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Charcot-Marie-Tooth Disease and Related Inherited Neuropathies

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Abbreviations used in this paper: CIDP, chronic inflammatory demyelinating polyneuropathy; CMT, Charcot-Marie-Tooth disease; CMTX, X-linked CMT; CNS, central nervous system; DSS, Dejerine-Sottas syndrome; FAP, familial amyloidotic polyneuropathy; FISH, fluorescence in situ hybridization; HMSN, hereditary motor and sensory neuropathies; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; NCV, nerve conduction velocities; PFGE, pulse-field gel electrophoresis; PMD, Pelizaeus-Merzbacher disease; SMA, spinal muscular atrophy.

Introduction

In 1886, Charcot and Marie [29] described an unusual slowly progressive form of muscular atrophy characterized by weakness and wasting of the feet and leg muscles followed by involvement of the hands. That same year, Tooth [169] independently described the peroneal type of progressive muscular atrophy with essentially the same clinical features. The inherited nature of this disease was noted in both cases even before Mendel's laws were ``rediscovered.'' It was Tooth, however, who correctly postulated that the disease is due to a neuropathy and not a myelopathy as proposed by Charcot and Marie. Subsequently, Dejerine and Sottas [36] reported cases of the progressive hypertrophic interstitial neuropathy of childhood. Postmortem studies in these patients revealed marked nerve swelling with the histologic appearance of onion bulbs. Since that time, associated clinical features have been described, including tremors and ataxia (Roussy-Levy syndrome) [152], deafness, optic atrophy, retinitis pigmentosa, and others [115]. The association of these clinical features with Charcot-Marie-Tooth disease (CMT) may represent coinherited or different genetic disorders.

CMT is the most common inherited disorder of the peripheral nervous system and 1 of the most common genetic diseases in humans, with an estimated frequency of 1 in 2,500 individuals [157]. CMT is actually a heterogeneous group of disorders of the peripheral nerves also referred to as the hereditary motor and sensory neuropathies (HMSN) [37]. Based on electrophysiologic and pathologic studies, CMT has been divided into 2 large distinct groups [40,41]. CMT type 1 (CMT1, HMSNI), the demyelinating form, exhibits moderately to severely reduced motor nerve conduction velocities (NCV), absent muscle stretch reflexes, and onion bulb formation on the nerve biopsy. CMT type 2 (CMT2, HMSNII), the neuronal form, shows normal or mildly reduced motor NCVs and decreased amplitude, normal muscle stretch reflexes, and no hypertrophic features on the nerve biopsy. This classification implied that the demyelinating form of CMT1 may be caused by an abnormality of Schwann cells Figure 1. Remarkable advances in our understanding of the molecular etiology of CMT have been made in the past 7 years through molecular genetic studies [4,97,131,142,148,149]. Linkage analyses using large families with CMT have revealed several loci responsible for this phenotype. Using a combination of positional cloning and candidate gene strategies, 3 genes have been identified that are associated with CMT. These studies revealed 2 very different mutational mechanisms that can lead to this disease: DNA duplication and point mutation. In fact, it has now been demonstrated that DNA rearrangements caused by reciprocal recombination are responsible for both CMT1A and the related but clinically distinct hereditary neuropathy with liability to

pressure palsies (HNPP). The objective of this article is to summarize the molecular genetic studies of CMT and related neuropathies with particular emphasis on clinical implications for the diagnosis, genetic counseling, and treatment of patients.

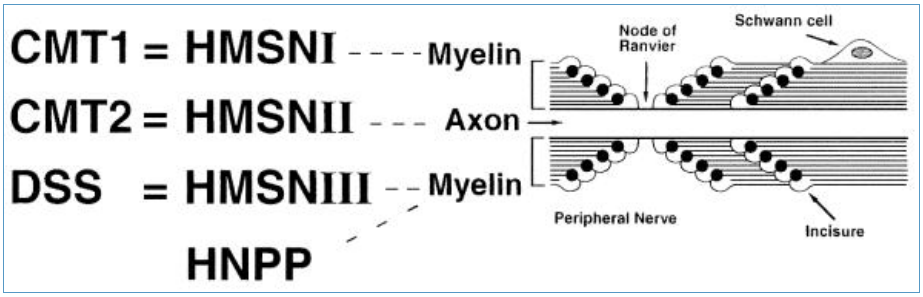

Figure 1. Schematic structure of the peripheral nerve. There are 2 types of hereditary peripheral neuropathies: those affecting the axon and those affecting Schwann cells of the myelin sheath. The cell type affected in each hereditary neuropathy is shown. CMT1 (HMSNI), DSS (HMSNIII), and HNPP are due primarily to a Schwann cell defect and thus affect the peripheral nerve myelin. CMT2 (HMSNII), which can be distinguished electrophysiologically from CMT1, DSS, and HNPP, appears to be caused by a neuronal (axon) defect.

Clinical Features of CMT and Related Disorders

CMT polyneuropathy syndrome is characterized by an insidious onset and slowly progressive weakness of the distal limb muscles [50,99]. The symptoms usually appear within the first 2 decades of life. Muscle weakness starts in the feet and legs. As a result of weakness of the dorsiflexor muscles of the feet, patients frequently trip over objects on the floor and sprain their ankles. Also, the foot drops with each step and forces the patient to lift the knee, giving the ``steppage" or ``equine" gait. Pes cavus deformity is not seen early in the course of the disease but develops with age. Atrophy of the leg muscles gives the ``stork leg" or inverted champagne bottle appearance and is prominent in slender and severely affected patients. Patients commonly complain of leg cramps after long walks and poor tolerance to cold weather probably due to loss of muscle mass. Weakness of the intrinsic hand muscles usually occurs late in the course of the disease but may not be related to the degree of leg weakness or atrophy and is not related to the age of the patient. The most frequent complaint concerning involvement of the hands is difficulty in using zippers and buttons and manipulating small objects that require fine finger movements and approximation of the thumb with other fingers. In severe cases, claw hand deformities may be seen. Muscle stretch reflexes disappear early at the ankle and later in the patellar and upper limbs. Sensory symptoms are rare, but mild sensory loss to pricking pain in the legs in a stocking distribution has been noted. There is a wide range of variation in clinical severity among unrelated individuals [99] and affected family members [80] and even in identical twins [51].

There are 2 major forms of CMT distinguishable by electrophysiologic and neuropathologic studies. Patients with CMT1 show moderately to severely slowed motor and sensory NCVs [84]. The median motor NCVs in patients with CMT1 usually are less than 42 m/sec [40]. A motor NCV value of 38 m/sec in the median nerve is often used as the division to separate CMT1 from CMT2 [62]. There are some exceptional cases, however, so these figures should be used as a guide only. In a recent study of 83 patients with CMT1 whose genotypes were confirmed by molecular analysis [80], median motor NCVs were slowed to less than 43 m/sec in all affected cases. The conduction abnormalities in CMT1 are uniform, symmetric, and bilaterally distributed from ipsilateral nerves and between proximal and distal nerve segments, suggesting that primarily Schwann cells are affected [81,171]. Electrophysiologic abnormalities in CMT1 are usually evident by 2 years of age before the onset of clinical symptoms [9,99,124]. After 5 years of age, NCVs do not significantly change [57,83,153]. These findings suggest that NCV studies can be an accurate indicator of affected status in CMT1 even before the onset of the disease. The severity of the disease does not correlate with the degree of conduction slowing but does correlate with the amplitude reduction of compound muscle action potentials, implying secondary axonal degeneration. The degree of conduction slowing at an early age is associated with the severity of neurologic deficit at a later age [38]. Peripheral nerve biopsies from patients with CMT1 show a decreased number of myelinated fibers and hypertrophic changes due to onion bulb formations. These onion bulb structures consist of circumferentially directed Schwann cells and their processes around myelinated and demyelinated internodes [56,98]. In some slender patients with CMT1, these

pathologic findings produce enlargement of the nerves that may be palpated (ulnar, peroneal) and may occasionally be visible (greater auricular). Interestingly, in CMT1 identical twins, the twin with more palpable hypertrophy had a less severe clinical symptomatology, suggesting that hypertrophy plays a compensatory role [51]. This may reflect either a protective effect of interstitial nerve hypertrophy on axon function or, alternatively, that hypertrophy may represent a better ability to restore lost function through mechanisms such as remyelination [51]. In contrast to CMT1, patients with CMT2 exhibit normal or mildly reduced motor NCVs and peripheral nerves of CMT2 patients show axonal loss with few, if any, onion bulbs.

X-linked CMT (CMTX) is similar to CMT1 clinically and neuropathologically. Male patients with CMTX are more severely affected than female patients. In electrophysiologic studies of known CMTX families, affected men have slow motor NCVs (<40 m/sec), whereas affected or carrier females exhibit intermediate motor NCVs (>40 m/sec) [126]. Some female cases of CMTX may be difficult to distinguish from CMT2 on the basis of electrophysiologic studies alone. Roussy and Levy [152] described some patients with hypertrophic neuropathy and essential tremor. This syndrome is not a distinct clinical entity because essential tremors are reported in 25%-40% of CMT patients [22,99], indicating that essential tremor may simply be part of the CMT phenotype in some patients or a coinherited disease in others.

Dejerine-Sottas syndrome (DSS; HMSNIII) is a rare disorder that shares considerable clinical, electrophysiologic, and pathologic overlap findings with CMT1. Onset in infancy, which may manifest as delayed motor milestones, and clinical severity are the hallmarks of DSS. Motor NCVs are markedly slowed (usually <10 m/sec), and peripheral nerves from DSS patients always show onion bulb formations, often with double basal lamina. However, homozygous patients with CMT1 may show the same features [82,100]. Cerebrospinal fluid protein levels are often markedly elevated as well. Congenital hypomyelinating neuropathy, another rare hereditary neuropathy, is characterized by a severe polyneuropathy of early infancy [61]. The pathologic findings of peripheral nerves from these patients exhibit thin myelin sheaths or complete absence of myelin. In some cases, lethal arthrogryposis (tightly contractured joint) multiplex congenital is associated with this disease [30]. It seems that congenital hypomyelinated neuropathy includes several heterogeneous disorders. Some of them may be the most severe form of DSS [37].

HNPP, also known as tomaculous neuropathy, was first described in a family with 3 generations of affected members who had recurrent peroneal neuropathy after digging potatoes in a kneeling position [34]. It is clinically distinct from CMT Table 1. Clinical features include periodic episodes of numbness, muscular weakness, and atrophy after relatively minor compression or trauma to the peripheral nerves [33,44]. The axillary, median, radial, ulnar, and peroneal nerves are the most commonly affected nerves. Entrapment neuropathies, such as carpal tunnel syndrome, are frequent manifestations of HNPP. Electrophysiologic studies sometimes show mildly slowed NCVs with conduction blocks in affected patients and asymptomatic carriers [42,54,94,171]. Peripheral nerves from HNPP patients show segmental demyelination and remyelination with tomacula or sausage-like focal thickening of the myelin sheaths [5,18,35,105]. Electron microscopy of tomacula demonstrates loss of myelin compaction [184], implying an adhesion role for the protein effected in HNPP patients.

	CMT1	HNPP
General clinical features	Slowly progressive, symmetric	Episodic, asymmetric
Antecedent features	None	Minor nerve compression or trauma
Electrophysiology	Decreased motor NCV	Conduction block
Neuropathology	Onion bulbs	Tomacula
Molecular	Duplication	Deletion

Abbreviations: CMT1 = Charcot-Marie-Tooth disease type I; HNPP = hereditary neuropathy with liability to pressure palsies; NCV = nerve conduction velocities.

Table 1. Contrasting features of CMT1 and HNPP

CMT, HNPP, and DSS: Modes of Inheritance

CMT is a genetically heterogeneous group of disorders Table 2. The inheritance patterns of CMT

may be autosomal dominant, X-linked, or autosomal recessive. Autosomal dominant CMT1 is the most frequently observed pattern and is subclassified based on genetic linkage studies as CMT1A (Mendelian Inheritance in Man [MIM, [115][1]] entry number 118220), CMT1B (MIM 118200), and CMT1C (MIM 601098). In most autosomal dominant CMT1 families, the locus for the disease is linked to DNA makers in 17p11.2-p12 and is designated CMT1A [177]. The related neuropathy HNPP (MIM 162500) is transmitted in an autosomal dominant manner and is also mapped to 17p11.2-p12 [24], although genetic heterogeneity has been reported [109]. CMT1B families with linkage to 1q21.2-q23 [92] are rare, and autosomal dominant CMT1C is not linked to either chromosome 1 or 17 [26,28]. The X-linked form of CMT, CMTX (MIM 302800), maps to proximal Xq13.1 [11,49]. Autosomal recessive CMT1, recently designated CMT4, is relatively rare and appears to be genetically heterogeneous. One form, CMT4A (MIM 214400), was mapped to 8q13-q21.1 [7]. CMT2 has been estimated to occur much less frequently than CMT1 [62] and is inherited in an autosomal dominant manner. Two loci for CMT2 have been described. One locus, CMT2A (MIM 118210), has been mapped to 1p35-p36 [8] and the other, CMT2B (MIM 600882), to 3q [87]. Most cases of DSS (MIM 145900) appear sporadic, but both autosomal recessive and dominant alleles have been reported [36,143]. Clinical features of each genotype are shown in Table 3.

Inheritance Pattern	Type	Locus	Gene	MIM Number
Autosomal dominant	CMT1A	17p11.2-p12	*PMP22*	601097
	CMT1B	1q21.2-q23	*MPZ*	159440
	CMT1C	not 1 or 17	—	601098
	CMT2A	1p35-p36	—	118210
	CMT2B	3q	—	600882
X-linked	CMTX	Xq13.1	*Cx32*	304040
Autosomal recessive	CMT-AR (CMT4A)	8q13-q21.1	—	214400

Abbreviations: MIM = *Mendelian Inheritance in Man* (reference 115, see also footnote 1 in text); *PMP22* = peripheral myelin protein 22; *MPZ* = myelin protein zero; *Cx32* = connexin32.

