

Autosomal dominant axonal Charcot-Marie-Tooth disease type 2 (CMT2G) maps to chromosome 12q12–q13.3

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Charcot-Marie-Tooth (CMT) disease is a clinically and genetically heterogeneous group of disorders that involve the peripheral nervous system.¹ It is characterised by progressive distal neurogenic muscular atrophy and weakness that initially affects the peroneal muscles and later the hands. Charcot-Marie-Tooth disease type 1 (CMT1), also called hereditary motor and sensory neuropathy type I (HMSN I), is a dominantly inherited demyelinating neuropathy characterised by reduced nerve conduction velocities (NCV) (motor median NCV <38 m/s). Charcot-Marie-Tooth disease type 2 (CMT) 2, or HMSN II, is a dominantly inherited axonal neuropathy characterised by normal or slightly reduced NCV. Both autosomal dominant CMT1 and autosomal dominant CMT2 are genetically heterogeneous, with five and six loci, respectively.² Most patients with CMT1 have a 1.4 Mb tandem duplication on chromosome 17p11.2 (CMT1A (MIM 118220)).^{3–4} Other patients with CMT1 may have point mutations in the peripheral myelin protein 22 gene (*PMP22* in CMT1A (MIM 60197)),⁵ myelin protein zero gene (*MPZ* in CMT1B (MIM 159440)),⁶ lipopolysaccharide induced tumour necrosis factor gene (*LITAF* in CMT1C (MIM 603795)),⁷ early growth response 2 gene (*EGR2* in CMT1D (MIM 129010)),⁸ or the gap junction protein beta 1 gene (*GJB1* in CMT1X (MIM 304040)).⁹ Patients with CMT2 may have point mutations in the kinesin family member 1B gene (*KIF1B* in CMT2A (MIM 605995)),¹⁰ RAB7, member RAS oncogene family (*RAB7* in CMT2B (MIM 602298)),¹¹ glycyl tRNA synthetase (*GARS* in CMT2D (MIM 600287)),¹² or neurofilament light polypeptide (*NEFL* in CMT2E (MIM 607684)).¹³ The genes for CMT2C and CMT2F have not been identified yet.^{14–15} Some patients with CMT2 have also been reported to have specific mutations in the *MPZ* gene.^{16–17}

METHODS

We previously described a large Spanish family diagnosed with autosomal dominant CMT2.¹⁸ For this study, we enlarged the pedigree to 28 people, of whom 14 were diagnosed as affected (fig 1). The age at onset was 9–76 (mean 29) years. Most patients developed symptoms in the second decade of life. The disease, which presented with foot deformity and difficulty walking, showed a very slow progression. Patients were mildly disabled. Ankle reflexes were absent or hypoactive in all patients, whereas knee reflexes sometimes were preserved. Mild stocking hypaesthesia was seen. The upper limbs were involved in only two patients. Scoliosis, pupillary abnormalities, foot ulcers, deafness, diaphragm and vocal cord paralysis, nerve enlargement, optic atrophy, tremor, and ataxia were absent.

Electrophysiological findings were updated for this study. Briefly, we found slight slowing of motor NCV (77–93% of lower limit of normal) in 30% of nerves tested. Interestingly, five patients had entirely normal NCV values. Distal compound motor action potentials and sensory nerve action potentials in the lower limbs had low amplitudes or were

Key points

- Charcot-Marie-Tooth (CMT) neuropathies are heterogeneous clinically and genetically. For the autosomal dominant axonal type of CMT or CMT type 2 (CMT2), six loci and four genes have been reported.
- A genome-wide scan was performed in a Spanish family with autosomal dominant CMT2 not linked to the known CMT2 loci and conclusive linkage with a chromosome 12q13.13 marker was obtained. Fine mapping localised this novel CMT2 locus to a 13.2 Mb (12.8 cM) interval between D12S1663 and D12S1644 at 12q12–q13.3.
- The candidate genes *advillin (AVIL)*, *centaurin gamma 1 (CENTG1)*, a member of the RAS oncogene family (*RAB5B*), and the desert hedgehog homologue (*Drosophila*) (*DHH*) were excluded.
- As the CMT2 neuropathy in this family represents a novel genetic entity, it was designated CMT2G.

