Genetics of Charcot-Marie-Tooth disease type 4A: mutations, inheritance, phenotypic variability, and founder effect


C hartoc-Marie-Tooth (CMT) disease is a motor and sensory neuropathy with clinical and genetic heterogeneity. Patients usually present in the first or second decade of life with distal muscle atrophy in the legs, areflexia, foot deformity (mainly pes cavus), and steppage gait. In most cases, hands are also involved as the disease progresses. CMT is the most frequent inherited neuropathy, with a prevalence in Spain of 28 in 100,000. Based on electrophysiologic studies and histopathologic findings in nerve biopsies, CMT has been subcategorised into two main and distinct neuropathies: (i) demyelinating CMT (CMT1, MIM 118200) associated with reduction in a nerve conduction velocities (NCVs) in all nerves and segmental demyelination and remyelination ("onion bulbs"); and (ii) axonal CMT (CMT2, MIM 118220) associated with normal or almost normal NCVs and loss of myelinated axons. Other phenotypes are associated with motor and sensory nerve involvement: Dejérine-Sottas neuropathy (DSN, MIM 145900) is a severe demyelinating neuropathy with onset in infancy, delayed motor milestones, and NCVs less than 10 m/s; congenital hypomyelinating neuropathy (CHN, MIM 605253) is a dysmyelinating neuropathy characterised by infantile hypotonia, distal muscle weakness, and marked reduction of NCVs; hereditary neuropathy with liability to pressure palsies (HNPP, MIM 162500) is a milder sensory and motor neuropathy with periodic episodes of numbness, muscular weakness, and atrophy.

Genetic heterogeneity is characteristic of the disease not just because of the large number of genes and loci associated with CMT (currently 21 genes), but also because the disease may segregate with different Mendelian patterns: autosomal dominant demyelinating neuropathy, CMT1B; however, some mutations in MPZ have also been found in patients with axonal neuropathy (CMT2-P3). Moreover, some patients with mutation in MPZ expressed the disease as either DSN or CHN. On the other hand, mutations in the same gene may be expressed with a different Mendelian pattern. Mutations in the MPZ gene are expressed as dominant mutations, but there are some mutations in MPZ that convey an autosomal recessive trait.

CMT disease caused by mutations in the ganglioside-induced differentiation-associated protein 1 (GDAP1) gene is a severe autosomal recessive neuropathy originally reported in families with either demyelinating CMT4A neuropathy (MIM 214400) or axonal neuropathy with vocal cord paresis (MIM 607706), which maps to the CMT4A locus on chromosome 11q12-q13. In some families, mutations in GDAP1 gene are expressed as dominant mutations, but there are some mutations in GDAP1 that convey an autosomal recessive trait.

We investigated the genetics and inheritance of the GDAP1 gene and phenotype expression in a series of 106 isolated and 19 familial cases with Charcot-Marie-Tooth disease and Spanish ancestry, for whom mutations in the MPZ, MPZ, and GJB1 genes had previously been excluded.

We also investigated the existence of founder effects for some recurrent mutations and the origin of these mutations in patients from different countries.

We found mutations in seven isolated patients, three autosomal recessive families, and two autosomal dominant families. Six out of seven isolated patients were homozygotes or compound heterozygotes with autosomal recessive inheritance and one patient carried a de novo dominant mutation. The mutation detection rate in the sporadic patients was 5.6%. Patients with homozygous or compound heterozygous genotypes showed a severe disease, whereas heterozygous patients from the two autosomal dominant families that segregated the R120W mutation showed a milder phenotype.

We also reported a de novo mutation, T157P, which has not been previously described. Haplotypic analysis of the CMT4A locus confirmed a unique origin for the Q163X mutation in 13 Spanish chromosomes and six American Hispanic chromosomes. A common origin for two Spanish chromosomes and two Moroccan chromosomes carrying the S194X mutation was also confirmed.

We concluded that: (i) although it used to be considered that CMT4A was inherited as an autosomal recessive disorder, some mutations may be expressed in heterozygous patients and segregate dominantly in some families; (ii) GDAP1 mutations are relatively frequent in our population, thus, the gene could be included in the routine genetic testing of CMT regardless of the inheritance pattern; and (iii) the most frequent mutation, Q163X, is the result of a founder effect as the consequence of a unique origin.

