMT except in specific ethnic groups. There is a wide spectrum of disease severity associated with CMT1, from classical CMT1, which is usually at the mild/moderate end to the more severe demyelinating neuropathies, Dejerine–Sottas disease (DSD) and congenital hypomyelinating neuropathy (CHN). Classical CMT1 is characterized clinically by distal muscle

wasting, weakness, and sensory loss with reduced tendon reflexes and usually a variable degree of foot deformity. Pathologically, classical onion bulbs are seen resulting from repeated segmental de- and remyelination. DSD is a more severe hypertrophic polyneuropathy of early onset with more severe motor slowing on nerve conduction studies (NCS) and nerve biopsies showing severe hypomyelination with basal lamina onion bulbs. CHN is a rare, severe childhood neuropathy, presenting with muscle weakness at birth or infancy with absent or very slow MCVs and nerve biopsy findings of markedly reduced or absent myelin. CMT1, DSD, and CHN are now considered to be variants of CMT1 as mutations in the same genes are responsible for all three phenotypes. Although all of the above clinical syndromes are characterized by demyelination to varying degrees, it has been recognized for many years that the wasting and weakness seen in CMT1, and consequently the impairment associated with the disease, is caused by axonal degeneration (Krajewski et al., 2000). This is very important in both understanding the pathogenesis of CMT1 and in planning therapies for the future.

AD CMT1 can now be classified using molecular genetics (first as loci were described and laterally as the causatives genes themselves were identified) into four types A, B, C, and D with the causative genes for types A, B, and D also causing DSD, CHN, or both (Table 1). Although the normal function of the causatives genes for AD CMT1 are not fully understood, there have been major advances in the understanding of both the function of these genes and of the pathogenesis of neuropathy when they are mutated. Recent exciting transgenic studies have identified agents to be studied in trials for CMT1A, the commonest form of AD CMT1.

CMT1A

Duplication of Chromosome 17p11.2-12 and Point Mutations in the Peripheral Myelin Protein 22 Gene

Genetics

In 1989, a large subgroup of CMT1 kindreds were linked to chromosome 17p11.2 (Raeymaekers et al., 1989; Vance et al., 1989) and this form of CMT1 was termed CMT1A. In 1991, two independent reports

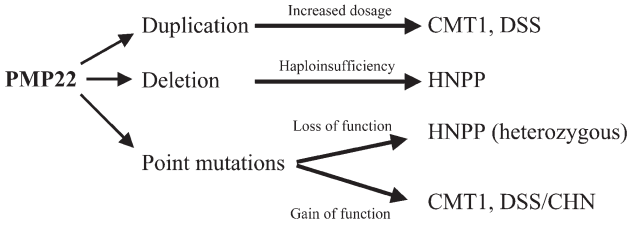

Fig. 3. Flow diagram showing the potential pathways and pathogenicity of the various defects in the *PMP22* gene.

appeared describing a large segmental duplication within band 17p11.2, involving about 1.4 Mb of DNA (Lupski et al., 1991; Raeymaekers et al., 1991). The complete *PMP22* gene was mapped within the duplicated region and the finding that point mutations in *PMP22* also caused CMT1A confirmed that *PMP22* was the causative gene for CMT1A (Valentijn et al., 1992). This was and still is the most important advance in the understanding of the molecular genetics of CMT as the chromosome 17 duplication remains the major cause of CMT accounting for about 70% of all cases of CMT1 (Nelis et al., 1996). Shortly after the chromosome 17 duplication was described as the cause of CMT1A, it was reported that a deletion of the same section of chromosome 17 caused hereditary neuropathy with liability to pressure palsies (HNPP), an autosomal-dominant condition characterized by episodic recurrent pressure palsies at points of nerve entrapment (Chance et al., 1993). The chromosome 17 duplication has been described in populations throughout the world and testing for the duplication is reasonably widely available. The vast majority of patients have the classical 1.4 Mb chromosome 17 duplication but occasional patients have been described with smaller duplications (Valentijn et al., 1993). Many methods are currently used to detect the duplication including polymerase chain reaction (PCR) detection of three alleles using multiple polymorphic short-tandem repeats (STRs) (microsatellites), fluorescent *in situ* hybridization (FISH), and junction fragment analysis (PFGE) (Lupski and Chance, 2005). The above methods have the advantage of also detecting the deletion associated with HNPP.

PMP22 point mutations also cause CMT1A and rarely HNPP but more commonly cause the more severe forms of CMT1 (DSD and CHN) (Fig. 3). The type of *PMP22* point mutations described include missense, nonsense, splice site, and frameshift

mutations. Missense mutations in the *PMP22* gene were originally described in two spontaneous mouse mutants termed trembler (Tr) and trembler-J (Tr-J) (Suter et al., 1992a,b) and the same mutations were subsequently found in humans; the Tr mutation (Gly150Asp) causing DSD in a mother and son (Ionasescu et al., 1997) and the Tr-J mutation (Leu16Pro) causing AD CMT1A (Valentijn et al., 1992). Other *PMP22* point mutations including *de novo* mutations (accounting for about 25% of *PMP22* mutations), are often associated with the more severe forms of CMT, DSD, and CHN (Suter et al., 1992a,b; Valentijn et al., 1992; mutation database of inherited peripheral neuropathies http://www.molgen.ua.ac.be/CMT). Frame shift, splice site, and nonsense mutations are rare and are usually associated with HNPP, as expected, as they usually represent null alleles and result in haploinsufficiency (Lenssen et al., 1998; Nelis et al., 1999; Meuleman et al., 2001; Abe et al., 2004; Lupski and Chance, 2005; Zephir et al., 2005). Although most *PMP22* point mutations are dominant, causing disease in the heterozygous state, CMT1 can also be caused by rare AR *PMP22* mutations, Arg157Trp and Arg157Gly (Roa et al., 1993; Parman et al., 1999; Numakura et al., 2000). The role of the *PMP22* Thr118Met mutation in causing an inherited neuropathy is uncertain; it has been suggested that this change is a polymorphism but there are also reports that it may act as a loss of function mutation causing HNPP (or making HNPP more severe if found on the nondeleted allele) or modulating the CMT1 phenotype in patients with the chromosome 17 duplication (Roa et al., 1993; Nelis et al., 1997; Mersiyanova et al., 2000a; Young et al., 2000; Marques et al., 2003). The Thr118Met mutation has not been described in the homozygous state but when identified this will be the true test of this mutations pathogenicity.

