Phenotypical Features of a Moroccan Family With Autosomal Recessive Charcot-Marie-Tooth Disease Associated With the S194X Mutation in the GDAP1 Gene

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Background: The first locus for demyelinating autosomal recessive Charcot-Marie-Tooth (ARCMT) disease was identified in 8q13, where mutations in GDAP1 have been found. Mutations in the same gene have been detected in families with axonal ARCMT disease.

Objective: To determine the clinical, electrophysiologic, and morphologic characteristics of a consanguineous Moroccan family with ARCMT disease associated with the S194X mutation in the GDAP1 gene.

Methods: Four patients from a consanguineous Moroccan family were examined clinically and electrophysiologically. In one patient, a morphometric and ultrastructural study of a peroneal nerve biopsy sample was performed. Mutation in the coding region of the GDAP1 gene was identified by direct sequencing.

Results: Neuropathy was evident early in childhood, walking was delayed in one patient, and onset of symptoms occurred before 18 months in the others. The phenotype was severe: foot deformities and disabilities involving the hands and feet developed toward the end of the first decade, followed by involvement of proximal muscles in the lower limbs, leading to loss of autonomy. Electrophysiologic findings were consistent with an axonal form of CMT disease: motor nerve conduction velocities, recordable in one patient only, were greater than 40 m/sec. Sensory nerve action potentials were either abolished or substantially reduced in amplitude. The morphologic data supported the diagnosis of axonal neuropathy, showing a marked reduction in myelinated fibers and signs of axonal regeneration, including frequent pseudo–onion bulb formations. The 4 patients in this family were homozygous for the S194X mutation in the GDAP1 gene.

Conclusion: Electrophysiologic and pathological findings support the hypothesis of an axonal disorder in this ARCMT family with the S194X mutation in the GDAP1 gene.

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ping the CMT4A locus has recently been demonstrated in a Tunisian family with pyramidal tract involvement.17 More recently, mutations in GDAP1 were identified in 3 Spanish families with axonal ARCMT disease linked to 8q21,18 showing that mutations in GDAP1 caused axonal and demyelinating ARCMT disease.

We report the results of a detailed clinical, electrophysiologic, and pathological study of 4 siblings from a Moroccan family with ARCMT disease and the S194X mutation in the GDAP1 gene.

ELECTROPHYSIOLOGIC STUDY

Nerve conduction velocities were recorded with stimulating and recording surface electrodes. Median and ulnar compound muscle action potentials (CMAPs) were recorded from the abductor pollicis brevis and abductor digitii quinti muscles, respectively, with stimulation at the wrist and elbow. The peroneal CMAP was recorded from the extensor digitorum brevis muscle, with stimulation at the ankle and knee. Distal motor latency, MNCV, and distal CMAP amplitude were measured. Median and ulnar sensory nerve action potentials were obtained orthodromically at the wrist after stimulation at the third and fifth digits, respectively. The sural sensory nerve action potential was recorded antidromically at the ankle after stimulation at the calf. Sensory nerve action potential amplitude and sensory nerve conduction velocity were measured. Electromyography with a concentric needle electrode was performed at least in the tibialis anterior and the first dorsalis interosseus muscles.

The electrophysiologic examination protocol was performed in all patients and at-risk relatives.

PATHOLOGICAL STUDY

A superficial peroneal nerve biopsy sample was obtained from patient V:5 at age 15 years after informed consent was pro-

Figure 1. Pedigree of family RBT-087 with autosomal recessive Charcot-Marie-Tooth disease associated with the S194X mutation in the GDAP1 gene. Black symbols identify affected individuals; circles, females; squares, males; roman numerals, generations; and arabic numbers, individuals. Genotypes are indicated for 6 markers flanking the GDAP1 gene. For the GDAP1 gene, “m” and “wt” correspond to the mutant and wild-type alleles, respectively. Electrophoretograms of the sequence at the mutation site in exon 5 are represented for the heterozygous parent (patient IV:4), the index case (patient V:13), and the healthy homozygous at-risk sibling (patient V:15).
vided. The specimen was fixed in buffered 2.5% glutaraldehyde, postfixed in osmium tetroxide, and embedded in epoxy resin. Semithin sections (0.5 µm) were stained with toluidine blue for light microscopic examination. Ultrathin sections were contrasted with lead citrate and uranyl acetate for electron microscopy. The density of myelinated fibers was determined on the whole intrafascicular area. The external and axon diameters of myelinated fibers were measured on the semithin sections using a semiautomatic image analyzer (ASM Leitz, Heidelberg, Germany); the g-ratio (axon diameter–fiber diameter) was calculated.