Key points

- We investigated the genetics and inheritance of the GDAP1 gene and phenotype expression in a series of 106 isolated and 19 familial cases with Charcot-Marie-Tooth disease and Spanish ancestry, for whom mutations in the MPZ, MPZ, and GJB1 genes had previously been excluded.
- We also investigated the existence of founder effects for some recurrent mutations and the origin of these mutations in patients from different countries.
- We found mutations in seven isolated patients, three autosomal recessive families, and two autosomal dominant families. Six out of seven isolated patients were homozygotes or compound heterozygotes with autosomal recessive inheritance and one patient carried a de novo dominant mutation. The mutation detection rate in the sporadic patients was 5.6%.
- Patients with homozygous or compound heterozygous genotypes showed a severe disease, whereas heterozygous patients from the two autosomal dominant families that segregated the R120W mutation showed a milder phenotype.
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Abbreviations: CHN, congenital hypomyelinating neuropathy; CMAP, compound motor action potential; CMT disease, Charcot-Marie-Tooth disease; DSN, Dejerine-Sottas neuropathy; NCVs, nerve conduction velocities; SNAP, sensory nerve action potential.
chromosome 8q21.1. GDAP1 is a 358 amino acid protein whose function is not well known. It is expressed in both the central and peripheral nervous system.15 17 A putative role as glutathione S-transferases has been postulated for GDAP1.16 17

Mutations in the GDAP1 gene have been observed particularly in patients from Mediterranean countries,17 18–22 but also in those from other European regions.17 23 24 The most prevalent mutation in Spain is Q163X,14 which has also been found in three North American Hispanic families.25 Moreover, S194X, the most frequent mutation in North African countries—Morocco, Tunisia15 16—has also been found in Spain.14 Haplotype analysis of one Moroccan family and one Spanish family suggested a common origin of the S194X mutation found in both countries.18

We report here the genetics of CMT4A investigated through genetic analysis of the GDAP1 gene and locus in a series 125 isolated or familial CMT patients with Spanish ancestry. We show that the most frequent mutation, Q163X, has a common origin in families from both Spain and North America. We also present genetic data suggesting that CMT4A displays both autosomal recessive and autosomal dominant inheritance, and we document a possible correlation between the severity of the disease and genetic status.

METHODS

Patients

A cohort of 161 patients belonging to 125 families with Spanish ancestry and with a diagnosis of CMT disease, either axonal or demyelinating, was available for genetic analysis of GDAP1. The cohort was distributed as follows: 106 isolated cases, 13 families with autosomal recessive inheritance (categorised thus because more than one sib was affected and parents were normal by examination or history), and six families with autosomal dominant inheritance. Consanguinity was observed in 10 isolated cases and three families. In all cases mutations in the MP22, MPZ, and GJB1 genes had previously been excluded. Mutation analysis25 and clinical descriptions26 for families LF38, LF249, and LF20 has previously been reported. Mutation studies and clinical data of the Hispanic families HOU531, HOU364, and HOU726, have also been reported elsewhere.27 Informed consent was obtained from patients and relatives before genetic studies. The study was approved by both the Hospital Universitari La Fe and the CSIC Institutional Boards on Bioethics.

SSCP analysis and DNA sequencing

The primers used for amplification of exons 1–6 have been reported elsewhere except a new direct primer for exon 1. The new designed primer is: 5’-GGCGCTTCCTCCTGCGAGGAGG TACC-3’. PCR conditions were set as follows: 4 min initial denaturation at 95°C, 35 cycles of 30 s denaturation at 94°C, 30 s annealing and elongation at 54–69°C (exon 1, 68°C; exon 2, 55°C; exon 3, 60°C; exon 4, 54°C; exon 5, 60°C; and exon 6, 69°C), and a 7 min final extension at 72°C.

For single-strand conformation polymorphism (SSCP) analysis, 5 μl of PCR products were diluted in 3 μl of 250 mM EDTA, 98% deionised formamide, 0.25% xylene cyanol, and 0.25% bromophenol blue. DNA was denatured for 10 min at 95°C and was kept on ice for more than 2 min. Then 6 μl of the mix was loaded onto 12% polyacrylamide with or without 5% glycerol. The non-denaturing gels were run at 800 V for 16 h at room temperature and visualised by silver staining.

