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Report

Dominant Intermediate Charcot-Marie-Tooth Neuropathy Maps to Chromosome 19p12-p13.2

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The hereditary disorders of peripheral nerve form one of the most common groups of human genetic diseases, collectively called Charcot-Marie-Tooth (CMT) neuropathy. Using linkage analysis we have identified a new locus for a form of CMT that we have called "dominant intermediate CMT" (DI-CMT). A genomewide screen using 383 microsatellite markers showed strong linkage to the short arm of chromosome 19 (maximum LOD score 4.3, with a recombination fraction (θ) of 0, at D19S221 and maximum LOD score 5.28, $\theta = 0$, at D19S226). Haplotype analysis performed with 14 additional markers placed the DI-CMT locus within a 16.8-cM region flanked by the markers D19S586 and D19S546. Multipoint linkage analysis suggested the most likely location at D19S226 (maximum multipoint LOD score 6.77), within a 10-cM confidence interval. This study establishes the presence of a locus for DI-CMT on chromosome 19p12-p13.2.

Charcot-Marie-Tooth (CMT) neuropathy, otherwise known as "hereditary motor and sensory neuropathy" (HMSN), is one of the most common groups of human hereditary disorders. The CMT syndrome includes many hereditary disorders of peripheral nerve affecting both motor and sensory neurons. The CMT phenotype is characterized by progressive weakness and atrophy of distal muscles, high arched feet (*pes cavus*), and loss of deep-tendon reflexes. CMT can be divided into two subgroups: CMT I, disorders of Schwann cells with nerve-conduction slowing, and CMT II, disorders of the distal portions of neurons, also known as the "axonal neuropathies" (Dyck and Lambert 1968). The known causes of CMT I are a 1.5-mb DNA duplication on chromosome 17p11.2-p12 (CMT1A [MIM 118220]) (Lupski et al. 1991; Raeymaekers et al. 1991) causing trisomy of the peripheral myelin protein 22 gene (*PMP22* [GenBank accession number L03203]) (Matsunami et al. 1992; Patel et al. 1992; Timmerman et al. 1992; Valentijn et al. 1992*b*), point mutations in connexin 32 (*Cx32/GJB1* [GenBank accession number XM_047682] and CMT1X [MIM 302800]; Bergoffen et al. 1993), point mutations of two myelin genes, peripheral myelin protein 22 (*PMP22* in CMT1A; Valentijn et al. 1992*a*), myelin protein zero (*MPZ/Po* [GenBank accession numbers D10537 and D90501] in CMT1B [MIM 118200]; Hayasaka et al. 1993), and mutations in the transcription factor (*EGR2* [GenBank accession number AF139463]; Warner et al. 1998). Motor-nerve conduction in the most common form of CMT type I (CMT1A) is typically ~20 m/s and is usually <40 m/s (Nicholson 1991). Males with the next-most-common form (CMT1X) have median conduction velocities <45 m/s (Nicholson and Nash 1993).

In CMT II, median nerve-conduction velocity is usually >38 m/s (Harding and Thomas 1980) or >45 m/s (Dyck and Lambert 1968). Nerve conduction is not slowed until axonal degeneration occurs; then, as large fibers are lost, mild slowing of conduction occurs. Eventually, when all fibers are lost, no responses are obtained. We have used the value of 45 m/s to define the cutoff between CMT I and CMT II, since this value is in agreement with both Dyck and Lambert's definition and with our results for CMT1A and CMT1X males.

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Table 1

Two-Point LOD Scores between the Dominant Intermediate CMT Locus and Microsatellite Markers on Chromosome 19p

	LOD AT θ =						
MARKER	.00	.01	.05	.10	.20	.30	.40
D19S912	−3.46	−1.59	−.40	−.05	.06	−.02	−.08
D19S922	−7.50	−3.35	−1.41	−.74	−.39	−.40	−.27
D19S586	−.23	3.19	3.54	3.38	2.69	1.75	.71
D19S584	4.40	4.32	3.97	3.51	2.53	1.48	.47
D19S1165	4.56	4.48	4.18	3.78	2.89	1.88	.81
D19S221	4.30	4.20	3.83	3.34	2.29	1.20	.27
D19S558	5.59	5.51	5.18	4.74	3.75	2.60	1.29
D19S930	2.83	2.77	2.54	2.24	1.60	.94	.34
D19S226	5.28	5.20	4.86	4.41	3.44	2.34	1.13
D19S244	3.59	3.52	3.20	2.81	2.00	1.20	.47
D19S199	2.80	2.75	2.52	2.21	1.58	.92	.33
D19S410	3.81	3.74	3.44	3.05	2.21	1.32	.46
D19S546	−8.59	−1.92	−.17	.47	.81	.70	.40
D19S568	−5.61	−1.67	−.85	−.51	−.25	−.13	−.04
D19S875	−3.74	−.54	.54	.87	.78	.32	−.11
D19S882	−7.94	−1.33	.06	.56	.81	.67	.35