MOLECULAR ANALYSIS

Blood samples from the 17 individuals were obtained after informed consent was provided. Genomic DNA was extracted using standard procedures. Family members were genotyped with fluorescent microsatellite markers to test linkage to known CMT loci in 5q23-q33,12 8q13-q21,6 8q24,19 11q23,20 and 1q21.14 Pairwise and multipoint lod scores were calculated using the MLINK and LINKMAP programs of the FASTLINK package,21 assuming a fully penetrant AR trait with a disease-allele frequency of 0.0001 and an equal recombination fraction in males and females.

Each exon of the GDAP1 gene was amplified by polymerase chain reaction using primers previously published.18 The 5’/H11032 3’/H11032 and 3’/H11032 5’/H11032 strands of the polymerase chain reaction products were sequenced with a BigDye Terminator sequencing kit (ABI 3100), and sequence chromatograms were analyzed using a software program (SeqScape version 1.1) (all from PE Applied Biosystems, Foster City, Calif).

RESULTS

Clinical findings are given in Table 1. Onset was early in childhood (<3 years) in all patients. The index case, patient V:13, had hypotonia at birth and delayed development of early motor milestones. She walked without help at age 4 years. Her cousins had normal development of early motor milestones but had difficulty walking from the beginning, in particular because of foot deformities. Symptoms consisted of distal weakness and wasting of legs, predominantly in peroneal muscles, with severe foot deformities of the pes equinovarus type (Figure 2). All patients had total areflexia and loss of proprioception in the lower limbs. Progression of the disease was severe, with involvement of proximal and distal muscles of the lower limbs in patient V:13, but pre-

Table 1. Clinical Findings in Patients With Autosomal Recessive Charcot-Marie-Tooth Neuropathy Associated With the S194X Mutation in the GDAP1 Gene

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>V:13</th>
<th>V:7</th>
<th>V:4</th>
<th>V:3</th>
</tr>
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<tbody>
<tr>
<td>Age at onset, y</td>
<td>&lt;1</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hypotonia at birth</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Age when walking</td>
<td>4 y</td>
<td>12 mo</td>
<td>&lt;18 mo</td>
<td>&lt;18 mo</td>
</tr>
<tr>
<td>Age at examination, y</td>
<td>15</td>
<td>13</td>
<td>&lt;18 mo</td>
<td>15</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>14</td>
<td>10</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Distal motor deficit</td>
<td>ULS + LLs</td>
<td>ULS + LLs</td>
<td>ULS + LLs</td>
<td>ULS + LLs</td>
</tr>
<tr>
<td>Proximal motor deficit</td>
<td>ULS + LLs</td>
<td>LLs</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Distal muscle atrophy</td>
<td>ULS + LLs</td>
<td>ULS + LLs</td>
<td>ULS + LLs</td>
<td>ULS + LLs</td>
</tr>
<tr>
<td>Proximal muscle atrophy</td>
<td>ULS + LLs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>ULS + LLs</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Proprioception</td>
<td>LLs</td>
<td>LLS</td>
<td>LLs</td>
<td>LLS</td>
</tr>
<tr>
<td>Areflexia</td>
<td>ULS + LLs</td>
<td>ULS + LLs</td>
<td>ULS + LLs</td>
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</tr>
<tr>
<td>Foot deformities</td>
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<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Functional disability</td>
<td>ULS</td>
<td>Clavilike fingers</td>
<td>Clavilike fingers</td>
<td>Clavilike fingers</td>
</tr>
<tr>
<td>LLS</td>
<td>Wheelchair bound</td>
<td>Walks with crutches</td>
<td>Walks with crutches</td>
<td>Walks with crutches</td>
</tr>
</tbody>
</table>

Abbreviations: LLs, lower limbs; ULS, upper limbs.

Figure 2. Patient V:5. Notice the severe pes equinovarus deformities and the clavilike fingers.