PMP22 *Function*

To begin to elucidate how the various alterations of *PMP22* cause CMT1, it is important to review the function of normal *PMP22* in the peripheral nervous system (PNS). Despite *PMP22* mutations being the major cause of CMT, less is known about the normal function of *PMP22* compared with other proteins that have subsequently been described to be important in CMT. Peripheral myelin protein (PMP) 22 is a hydrophobic 22-kDa glycoprotein of

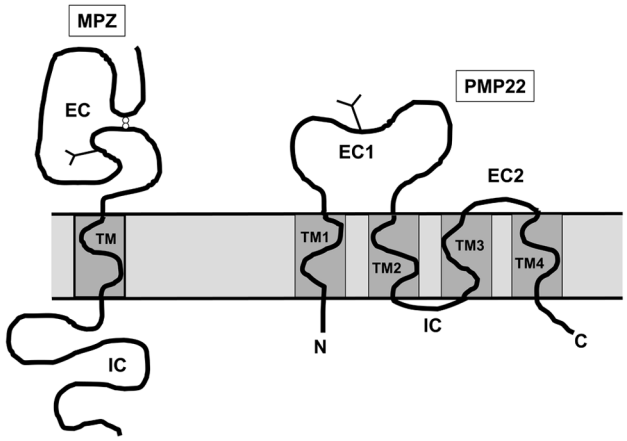

Fig. 4. Transmembrane structure of *MPZ* and *PMP22*.

160 amino acids with four transmembrane domains mainly expressed by myelinating Schwann cells in the PNS and regulated by two alternatively used promoters, one being a myelin-specific promoter (Fig. 4). *PMP22* localizes almost exclusively to compact myelin (Snipes et al., 1992; Naef and Suter, 1998) and makes up approx 2–5% of total PNS myelin protein and is thought to be of importance in myelin formation and maintenance. Although the functions of *PMP22* are largely unknown, it is thought to have a role in the initiation of myelin spirals, regulation of growth and differentiation of Schwann cells and control of thickness and stability of myelin sheaths (Vallat, 2003).

Much of the information about the normal function of *PMP22* comes from studies on animal models. *PMP22* knockout mice (KO) (PMP–/–) have delayed onset of myelination and subsequently develop demyelination, axonal loss, and associated functional impairment (Adlkofer et al., 1995; Sancho et al., 1999). Heterozygous KO mice (*PMP22*–/+) carrying one copy of *PMP22* develop a syndrome similar to HNPP (Adlkofer et al., 1997a). Transgenic animals carrying additional copies of the *PMP22* gene under the control of its own regulatory elements show dose-dependent dysmyelinating and demyelinating neuropathies similar to those observed in human patients (Magyar et al., 1996; Sereda et al., 1996; Sancho et al., 1999). Finally, mice carrying *PMP22* point mutations (Tr, Tr-J, Tr-m1H, and m2H) and a mouse with a *PMP22* deletion (Tr-Ncnp) also develop a severe demyelinating neuropathy usually more severe than the overexpressing

transgenic mice (Suter et al., 1992a,b; Sereda et al., 1996; Suh et al., 1997; Isaacs et al., 2000). These studies confirm that *PMP22* is required for the formation and maintenance of PNS myelin. A recent interesting study in mutant mice, using comparative expression profiling of mutant and wild-type sciatic nerves, has shown for the first time that *PMP22* probably has a primary role in the regulation of Schwann cell proliferation (Giambonini-Brugnoli et al., 2005).

Pathogenesis of CMT1A Owing to the Chromosome 17 Duplication

The original finding of *PMP22* within the duplicated chromosome 17 region suggested that a gene-dosage effect leading to overexpression of *PMP22* is the cause of CMT1A (Lupski and Chance, 2005). There is a good deal of evidence to support this notion; in patients with small duplications (Ionasescu et al., 1993) or deletions (King et al., 1998), the *PMP22* gene was always included within the change. Genetically engineered rats and mice that express multiple copies of the *PMP22* gene under the control of their own regulatory elements, show similar dose-dependent dysmyelinating and demyelinating neuropathies to those observed in human patients (Magyar et al., 1996; Sereda et al., 1996; Sancho et al., 1999). A further interesting transgenic mouse model was developed in which the overexpression of the mouse *pmp22* gene could be regulated by tetracyclinine administration (Perea et al., 2001). Overexpression of the mouse *pmp22* gene caused demyelination, myelination was nearly normal when the expression was switched off throughout life. When expression was switched off in adult mice, demyelination could be largely corrected within a few months, although Schwann cells were still sensitive to subsequent overexpression; this also supports the dosage hypothesis (Perea et al., 2001). Human studies have also suggested that gene dosage is important. Ultrastructural immunocytochemical quantitative analysis of *PMP22* expression in nerve biopsies of humans with CMT1A resulting from the chromosome 17 duplication showed elevated expression of *PMP22* compared with controls in keeping with a dosage effect (Yoshikawa et al., 1994; Vallat et al., 1996). Also, the phenotype associated with the chromosome 17 duplication varies between patients suggesting other genetic and environmental influences are active, rare patients with four copies of *PMP22* usually have a more severe neuropathy suggesting that gene dosage is important, but the disease phenotype is not determined solely by the number of copies of the *PMP22* gene (Lupski et al., 1991; LeGuern et al., 1997).