Mutation screening was performed by direct sequencing of purified PCR products (Qiagen, Hilden, Germany) in an ABI PRISM 3100 sequencing analyser by using fluorescent dideoxynucleotides and one of the PCR primers. All sequences on both strands were determined.

Microsatellite and SNP genotyping

Genotyping for the six microsatellite markers linked to the CMT4A locus was performed using a similar PCR protocol: 4 min initial denaturation at 95°C, 35 cycles of 30 s denaturation at 94°C, 30 s annealing and elongation at 55°C (D8S279, D8S286, and D8S551) or 58°C (D8S1474, D8S1289, and D8S84), and a 7 min final extension at 72°C. PCR products were run on a 12% non-denaturing polyacrylamide gel at 800 V for 10 h at room temperature. Allele fragments were visualised by silver staining. Allelic numbers for every marker except D8S1474 are according to the Genome Database (http://www.gdb.org/), D8S1474 alleles and frequencies were established in the general Spanish population. The determination of haplotype phase was based either on homozygosity or on analysis of parental samples, which allowed us to fully or partially define the phase.

Analysis of the c.507T/G single nucleotide polymorphism (SNP) was performed by PCR amplification of exon 4 and restriction digestion with DdeI. After digestion the presence of two bands of 168 and 120 bp indicates allele T, whereas a 288 bp undigested band indicates allele G. Both rs1029592 and rs9594242 SNPs (UCSC Human Genome Browser, Human Genome Working Draft, http://genome.ucsc.edu/goldenPath/ septTracks.html) were investigated by SSCP analysis.

Estimation of Q163X mutation age was performed by means of the maximum likelihood method implemented in the program BDMC21 v2.1 (available at http://www.rannala. org/labpages/software.html).27 The program parameter setting we used were: growth rate = 0.005, sample fraction = 0.0000325 (assuming a carrier frequency of 1/200 in the general population), a total population size of 40 million individuals, and a mutation rate of short tandem repeat (STR) linked markers of 0.0001. Program data settings were: 13 mutant copies, which are the mutant alleles in our sample, and two segregating sites. Program option settings were: conditional on copy number = yes, number of Monte Carlo replicates = 10 000, initial time = 10, final time = 500, and interval increments = 10.

Exclusion of false paternity was performed by using 10 microsatellite markers with high heterozygosity from the CHLC Human Screening Set/Weber version 6 (Research Genetics, Huntsville, AL, USA): D1S518, D2S1326, D3S1249, D4S2368, D5S2494, D6S1956, D7S1808, D8S1477, D9S301, and D10S1432.

RESULTS

Mutation analysis

In order to investigate the frequency and type of GDAP1 mutations in the Spanish population, we screened each coding exon and flanking intronic sequences of GDAP1 for mutations in a series of 125 CMT probands from unrelated families or isolated cases. All patients had Spanish ancestry. We observed mutations in 12 probands. The mutations described elsewhere—Q163X, S194X, and T288fsX290—were found in one or more additional families. Three novel mutations were found (table 1). One patient with an S194X mutation in one chromosome presented a 4 bp AAAG deletion on the other chromosome. This deletion is a frameshift mutation that generates a stop codon at position 145 (E114fsX145) and predicts a major disruption of GDAP1 synthesis. Two mutations were missense amino acid changes, R120W and T157P. The R120W mutation was found in the heterozygous state in two families segregating the CMT phenotype as an autosomal dominant trait and the T157P mutation was detected in one sporadic case again expressing the disease as a dominant trait (fig 1). We found no other
mutations in the dominant patients after sequencing all exons. Comparison of the mutated amino acids with the corresponding amino acids in the orthologous genes of GDAP1 in mouse, rat, and zebrafish, and the paralogous gene GDAPILL, mapped on human chromosome 20, and its orthologues in mouse, rat, and zebrafish revealed that the two missense mutations were non-conservative substitutions that altered highly conserved amino acids (table 1). Moreover, we did not find these nucleotide changes in 196 control chromosomes in individuals from the general Spanish population, suggesting again that neither R120W nor T157P are neutral polymorphisms. In short, we found 21 chromosom...
contrast, patients from the dominant families LF292 and LF293, which carry the identical mutation R120W, show a mild phenotype with onset at the end of second decade and very slow evolution. They are currently able to walk and need no orthopaedic devices. Muscle strength and deep tendon reflexes were more affected in recessive than in dominant patients. A hoarse voice was evident in patients from seven of eight recessive families but not in patients from dominant families. The sporadic patient from family VAL8 is a 9 year old girl who shows a severe phenotype with early onset of symptoms in the first year of life, moderately reduced distal strength in lower limbs, absent tendon reflexes, and optic atrophy.