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dominating in distal muscles in the other patients. Weakness of the upper limbs, particularly in the hand muscles, developed late in the first decade, with clawing of the fingers in all patients. The index case developed severe weakness of the proximal muscles and became wheelchair bound at age 16 years. Her cousins needed crutches for walking at 13, 15, and 20 years of age. All patients had mild scoliosis. There was no cranial nerve involvement or cerebellar or pyramidal signs. Clinically enlarged nerves were not obvious in any patients. Intellectual function was normal in all patients.

**ELECTROPHYSIOLOGIC FINDINGS**

The results of the electrophysiologic examination are given in Table 2. No motor or sensory responses could be elicited in patients V:4, V:7, and V:13. In patient V:5, no motor or sensory action potentials were obtained in the lower limbs. The CMAP amplitudes in the upper limbs were greatly reduced, distal motor latencies were delayed, and MNCVs of the median and ulnar nerves were slightly reduced (40-50 m/s). Needle electromyographic examination showed a reduced recruitment pattern in the proximal muscles. Voluntary activity was absent in distal muscles. These data are consistent with an axonal form of CMT disease.

**PATHOLOGICAL FINDINGS**

The morphometric analysis showed marked loss of myelinated fibers, with a density of 3243/mm², which is very low compared with an age-matched control. The size of the myelinated fiber was distributed unimodally, with loss of large-diameter fibers and a shift toward smaller diameters (Figure 3). No obvious signs of demyelination or typical onion bulb formations were seen. Myelin structure was normal, without aspects of uncompaction. Only occasional fibers had thin myelin sheaths. The mean g-ratio (axon diameter–total fiber diameter) was 0.73, which is only slightly higher than the reference value of 0.70. Rare clusters of regeneration were observed, and they were sometimes surrounded by concentrically arranged Schwann cell processes, giving an appearance of an onion bulb. More frequently, these pseudo–onion bulbs consisted of a single myelinated fiber surrounded by Schwann cell processes enclosing unmyelinated axons (Figure 4).

**MOLECULAR ANALYSIS FINDINGS**

Bipoint and multipoint analyses excluded linkage to 5q, 8q24 (NDRG1), 11q23 (MTMR2), and 1q (Lamin A/C) loci (data not shown). In contrast, bipoint lod scores were positive for 4 markers at the 8q13 locus (GDAP1 gene) (Table 3), 3 of which (D8S526, D8S1144, and D8S164) had maximum lod scores greater than the threshold of +3. These results strongly supported linkage to the GDAP1 gene.

We initially tested 2 affected individuals (patients V:7 and V:13) for mutations in GDAP1 by direct sequencing of the 6 exons. A C→G transition in exon 5 resulted in the nonsense S194X mutation (Figure 1). This mutation causes truncation of the protein in the glutathione S-transferase domain and a probable loss of function. Direct sequencing of GDAP1 exon 5 showed that the 4 affected individuals (patients V:4, V:5, V:7, and V:13) were homozygous and that their parents (patients III:1, III:2, III:3, and III:4) were heterozygous for the S194X mutation. At-risk members (patients V:8, V:10, V:11, V:12, and V:14) were heterozygous, and patient V:15 did not carry the mutation.

In this detailed description of the clinical, electrophysiologic, and pathological phenotype of 8q-linked ARCMT...
neuropathy in a consanguineous Moroccan family, the patients were homozygous for the nonsense S194X mutation in exon 5 of the GDAP1 gene. This mutation has already been reported, in the heterozygous state, in a family (LF249) of Spanish origin with an axonal form of CMT disease and, in the homozygous state, in a Tunisian family (DUK 1402) with demyelinating CMT disease.

In the family we studied, age at onset was early. The patients either began walking late (>1.5 years) or were disabled from the start. The major sign of onset was pronounced foot deformity, with a deficit in peroneal muscles. In the first description of families with linkage to 8q13 by Ben Othmane et al, onset occurred before age 2 years. In families with the GDAP1 gene mutation reported by Cuesta et al, onset occurred in childhood, but it was not specified whether patients had delayed early developmental milestones. Ouvrier et al and Gabreels-Festen et al also described CMT families with early onset.