Table 2. Genetic heterogeneity of Charcot-Marie-Tooth disease

Subtypes	Inheritance	Age of Onset	Early Symptoms	Muscle Stretch Reflexes	Motor NCVs	Pathological Features
CMT1A	AD	First 2 decades of life	Distal leg muscle weakness	Absent	Slowed	Decreased number of myelinated fibers, onion bulbs
CMT1B	AD	"	"	"	"	"
CMT1C	AD	"	"	"	"	"
CMTX	X-linked	"	"	"	"	"
DSS	AR? or AD	Congenital, infantile and juvenile	Severe muscle weakness in the extremities	"	Severely slowed	More severe than that of CMT1
CMT-AR	AR	First decade of life	Distal muscle weakness	"	"	Hypomyelination
HNPP	AD	All ages	Periodic episodes of numbness and muscle weakness	Normal	Conduction block	Tomacula
CMT2	AD	Usually the first 2 decades of life, up to the 7th decade	Distal leg muscle weakness	Normal	Normal	Decreased number of large myelinated fibers (axonal degeneration)

Abbreviations: See previous tables. AD = autosomal dominant; AR = autosomal recessive; DSS = Dejerine-Sottas syndrome.

Table 3. Clinical features of CMT and HNPP

([1]) Mendelian Inheritance in Man is available electronically as Online Mendelian Inheritance in Man (OMIM), accessible through World Wide Web (http://www3.ncbi.nlm.nih.gov/omim/).

Allan [2] used CMT as a model to support his proposal of a relation between hereditary pattern, the behavior of genes, and clinical severity. He postulated that recessive disorders are usually of earlier onset, more clinically severe, and less variable in their clinical expression because there are 2 mutant genes. Dominant disorders, in contradistinction to recessive disorders, are of later onset, less severe, and more clinically variable because the 1 normal gene may mitigate the effects of the mutant gene.

Sporadic Demyelinating Peripheral Neuropathies

Diagnosis of sporadic cases of CMT without a family history can be difficult. There are no distinct clinical symptoms and signs that distinguish CMT from other chronic inherited or acquired neuropathies. However, the presence of pes cavus and hypertrophic nerves is more suggestive of a

hereditary form of polyneuropathy than an acquired form. Careful clinical examination and electrophysiologic study of asymptomatic family members may reveal the hereditary nature of the disease; however, sporadic cases also include patients with de novo mutations. If the sporadic case exhibits clinical features of demyelinating polyneuropathy, there are several diseases to be considered. However, the electrophysiologic findings of uniform conduction slowing characterize CMT1 in distinction to acquired demyelinating polyneuropathies, which feature multiple conduction abnormalities. It is particularly important, but sometimes difficult, to distinguish between CMT or HNPP and chronic inflammatory demyelinating polyneuropathy (CIDP). Conduction blocks are found in CIDP, multifocal motor neuropathy, and other acquired demyelinating polyneuropathies. However, conduction blocks have also been reported in rare cases of CMT1 and are a consistent feature of HNPP. Although onion bulbs in the nerve biopsy are most frequently present in CMT1, they can be found in CIDP. Protein levels in cerebrospinal fluids are elevated in most patients with CIDP, but mild elevation of protein levels is often encountered in CMT1 and more frequently in DSS. Furthermore, in some patients, CIDP has occasionally been reported to occur in association with CMT1 [43,55]. In these sporadic cases, the molecular analysis of CMT may be the most useful and accurate diagnostic test. If there are associated neurologic and physical features such as central nervous system (CNS) involvement, other metabolic diseases should be considered such as Refsum disease or metachromatic or globoid cell leukodystrophy. Laboratory tests may demonstrate the presence of paraproteinemia in multiple myeloma-related neuropathy, and a medical history may reveal the presence of cancer, diabetes mellitus, diphtheria, etc., which result in demyelinating neuropathy.

DNA Rearrangements and Gene Dosage as Mechanisms for CMT1A and HNPP

Molecular genetic analysis of CMT1A and HNPP revealed a novel disease-causing mechanism in humans that involves a large inherited DNA rearrangement. Most CMT1A patients have a 1.5-Mb tandem DNA duplication in 17p11.2-p12 that segregates with the disease phenotype [100,133,135] Figure 2. Failure to account for the segmental trisomy due to duplication can lead to the misinterpretation of marker genotypes for affected individuals, the identification of false recombinants, and the incorrect mapping of the disease locus [95,100,113,125]. The tandem nature of the duplication is demonstrated both by physical mapping [133] and by 2-color fluorescence in situ hybridization (FISH) analysis. Probes from different regions of the duplicated segment always revealed equidistant signals consistent with a tandem and not inverted duplication [175]. The CMT1A duplication was originally identified in 6 French-Acadian families and 1 Ashkenazi Jewish CMT1A family [100] and independently described in 12 European CMT1A families [135]. The CMT1A duplication has now been found in multiple families of different ethnic origin and in multiple unrelated patients with CMT1 [6,20,28,58,59,67,69,70,100,101,104,106,116,117,123,125,133,135,136,142,155,183]. The size of the CMT1A duplication is apparently identical in most patients with CMT1 and faithfully transmitted in families with CMT1A [100,101,123,136,142,183]. The frequency of the CMT1A duplication in patients with CMT1 has now been firmly established at 70% based on 3 large independent studies [75,123,183]. De novo duplications appear to arise at a relatively high frequency as well [15,70,106]. In a study by Hoogendijk et al [70], 9 of 10 sporadic patients with CMT1 were found to have the CMT1A duplication. In the overwhelming majority of de novo duplication cases examined [15,67,129,183], the duplication mutation is of paternal origin, suggesting that a male-specific factor may mediate the DNA rearrangement during spermatogenesis, resulting in a sex-predilection for the new mutation [129]. However, a rare patient with a de novo duplication of maternal origin has been reported [15].

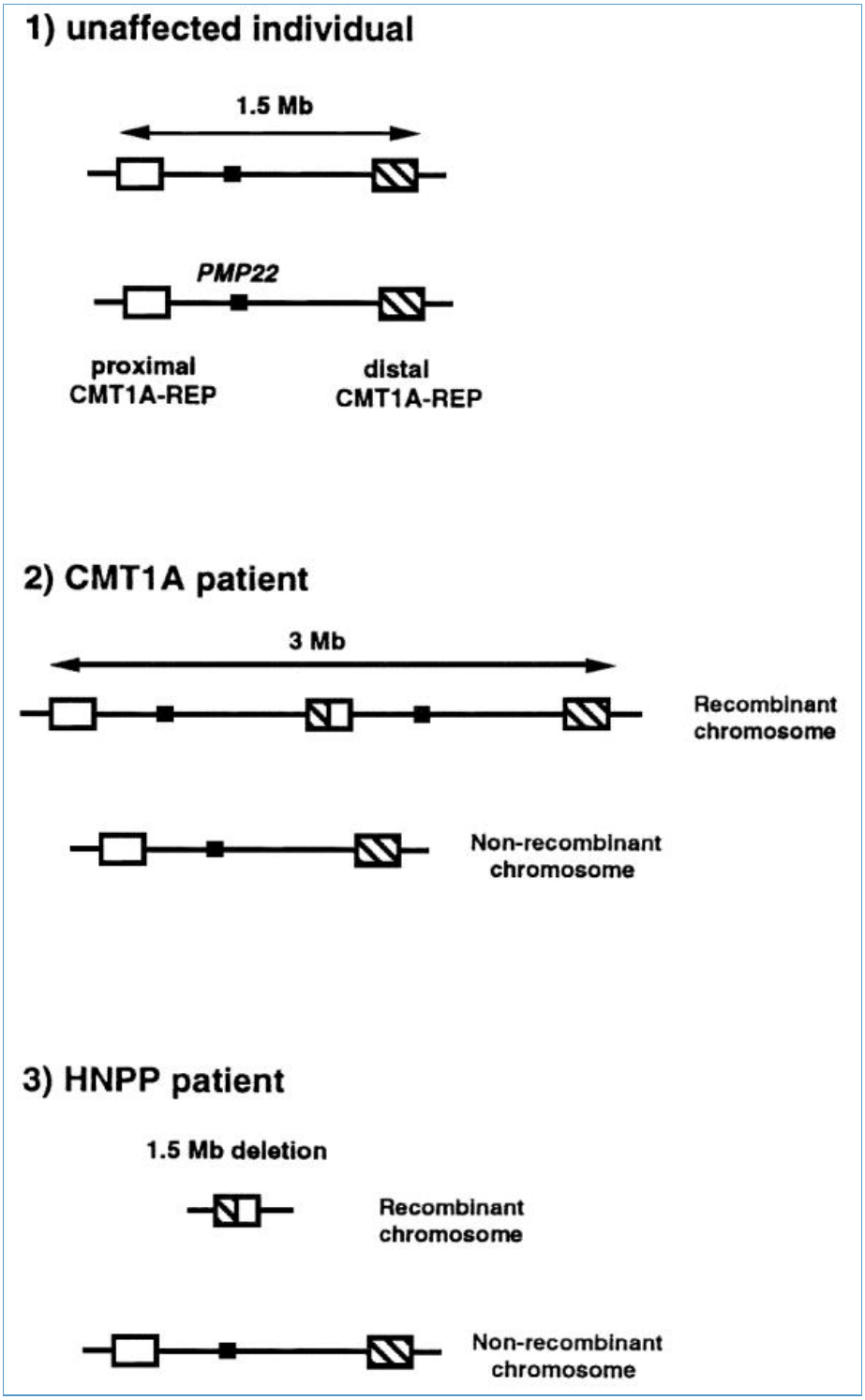

Figure 2. A 1.5-Mb region duplicated in CMT1A and deleted in HNPP. The 1.5-Mb monomer unit duplicated/deleted in 17p11.2-p12 is shown in 1. Open and shadowed boxes represent proximal and distal CMT1A-REPs flanking the 1.5-Mb region. The filled box represents the PMP22 gene that lies completely within the region duplicated in CMT1A and deleted in HNPP patients. This region is duplicated in most patients with CMT1A [2] and deleted in most patients with HNPP (3).

In contrast to duplication, HNPP is associated with a 1.5-Mb deletion in 17p11.2-p12 Figure 2. Interestingly, all DNA markers duplicated in CMT1A patients are deleted in patients with HNPP [24]. In fact, the deletion boundaries for the HNPP deletion map to the duplication junction boundaries for the CMT1A duplication [24,133]. The region of 17p11.2-p12 deleted in HNPP is the same as that duplicated in CMT1A as shown by the detection of predicted junction fragments [23,94,142]. The HNPP deletion has also been found in multiple families of different ethnic groups and in multiple unrelated HNPP patients [24,91,94,107,110,123,142,144,156,167,178]. Two de novo HNPP deletions have been reported to be of maternal origin [90,139].

The constant size of the CMT1A duplication and HNPP deletion suggests that an intrinsic structural feature of the chromosomal region in 17p11.2-p12 is involved in the mechanism that leads to a stably inherited DNA rearrangement. Duplication of this 1.5-Mb region predicts the generation of novel DNA fragments containing the junction from the recombinant chromosome carrying the CMT1A duplication Figure 3. Multiple predicted junction fragments were demonstrated by pulse-field gel electrophoresis (PFGE) in many CMT1 families, unrelated patients with CMT1, and de novo CMT patients [100,136,183]. Physical mapping of the CMT1A duplication region determined that this 1.5-Mb monomer unit is flanked by complex low copy number repeats: the CMT1A-REP [133] Figure 3. An unequal crossing-over model was initially proposed based on the segregation of paternal alleles in a de novo CMT1A duplication patient [135]. The CMT1A-REP is present in 2 copies on nonrecombinant chromosomes and 3 copies on CMT1A duplication chromosomes [133]. In the case of the 1.5-Mb HNPP deletion, several junction fragments specific to HNPP have also been found in most patients [23,94,142,144,167]. As one might expect, the CMT1A-REP is present in only 1 copy on the HNPP deletion chromosome [23,89,94]. These findings are consistent with a model of unequal crossing-over mediated by the CMT1A-REP repeat regions Figure 3. This reciprocal rearrangement is postulated to occur preferentially during male meiosis as illustrated in Figure 3. Subsequently, a recombination ``hot spot" within the CMT1A-REPs was identified in a large study of CMT1A and HNPP patients [140]. The crossing-over event in most CMT1A duplication and HNPP deletion patients examined occurred within a 1.7-Kb interval within the approximate 30-Kb region of homology between misaligned CMT1A-REPs. Interestingly, this recombination hot spot occurred adjacent to a mariner transposon-like element. This study confirmed that the 1.5-Mb CMT1A duplication and the 1.5-Mb HNPP deletion are the products of a reciprocal recombination event [140]. Although in most cases CMT1A results from a 1.5-Mb tandem duplication, smaller duplications have been reported in 3 patients [76,129,173]. In 1 of these cases [173], a 460-Kb duplication was observed. Smaller deletions have also been reported in a few HNPP patients [123]. These aberrantly sized duplications and deletions in 17p11.2-p12 proved essential to understanding the underlying molecular mechanism and gene involved in both disorders [141].

