

# Charcot-Marie-Tooth Disease: Seventeen Causative Genes

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Charcot-Marie-Tooth disease (CMT) is the most common form of inherited motor and sensory neuropathy. Moreover, CMT is a genetically heterogeneous disorder of the peripheral nervous system, with many genes identified as CMT-causative. CMT has two usual classifications: type 1, the demyelinating form (CMT1); and type 2, the axonal form (CMT2). In addition, patients are classified as CMTX if they have an X-linked inheritance pattern and CMT4 if the inheritance pattern is autosomal recessive. A large amount of new information on the genetic causes of CMT has become available, and mutations causing it have been associated with more than 17 different genes and 25 chromosomal loci. Advances in our understanding of the molecular basis of CMT have revealed an enormous diversity in genetic mechanisms, despite a clinical entity that is relatively uniform in presentation. In addition, recent encouraging studies - shown in CMT1A animal models - concerning the therapeutic effects of certain chemicals have been published; these suggest potential therapies for the most common form of CMT, CMT1A. This review focuses on the inherited motor and sensory neuropathy subgroup for which there has been an explosion of new molecular genetic information over the past decade.

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**Key Words** : Charcot-Marie-Tooth disease, Neuropathy, Axon, Gene, Mutation

## INTRODUCTION

Charcot-Marie-Tooth disease (CMT) is the most common form of inherited motor and sensory neuropathy.<sup>1</sup> CMT is genetically and clinically a heterogeneous disorder of the peripheral nervous system, and mutations of many CMT genes are known to be responsible for the development of a variety of distinct phenotypes.<sup>2</sup> In 1886, Charcot and Marie in France and, independently, Tooth in the United Kingdom described hereditary motor and sensory neuropathies for the first time (Fig. 1).<sup>3,4</sup> Today, the classification of CMT has been revised and

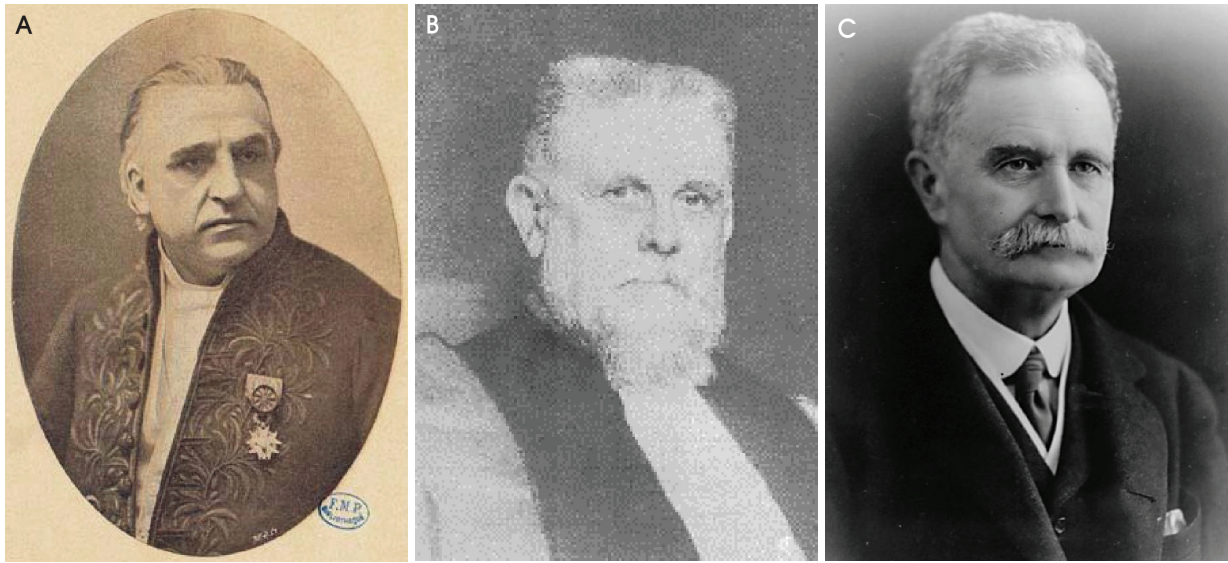
extended based on clinical features and electrophysiological, histopathological, and genetic findings.<sup>5</sup>

Autosomal-dominant inherited CMT is usually classified as type 1, the demyelinating form (CMT1), or type 2, the axonal form (CMT2).<sup>6</sup> CMT1 patients have severely reduced nerve conduction velocities (NCVs). The upper limit of NCV for the motor median nerve in CMT1 patients is 38 m/s.<sup>7</sup> Histopathological examinations of peripheral nerve biopsies frequently reveal extensive segmental demyelination and remyelination.<sup>8</sup> The primary defect of CMT2 patients is neuronal.<sup>9</sup> We classify patients as having CMTX if they have an X-linked inheritance pattern, and CMT4 if the inheritance pattern

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**Figure 1.** Contemporary portraits of Charcot (A), Marie (B), and Tooth (C). In 1886, Frenchmen Jean Martin Charcot (1825~1893) and Pierre Marie (1853~1940), and Briton Howard Henry Tooth (1856~1925), described hereditary motor and sensory neuropathies for the first time.

is autosomal recessive.<sup>9</sup>

Considerable new information about the pathophysiology and causative genes of CMT has recently become available.<sup>2</sup> To date, mutations causing inherited neuropathies have been associated with at least 17 different genes, and chromosomal loci have been identified in more than 25 others (see Table 1).<sup>6</sup> These investigations are helpful not only for the pathophysiologic studies of peripheral neuropathies but also the clinical and genetic classification of complex peripheral nerve disease. Onapristone, ascorbic acid, and neurotrophin-3 (NT3) have recently been introduced for the treatment of CMT.<sup>10-12</sup> In this review, we focus on the 17 gene mutations that are known to cause CMT, and discuss the biological mechanisms of the peripheral neuropathies associated with myelin and axons.