unobtainable. Electromyography of tibialis anterior muscles showed chronic neurogenic alterations. The histological study of two sural nerve biopsies and a sciatic nerve and its branches that we dissected in an amputated leg of patient 117.3 showed loss of myelinated fibres with a proximal to distal gradient, clusters of regenerating fibres, and atrophic axons.¹⁸ Autopsy of patient 117.102 showed loss of anterior horn and dorsal root ganglion neurons in the lumbosacral segments and degeneration of the fasciculus gracilis. Morphometric evaluation of the L5 ventral and dorsal roots showed a normal number of myelinated fibres, while diameter histograms were shifted to the left because of a significant loss of large myelinated fibres and regeneration.¹⁸

DNA from 28 individuals, of whom 11 were affected, was available for genetic analysis. Informed consent was obtained according to the Declaration of Helsinki, and protocols were approved by the Institutional Review Board of the Marqués de Valdecilla University Hospital. We previously had excluded the CMT1A tandem duplication at 17p11.2 and mutations in *PMP22*, *MPZ*, and *NEFL* (data not shown). Furthermore, we performed genetic linkage studies and excluded known CMT2 loci with short tandem repeat markers from these regions (data not shown). We performed a genome-wide scan with 382 short tandem repeat markers of the ABI Prism Linkage Mapping Set (version 2.5; Applied Biosystems, Foster City, CA, USA), which had an average intermarker distance of 10 cM. Markers were amplified by polymerase chain reaction (PCR) on a PTC-220 DNA Engine DYAD (MJ Research, Waltham, MA, USA) and pooled with a Biomek FX

Laboratory Workstation (Beckman Coulter, Fullerton, CA, USA). We performed and processed fragment analysis by capillary electrophoresis on an ABI Prism 3700 DNA Analyzer (Applied Biosystems, Foster City, CA, USA) and with GeneScan Analysis software (version 3.5; Applied Biosystems, Foster City, CA, USA) and Genotyper software (version 3.7; Applied Biosystems, Foster City, CA, USA). We performed genetic fine mapping with additional short tandem repeat markers selected from the ABI Prism Linkage Mapping Set HD-5 (Applied Biosystems, Foster City, CA, USA) (D12S1682, D12S1640, and D12S1663) or UCSC Human Genome Browser (April 2003 Freeze) and the genome database (D12S1687, D12S1713, D12S1632, D12S1644, and D12S90).

We computed two point linkage between the disease gene and each marker with Linkage software (version 5.1) and Fastlink software (version 2.1, freely available).^{19, 20} We scored CMT2 as a 90% penetrant autosomal dominant trait with a gene frequency of 0.0001. We assumed equal recombination rates between men and women. For each short tandem repeat marker, we set the number of alleles in the logarithm of odds (LOD) score calculations at the observed number of alleles in the pedigree (N) and the allele frequencies at 1/N.

We designed primers for PCR amplification of the coding region of the candidate genes with Primer3 (*RAB5B*) or our in house software SNPbox (*AVIL*, *CENTG1*) (S. Weckx *et al*, personal communication, 2003) (table 2, supplementary data) or used published primers (*DHH*).²¹ We sequenced the PCR products, which were prepared for sequencing with the PCR Product Pre-Sequencing Kit (USB Corporation, Cleveland, OH, USA), with the BigDye Terminator Cycle Sequencing kit and AmpliTaq DNA polymerase FS (Applied Biosystems, Foster City, CA, USA). We removed unincorporated dye terminators with MultiScreen 96-well filtration plates (Millipore, Bedford, MA, USA). We performed electrophoresis on an ABI Prism 3730 DNA analyser (Applied Biosystems, Foster City, CA, USA). We collected sequencing data with the ABI DNA Sequencing Analysis software (version 3.6) and analysed them with the SeqMan II software (version 5.06 DNASTAR, Madison, WA, USA).