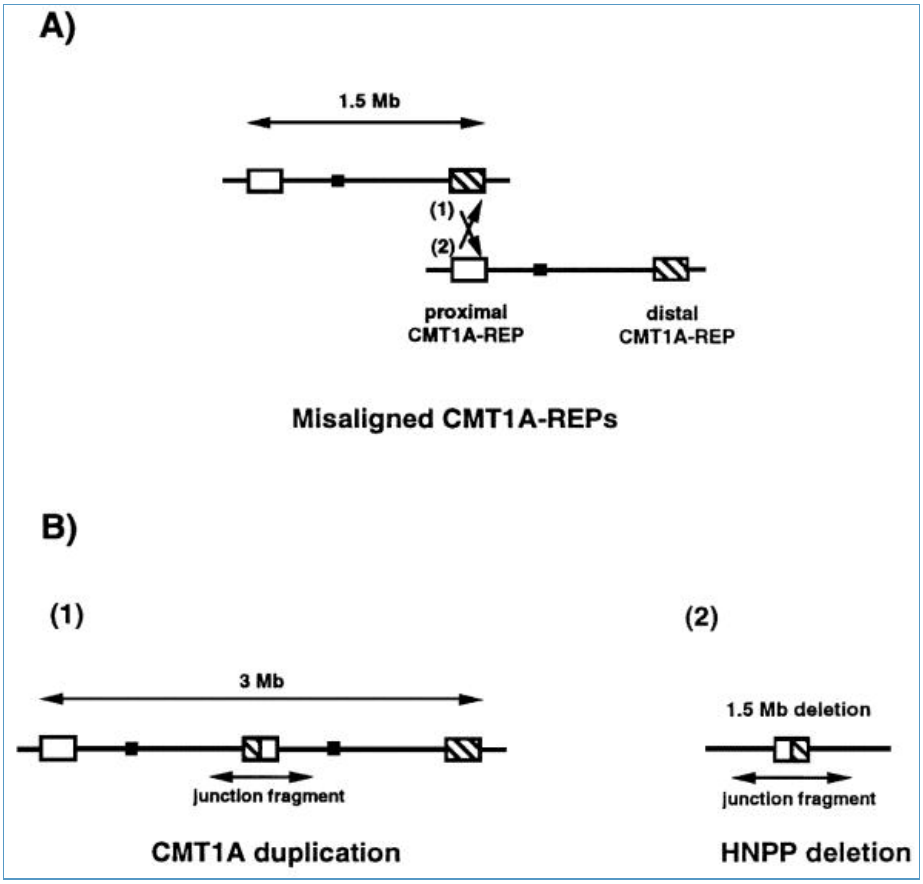

Figure 3. Proposed homologous recombination model of unequal crossing-over leading to the CMT1A duplication and HNPP deletion. The proximal (open box) and distal (shadowed box) CMT1A-REPs can misalign during meiosis as illustrated in A. An unequal crossing-over event occurs between misaligned CMT1A-REP elements via homologous recombination. There are 2 reciprocal recombination products for this recombinant event (B). Recombination pathway (1) leads to the CMT1A tandem duplication of 3.0 Mb, whereas recombination pathway (2) leads to the 1.5-Mb HNPP

deletion.

Several models have been proposed to explain how the CMT1A duplication causes the clinical phenotype of CMT1. Cumulative evidence strongly supports a gene dosage model in which trisomy for a critical gene or genes within the duplicated region results in increased expression, leading to the CMT1A disease phenotype. Four patients with CMT1 with rare large cytogenetically visible duplications of 17p encompassing the CMT1A duplication region have also been found [25,103,146,147,172]. These patients exhibited distal weakness and wasting with uniformly decreased NCVs as part of their overall complex clinical phenotype. Moreover, these larger duplications have different distinct breakpoints that strongly argue against the gene interruption model. Also, 3 patients homozygous for the CMT1A duplication have been identified [82,100] who exhibited a more severe clinical phenotype than their heterozygous duplication siblings and parents and that of unrelated heterozygous duplication patients. These findings comprise some of the initial evidence that the CMT1A phenotype results from a gene dosage effect.

The PMP22 Gene in CMT and HNPP

Based on size alone, the region duplicated in CMT1A is likely to contain 30-50 genes, of which 1 or many could be critical to development of the phenotype. However, the discovery of a mouse mutant with a similar phenotype to CMT suggested that 1 gene plays a critical role in the disorder. The trembler and allelic trembler (^{J}) mutations in mice are characterized by severe hypomyelination and continuing Schwann cell proliferation. Autosomal dominant mutations in the peripheral myelin protein 22 (pmp22) gene were found in both mice [162,166]. Pmp22 is an approximate 22-kDa glycosylated myelin protein predicted to contain 4 transmembrane domains Figure 4 [163]. Two amino acid substitutions, a Gly150-Asp and a Leu16Pro, predicted by point mutations found in trembler and trembler^{J} mice lie deep within the fourth and first transmembrane domains of the theoretical protein structure Figure 4. Murine pmp22 was mapped to mouse chromosome 11 in a region of synteny with human chromosome 17p. These observations suggested that the human PMP22 gene might be involved in CMT1.

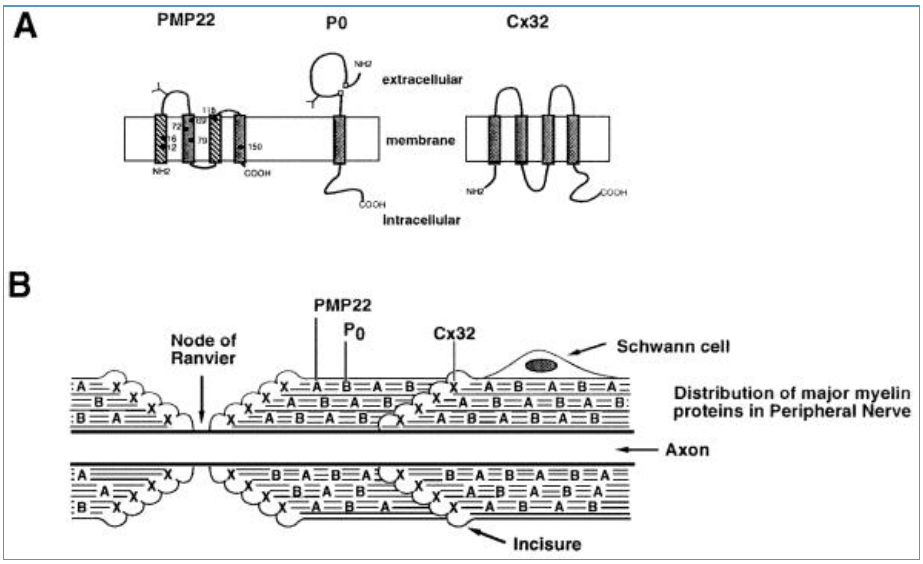

Figure 4. Schematic diagram of myelin proteins associated with CMT and their distribution in peripheral nerve. (A) PMP22 consists of an approximate 18-kDa core of 160 amino acids containing 4 putative transmembrane domains and an approximate 4-kDa carbohydrates group linked to an asparagine 41 (indicated by the Y-shaped symbol). The closed circles denote the positions of the mutations associated with CMT1A [16,79,117], DSS [12,69,72], Trembler [150], and Trembler^{J} [16] mice. P0 is an approximate 28-kDa adhesive glycoprotein derived from a precursor protein of 248 amino acids that consists of a single extracellular domain, a transmembrane domain, and an intracellular domain. The extracellular domain contains an N-glycosylation site (indicated by the Y-shaped symbol) and 2 cysteines at 50 and 127 (open squares) that are proposed to be responsible for the structural integrity of the immunoglobulin-like domain. Cx32 is an approximate 32-kDa junction protein of 283 amino acids and a member of the connexon forming family of proteins that are assembled into hexamers in the plasma membrane. (B) PMP22 and P0 are components of Schwann cells that make up the compact myelin. Cx32 is localized to noncompact myelin (Schmidt-

Lanterman clefts and the lateral loop of the myelin sheath) in Schwann cells. The distribution of PMP22, P0, and Cx32 in the myelin sheath [60] are indicated by symbols representing the disorders associated with CMT1A (A), CMT1B (B), and CMTX (X).

Several groups simultaneously mapped the PMP22 gene within the region duplicated in CMT1A [114,132,168,175]. It has also been shown that PMP22 is highly expressed in the human peripheral nerve [132]. Subsequently, it was demonstrated that PMP22 maps some distance away from breakpoint junctions of the CMT1A duplication patients and is not disrupted by the duplication event [133]. These observations implied that 3 copies of PMP22 might lead to the CMT1A phenotype. More definitive proof that PMP22 is directly involved in the disorder came from the identification of point mutations within the PMP22 gene in patients with CMT1A who did not have the 1.5-Mb CMT1A duplication [145,174]. A missense mutation in a CMT1A family without the duplication predicted a Leu16Pro substitution identical to that of the mouse trembler^{J} mutation [174]. A de novo mutation that predicted a Ser79Cys substitution was also identified in a sporadic CMT1A patient [145]. A 5 prime splice site mutation in the PMP22 gene has also been described in 2 patients with CMT1 [121], but how this mutation causes CMT1A is unclear. Furthermore, there are no PMP22 coding region mutations in multiple CMT1A duplication patients examined [180]. Moreover, decreased NCV characteristic of CMT1 is observed in rare 17p partial trisomy patients only if the duplicated region contains PMP22 [147], and PMP22 maps to the region duplicated in 3 patients with CMT1 with smaller duplications [76,129,141,173]. Autosomal dominant CMT1A, therefore, appears to be caused by an increase in the copy number of the PMP22 gene or by apparently gain-of-function point mutations in this gene.

Molecular analysis of the PMP22 gene in patients with DSS also revealed 2 patients with point mutations [143]. One is a de novo mutation that yields a Met69Lys substitution and the other mutation, in an unrelated patient, leads to a Ser72Leu substitution Figure 4. The latter mutation has been reported in 1 other patient with DSS [77]. Recently, a de novo mutation that predicts a His12Gln substitution was described in a patient with DSS [176]. The heterozygous state of these mutations suggest that DSS can result from dominant point mutation alleles of the PMP22 gene. These molecular findings demonstrate that instead of being 2 completely distinct disease entities, DSS and CMT1A represent a spectrum of related clinical findings due to allelic heterogeneity underlying these disorders [143].

As described previously, HNPP is most frequently associated with a 1.5-Mb deletion in 17p11.2-p12. In 1 HNPP family without the 1.5-Mb deletion, a frameshift mutation in the PMP22 gene leading to a null allele (a frameshift at Ser7 generating a nonsense codon at codon 36) was identified [127]. This mutation confirmed the hypothesis that a decrease in copy number or a loss-of-function mutation in the PMP22 gene leads to the HNPP phenotype. An apparent recessive PMP22 point mutation associated with CMT1A has also been identified in a family with both CMT1A and HNPP [144]. A compound heterozygote patient exhibiting CMT1 carried a point mutation (predicting a Thr118Met substitution) of the PMP22 gene on 1 chromosome and a 1.5-Mb HNPP deletion on the homologous chromosome. This severely affected CMT1A-like patient had a 52-year-old son who carried this point mutation in PMP22 but did not exhibit signs of the CMT phenotype clinically or electrophysiologically. However, 2 other sons heterozygous for the 1.5-Mb HNPP deletion clearly had HNPP. These findings suggest the presence of an autosomal recessive point mutation allele in PMP22.

The PMP22 protein is mainly localized to the compact myelin in Schwann cells where it comprises about 2%-5% of the total myelin protein [158]. The PMP22 gene was initially identified as a growth arrest-specific gene (gas-3) expressed in quiescent cultured fibroblast cells [108]. Subsequently, this gene was shown to encode a myelin protein [160,182]. Two kinds of transcripts of the PMP22 gene are expressed in a tissue-specific manner from 2 promoters located upstream of 2 alternative 5 prime-noncoding exons. High levels of 1 transcript are associated with myelin formation, whereas the other transcript is predominantly in nonneural tissues and in growth-arrested fibroblasts [3,17,164,186]. Thus, the PMP22 gene is regulated by a complex mechanism consistent with a possible dual function of PMP22 in myelination and cell growth [163]. As previously stated, trisomy for PMP22 appears to cause CMT in CMT1A duplication patients. This gene dosage mechanism is supported by the detection of elevated levels of PMP22 mRNA in the peripheral nerves of patients with the CMT1A duplication [185]. Indeed, this gene dosage effect of PMP22 is also observed in pmp22-deficient mice. The homozygous pmp22-deficient mice (pmp22$^{-/-}$) showed

retardation of myelin formation and sausage-like hypermyelination structures (tomacula) at a young age followed by severe demyelination. Heterozygous mice (pmp22 ($^{+/-}$)) are less affected but have tomacula comparable with the pathology observed in HNPP patients [1].

Most of the PMP22 mutations associated with CMT1A, DSS, trembler, and trembler^{J} lie in the putative transmembrane domains of the protein, suggesting that the membrane-associated domain is particularly sensitive to structural changes that affect the function of the PMP22 protein. The finding of uncompacted myelin in HNPP patients supports a structural and perhaps an adhesive role for PMP22 in myelin compaction. Interestingly, a structural analogue of PMP22 in the CNS, the proteolipid protein (PLP) gene, is also dosage sensitive. PLP is a major myelin protein in the CNS and has 4 putative transmembrane domains similar to PMP22 [165]. Mutations in the PLP gene are associated with the CNS myelin disorder Pelizaeus-Merzbacher disease (PMD) [72]. Duplication of a region containing the entire PLP gene results in a PMD phenotype [31,45] just as duplications encompassing the PMP22 gene result in a CMT1A phenotype [148]. Overexpression of DM20 mRNA, alternatively spliced PLP transcript, was also observed in 2 brothers with PMD who did not have coding exon mutations [21]. Furthermore, transgenic mice that overexpress the wild-type PLP gene reveal a dysmyelinating phenotype similar to that observed in PMD [79,138].

Genes Associated With Other Forms of CMT

The discovery of a peripheral myelin protein, PMP22, involved in CMT1A prompted the search for other myelin proteins using linkage analysis and a candidate gene approach. The CMT1B locus was first linked to the Duffy blood group locus on 1q21 using polymorphic protein markers [13]. The myelin protein zero (MPZ) gene encoding P0 maps to the 1q22-q23 region [92]. P0 is a 28-kDa glycoprotein that constitutes half of the peripheral myelin protein. Mutational analysis of the MPZ gene in patients with CMT1B indeed identified point mutations [63]. Two de novo mutations of MPZ in patients with DSS have also been identified [64]. Interestingly, a mutation that predicts a Ser63Cys substitution is associated with DSS, whereas a 3-bp deletion of this Ser codon results in CMT1B [86,131]. More than 20 mutations associated with CMT1B or DSS have been found in MPZ [63-66,68,86,88,120,122,123,137,150,161,179]. Clinical manifestations of MPZ mutations can include congenital hypomyelination (LE Warner and JR Lupski, unpublished data).