### GENES ASSOCIATED WITH DEMYELINATING NEUROPATHY

Myelin plays an important role in the saltatory transmission of impulses along neuronal extensions.<sup>8</sup> As part of the process of myelination, myelin-forming Schwann cells trap large-caliber axons within their plasma mem-

branes during the development of the peripheral nervous system.<sup>13</sup> Faulty communication between Schwann cells and neurons, due to genetic defects, frequently leads to these peripheral neuropathies.<sup>8</sup>

#### 1. *PMP22*

The peripheral myelin protein 22 (*PMP22*) gene is located within the duplication region. Several lines of evidence implicate alterations in gene dosage of *PMP22* as the main factor underlying the CMT1A phenotype.<sup>14,15</sup> This means that patients carrying one extra copy of *PMP22* develop CMT1A, while patients with HNPP (hereditary neuropathy with liability to pressure palsies) deletion have only one copy of *PMP22* (Fig. 2).

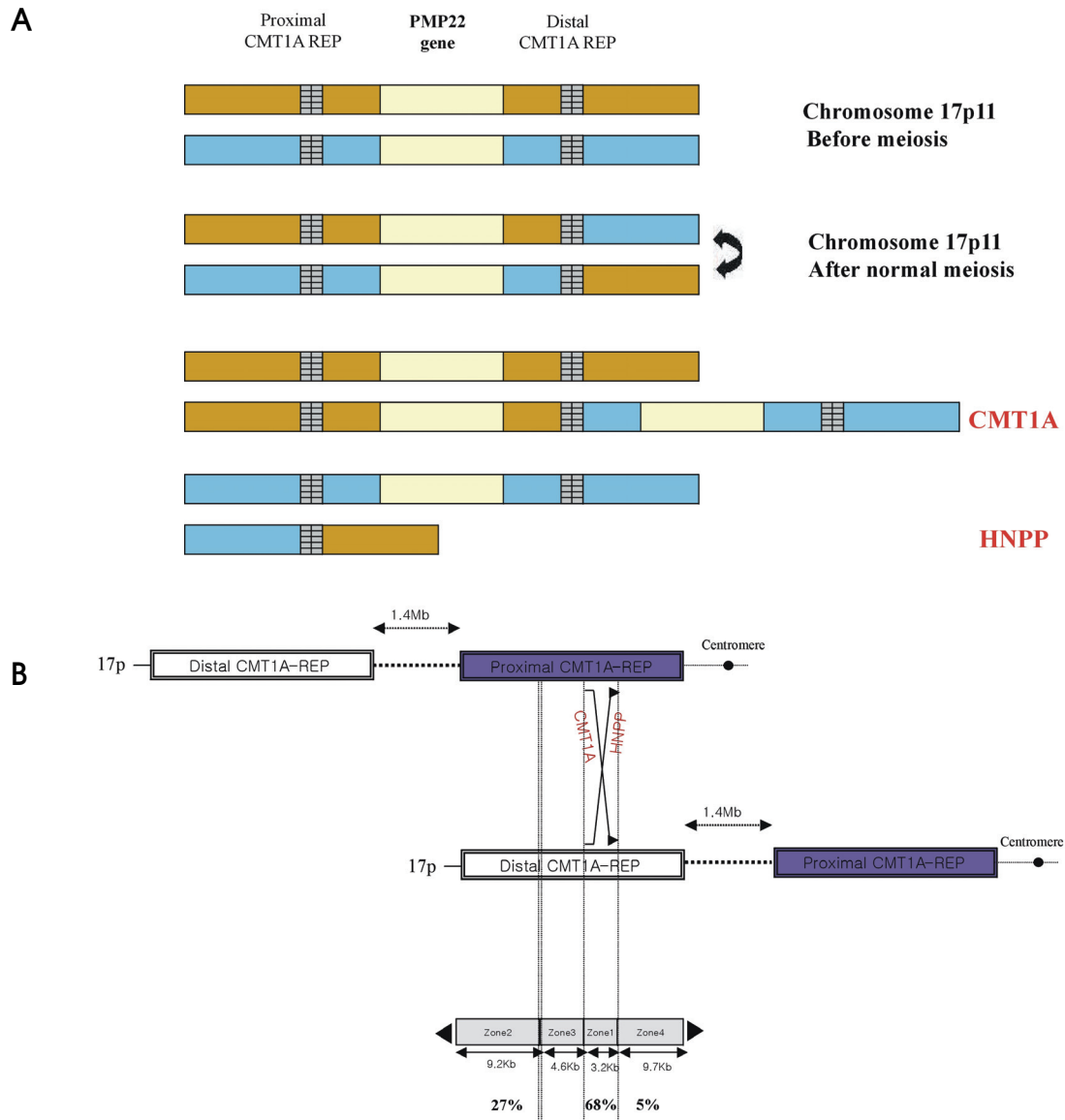
##### 1) *PMP22* duplication

Tandem duplication of the CMT1A region within chromosome 17p11.2-p12, including the *PMP22* gene, is the most frequent cause of CMT type 1.<sup>16</sup> This duplication is caused by an unequal crossover event between two homologous repetitive elements flanking the 1.4-Mb region.<sup>16</sup> Approximately 50% of all CMT patients have this duplication, as do at least 70% of all patients with CMT1.<sup>17</sup> Patients carrying one extra copy of *PMP22*

Table 1. A list of causable seventeen mutations of hereditary motor and sensory neuropathies

Gene	Phenotype	Inheritance	Locus	Protein	Mutation	Testing method
<b>Genes associated with demyelinating neuropathy</b>						
<i>PMP22</i>	CMT1A CMT1A DSS CH	AD AD	17p11.2	Peripheral myelin protein 22	Duplication Point mutation	FISH, STR, Southern blot, Pulse-field gel electrophoresis Sequencing, mutation scanning, mutation analysis
<i>PMP22</i>	HNPP	AD	17p11.2	Peripheral myelin protein 22	Deletion Point mutation /small deletion	Mutation analysis, STR, FISH, long PCR-RFLP, Southern blot Sequencing, mutation scanning, mutation analysis
<i>EGR2</i>	CMT1D DSS CH CMT4E	AD AR	10q21.1-q22.1	Early growth response protein 2	Point mutation	Sequencing, mutation scanning, mutation analysis
