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Report

Mapping of Charcot-Marie-Tooth Disease Type 1C to Chromosome 16p Identifies a Novel Locus for Demyelinating Neuropathies

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Charcot-Marie-Tooth (CMT) neuropathy represents a genetically heterogeneous group of diseases affecting the peripheral nervous system. We report genetic mapping of the disease to chromosome 16p13.1-p12.3, in two families with autosomal dominant CMT type 1C (CMT1C). Affected individuals in these families manifest characteristic CMT symptoms, including high-arched feet, distal muscle weakness and atrophy, depressed deep-tendon reflexes, sensory impairment, slow nerve conduction velocities, and nerve demyelination. A maximal combined LOD score of 14.25 was obtained with marker D16S500. The combined haplotype analysis in these two families localizes the CMT1C gene within a 9-cM interval flanked by markers D16S519 and D16S764. The disease-linked haplotypes in these two pedigrees are not conserved, suggesting that the gene mutation underlying the disease in each family arose independently. The epithelial membrane protein 2 gene (*EMP2*), which maps to chromosome 16p13.2, was evaluated as a candidate gene for CMT1C.

Charcot-Marie-Tooth disease (CMT; also known as "hereditary motor and sensory neuropathy") is a group of disorders characterized by degenerative changes in peripheral motor and sensory nerves. CMT is transmitted most frequently in an autosomal dominant manner and affects ~1 in 2,000 individuals (Skre 1974), making it one of the most common inherited neurological diseases. CMT leads to progressive distal muscle weakness affecting the upper and lower limbs, with loss of sensation. Clinical signs may range from a lack of symptoms to marked muscle weakness, and, in rare cases, patients may become wheelchair dependent.

CMT type I (CMT1) is characterized by demyelination and reduced (<40 m/s) nerve conduction velocities (NCVs) (Dyck and Lambert 1968). In CMT type II (CMT2), there is axonal loss, with normal or only mildly reduced NCVs (Dyck and Lambert 1968). CMT3 (MIM 145900), also known as "Dejerine-Sottas disease," may be inherited as an autosomal recessive or autosomal dominant trait and is characterized by severe hypomyelination, markedly reduced NCVs, and infantile onset (Lyon 1969; Kennedy et al. 1977). CMT4 is inherited as an autosomal recessive trait, with patients displaying early disease onset and rapid distal limb atrophy (Ben Othmane et al. 1993). In addition to autosomal forms of CMT, X-linked dominant inheritance also has been well characterized (Bergoffen et al. 1993).

On the basis of genetic-linkage and gene-sequence analysis, CMT1 has been divided into four subtypes. CMT1A (MIM 118220) is associated with a 1.4-Mb duplication on chromosome 17p11.2-p12 (Lupski et al. 1991; Raeymaekers et al. 1991) with a gene-dosage effect for peripheral myelin protein (PMP-22 [MIM 601097]) (Matsunami et al. 1992; Patel et al. 1992; Timmerman et al. 1992; Valentijn et al. 1992*b;* Warner et al. 1996). PMP-22 point mutations have been found in rare patients with CMT1A who lack the duplication (Valentijn et al. 1992*a;* Roa et al. 1993; Nelis et al. 1994). CMT1B (MIM 118200) results from mutations in the gene on chromosome 1 encoding myelin protein zero (MPZ [MIM 159440]; also known as "Po protein"), a major structural protein of peripheral mye-