P0 is localized to the compact myelin in the peripheral nerve and consists of a glycosylated extracellular domain, a single transmembrane domain, and a cytoplasmic domain Figure 4. Although some mutations associated with CMT1B have been found in the transmembrane or intracellular domain, most of the mutations occur in the extracellular domain. The extracellular portion of the protein contains an immunoglobulin-like domain that may allow P0 to act as a homophilic adhesion molecule, facilitating the tight compaction of the apposed extramembrane faces along the intraperiod line of myelin [163]. In support of this hypothesis, the most striking features in mice homozygous for a null mutation in P0 were the absence of regular intraperiod line and widening of the intraperiod spaces [52]. P0 also seems to be dosage sensitive. In 1 study of P0-deficient mice [112], homozygous mice ($P0^{-/-}$) demonstrated severe demyelination at a very young age, whereas heterozygous mice ($P0^{+/-}$), which initially appear to have normal myelination, eventually developed a progressive demyelination after 4 months of age. The pathology of these P0 knockout mice is similar to that of DSS in the homozygote ($P0^{-/-}$) and more mildly affected CMT1B patients in the heterozygote ($P0^{+/-}$).

CMTX has been mapped to Xq13.1. Connexin 32 (Cx32) is a 32-kDa gap junction protein that forms connexons in many tissues and also maps to this locus. Mutational analysis in patients with CMTX of the Cx32 gene revealed several point mutations [10]. In the peripheral nerve, Cx32 localizes to the nodes of Ranvier and at the Schmidt-Lanterman incisures (noncompact myelin) [10]. Multiple Cx32 gene mutations that lead to single amino acid substitutions, codon deletions, stop codons, or frameshifts have now been identified [10,16,47,73,123,128]. In fact, more than 30 mutations in the Cx32 gene associated with CMTX have already been reported. The diversity of these mutations suggests that all regions of the Cx32 protein, not just the transmembrane domain, are important for its function. Cx32 is a member of a family of similar transmembrane-associated proteins that form membrane-spanning half channels called connexons [159]. Connexons interact

with connexon proteins on the surface of adjacent cells for transport of ions and small molecules. Cx32 structurally resembles PMP22 in that they both contain 4 putative transmembrane domains in similar orientation [159] Figure 4.

Clinical Implications

The CMT1A duplication has been identified in >70% of patients with CMT1 [75,123,183]. Given this high frequency, the detection of the CMT1A duplication is a useful molecular test in patients with inherited and sporadic peripheral neuropathies because it is a biologic marker for the disease [142]. The CMT1A duplication can be identified by several methods [100], including dosage differences of alleles at restriction fragment length polymorphisms, presence of 3 alleles at a highly polymorphic locus by polymerase chain reaction, FISH analysis using probes from the duplicated region, and detection of the junction fragment specific to the CMT1A duplication by PFGE or Southern blot analysis. Each method has advantages and disadvantages. In the first 2 methods, the informativeness depends on the heterozygosity of the markers. At present, several highly polymorphic markers in the CMT1A duplicated region have been developed [14,32,100]. FISH analysis of interphase nuclei from patients can graphically visualize the submicroscopic 1.5-Mb CMT1A duplication [100]. The detection of CMT1A specific junction fragments using PFGE appears to be the most informative DNA diagnostic test currently available commercially. Although relatively labor intensive, PFGE methods followed by Southern blot analysis can be used to detect the large junction fragments associated with both CMT1A and HNPP. Use of a CMT1A-REP probe enables a single test to detect either CMT1A duplication-specific or HNPP deletion-specific junction fragments [23,142] Figure 3. Interestingly, molecular analysis has detected the HNPP deletion in some patients diagnosed with CMT1 [142], suggesting clinical overlap with CMT1 in more severe HNPP cases. In the future, simple genomic Southern blot analysis methods, currently being developed to detect small novel junction fragments from the recombinant chromosomes of CMT1A and HNPP patients, may prove to be the diagnostic method of choice [140]. In an individual with a clinical or electrophysiologic diagnosis of CMT1 [81], detection of the CMT1A duplication confirms the diagnosis and makes it possible to diagnose or rule out other family members who are at risk using a simple blood test. This test can even be used for prenatal diagnosis of CMT1A [93,119]. With respect to prognosis, longitudinal studies of CMT1A duplication patients over 22 years show no significant change of motor NCVs and very slow clinical deterioration of the motor deficit [83]. Patients with CMT1 without the duplication and patients with DSS can now be directly screened for mutations in the PMP22, MPZ, and Cx32 genes. Point mutations in PMP22 appear to lead to a more severe clinical phenotype than duplication of PMP22 [71,96,145]. As mutations in Cx32 are more frequently observed [74,123], the Cx32 gene should be the first gene screened if X-linked segregation has not been ruled out.

Although the DSS has been reported as an autosomal recessive or sporadic phenotype, it now appears to be caused by new dominant mutations of the PMP22 or MPZ genes. Sporadic cases may be explained by de novo autosomal mutation. In retrospect, the affected brother and sister initially described by Dejerine and Sottas [36] may have been caused by gonadal mosaicism of an autosomal dominant mutation and not a recessive allele as initially described based on inheritance patterns. However, autosomal recessive CMT1 cases that seem to be similar to patients with DSS have been described [48]. Further molecular studies of these patients may confirm whether cases of autosomal recessive DSS exist. At the present time, DSS seems to be a variant of CMT1 rather than a separate syndrome.

HNPP may be more difficult to clinically diagnose because it is a milder transient disease. The exact prevalence of HNPP is still unknown in part due to the variable expressivity of the phenotype. However, the frequency of new mutation may be similar in CMT1 and HNPP given the molecular etiology that generates the CMT1A duplication and HNPP deletion. HNPP should be considered in the differential diagnosis of all patients with a recurrent demyelinating polyneuropathy, a compressive mononeuropathy, or mononeuropathies multiplex of undetermined etiology because NCVs in all these disorders can show conduction blocks [5,24,42,142,171]. Early diagnosis of HNPP can promote preventive measures to avoid nerve pressure or trauma associated with particular vocations or activities [97].

Several other clinical features have been described that can be associated with the CMT syndrome. These include spastic paraparesis, ataxia, tremor, deafness, optic atrophy, retinitis pigmentosa, Marfan-like appearance, calf hypertrophy [170], absent eye brows, and even mental retardation. Some of these features may be due to both a high frequency of the CMT1A duplication and a coincidental mutation of an independent gene [101]. Molecular analysis in these patients could reveal whether these variants are due to the same gene or independent genes of coinherited disorders. However, an intriguing possibility that needs to be investigated further is that certain alleles of other genes located within the 1.5-Mb CMT1A duplication may manifest dosage-sensitive phenotypes. Linkage studies have been performed in some CMT families with associated features. A locus for X-linked recessive CMT associated with mental retardation or spastic paraparesis has been mapped to Xp22 and Xq26, respectively [78]. In these families, electrophysiologic studies revealed slowing of motor NCVs. A locus for X-linked recessive axonal hereditary motor and sensory neuropathy with deafness and mental retardation has also been mapped to Xq24-q26 [134]. Studies of evoked potentials on CMT patients reported brain dysfunction in some cases using visual, somatosensory, and auditory evoked potentials [74].

Differential Diagnosis

There are other inherited neuropathies in the differential diagnosis of CMT. CMT is a motor and sensory neuropathy, but sensory loss is usually mild. If there is no sensory disturbance on neurologic examination, the distal form of spinal muscular atrophy (SMA) should be considered. However, joint contractures seen in the distal form of SMA are not seen in CMT. On the contrary, if sensory or autonomic involvement is a primary symptom, familial amyloidotic polyneuropathy (FAP) or hereditary sensory and autonomic neuropathy (HSAN) should be considered. FAP is another autosomal dominant inherited polyneuropathy characterized by extracellular amyloid deposits. The amyloid fibrils, which consist of variant transthyretin, apolipoprotein A1, or gelsolin, result from single amino acid substitutions in these proteins [118]. Symptoms usually develop between 20 and 45 years of age. Sensory neuropathy in the lower limbs and autonomic dysfunction are early features. HSAN is also in the collection of heterogeneous disorders characterized by the loss of several modalities of sensation with less prominent motor or autonomic disturbance. The inheritance patterns of HSAN are autosomal dominant or recessive. In some families with HSAN, peroneal muscular atrophy has been described as a prominent feature [39,46].

Refsum disease (MIM 266500) is a rare autosomal recessive disorder characterized by retinitis pigmentosa, ataxia, and chronic polyneuropathy. These neurologic features are due to the accumulation of phytantic acid in the nervous system. The age of onset for this disease is usually between 10 and 30 years of age, and the polyneuropathy is of the demyelinating type. Electrophysiologic studies in these patients can show markedly reduced NCVs. As in severe cases of CMT, the peripheral nerves may be palpably enlarged. Clinical presence of ataxia and retinitis pigmentosa, or the laboratory determination of phytantic acid level in serum or detecting a defect of phytantic acid alpha-oxidation, may be helpful in distinguishing Refsum disease from CMT.

Hereditary neuralgic amyotrophy (HNA; MIM 162100) is another autosomal dominant disease characterized by painful episodes of brachial palsy frequently beginning in the second decade of life. It is not a generalized polyneuropathy. Hypotelorism and other minor dysmorphic features are described in some pedigrees. The tomacula associated with HNPP are detected by nerve biopsies of some patients with HNA. However, the focal radicular nature of the disorder and linkage analysis suggests HNA and HNPP are clinically and genetically distinct entities, respectively [27,53]. Molecular detection of the HNPP deletion is the most useful test to distinguish between these 2 disorders.

Differentiation of sporadic demyelinating peripheral neuropathy was mentioned previously. In all such sporadic cases, the detection of the CMT1A duplication by molecular analysis may be the most useful diagnostic test. Mutation analysis of the Cx32 gene may be useful in nonduplication patients because of its relatively high mutation frequency [123]. In the case of sporadic patients with chronic axonal polyneuropathy, it may be more difficult to differentiate between CMT2 and acquired polyneuropathies. Acquired diseases may be ruled out by clinical examination, laboratory tests, radiologic examination, cerebrospinal fluid analysis, electrophysiology, and nerve biopsies.

Finally, a rare form of autosomal dominant distal myopathy may have similar phenotypic expression to that of CMT with distal weakness and wasting of limb muscles [111,181]. However, the NCVs are normal, the electromyogram is myopathic, and the muscle enzymes (creatine kinase) are elevated. The diagnosis of distal myopathy is confirmed by a muscle biopsy.

Therapy

Although there is no specific pharmacologic or molecular therapy for CMT at present, symptomatic treatment, supportive therapy, and genetic counseling are available for CMT patients. The primary manifestation of CMT is distal limb muscle weakness. Muscle imbalance in patients cause foot and hand deformities, the effects of which can be ameliorated by physical therapy, braces, or sometimes surgery. Pes cavus is often observed in CMT [19,154]. Ankle sprains should be treated as soon as possible because they may lead to ligament laxity and further instability. Although patients with CMT should avoid fatigue and injury, muscle and heel cord strengthening exercises may help to improve function in the extremities [130]. Muscle and heel cord stretching exercises are useful in the early prevention of some deformities. High top shoes, boots, or ankle-foot or thoses are often used in patients with CMT to provide stability. Such devices improve the patient's ability to walk and decrease the risk of injury. Adaptive devices such as railings may also be helpful. Surgical release of the contractures and tendon transplants are indicated in some severe cases.

DNA testing for CMT and HNPP has made it possible to determine the molecular basis for the neuropathy in individual probands and families [12]. The identification of the CMT1A duplication or HNPP deletion establishes an exact molecular form of the disease and a secure diagnosis in that family. Furthermore, it makes it possible to diagnose or exclude with a simple blood test other family members who are at risk of developing the disease, enables prenatal diagnosis to be offered, and may provide prognostic information [96]. For genetic counseling purposes, it is important to accurately diagnose new mutation cases and distinguish whether the inheritance of the CMT is autosomal dominant or X-linked. In families with CMTX, there is no male-to-male transmission, and the affected men usually have more severe symptoms than affected women. In the future, knowing the genotype will be valuable for patients with CMT if effective drugs or somatic gene therapies are developed [148,151].

A fundamental understanding of the underlying disease processes could provide a foundation for the development of therapeutic regimens for CMT. As the PMP22 gene is dosage sensitive, the fine modulation of expression of this gene in patients with CMT1A duplication by using antisense nucleic acid constructs, ribozyme, or conventional gene replacement therapies seems well beyond the capabilities of current gene therapy protocols [142,148]. It is feasible, however, that a therapeutic titer of antisense PMP22 nucleotides could be determined for individual patients. Such a therapeutic regime would most likely result in the exchange of the more severe CMT1A symptoms for the less debilitating HNPP symptoms, which result from underexpression of PMP22. In the case of point mutations in CMT1-related genes, a different strategy must be used. Somatic gene replacement therapy may be an option in these cases. Further molecular studies of myelin gene promoters and Schwann cell proliferation are necessary to develop robust gene therapy protocols. Apart from gene therapy, conventional drug design could lead to a viable therapeutic regimen. It was recently found that progesterone, which is produced by Schwann cells, promotes myelin formations during nerve regeneration [85]. Thus, progesterone, and perhaps other steroids, may affect the expression of myelin genes that are responsible for the phenotype of CMT. Effective therapeutic regimens using steroids or other drugs can now be tested on pmp22 and P0 knockout mice developed by investigators, and pmp22 overexpressing mice and rats that are presently being developed in several laboratories, in addition to the trembler mice originally identified.