The only known mutations causing CMT II are mutations in the neurofilament light gene (*NEFL* [GenBank accession number X05608]) in CMT2E (MIM 162280; Mersiyanova et al. 2000), the *MPZ/Po* (Marrosu et al. 1998; Senderek et al. 2000), and the microtubule motor KIF1Bβ gene (*KIF1Bβ* [GenBank accession number AB023656]) in CMT2A (MIM 118210; Zhao et al. 2001).

We have used the term "intermediate conduction velocity" to describe CMT families with nerve-conduction velocities, in different affected individuals, that overlap the division between CMT I and CMT II (45 m/s). A functional definition is to use the term for families with a range of nerve-conduction velocities, including both the CMT I and CMT II ranges. There has been controversy about whether an intermediate form of CMT exists; however, families of this type have been reported (Salisachs 1974; Davis et al. 1978). An Italian family has been described with a dominantly inherited form of CMT with intermediate median motor-nerve–conduction velocities (Rossi et al. 1985; Villanova et al. 1998). Two *MPZ/Po* mutations are associated with intermediate conduction velocities (De Jonghe et al. 1999; Mastaglia et al. 1999). We have identified a large family (DI-CMT310) with conduction velocities ranging from 24 to 54 m/s. The sural-nerve biopsy in this family shows axonal degeneration, loss of large-diameter fibers, rare segmental demyelination, and remyelination with onion bulb formation, as in the family reported by Villanova et al. (1998).

Genomic DNA was extracted from peripheral blood leukocytes, using standard techniques. A genomewide linkage screen was performed at the Australian Genome Research Facility, using 383 microsatellite markers from the ABI Prism Linkage Mapping Set Version 2 (PE Applied Biosystems). DI-CMT was assumed to be an autosomal dominant trait with a penetrance of 90% by age 20 years. The disease allele had a frequency of .0001, with a phenocopy rate of 0. Male and female recombination rates were considered to be equal. Marker allele frequencies were set at $1/n$, where n is the number of alleles observed. When marker allele frequencies were varied using available population data, this had little or no effect on the LOD score results. Information on additional markers to confirm and refine the interval were accessed through the Genome Database, and samples were PCR amplified as described elsewhere (Nicholson et al. 1996). Linkage analysis was performed using the MLINK and Linkmap programs of the Linkage package (V5.1) (Lathrop et al. 1984) in the Fastlink implementation (version 4.1p; Cottingham et al. 1993). Both two-point and multipoint analyses were performed. For multipoint analysis, the genetic distances between loci were obtained from the Marshfield sex-averaged linkage map and were converted to recombination fractions using Haldane's mapping function. The $Z_{max} - 1$ method was used to determine the 95% confidence limits and support interval for the DI-CMT locus (Conneally et al. 1985).

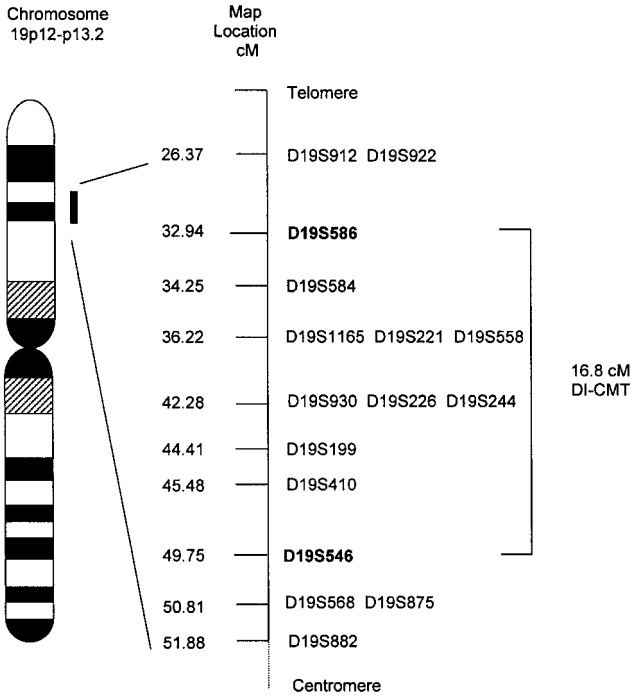

Figure 1 Genetic map (sex averaged) of chromosome 19 markers used in this study. The genetic distances were obtained from the Marshfield map. Loci that appear on the same line map to the same genetic location. The order of these markers was obtained from the chromosome 19 p-arm metric physical map. Markers defining the DI-CMT genetic interval are shown in boldface.