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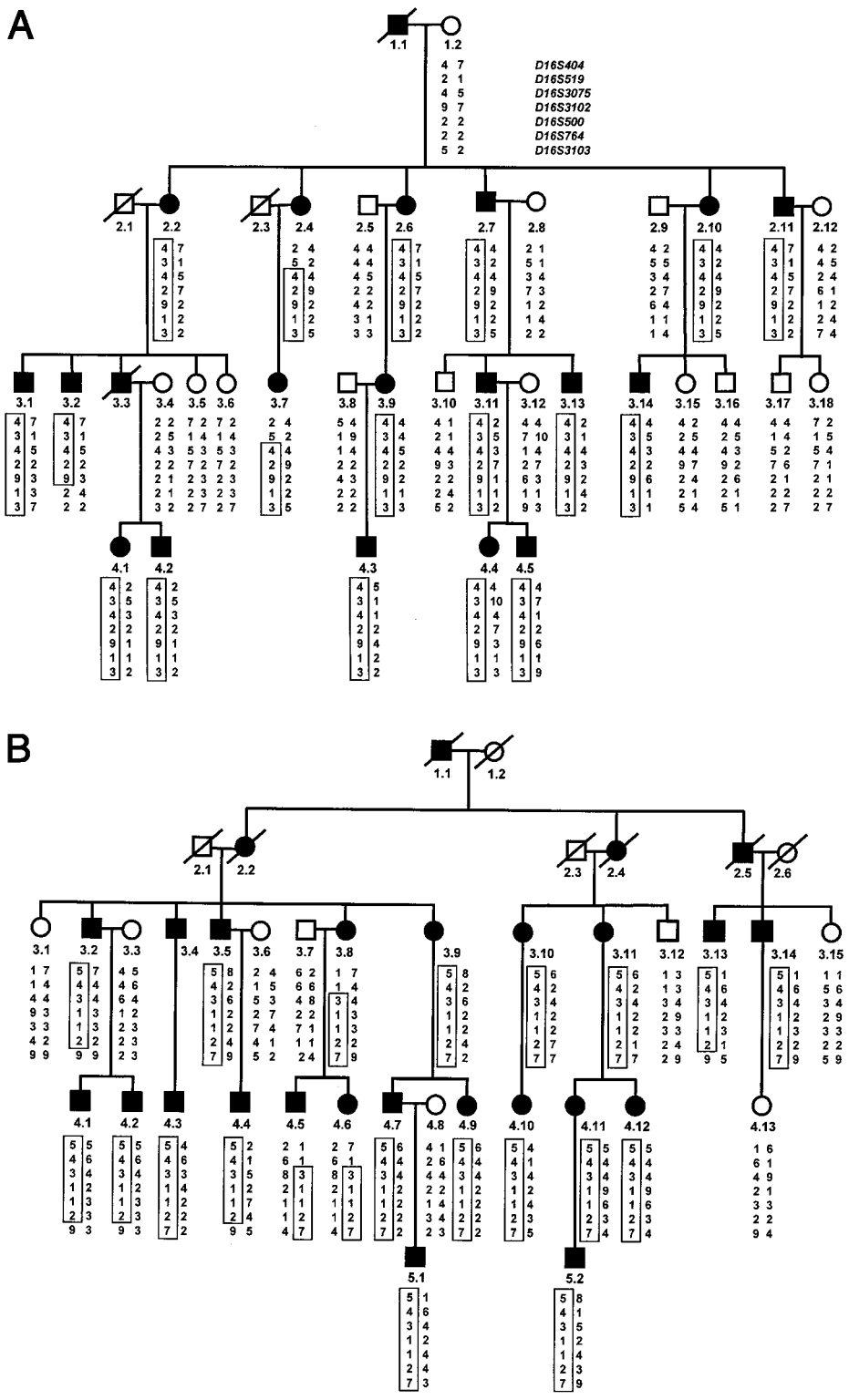

Figure 1 Haplotype analysis in pedigrees K1550 (*A*) and K1551 (*B*). Affected individuals are denoted by blackened symbols, males are denoted by squares, females are denoted by circles, and deceased persons are indicated by a diagonal line through a symbol. Markers are listed from telomere (*top*) to centromere (*bottom*) and are the same in both pedigrees. The CMT1C-linked haplotype is boxed.

Table 1

Pedigrees K1550 and K1551: LOD Scores with Chromosome 16p Markers

Marker (Position) and Pedigree[a]	LOD Score at Recombination Fraction (θ) = .0	.01	.05	.1	.2	.3	.4	Z_{max}	θ_{max}
D16S404 (16.7):									
K1550	−∞	.46	1.56	1.79	1.60	1.11	.53	1.793	.114
K1551	−∞	3.07	4.03	4.07	3.44	2.43	1.18	4.105	.076
K1550+K1551	−∞	3.53	5.59	5.86	5.04	3.54	1.71		
D16S519 (19.7):									
K1550	3.62	4.83	5.07	4.78	3.83	2.65	1.34	5.083	.038
K1551	−∞	3.37	3.70	3.53	2.80	1.86	.80	3.706	.046
K1550+K1551	−∞	8.20	8.77	8.31	6.63	4.51	2.14		
D16S307 (21.8):									
K1550	3.27	3.20	2.91	2.54	1.81	1.11	.50	3.270	.000
K1551	4.07	4.00	3.71	3.32	2.47	1.56	.66	4.070	.000
K1550+K1551	7.34	7.20	6.62	5.86	4.28	2.67	1.66		
D16S310 (23.1):									
K1550	5.74	5.64	5.25	4.74	3.67	2.53	1.32	5.740	.000
K1551	5.58	5.48	5.06	4.51	3.35	2.11	.84	5.580	.000
K1550+K1551	11.32	11.12	10.31	9.25	7.02	4.64	1.40		
D16S500 (27.0):									
K1550	6.97	6.86	6.39	5.80	4.53	3.16	1.67	6.970	.000
K1551	7.28	7.15	6.64	5.96	4.53	2.96	1.3	7.280	.000
K1550+K1551	14.25	14.01	13.03	11.76	9.06	6.12	2.97		
D16S764 (28.7):									
K1550	−∞	3.59	3.92	3.76	3.08	2.21	1.19	3.923	.047
K1551	2.93	2.89	2.69	2.41	1.79	1.07	.35	2.930	.000
K1550+K1551	−∞	6.48	6.61	6.17	4.87	3.28	1.54		
D16S310 (31.1):									
K1550	−∞	4.00	4.31	4.10	3.32	2.35	1.25	4.310	.043
K1551	−∞	−.26	.89	1.16	1.06	.70	.31	1.180	.125
K1550+K1551	−∞	3.74	5.20	5.26	4.38	3.05	1.56		