Summary

Charcot-Marie-Tooth disease (CMT) was initially described more than 100 years ago by Charcot, Marie, and Tooth. It was only recently, however, that molecular genetic studies of CMT have uncovered the underlying causes of most forms of the diseases. Most cases of CMT1 are associated

with a 1.5-Mb tandem duplication in 17p11.2-p12 that encompasses the PMP22 gene. Although many genes may exist in this large duplicated region, PMP22 appears to be the major dosage-sensitive gene. CMT1A is the first autosomal dominant disease associated with a gene dosage effect due to an inherited DNA rearrangement. There is no mutant gene, but instead the disease phenotype results from having 3 copies of a normal gene. Furthermore, these findings suggest that therapeutic intervention in CMT1A duplication patients may be possible by normalizing the amount of PMP22 mRNA levels. Alternatively, CMT1A can be caused by mutations in the PMP22 gene. Other forms of CMT are associated with mutations in the MPZ (CMT1B) and Cx32 (CMTX) genes. Thus, mutations in different genes can cause similar CMT phenotypes. The related but more severe neuropathy, Dejerine-Sottas syndrome (DSS), can also be caused by mutations in the PMP22 and MPZ genes. All 3 genes thus far identified by CMT researchers appear to play an important role in the myelin formation or maintenance of peripheral nerves. CMT1A, CMT1B, CMTX, hereditary neuropathy with liability to pressure palsies (HNPP), and DSS have been called myelin disorders or ``myelinopathies." Other demyelinating forms, CMT1C and CMT-AR, may be caused by mutations of not yet identified myelin genes expressed in Schwann cells.

The clinically distinct disease HNPP is caused by a 1.5-Mb deletion in 17p11.2-p12, which spans the same region duplicated in most CMT1A patients. Underexpression of the PMP22 gene causes HNPP just as overexpression of PMP22 causes CMT1A. Thus, 2 different phenotypes can be caused by dosage variations of the same gene. It is apparent that the CMT1A duplication and HNPP deletion are the reciprocal products of a recombination event during meiosis mediated through the CMT1A-REPs. CMT1A and HNPP could be thought of as a ``genomic disease" more than single gene disorders. Other genetic disorders may also prove to arise from recombination events mediated by specific chromosomal structural features of the human genome [102]. Further studies on the recombination mechanism of CMT and HNPP might reveal the causes of site specific homologous recombination in the human genome. The discovery of the PMP22 gene in the 1.5-Mb CMT1A duplication/HNPP deletion critical region also suggests that the clinical phenotype of chromosome aneuploid syndromes may result from the effect of a small subset of dosage-sensitive genes mapping within the region of aneuploidy.

The understanding of the molecular basis of CMT1 and related disorders has allowed accurate DNA diagnosis and genetic counseling of inherited peripheral neuropathies and will make it possible to develop rational strategies for therapy. As several loci for CMT2 have been identified, the genes responsible for CMT2 will most likely be disclosed using positional cloning and candidate gene approaches in the near future.

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REFERENCES

1. Adlkofer K, Martini R, Aguzzi A, Zielasek J, Toyka KV, Suter U. Hypermyelination and demyelinating peripheral neuropathy in Pmp22-deficient mice. Nature Genet 11: 274-80, 1995. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

2. Allan W. Relation of hereditary pattern to clinical severity as illustrated by peroneal atrophy. Arch Intern Med 63: 1123-1131, 1939. **ExternalResolverBasic** | [Context Link]

3. Baechner D, Liehr T, Hameister H, Altenberger H, Grehl H, Suter U, Rautenstrau beta B. Widespread expression of the peripheral myelin protein-22 gene (pmp22) in neural and non-neural tissues during murine development. J Neurosci Res 42: 733-41, 1995. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

4. Ballabio A, Zoghbi HY. Charcot-Marie-Tooth disease and hereditary neuropathy with liability to pressure palsies. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill, p. 4569, 1995. [Context Link]

5. Behse F, Buchthal F, Carlsen F, Knappeis GG. Hereditary neuropathy with liability to pressure palsies: Electrophysiological and histopathological aspects. Brain 95: 777-94, 1972. ExternalResolverBasic | Bibliographic Links | [Context Link]

6. Bellone E, Mandich P, Mancardi GL, Schenone A, Uccelli A, Abbruzzese M, Sghirlanzoni A, Pareyson D, Ajmar F. Charcot-Marie-Tooth (CMT) la duplication at 17p11.2 in Italian families. J Med Genet 29: 492-3, 1992. ExternalResolverBasic | Bibliographic Links | [Context Link]

7. Ben Othmane K, Hentati F, Lennon F, Ben Hamida C, Blel S, Roses AD, Pericak-Vance MA, Ben Hamida M, Vance JM. Linkage of a locus (CMT4A) for autosomal recessive Charcot-Marie-Tooth disease to chromosome 8q. Hum Mol Genet 2: 1625-1628, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

8. Ben Othmane K, Middleton LT, Loprest LJ, Wilkinson KM, Lennon F, Rozear MP, Stajich JM, Gaskell PC, Roses AD, Pericak-Vance MA, Vance JM. Localization of a gene (CMT2A) for autosomal domomant Charcot-Marie-Tooth disease type 2 to chromosome 1p and evidence of genetic heterogeneity. Genomics 17: 370-5, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

9. Berciano J, Combarros O, Calleja J, Polo JM, Leno C. The application of nerve conduction and clinical studies to genetic counseling in hereditary motor and sensory neuropathy type I. Muscle Nerve 12: 302-6, 1989. ExternalResolverBasic | Bibliographic Links | [Context Link]

10. Bergoffen J, Scherer SS, Wang S, Scott MO, Bone LJ, Paul DL, Chen K, Lensch MW, Chance PF, Fischbeck KH. Connexin mutations in X-linked Charcot-Marie-Tooth disease. Science 262: 2039-2042, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

11. Bergoffen J, Trofatter J, Pericak-Vance MA, Haines JL, Chance PF, Fischbeck KH. Linkage localization of X-linked Charcot-Marie-Tooth disease. Am J Hum Genet 52: 312-8, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

12. Bird TD, Bennett RL. Why do DNA testing? Practical and ethical implications of new neurogenetic tests. Ann Neurol 38: 141-6, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

13. Bird TD, Ott J, Giblett ER. Evidence for linkage of Charcot-Marie-Tooth neuropathy to the Duffy locus on chromosome 1. Am J Hum Genet 34: 388-94, 1982. ExternalResolverBasic | Bibliographic Links | [Context Link]

14. Blair IP, Kennerson ML, Nicholson GA. Detection of Charcot-Marie-Tooth type 1A duplication by the polymerase chain reaction. Clin Chem 41: 1105-1108, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

15. Blair IP, Nash J, Gordon MJ, Nicholson GA. Prevalence and origin of de novo duplications in Charcot-Marie-Tooth disease type 1A: First report of a de novo duplication with a maternal origin. Am J Hum Genet 58: 472-6, 1996. ExternalResolverBasic | Bibliographic Links | [Context Link]

16. Bone LJ, Dahl N, Lensch MW, Chance PF, Kelly T, Le Guern E, Magi S, Parry G, Shapiro H, Wang S, Fischbeck KH. New connexin32 mutations associated with X-linked Charcot-Marie-Tooth disease. Neurology 45: 1863-1866, 1995. [Context Link]

17. Bosse F, Zoidl G, Wilms S, Gillen CP, Kuhn HG, Muller HW. Differential expression of two mRNA species indicates a dual function of peripheral myelin protein PMP22 in cell growth and myelination. J Neurosci Res 37: 529-37, 1994. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

18. Bradely WG, Madrid R, Thrush DC, Campbell MJ. Recurrent brachial plexus neuropathy. Brain 98: 381-98, 1975. [Context Link]

19. Brewerton DA, Sandifer PH, Sweetnam DR. ``Idiopathic" pes cavus: An investigation into its aetiology. Br Med J 2: 659-61, 1963. [Context Link]

20. Brice A, Ravise N, Stevanin G, Gugenheim M, Bouche P, Penet C, Agid Y, the French CMT Research Group. Duplication within chromosome 17p11.2 in 12 families of French ancestry with Charcot-Marie-Tooth disease type 1a. J Med Genet 29: 807-12, 1992. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

21. Carango P, Funanage VL, Quiros RE, Debruyn CS, Marks HG. Overexpression of DM20 messenger RNA in two brothers with Pelizaeus-Merzbacher disease. Ann Neurol 38: 610-7, 1995. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

22. Cardoso FEC, Jankovic J. Hereditary motor-sensory neuropathy and movement disorders. Muscle Nerve 16: 904-10, 1993. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

23. Chance PF, Abbas N, Lensch MW, Pentao L, Roa BB, Patel PI, Lupski JR. Two autosomal dominant neuropathies result from reciprocal DNA duplication/deletion of a region on chromosome 17. Hum Mol Genet 3: 223-8, 1994. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

24. Chance PF, Alderson MK, Leppig KA, Lensch MW, Matsunami N, Smith B, Swanson PD, Odelberg SJ, Disteche CM, Bird TD. DNA deletion associated with hereditary neuropathy with liability to pressure palsies. Cell 72: 143-51, 1993. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

25. Chance PF, Bird TD, Matsunami N, Lensch MW, Brothman AR, Feldman GM. Trisomy 17p associated with Charcot-Marie-Tooth neuropathy type 1A phenotype: Evidence for gene dosage as a mechanism in CMT1A. Neurology 42: 2295-2299, 1992. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

26. Chance PF, Bird TD, O'Connell P, Lipe H, Larouel J-M, Leppert M. Genetic linkage and heterogeneity in type I Charcot-Marie-Tooth disease (hereditary motor and sensory neuropathy type I). Am J Hum Genet 47: 915-25, 1990. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

27. Chance PF, Lensch MW, Lipe H, Brown RH Sr, Brown RH Jr, Bird TD. Hereditary neuralgic amyotrophy and hereditary neuropathy with liability to pressure palsies: Two distinct genetic disorders. Neurology 44: 2253-2257, 1994. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

28. Chance PF, Matsunami N, Lensch W, Smith B, Bird TD. Analysis of the DNA duplication 17p11.2 in Charcot-Marie-Tooth neuropathy type 1 pedigrees: Additional evidence for a third autosomal CMT1 locus. Neurology 42: 2037-2041, 1992. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

29. Charcot J-M, Marie P. Sur une forme particulaiere d'atrophie musculaire progressive souvent familiale debutant par les pied et les jambes et atteignant plus tard les mains. Rev Med 6: 97-138, 1886. [Context Link]

30. Charnas L, Trapp B, Griffin J. Congenital absence of peripheral myelin: Abnormal Schwann cell development causes lethal arthrogryposis multiplex congenita. Neurology 38: 966-74, 1988. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

31. Cremers FPM, Pfeiffer RA, van de Pol TJR, Hofker MH, Kruse TA, Wieringa B, Ropers HH. An interstitial duplication of the X chromosome in a male allows physical fine mapping of probes from the Xq13-q22 region. Hum Genet 77: 23-27, 1987. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

32. Cudrey C, Chevillard C, Le Paslier D, Vignal A, Passage E, Fontes M. Assignment of microsatellite sequences to the region duplicated in CMT1A (17p12): A useful tool for diagnosis. J Med Genet 32: 231-3, 1995. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

33. Davies DM. Recurrent peripheral-nerve palsies in a family. Lancet 2: 266-8, 1954. **ExternalResolverBasic** | [Context Link]

34. De Jong JGY. Over families met hereditaire dispositie tot het optreden van neuritiden gecorreleered met migraine. Psychiatr Neurol Bull 50: 60-76, 1947. [Context Link]

35. Debruyne J, Dehaene I, Martin JJ. Hereditary pressure-sensitive neuropathy. J Neurol Sci 47: 385-94, 1980. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

36. Dejerine J, Sottas J. Sur la nevrite interstitielle, hypertrophique et progressive de l'enface. C R Soc Biol 45: 63-96, 1893. [Context Link]

37. Dyck PJ, Chance PF, Lebo R, Carney JA. Hereditary motor and sensory neuropathies. In: Dyck PJ, Thomas PK, Griffin JW, Low PW, Poduslo JF, eds. Peripheral neuropathy. 3rd ed. Philadelphia: WB Saunders Co., p. 1094, 1993. [Context Link]

38. Dyck PJ, Karnes JL, Lambert EH. Longitudinal study of neuropathic deficits and nerve conduction abnormalities in hereditary motor and sensory neuropathy type 1. Neurology 39: 1302-1308, 1989. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

39. Dyck PJ, Kennel AJ, Magal IV, Kraybill EN. A Virginia kinship with hereditary sensory neuropathy: Peroneal muscular atrophy and pes cavus. Mayo Clin Proc 40: 685-94, 1965. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

40. Dyck PJ, Lambert EH. Lower motor and primary sensory neuron diseases with peroneal muscular atrophy. I. Neurologic, genetic, and electrophysiologic findings in hereditary polyneuropathies. Arch Neurol 18: 603-18, 1968. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

41. Dyck PJ, Lambert EH. Lower motor and primary sensory neuron diseases with peroneal muscular atrophy. II. Neurologic, genetic, and electrophysiologic findings in various neuronal degenerations. Arch Neurol 18: 619-25, 1968. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

42. Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified neuropathies yields improved diagnosis. Ann Neurol 10: 222-6, 1981. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

43. Dyck PJ, Swanson CJ, Low PA, Bartleson JD, Lambert EH. Prednisone-responsive hereditary motor and sensory neuropathy. Mayo Clin Proc 57: 239-46, 1982. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

44. Earl CJ, Fullerton PM, Wakefield GS, Schutta HS. Hereditary neuropathy, with liability to pressure palsies. Q J Med 33: 481-98, 1964. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

45. Ellis D, Malcolm S. Proteolipid protein gene dosage effect in Pelizaeus-Merzbacher disease. Nature Genet 6: 333-4, 1994. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

46. England AC, Denny-Brown D. Severe sensory changes, and trophic disorders, in peroneal muscular atrophy (Charcot-Marie-Tooth type). Arch Neurol Psychiatry 67: 1-22, 1952. **ExternalResolverBasic** | [Context Link]