It is noteworthy that electrophysiologic studies indicated that all patient except for probands from families LF127 and LF135 showed normal or mildly reduced NCVs. In these two patients, however, both compound motor action potential (CMAP) and sensory nerve action potential (SNAP) were more affected in recessive than in dominant families. Seven out of 13 Spanish chromosomes shared the complete haplotype, while we found variations in some STRs in the remaining six chromosomes. Analysis of all markers again suggested the presence of a common ancestral haplotype 7-3-5-G-3-6-6. The observed allele variations represent a change of just one repeat that could be produced by mutation. Thus, we suggested that the three haplotypes represent a common ancestral haplotype (the C and F chromosomes) caused by mutations of repeat elements. We postulated that the Q163X mutation originated once in the Iberian peninsula and that the present patients and families segregating the CMT4A phenotype are the consequence of a founder effect.

To confirm this hypothesis we extended haplotype analysis with more STRs. Analysis of all markers again suggested the presence of a common ancestral haplotype 7-3-5-G-3-6-6. Seven out of 13 Spanish chromosomes shared the complete haplotype, while we found variations in some STRs in the other six chromosomes (fig 4). We observed different alleles at markers D8S286 and D8S1829 on chromosomes C. This finding suggests chromosome C derived from the ancestral chromosome after several mutation or recombination events.

### Table 1 Mutations in the GDAP1 gene of CMT4A patients

<table>
<thead>
<tr>
<th>Exon</th>
<th>Nucleotide change</th>
<th>Effect on coding sequence</th>
<th>Number of mutant chromosomes</th>
<th>Corresponding amino acid in mouse, rat, and zebrafish GDAP1, and in human, mouse, rat, and zebrafish GDAP1L1</th>
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<td>c.342-345delAAAG</td>
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Figure 2. Physical map of the CMT4A locus. The GDAP1 gene is indicated as a box. Linked microsatellite markers are indicated at the top. The rs1025928 SNP at the D8S279 locus is shown at the bottom.

Figure 3. Map of Spain showing the 17 autonomous regions. Chromosomes bearing Q163X mutations are represented as filled circles: there are seven in the Basque Country, four in the Valencia region, and two in Castile and Leon.

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However, since flanking markers D8S279 (allele 7 represents 0.08% of normal chromosomes) and D8S84 (allele 6 represents 0.54% of normal chromosomes) did not change with regard to the common haplotype, we suggest a unique origin for the Q163X mutation in patients from the Iberian peninsula. Interestingly, we observed that four of the Hispanic chromosomes shared the same haplotype, whereas chromosome S has the identical haplotype and they are Hispanic in origin, a founder mutation originating in the Iberian peninsula was postulated. To confirm this hypothesis we compared haplotypes at the D8S279 locus with those of the Spanish patients. We observed that four of the Hispanic chromosomes shared the common haplotype C-T-5-G-3-6-6 with Spanish chromosomes. The other two chromosomes showed allelic differences for the proximal markers rs1025928 and D8S279 (fig 4).

These data confirm that the Q163X mutation in patients from both sides of the Atlantic has a common ancestral origin and suggest the existence of a founder effect for the Q163X mutation in the Iberian peninsula. Interestingly, we observed identical variation at locus D8S279 in both Spanish and Hispanic chromosomes. These findings suggest two possible hypotheses about migration: first, the Q163X mutation moved from Spain to America once, probably associated with allele 7, and later the other haplotypes appeared either by recombination or by mutation; second, the Q163X mutation arrived into America in more than one migration movement.

We also applied haplotype analysis to the other mutations each found in two chromosomes: S194X and T288fsX290 (fig 5). We observed that every mutation could be associated with a unique haplotype confirming a unique origin for each one. The S194X mutation was associated with a common D8S551 to D8S84 haplotype in the two Spanish chromosomes. By studying the extended haplotype in the Moroccan family, we confirmed that S194X mutations have a common origin.