[a] Markers are shown in order given by Dib et al. (1996), from telomere to centromere. Marker map positions (in cM) are based on the Généthon and Marshfield human sex-averaged linkage maps.

lin (reviewed by Lupski [1998]). The CMT1C (MIM 300200) designation was suggested on the basis of genetic evidence, when linkage to regions on chromosomes 17 and 1 were excluded in two CMT1 pedigrees (K1550 and K1551) (Chance et al. 1990, 1992). The CMT1D gene maps to chromosome 10 and is associated with mutations in the early growth response 2 gene (*EGR2* [MIM 129010]), also known as "*Krox-20*" (Warner et al. 1998). In the present article, we describe the mapping of the CMT1C locus to chromosome 16 and the evaluation of the epithelial membrane protein 2 gene (*EMP2* [MIM 602334]) as a candidate gene.

Under a protocol of informed consent approved by the institutional review board of the University of Washington, Seattle, 15–20 ml of blood were drawn, by venipuncture, to obtain high-molecular-weight DNA, as described previously (Neitzel 1986). Pedigrees K1550 and K1551 are of Irish and English descent, respectively, and are depicted in figures 1*A* and *B*, respectively. Male-to-male transmission is observed in both families, confirming autosomal dominant inheritance. Affected individuals in both pedigrees met widely accepted criteria for CMT1, including distal muscle weakness and atrophy, depressed deep-tendon reflexes, and sensory impairment (Dyck and Lambert 1968). The mean ulnar (16.7 m/s [$n = 3$] and 25.3 m/s [$n = 8$], for K1550 and K1551, respectively), median (23 m/s [$n = 5$] and 25.8 m/s [$n = 12$]), and peroneal (20.4 m/s [$n = 4$], 21 m/s [$n = 6$]) motor-nerve conduction velocities of affected K1550 and K1551 individuals are consistent with CMT1. One affected person (individual 2.7) in pedigree K1550 was examined further, by sural-nerve biopsy, which demonstrated "onion bulb hypertrophy" typical of demyelinating CMT.

A genomewide scan (ABI PRISM Linkage Mapping Set Version 2; PE Biosystems) was performed in pedigrees K1550 and K1551, with informative microsatellite markers (Dib et al. 1996) spaced at ~10-cM intervals. PCR was performed under the conditions recommended by the manufacturer (PE Biosystems). PCR products were multiplexed and separated by capillary electrophoresis using an ABI PRISM 310 Genetic Analyzer (PE Biosystems). Microsatellite marker-allele data were analyzed by GENESCAN version 3.1.2 and GENOTYPER

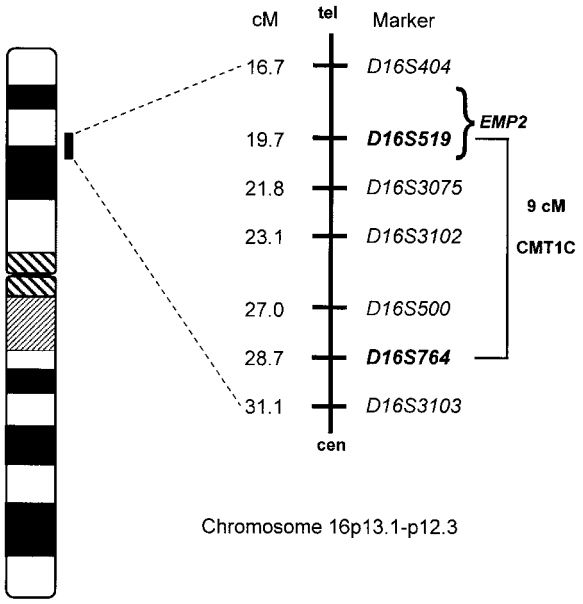

Figure 2 CMT1C-containing region of 16p. The CMT1C genetic interval on chromosome 16p13.1-p12.3 is indicated by a bracket ( ]), with flanking markers shown in boldface. Marker map order and position are based on the Généthon and Marshfield human sex-averaged linkage maps. The approximate location of *EMP2,* based on previous radiation hybrid mapping, is indicated by a brace (}).

