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SHORT COMMUNICATION

Novel mutation in the *HSN2* gene in a Korean patient with hereditary sensory and autonomic neuropathy type 2

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Abstract Hereditary sensory and autonomic neuropathies (HSAN) are a group of clinically and genetically heterogeneous disorders that are associated with sensory dysfunction. Among these, HSAN type 2 (HSAN2; MIM 201300) is a rare recessive disease that is characterized by an early age of onset with distal and proximal sensory loss, dysfunction of the autonomic nervous system, loss of the tendon reflex, the presence of various mutilations, and the slow progression of the disease over time. The authors report a Korean patient with the clinical features of HSAN2, who was compound heterozygous for two loss-of-function mutations in the *HSN2* gene: c.217C > T (Gln73X) and c.1134_1135insT (Asp379fsX1). The Gln73X mutation was a novel mutation while the Asp379fsX1 mutation has recently been reported in a Japanese patient with HSAN2. These results expanded the spectrum of mutations of the *HSN2* gene by identifying a novel truncating mutation in a Korean patient and further support the hypothesis that *HSN2* is a causative gene for HSAN2.

Keywords Hereditary sensory and autonomic neuropathies · HSAN2 · *HSN2* · Mutation · Korean

Introduction

Hereditary sensory and autonomic neuropathies (HSANs) are a group of clinically and genetically heterogeneous disorders that are associated with sensory dysfunction. Among these, HSAN type 2 (HSAN2; MIM 201300) is a rare recessive disease that was first clearly described in 1973 (Ota et al. 1973). HSAN2 is characterized by an early age of onset with distal and proximal sensory loss, dysfunction of the autonomic nervous system, loss of the tendon reflex, the presence of various mutilation and the slow progression of the disease over time (Kondo and Horikawa 1974; Murray 1973). Mutations in a novel gene named *HSN2* at 12p13.33 have been identified as being the cause of HSAN2 in Canadian and Lebanese patients (Lafreniere et al. 2004; Riviere et al. 2004; Roddier et al. 2005). In addition, three Caucasian patients and a Japanese patient have recently been reported to carry different mutations of the *HSN2* gene, which implies the genetic homogeneity of the rare disease (Coen et al. 2006; Takagi et al. 2006). In

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the present study, we report on a Korean patient with HSAN2 carrying compound heterozygous mutations in the *HSN2* gene.

Patients and methods

A 28-year-old male patient presented with slowly progressive sensory loss involving all the sensory modalities in the upper and lower limbs for the previous 17 years. The man suffered from loss of sensation and insensitivity to pain, leading to ulcerative lesions on the feet and hands, bacterial infection, and amputation of both lower legs and several fingers. On neurological examination, the deep tendon reflexes were reduced on the wrists and knees, and the proximal muscle motor strength was intact. No significant autonomic signs were detected except for dry hands. The sympathetic skin response recorded from the palms was normal and other autonomic function tests including heart rate at deep breathing, blood pressure change at Valsalva maneuver, and heart rate change on the tilt-bed test showed no significant abnormalities. Nerve conduction study showed distal sensory dominant polyneuropathy. Pathologic examination of the sural nerve biopsy revealed marked loss of myelinated fibers, rare myelin ovoids, and endoneurial fibrosis (Fig. 1a). Electron microscopic examination showed severe loss of large and small myelinated nerve fibers, relatively preserved unmyelinated nerve fibers, and the lack of onion-bulb structures, and segmental demyelination and remyelination (Fig. 1b). Endoneurial spaces were increased by deposition of collagen fibrils. He denied a family history of neuromuscular disease.

After we had obtained informed consent, blood samples were collected from the patient and his family members (Fig. 2). The youngest brother was unavailable for the study. The genomic DNA was isolated from the peripheral blood leukocytes using a Wizard genomic DNA purification kit following the manufacturer's instructions (Promega, Madison, WI, USA). The *HSN2* gene was amplified by polymerase chain reaction (PCR) by using the appropriate primers designed by the authors (available upon request) and a thermal cycler (Model 9700; Applied Biosystems, Foster City, CA, USA). The direct sequencing was performed with the BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems) on an ABI Prism 3100 genetic analyzer (Applied Biosystems).