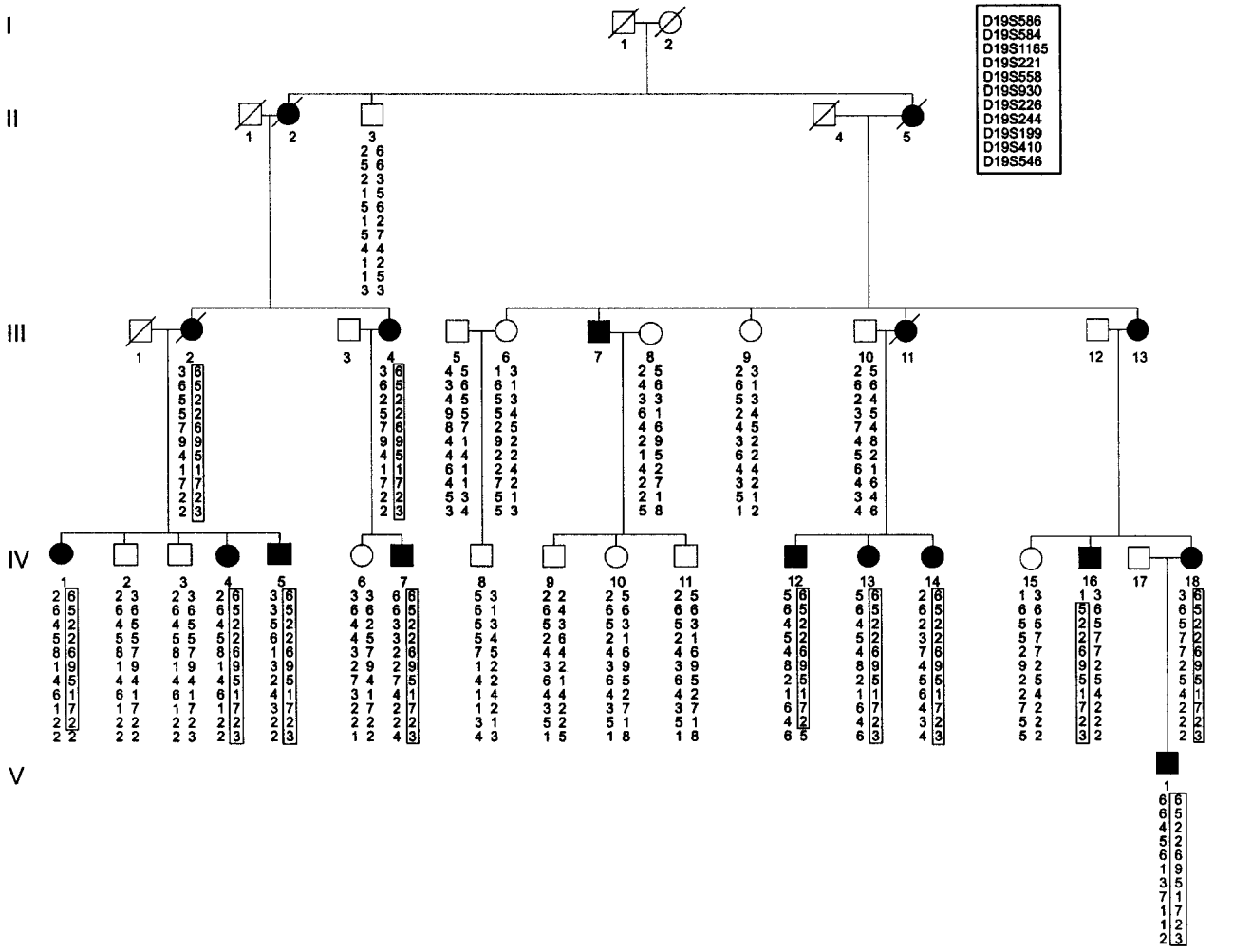

Figure 2 Haplotype analysis of markers from chromosome 19p12-p13.2 in family (DI-CMT310) with autosomal dominant intermediate CMT. The haplotype segregating with the disease is boxed. The markers are presented in order from telomere (*top*) to centromere (*bottom*). Blackened symbols denote affected individuals, and unblackened symbols denote unaffected individuals. Individuals are numbered consecutively in each generation, from left to right. Individuals IV-1 and IV-12 define the centromeric boundary of the disease at D19S546, whereas individual IV-16 defines the telomeric boundary at D19S586.

