Novel mutation of the mitofusin 2 gene in a family with Charcot-Marie-Tooth disease type 2 (CMT2A).

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because the patient's mother displayed the intron 3 mutation and the patient's father displayed the exon 6 mutation in heterozygous states, respectively. The patient had worsening proximal weakness of upper and lower limbs at 9 years, starting to restrict activities such as climbing stairs. There were no signs of deteriorating cardiac function, and cardiac treatment has not been necessary.

Data on the consequences of sarcoglycan-deficiency on expression, assembly, and trafficking of dystrophin are rather scarce,[4–10] in particular for γ-sarcoglycan. Deletion of 525-T causes a frameshift mutation within the extracellular region of γ-sarcoglycan.[1] This causes loss of immunostaining plus reduced immunoreactivity for dystrophin,[1–3] and on immunoblots.[11] However, this feature has not been described in other mutations of γ-sarcoglycan, raising the question whether this specific mutation, and not disruption of γ-sarcoglycan in general, is responsible for the reduction in dystrophin expression.[2] We can only speculate about the impact of the intron 3-mutation c.298-1G>A described here. However, this mutation affects a highly conserved splice region and obviously leads to a major disruption of γ-sarcoglycan; it may, in fact also influence dystrophin expression.

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NOVEL MUTATION OF THE MITOFUSIN 2 GENE IN A FAMILY WITH CHARCOT–MARIE–TOOTH DISEASE TYPE 2

Charcot–Marie–Tooth disease type 2A (CMT2A) is the most frequent form of CMT2. It is caused by mutations in the nuclear-encoded mitochondrial gene mitofusin 2 (*MFN2*).[1–4] *MFN2* mutations are mainly missense substitutions in GTPase in the linker domain between this and the first coiled-coil region and in the second coiled-coil domain.[5]

We describe 2 patients, a mother and daughter, who are affected with CMT2A caused by a new mutation of the *MFN2* gene.

A 68-year-old woman came to our attention for longstanding gait disorder. Family history was negative. She married at age 25 years and had 6 children, 4 sons (ages 40, 38, 37, and 34 years, respectively) and 2 daughters (ages 33 and 31 years) (Fig. 1A). In her past medical history, she had developed, after the third and fourth delivery (at ages 29 and 32, respectively), weakness and sensory loss in the anterior compartments of both legs and was diagnosed with mononeuropathy secondary to distocic delivery. At age 44 years, neurophysiologic examination revealed signs of diffuse denervation, and lower motor neuron disease was diagnosed.

When we first saw her, at age 68, she had an ataxic-steppage gait, severe lower limb atrophy, weakness, and areflexia. Neurophysiologic studies showed a sensory–motor axonal polyneuropathy [right fibular nerve motor conduction velocity (MCV) 40 m/s, compound muscle action potential (CMAP) amplitude 0.1 mV; left fibular nerve MCV 40 m/s, CMAP amplitude 0.6 mV; right sural nerve CV 40 m/s, sensory nerve action potential (SNAP) amplitude 1.7 μV; left median nerve sensory conduction velocity (SCV) index finger–wrist 46 m/s, SNAP amplitude 1.7 μV; left ulnar nerve SCV little finger–wrist 56 m/s, SNAP amplitude 1.1 μV]. Molecular genetic analysis ruled out duplication and deletion of the peripheral myelin protein 22 gene (*PMP22*), whereas direct sequencing of *MFN2* revealed a heterozygous nucleotide substitution c.864G>C (p.E288D) in exon 9 (Fig. 1B). Of the 6 children of the proband, a daughter (II-5; Fig. 1A), currently age 33 years, had complained since age 22 of slight right foot drop. She had distal atrophy of the lower limbs, distal weakness of the right leg, and lower limb areflexia. Neurophysiologic examination showed sensory–motor axonal polyneuropathy (right tibial nerve MCV 42 m/s, CMAP amplitude 1.4 mV; left