RESULTS

In the initial genomewide search, significant linkage to marker D12S368 (LOD score $z = 4.10$ at $\theta = 0$) and suggestive linkage to the neighbouring marker D12S85 (LOD score $z = 2.92$ at $\theta = 0$) were obtained on chromosome 12q13.1 (table 1). We performed genetic fine mapping with additional

short tandem repeat markers. Table 1 summarises the two point LOD scores. Segregation analysis in the family identified the disease haplotype in all patients (163, 171, 122, 210, 275, and 213) with markers D12S1687, D12S1713, D12S85, D12S368, D12S1604, and D12S1632 (fig 1). Two key meiotic recombinants were identified between D12S1663 and D12S1687 in patient 117.9 and between D12S1632 and D12S1644 in patient 117.16. These two recombinants assigned the CMT2 gene to a 13.2 Mb region (UCSC Human Genome Browser, April 2003 Freeze) between centromeric D12S1663 and telomeric D12S1644 at 12q12–q13.3. Simultaneous with the fine mapping, we screened four candidate genes in the linked region: *avillin* (*AVIL*), centaurin gamma 1 (*CENTG1*), *RAB5B* member RAS oncogene family (*RAB5B*), and desert hedgehog homologue (*Drosophila*) gene (*DHH*). Sequence analysis of the complete coding regions of the genes showed a nucleotide change in intron 13 (c.1550–49C>T) of *CENTG1*. Segregation analysis of this non-coding single nucleotide polymorphism in the family indicated that the single nucleotide polymorphism was transmitted with the CMT2 phenotype, except in one patient (117.16). This recombination event was confirmed by marker D12S1644 in the same patient (figs 1 and 2). The *CENTG1* single nucleotide polymorphism is not related, therefore, to the disease in this family affected by CMT2. In addition, analysis of 154 control chromosomes did not identify the c.1550–49C>T single nucleotide polymorphism, which suggests that this single nucleotide polymorphism is rare.

DISCUSSION

We report a novel genetic locus of a 12.8 cM linkage region at 12q12–q13.3 in a Spanish autosomal dominant family with CMT2. It is the seventh locus for autosomal dominant CMT2, so we designated it *CMT2G*. The CMT2 region is covered by one sequenced contig (NT_029419) and contains more than 300 genes (UCSC Human Genome Browser, April 2003 Freeze). We screened the coding region of four candidate genes in the linked region. *AVIL* and *CENTG1* were considered functional candidates, as they are expressed in the peripheral nervous system (Verpoorten *et al.*, unpublished data, 2003). *RAB5B* was considered a good candidate, as it is highly homologous to *RAB7*—the gene in which mutations cause *CMT2B*.¹¹ *DHH* may be involved in perineurial development in peripheral nerves.²² No disease causing mutations were detected, which excluded these four genes as the CMT2 genes.

Table 1 Two point LOD scores between the CMT2 locus and short tandem repeat markers on chromosome 12q12–q13.3

Marker	LOD score at recombination fraction (θ)								
	0.00	0.001	0.01	0.05	0.10	0.20	0.30	0.40	
D12S364	-6.38	-2.82	-0.83	0.55	1.05	1.24	1.00	0.51	
D12S310	1.16	1.16	1.15	1.08	0.98	0.79	0.56	0.30	
D12S1682	-3.54	-1.28	-0.28	0.43	0.68	0.79	0.67	0.40	
D12S1617	-5.09	-1.52	0.43	1.65	1.98	1.92	1.44	0.72	
D12S1640	0.84	0.84	0.85	0.87	0.86	0.74	0.55	0.30	
D12S345	-3.53	-0.49	0.47	0.99	1.05	0.86	0.52	0.17	
D12S1663	-0.70	1.30	2.24	2.66	2.61	2.15	1.49	0.71	
D12S1687	2.64	2.64	2.62	2.51	2.32	1.84	1.25	0.56	
D12S1713	2.64	2.64	2.62	2.51	2.32	1.84	1.25	0.56	
D12S85	2.92	2.92	2.90	2.77	2.56	2.04	1.39	0.63	
D12S368	4.10	4.10	4.06	3.86	3.55	2.82	1.94	0.93	
D12S1604	4.08	4.08	4.04	3.84	3.54	2.81	1.94	0.93	
D12S1632	4.56	4.55	4.49	4.18	3.78	2.93	1.98	0.94	
D12S1644	-3.95	-0.95	0.05	0.71	0.91	0.93	0.74	0.42	
D12S90	-3.02	-0.04	0.94	1.52	1.62	1.43	1.00	0.46	
D12S83	-0.70	1.30	2.24	2.66	2.61	2.15	1.49	0.71	