<i>LITAF</i>	CMTIC CMT4F CMT4B1 CMT4B2	AD AR AR AR	16p13.1-p12.3 19q13.1-q13.2 11q22 11p15	SIMPLE Periaxin Myotubularin-related protein 2 SET binding factor 2	Point mutation Point mutation Point mutation Point mutation	Sequencing, mutation analysis Sequencing, Sequencing, Sequencing,
<b>Genes associated with axonal neuropathy</b>						
<i>MFN2</i>	CMT2A	AD	1p36.2	Mitofusin 2	Point mutation	Sequencing,
<i>KIF1B</i>	CMT2A	AD	1p36.2	Kinesin-like protein KIF1B	Point mutation	Sequencing,
<i>RAB7</i>	CMT2B	AD	3q21	Ras-related protein Rab-7	Point mutation	Sequencing,
<i>HSP27</i>	CMT2F dHMN	AD AD	7q11-21	Small heat shock protein 27	Point mutation	Sequencing,
<i>GARS</i>	CMT2D	AD	7p15	Glycyl-tRNA synthetase	Point mutation	Sequencing,
<b>Genes associated with both demyelinating and axonal neuropathies</b>						
<i>MPZ</i>	CMT1B DSS CH CMT2	AD AD AD	1q22	Myelin protein zero	Point mutation	Sequencing, mutation scanning, mutation analysis
<i>NEFL</i>	CMT2E CMT1 DSS	AD AD	8p21	Neurofilament triplet L protein	Point mutation	Sequencing,
<i>GJB1</i>	CMTX	X-linked	Xq13.1	Gap junction beta-1 protein (connexin 32)	Point mutation Deletions (rare)	Sequencing, mutation scanning, mutation analysis
<i>GDAPI</i>	CMT4A	AR	8q13-q21.1	Ganglioside-induced differentiation protein-1	Point mutation Point mutation	Sequencing,
<b>Genes with unknown function</b>						
<i>Gigaxonin</i>	GAN	AR	16q24.1	Gigaxonin	Point mutation	
<i>KIAA1985</i>	CMT4C	AR	5q32		Point mutation	

AD; autosomal dominant, AR; autosomal recessive, CMT; Charcot-Marie-Tooth disease, DSS; Dejerine-Sottas syndrome, HNPP; hereditary neuropathy with liability to pressure palsy, CH; congenital hypomyelination, GAN; giant axonal neuropathy, dHMN; distal hereditary motor neuropathy.



**Figure 2.** (A) CMT1A duplication and HNPP deletion are reciprocal products of a recombination event (unequal crossing-over) during meiosis, mediated by the flanking repeat elements (CMT1A-REPs). (B) Genomic map of the chromosome 17p11.2-p12. The genomic structure of the CMT1A/HNPP region (telomere-to-centromere orientation). Proximal and distal CMT1A-REPs are shown as vertical boxes.