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### Table: GDAP1 haplotypes associated with the Q163X mutation

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<th>Family</th>
<th>Chromosome no.</th>
<th>rs1025928</th>
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<th>D8S286</th>
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<th>D8S1474</th>
<th>D8S1829</th>
<th>D8S84</th>
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</table>

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**Figure 4** GDAP1 haplotypes associated with the Q163X mutation. The figure shows haplotypes associated with the 13 Spanish chromosomes (A to M) and the six (N to S) Hispanic North American chromosomes bearing the Q163X mutation. Families are indicated in the first column. Ethnic origin is indicated. A grey colour code is used to identify the marker alleles shared by all chromosomes. Alleles for some markers diverge from the common ancestral haplotype. Light grey labelling indicates that it may have been generated by mutation (mut); by contrast, white labelling suggests that it was the result of a recombination event (rec).
origin in Spain and Morocco, as previously reported by Nellis et al. The two chromosomes bearing the T288fsX290 mutation shared a common haplotype between markers D8S279 and c.507G/T, but differed in the three distal markers. This difference suggests that a recombination event occurred between GDAP1 and D8S1474.

**DISCUSSION**

The genetics of motor and sensory hereditary neuropathies is complex. These disorders show a wide phenotypic and genetic heterogeneity. We addressed the genetics of CMT4A in a series of 125 unrelated families with Spanish ancestry. We found six different mutations in GDAP1, five previously reported and one new mutation, in 12 families. Interestingly, we found mutations in seven isolated cases, three autosomal recessive families previously reported, and two autosomal dominant families. Six out of seven sporadic patients were homozygotes or compound heterozygotes, whereas one patient was heterozygous for the T157P mutation that originated as a de novo mutation and, hence, was expressed as a dominant mutation. In any case there was a history of consanguinity. The seven sporadic patients represent a detection rate of 5.6% in the 106 isolated cases of the series, a screening yield suggesting that GDAP1 testing may be indicated in the mutation analysis of isolated CMT patients. Nevertheless, as no mutation has been reported in isolated cases from other series, inclusion of GDAP1 in the molecular diagnosis routine of CMT may depend on the prevalence of CMT4A in each country.

Autosomal dominant inheritance has not previously reported in CMT patients and families with GDAP1 gene mutations. Patients from families LF292 and LF293 carried the R120W mutation and segregated the disease as an autosomal dominant trait. They showed a mild phenotype with age of onset in the second decade or even later and are still walking (I-1 in family LF292 is 70 years old). This mild phenotype in heterozygous patients is in contrast with the autosomal recessive patients from families LF292 and LF293 carried the R120W mutation and segregated the disease as an autosomal recessive trait. They showed a mild phenotype with age of onset in the second decade or even later and are still walking (I-1 in family LF292 is 70 years old). This mild phenotype in heterozygous patients is in contrast with the autosomal recessive patients from families LF292 and LF293.

The Q163X mutation is clearly the most frequent mutation in Spain. It has not been found in patients from other countries except for three Hispanic North American families. These three families shared a common associated haplotype indicating a founder mutation with a possible origin in the Iberian peninsula. Haplotype analysis suggests that the Q163X mutation in several families from different regions in Spain is the consequence of a founder effect that we have dated to many centuries ago, and confirms the Spanish origin of the mutant chromosomes in the Hispanic families. Interestingly, identical variations at markers rs1025928 and D8S279 found in the Spanish chromosomes (chromosomes E, H, and J) were also observed in the Spanish chromosomes (chromosomes R and S). This coincidence suggests that D8S279 divergence might have occurred before carrier individuals went to America. Thus, the most likely series of events is that Q163X migrated from the Iberian peninsula to America in three separate migrations. Seven out of 13 Spanish chromosomes are from the Basque Country, six of them from two valleys close together in the province of Guipuzkoa. Chromosomes H and J have been found in two Basque patients while the other Basque patients carry the common ancestral chromosomes also found in other Spanish patients. Since chromosomes H and J are identical to chromosomes S and R, respectively, we propose that the latter arrived in Peru from the Basque Country. By contrast, determination of the origin of the four Costa Rican chromosomes is more difficult because we have no data on the origin of the mutation or the distribution of the ancestral chromosomes in the Iberian peninsula.

We estimated the age of the Q163X mutation to be 33,000 years, which makes it a relatively ancient mutation. It predates the most recent Neolithic expansion of modern humans into Europe, roughly 10,000–15,000 years ago, and corresponds more closely with the early Paleolithic expansion. It is interesting to speculate that the mutation may have originated in or arrived into the Basque Country and then extended to the rest of the Iberian peninsula.