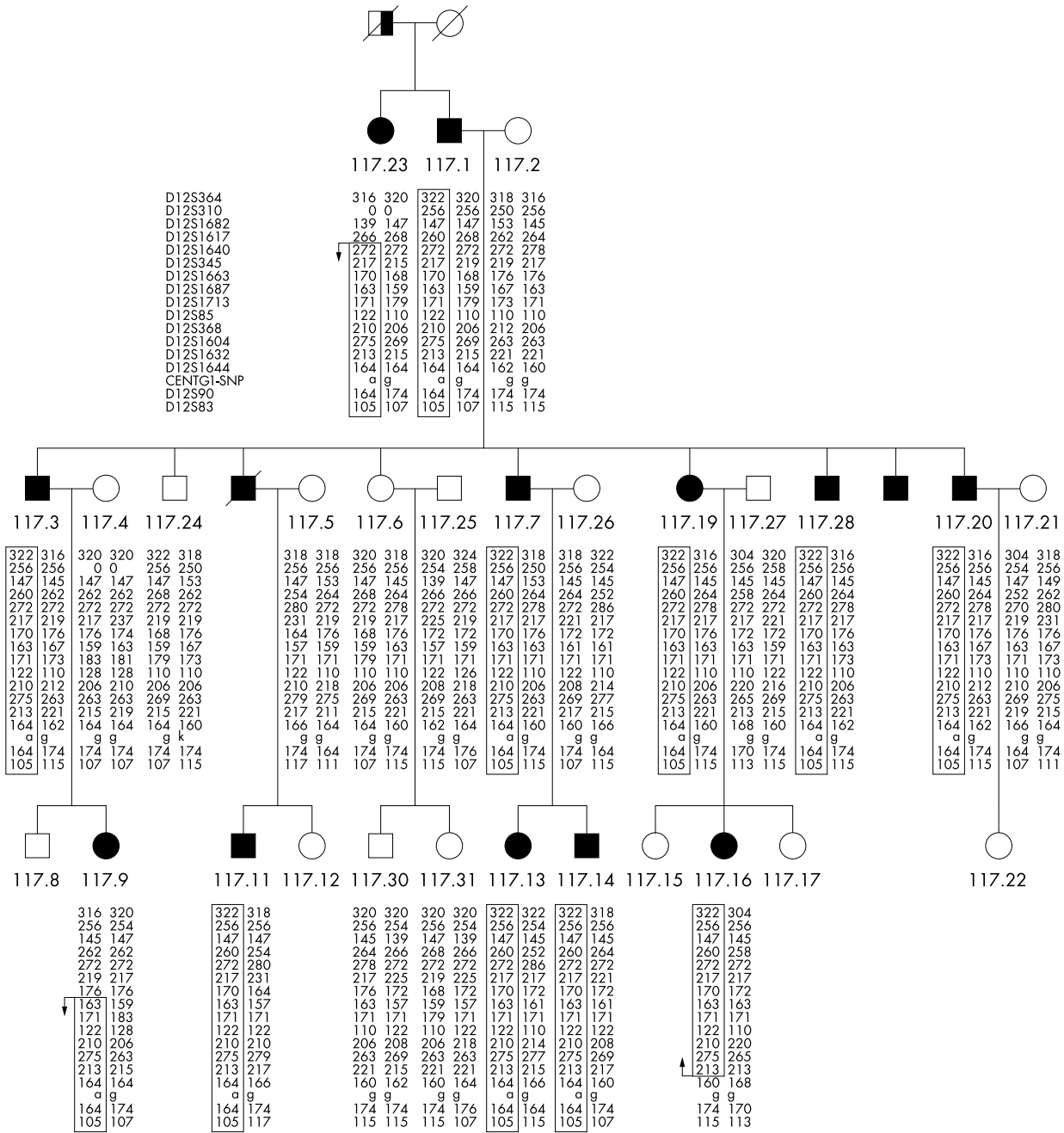


Figure 1 Haplotype analysis in the pedigree of the Spanish autosomal dominant family with CMT2 CMT-117. For confidentiality reasons, we did not reveal the genotypes of the asymptomatic people who were at risk in the youngest generation. Alleles were sized according to the Centre d'Etude du Polymorphisme Humain (CEPH) control DNA (1347.02) and are shown in base pairs. Short tandem repeat markers are shown from centromere (top) to telomere (bottom). The haplotype associated with the disease is boxed. Patient 117.9 defines the centromeric border of the disease at D12S1663, while patient 117.16 defines the telomeric border at D12S1644. ● affected woman; ■ affected man; ○ unaffected woman; □ unaffected man; ◐ man of unknown status; / deceased; 0 failed genotype.