Table 3. Two-Point LOD Scores for Linkage Between the GDAP1 Locus and the Informative 8q13 Markers in the Consanguineous Moroccan Family

<table>
<thead>
<tr>
<th>Markers</th>
<th>0.0</th>
<th>0.01</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>Z(_{\text{max}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>D8S533</td>
<td>-0.95</td>
<td>0.98</td>
<td>1.34</td>
<td>1.23</td>
<td>0.78</td>
<td>0.39</td>
<td>0.15</td>
<td>1.34</td>
</tr>
<tr>
<td>D8S526</td>
<td>3.29</td>
<td>3.21</td>
<td>2.88</td>
<td>2.46</td>
<td>1.65</td>
<td>0.90</td>
<td>0.29</td>
<td>3.29</td>
</tr>
<tr>
<td>D8S551</td>
<td>2.96</td>
<td>2.88</td>
<td>2.56</td>
<td>2.16</td>
<td>1.40</td>
<td>0.72</td>
<td>0.23</td>
<td>2.96</td>
</tr>
<tr>
<td>D8S1144</td>
<td>3.63</td>
<td>3.55</td>
<td>3.20</td>
<td>2.77</td>
<td>1.91</td>
<td>1.11</td>
<td>0.43</td>
<td>3.63</td>
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<tr>
<td>D8S541</td>
<td>2.03</td>
<td>1.98</td>
<td>1.76</td>
<td>1.49</td>
<td>0.99</td>
<td>0.54</td>
<td>0.20</td>
<td>2.03</td>
</tr>
<tr>
<td>D8S271</td>
<td>-infini</td>
<td>-3.16</td>
<td>-1.34</td>
<td>-0.74</td>
<td>-0.33</td>
<td>-0.16</td>
<td>-0.05</td>
<td>2.03</td>
</tr>
</tbody>
</table>

Figure 4. A, Transverse semithin section of the peroneal nerve of patient V:5 showing a severe reduction in the density of myelinated fibers and loss of large-caliber myelinated fibers (toluidine blue, original magnification ×100). B, Electron micrograph showing an axon with myelin of normal thickness (contrasted with lead citrate–uranyl acetate, original magnification ×15 000). C, Electron micrograph showing a pseudo–onion bulb formation consisting of small myelinated fibers surrounded by Schwann cell processes enclosing unmyelinated axons (arrows) (contrasted with lead citrate–uranyl acetate, original magnification ×6 000). D, Electron micrograph showing a regenerative cluster consisting of 2 adjacent, thinly myelinated axons surrounded by flattened Schwann cell processes, giving an onion bulb–like appearance (contrasted with lead citrate–uranyl acetate, original magnification ×5 000).
set, some of which had AR inheritance and a neuronal type of the disease. However, the genes responsible were not identified.

In the Moroccan family we studied, the clinical signs were dominated by distal muscle weakness and wasting in the 4 limbs, with early pronounced pes equinovarus deformities. Proximal muscles became involved in the index case at age 16 years and was responsible for an early loss of the ability to walk. The hand muscles were severely involved by the end of the first decade in all patients. Clinical progression was thus severe, with important functional disability of both hands and feet developing during the second decade. The severity of the disease, which caused disability by the end of the first decade, was also noted in the families described by Cuesta et al.18 The families studied by Ben Othmane et al6 and Baxter et al2 also had a severe phenotype, but no details were given about the progression of the disease. The involvement of proximal lower limb muscles could be considered a hallmark of severity in CMT disease, since it is the primary cause of the loss of autonomy in walking. This finding is not specific to ARCMFT disease with mutations in the GDAP1 gene; it also has been reported in demyelinating ARCMT disease caused by mutations in MTMR224 and in axonal ARCMT disease caused by mutations in the LMNA gene.15