The duplication and deletion result from nonallelic homologous recombination between highly homologous 24-kb low copy repeats in 17p11.2, termed "CMT1A-REPs" (Reiter et al., 1996; Inoue et al., 2001). During meiosis, if the proximal copy of CMT1A-REP pairs with the distal copy from the other chromosome homolog, recombination between nonallelic CMT1A-REP copies results in duplication. This unequal crossing-over model predicts a tandem CMT1A duplication structure with the presence of three copies of CMT1A-REP, including a recombinant CMT1A-REP copy in which the crossover occurred (Pentao et al., 1992). Studies in nonhuman primates determined that the origin of the CMT1A-REP occurred during speciation between chimpanzee and gorilla (Kiyosawa and Chance, 1996; Boerkoel et al., 1999). CMT1A accounts for approx 70% of all inherited neuropathies (in different population the prevalence ranges from 60 to 90%), about 20% of cases appear sporadically and some represent *de novo* mutations, the duplicated region is usually of paternal origin (Palau et al., 1993; De Jonghe et al., 1997; Dubourg et al., 2001; Mostacciuolo et al., 2001). Mosaicism has also been reported in CMT1A (Sorour et al., 1995). How exactly increased expression of *PMP22* causes CMT1A is yet to be understood but it is thought that the increase in PMP22 protein in compact myelin may either destabilize the myelin sheath or overexpression may result in demyelination because *PMP22*, in Schwann cells, acts like a growth arrest gene (Hanemann et al., 1997). There is also good evidence from overexpressing transgenic animals that *PMP22* accumulates in perinuclear aggregates called aggresomes (Notterpek et al., 1999; Ryan et al., 2002).

Pathogenesis of CMT1A Resulting From PMP22 *Point Mutations*

Comparison of human and animal models with *PMP22* point mutations and deletions, with *PMP22* knockout mice or *PMP22*-duplicated rodents suggests there is strong evidence that most *PMP22*

mutations act by causing a toxic gain of function (Adlkofer et al., 1997b; Naef et al., 1997) (Fig. 3). The mechanism of this gain of function is thought to be largely owing to impaired intracellular trafficking where the mutant *PMP22* does not reach the plasma membrane (Naef et al., 1997; Brancolini et al., 2000). In vitro and in vivo studies have shown overloaded endoplasmic reticulum (ER)—Golgi compartments with mutant protein aggregates as a consequence of *PMP22* point mutations (D'Urso and Muller, 1997; D'Urso et al., 1997). The mutant *PMP22* Tr protein can also form heterodimers with the wild-type PMP22 protein, sequestering it from normal trafficking in the cell, potentially explaining dominant inheritance (Tobler et al., 1999). However, mechanistically it remains unclear how this could interfere with myelin stability and cause demyelination. One possible hypothesis is that different proteins form complexes within the lipid bilayer and/or between the myelin membranes (D'Urso et al., 1999). There is also evidence that *PMP22–MPZ* complexes are formed at the plasma membrane and participate/stabilize myelin compaction. This would explain how *PMP22* and *MPZ* mutations can cause a similar and varied phenotypic picture (D'Urso et al., 1999, 1998).

A type of aggregate, the aggresome, accumulates misfolded proteins destined for degradation by the ubiquitin–proteasome pathway. Mutant, misfolded *PMP22* overload the proteasome and promote aggresome formation. There is evidence to suggest that Schwann cells have the ability to eliminate aggresomes by a mechanism that is enhanced when autophagy is activated and is primarily prevented when autophagy is inhibited (Fortun et al., 2003). This is also evidence to suggest that different PMP22 mutations differ in the degree of protein aggregation; this might influence clinical phenotype (Tobler et al., 2002). Recently it has been shown that the myelin basic protein, an endogenous Schwann cell proteasome substrate, associates with *PMP22* aggregates in affected nerves. These nerves have reduced proteasome activity coupled with the accumulation of ubiquitinated substrates, and the recruitment of proteasomal pathway constituents form aggregates. This recent data reveal a further mechanism by which altered degradation of Schwann cell proteins might contribute to the pathogenesis of certain *PMP22* neuropathies (Fortun et al., 2005).

Implications for Therapy for CMT1A From Animal Models

Recent animal model studies of CMT1A also have begun to provide the first therapeutic options in CMT. The steroid hormone progesterone has been shown to stimulate *PMP22* gene expression both in cultured Schwann cells and in adult mice (Melcangi et al., 1999a,b). Using a rat model of CMT1A with extra copies of the *PMP22* gene, Sereda and colleagues (2003) demonstrated that the progesterone antagonist onapristone reduced overexpression of *PMP22* and improved the CMT phenotype in male mice. Another important paper from Passage and coworkers (2004) studied mutant mice overexpressing *PMP22* and found that treatment with ascorbic acid resulted in amelioration of the CMT1A phenotype, as measured by improved motor function and increased survival. The treated mice showed a 10-fold decrease in *PMP22* RNA in sciatic nerves. This group also noted that ascorbic acid is a promoter of myelination, and proposed a mechanism of *PMP22* suppression through inhibition of cAMP. These recent therapeutic studies in mice and their optimistic results have led to the planning of clinical trials, initially with ascorbic acid, in patients with CMT1A secondary to the chromosome 17 duplication.

CMT1B

Mutations in the Myelin Protein Zero Gene

Genetics

The first linkage described in CMT was described for CMT 1B. In 1982, linkage was described to the Duffy (Fy) blood group on chromosome 1, in an AD CMT1 kindred first identified in 1962 (Bird et al., 1982). In 1993, myelin protein zero (*MPZ*) was identified as the causative gene for CMT 1B (Hayasaka et al., 1993a,b). CMT 1B is much less common than CMT1A and mutations in the *MPZ* gene account for less than 5% of CMT1 cases (Nelis et al., 1996). To date, there are more than 100 mutations known, most of which are missense. Over the last decade, a variety of clinical phenotypes have been identified associated with *MPZ* mutations including an AD demyelinating neuropathy (CMT1B) and a more severe disorder with very slow nerve conduction studies and a phenotype compatible with

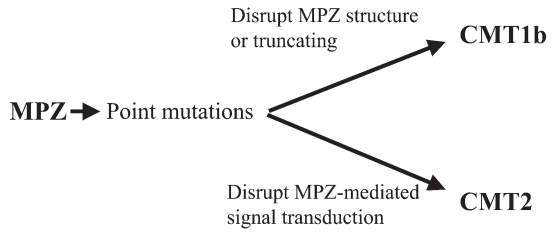

Fig. 5. Flow diagram showing the potential pathways and pathogenicity of the various defects in the *MPZ* gene.

