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RECESSIVE HEREDITARY MOTOR AND SENSORY NEUROPATHY CAUSED BY *IGHMBP2* GENE MUTATION

Hereditary motor and sensory neuropathy (HMSN), also known as Charcot-Marie-Tooth disease (CMT), is a genetically heterogeneous disorder that affects both sensory and motor peripheral nerves. HMSN is characterized by distal and symmetric muscle atrophy in the lower limbs and hands, foot abnormalities, and distal sensory loss. It is associated with more than 50 causative genes or loci; however, the genetic cause remains undetermined in almost 50% of HMSN cases.[1,2]

We initially observed 2 patients from a nonconsanguineous family who were affected by autosomal recessive early-onset HMSN. The proband (II-2) was born at full term with unremarkable perinatal history. At 1 year of age, he experienced noticeable distal lower limb muscle weakness and slight upper limb muscle weakness. In addition, his early motor milestones were delayed. When he began walking at 1.5 years of age, gradual weakness developed in his lower limbs and resulted in bilateral foot drop and gait disturbance. Neurologic examination at 8 years of age revealed muscle weakness and atrophy of the bilateral distal muscles, predominantly in the lower limbs. Steppage gait, pes cavus, and scoliosis were noted. Loss of light touch, pain, and vibration sensations in the feet and hands was also observed, presenting as glove and stocking syndrome (figure e-1 and table e-1 on the *Neurology*® Web site at Neurology.org).

Supplemental data at Neurology.org

The electroneuromyography results for the proband revealed that lower limb motor responses were not elicited by stimulation of the peroneal and tibial nerves. Sensory nerve action potentials were also absent following stimulation of the bilateral sural nerves. In the upper limbs, decreased motor amplitudes with reduced nerve conduction velocities occurred in the ulnar and median nerves, and sensory nerve conduction velocities and action potentials were remarkably decreased. Needle EMG showed a neurogenic pattern of muscle degeneration. The proband's 5-year-old sister (II-3) experienced distal limb weakness from 1 year of age and experienced a very similar disease progression. She presented with atrophies of bilateral distal muscles and scoliosis at 6 years of age. Loss of sensory abilities and electrophysiologic findings were also similar to those of the proband (table e-2).

In order to identify the disease-associated genetic abnormality of this pedigree, we had previously excluded 50 known HMSN genes by targeted high-throughput sequencing. Because we did not identify any known HMSN gene mutations, we performed exome sequencing in the proband. Using ANNOVAR and previously described methods (table e-3),[3,4] we obtained a list of candidate genes; 2 novel compound heterozygous mutations in the *IGHMBP2* gene, c.344C>T (p.Thr115Met) and c.1794G>C (p.Asn598Lys), were highlighted. The *IGHMBP2* gene c.344C>T variant is listed in the dbSNP as rs181657861, with an estimated minor allele frequency of 0.00054 in the Exome Variant Server (EVS; 1/12,987) having no identified homozygote, whereas the c.1794G>C variant is not listed in the EVS, and the 2 mutations passed SIFT and PolyPhen-2 filtering. Therefore, both variants are rare and predicted to be pathologic. In addition, we found that the 2 mutations were fully cosegregated with the HMSN phenotype and absent in 500 ethnically matched controls, thereby confirming the pathogenicity (figure e-2).

Mutations in *IGHMBP2* have previously been associated with spinal muscular atrophy with accompanying respiratory distress type 1 (SMARD1), which is characterized by low birth weight, progressive distal muscle weakness, and life-threatening respiratory failure due to diaphragmatic dysfunction before 12 months of age.[5,6] However, a recent study revealed that truncating and missense mutations in *IGHMBP2* could also lead to CMT.[7] Our proband presented with progressive weakness and sensory loss in distal limbs without any history of respiratory distress. As sensory neuropathy and history of respiratory distress are useful discriminating factors between HMSN and SMARD1, the clinical findings of this pedigree supported the diagnosis of HMSN rather than SMARD1.

IGHMBP2 is thought to be involved in immunoglobulin class switching, pre-mRNA processing, and regulation of transcription.[6] However, the precise pathophysiologic mechanisms for disease and the reasons for the varied phenotypes associated with *IGHMBP2* mutations are still unknown. One explanation is that *IGHMBP2* mutations underlying CMT usually lead to much higher residual protein levels than *IGHMBP2* mutations underlying SMARD1. These findings indicate that partial loss of *IGHMBP2* function may lead to a milder phenotype than complete loss of gene function.[6] Further evidence is still needed to clarify the effects of different *IGHMBP2* mutations.

Our results support the findings of Cottenie et al.[7] and demonstrate 2 additional mutations in the *IGHMBP2* gene associated with HMSN rather than SMARD1. Our findings suggest that genetic screening for *IGHMBP2* mutations should be considered in patients with recessive HMSN.

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