



## Paroxysmal itch caused by gain-of-function Na<sub>v</sub>1.7 mutation

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### ABSTRACT

Itch is a common experience. It can occur in the course of systemic diseases and can be a manifestation of allergies or a consequence of diseases affecting the somatosensory pathway. We describe a kindred characterized by paroxysmal itch caused by a variant in *SCN9A* gene encoding for the Na<sub>v</sub>1.7 sodium channel. Patients underwent clinical and somatosensory profile assessment by quantitative sensory testing, nerve conduction study, autonomic cardiovascular reflex, and sympathetic skin response examination, skin biopsy with quantification of intraepidermal nerve fiber density, and *SCN9A* mutational analysis. The index patient, her mother, and a sister presented with a stereotypical clinical picture characterized by paroxysmal itch attacks involving the shoulders, upper back, and upper limbs, followed by transient burning pain, and triggered by environmental warmth, hot drinks, and spicy food. Somatosensory profile assessment demonstrated a remarkably identical pattern of increased cold and pain thresholds and paradoxical heat sensation. Autonomic tests were negative, whereas skin biopsy revealed decreased intraepidermal nerve fiber density in 2 of the 3 patients. All affected members harbored the 2215A>G I739V substitution in exon 13 of *SCN9A* gene. Pregabalin treatment reduced itch intensity and attack frequency in all patients. The co-segregation of the I739V variant in the affected members of the family provides evidence, for the first time, that paroxysmal itch can be related to a mutation in sodium channel gene.

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## 1. Introduction

Itch is a common manifestation in systemic diseases, including malignancies, hematological disorders, uremia, and allergies. When it occurs in patients with neurological diseases involving the somatosensory pathway, as in post-herpetic neuralgia (PHN), multiple sclerosis, or peripheral neuropathies, it is defined as neuropathic itch [6]. Its distribution depends on the underlying disease, being localized, for example, at the distal lower limbs in polyneuropathies or in the dermatome affected by PHN (eg, face or trunk). Neuropathic pain can be variably associated with burning pain that does not necessarily evoke scratching. Itch and neuropathic pain have specific peripheral receptors [6,23] and

distinct neural pathways [16]. In particular, it has been demonstrated that cowhage-induced itch is mediated by both C and A $\delta$  fibers, whereas histamine-dependent itch is mediated by C fibers alone [26]. However, neuropathic itch occurs in a limited percentage of patients with small-fiber neuropathy (SFN) [5], and its pathogenesis is largely unknown.

SFN is a relatively common disorder of A $\delta$  and C nerve fibers characterized by neuropathic pain, usually presenting with burning or sunburn-like quality and length-dependent distribution, and variably associated with autonomic disturbances [21]. Most recently, targeting screening of genes encoding for Na<sub>v</sub>1.7 and Na<sub>v</sub>1.8  $\alpha$  subunits of sodium channels have led to the identification of novel mutations in SFN patients [9,10], opening a new window upon the pathogenesis of neuropathic pain in peripheral neuropathies.

Na<sub>v</sub>1.7, encoded by the *SCN9A* gene, is widely expressed in dorsal root ganglions (DRG) and sympathetic ganglion neurons [29] and their small-diameter axons [25], where it modulates cell

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excitability and channel functioning [7]. Gain-of-function mutations identified in SFN have been found to cause distinct biophysical changes in nociceptors and sympathetic neurons, resulting from impaired slow inactivation, depolarized slow and fast inactivation, and enhanced resurgent currents in the mutant channels [11,12]. Overall, these findings indicate that sodium channel-related painful SFN represents a novel and distinct nosologic condition occurring either in sporadic or, more rarely, in familial cases [9,10,14].

Here we describe a kindred with a novel and remarkably stereotypical phenotype characterized by paroxysmal itch over the trunk and proximal upper extremities, together with reduced intraepidermal nerve fiber (IENF) density, abnormal sensory thresholds, and good response to pregabalin treatment. Each of the 3 affected subjects harbored a variant in *SCN9A* (c.2215A>G; I739V) previously described in 3 unrelated SFN patients whose disorders were sporadic [9,11,12]. Our observations provide evidence, for the first time, of a genetic background for neuropathic itch, and widen the spectrum of sodium channel-related painful disorders.