Haplotypes were assigned on the basis of the minimization of intermarker recombination.

Prior to performance of a genome screen on family DI-CMT310, all known CMT I (CMT1A, CMT1B) and CMT II (CMT2A, CMT2B [MIM 600882], CMT2C [MIM 606071], CMT2D [MIM 601472], CMT2E) loci were excluded by either linkage analysis or mutation screening (data not shown). Simulation studies indicated that the family could independently demonstrate linkage (LOD score > 3.0) and was capable of excluding 11.6 cM on either side of an unlinked marker (data not shown). A genome screen was subsequently undertaken using markers spaced, on average, at 10-cM intervals. Linkage was established to chromosome 19p12-p13.2 when significant LOD scores were obtained with the consecutive markers D19S221 and D19S226 (table 1). No other markers analyzed from the genome screen gave a LOD score $\geq$3.0. Fourteen additional markers were then tested in the family. The results of the two-point analysis between the disease phenotype and the additional marker loci are shown (table 1). Extended haplotypes of individuals were constructed according to the order of both the Marshfield genetic map and the chromosome 19 p-arm metric physical map (fig. 1). Haplotype analysis detected no recombination between DI-CMT and seven closely linked markers (D19S584, D19S1165, D19S221, D19S558, D19S226, D19S244, and D19S410). The markers D19S930 and D19S199 did not generate a LOD score of 3.0, but the alleles from these markers formed part of the disease haplotype seg-

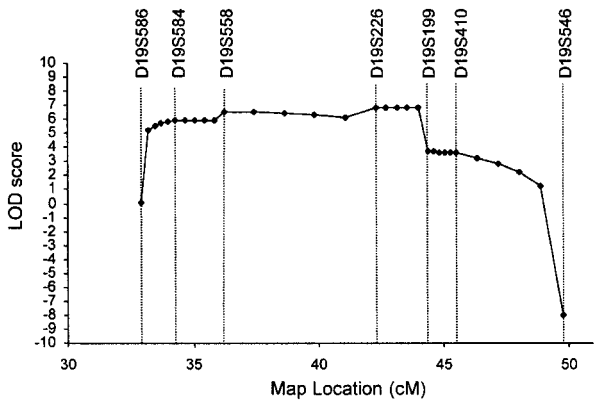

Figure 3 Multipoint localization of dominant intermediate CMT. Genetic location (distance, in cM, from the telomere of chromosome 19p) is plotted against the multipoint LOD score. Markers used in the multipoint analysis are shown. A maximum multipoint LOD score of 6.77 was obtained for D19S226 at 42.28 cM. The markers D19S586 and D19S199 flank the 10-cM confidence interval.

regating in this family (fig. 2). On the basis of the analysis, the proximal recombination site is between D19S546 and D19S410, as observed in two affected individuals (IV-1 and IV-12), and the distal recombination site is between D19S586 and D19S584 as observed in a single affected family member (IV-16). These results suggest the localization of DI-CMT to be within a 16.8-cM interval between D19S586 and D19S546. Multipoint linkage analysis was performed using the markers D19S586, D19S584, D19S558, D19S226, D19S199, D19S410, and D19S546. The most likely location for DI-CMT is D19S226, with a maximum multipoint LOD score of $Z = 6.77$. By use of the $Z_{max} - 1$ method, the inferred location of the DI-CMT locus has been narrowed to within a 10-cM confidence interval (8.2 cM telomeric and 1.8 cM centromeric to D19S226; see fig. 3).

Although the 16.8-cM interval containing the DI-CMT locus is too large for practical positional cloning, the region has been almost completely sequenced. Refinement of the critical interval, however, will be required before mutation screening of expressed sequences within the region is undertaken. The chromosome 19 p-arm metric physical map (Lawrence Livermore Laboratory) has listed 53 genes that have been mapped on a cosmid contig in the interval between D19S586 and D19S546. Several other diseases and associated genes have been mapped to the same region as DI-CMT. They include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (*NOTCH3;* Joutel et al. 1996), episodic ataxia and familial hemiplegic migraine (*CACNLA1A4*; Jodice et al. 1997), and, more recently, a locus for autosomal dominant polycystic liver disease was mapped to this region (Reynolds et al. 2000).

