

## Late-onset hereditary sensory and autonomic neuropathy type 2B caused by novel compound heterozygous mutations in *FAM134B* presenting as chronic recurrent ulcers on the soles

Sir,

A 38-year-old man from a nonconsanguineous Chinese family presented with a 23-year history of recurrently flared erythema, swelling and pain on the toes and forefeet. Twenty years ago, mutilating ulceration with discharges of sequestrum subsequent to the flared lesion were present on his soles; later the ulceration became painless and healed spontaneously with scars. He had difficulty in walking three years before his presentation and was diagnosed as leprosy and peripheral neuropathy that showed poor response to the treatments. Examination showed deformity of multiple toes and plantar ulceration on the right forefoot [Figure 1a], associated with onychodystrophy, localized plantar hyperkeratosis and scars on both feet. All muscle groups and tendon reflexes were normal. Roentgen-ray revealed pedal acro-osteolysis and resorption of the terminal phalanges and metatarsal bones of the first and second toes on both feet [Figure 1b]. Electromyography revealed mildly slow sensory and motor nerve conduction velocities as well as decreased sensory nerve action potential in the lower limbs [Table 1]; however, no myogenic involvement was present. Nerve biopsy was denied. Laboratory tests including complete blood cell count, biochemical profiles, serum creatine kinase-MB, immunoglobulin, complements and autoimmune antibodies were within the normal range or negative. During a four-year follow-up, progressive osteolysis on the left middle finger was present. The patient showed poor response to palliative treatments.

The proband's 30-year-old brother and 47-year-old sister had similar conditions starting in their second decade; however, both patients were absent for finger-osteolysis till the present submission. All three affected siblings had progressive pedal acro-osteolysis but lacked distal numbness and weakness in the extremities, and their temperature and touch sensation were slightly impaired. The sister had the most severe



**Figure 1a:** Malformation of both feet associated with localized plantar hyperkeratosis and scars, and ulceration on the right forefoot



**Figure 1b:** Radiology reveals acro-osteolysis and resorption of the terminal phalanges and metatarsal bones of the first and second toes

acro-osteolysis. All their siblings including another three normal women had normal birth and normal developmental

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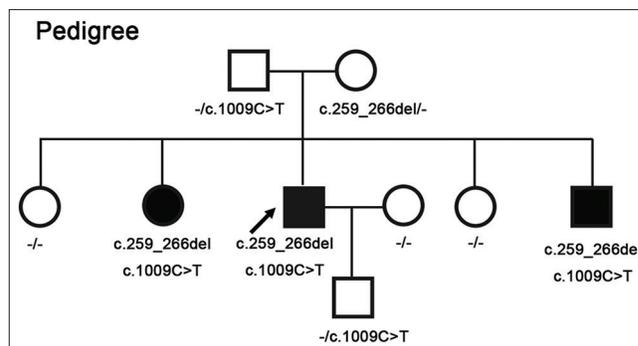
**Table 1: Nerve conduction studies**

Site	Distal latency (ms)	Amplitude	Velocities (m/S)
<b>Sensory nerve conduction study</b>			
Median, R			
Thumb	1.96	13.7 $\mu$ V	45.9
Middle finger	2.34	34.2 $\mu$ V	59.8
Ulnar, R			
Wrist	2.42	27.0 $\mu$ V	49.6
Sural, R			
Sural, L	2.82	7.8 $\mu$ V	46.1
Superficial peroneal nerves			
Superficial peroneal nerve, L	1.92	9.6 $\mu$ V	52.1
Superficial peroneal nerve, R	3.30	8.1 $\mu$ V	42.4
<b>Motor nerve conduction study</b>			
Median, L	3.50	11.34 mV	57.1
Ulnar, L	2.86	13.57 mV	83.9
Peroneal, L	5.95	2.0 mV	50.4
Peroneal, R	4.5	2.24 mV	42.2

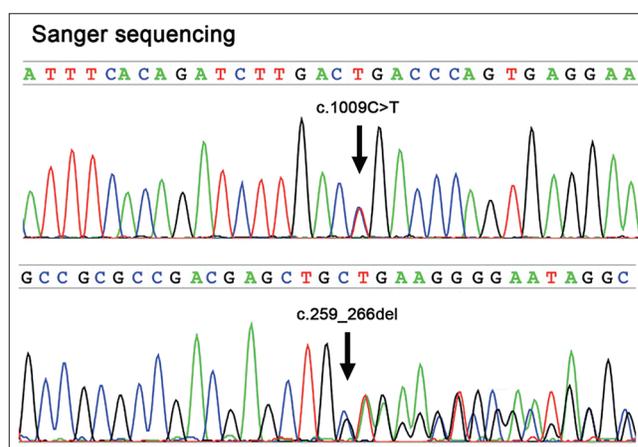
milestones. They had normal sensations, proprioception and vibration, and pupillary reaction to light, and were absent for autonomic symptoms including cough, gastro-oesophageal reflux, postural hypotension, urinary incontinence, excessive sweating, hypesthesia, as well as hypalgesia.