## 2. Methods

The study was approved by the Ethic Committee of the IRCCS Foundation “Carlo Besta” Neurological Institute, Milan, Italy.

### 2.1. Pain and autonomic symptom questionnaires

In all of the family members, we recorded the score of the Douleur Neuropathique en 4 Questions (DN4; range 0–10) [4], Neuropathic Pain Symptoms Inventory (NPSI; total score is the sum of the subscores corresponding to the mean scores of the items belonging to each of the 5 pain dimension) [24], SFN Symptom Inventory Questionnaire (SFN-SIQ; range 0–12) [2], and the abbreviated Composite Autonomic Symptom Score (COMPASS 31; range 0–100) [30].

### 2.2. Somatosensory thresholds assessment

Quantitative sensory testing (QST) was performed using a panel of 10 parameters encompassing thermal and mechanical stimuli that we considered more relevant to the clinical picture. Tests were performed at the dorsal hand, dorsal foot, and shoulder bilaterally. Pain intensity was scored using an 11-point numeric rating scale (NRS).

#### 2.2.1. Thermal stimuli

Warm detection threshold (WDT) and cold detection threshold (CDT), as well as cold pain threshold (CPT) and heat pain threshold (HPT), stimuli have been assessed. Abnormal sensations including paradoxical heat sensation (PHT) during alternating cold and warm stimulation, errata sensation, thermal allodynia or hyperalgesia, and aftersensation were also recorded. Thermal stimuli were assessed by the Medoc™ device (Medoc™ Thermal Sensory Analyser, TSA-2001, Ramat Yishai, Israel) using a 30- to 30-mm probe with the method of limits, with ramp stimuli of 1 °C/s from 32 °C. Values were compared with available age- and gender-matched normative values. Results above the 95th percentile were considered abnormal.

#### 2.2.2. Mechanical stimuli

Patients underwent assessment of mechanical detection threshold (MDT), including thresholds for pinprick (mechanical pain threshold [MPT]) and pressure pain threshold (PPT), vibratory detection thresholds (VDT), dynamic mechanical allodynia

(DMA), and pain summation to repetitive pinprick stimuli (wind-up ratio [WUR]).

The MDT was measured with a standardized set of modified von Frey hairs (SenseLab, Somedic von Frey Aesthesiometer, Sweden; range 0.26 mN to 490 mN) using the method of limits making 5 threshold determination. The MPT was measured with a standardized set of pinprick stimuli (PinPrick; MRC Systems GmbH, Germany; highest intensity used 512 mN) and WUR by a series of 10 repetitive pinprick stimuli (1/s applied within an area of 1 cm<sup>2</sup>) at the same intensity (256 mN). The VDT was performed with a graded Rydel-Seiffer tuning fork (64 Hz, 8/8 scale) placed over the head of humerus, scapula, ulna styloid process, and internal malleolus. The PPT was performed with a pressure gauge device (FDN200; Wagner Instruments, Riverside, CT, USA) able to exert forces up to 20 kg/cm<sup>2</sup> with increasing ramp of 50 kPa/s.

### 2.2.3. Sensory profile analyses

We created profiles of sensory changes using the z transformation of QST [28] to obtain a z score (mean patient–mean controls)/standard deviation [SD] of controls. We obtained an individual QST profile with normal distribution of the parameters, in which z-score values above 0 indicated gain-of-function (eg, hyperalgesia, allodynia, hyperpathia) and those below 0 indicated loss-of-function (eg, hypoesthesia, hypoalgesia). z Score values around 0 were considered corresponding to the mean of healthy control subjects. Findings were compared with normative reference values from a cohort of 80 age- and gender-matched healthy subjects tested at the same body sites (eg, dorsal hand, dorsal foot, and shoulder) in our laboratory.

### 2.3. Skin biopsy

Skin biopsy was performed using a 3-mm disposable device 10 cm above the lateral malleolus in the territory of the sural nerve. The procedure was performed with local anesthesia (2% lidocaine) under sterile technique. No suturing was needed. Three sections randomly chosen from each specimen were immunostained with polyclonal rabbit anti-protein gene product 9.5 antibody (PGP9.5; Ultracclone), and the innervation density (IENF/mm) was compared with published age- and gender-adjusted normative values [20].