DSD or CHN (Shy et al., 2005). This initial spectrum of phenotypes was similar to the spectrum of phenotypes described with *PMP22* mutations. In the late 1990s, a surprising report suggested that an *MPZ* mutation caused an axonal neuropathy, compatible with CMT2 (Marrosu et al., 1998) and CMT2 secondary to other *MPZ* mutations have been described subsequently. This suggests that the spectrum of phenotypes with *MPZ* mutations is broader than with *PMP22* mutations (Fig. 5).

MPZ mutations are usually autosomal-dominant, although some are *de novo* mutations and there is evidence of rare somatic and germline mosascism (Fabrizi et al., 2001). In clinical practice, many may be present without an apparent family history (Shy et al., 2005). Analysis of the *MPZ* gene is now carried out by DHPLC or by direct sequencing and is now widely available.

MPZ Function

MPZ is a transmembrane protein of 219 amino acids made up of six exons, and is a member of the immunoglobulin gene superfamily. Structurally it is made up of a single immunoglobulin like extracellular domain (124 amino acids), a single transmembrane domain (25 amino acids), and a single cytoplasmic domain (69 amino acids) (Fig. 4). Most MPZ mutations described to cause a neuropathy are located in the extracellular domain. Posttranslational modification occurs extensively in the ER and Golgi apparatus including the addition of an *N*-linked oligosaccharide in the extracellular domain, sulfation, acylation, and phosphorylation (D'Urso et al., 1990; Shy et al., 2005). MPZ is expressed by Schwann cells and comprises about 50% of peripheral myelin proteins and is known to be necessary for normal myelin structure and function. Like other members of the immunoglobulin gene superfamily, *MPZ* is a homophilic adhesion molecule (Filbin et al., 1990). MPZ is thought to wrap the myelin membrane together, the extracellular domain forms homotetramers within the plane of the membrane, a doughnut-like structure with a hole that interacts with the opposing homotetramer (Shapiro et al., 1996). Absence of *MPZ* in knockout mice cause myelin to be uncompacted (Giese et al., 1992) and heterozygous knockout mice show normal myelination initially but later develop a mild demyelinating neuropathy (Martini et al., 1995). All of the above confirms the essential role of *MPZ* in myelination. The cytoplasmic domain is also necessary for homotypic adhesion (Filbin et al., 1999). *MPZ* also has a regulatory role in myelination, which is probably a consequence of the *MPZ*-mediated signal transduction cascade (Xu et al., 2000; Menichella et al., 2001).

Pathogenesis of MPZ-Associated CMT

From the heterozygous knockout mouse described earlier, which has a mild phenotype, it was postulated that most *MPZ* mutations cause disease by a toxic gain-of-function or dominant-negative effects rather than pure loss of function (Berger et al., 2002). Unlike some other forms of CMT, genotype–phenotype studies have been very useful in helping to understand the pathogenesis *MPZ*-related neuropathies.

Shy and colleagues (2004) used 13 patients with *MPZ* mutations that they had studied and also used 64 patients with *MPZ* mutations in the literature with sufficient clinical details to be useful to perform a detailed genotype–phenotype study. They identified two distinct phenotypes including an early-onset (prewalking) disease with slow nerve conduction velocity in which dysmyelination is the major pathological feature and a late (adult)-onset disease with only moderately slow nerve conduction velocity in which axonal degeneration is the major pathological feature. There were a number of mutations that did not fit into this classification where there was phenotypic variability with the same mutation and some patients having an early onset and some a late onset neuropathy, which occurred in and between families. Electrophysiology in these two groups revealed that the early-onset group had a mean median MCV of 8.6 ± 4 m/s, whereas the late-onset group had only mildly slowed

MCVs (mean median 32 ± 9 m/s) and several patients has MCVs greater than 50 m/s. The neuropathological characteristics in sural nerve biopsies from patients with *MPZ* mutations also suggest two phenotypes, although certain families have been reported with unusual neuropathological features that do not comply with this classification such as segmental conduction abnormalities and myelin thickenings in the Val102fs null mutation of *MPZ* gene (De Angelis et al., 2004). Abnormalities of myelin are the prominent feature of nerve biopsies from early-onset patients, pathological features include loss of myelinated axons, demyelination, and remyelination in teased fibers and onion bulb formation. Electron microscopy (EM) studies have revealed a further subdivision with some individuals with extensive areas of uncompacted myelin and others with focally folded myelin (Gabreels-Festen et al., 1996). Axonal degeneration and regeneration has been a prominent feature in the biopsies from patients with late-onset CMT and an *MPZ* mutation with demyelination less evident. Loss of myelinated fibers of all calibers is also an important feature (Marrosu et al., 1998; Chapon et al., 1999; De Jonghe et al., 1999; Senderek et al., 2000; Shy et al., 2004). EM studies in late-onset cases show little segmental demyelination and infrequent compaction abnormalities and tomacula formation. From their genotype–phenotype study, Shy and colleagues concluded that addition of either a charged amino acid or altering a cysteine residue in the extracellular domain caused a severe early-onset neuropathy as do mutations, which cause truncation of the cytoplasmic domain or alteration of an evolutionary conserved amino acid. These types of mutations are thought to significantly disrupt tertiary *MPZ* structure and consequently interfere with myelin compaction and adhesion. They also suggested that mutations, which disrupt *MPZ*-mediated signal transduction and Schwann cell interactions cause late onset neuropathy as less severe alterations of myelin structure would occur.