Informed consent was obtained from each participated individual of the family. Whole-exome sequencing using the genomic DNA extracted from peripheral blood of the proband revealed two novel heterozygous mutations in *FAM134B* (c.1009C>T, p.Arg337\*; c.259\_266del, p.Leu87Glufs\*51) which were confirmed by Sanger sequencing [Figures 2a and b]. The other two affected siblings also harbored the same mutations. Their father as well as the proband’s son were carriers of c.1009C>T and their mother was a carrier of c.259\_266del [Figures 2a and b], respectively.

A diagnosis of hereditary sensory and autonomic neuropathy type 2B was confirmed for the family. Compared with other subtypes of hereditary sensory and autonomic neuropathies, patients with hereditary sensory and autonomic neuropathy type 2, with highly variable progression, always have progressively reduced sensation to pain, temperature and touch in limbs with normal mental development and minimal autonomic dysfunction, their muscle weakness and wasting are usually absent or only mild. Hereditary sensory and autonomic neuropathy type 2 is comprised of four subtypes (2A, 2B, 2C and 2D). Hereditary sensory and autonomic neuropathy type 2B is a rare autosomal recessive disorder characterized by early-onset, pronounced sensory and autonomic dysfunction with or without distal motor abnormality.<sup>1</sup> Patients with hereditary sensory and autonomic neuropathy type 2B usually present with chronic acral-osteomyelitis, recurrent infection, leading to painless mutilating ulceration and distal deformity<sup>1,2</sup>



**Figure 2a:** Pedigrees of the described family with hereditary sensory and autonomic neuropathy type 2B. Filled boxes indicate affected individuals with compound heterozygous mutations in *FAM134B* (c.1009C>T, p.Arg337\*; c.259\_266delCTGAGCTG, p.Leu87Glufs\*51). Their mother was a carrier of c.259\_266del and their father as well as the proband’s son were carriers of c.1009C>T, respectively



**Figure 2b:** Sanger sequencing of the *FAM134B* gene (NM 001034850) reveals compound heterozygous mutations (c.1009C>T, p.Arg337\*; c.259\_266delCTGAGCTG, p.Leu87Glufs\*51) in the proband

which, sometimes, may be the main symptoms for the patients presenting to the dermatologist. Other cutaneous associations include excessive sweating, recurrent flares of erythema, nail dystrophy or loss, palmoplantar hyperkeratosis, widespread scarring, hypopigmentation and painful callus and fixed joint deformities.<sup>1,2</sup> However, those symptoms are atypical and nonspecific. When a patient presents with recurrent chronic acro-osteomyelitis and one or more cutaneous features mentioned above, the diagnosis of hereditary sensory and autonomic neuropathy type 2B should be considered and a comprehensive evaluation of neurological manifestations or genetic testing should be performed.

Hereditary sensory and autonomic neuropathy type 2B is caused by recessive mutations of *FAM134B*, that encodes for a cis-Golgi transmembrane protein, also known as JK1, and renamed as reticulophagy regulator 1 by Human Genome Organization Gene Nomenclature Committee (<http://www.genenames.org/>) recently.<sup>3</sup> Mutations in *FAM134B* lead to alterations of the cis-Golgi compartment that is crucial for

the distribution and processing of proteins and lipids. As a result, loss of function in *FAM134B* results in apoptosis and degeneration of sensory and autonomic neurons. Till now, nine mutations in *FAM134B* (c.433C>T, c.471C>T, c.646G>A, c.873 + 2T>C, c.926C>G, c.17del, c.826del, c.1009C>T, c.259\_266del) have been reported underlying hereditary sensory and autonomic neuropathy type 2B; all these mutations are predicted to be loss-of-function.<sup>1-5</sup> These patients are novel entities with a relatively late onset of the symptoms associated with atypical cutaneous alterations, and with novel compound heterozygous truncated mutations in *FAM134B*. Owing to the rarity of hereditary sensory and autonomic neuropathy type 2B, it is necessary to have further study and accumulate more cases to unravel the genotype-phenotype correlation of *FAM134B*-associated hereditary sensory and autonomic neuropathy type 2B and the cutaneous complications in the future.

Treatment strategies are still challenging. Preventive and symptomatic management including padded shoe-wear as well as gait and posture modification may be helpful.

The main limitations of the present work are that we have not studied the mechanisms of present compound heterozygous mutations.

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#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

#### Conflicts of interest

There are no conflicts of interest.

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