Results

Two mutations in the *HSN2* gene were identified in the patient. One was a heterozygous nonsense mutation (c.217C > T; Gln73X) and the other was a 1-bp insertion mutation (c.1134_1135insT; Asp379fsX1). The Gln73X was a novel mutation while the Asp379fsX1 has recently been reported in a Japanese patient with HSAN2 (Takagi et al. 2006). Because the patient's mother was a heterozygous carrier of the Asp379fsX1 mutation and all the tested siblings were heterozygous carriers of the Gln73X mutation (Fig. 1), the Gln73X mutation seemed to be derived from the patient's deceased father. This mutation was not found in 100 control chromosomes.

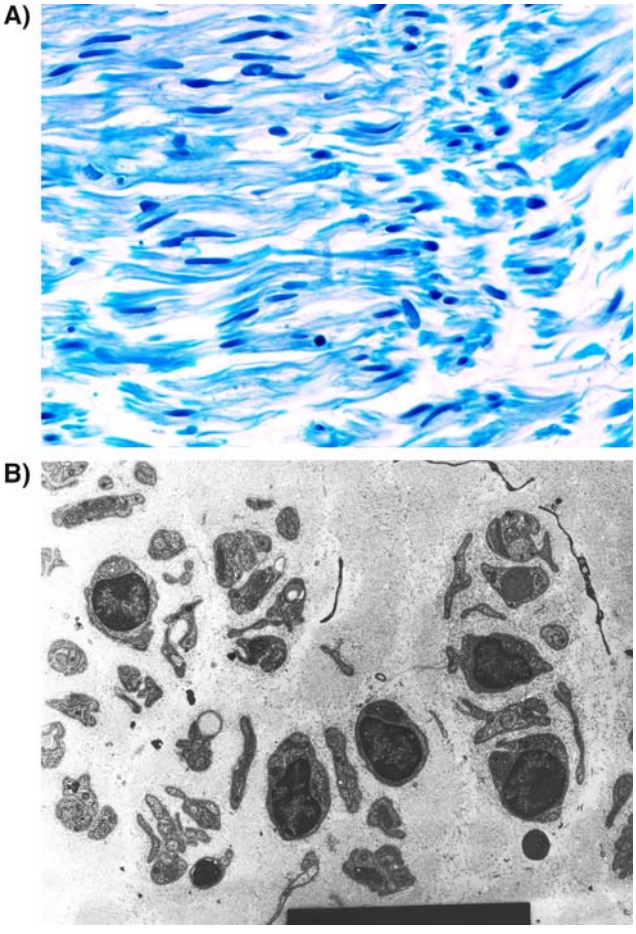

Fig. 1 **a** Light microscopy of the sural nerve shows marked loss of myelinated fibers, rare myelin ovoids, and endoneurial fibrosis (Luxol-fast blue, ×400). **b** At the electron microscopical level, severe loss of large and small myelinated nerve fibers is demonstrated with relatively preserved unmyelinated fibers and increased accumulation of endoneurial collagen fibrils (original magnification ×3,500)