A second mutation, S194X, has been described both in Spanish families and in Tunisian families from the countries referred to as the Maghreb (Morocco, Algeria, and Tunisia). As previously reported, we have confirmed the common origin of this mutation in two unrelated Spanish families and one Belgian family with Moroccan ancestry. Moreover, we also observed that the T288fsX290 mutation, found in two chromosomes from unrelated families, has a common origin. In total, we have demonstrated that these mutations in the Spanish population are the consequence of founder effects.

In summary, both the genetics of the GDAP1 gene and clinical expression of CMT4A neuropathy is complex. Most families segregate the neuropathy as a recessive trait although some families show dominant segregation of mutations that may be associated with a milder phenotype.
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<thead>
<tr>
<th>Family proband</th>
<th>Mutations</th>
<th>Age (years)/gender</th>
<th>Age at onset</th>
<th>Presenting symptom</th>
<th>Age of walking (months)</th>
<th>Age wheelchair needed</th>
<th>Muscle weakness</th>
<th>Sensory disturbance</th>
<th>Hoarse voice</th>
<th>Deep tendon reflexes</th>
<th>Motor NCV/CMAP (m.s⁻²/mV)</th>
<th>Sensory NCV/SNAP (m.s⁻²/mV)</th>
<th>Sural nerve biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal recessive</td>
<td></td>
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</tr>
<tr>
<td>LF249</td>
<td>Q163X/S194X</td>
<td>46/M</td>
<td>18 months</td>
<td>Gait clumsy, frequent falls</td>
<td>12</td>
<td>12</td>
<td>Dist. LL 0/5, dist. UL 0/5</td>
<td>Decreased P, V, T, Po</td>
<td>Yes (vocal cord paresis)</td>
<td>Absent</td>
<td>Median nerve: NR/NR</td>
<td>Sural nerve: 37/1.3</td>
<td>Reduced number of large myelinated fibres, occasional onion bulbs and regenerative clusters</td>
</tr>
<tr>
<td>LF20</td>
<td>Q163X/T288fs</td>
<td>42/M</td>
<td>Birth</td>
<td>Floppy infant, retarded milestones</td>
<td>24</td>
<td>9</td>
<td>Dist. LL 0/5, dist. UL 0/5</td>
<td>Decreased P, V, T, Po</td>
<td>Yes (vocal cord paresis)</td>
<td>Absent</td>
<td>Median nerve: NR/NR</td>
<td>Sural nerve: 46.3/0.2</td>
<td>Reduced number of large myelinated fibres, occasional onion bulbs and regenerative clusters</td>
</tr>
<tr>
<td>LF38</td>
<td>Q163X/Q163X</td>
<td>56/M</td>
<td>2 years</td>
<td>NA</td>
<td>Delayed</td>
<td>30</td>
<td>Dist. LL 0/5, dist. UL 0/5</td>
<td>Decreased P, V, T, Po</td>
<td>Yes</td>
<td>Absent</td>
<td>Median nerve: NR/NR</td>
<td>Normal NCVs</td>
<td>Reduced number of large myelinated fibres, no onion bulbs</td>
</tr>
<tr>
<td>LF127</td>
<td>S194X/T288fs</td>
<td>13/F</td>
<td>2 years</td>
<td>Walking problems</td>
<td>11</td>
<td>13</td>
<td>Prox. LL 4/5, dist. LL 0/5</td>
<td>Normal</td>
<td>Yes</td>
<td>Absent</td>
<td>Median nerve: NR/NR</td>
<td>Sural nerve: 53/3</td>
<td>Reduced number of large myelinated fibres, occasional onion bulbs and regenerative clusters</td>
</tr>
<tr>
<td>LF135</td>
<td>Q163X/Q163X</td>
<td>17/F</td>
<td>18 months</td>
<td>Walking problems</td>
<td>NA</td>
<td>NA</td>
<td>Dist. LL 0–1/5, dist. UL 2/5</td>
<td>Normal</td>
<td>Yes</td>
<td>Absent</td>
<td>Median nerve: 26/0.7</td>
<td>Normal NCV with reduced SNAP</td>
<td></td>
</tr>
<tr>
<td>VAL1</td>
<td>Q163X/Q163X</td>
<td>54/F</td>
<td>14 months</td>