Chromosome 12q contains several loci for neuromuscular disorders: CMT2C at 12q23–q24,¹⁴ dominant congenital distal spinal muscular atrophy at 12q23–q24,²³ distal hereditary motor neuropathy type II (distal HMN II) at 12q24,²⁴ spinocerebellar ataxia type 2 (SCA2; gene *SCA2*) at 12q24,²⁵ scapuloperoneal spinal muscular atrophy (SPSMA) at 12q24.1–q34.31,²⁶ scapuloperoneal muscular dystrophy (SPMD) at 12q15–q23.1,²⁷ gonadal dysgenesis with minifascicular neuropathy (gene *DHH*) at 12q13.1,²¹ spastic paraplegia type 10 (SPG10; gene *KIF5A*) at 12q13.3,²⁸ centronuclear myopathy (gene *MYF6*) at 12q21,²⁹ and restless

leg syndrome at 12q12–q21.³⁰ Only the gonadal dysgenesis with minifascicular neuropathy region overlaps with the *CMT2G* region. The gene associated with this disorder, *DHH*, was excluded by mutation analysis.

The electrophysiological and pathological findings in the Spanish pedigree affected by CMT showed that the neuropathy primarily is axonal and therefore can be classified as CMT2.^{31–32} The clinical phenotype is characterised by a classic, although mild, peroneal muscular atrophy syndrome. Additional features were absent, which indicates that this neuropathy presents as a pure variant of CMT.

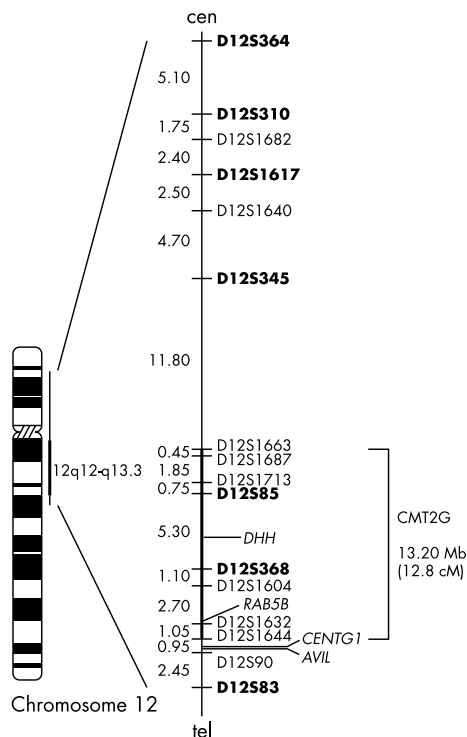


Figure 2 Genetic map of chromosome 12q12–q13 region. Physical distances between the markers (Mb) were obtained from the UCSC Human Genome Browser (April 2003 Freeze). A bold line indicates the CMT2G region. Markers in bold are from the ABI Prism Linkage Mapping Set (version 2.5).

Conclusion

We report a novel genetic locus of a 12.8 cM linkage region at 12q12–q13.3 in a Spanish autosomal dominant CMT2 family. Clinical and genetic analysis of additional CMT2 families will help to fine map the locus and identify the genetic defect that causes CMT2G.

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Electronic database information

- Inherited peripheral neuropathies mutation database (IPNMDB) (<http://molgen-www.uia.ac.be/CMTMutations/>)
- Genome database (<http://www.gdb.org/>)
- Online Mendelian inheritance in man (OMIM) (<http://www.ncbi.nlm.nih.gov/omim>)
- Primer3 (http://www-genome.wi.mit.edu/cgi-bin/primer/primer3_www.cgi)
- UCSC Human Genome Browser (<http://genome.ucsc.edu/goldenPath/septTracks.html>)
- Fastlink (<http://www.ncbi.nlm.nih.gov/CBBresearch/schaffer/fastlink.html>)

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