### 2.4. Histamine skin testing

Histamine reaction test was performed by skin prick of 0.1% histamine using a 30-gauge needle at the dorsum of the shoulder in the index patient [15]. Reaction was evaluated during 30 minutes of observation, and the intensity of evoked sensations were measured by the NRS. The wheal and flare response was qualitatively evaluated. The response to mechanical stimuli (10.8 mN, 26 mN, and 490 mN von Frey hairs) (Somedic von Frey Aesthesiometer, SenseLab, Sweden) upon the site of injection and in a surrounding area of 1 to 10 mm was examined.

### 2.5. Cardiovascular reflexes and sympathetic skin response

All tests were performed under standardized conditions. Patients underwent cardiovascular parasympathetic (heart rate response to deep-breathing test and Valsalva maneuver) and sympathetic (blood pressure response to tilt-table testing at 60° during isometric exercise and Valsalva maneuver) function assessment under continuous electrocardiogram and blood pressure monitoring. Manual blood pressure was recorded every minute during the tilt-table testing. Sympathetic skin responses were recorded using a standard technique from the palms and soles [1].

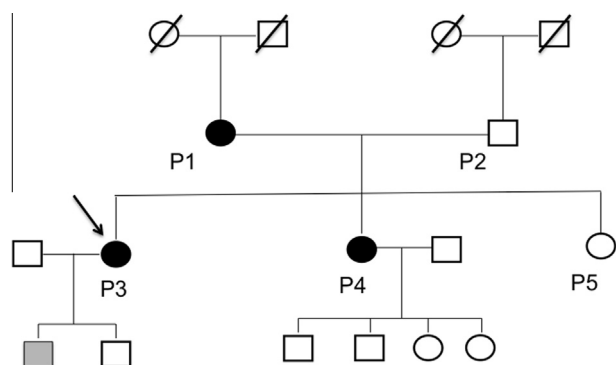
## 2.6. SCN9A mutation analysis

Mutational analysis was performed at the IRCCS Foundation “Carlo Besta” Neurological Institute in Milan, Italy. Genomic DNA was extracted from whole blood using QIAamp DNA Blood Maxi Kit (Qiagen). All coding exons and flanking intronic sequences, and exons encoding 5′ and 3′ untranslated sequences within the complementary DNA, were amplified by polymerase chain reaction (PCR). Primers specific for SCN9A exons were designed using Primer3-input software (version 4.0). Forward primer, 5′CAGACAAATGGCTGACTCCA 3′, and reverse primer 5′GCTGCAGATTCATCTGACATAA 3′, were used to amplify exon 13. Polymerase chain reaction products were purified by ExoSAP-IT (USB-Affymetrix, Cleveland, OH), and sequenced by bidirectional sequencing using the BigDye Terminator v3.1 Cycle Sequencing Kit (Life Technologies, Foster City, CA) on an ABI PRISM 3130 Genetic Analyzer (Life Technologies). The obtained sequences were analyzed with SeqScape v.3 software (Life Technologies). Genomic sequences were compared with reference Nav1.7 complementary DNA (NM\_002977.3) to identify sequence variations, using Alamut Mutation-Interpretation Software (Interactive-Biosoftware). A control panel of DNA from 100 healthy, Dutch, white individuals (200 chromosomes) was screened for all new mutations. The NCBI SNP database, the Human Gene Mutation Database (HGMD), and the 1000 genomes project ([www.1000genomes.org/data](http://www.1000genomes.org/data)) were also screened.