<td>Muscle weakness, frequent falls</td>
<td>10</td>
<td>10</td>
<td>Prox. LL 2/5, dist. LL 0/5</td>
<td>Normal</td>
<td>Yes (vocal cord paresis)</td>
<td>Absent</td>
<td>Median nerve: NR/NR</td>
<td>Sural nerve: 46.3/0.2</td>
<td>Reduced number of large myelinated fibres, occasional onion bulbs and regenerative clusters</td>
</tr>
<tr>
<td>VAL3</td>
<td>Q163X/Q163X</td>
<td>19/M</td>
<td>18 months</td>
<td>Muscle weakness and atrophy</td>
<td>17</td>
<td>7</td>
<td>Prox. LL 2/5, dist. LL 0/5</td>
<td>Normal</td>
<td>Yes</td>
<td>Absent</td>
<td>Median nerve: 41/1.4</td>
<td>Sural nerve: NR/NR</td>
<td>Reduced number of large myelinated fibres, occasional onion bulbs and regenerative clusters</td>
</tr>
<tr>
<td>VAL4</td>
<td>Q163X/Q163X</td>
<td>53/M</td>
<td>17 months</td>
<td>Foot walking problems, Retarded milestones</td>
<td>14–15</td>
<td>Prox. LL 3–4/5, dist. LL 0/5</td>
<td>Normal</td>
<td>Yes (vocal cord paresis)</td>
<td>Absent</td>
<td>Median nerve: 26/0.7</td>
<td>Normal NCV with reduced SNAP</td>
<td></td>
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</tr>
<tr>
<td>VAL5</td>
<td>Q163X/E114fs</td>
<td>4/M</td>
<td>17 months</td>
<td>Muscle weakness and atrophy, clumsiness, gait instability, Delayed gait</td>
<td>15</td>
<td>Walking</td>
<td>Prox. LL 3–4/5, dist. LL 0/5</td>
<td>Normal</td>
<td>No</td>
<td>Absent</td>
<td>Median nerve: NR/NR</td>
<td>Normal NCVs and SNAPs</td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant</td>
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</tr>
<tr>
<td>LF292</td>
<td>R120W/+</td>
<td>36/M</td>
<td>18 years</td>
<td>Foot pain, stepagge gait</td>
<td>NA</td>
<td>Walking</td>
<td>Dist. LL 3–4/5</td>
<td>Reduction of pain and profound sensations</td>
<td>No</td>
<td>Normal except ankle reflexes</td>
<td>Normal NCVs and SNAPs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF293</td>
<td>R120W/+</td>
<td>34/M</td>
<td>14 years</td>
<td>Muscle weakness and atrophy, clumsiness, gait instability, Delayed gait</td>
<td>NA</td>
<td>Walking</td>
<td>Dist. LL 4/5</td>
<td>Normal</td>
<td>No</td>
<td>Normal except ankle reflexes</td>
<td>Peroneal nerve: 45/mild reduction of SNAP 45/15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAL8</td>
<td>T157P/+</td>
<td>10/F</td>
<td>12 months</td>
<td>Muscle weakness and atrophy, clumsiness, gait instability, Delayed gait</td>
<td>15 months</td>
<td>Walking</td>
<td>Prox. LL 5/5, dist. LL 2–3/5</td>
<td>Reduced</td>
<td>No</td>
<td>Absent</td>
<td>Median nerve: NR/NR</td>
<td>Normal NCVs and SNAPs</td>
<td></td>
</tr>
</tbody>
</table>

CMAP, compound motor action potential; LL, lower limbs; SNAP, sensory nerve action potential; UL, upper limbs (the Medical Research Council (MRC) scale is used); sensory disturbance: P, pinprick; Po, positional; T, touch; V, vibratory. NA, not available; ND, not done; NR, not recorded.
Finally, most of the mutations causing the rare disease of CMT4A originated once in human history.

ACKNOWLEDGEMENTS

We are grateful for the kind collaboration of patients and families. We also thank Dr E N elites and Dr V Timmerman for providing DNA samples from family PN860.

ELECTRONIC-DATABASE INFORMATION


REFERENCES

Genetics of Charcot-Marie-Tooth disease type 4A: mutations, inheritance, phenotypic variability, and founder effect


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