

**Mutation in *FAM134B* causing hereditary sensory neuropathy with spasticity in a Turkish family**

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**Keywords**

!) Autosomal recessive

2) *FAM 134 B*

3) Hereditary neuropathy

4) Sensory and autonomic neuropathy

5) Spasticity

**Running title: HSAN with spasticity**

Hereditary sensory and autonomic neuropathy (HSAN) type 2 is a rare autosomal recessive disease that was first described by Ota *et al* in 1973 (1). We report the clinical and pathological findings of 2 siblings with HSAN type 2 due to a homozygous mutation in *FAM134B*.

### Case reports:

Patient 1 A 41- year-old man, born from first degree cousins, did not show any obvious motor delay until the age of 2, when he started to have difficulty in walking. He experienced recurrent painless foot infections and ulcers from age 8. He was admitted to the Neurology Department of the İstanbul Medical Faculty at age 24 and was followed up afterwards. On examination, he had both proximal and distal weakness in the lower extremities, his gait was spastic, and he had glove and stocking distribution hypesthesia and hypalgesia. Vibration sense was impaired distally. He complained of urge incontinence, excessive sweating, and occasional orthostatic dizziness. He had hyperkeratosis of hands and feet (Figure 1 A).

Patient 2 His sister was did not walk until the age 3 years and had difficulty in walking since then. She experienced foot ulcerations starting from childhood, and the first toe of the right foot was amputated at the age 5 (Figure 1 B). Her neurological examination was similar to her brother's and she too had autonomic involvement and a spastic gait (Figure 1 C).

In both patients electrodiagnostic findings indicated the presence of axonal neuropathy involving motor and sensory fibers. Sural nerve biopsy showed loss of myelinated fibers.

Cranial and spinal magnetic resonance imaging of both patients was normal.

A previously unreported homozygous single nucleotide deletion was identified in both patients (Supplemental figure – available online). Hypothetically, the mutation c.826delA, introduces a stop codon 21 nucleotides downstream of the deletion site (p.Ser276Valfs\*8).

Although healthy controls have not been screened for the mutation, it was not present in 2 databases, the dbSNP-1000 genomes study, and the HGMD Professional 2013.2, confirming the causative role of the variation in the family. Four different homozygous truncating loss-of-

function mutations were reported previously in the *FAM134B* gene (613114.0001-613114.0004) by Kurth *et al* (2).

Kurth *et al.* report 4 unrelated families with autosomal recessive inheritance of hereditary sensory and autonomic neuropathy (2). The symptoms of our patients started similarly in the first decade, presenting with pronounced motor and sensory impairment in the lower extremities, accompanied by ulcerations, autonomic abnormality, and hyperkeratosis of palms and soles (3). Our electrodiagnostic and histopathological studies, along with the clinical features, were compatible with previous reports (4, 5).

This syndrome of combined mutilating hereditary sensory neuropathy and spastic paraplegia is a very rarely documented autosomal recessive disease. (6, 7). Our patients presented with spastic weakness, which has not been reported previously in HSAN type 2 B. Koy *et al.* proposed that there might be a “Turkish variant” of sensory and autonomic neuropathy that presents with central nervous system involvement.(8) This may also explain the presence of spasticity in our patients.

This report suggests that spasticity can be a feature of *FAM134B*-associated HSAN type II.

### Figure Legend

Figure 1: Clinical presentation and pedigree of FAM 134B

A. Palmar hyperkeratosis of the index man

B. Amputated greater toe of

C. Pedigree: The parents of the patients are first-degree cousins. Only DNA samples from the father, mother, sister, and son were available. The filled arrow shows our index patient, the striped arrow his affected sister. A square indicates a man; a circle a woman; a filled symbol represents 'affected'; a slanted line through a symbol indicates that the individual is deceased.