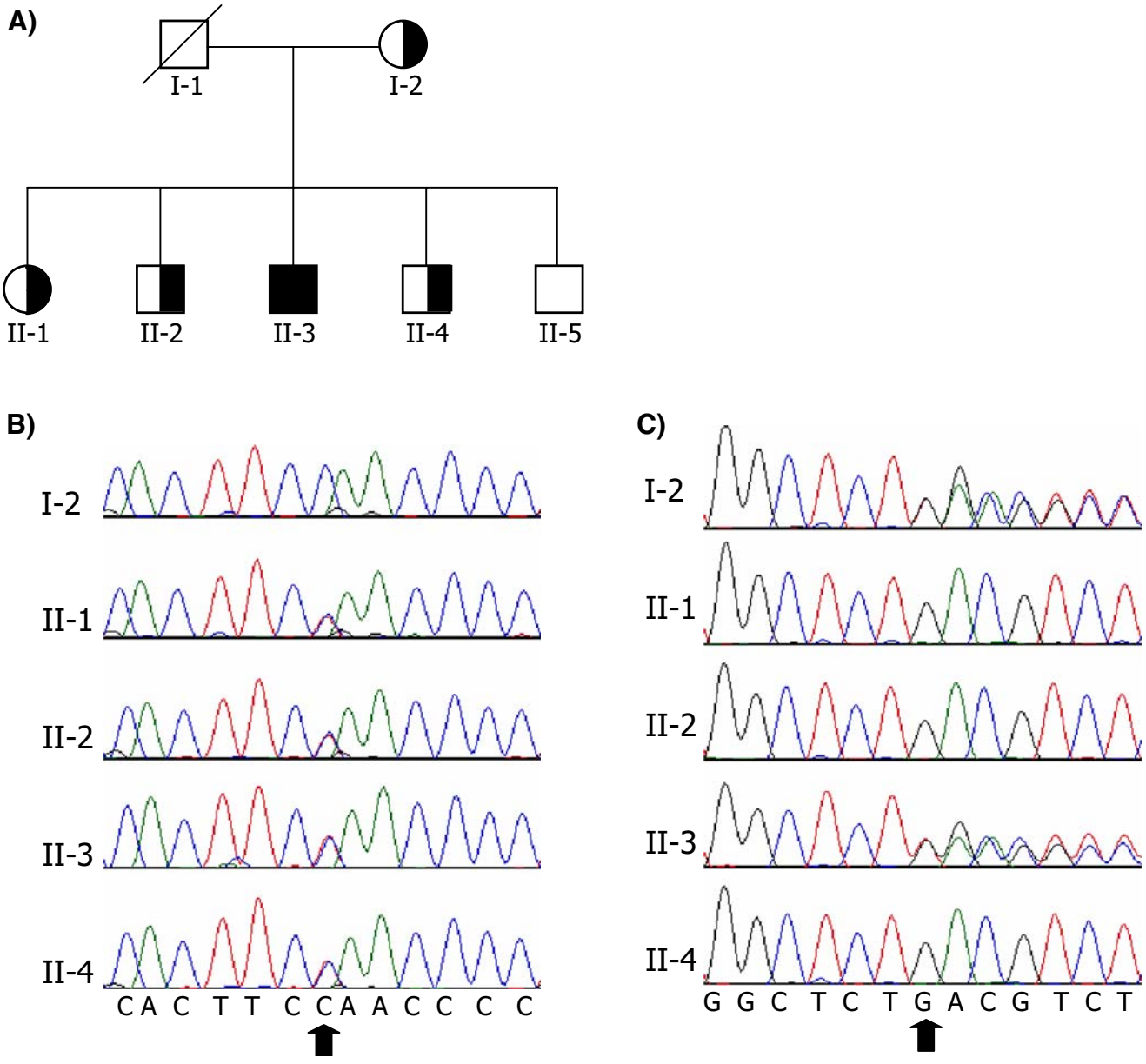

Fig. 2 **a** Pedigree of the family with hereditary sensory and autonomic neuropathy type II (HSAN2). *Circle* female; *square* male; *black symbol* affected; *half-filled symbol* obligate heterozygote; *diagonal line* deceased. Direct sequencing of the *HSN2* gene in this family revealed two mutations (*arrows*): **b** a heterozygous nonsense mutation (c.217C > T; Gln73X) and **c** a 1-bp insertion mutation (c.1134_1135insT; Asp379fsX1)

Discussion

The autosomal recessive disorder HSAN2 results from segmental demyelination and the loss of axons in the peripheral nervous system (Kondo and Horikawa 1974; Murray 1973). Although the function of HSN2 protein remains to be determined, the identification of disease-associated mutations would provide considerable insight into the structural and function of HSN2 protein. Thus far, only ten different mutations have been reported in French Canadian, Lebanese, European, and Japanese patients with HSAN2 (Coen et al. 2006; Lafreniere et al. 2004; Riviere et al. 2004; Roddier et al. 2005; Takagi et al. 2006). Lafreniere et al. (2004) demonstrated that one mutation (c.594delA; Glu198fsX10) had a founder effect in a large Newfoundland HSAN2 family and Roddier et al. (2005) showed that two ancestral chromosomes carrying two

distinct *HSN2* mutations [(.943C > T [Gln315X], c.918-919insA [Ser307fsX13]) were responsible for the HSAN2 in the French Canadian population.

This study documents the existence of a Korean family with HSAN2 and also describes two mutations, including one novel mutation identified in this patient. The c.1134_1135insT (Asp379fsX1) mutation has been found in a Japanese HSAN2 patient whose parents and grandparents were consanguineous. Like all *HSN2* mutations found to date (Coen et al. 2006; Lafreniere et al. 2004; Riviere et al. 2004; Roddier et al. 2005; Takagi et al. 2006), the novel Gln73X mutation found in this study was predicted to be deleterious, leading to a loss of function of the HSN2 protein.

In conclusion, we enlarged the spectrum of mutations of the *HSN2* gene by identifying a novel truncating mutation in a Korean patient who was diagnosed with HSAN2. To our knowledge, this is the first report of a genetically confirmed case of HSAN2 in the Korean population, which shows the genetic homogeneity of this rare disease.

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