DI-CMT shares clinical features with CMT I and CMT II. Genes identified for CMT type I and II could give clues to positional candidate genes for DI-CMT. Currently, 30 genetic loci have been identified for distinct forms of CMT; however, only 10 genes have been identified (Meuleman et al. 2000). Genes associated with recessive peripheral neuropathies include the gene encoding the phosphatase myotubularin-related protein 2 (*MTMR2* [GenBank accession number NM_003912]; Bolino et al. 2000), a protein involved with cell-cycle regulation and signal transduction (*NDRG1* [GenBank accession number XM_051273]; Kalaydjieva et al. 2001), a receptor for a neurotrophic factor (*NTRK1/TrkA* [GenBank accession number XM_043533]; Bodzioch et al. 2001; Houlden et al. 2001), and a protein (periaxin) associated with myelinating Schwann cells (*PRX* [GenBank accession number XM_047407]; Guilbot et al. 2001). The genes involved with dominant CMT I and CMT II represent a spectrum of proteins with diverse functions ranging from a structural protein (*PMP22*), an adhesion molecule (*MPZ/Po*), a transcription factor (*EGR2*), a mitochondrial transport protein (*KIF1Bβ*), and a cytoskeletal protein (*NEFL*). All these genes are expressed in peripheral nerve and play a role in Schwann cell biology and myelination (*PMP22* and *MPZ/Po*), axonal structure (*NEFL*), axonal transport (*KIF1Bβ*), and differentiation of the myelinating Schwann cell (*EGR2*). Possible candidates for DI-CMT, on the basis of their expression profiles in peripheral nerve and spinal cord, respectively, include the growth differentiation factor 1 gene (*GDF-1*; Lee 1991) and the brain-specific membrane anchored protein gene (*BSMAP;* Elson et al. 1999). *BSMAP* was localized to the DI-CMT interval, according to the Unified Database for Human Genome Mapping (Weizmann Institute). In addition to these two genes, the protein kinase C substrate 80K-H (*PRKCSH*) could also be a positional candidate, because of its potential role in neuronal signal transduction (Ophoff et al. 1996). Screening of these genes is currently being performed. The remaining genes in the region have reported tissue expression or possible functions that eliminate their role as strong positional candidates for this disease.

Another possible clue to mechanisms involved in dominant intermediate CMT is given by the *Cx32/GJB1* gene mutated in CMT1X. CMT1X has a mixed axonal and demyelinating appearance on biopsy, and affected males have slowing of nerve-conduction velocities due to demyelination. Connexin 32 is a protein that forms channels between myelin lamellae and the myelin/axonal interface. Mutations in connexin 32 disrupt the connexin channel between myelin lamellae and axons, resulting in degeneration of both myelin and axons. Dominant intermediate CMT could be caused by a gene with a similar function.

Linkage studies localizing DI-CMT to 19p12-13.2 have shown that dominant intermediate CMT exists as

a separate genetic entity. Because the disease shows both axonal and demyelinating features, identification of the gene involved with this disorder may elucidate axonal and myelin interactions. Such interactions are relevant to understanding secondary axonal degeneration, a direct cause of disability in both axonal and demyelinating neuropathies.

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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://research.marshfieldclinic.org/genetics/Map_Markers/maps/IndexMapFrames.html

Chromosome 19 p Arm Metric Physical Map, Lawrence Livermore Laboratory, http://greengenes.llnl.gov/genome-bin/loadmap?region=mp

GenBank, http://www.ncbi.nlm.nih.gov/ (for *PMP22* [accession number L03203], *Cx32/GJB1* [accession number XM_047682], *MPZ/Po* [accession number D10537 D90501], *EGR2* [accession number AF139463], *MTMR2* [accession number NM_003912], *NDRG1* [accession number XM_051273], *NTRK1/TrkA* [accession number XM_043533], *PRX* [accession number XM_047407], *NEFL* [accession number X05608], *KIF1Bβ* [accession number AB023656])

Genome Database, http://www.gdb.org/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for CMT1A [MIM 118220], CMT1B [MIM 118200], CMT1X [MIM 302800], CMT2A [MIM 118210], CMT2B [MIM 600882], CMT2C [MIM 606071], CMT2D [MIM 601472], and CMT2E [162280])

Unified Database for Human Genome Mapping, Weizmann Institute, http://bioinformatics.weizmann.ac.il/udb/

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