develop CMT1A, whereas entire, or even partial, deletion of the 17p11.2-p12 region causes HNPP. Duplication or deletion of the 1.4-Mb fragment is the primary causative mutation, but it is not found in all cases of CMT1A and HNPP.<sup>18</sup> In rare cases, missense or frame-shift mutations in the *PMP22* gene lead to CMT1A and HNPP.<sup>19,20</sup> The symptoms occurring in mice carrying an additional copy of *PMP22* are similar to those of patients with human

peripheral myelin protein duplication.<sup>21</sup>

It has been reported that the administration of the selective progesterone receptor antagonist onapristone reduces overexpression of *PMP22* and impairs the CMT phenotype, without obvious side-effects.<sup>10</sup> In addition, Passage et al. reported, with their mouse model of CMT1A, that ascorbic acid had an important effect in myelination and in reducing *PMP22* concentrations to

levels below those necessary to induce the disease phenotype.<sup>11</sup>

## 2) *PMP22* deletion

HNPP patients are characterized by recurrent pressure palsies and nerve biopsies from them show sausage-like swellings (tomacula) of the myelin sheaths.<sup>22</sup> Deletion of the chromosome 17p11.2-p12 region that includes *PMP22* frequently provides the genetic basis of hereditary peripheral demyelinating neuropathy such as HNPP (Fig. 2).<sup>23,24</sup> Mutations and altered dosage of the *PMP22* gene are regarded as the main reasons for hereditary peripheral neuropathies.<sup>25,26</sup> Deletion is the most frequent mutation, but is not found in all cases of HNPP. In rare cases, frame-shift mutations in the *PMP22* gene lead to HNPP.<sup>19,20</sup>

Clinical assessments of HNPP patients are generally less severe than those of CMT1A patients.<sup>26-28</sup> HNPP usually develops as a painless neuropathy after minor trauma or compression. The mean ages of onset of HNPP and CMT1A are not significantly different; however, onset in the preteens was found to be more frequent in CMT1A than in HNPP.<sup>27,28</sup>

## 3) *PMP22* point mutation

Although the point mutation of the *PMP22* gene is rare, it is also a cause of CMT1A and HNPP.<sup>19,20,29</sup> Patients carrying the *PMP22* point mutation of the *PMP22* gene show similar clinical features to those carrying duplication or deletion.<sup>20,29</sup> However, in rare cases, patients with *PMP22* point mutations show an early age of onset and severe phenotypes, such as Déjérine-Sottas syndrome (DSS).<sup>30</sup> In addition, audiological evaluation can reveal auditory neuropathy in the affected individual with a frame-shift mutation Ala106fs (318delT) in the *PMP22* gene.<sup>31</sup>

## 2. *EGR2*

The early growth response 2 (*EGR2*) gene encodes a zinc finger transcription factor that plays a major role in myelination of peripheral nerves.<sup>32</sup> *EGR2* mutations are associated with a dominantly inherited severe form of CMT1, giving syndromes of congenital hypomyelination

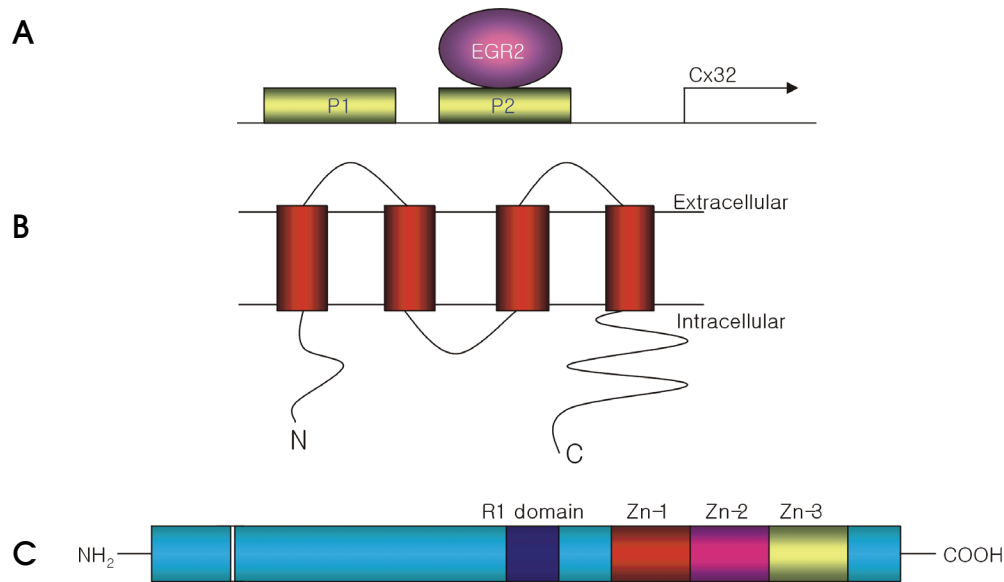
(CH), DSS, or CMT4E with recessive inheritance.<sup>33</sup> Disruption of the *EGR2* gene in mice blocks the development of Schwann cells at the promyelinating stage and causes demyelinating peripheral neuropathy by preventing PNS myelination.<sup>34</sup> Thus, the normal expression of the *EGR2* gene is very important in the process of Schwann cell development.<sup>34</sup> In a recent study, overexpression of *EGR2* in Schwann cells strongly increased the expression of other myelin-related genes; therefore, *EGR2* mutation may cause a demyelinating form of CMT.<sup>35</sup>

