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LETTER TO THE EDITOR

SCN11A variant as possible pain generator in sensory axonal neuropathy

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Dear Editor,

Voltage-gated sodium channel (NaV) Nav1.9 is expressed in dorsal root ganglion and their axons and has been shown to play an important role both in regulating sensory neuron excitability and in pain signaling [1]. Heterozygous missense mutations in the SCN11A gene encoding NaV1.9 have been recently described in individuals with painful peripheral neuropathy [2]. It is thought that enhanced NaV channel activity may directly contribute to the pain because some of the missense variants identified depolarize resting membrane potential of dorsal root ganglion neurons through a gain-of-function mechanism, enhance spontaneous firing, and increase evoked firing of these neurons [2]. A recent report on SCN11A variants influencing postoperative pain sensitivity suggests that Nav1.9 can be considered among the main effectors of peripheral inflammatory and neuropathic pain hypersensitivity [1, 3] and should be regarded as an attractive target while searching more effective treatments of pain.

We describe the case of a 48-year-old male was referred to our neurology outpatient clinic with a 1-year history of hypo/anesthesia and paresthesia in both legs, gradually disseminating to his hands. He also suffered from episodes of stabbing pain and electric-like pain in his arms, legs, thorax, and rachis. Physical examination showed normal strength and decreased vibration sense at both ankles and knees, abolished deep tendon reflexes, and hypo/anesthesia in distal segments of the legs and arms. Family and past medical history were unremarkable. Nerve conduction studies (NCS) showed absent sensory action potential in all sensory nerves investigated (median, ulnar, radial, sural, and superficial peroneal nerves, bilaterally) compatibly with an A beta fibers damage. Conversely, all NCS of the motor nerves were unremarkable. Sympathetic skin response gave normal results. Sural nerve biopsy (Fig. 1) showed a significant reduction in density of myelinated fibers affecting the fibers with a larger caliber, aspects of axonal atrophy and degeneration, very rare axonal regeneration clusters, and degenerative aspects of the unmyelinated fibers with collagen pocket. Unmyelinated axons were relatively spared compared with the loss of myelinated nerve. A muscle biopsy excluded epineural lymphohistiocytic deposits, vasculitic signs, and amyloid deposits. A muscle biopsy was unremarkable. Cerebrospinal fluid examination, tests for neurotropic viruses, and immunological screening were all negative. The latter comprised the search for anti-ganglioside antibodies and the ANA, ENA, ANCA screening including Ro/SSA and La/SSB auto-antibodies. Vitamin deficiencies, sarcoidosis, amyloidosis, and other systemic diseases were excluded. In the screening tests, we did not find any onconeuronal antibodies; specifically, anti-CV2 and anti-Hu antibodies were absent. On the other hand, a PET scan performed 2 years after the symptoms onset excluded an underlying neoplasm.

Using a multigene targeted resequencing panel we investigated the coding exons and flanking introns of 113 genes known to be associated with inherited peripheral neuropathies. In the proband, we identified the heterozygous c.2458A > T/p.Asn820Tyr mutation in SCN11A (NM_014139.2) (Fig. 2). The mutation was confirmed by Sanger sequencing and it is predictably damaging when examined in silico using SIFT and FATHMM software.

The novel mutation, affecting a residue conserved throughout the vertebrate and invertebrate proteins, was ultra-rare (MAF 7.731e-5) in ExAc (http://exac.broadinstitute.org/) and with zero homozygous in gnomAD (http://gnomad.broadinstitute.org/). According to ACMG guidelines for Interpretation for Sequences Variants, the c.2458A > T/p.Asn820Tyr variant may be classified as "likely pathogenic"