version 2.0 (PE Biosystems). Amplification products generated with the ABI panel sets were sized according to CEPH control DNA (1347-02) and were assigned allele numbers consistent with the Marshfield and CEPH designations (Center for Medical Genetics, Marshfield Medical Research Foundation Web site; Fondation Jean Dausset–CEPH Web site). New alleles not reported in the CEPH database include a 205-bp product (designated "allele 9" in the present study) for marker D16S500, a 202-bp product (designated "allele 9") for marker D16S3075, and a 159-bp product (designated "allele 10") for marker D16S519. Two markers, D16S764 and D16S519, were obtained from Research Genetics. Under a model of autosomal dominant inheritance, pairwise LOD scores were calculated using the LINKAGE computer program package version 5.1 (Lathrop et al. 1985). Equal recombination rates in males and females were assumed, and a CMT1-gene frequency of 0.0005 (Skre 1974) was used for the calculations. Equal microsatellite marker-allele frequencies were employed in the analyses, unless CEPH allele frequencies were available. Haplotypes were constructed on the basis of known marker orders (Dib et al. 1996).

A combined maximal LOD score (Z_{max}) of 14.25 was obtained with marker D16S500, establishing linkage to chromosome 16. Significant LOD scores ($Z_{max} > 3$) were obtained with multiple markers from chromosome 16p13.1-p12.3, in both pedigrees (table 1). Haplotype analysis indicated that three markers—D16S3075, D16S3102, and D16S500—were nonrecombinant with the CMT1C phenotype in family K1550 (fig. 1*A*). Individual 2.4 displayed a crossover between markers D16S519 and D16S3075, defining D16S519 as a distal flanking marker. Individual 3.2 displayed a crossover between markers D16S500 and D16S764, defining D16S764 as a proximal flanking marker. In pedigree K1551, haplotype analysis determined that four markers—D16S3075, D16S3102, D16S500, and D16S764—were nonrecombinant with the CMT1C phenotype (fig. 1*B*). Individual 3.8 demonstrated a crossover between markers D16S519 and D16S3075, confirming D16S519 as a distal flanking marker. Individuals 3.2, 3.13, and 4.4 showed crossovers between markers D16S764 and D16S3103. The combined analysis in these two families suggests that the CMT1C gene maps within a 9-cM interval between markers D16S519 and D16S764 (fig. 2). Although no public human-genome database contains contiguous sequence that spans markers D16S519 and D16S764, available sequence information indicates the presence of ⩾20 genes in this interval on chromosome 16p.

EMP2 has been mapped to chromosome 16p13.2 (Liehr et al. 1999) and is a member of the *PMP-22* gene family (Taylor and Suter 1996). Given the coincident map position of *EMP2* and CMT1C, the coding exon and flanking intron nucleotide sequence for *EMP2* (GenBank accession numbers NT_019611 and X94770) were compared between affected and unaffected family members in pedigrees K1550 and K1551 (table 2), but no disease-associated mutations were detected. An *EMP2* C/T single-nucleotide polymorphism (SNP) is present 14 bp 5′ of the AG splice-acceptor site in the third coding exon. Some affected individuals in both pedigrees are heterozygous at the C/T SNP, suggesting that the *EMP2* gene is not deleted in individuals with CMT1C. In an effort to genetically map *EMP2* relative to CMT1C, we directly sequenced this area in key individuals (2.4 and 3.7 from K1500 and 3.7, 3.8, 4.5, and 4.6 from K1551), including those displaying crossover events between D16S519 and D16S3075. The C/T SNP was uninformative in family K1551, since affected individual 3.8 was T/T homozygous. In pedigree K1550, the genotype of unaffected individual 1.2 was T/T, and three of her affected offspring (2.2, 2.4, and 2.7) were C/T heterozygous, suggesting that the C allele was carried on the affected chromosome inherited from the father (1.1). Individual 2.4 transmitted the C allele to her affected daughter (3.7). Inheritance of the C/T SNP in family K1550 suggests that *EMP2* is contained within the nonrecombinant CMT-linked haplotype and that it therefore cannot be eliminated as a candidate gene on the basis of map position alone.