A CMT family with two missense mutations in different genes has been reported.<sup>36</sup> A R359W mutation in *EGR2* was shared by the affected daughter and her father. In addition, she had a V136A mutation in *GJB1*, which was determined to be a *de novo* mutation. The daughter with two different gene mutations showed more severe clinical, electrophysiological, and histopathological phenotypes than her father, who had only the *EGR2* mutation. These phenotypic differences between the proband and her father may have been caused by an altered effect of the genetic modifier in *EGR2*, or by the additive effect of the *EGR2* and *GJB1* mutations.<sup>36</sup>

The *EGR2* gene regulates the expressions of myelin genes, including *GJB1*, *PMP22*, *P0*, and *PRX* in a dominant-negative manner.<sup>37,38</sup> Mutations in *EGR2* prevent Schwann cell development, and lead to the development of demyelinating neuropathy via the regulation of *GJB1* expression (Fig. 3).<sup>37</sup> Moreover, it is known that the R359W mutation in *EGR2* reduces transcriptional activity in *GJB1*.<sup>38</sup>

## 3. *LITAF*

Mutations in the *LITAF* (lipopolysaccharide-induced tumor necrosis factor- $\alpha$  factor, also referred to as *SIMPLE*) gene cause the demyelinating autosomal dominant disease CMT1C.<sup>9</sup> Patients with CMT1C have decreased NCVs of 20~25 m/s, along with mild weakness and sensory loss that first presents within the first two decades of life.<sup>39</sup> They show very similar clinical findings to CMT1A. *SIMPLE* is a protein encoded by the *LITAF* gene and may interact with Nedd4, an E3 ubiquitin ligase.<sup>40</sup> Although *SIMPLE* is expressed in



**Figure 3.** Genomic structures of *GJB1* (A) and *EGR2* (B). The *EGR2* gene encodes a zinc finger transcription factor that plays a major role in myelination of the peripheral nerves, and the *EGR2* gene regulates the expressions of *GJB1*. Thus, mutations in *EGR2* prevent Schwann cell development and lead to the development of demyelinating neuropathy (C).

many cell types, when mutated it seems to cause only a demyelinating neuropathy. The disease specificity may result from the impaired degeneration of specific Schwann cell proteins.<sup>40</sup>

#### 4. *PRX*

CMT4F is a severe form of recessive CMT that has been defined in a large Lebanese family with mutations in the periaxin (*PRX*) gene on chromosome 19.<sup>41</sup> Nerve conduction is markedly slowed and onion bulbs are observed on sural nerve biopsies. *PRX* is a protein specifically expressed by myelinating Schwann cells.<sup>42</sup> In adult myelinated fibers, *PRX* is found in the abaxonal membrane.<sup>38</sup> During development, *PRX* is found in the adaxonal membrane or periaxonal cytoplasm of the myelinating Schwann cell and may have some additional function.<sup>43,44</sup> Furthermore, an isoform of *PRX* is targeted to the nucleus of embryonic Schwann cells, suggesting that this protein can shuttle between the nucleus and cortical signaling or adherence complexes. Histopathological analysis of a nerve biopsy from a CMT4F patient revealed disruption of the connection between the paranodal loop and the adjacent axon; structural abnor-

mality of the paranode was also present.<sup>45</sup>

#### 5. *MTMR2*

Mutations in the gene encoding myotubularin-related phosphatase 2 (*MTMR2*) cause a severe autosomal-recessive, demyelinating neuropathy, CMT4B1, which has also been called hereditary motor and sensory neuropathy with focally folded myelin sheaths.<sup>46</sup> *MTMR2* contains a homologous 10-amino acid sequence with an active site for both tyrosine and serine phosphate.<sup>47</sup> The function of *MTMR2* is not yet known. However, teased fibers from sural nerve biopsy samples showed segmental demyelination associated with redundant loops of myelin, suggesting that *MTMR2* has an important role in the regulation of myelin wrapping.<sup>48</sup>

#### 6. *SBF2*

Mutations in *MTMR13/SBF2* have been identified in severe autosomal recessive demyelinating CMT, CMT4B2.<sup>49</sup> *SBF2* is located on chromosome 11p15 and is also known as myotubulin-related protein 13 (*MTMR13*). *MTMR13/SBF2* is a homologue of *MTMR2*, which

causes CMT4B1.<sup>49</sup> This is probably the reason for CMT4B2 neuropathy resembling that of CMT4B1 both clinically and pathologically. These peripheral neuropathies show very severe disabilities in infancy and extremely slow NCVs. Sometimes patients are wheelchair-bound by adulthood. Because the pathological findings of CMT4B1 and CMT4B2 are found simultaneously with the misfoldings of myelin, they probably share a common pathological mechanism. *SBF2* might regulate phosphatase activity by interacting with *MTMR2*.<sup>9</sup>