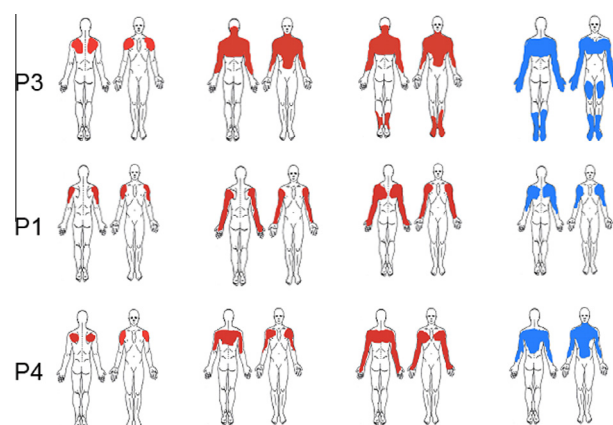
## 3. Results

### 3.1. Clinical description

The index patient was a 37-year-old woman (P3; Fig. 1) was referred to the Neuropathic Pain Clinic of the University Hospital of Udine, Italy, because of intense itch attacks which started at the age of 15 years and gradually worsened in intensity and frequency over time. Itch attacks involved her shoulders, upper back, and upper limbs; occurred more frequently during the summer; and were triggered by environment warmth, hot drinks, and spicy food (Fig. 2). The attacks lasted 2 to 4 hours; their frequency was 3 to 4 per day, and they were followed by episodic flushing at the upper body. At the age of 34 years, she had started complaining of prolonged burning pain that followed the itch attacks. The neurological examination revealed tactile hypoesthesia and hypoalgesia over the shoulders and upper back. The von Frey hair test confirmed the hypoesthesia over the upper back (166 mN; normal value  $0.6 \pm 0.2$ ) and feet (50.0 mN; normal value  $0.8 \pm 0.2$ ) with normal values on the dorsal hands (0.26 mN; normal value  $0.5 \pm 0.1$ ). She scored 10 for the intensity of itch during the attacks



**Fig. 1.** Genealogic tree of the family harboring the I739V variant in SCN9A. Arrow indicates the index patient.



**Fig. 2.** Development of itch attacks and ensuing burning pain over time (red) and distribution of sensory abnormalities (blue) at clinical and quantitative sensory testing in the 3 affected members of the family.

and 8 for the ensuing burning pain. The DN4 score was 7, the NPSI score was 24 (pins and needles = 0; hot/burning = 4; numb = 0; electric shock = 0; evoked pain = 20); the SFN-SIQ score was 11, including 3 autonomic complaints (hot flushing, orthostatic dizziness, sweating); and the COMPASS score was 30. Cardiovascular autonomic function tests were normal; in particular, they did not show orthostatic hypotension or persistent orthostatic tachycardia. Sympathetic skin responses were also normal. Skin biopsy showed reduced IENF density (3.4/mm; fifth percentile 7.1/mm). Histamine test evoked mild warm sensation (NRS = 3) occurring after 186 seconds and lasting 390 seconds, without itch sensation; wheal and skin flare did not occur (anergic reaction).

The mother (P1; Fig. 1) was 65 years at the time of our evaluation. At the age of 55 years, she had undergone cardiac ablation for arrhythmia of unknown origin. At the age of 54 years, she had started to complain of episodic itch attacks over the shoulder, upper back, and upper limbs that were triggered by warmth, hot drinks, and spicy food. The attacks lasted about 2 hours, and their frequency was 5 per month. About 5 years after the onset of symptoms, the patient experienced burning pain and episodic flushing at the upper body and hands after the itch attacks. The neurological examination showed tactile hypoesthesia and hypoalgesia over the shoulders, upper back, and distal legs (Fig. 2). The von Frey hair test confirmed the hypoesthesia over the upper back (81.4 mN; normal value  $0.6 \pm 0.3$ ) and feet (235 mN; normal value  $1.2 \pm 0.4$ ) with normal values at dorsal hands (0.33 mN; normal value  $0.7 \pm 0.3$ ). She scored 8 for the intensity of itch during the attacks and 6 for the intensity of the ensuing burning pain. The DN4 score was 1; the NPSI score was 14 (pins and needles = 0; hot/burning = 3; numb = 0; electric shock = 0; evoked pain = 11), the SFN-SIQ score was 4; and the COMPASS score was 10. Cardiovascular autonomic reflex tests and sympathetic skin responses were normal. Skin biopsy showed reduced IENF density (2.7/mm; fifth percentile 3.2/mm).