There are a number of possible mechanisms behind the phenotypic differences that certain MPZ mutations cause. Early-onset disease is mainly caused by mutations which disrupt *MPZ* structure or truncate the cytoplasmic domain. These mutations might directly alter myelination after being incorporated into the myelin sheath or they might indirectly affect the myelinating Schwann cell by instigating protein misfolding and/or altered intracellular transport. The former seems to be the more common mechanism as several MPZ mutations causing early-onset disease, have been shown to be incorporated into myelin (Shames et al., 2003). In late-onset disease a direct mechanism seems less likely but one possible pathogenic route leading to axonal degeneration is a subtle abnormality of the myelin sheath causing an alteration in the Schwann cell axon interactions. As stated above for *PMP22* mutations there is also evidence that *MPZ* and *PM22* form complexes in the myelin membrane that may be relevant in the pathogenesis of both diseases (D'Urso et al., 1998, 1999).

The role of the immune system in the pathogenesis of *MPZ*-related neuropathies is also of interest. Clinical improvement has been documented in a late onset case treated with steroids (Donaghy et al., 2000). In heterozygous knockout *MPZ* mice, T lymphocytes were observed in nerve biopsies. The phenotype was improved in these mice by breeding the mice into null mutants for the recombinant activating gene 1, in which the mice cannot generate an immune response and the phenotype worsened again by transplantation of bone marrow from wild-type mice (Schmid et al., 2000). Whether these studies have any relevance to patients with *MPZ* mutations has yet to be determined.

CMT1C

Mutations in the Lipopolysaccharide–Induced TNF Factor Gene/Small Integral Membrane Protein of Lysosome/Late Endosome (SIMPLE)

Genetics

As discussed in this review, there is considerable genetic heterogeneity in CMT type 1 (Reilly, 2000; Lupski and Chance, 2005). Chance and colleagues (1990) identified three CMT1 pedigrees that were not linked to chromosome 1 or 17, this form of CMT was termed type 1C (Table 1). CMT1C was linked to chromosome 16p13.1 (Street et al., 2002) and mutations in the *LITAF* gene have been described as causing this type of CMT1 (Street et al., 2003; Bennett et al., 2004; Saifi et al., 2005). To date, there have been six mutations (Table 2). The usual phenotype is that of typical CMT1 with an AD demyelinating

Table 2
LITAF Mutations With the Associated Phenotype

LITAF mutation	Position	Inheritance	Phenotype	Upper limb MNCV	Nerve biopsy	References
Thr49Met	146 C > T	Dominant	CMT2	43 m/s	Axonal loss	Saifi et al. (2005)
Gly112Ser	334 G > A	AD/Sporadic	CMT1	Mean Ulnar 25.3 m/s	ND	Bennett et al. (2004); Saifi et al. (2005); Street et al. (2003)
Thr115Asn	344 C > A	AD	CMT1	Mean Ulnar 16.7 m/s	Onion bulbs	Bennett et al. (2004); Saifi et al. (2005); Street et al. (2003)
Trp116Gly	346 T > G	AD	CMT1	Mean Ulnar 19.2 m/s	ND	Bennett et al. (2004); Street et al. (2003)
Leu122Val	364 T > G	Sporadic	CMT1	25.7 m/s	Onion bulbs	Saifi et al. (2005)
3′UTR	671 T > C	Parents died young	CMT1	Absent response	ND	Saifi et al. (2005)

LITAF, lipopolysaccharide-induced TNF factor gene; UTR, untranslated region; AD, autosomal-dominant; CMT, Charcot-Marie-Tooth disease; ND, not done.

neuropathy usually with an age of onset in childhood, although one patient diagnosed with CMT2 has been found to have a *LITAF* mutation (Street et al., 2003; Bennett et al., 2004; Saifi et al., 2005). The initial symptoms are *pes cavus* or an abnormal gait and then the classical features of CMT with distal weakness and wasting in the limbs, depressed tendon reflexes, and sensory impairment. Peripheral nerves were hypertrophied in two of the seven original families reported (Street et al., 2003; Bennett et al., 2004; Saifi et al., 2005). Some atypical features were observed such as exacerbation during pregnancy and early-onset hearing loss (Saifi et al., 2005).

Electrophysiology in the majority of families has been in the demyelinating range (Street et al., 2003; Bennett et al., 2004; Saifi et al., 2005) with velocities in the axonal range found in only one family (Saifi et al., 2005). Bennett studied one family in detail (Family K2900, Trp116Gly), finding a reduction in SNCV of 31 m/s in the sural, 35.5 m/s in the median (Bennett et al., 2004). MNCVs, where available in the other families from this paper with likely pathogenic mutations are as follows; median was between 15 and 39.4 m/s, ulnar 15 and 25.3 m/s and peroneal 7.5 and 27 m/s (Bennett et al., 2004). In family K2900 temporal dispersion was noted in two individuals (3 out of 12 motor nerves), this is not typical in CMT (Bennett et al., 2004). A further patient in a subsequent study was identified with a Thr49Met mutation and nerve conduction velocities in the axonal range (upper MCV and SCV both 43 m/s) with conduction block as well as temporal dispersion. Sural nerve biopsy in this case was reported to show axonal loss (Saifi et al., 2005). Sural nerve biopsies from cases with the more typical CMT1 phenotype and a *LITAF* mutation Thr115Asn (Bennett et al., 2004) and Leu122Val (Saifi et al., 2005) showed numerous onion bulbs, consistent with demyelination.

SIMPLE Function and Pathogenesis of SIMPLE-Related CMT

There is speculation regarding the normal cellular function and the mechanism(s) of action of *LITAF* mutations. Originally two transcripts, encoding different proteins, LITAF, and SIMPLE, were reported, (Polyak et al., 1997; Myokai et al., 1999; Moriwaki et al., 2001), but a very recent study showed that the LITAF transcript appears to result from a DNA-sequencing error suggesting that SIMPLE is the only true transcript from this gene (Saifi et al., 2005). The authors also suggest that there are a number of possible functions of this gene including involvement in the ubiquitin-mediated proteosome pathway and interactions through the PPXY motif and PSAP motifs with other proteins, disturbances of which may underlie the neuropathy in SIMPLE-related

CMT. Further functional studies will help resolve the disease-causing mechanism. A recent interesting paper reports a patient with early onset CMT and two mutations in CMT1 genes, one the common chromosome 17 duplication and the other a SIMPLE mutation, whereas both parents carried only one mutated gene and had minimal signs of CMT. This might suggest that SIMPLE mutations can severely affect the phenotype usually seen with the chromosome 17 duplication (Meggouh et al., 2005).