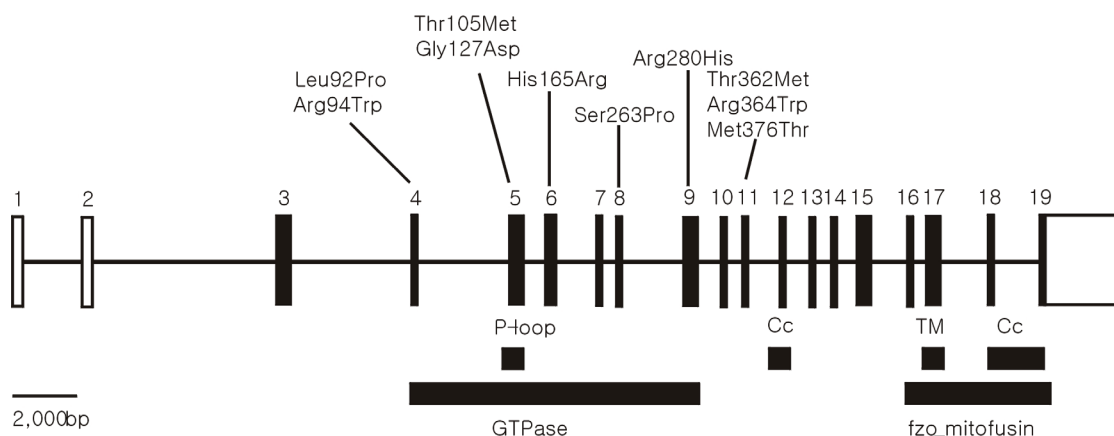
**GENES ASSOCIATED WITH AXONAL NEUROPATHY**

1. *MFN2*

By linkage analysis and screening genes linked to the CMT2A locus, Züchner et al. first identified several mutations in the mitofusion 2 (*MFN2*) gene.<sup>50</sup> Subsequently, additional *MFN2* mutations were reported in CMT2A patients (Fig. 4).<sup>51,52</sup> Thus, mutations in *MFN2* are now considered to provide the genetic basis of the CMT2A phenotype. Mitofusin 2 encodes an outer mitochondrial membrane protein which, in cooperation with the MFN1 isoform, has important roles in the regulation of mitochondrial fusion,<sup>53-55</sup> a function essential for metabolic activity in eukaryotic cells.<sup>56</sup> It has also been

suggested that *MFN2* may be associated with maintaining mitochondrial membrane potentials.<sup>57</sup> Moreover, *MFN2*-deficient mice die in mid-gestation and display fragmented mitochondria.<sup>54</sup> It is also believed, from a few population-based studies, that *MFN2* mutations are most common in CMT2.<sup>58</sup> Recently, axonal CMT neuropathy with visual impairment due to optic atrophy - designated as hereditary motor and sensory neuropathy type VI (HMSN VI) - has also been shown to be caused by mutations in the *MFN2* gene.<sup>59</sup> It is well known that HMSN VI is an axonal CMT neuropathy with optic atrophy. However, the differences between CMT2A and HMSN VI with *MFN2* mutations remain to be clarified. It appears that mutational loci with high frequency might exist in *MFN2* at the 94th, 105th, 280th, and 364th codons.<sup>60</sup>

Ethnic population data on *MFN2* mutations are limited because the relevance of the *MFN2* mutation to CMT2 has been reported only recently.<sup>50</sup> Züchner et al. reported 7 mutations (19%) in 36 CMT2 families representing several ethnic groups; a Japanese group reported 7 mutations (9%) in 81 axonal or unclassified CMT patients,<sup>47</sup> and an American study found 3 mutations (23%) in 13 CMT2 families.<sup>50-52</sup> In addition, *MFN2* mutations have been identified in 22% of Korean CMT2 families.<sup>60</sup> The mutation frequency observed by the Japanese group was lower than that found in the other studies, which may be due to sampling or analytical



**Figure 4.** Genomic structure and mutations of *MFN2*. Solid black boxes and solid white boxes indicate protein coding sequences and untranslated sequences, respectively. P, loop; GTP, binding-site motif; Cc, coiled-coil domain; TM, transmembrane domain; GTPase, GTPase functional domain; fzo mitofusin, fzo mitofusin functional domain.

differences or perhaps to different genetic backgrounds. Kijima et al. performed denaturing high-performance liquid chromatography (HPLC) prior to sequence analysis, a process that may have reduced the detection rate.<sup>51</sup>

Mutations in the *MFN2* gene are now viewed as the primary cause of axonal autosomal-dominant CMT2A, and it has therefore been suggested that these patients should be screened for *MFN2*. However, clinical and electrophysiological phenotypes of CMT patients with *MFN2* mutations were significantly different in early- and late-onset groups, and optic atrophy was found only in CMT2 patients with unusually severe phenotypes with an early onset age. In addition, *MFN2* mutations show variable central nervous system (CNS) involvements.

## 2. *KIF1B*

Following the mapping of CMT2A to the short arm of chromosome 1, 1p35-p36, a missense mutation was detected in *KIF1B* in a Japanese CMT2A family.<sup>61</sup> However, no other mutation has been identified in *KIF1B*, and it is therefore believed that another gene is involved.<sup>62,63</sup> The kinesin superfamily is responsible for microtubule-dependent transport of a variety of organelles and vesicles.

## 3. *RAB7*

It has been reported that mutations in the ras-related protein rab-7 (*RAB7*) gene cause the axonal form of CMT known as CMT2B.<sup>64</sup> *RAB7* is a member of the Rab family of small G proteins, which regulate intracellular vesicle traffic. *RAB7* and its effector protein, RILP, have been shown to play a role in lysosomal transport by inducing the recruitment of dynein-dynactin motors.<sup>65</sup> Mutations in dynactin also cause axonopathy, suggesting that two separate diseases may share a common pathway.