The 42-year-old sister (P4; Fig. 1) has started experiencing, at the age of 39 years, itch attacks over the shoulders, upper back, and upper limbs that were triggered by warmth, hot drinks, and spicy food. The attacks lasted about 2 hours, and their frequency was 3 per month. About 3 years after the onset of symptoms, the patient complained of intense burning pain and flushing at the upper body after the itch attacks. The neurological examination revealed mild tactile hypoesthesia and hypoalgesia at the shoulders and upper back (Fig. 2). The von Frey hair test confirmed the hypoesthesia over the upper back (81.4 mN; normal value  $0.6 \pm 0.2$ ), whereas values at the dorsal hand (0.33 mN; normal value  $0.5 \pm 0.1$ ) and feet (0.63 mN; normal value  $0.8 \pm 0.2$ ) were

normal. The patient scored 6 for the intensity of itch during the attacks and 8 for the ensuing burning pain. The DN4 score was 3; the NPSI score was 7 (pins and needles = 0; hot/burning = 0; numb = 0; electric shock = 0; evoked pain = 7); the SFN-SIQ score was 5; and the COMPASS score was 8. Cardiovascular autonomic function tests and sympathetic skin responses were normal. Skin biopsy showed normal IENF density (6.8/mm; fifth percentile 5.7/mm).

The 5-year-old son of the index patient (Fig. 1, gray box) was reported to complain of itch attacks during the summer. The parents did not consent to perform neurological or genetic investigations.

### 3.2. Peripheral neuropathy and systematic diseases screening

All known causes of neuropathy including impaired glucose tolerance, diabetes mellitus, Fabry's disease, celiac disease, human immunodeficiency virus, sarcoidosis, malignancies, and dermatologic and allergic illnesses were ruled out by appropriate screening [21].

### 3.3. Nerve conduction study and quantitative sensory findings

Sensory and motor nerve conduction studies at all limbs were unremarkable in all patients. QST abnormalities were more severe over the upper back than over the dorsal hand and dorsal foot. Recordings demonstrated increased CPT and HPT, and PHT with a remarkably identical pattern in all affected members of the family

(Fig. 3). None of the patients experienced itch or pain during or after the QST examination.