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**Abbreviations:**

HSAN: Hereditary sensory and autonomic neuropathy

## References

- 1) Ota M, Ellefson RD, Lambert EH, Dyck PJ. Hereditary sensory neuropathy, type II. Clinical, electrophysiologic, histologic, and biochemical studies of a Quebec kinship. *Arch Neurol* 1973;29 :23-37.
- 2) Kurth I, Pamminger T, Hennings JC, Soehendra D, Huebner AK, Rotthier A, Baets J, Senderek J, Topaloglu H, Farrell SA, Nürnberg G, Nürnberg P, De Jonghe P, Gal A, Kaether C, Timmerman V, Hübner CA. Mutations in FAM134B, encoding a newly identified Golgi protein, causing severe sensory and autonomic neuropathy. *Nat Genet.* 2009 ;41:1179-81.
- 3) Murphy SM, Davidson GL, Brandner S, Houlden H, Reilly MM. Mutation in FAM134B causing severe hereditary sensory neuropathy. *J Neurol Neurosurg Psychiatry.* 2012; 83:119-20.
- 4) Bouhouche A, Benomar A, Bouslam N, Ouazzani R, Chkili T, Yahyaoui M. Autosomal recessive mutilating sensory neuropathy with spastic paraplegia maps to chromosome 5p15.31–14.1. *Eur J Hum Genet* 2005; 14: 249–252.
- 5) Koy A, Freynhagen R, Mayatepek E, Tibussek D. Hereditary sensory and autonomic neuropathy with autonomic crises: a Turkish variant of familial dysautonomia? *J Child Neurol* 2012; 27:191-6.
- 6) Christopher JK, Peter JD. HSANs: Clinical features, pathologic classification and molecular genetics. In: Dyke PJ, Thomas PK, eds. *Peripheral Neuropathy*. 4th ed. Philadelphia: Elsevier Saunders; 2005: p 1809-1844.
- 7) Lafreniere RG, MacDonald ML, Dube MP, MacFarlane J, O' Driscoll M, Brais B et al. Identification of a novel gene (HSN2) causing hereditary sensory and autonomic neuropathy type II through the Study of Canadian Genetic Isolates. *Am J Hum Genet.* 2004; 74:1064-73.

8) Thomas P K, Misra V P, King H M, Muddle J R, Wroe S, Bhatia K P, Anderson M, Cabello A, Vilchez J, Wadia N H. Autosomal recessive hereditary sensory neuropathy with spastic paraplegia. *Brain* 1994; 117: 651-659.

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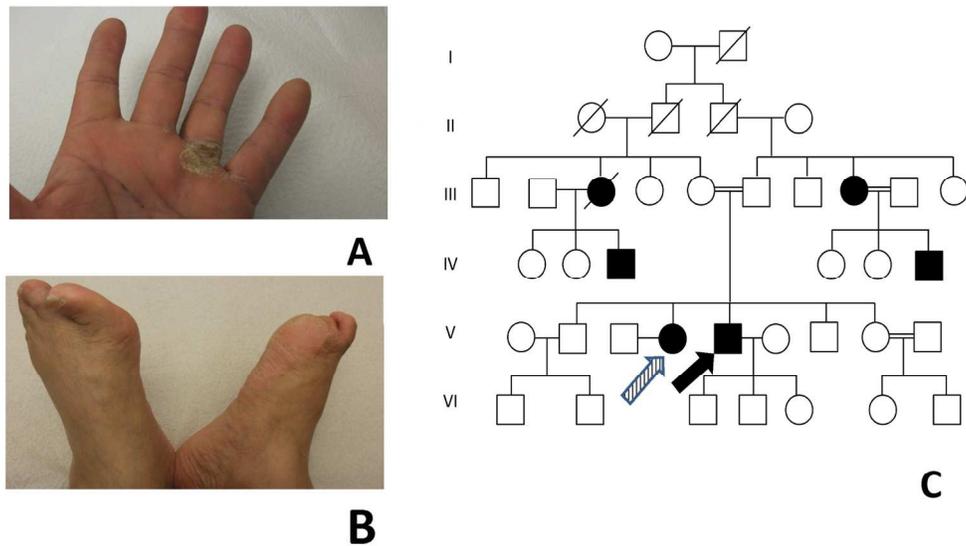


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179x106mm (300 x 300 DPI)

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Sequence 1  
Sequence 2