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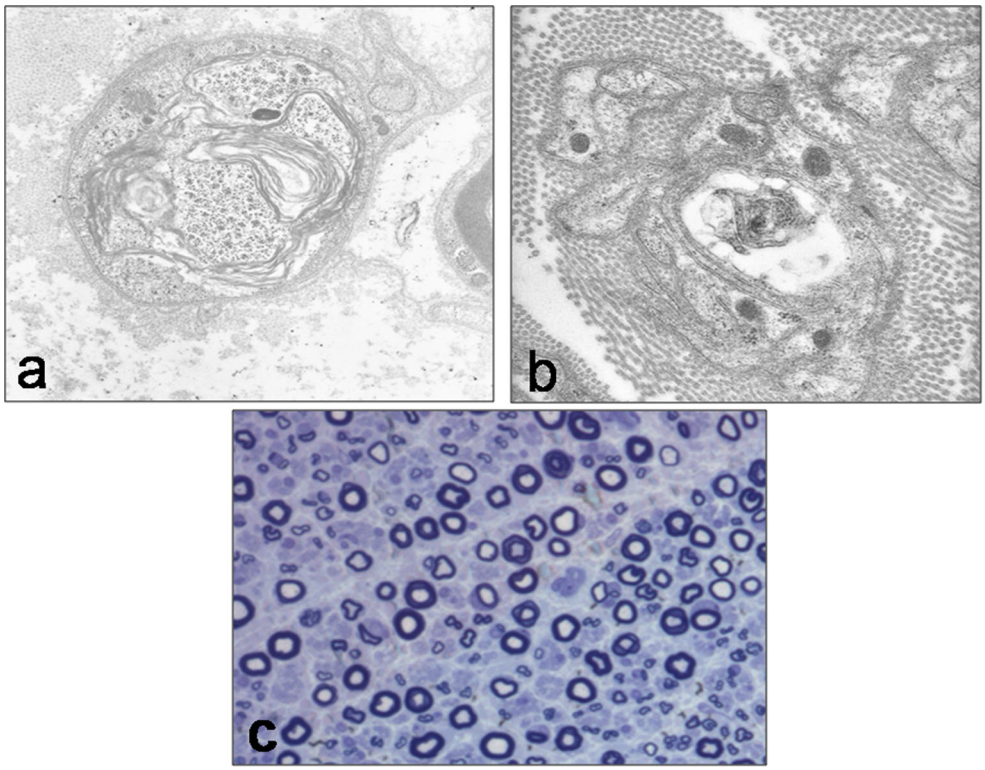

Fig. 1 Sural nerve biopsy. Transmission electron microscopy: **a** active axonal degeneration (o.m. × 7800); **b** degenerative aspects of unmyelinated axons with collagen pockets (o.m. × 21000) Semithin section (toluidine blue, original magnification × 400); **c** reduction of density of myelinated fibers

[4]. Asn820 is located at the end of segment S6 of second transmembrane domain, where previously pathogenic mutations associated with familial episodic pain [3] and loss of pain perception have been described [5]. The genetic test done on the 28-year-old daughter showed the same mutation of the father, although she had no sign and symptoms of polyneuropathy, nor episodes of pain. The clinical history of the parents was negative for neurological diseases or pain syndromes. Duloxetine 60 mg/day, gabapentin up 1200 mg/day, and pregabalin up 300 mg/day were started one after another, without significant symptom relief. Once a molecular diagnosis was reached, we did put the patient on treatment with voltage-gated sodium channel blockers (oxcarbazepine, 900 mg/day) with a significant reduction of the frequency of the sharp pain episodes.

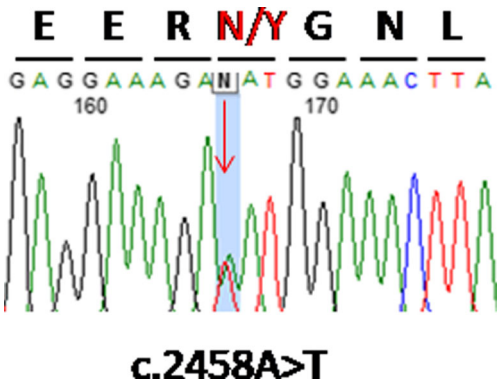

Fig. 2 DNA sequence chromatogram of the region flanking the heterozygous c.2458A > T/p.Asn820Tyr mutation in SCN11A identified in the patient

Voltage-gated sodium channel mutations cause genetic pain disorders that range from severe paroxysmal pain to a congenital inability to sense pain [3, 5]. Previous studies on NaV1.7 and NaV1.8 established clear relationships between perturbations in channel function and divergent clinical phenotypes. By contrast, no clear relationship between channel dysfunction and clinical phenotype has yet emerged from early work on NaV1.9 mutations since Nav1.9 is exclusively expressed in nociceptive neurons. Mutations in the gene encoding NaV1.9 have recently been associated with either loss of pain perception [5] or familial episodic pain and painful peripheral neuropathy [6]. Regardless of clinical phenotype, mutations in NaV1.9 channels show hyperpolarizing shifts in channel activation, which is consistent with a gain-of-function mechanism. Our patient carrying c.2458A > T/p.Asn820Tyr mutation in SCN11A was affected by sensory polyneuropathy with sharp episodes of pain. Although it is not possible to state that this mutation is responsible for the sensory axonal polyneuropathy, the use of a voltage-gated sodium channel blocker resulted in significant clinical improvement, possibly by reducing the spontaneous and evoked firing of the affected dorsal root ganglion and their axons and decreasing the density of sodium channels around the lesion. Search for mutations in SCN11A should be considered in subjects with painful sensory polyneuropathy, irrespective of

the neuropathy type, offering a valid therapeutic opportunity for the relief of pain.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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