Table 2

Genomic Intronic Primer Sequences to Amplify *EMP2* Coding Exons

Coding Exon	PCR Primer (5′→3′)		Product Size (bp)	Annealing Temperature (°C)
	Forward	Reverse		
1	actgcaggtatgacgacc	acctagtctctggtatgc	487	60
2	acctcctgagtcagtctgc	ggagtatgcagtgagtgg	367	65
3	tgctcagaccatgtagacg	acgtcccactgtggtacagc	488	65
4	tacccagggtgcactgtgg	gaatgtggattctgtactgc	291	65

The bifunctional apoptosis regulator gene (*BAR*) is another potential candidate gene for CMT1C. *BAR* appears to encode a scaffold protein that is able to modulate both (1) the extrinsic apoptotic pathway activated by extracellular ligands binding to membrane-spanning tumor-necrosis–factor receptors and (2) the intrinsic apoptotic pathway triggered by mitochondrial release of cytochrome c (Zhang et al. 2000). Like *BAR*, the *PMP-22* gene underlying CMT1A also regulates programmed cell death (Brancolini et al. 1999).

CMT demonstrates extensive genetic heterogeneity, with nine different genes thus far identified that, when altered, can give rise to a CMT phenotype. These CMT genes are *PMP-22, MPZ, EGR2,* the connexin-32 gene (*Cx-32* [MIM 304040]), the neurofilament-light gene (*NF-L* [MIM 162280]) (Mersiyanova et al. 2000; De Jonghe et al. 2001), the myotubularin-related protein 2 gene (*MTMR2* [MIM 603557]) (Bolino et al. 2000), N-myc downstream-regulated gene 1 (*NDRG1* [MIM 605262]) (Kalaydjieva et al. 2000), the periaxin gene (*PRX* [MIM 605725]) (Boerkoel et al. 2001; Guilbot et al. 2001), and the b isoform of kinesin superfamily motor protein B gene (*KIF1Bb*) (Zhao et al. 2001). The proteins encoded by these genes are involved in a variety of cellular functions, including cytoskeletal scaffolding (in the case of *NF-L*), the transport of small molecules within and across the myelin sheath (in the case of *Cx-32*), signal transduction (in the case of *MTMR2*), cell arrest/proliferation and differentiation (in the case of *PMP-22, NDRG1,* and *EGR2*), myelin maintenance and formation (in the case of *MPZ* and *PRX*) (Gillespie et al. 2000), and axonal transport (in the case of *KIF1Bb*).

In the present study, we have firmly established the category of CMT1C and have identified an additional locus for CMT, on chromosome 16. Therefore, patients diagnosed clinically with CMT1 may have alterations in *PMP-22* (in the case of CMT1A), *MPZ* (in the case of CMT1B), an unidentified gene on chromosome 16 (in the case of CMT1C), or *EGR2* (in the case of CMT1D). The CMT1A duplication on chromosome 17p11.2-p12, which contains *PMP-22,* accounts for ~70% of all cases of CMT1 (Wise et al. 1993). The remaining 30% of CMT1 cases may be caused by *PMP-22, MPZ, EGR2,* or chromosome 16 gene mutations. We cannot predict the contribution that CMT1C gene mutations will make to the remaining 30% of CMT1 cases. However, it is noteworthy that two unrelated families with CMT1C that have been discussed in the present article were identified in a limited geographical region of the Pacific Northwest. The CMT1C-linked haplotypes—4-3-4-2-9-1-3 in K1550 and 5-4-3-1-1-2-7 in K1551—are not conserved, suggesting that the gene mutation underlying the disease in each family arose independently; this raises the possibility that mutations in the CMT1C gene might not be rare. Discovery of the CMT1C gene will allow investigators to determine the contribution of CMT1C gene mutations to the 30% of CMT1 cases not accounted for by the duplication of *PMP-22* and will further our understanding of the basic processes controlling myelination.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Center for Medical Genetics, Marshfield Medical Research

Foundation, http://www.marshfieldclinic.org/research/genetics/

Fondation Jean Dausset–CEPH, http://www.cephb.fr/

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for *EMP2* genomic and cDNA [accession numbers NT_019611 and X94770, respectively])

Généthon, http://www.genethon.fr/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for CMT1C [MIM 601098], EMP2 [MIM 602334], CMT3 [MIM 145900], CMT1A [MIM 118220], CMT1B [MIM 118200], PMP-22 [MIM 601097], MPZ [MIM 159440], EGR2 [MIM 129010], Cx-32 [MIM 304040], NF-L [MIM 162280], MTMR2 [MIM 603557], NDRG1 [MIM 605262], and PRX [MIM 605725])

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