CMT1D

Mutations in the Early Growth Response 2 Gene

Genetics

Mutations in the early growth response 2 (*EGR2*) gene on chromosome 10q21-22 were described as causing AD CMT1 (termed CMT 1D) and DSD in 1998 (Warner et al., 1998). Since then, it has been recognized that *EGR2* mutations, like mutations in *PMP22*, and *MPZ*, can cause a wide range of phenotypes from CMT1 to DSD or CHN (Table 3) (Warner et al., 1998; Timmerman et al., 1999) (Fig. 6).

AD and *de novo* heterozygous, AR homozygous as well as a compound heterozygous mutations have been identified, although they are rare and probably account for less than 1% of CMT (Warner et al., 1998; Boerkoel et al., 2002). The clinical features seen with EGR2 mutations are broadly similar to those seen with PMP2 and MPZ ranging from the least severe CMT1 phenotype, characterized by a slowly progressive distal muscle atrophy and decreased motor nerve conduction velocities with onset in late childhood or adulthood, to DSD, in which similar features are exhibited with increased severity (i.e., slower NCVs and earlier age of onset) (Warner et al., 1999), and finally to CHN, which like Krox20 homozygous knockout mice have hypomyelination of the PNS (Harati and Butler, 1985) and in one particular mutation group (Arg359Trp) can cause death by age 6 yr with respiratory compromise and cranial nerve involvement.

Sural nerve biopsy in the Arg359Trp DSD mutation showed a severe loss of myelinated and unmyelinated fibers, classic onion bulbs and focally folded myelin sheaths. In the double mutant CHN Ser382Arg and Asp383Tyr the sural nerve also showed profound absence of myelin in virtually all axons and only two or three normally myelinated axons across the entire cross section of the nerve were preserved.

EGR2 Function

EGR2 is a zinc finger transcription factor that plays a crucial role in PNS development (Mirsky and Jessen, 1999) (Fig. 6). The gene encoding EGR2 is on chromosome 10q21-22 and is formed by two exons. Expression of EGR2 starts before myelination onset in mice and rats and continues throughout life (Zorick et al., 1999). EGR2 has been shown to regulate the expression of genes crucial for PNS myelination including *PMP22*, *MPZ*, gap junction protein β 1, and Periaxin and also to be important for the synthesis of lipids (Nagarajan et al., 2001; Berger et al., 2002; Leblanc et al., 2005). The mouse ortholog of *EGR2* is Krox20 (Chavrier et al., 1989). Analysis of mouse knockouts has demonstrated that Krox20 is important for a number of functions including PNS myelination. In these knockout mice Schwann cells are blocked at an early stage of differentiation with reduction in major components of compacted myelin such as MPZ and myelin basic protein (Schneider-Maunoury et al., 1993). A recent homozygous mouse model using hypomorphic EGR2 alleles (which can survive up to 3 wk postnatally unlike the perinatal lethality of EGR2 null mice) also developed a syndrome similar to CHN in humans (Le et al., 2005a). Functionally these mice had downregulation of myelination related genes and upregulation of genes associated with immature and promyelinating Schwann cells again confirming the importance of EGR2 in myelination.

Pathogenesis of EGR2-Related CMT

Functional studies (Bellone et al., 1999; Warner et al., 1999; Warner and Lupski, 2005) indicate that mutations within the zinc fingers of the EGR2 gene affect DNA binding to a *cis*-acting regulatory site in vitro. The R1 domain mutation (Ile268Asn) prevents interaction of EGR2 with the NAB corepressors and thereby increases transcriptional activity. Ile268Asn is a recessive mutation and all the dominant mutations are found in the zinc fingers (Fig. 6). The severity of the EGR2-related CMT correlates directly with the functional abnormalities although this correlation is based on a limited number of mutations. The dominant zinc finger mutations are thought to act

Table 3
EGR2 Mutations and Clinical Details

EGR2 mutation	Position	Inheritance	Phenotype	MNCV m/s	Nerve biopsy	References
Ile268Asn	803 T > A	Recessive	CHN	3	Absent MF	Warner et al. (1998)
Asp355Val	1064 A > T	Sporadic	Severe CMT1	<19	Mild loss MF, OB	Bellone et al. (1999)
Arg359Trp	1075 C > T	Sporadic	DSD with CN CMT1	≤8 (n = 3) 24.2 (n = 1)	Severe loss MF, OB	Boerkoel et al. (2001); Choi et al. (2004); Taroni et al. (1999); Timmerman et al. (1999)
Arg381Cys	1141 C > T	Sporadic	CMT1 late onset	≤27	Severe loss MF, OB	Yoshihara et al. (2001)
Arg381His	1142 G > A	Dominant	CMT1 with CN	≤28	Severe loss MF, OB	Latour et al. (1999); Pareyson et al. (2000); Warner et al. (1998)
Ser382Arg/ Asp383Tyr	1146 T > G/ 1147 G > T	Sporadic	CHN	≤8	Absent MF, OB	Warner et al. (1998)
Asp383Tyr	1147 G > T	Sporadic	DSD	7.8	Severe loss MF, OB	Numakura et al. (2003)
Arg409Trp	1225 C > T	Dominant	CMT1	≤32	N/A	Warner et al. (1998)
Gly451Val	1352 G > T	Sporadic	CMT ?type	N/A	N/A	Takashima et al. (2001)

CMT, Charcot-Marie-Tooth disease; EGR2, early growth response 2 gene; DSD, Dejerine–Sottas disease; CHN, congenital hypomyelinating neuropathy; MF, myelinated fibers; OB, onion bulbs; n, number of reported cases; N/A, not available; CN, cranial nerve palsies.