## 4. *sHSP27*

Mutations of the small heat-shock proteins (sHSPs) are reported to cause either CMT2 or a distal hereditary

motor neuropathy (dHMN).<sup>66</sup> It is known that *sHSPs* are part of a protein superfamily sharing 85 amino acid residues in a C-terminal region known as the  $\alpha$ -crystalline domain, although the function of sHSP is unclear. However, it is believed that sHSP27 is associated with protection from apoptosis and stabilization of the cytoskeleton.<sup>67</sup> Irobi et al.<sup>66</sup> reported that mutations in the  $\alpha$ -crystalline domain of *sHSP22* cause dHMN type II; Evgrafov et al.<sup>68</sup> suggested that mutations in the  $\alpha$ -crystalline and C-terminal tail of *sHSP27* cause either CMT2F or another dHMN. It seems that *sHSP22* and *sHSP27* interact with each other, and both diseases involve common mechanisms.<sup>69,70</sup>

## 5. *Glycyl-tRNA synthetase*

*Glycyl-tRNA synthetase* is known to cause CMT2D.<sup>71</sup> In four families with CMT2D, mutation of *Glycyl-tRNA synthetase* provided the first example of an aminoacyl tRNA synthetase which was related to human genetic disease.<sup>71</sup> Why a mutation in a tRNA synthetase should cause only a chronic neuropathy but spare other organ systems is both unknown and surprising.

### GENES ASSOCIATED WITH BOTH DEMYELINATING AND AXONAL NEUROPATHIES

#### 1. *MPZ*

Mutations in the myelin protein zero (*MPZ*) gene, which is located on chromosome 1q21-q22, are present in CMT1B, CMT type 2, DSS, and CH neuropathy.<sup>72,73</sup> It is proposed that the nature and position of the *MPZ* mutations largely determine the axonal and demyelinating phenotypes. *MPZ* is highly expressed by myelinating Schwann cells and in more than half the protein in the peripheral myelin sheet. The clinical, electrophysiological, and histopathological findings appear to be heterogeneous for *MPZ* mutations.<sup>74</sup> Furthermore, the same mutation can cause different degrees of disease severity in different patients.<sup>75</sup>

The protein consists of 248 amino acids and a single extracellular immunoglobulin-related domain (which

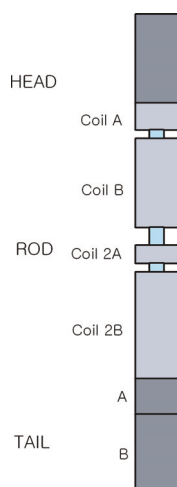


mediates homophilic adhesion), a transmembrane domain, and a short basic intracellular domain.<sup>76</sup> *MPZ* knock-out mice show abnormal regulation of myelin gene expression such as upregulation of *MAG* and *PLP* and down-regulation of *PMP22*.<sup>77</sup> The myelination regulatory mechanism of *MPZ* is through adhesion-mediated signal transduction.<sup>78</sup> By this hypothesis, the in vitro mutations of *MPZ* are associated with decreased *MPZ*-mediated adhesion and these changes cause the more severe clinical features.

## 2. *NEFL*

Neurofilament light-chain polypeptide (*NEFL*) is one of the most abundant cytoskeletal components of the neuron.<sup>79</sup> The *NEFL* gene encoding the neurofilament plays an important role in axonal structure, including that of the extensive fibrous network in the cytoplasm of the neuron (Fig. 5).<sup>79</sup> Mutations in the *NEFL* gene usually cause axonal CMT2E neuropathy, but recent studies found that *NEFL* mutations cause the demyelinating forms of neuropathy common to CMT1 and DSS.<sup>80</sup>

Nerve conduction studies of CMT2E patients showed



**Figure 5.** Structure of the *NEFL* protein, which is one of the most abundant cytoskeletal components of the neuron. The *NEFL* gene encoding the neurofilament light chain plays an important role in axonal structure, including an extensive fibrous network in the cytoplasm of the neuron.

that NCV is not decreased severely. These findings suggest that the pathophysiological mechanism of the neuropathy is primary axonal damage.<sup>81</sup> A patient with *NEFL* gene mutation shows proximal muscle weakness, normal NCV, and reduced motor and sensory nerve action potential amplitudes, findings compatible with typical CMT2. Transgenic mice harboring loss of *NEFL* genes show a normal phenotype; however, NCVs are severely reduced.<sup>82,83</sup> Mutation of the *NEFL* gene could be the cause of both CMT1 and CMT2 neuropathies. Population data on the mutation frequencies of the *NEFL* gene are very limited. The frequencies of *NEFL* were 4.8% in Koreans and 2.2% in Caucasian CMT patients.<sup>84,85</sup>

## 3. *GJB1*

CMTX is the second-most-frequent form of CMT, and is caused by mutations in the gene for gap junction protein beta 1 (*GJB1*: connexin 32, Cx32), which maps to chromosome Xq13.<sup>86,87</sup> CMTX patients display the distinctive criterion of an X-linked mode of inheritance; that is, an absence of man-to-man transmission and a more severe disease phenotype in affected males than in affected females of the same age.<sup>88</sup> Motor nerve conduction is slower in CMTX males, but ranges from slightly reduced to normal in females.<sup>89</sup> The nature of the neuropathy in CMTX remains controversial, and it could be a primary axonal neuropathy or a primary demyelinating neuropathy with secondary axonal degeneration.<sup>90,91</sup>