In contrast to the 3 previously described Spanish families, in which the patients were either homozygous or compound heterozygous for the Q163X mutation,18 our patients had neither vocal cord paralysis with a hoarse voice nor cranial nerve or central nervous system involvement. These signs, which also seemed to be absent in the family DUK1402,7 in which patients were homoallelic for S194X, might be associated with some mutations other than S194X. In other types of CMT disease, mutations resulting in a CMT phenotype with additional clinical signs have been described in the P0 gene (CMT1B), in which the Thr124Met and Glu97Val mutations are associated with a neuronal phenotype.16,17 In the family DUK1402,7 in which patients were homoallelic for S194X, might be associated with some mutations other than S194X. In other types of CMT disease, mutations resulting in a CMT phenotype with additional clinical signs have been described in the P0 gene (CMT1B), in which the Thr124Met and Glu97Val mutations are associated with a neuronal phenotype.16,17 In the family DUK1402,7 in which patients were homoallelic for S194X, might be associated with some mutations other than S194X. In other types of CMT disease, mutations resulting in a CMT phenotype with additional clinical signs have been described in the P0 gene (CMT1B), in which the Thr124Met and Glu97Val mutations are associated with a neuronal phenotype.16,17 In the family DUK1402,7 in which patients were homoallelic for S194X, might be associated with some mutations other than S194X. In other types of CMT disease, mutations resulting in a CMT phenotype with additional clinical signs have been described in the P0 gene (CMT1B), in which the Thr124Met and Glu97Val mutations are associated with a neuronal phenotype.16,17 In the family DUK1402,7 in which patients were homoallelic for S194X, might be associated with some mutations other than S194X. In other types of CMT disease, mutations resulting in a CMT phenotype with additional clinical signs have been described in the P0 gene (CMT1B), in which the Thr124Met and Glu97Val mutations are associated with a neuronal phenotype.16,17

The electrophysiologic data were in line with the clinical severity, since no motor response could be recorded in 3 patients because of the degree of muscle atrophy. The sensory potentials were abolished as well, and only patient V:5 had measurable MNCV with values greater than 40 m/s for the median and ulnar nerves and very reduced CMAP amplitudes. These results are concordant with an axonal form of CMT neuropathy, as defined by electrophysiologic criteria. Results of needle electromyographic examination showed that proximal and distal muscles were denervated, consistent with the clinical deficit. In the families described by Cuesta et al.,18 the median and ulnar MNCVs, when recordable, were also greater than 40 m/s, with substantially reduced or abolished sensory nerve action potentials.

The pathological study in patient V:5 showed severe loss of myelinated fibers and a shift toward myelinated fibers with smaller diameters. There were no obvious signs of demyelination. Typical onion bulb formations were not observed, but there were many pseudo–onion bulbs consisting of either a single myelinated axon surrounded by Schwann cell processes enclosing unmethylated axons or a regenerating cluster of axons surrounded by concentrically arranged Schwann cell processes. These aspects are considered signs of axonal regeneration rather than excesses of Schwann cell proliferation indicative of a demyelinating disorder. The same features have been described in X-linked CMT disease due to connexin 32 mutations.29,30 Furthermore, the thickness of the myelin sheath in relation to axon diameter, represented by the g-ratio, remained in the reference range. These findings are in favor of an axonal neuropathy and are in accordance with the electrophysiologic findings.

Mutations in the GDAP1 gene have been reported to be responsible for demyelinating and axonal ARCMT diseases.5,6 The same is true of mutations in the P0 gene that can cause either demyelinating or axonal neuropathy (see the Inherited Peripheral Neuropathies Mutation Database Web site: http://molgen-www.uia.ac.be/CMTMutations/). In both diseases, there is no clear correlation between the location or the type (missense, nonsense, deletion, or frame-shift) of mutation and the phenotype. For CMTX, it has long been debated whether the pathologic process is demyelinating or axonal. It seems that the process is composite, with demyelinating and axonal components that vary among patients without a clear correlation with the genotype.31,32 In GDAP1, the same mutation, S194X, has been associated, in the homozygous state, with demyelinating and axonal CMT phenotypes, like the Asp61Asn and Thr124Met mutations in the P0 gene.25,33,34 However, the severity of the CMT disease associated with GDAP1 mutations makes it difficult to characterize the pathologic process, since the patients are often examined after its active phase. The timing of the pathologic events, demyelination and axonal loss, might thus not be precisely defined. Because the GDAP1 gene is expressed in Schwann cells and neurons,18 a mixed process might result.

The function of the GDAP1 gene in the peripheral nerve and central nervous system is still unknown but would probably help correlate the mutation and its functional and histopathologic consequences. Cellular and animal models will help answer these questions.

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