47. Fairweather N, Bell C, Cochrane S, Chelly J, Wang S, Mostacciuolo ML, Monaco AP, Haites NE. Mutations in the connexin 32 gene in X-linked dominant Charcot-Marie-Tooth disease (CMTX1). Hum Mol Genet 3: 29-34, 1994. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

48. Gabreels-Festen AAWM, Gabreels FJM, Jennekens FGI, Joosten EMG, Janssen-van Kempen TW. Autosomal recessive form of hereditary motor and sensory neuropathy type I. Neurology 42: 1755-1761, 1992. [Context Link]

49. Gal A, Mucke J, Theile H, Wieacker PF, Ropers H-H, Wienker TF. X-linked dominant Charcot-Marie-Tooth disease: Suggestion of linkage with a cloned DNA sequence from the proximal Xq. Hum Genet 70: 38-42, 1985. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

50. Garcia CA. The clinical features of Charcot-Marie-Tooth disorders. In: Parry GJ, ed. Charcot-Marie-Tooth disorders: A handbook for primary care physicians. Upland, PA: Charcot-Marie-Tooth Association, p. 5, 1995. [Context Link]

51. Garcia CA, Malamut RE, England JD, Parry GS, Liu P, Lupski JR. Clinical variability in two pairs of identical twins with the Charcot-Marie-Tooth disease type 1A duplication. Neurology 45: 2090-2093, 1995. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

52. Giese KP, Martini R, Lemke G, Soriano P, Schachner M. Mouse Po gene disruption leads to hypomyelination, abnormal expression of recognition molecules, and degeneration of myelin and axons. Cell 71: 565-76, 1992. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

53. Gouider R, LeGuern E, Emile J, Tardieu S, Cabon F, Samid M, Weissenbach J, Agid Y, Bouche P,

Brice A. Hereditary neuralgic amyotrophy and hereditary neuropathy with liability to pressure palsies: Two distinct clinical, electrophysiologic, and genetic entities. Neurology 44: 2250-2252, 1994. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

54. Gouider R, LeGuern E, Gugenheim M, Tardieu S, Maisonobe T, Leger JM, Vallat JM, Agid Y, Bouche P, Brice A. Clinical, electrophysiologic, and molecular correlations in 13 families with hereditary neuropathy with liability to pressure palsies and a chromosome 17p11.2 deletion. Neurology 45: 2018-2023, 1995. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

55. Gregory R, Thomas PK, King RHM, Hallam PLJ, Malcolm S, Hughes RAC, Harding AE. Coexistence of hereditary motor and sensory neuropathy type 1a and IgM paraproteinemic neuropathy. Ann Neurol 33: 649-52, 1993. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

56. Griffin JW. Pathologic changes in Charcot-Marie-Tooth disorders. In: Parry GJ, ed. Charcot-Marie-Tooth disorders: A handbook for primary care physicians. Upland, PA: Charcot-Marie-Tooth Association, p. 29, 1995. [Context Link]

57. Gutmann L, Fakadej A, Riggs JE. Evolution of nerve conduction abnormalities in children with dominant hypertrophic neuropathy of the Charcot-Marie-Tooth type. Muscle Nerve 6: 515-9, 1983. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

58. Guzzetta V, Santoro L, Gasparo-Rippa P, Ragno M, Vita G, Caruso G, Andria G. Charcot-Marie-Tooth disease: Molecular characterization of patients from Central and Southern Italy. Clin Genet 47: 27-32, 1995. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

59. Hallam PJ, Harding AE, Berciano J, Barker DF, Malcolm S. Duplication of part of chromosome 17 is commonly associated with hereditary motor and sensory neuropathy type I (Charcot-Marie-Tooth type 1). Ann Neurol 31: 570-2, 1992. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

60. Haney C, Snipes J, Shooter EM, Suter U, Garcia CA, Griffin JW, Trapp BD. Ultrastructural distribution of PMP22 in Charcot-Marie-Tooth disease type 1A. J Neuropathol Exp Neurol 55: 290-9, 1996. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

61. Harati Y, Butler IJ. Congenital hypomyelinating neuropathy. J Neurol Neurosurg Psychiatry 48: 1269-1276, 1985. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

62. Harding AE, Thomas PK. The clinical features of hereditary motor and sensory neuropathy types I and II. Brain 103: 259-80, 1980. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

63. Hayasaka K, Himoro M, Sato W, Takada G, Uyemura K, Shimizu N, Bird TD, Conneally PM, Chance PF. Charcot-Marie-Tooth neuropathy type 1B is associated with mutations of the myelin Po gene. Nature Genet 5: 31-34, 1993. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

64. Hayasaka K, Himoro M, Sawaishi Y, Nanao K, Takahashi T, Takada G, Nicholson GA, Ouvrier RA, Tachi N. De novo mutation of the myelin P0 gene in Dejerine-Sottas disease (hereditary motor and sensory neuropathy type III). Nature Genet 5: 266-8, 1993. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

65. Hayasaka K, Ohnishi A, Takada G, Fukushima Y, Murai Y. Mutation of the myelin Po gene in Charcot-Marie-Tooth neuropathy type 1. Biochem Biophys Res Commun 194: 1317-1322, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

66. Hayasaka K, Takada G, Ionasescu VV. Mutation of the myelin Po gene in Charcot-Marie-Tooth neuropathy type 1B. Hum Mol Genet 2: 1369-1372, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

67. Hertz JM, Borglum AD, Brandt CA, Flint T, Bisgaard C. Charcot-Marie-Tooth disease type 1A: The parental origin of a de novo 17p11.2-p12 duplication. Clin Genet 46: 291-4, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

68. Himoro M, Yoshikawa H, Matsui T, Mitsui Y, Takahashi M, Kaido M, Nishimura T, Sawaishi Y, Takada G, Hayasaka K. New mutation of the myelin Po gene in a pedigree of Charcot-Marie-Tooth neuropathy type 1. Biochem Mol Biol Int 31: 169-73, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

69. Holmberg BH, Holmgren G, Nelis E, Van Broeckhoven C, Westerberg B. Charcot-Marie-Tooth disease in northern Sweden: Pedigree analysis and the presence of the duplication in chromosome 17p11.2. J Med Genet 31: 435-41, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

70. Hoogendijk JE, Hensels GW, Gabreels-Festen AAWM, Gabreels FJM, Janssen EAM, de Jonghe P, Martin J-J, Van Broeckhoven C, Valentijn LJ, Baas F, de Visser M, Bolhuis PA. De-novo mutation in hereditary motor and sensory neuropathy type I. Lancet 339: 1081-2, 1992. ExternalResolverBasic | Bibliographic Links | [Context Link]

71. Hoogendijk JE, Janssen EAM, Gabreels-Festen AAWM, Hensels GW, Joosten EMG, Gabreels FJM, Zorn I, Valentijn LJ, Baas F, Ongerboer de Visser BW, de Visser M, Bolhuis PA. Allelic heterogeneity in hereditary motor and sensory neuropathy type Ia (Charcot-Marie-Tooth disease type 1a). Neurology 43: 1010-1015, 1993. Ovid Full Text | ExternalResolverBasic | Request Permissions | Bibliographic Links | [Context Link]

72. Hudson LD, Puckett C, Berndt J, Chan J, Gencic S. Mutation of the proteolipid protein gene PLP in a human X chromosome-linked myelin disorder. Proc Natl Acad Sci USA 86: 8128-8131, 1989. ExternalResolverBasic | Bibliographic Links | [Context Link]

73. Ionasescu V, Searby C, Ionasescu R. Point mutations of the connexin32 (GJB1) gene in X-linked dominant Charcot-Marie-Tooth neuropathy. Hum Mol Genet 3: 355-8, 1994. [Context Link]

74. Ionasescu VV. Charcot-Marie-Tooth neuropathies: From clinical description to molecular genetics. Muscle Nerve 18: 267-75, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

75. Ionasescu VV, Ionasescu R, Searby C. Screening of dominantly inherited Charcot-Marie-Tooth neuropathies. Muscle Nerve 16: 1232-1238, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

76. Ionasescu VV, Ionasescu R, Searby C, Barker DF. Charcot-Marie-Tooth neuropathy type 1A with both duplication and non-duplication. Hum Mol Genet 2: 405-10, 1993. ExternalResolverBasic |

Bibliographic Links | [Context Link]

77. Ionasescu VV, Ionasescu R, Searby C, Neahring R. Dejerine-Sottas disease with de novo dominant point mutation of the PMP22 gene. Neurology 45: 1766-1767, 1995. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

78. Ionasescu VV, Trofatter J, Haines JL, Summers AM, Ionasescu R, Searby C. Heterogeneity in X-linked recessive Charcot-Marie-Tooth neuropathy. Am J Hum Genet 1075-1083, 1991. **ExternalResolverBasic** | [Context Link]

79. Kagawa T, Ikenaka K, Inoue Y, Kuriyama S, Tsujii T, Nakao J, Nakajima K, Aruga J, Okano H, Mikoshiba K. Glial cell degeneration and hypomyelination caused by overexpression of myelin proteolipid protein gene. Neuron 13: 427-42, 1994. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

80. Kaku DA, Parry GJ, Malamut R, Lupski JR, Garcia CA. Nerve conduction studies in Charcot-Marie-Tooth polyneuropathy associated with a segmental duplication of chromosome 17. Neurology 43: 1806-1808, 1993. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

81. Kaku DA, Parry GJ, Malamut R, Lupski JR, Garcia CA. Uniform slowing of conduction velocities in Charcot-Marie-Tooth polyneuropathy type 1. Neurology 43: 2664-2667, 1993. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

82. Killian JM, Kloepfer HW. Homozygous expression of a dominant gene for Charcot-Marie-Tooth neuropathy. Ann Neurol 5: 515-22, 1979. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

83. Killian JM, Tiwari PS, Jacobson S, Jackson RD, Lupski JR. Longitudinal studies of the duplication form of Chracot-Marie-Tooth polyneuropathy. Muscle Nerve 19: 74-78, 1996. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

84. Kimura J. Electrodiagnosis in diseases of nerve and muscle: Principles and practice. Philadelphia: F.A. Davis Co., 1989. [Context Link]

85. Koenig HL, Schumacher M, Ferzaz B, Do Thi AN, Ressouches A, Guennoun R, Jung-Testas I, Robel P, Akwa Y, Baulieu E-E. Progesterone synthesis and myelin formation by Schwann cells. Science 268: 1500-1503, 1995. [Context Link]

86. Kulkens T, Bolhuis PA, Wolterman RA, Kemp S, te Nijenhuis S, Valentijn LJ, Hensels GW, Jennekens FGI, de Visser M, Hoogendijk JE, Baas F. Deletion of the serine 34 codon from the major peripheral myelin protein Po gene in Charcot-Marie-Tooth disease type 1B. Nature Genet 35-39, 1993. **ExternalResolverBasic** | [Context Link]

87. Kwon JM, Elliott JL, Yee W, Ivanovich J, Scavarda NJ, Moolsintong PJ, Goodfellow PJ. Assignment of a second Charcot-Marie-Tooth type II locus to chromosome 3q. Am J Hum Genet 57: 853-8, 1995. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

88. Latour P, Blanquet F, Nelis E, Bonnebouche C, Chapon F, Diraison P, Ollagnon E, Dautigny A, Pham-Dinh D, Chazot G, Boucherat M, Van Broeckhoven C, Vandenberghe A. Mutations in the myelin

protein zero gene associated with Charcot-Marie-Tooth disease type 1B. Hum Mutat 6: 50-54, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

89. Le Guern E, Gouider R, Lopes J, Abbas N, Gugenheim M, Tardieu S, Ravise N, Leger J-M, Vallat J-M, Bouche P, Agid Y, Brice A, the French CMT Collaborative Research Group. Constant rearrangement of the CMT1A-REP sequences in HNPP patients with a deletion in chromosome 17p11.2: A study of 30 unrelated cases. Hum Mol Genet 4: 1673-1874, 1995. ExternalResolverBasic | [Context Link]

90. Le Guern E, Gouider R, Ravise N, Lopes J, Tardieu S, Gugenheim M, Abbas N, Bouche P, Agid Y, Brice A. A de novo case of hereditary neuropathy with liability to pressure palsies (HNPP) of maternal origin: A new mechanism for deletion in 17p11.2? Hum Mol Genet 5: 103-6, 1996. ExternalResolverBasic | Bibliographic Links | [Context Link]

91. Le Guern E, Sturtz F, Gugenheim M, Gouider R, Bonnebouche C, Ravise N, Gonnaud P-M, Tardieu S, Bouche P, Chazot G, Agid Y, Vandenberghe A, Brice A. Detection of deletion within 17p11.2 in 7 French families with hereditary neuropathy with liability to pressure palsies (HNPP). Cytogenet Cell Genet 65: 261-4, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

92. Lebo RV, Chance PF, Dyck PJ, Redila-Flores MT, Lynch ED, Golbus MS, Bird TD, King MC, Anderson LA, Hall J, Wiegant J, Jiang Z, Dazin PF, Punnett HH, Schonberg SA, Moore K, Shull MM, Gendler S, Hurko O, Lovelace RE, Latov N, Trofatter J, Conneally PM. Chromosome 1 Charcot-Marie-Tooth disease (CMT1B) locus in the Fc gamma receptor region. Hum Genet 88: 1-12, 1991. ExternalResolverBasic | Bibliographic Links | [Context Link]

93. Lebo RV, Martelli L, Su Y, Li L, Lynch E, Mansfield E, Pua K-H, Watson DF, Chueh J, Hurko O. Prenatal diagnosis of Charcot-Marie-Tooth disease type 1A by multicolor in situ hybridization. Am J Med Genet 47: 441-50, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

94. Lorenzetti D, Pareyson D, Sghirlanzoni A, Roa BB, Abbas NE, Pandolfo M, Di Donato S, Lupski JR. A 1.5-Mb deletion in 17p11.2-p12 is frequently observed in Italian families with hereditary neuropathy with liability to pressure palsies. Am J Hum Genet 56: 91-98, 1995. [Context Link]