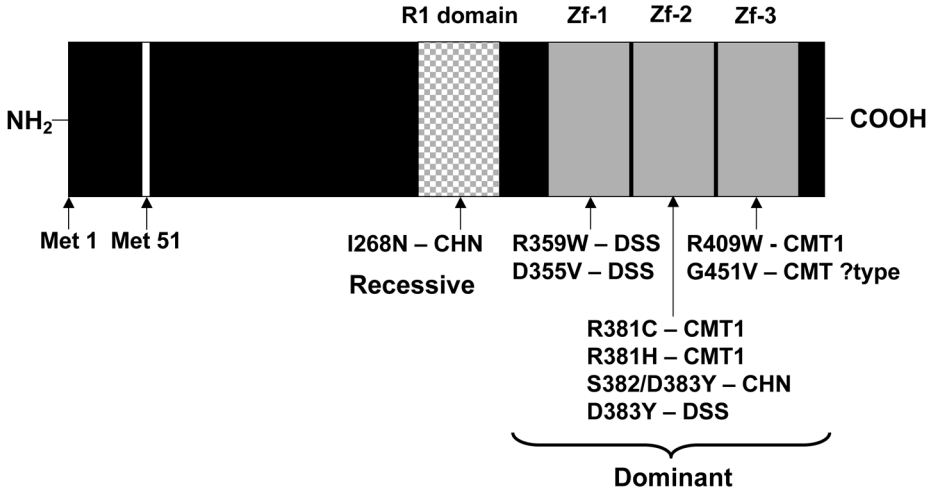

Fig. 6. Structure of the EGR2 gene indicating the location of mutations. Met 1 and Met 51 = alternate start sites. ZF, zinc finger domain.

as dominant-negative or gain-of-function mutations as heterozygous knockout mice are phenotypically normal (Schneider-Maunoury et al., 1993). The phenotype seems to correlate with residual DNA binding activity with complete loss of binding being associated with CMT1 and mutations with some residual binding activity being associated with the more severe DSD/CHN neuropathies (Warner et al., 1998). A complete understanding of the pathway from mutation to specific neuropathy phenotype will require the characterization of additional disease-associated mutations, the identification of downstream PNS-specific target genes of EGR2 and an understanding of the additional factors involved in EGR2 transcriptional regulation.

NAB proteins (NAB1 and NAB2) are critical transcriptional modulators of EGR2 in myelinating Schwann cells. In a similar way to EGR2 these proteins are essential for the differentiation of Schwann cells into the myelinating state. Knockout mice lacking NAB1 and NAB2 show severe congenital hypomyelination of peripheral nerves with Schwann cell development arresting at the promyelinating stage (Le et al., 2005b). The EGR2/ NAB protein complex is a key regulator of Schwann cell myelination and disruption of this complex is likely to lead to Schwann cell dysfunction in patients with EGR2 mutations (Le et al., 2005b). The NAB1 and NAB2 proteins are also candidate genes in peripheral neuropathy but genetic analysis of these genes has so far proven to be negative (Venken et al., 2002).

CMT 2E

Mutations in the Neurofilament Protein Light Polypeptide

Mutations in the neurofilament protein, light polypeptide gene (NEFL) were originally described as causing CMT2 (termed CMT 2E) but subsequently mutations have been shown to cause CMT with nerve conduction velocities in the demyelinating range and pathological changes not only of axonal degeneration but also the presence of small onion bulbs (Klein and Dyck, 2005). Giant axons on sural nerve biopsy have also been described in one family with an NEFL mutation (Fabrizi et al., 2004). The molecular genetics of CMT associated with NEFL mutations will therefore be dealt with more extensively in the review of AD CMT2 and will only be mentioned briefly here.

Genetics

In a large Russian family with axonal CMT, Mersiyanova and colleagues (Mersiyanova et al., 2000b) found linkage to chromosome 8p21 and subsequently they identified a Gln333Pro mutation in the NEFL gene. Other groups (Mersiyanova et al., 2000b; De Jonghe et al., 2001; Jordanova et al., 2003) identified further mutations as outlined in Table 4. NEFL mutations can cause both demyelinating and axonal phenotypes and as such should be screened for both in AD CMT1 and AD CMT2 (Table 4; Fig. 7).

NEFL Function and Pathogenesis of NEFL-Related CMT

Neurofilament light (NEFL) protein is found within the cytoskeleton of myelinated axons and is a member of the group of intermediate neurofilaments. Cytoplasmic intermediate filaments can be divided into five subclasses based on their biochemical properties, immunological specificity and tissue distribution: keratin in epithelial cells, vimentin filaments of mesenchymal origin, desmin in muscle, glial filaments in astrocytes, and neurofilaments (NF) in neurons. NFs are composed of three neuron specific proteins with molecular masses of 68 kD (NEFL), 125 kD (NF medium), and 200 kD (NF heavy) on SDS gel electrophoresis (Julian et al., 1987; Liu et al., 2004). Neurofilaments are important for the structure and also for the function of axons so it was no surprise that mutations in one of these (NEFL) caused CMT2. The finding of demyelinating CMT associated with NEFL is not that surprising considering the complex axonal–Schwann cell interactions that exist in the PNS. There was also the precedence of mutations in the major myelin protein MPZ, also causing both CMT1 and CMT2 (*see* section on CMT1B).

Transgenic mice bearing a target disrupted NEFL gene were generated by Zhu and colleagues (1997). The lack of NEFL gene produced not only the absence of NEFL protein but also a significant reduction in the NF medium and heavy chain proteins in the brain and sciatic nerve. These mice had hypertrophied axons but developed normally suggesting that mutations in humans do not cause a phenotype due to a simple loss of function (Berger et al., 2002). Crush injury to nerves in these mice developed clusters of axonal sprouts and eventual remyelination but at a slower rate suggesting NFs play a role in maturation