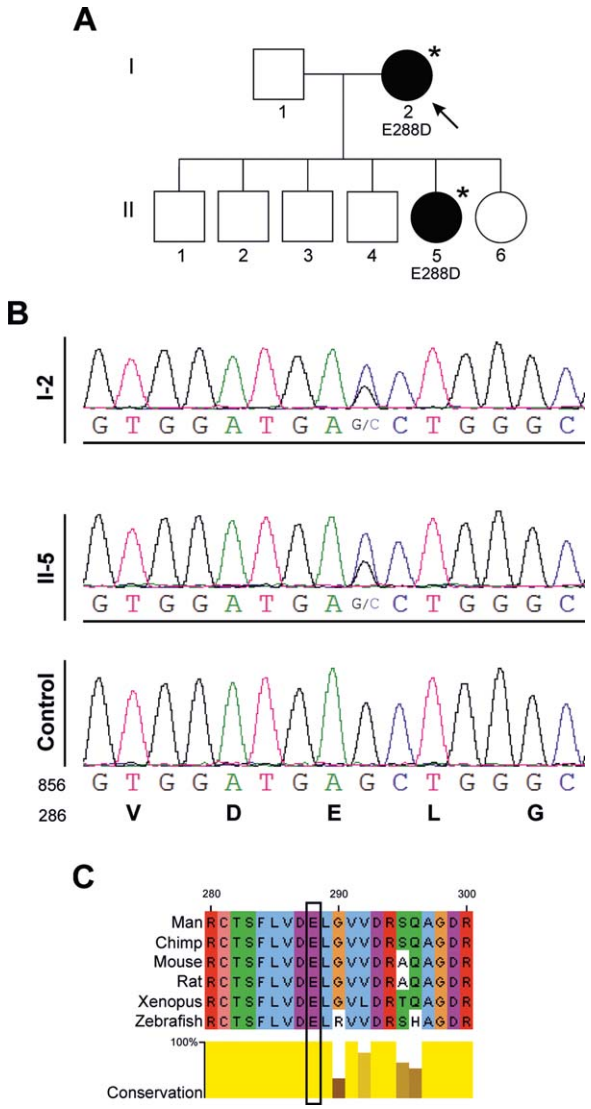

FIGURE 1. (A) Family pedigree (asterisk indicates DNA available). **(B)** Electropherograms obtained from the sequencing of exon 9 of *MFN2* show the presence of a heterozygous substitution c.864G>C in the proband I-2 and her daughter II-5. **(C)** Multiple alignment of MFN2 amino acid sequences reveal that E288 is highly conserved among vertebrates. Numbering refers to human sequence. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

tibial nerve MCV 40 m/s, CMAP amplitude 1.5 mV; right sural nerve CV 32 m/s, SNAP amplitude 3.4 μV; left median nerve SCV index finger–wrist 36 m/s, SNAP amplitude 1.3 μV; left ulnar nerve SCV little finger–wrist 36 m/s, SNAP amplitude 2.4 μV). In both patients, needle electromyography showed chronic and minimal active denervation. *MFN2* sequencing in the daughter confirmed the presence of a c.864G>C substitution.

MFN2 mutations are mainly dominantly inherited missense substitutions[5] that impair mitochondrial movement, probably with a gain-of-function mechanism.[6,7] The substitution c.864G>C, never described, is not reported in the Exome Variant Server or 1000 genome databases and was not found in 200 healthy controls, thus confirming that E288D is indeed a new mutation. The residue E288, located between GTPase and the first coiled-coil domain, is evolutionarily conserved (Fig. 1C). The prediction tools PolyPhen-2,[8] Mutation Taster,[9] and PROVEAN[10] all confirmed that E288D potentially affects protein function.

We have identified a new *MFN2* mutation associated with CMT2 and provided complete phenotypic characterization. *MFN2* mutations are the primary cause of CMT2,[5] and the identification of new mutations and associated phenotypes may facilitate diagnosis.

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COMPOUND MUSCLE ACTION POTENTIAL AMPLITUDE AND DISTAL POTENTIAL DURATION IN AXONAL NEUROPATHY

Prolonged distal compound muscle action potential duration (DCMAPD) can be helpful in diagnosing demyelinating neuropathies.[1,2] However, it is not known