95. Lupski JR. An inherited DNA rearrangement and gene dosage effect are responsible for the most common autosomal dominant peripheral neuropathy: Charcot-Marie-Tooth disease type 1A. Clin Res 40: 645-52, 1992. ExternalResolverBasic | Bibliographic Links | [Context Link]

96. Lupski JR. Molecular genetics of Charcot-Marie-Tooth disease and related peripheral neuropathies. In: Jameson JL, ed. Textbook of molecular medicine. Cambridge: Blackwell Scientific, 1996. [Context Link]

97. Lupski JR, Chance PF, Garcia CA. Inherited primary peripheral neuropathies: Molecular genetics and clinical implications of CMT1A and HNPP. JAMA 17: 2326-2330, 1993. [Context Link]

98. Lupski JR, Garcia CA. Molecular genetics and neuropathology of Charcot-Marie-Tooth disease type 1A. Brain Pathol 2: 337-49, 1992. [Context Link]

99. Lupski JR, Garcia CA, Parry GJ, Patel PI. Charcot-Marie-Tooth polyneuropathy syndrome: Clinical, electrophysiologic, and genetic aspects. In: Appel S, ed. Current neurology. Chicago: Mosby Yearbook, p. 1, 1991. [Context Link]

100. Lupski JR. Montes de Oca-Luna R, Slaugenhaupt S, Pentao L, Guzzetta V, Trask BJ, Saucedo-Cardenas O, Barker DF, Killian JM, Garcia CA, Chakravarti A, Patel PI. DNA duplication associated with Charcot-Marie-Tooth disease type 1A. Cell 66: 219-32, 1991. [Context Link]

101. Lupski JR, Pentao L, Williams LL, Patel PI. Stable inheritance of the CMT1A DNA duplication in two patients with CMT1 and NF1. Am J Med Genet 45: 92-96, 1993. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

102. Lupski JR, Roth JR, Weinstock GM. Chromosomal duplications in bacteria, fruit flies, and humans. Am J Hum 58: 21-27, 1996. [Context Link]

103. Lupski JR, Wise CA, Kuwano A, Pentao L, Parke JT, Glaze DG, Ledbetter DH, Greenberg F, Patel PI. Gene dosage is a mechanism for Charcot-Marie-Tooth disease type 1A. Nature Genet 1: 29-33, 1992. [Context Link]

104. MacMillan JC, Upadhyaya M, Harper PS. Charcot-Marie-Tooth disease type 1a (CMT1a): Evidence for trisomy of the region p11.2 of chromosome 17 in south Wales families. J Med Genet 29: 12-13, 1991. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

105. Madrid R, Bradley WG. The pathology of neuropathies with focal thickening of the myelin sheath (tomaculous neuropathy): Studies on the formation of the abnormal myelin sheath. J Neurol Sci 25: 415-48, 1975. **ExternalResolverBasic** | [Context Link]

106. Mancardi GL, Uccelli A, Bellone E, Sghirlanzoni A, Mandich P, Pareyson D, Schenone A, Abbruzzese M, Ajmar F. 17p11.2 duplication is a common finding in sporadic cases of Charcot-Marie-Tooth type 1. Eur Neurol 34: 135-9, 1994. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

107. Mandich P, James R, Nassani S, Defferrari R, Bellone E, Mancardi G, Schenone A, Abbruzzese M, Rocchi M, Ajmar F, Archidiacono N. Molecular diagnosis of hereditary neuropathy with liability to pressure palsies (HNPP) by detection of 17p11.2 deletion in Italian patients. J Neurol 242: 295-8, 1995. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

108. Manfioletti G, Ruaro ME, Del Sal G, Philipson L, Schneider C. A growth arrest-specific (gas) gene codes for a membrane protein. Mol Cell Biol 10: 2924-2930, 1990. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

109. Mariman ECM, Gabreels-Festen AAWM, van Beersum SEC, Jongen PJH, van de Looij E, Baas F, Bolhuis PA, Ropers HH, Gabreels FJM. Evidence for genetic heterogeneity underlying hereditary neuropathy with liability to pressure palsies. Hum Genet 93: 151-6, 1994. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

110. Mariman ECM, Gabreels-Festen AAWM, van Beersum SEC, Valentijn LJ, Baas F, Bolhuis PA, Jongen PJH, Ropers HH, Gabreels FJM. Prevalence of the 1.5-Mb 17p deletion in families with hereditary neuropathy with liability to pressure palsies. Ann Neurol 36: 650-5, 1994. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

111. Markesbery WR, Griggs RC, Leach RP, Lapham LW. Late onset hereditary distal myopathy. Neurology 24: 127-34, 1974. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

112. Martini R, Zielasek J, Toyka KV, Giese KP, Schachner M. Protein zero (PO)-deficient mice show myelin degeneration in peripheral nerves characteristic of inherited human neuropathies. Nature Genet 11: 281-6, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

113. Matise TC, Chakravarti A, Patel PI, Lupski JR, Nelis E, Timmerman V, Van Broekhoven C, Weeks DE. Detection of tandem duplications and implications for linkage analysis. Am J Hum Genet 54: 1110-1121, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

114. Matsunami N, Smith B, Ballard L, Lensch MW, Robertson M, Albertsen H, Hanemann CO, Muller HW, Bird TD, White R, Chance PF. Peripheral myelin protein-22 gene maps in the duplication in chromosome 17p11.2 associated with Charcot-Marie-Tooth 1A. Nature Genet 1: 176-9, 1992. ExternalResolverBasic | Bibliographic Links | [Context Link]

115. McKusick VA. Mendelian inheritance in man: A catalog of human genes and genetic disorders. 11th ed. Baltimore: Johns Hopkins University Press, 1994. [Context Link]

116. Mostacciuolo ML, Schiavon F, Angelini C, Miccoli B, Piccolo F, Danieli GA. Frequency of duplication at 17p11.2 in families of northeast Italy with Charcot-Marie-Tooth disease type 1. Neuroepidemiology 14: 49-53, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

117. Muller E, Mostacciuolo ML, Micaglio G, Angelini C, Danieli GA. Further evidence of a duplication in 17p11.2 in families with recurrence of HMSN Ia (Charcot-Marie-Tooth neuropathy type 1a). Hum Genet 90: 231-4, 1992. ExternalResolverBasic | Bibliographic Links | [Context Link]

118. Murakami T, Uchino M, Ando M. Genetic abnormalities and pathogenesis of familial amyloidotic polyneuropathy. Pathol Int 45: 1-9, 1995. [Context Link]

119. Navon R, Timmerman V, Lofgren A, Liang P, Nelis E, Zeitune M, Van Broeckhoven C. Prenatal diagnosis of Charcot-Marie-Tooth disease type 1A (CMT1A) using molecular genetic techniques. Prenat Diagn 15: 633-40, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

120. Nelis E, Timmerman V, De Jonghe P, Muylle L, Martin J-J, Van Broeckhoven C. Linkage and mutation analysis in an extended family with Charcot-Marie-Tooth disease type 1B. J Med Genet 31: 811-5, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

121. Nelis E, Timmerman V, De Jonghe P, Van Broeckhoven C. Identification of a 5 prime splice site mutation in the PMP-22 gene in autosomal dominant Charcot-Marie-Tooth disease type 1. Hum Mol Genet 3: 515-6, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

122. Nelis E, Timmerman V, De Jonghe P, Vandenberghe A, Pham-Dinh D, Dautigny A, Martin J-J, Van Broeckhoven C. Rapid screening of myelin genes in CMT1 patients by SSCP analysis: Identification of new mutations and polymorphisms in the Po gene. Hum Genet 94: 653-7, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

123. Nelis E, Van Broeckhoven C, and the European Collaborative Consortium. Estimation of the mutation frequencies in Charcot-Marie-Tooth disease type 1 (CMT1) and hereditary neuropathy with liability to pressure palsies (HNPP): A European collaborative study. Eur J Hum Genet 4: 25-33, 1996. ExternalResolverBasic | Bibliographic Links | [Context Link]

124. Nicholson GA. Penetrance of the hereditary motor and sensory neuropathy Ia mutation: Assessment by nerve conduction studies. Neurology 41: 547-52, 1991. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

125. Nicholson GA, Kennerson ML, Keats BJB, Mesterovic N, Churcher W, Barker D, Ross DA. Charcot-Marie-Tooth neuropathy type 1A mutation: Apparent crossovers with D17S122 are due to a duplication. Am J Med Genet 44: 455-60, 1992. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

126. Nicholson G, Nash J. Intermediate nerve conduction velocities define X-linked Charcot-Marie-Tooth neuropathy families. Neurology 43: 2558-2564, 1993. **Ovid Full Text** | **ExternalResolverBasic** | **Request Permissions** | **Bibliographic Links** | [Context Link]

127. Nicholson GA, Valentijn LJ, Cherryson AK, Kennerson ML, Bragg TL, DeKroon RM, Ross DA, Pollard JD, Mcleod JG, Bolhuis PA, Bass F. A frame shift mutation in the PMP22 gene in hereditary neuropathy with liability to pressure palsies. Nature Genet 6: 263-66, 1994. Erratum: Nature Genet 7: 113, 1994. [Context Link]

128. Orth U, Fairweather N, Exler M-C, Schwinger E, Gal A. X-linked dominant Charcot-Marie-Tooth neuropathy: Valine-38-methionine substitution of connexin32. Hum Mol Genet 3: 1966-1700, 1994. **ExternalResolverBasic** | [Context Link]

129. Palau F, Logren A, De Jonghe P, Bort S, Nelis E, Sevilla T, Martin J-J, Vilchez J, Prieto F, Van Broeckhoven C. Origin of the de novo duplication in Charcot-Marie-Tooth disease type 1A: Unequal nonsister chromatid exchange during spermatogenesis. Hum Mol Genet 2: 2031-2035, 1993. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

130. Parry GJ. Charcot-Marie-Tooth disorders: A handbook for primary care physicians. Upland, PA: Charcot-Marie-Tooth Association, 1995. [Context Link]

131. Patel PI, Lupski JR. Charcot-Marie-Tooth disease: A new paradigm for the mechanism of inherited disease. Trends Genet 10: 128-33, 1994. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

132. Patel PI, Roa BB, Welcher AA, Schoener-Scott R, Trask BJ, Pentao L, Snipes GJ, Garcia CA, Francke U, Shooter EM, Lupski JR, Suter U. The gene for the peripheral myelin protein PMP-22 is a candidate for Charcot-Marie-Tooth disease type 1A. Nature Genet 1: 159-65, 1992. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

133. Pentao L, Wise CA, Chinault AC, Patel PI, Lupski JR. Charcot-Marie-Tooth type 1A duplication appears to arise from recombination at repeat sequences flanking the 1.5 Mb monomer unit. Nature Genet 2: 292-300, 1992. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

134. Priest JM, Fischbeck KH, Nouri N, Keats BJB. A locus for axonal motor-sensory neuropathy with deafness and mental retardation maps to Xq24-q26. Genomics 29: 409-12, 1995. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

135. Raeymaekers P, Timmerman V, Nelis E, De Jonghe P, Hoogendijk JE, Baas F, Barker DF, Martin JJ, De Visser M, Bolhuis PA, Van Broeckhoven C, and the HMSN Collaborative Research Group. Duplication in chromosome 17p11.2 in Charcot-Marie-Tooth neuropathy type 1a (CMT1a). Neuromusc Dis 1: 93-97, 1991. **ExternalResolverBasic** | **Bibliographic Links** | [Context Link]

136. Raeymaekers P, Timmerman V, Nelis E, Van Hul W, De Jonghe P, Martin J-J, Van Brockhoven C, and the HMSN Collaborative Research Group. Estimation of the size of the chromosome 17p11.2 duplication in Charcot-Marie-Tooth neuropathy type 1a (CMT1a). J Med Genet 29: 5-11, 1992. ExternalResolverBasic | Bibliographic Links | [Context Link]

137. Rautenstrau beta B, Nelis E, Grehl H, Pfeiffer RA, Van Broeckhoven C. Identification of a de novo insertional mutation in Po in a patient with a Dejerine-Sottas syndrome (DSS) phenotype. Hum Mol Genet 3: 1701-2, 1994. [Context Link]

138. Readhead C, Schneider A, Griffiths I, Nave K-A. Premature arrest of myelin formation in transgenic mice with increased proteolipid protein gene dosage. Neuron 12: 583-95, 1994. [Context Link]

139. Reisecker F, Leblhuber F, Lexner R, Radner G, Rosenkranz W, Wagner K. A sporadic form of hereditary neuropathy with liability to pressure palsies: Clinical, electrodiagnostic, and molecular genetic findings. Neurology 44: 753-5, 1994. Ovid Full Text | ExternalResolverBasic | Request Permissions | Bibliographic Links | [Context Link]

140. Reiter LT, Murakami T, Koeuth T, Pentao L, Muzny DM, Gibbs RA, Lupski JR. A recombination hot spot responsible for two inherited peripheral neuropathies is located near a mariner transposon-like element. Nature Genet 12: 288-97, 1996. ExternalResolverBasic | Bibliographic Links | [Context Link]

141. Reiter LT, Murakami T, Warner LE, Lupski JR. DNA rearrangements affecting dosage sensitive genes. In: McCabe ERB, ed. Mental retardation and developmental disabilities research reviews: The molecular medicine of mental retardation and developmental disabilities. New York: John Wiley and Sons (in press). [Context Link]

142. Roa BB, Ananth U, Garcia CA, Lupski JR. Molecular diagnosis of CMT1A and HNPP. Lab Med Int 12: 22-24, 1995. [Context Link]

143. Roa BB, Dyck PJ, Marks HG, Chance PF, Lupski JR. Dejerine-Sottas syndrome associated with point mutation in the peripheral myelin protein 22 (PMP22) gene. Nature Genet 5: 269-73, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

144. Roa BB, Garcia CA, Pentao L, Killian JM, Trask BJ, Suter U, Snipes J, Ortiz-Lopez R, Shooter EM, Patel PI, Lupski JR. Evidence for a recessive PMP22 point mutation in Charcot-Marie-Tooth disease type 1A. Nature Genet 5: 189-94, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