Table 4
Mutations Identified in the NEFL Gene

NEFL mutation	Position	Phenotype	References
Glu7Lys	19 G > A	Unspecified CMT	Jordanova et al. (2003)
Pro8Arg	23 C > G	CMT1/2	De Jonghe et al. (2001); Jordanova et al. (2003)
Pro8Leu	23 C > T	CMT1	Jordanova et al. (2003)
Pro8Gln	23 C > A	CMT1	Jordanova et al. (2003)
Pro22Thr	64 C > A	CMT1	Yoshihara et al. (2002)
Pro22Ser	64 C > T	CMT1/2	Fabrizi et al. (2004); Georgiou et al. (2002)
Glyn89Lys	265 G > A	CMT1	Jordanova et al. (2003)
Asn97Ser	290 A > G	CMT1	Jordanova et al. (2003); Yoshihara et al. (2002)
Ala148Val	443 C > T	Unspecified CMT	Yoshihara et al. (2002)
Gln333Pro	998 A > C	CMT2	Mersiyanova et al. (2000b)
Leu334Pro	1001 T > C	CMT2	Choi et al. (2004)
Glu397Lys	1189 G > A	CMT1/CMT2	Choi et al. (2004); Zuchner et al. (2004)
Glu528Del	1582_1584del GAG	CMT1/?polymorphism	Yoshihara et al. (2002); Jordanova et al. (2003); Yamamoto et al. (2004)

CMT, Charcot-Marie-Tooth disease; NEFL, neurofilament protein light polypeptide gene; Del, deletion.

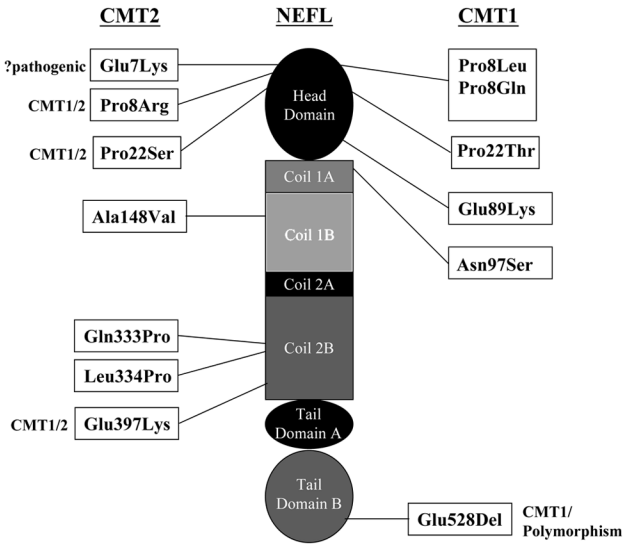

Fig. 7. NEFL mutations and their position shown on the NEFL protein.

of myelinated axons. Brownlees and colleagues (2002) used a transient expression system to demonstrate that the NEFL Pro8Arg and Gln333Pro mutations disrupted neurofilament assembly, axonal transport in mammalian cells, and neurons and perturbed the localization of mitochondria in neurons. The finding of mutations in NEFL as a cause of CMT was of particular interest as neurofilament proteins had already been described as being important in the pathogenesis of other neurological disorders including Alzheimer's disease, Parkinson's disease, motor neuron disease, and also a rare autosomal-recessive neuropathy, giant axonal neuropathy (Lupski, 2000).

Conclusions

The number of genes associated with CMT and their overlapping phenotypes has expanded and no doubt this expansion will continue over the next few years. From a clinician's perspective this makes the genetic diagnosis more complex, but it does increase the chance of identifying the genetic cause in a patient with inherited demyelinating neuropathy to over 95%. This makes DNA testing a very important investigation in this particular type of CMT. When the disease genes discussed above were first identified they initially were in families with clear autosomal-dominant demyelinating CMT. As more patients are analyzed the phenotype that a particular mutant gene can cause has expanded to include a range of severities as well as rare cases with axonal CMT2 (Table 5). The inheritance pattern has also expanded with AD, *de novo*, AR and

Table 5
Phenotypes Associated With Demyelinating CMT Genes

Phenotypes	CMT1	DSD	CHN	CMT2
Ch17p11.2 duplication	Yes	Yes	No	No
PMP22	Yes	Yes	Yes	No
MPZ	Yes	Yes	Yes	Yes
EGR2	Yes	Yes	Yes	No
NEFL	Yes	No	No	Yes
LITAF	Yes	No	No	Yes

CMT, Charcot-Marie-Tooth disease; *PMP22*, peripheral myelin protein 22 gene; *MPZ*, myelin protein zero gene; *EGR2*, early growth response 2 gene; *LITAF*, lipopolysaccharide-induced TNF factor gene; *NEFL*, neurofilament protein light polypeptide gene; DSD, Dejerine–Sottas disease; CHN, congenital hypomyelinating neuropathy.

somatic and germline mosaicism (Fabrizi et al., 2001) being identified in the most widely analysed genes such as MPZ.

Although there have been major advances in the understanding of both the normal function of the proteins translated from the causative genes for AD CMT1 and indeed for CMT in general and also in the pathogenesis of the neuropathies caused by these proteins when mutated, there remains many unanswered questions. These questions relate both to the individual disease mechanisms associated with each mutant gene but also to the emergence of common pathways in which these proteins play a role and which may be important in the pathogenesis of the neuropathy. Future studies of both the individual genes and then proteome analysis of the post translational pathways will be important.

Genotype–phenotype correlations have also been very useful in the investigation of many of the CMT disease genes and will be increasingly important as the range of phenotypes described with each gene broadens. So far these genotype–phenotype studies have been most useful in MPZ related neuropathies (Shy et al., 2004). Although the data is limited, there is some indication to suggest that EGR2 mutants might correlate with CMT phenotype and the in vitro functional consequences (Bellone et al., 1999; Warner et al., 1999). In CMT1A owing to the chromosome 17 duplication there is an immense spectrum of disease from clinically unaffected individuals through to DSD. The variation in phenotypes seen with this particularly common form of CMT strongly suggests that both environmental modifiers, as already suggested (Ginsberg et al., 2003), and genetic modifiers will also be important in determining the phenotype with the chromosome 17 duplication but also in other forms of CMT. The next step in identifying modulating genes will be microarray analysis, large scale analysis of genetic variation in the duplicated region and further association studies on polymorphisms in other neuropathy genes. The investigation of the molecular genetics of CMT is currently entering a very exciting phase especially as recent animal studies have stimulated the first therapeutic trials in CMT.

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