The *GJB1* gene is involved in the transport of small molecules within Schwann cells.<sup>92</sup> Gap junctions allow electrical communication between cells in the nervous system and *GJB1* mutations affect the function of gap junctions in the myelin sheath.<sup>93</sup> Gap junctions comprise intercellular channels among adjacent cells and they are distributed in the liver, kidneys, and CNS as well as the peripheral nerves.<sup>94</sup> Since the *GJB1* gene is expressed not only in Schwann cells but also in oligodendrocytes, *GJB1* mutation has been reported to cause CNS lesions.<sup>95</sup> There are over 200 mutations associated with various degrees of muscular weakness, atrophy, and sensory impairment. In studies of CMTX patients, muta-

tion of *GJBI* more or less destroyed the structure of the myelin and the action potential amplitude was more affected than the NCV.<sup>96</sup> Sural nerve biopsy confirmed that there was prominent axonal loss.<sup>97</sup>

The mutation frequency of *GJBI* in Korea (7.1%)<sup>85</sup> is considerably lower than in several European groups - Spain, 21.3%<sup>98</sup>; Finland, 19.0%<sup>99</sup>; Russia, 13.0%<sup>100</sup>; Italy, 16.7%<sup>101</sup>; Germany, 11.9%<sup>102</sup> - but is similar to that in Japan (5.6-5.7%).<sup>103,104</sup> It appears that mutations in *GJBI* are less frequent in East Asian CMT patients than in European patients.

#### 4. *GDAP1*

CMT4A is linked to 8q13-q21.1 and is caused by mutations in ganglioside-induced differentiated associated protein 1 (*GDAP1*), a novel protein of unknown function.<sup>105</sup> Clinical symptoms begin at an early age (before 10 years), with delayed developmental milestones of sitting or walking; weakness spreads to proximal muscles by the end of the first decade. However, sensory loss is mild. In other patients, hoarse voice and vocal cord paresis have been reported. Axonal and demyelinating phenotypes have been associated with *GDAP1* mutations, which could be the cause of both the demyelinating and axonal neuropathies.<sup>106</sup> The *GDAP1* gene is found in the nerve cell at an early stage of development but its expression is found in the Schwann cell.<sup>107</sup> It is not yet known if mutation of the *GDAP1* gene damages the nerve cell, Schwann cell, or both. However, a likely hypothesis is that mutation of the *GDAP1* gene disturbs signal transmission between Schwann cells and nerve cells.

### GENES WITH UNKNOWN FUNCTION

#### 1. *Gigaxonin*

Mutations in the Gigaxonin gene lead to a rare autosomal-recessive giant axonal neuropathy (GAN) affecting the peripheral nervous system and CNS.<sup>108</sup> Prominent axonal swelling occurs, with masses of tightly woven neurofilaments - commonly found near nodes of

Ranvier - producing an increase in axon caliber.<sup>109</sup> This causes the main stigmata of the disease. Abnormalities in the organization of neurofilaments are also found in the brains of these patients, and are the possible cause of the associated mental retardation.

GAN includes abnormal intermediate neurofilaments and displays the typically kinky-hair-like filaments. The mechanism of the disease is unknown, but the peripheral neuropathy is developed by the mutation of the *Gigaxonin* gene, which possibly induces changes in the axon transport system and a resulting deficiency in energy.

#### 2. *KIAA1985*

CMT4C is caused by homozygous or compound heterozygous mutations in the previously uncharacterized *KIAA1985* gene.<sup>110</sup> CMT4C is a childhood-onset disease associated with an early-onset scoliosis and a distinct Schwann cell pathology. Scoliosis is prominent early on and may precede weakness and sensory loss. The protein encoded by *KIAA1985* belongs to new vertebrate protein group whose function is not known. By means of comparative sequence alignment, it is possible to determine that this protein group includes the multiple SH3 and TRP domains which are associated with formation of protein polymers.<sup>110</sup>

### CONCLUSIONS

Seventeen genes that cause hereditary motor and sensory neuropathy have been described. Even though the severities of the clinical symptoms differ, CMT is caused by a single gene mutation and follows Mendel's law. Development of the disease is directly due to a genetic defect, which means that detection of the defect provides a positive diagnosis. Over the past decade, new information about the function of genes known to cause CMT and new rational treatment approaches for CMT1A have emerged.<sup>10-12</sup> Apparent therapeutic effects of certain chemicals tested in CMT1A animal models highlight the importance of exact and speedy determination of chromosome 17p11.2-p12 duplication in subjects with peripheral neuropathies.<sup>10,11</sup> A personalized therapy for patients

with CMT1A duplication might be possible in the near future. For this reason, the importance of rapid and accurate molecular diagnosis is again emphasized. Understanding mutations and their causes and clarifying the pathophysiological mechanisms of CMT is important not only for diagnosis but also for developing new therapies.

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