145. Roa BB, Garcia CA, Suter U, Kulpa DA, Wise CA, Mueller J, Welcher AA, Snipes GJ, Shooter EM, Patel PI, Lupski JR. Charcot-Marie-Tooth disease type 1A: Association with a spontaneous point mutation in the PMP22 gene. N Engl J Med 329: 96-101, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

146. Roa BB, Garcia CA, Wise CA, Anderson K, Greenberg F, Patel PI, Lupski JR. Gene dosage as a mechanism for a common autosomal dominant peripheral neuropathy: Charcot-Marie-Tooth disease type 1A. In: Epstein CJ, ed. Phenotypic mapping of Down syndrome and other aneuploid conditions. New York: Wiley-Liss Inc., p. 187, 1993. [Context Link]

147. Roa BB, Greenberg F, Gunaratne P, Sauer CM, Lubinsky MS, Kozma C, Meck JM, Magenis RE, Shaffer LG, Lupski JR. Duplication of the PMP22 gene in 17p partial trisomy patients with Charcot-Marie-Tooth type 1A neuropathy. Hum Genet 97:642-49, 1996. ExternalResolverBasic | Bibliographic Links | [Context Link]

148. Roa BB, Lupski JR. Charcot-Marie-Tooth disease and related inherited myelin disorders: Molecular genetics and implications for gene therapy. Institute of Laboratory Animal Resources (ILAR) News 36: 64-72, 1994. [Context Link]

149. Roa BB, Lupski JR. Molecular genetics of Charcot-Marie-Tooth neuropathy. In: Harris H, Hirschhorn K, eds. Advances in human genetics. New York: Plenum Press, p. 117, 1994. [Context Link]

150. Roa BB, Waner LE, Garcia CA, Russo D, Lovelace R, Chance PF, Lupski JR. Myelin protein zero (MPZ) gene mutations in nonduplication type 1 Charcot-Marie-Tooth disease. Hum Mutat 7: 36-45, 1996. ExternalResolverBasic | Bibliographic Links | [Context Link]

151. Rosenberg RN, Iannaccone ST. The prevention of neurogenetic disease. Arch Neurol 52: 356-62, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

152. Roussy G, Levy G. Sept cas d'une maladie familiale particuliere: Troubles de la marche, pieds bots et areflexie tendineuse generalisee avec accessoirement, legere maladresse des mains. Rev Neurol 1: 427-50, 1926. ExternalResolverBasic | [Context Link]

153. Roy EP, Gutmann L, Riggs JE. Longitudinal conduction studies in hereditary motor and sensory neuropathy type 1. Muscle Nerve 12: 52-55, 1989. ExternalResolverBasic | Bibliographic Links | [Context Link]

154. Sabir M, Lyttle D. Pathogeneis of pes cavus in Charcot-Marie-Tooth disease. Clin Orthop 175: 173-8, 1983. [Context Link]

155. Schiavon F, Mostacciuolo ML, Saad F, Merlini L, Siciliano G, Angelini C, Danieli GA. Non-radioactive detection of 17p11.2 duplication in CMT1A: A study of 78 patients. J Med Genet 31: 880-3, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

156. Silander K, Halonen P, Sara R, Kalimo H, Falck B, Savontaus M-L. DNA analysis in Finnish patients with hereditary neuropathy with liability to pressure palsies (HNPP). J Neurol Neurosurg Psychiatry 57: 1260-1262, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

157. Skre H. Genetic and clinical aspects of Charcot-Marie-Tooth's disease. Clin Genet 6: 98-118, 1974. ExternalResolverBasic | Bibliographic Links | [Context Link]

158. Snipes GJ, Suter U. Molecular anatomy and genetics of myelin proteins in the peripheral nervous system. J Anat 186: 483-94, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

159. Snipes GJ, Suter U. Molecular basis of common hereditary motor and sensory neuropathies in humans and in mouse models. Brain Pathol 5: 233-47, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

160. Spreyer P, Kuhn G, Hanemann CO, Gillen C, Schaal H, Kuhn R, Lemke G, Muller HW. Axon-regulated expression of a Schwann cell transcript that is homologous to a ``growth arrest-specific'' gene. EMBO J 10: 3661-3668, 1991. [Context Link]

161. Su Y, Brooks DG, Li L, Lepercq J, Trofatter JA, Ravetch JV, Lebo RV. Myelin protein zero gene mutated in Charcot-Marie-Tooth type 1B patients. Proc Natl Acad Sci USA 90: 10856-10860, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

162. Suter U, Moskow JJ, Welcher AA, Snipes GJ, Kosaras B, Sidman RL, Buchberg AM, Shooter EM. A leucine-to-proline mutation in the putative first transmembrane domain of the 22-kDa peripheral myelin protein in the trembler-J mouse. Proc Natl Acad Sci USA 89: 4382-4386, 1992. ExternalResolverBasic | Bibliographic Links | [Context Link]

163. Suter U, Snipes GJ. Biology and genetics of hereditary motor and sensory neuropathies. Annu Rev Neurosci 18: 45-75, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

164. Suter U, Snipes GJ, Schoener-Scott R, Welcher AA, Pareek S, Lupski JR, Murphy RA, Shooter EM, Patel PI. Regulation of tissue-specific expression of alternative peripheral myelin protein-22 (PMP22) gene transcripts by two promoters. J Biol Chem 269: 25795-25808, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

165. Suter U, Welcher AA, Snipes GJ. Progress in the molecular understanding of hereditary peripheral neuropathies reveals new insights into the biology of the periphral nervous system. Trends Neurosci 16: 50-56, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

166. Suter U, Welcher AA, Ozcelik T, Snipes GJ, Kosaras B, Francke U, Billings-Gagliardi S, Sidman RL, Shooter EM. Trembler mouse carries a point mutation in a myelin gene. Nature 356: 241-4, 1992. ExternalResolverBasic | Bibliographic Links | [Context Link]

167. Timmerman V, Lofgren A, Le Guern E, Liang P, De Jonghe P, Martin J-J, Verhalle D, Robberecht W, Gouider R, Brice A, Van Broeckhoven C. Molecular genetic analysis of the 17p11.2 region in patients with hereditary neuropathy with liability to pressure palsies (HNPP). Hum Genet 97: 26-34, 1996. ExternalResolverBasic | Bibliographic Links | [Context Link]

168. Timmerman V, Nelis E, Van Hul W, Nieuwenhuijsen BW, Chen KL, Wang S, Ben Othman K, Cullen B, Leach RJ, Hanemann CO, De Jonghe P, Raeymaekers P, van Ommen G-JB, Martin J-J, Muller HW, Vance JM, Fischbeck KH, Van Broeckhoven C. The peripheral myelin protein gene PMP-22 is contained within the Charcot-Marie-Tooth disease type 1A duplication. Nature Genet 1: 171-5, 1992. ExternalResolverBasic | Bibliographic Links | [Context Link]

169. Tooth H. The peroneal type of progressive muscular atrophy. London, England: Lewis, HK, 1886. [Context Link]

170. Uncini A, Di Muzio A, Chiavaroli F, Gambi D, Sabatelli M, Archidiacono N, Antonacci R, Marzella R, Rocchi M. Hereditary motor and sensory neuropathy with calf hypertrophy is associated with 17p11.2 duplication. Ann Neurol 35: 552-58, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

171. Uncini A, Di Guglielmo G, Di Muzio A, Gambi D, Sabatelli M, Mignogna T, Tonali P, Marzella R, Finelli P, Archidiacono N, Rocchi M. Differential electrophysiological features of neuropathies

associated with 17p11.2 deletion and duplication. Muscle Nerve 18: 628-35, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

172. Upadhyaya M, Roberts SH, Farnham J, MacMillan JC, Clarke A, Heath JP, Hodges ICG, Harper PS. Charcot-Marie-Tooth disease 1A (CMT1A) associated with a maternal duplication of chromosome 17p11.2-12. Hum Genet 91: 392-4, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

173. Valentijn LJ, Baas F, Zorn I, Hensels GW, de Visser M, Bolhuis PA. Alternatively sized duplication in Charcot-Marie-Tooth disease type 1A. Hum Mol Genet 2: 2143-2146, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

174. Valentijn LJ, Bass F, Wolterman RA, Hoogendijk JE, van den Bosch NHA, Zorn I, Gabreels-Festen AAWM, de Visser M, Bolhuis PA. Identical point mutations of PMP-22 in Trembler-J mouse and Charcot-Marie-Tooth disease type 1A. Nature Genet 2: 288-91, 1992. ExternalResolverBasic | Bibliographic Links | [Context Link]

175. Valentijn LJ, Bolhuis PA, Zorn I, Hoogendijk JE, van den Bosch N, Hensels GW, Stanton Jr VP, Housman DE, Fischbeck KH, Ross DA, Nicholson GA, Meershoek EJ, Dauwerse HG, van Ommen G-JB, Baas F. The peripheral myelin gene PMP-22/GAS-3 is duplicated in Charcot-Marie-Tooth disease type 1A. Nature Genet 1: 166-70, 1992. ExternalResolverBasic | Bibliographic Links | [Context Link]

176. Valentijn LJ, Ouvrier RA, van den Bosch NH, Bolhuis PA, Baas F, Nicholson GA. Dejerine-Sottas neuropathy is associated with a de novo PMP22 mutation. Hum Mutat 5: 76-80, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

177. Vance JM, Nicholson GA, Yamaoka LH, Stajich J, Stewart CS, Speer MC, Hung W-Y, Roses AD, Barker D, Pericak-Vance MA. Linkage of Charcot-Marie-Tooth neuropathy type 1a to chromosome 17. Exp Neurol 104: 186-9, 1989. ExternalResolverBasic | Bibliographic Links | [Context Link]

178. Verhalle D, Lofgren A, Nelis E, Dehaene I, Theys P, Lammens M, Dom R, Van Broeckhoven C, Robberecht W. Deletion in the CMT1A locus on chromosome 17p11.2 in hereditary neuropathy with liability to pressure palsies. Ann Neurol 35: 704-8, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

179. Warner LE, Roa BB, Lupski JR. Settling the myelin protein zero question in CMT1B. Nature Genet 11: 119-20, 1995. ExternalResolverBasic | Bibliographic Links | [Context Link]

180. Warner LE, Roa BB, Lupski JR. Absence of PMP22 coding region mutations in CMT1A duplication patients: Further evidence supporting gene dosage as a mechanism for Charcot-Marie-Tooth disease type 1A. Hum Mutat (in press). [Context Link]

181. Welander L. Miopathia distalis tarda hereditaria. Acta Med Scand 141 (suppl 265): 1-124, 1951. ExternalResolverBasic | [Context Link]

182. Welcher AA, Suter U, De Leon M, Snipes GJ, Shooter EM. A myelin protein is encoded by the homologue of a growth arrest-specific gene. Proc Natl Acad Sci USA 88: 7195-7199, 1991. ExternalResolverBasic | Bibliographic Links | [Context Link]

183. Wise CA, Garcia CA, Davis SN, Heju Z, Pentao L, Patel PI, Lupski JR. Molecular analyses of

unrelated Charcot-Marie-Tooth (CMT) disease patients suggest a high frequency of the CMT1A duplication. Am J Hum Genet 53: 853-63, 1993. ExternalResolverBasic | Bibliographic Links | [Context Link]

184. Yoshikawa H, Dyck PJ. Uncompacted inner myelin lamellae in inherited tendency to pressure palsy. J Neuropathol Exp Neurol 50: 649-57, 1991. Ovid Full Text | ExternalResolverBasic | Request Permissions | Bibliographic Links | [Context Link]

185. Yoshikawa H, Nishimura T, Nakatsuji Y, Fujimura H, Himoro M, Hayasaka K, Sakoda S, Yanagihara T. Elevated expression of messenger RNA for peripheral myelin protein 22 in biopsied peripheral nerves of patients with Charcot-Marie-Tooth disease type 1A. Ann Neurol 35: 445-50, 1994. ExternalResolverBasic | Bibliographic Links | [Context Link]

186. Zoidl G, Blass-Kampmann S, D'Urso D, Schmalenbach C, Muller HW. Retroviral-mediated gene transfer of the peripheral myelin protein PMP22 in Schwann cells: Modulation of cell growth. EMBO J 1122-1128, 1995. ExternalResolverBasic | [Context Link]

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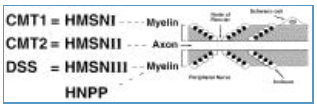

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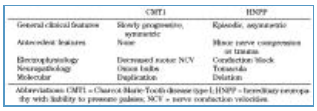

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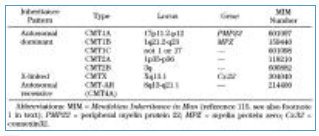

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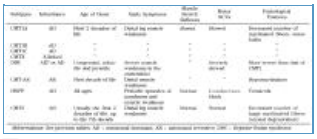

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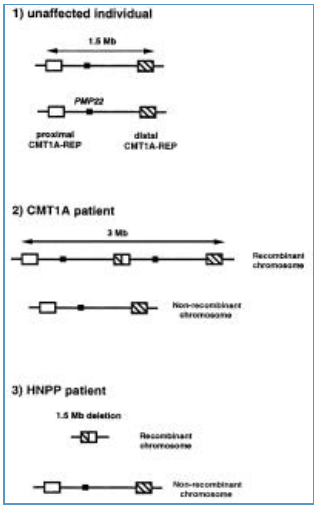

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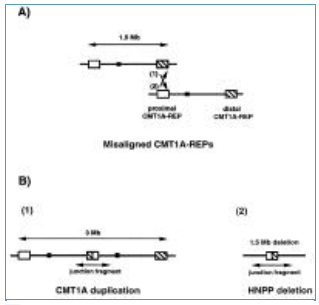

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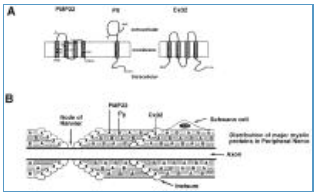

Figure 4

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