### 3.4. DNA analysis

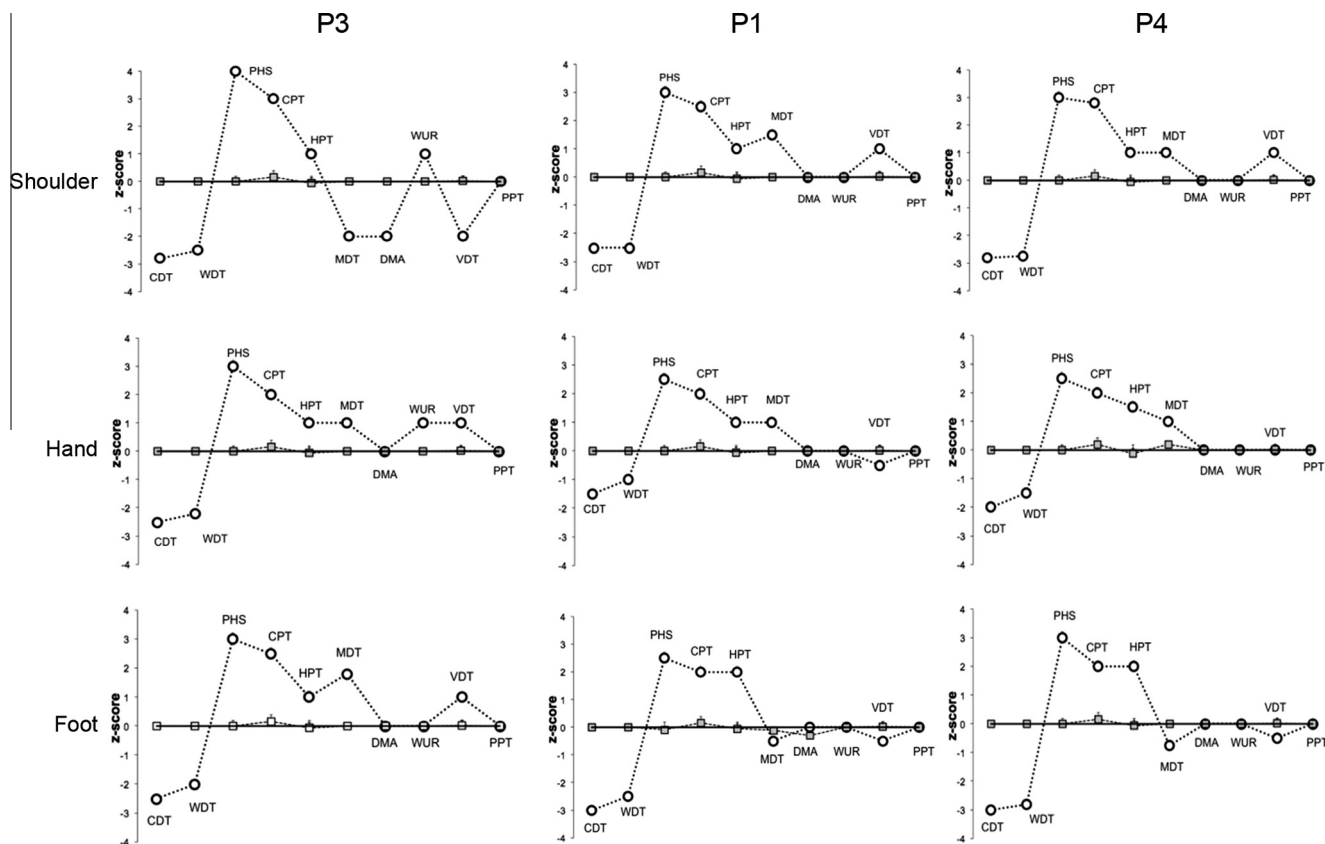
DNA analysis was performed in all available family members (P1, P2, P3, P4, and P5). The index patient and the affected family members (P3 and P4) harbored the 2215A>G I739V substitution in exon 13 of the *SCN9A* gene encoding for Na<sub>v</sub>1.7. The I739V substitution has previously been described in 3 unrelated patients with sporadic painful SFN and dysautonomia [9,11,12]. Previous patch-clamp studies showed that the I739V variant renders DRG neurons hyperexcitable [11] and superior cervical ganglion neurons hypoexcitable [12], providing a cell-electrophysiological basis for painful and dysautonomic symptoms in some patients.

### 3.5. Response to treatment

Pregabalin 300 mg daily provided excellent relief in all patients. As an example, after 2 years, in the index patient the itch attacks lasted only 10 minutes and their frequency decreased to 0 to 1 per day. The intensity of itch was 4 and that of burning pain 2.

## 4. Discussion

We reported a novel clinical syndrome associated with the I739V variant in *SCN9A* gene previously described in 3 unrelated



**Fig. 3.** Individual sensory profile measured by z score (mean patient–mean controls)/standard deviation [SD] of controls) in the 3 affected members of the family. Values above 0 indicate positive phenomena (eg, hyperalgesia, allodynia, hyperpathia); values below 0 indicate negative phenomena (eg, hypoesthesia, hypoalgesia). All data were compared with normative values from a cohort of 80 age- and gender-matched healthy subjects. Value above 2 standard deviations were considered pathological. The line with gray boxes indicates the values in healthy controls. CDT, cold-detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; PHS, paradoxical heat sensation; PPT, pressure pain threshold; WDT, warm-detection threshold; WUR, wind-up ratio.

patients with sporadic length-dependent painful and autonomic SFN. This variant was found to change the biophysical properties of the channel and to alter the excitability of small DRG neurons and the superior cervical ganglion neurons [9,11,12].

The present kindred was characterized by paroxysmal neuro-pathic itch attacks, mainly triggered by warmth and spicy food and followed by transient burning pain. Autonomic disturbances were limited to episodic flushing without evidence of cardiovascular or cholinergic sudomotor dysautonomia. Skin biopsy demonstrated a significant decrease of IENF density at the distal leg, consistent with the diagnosis of SFN in 2 of the 3 patients. The most striking findings were the quality and distribution of the paroxysmal phenomena, dominated by itch attacks with a remarkable proximal distribution presenting with an identical clinical and somatosensory threshold pattern in all of the affected members of the family. The neuropathic nature of itch was suggested by its overlap with impaired superficial sensation (eg, hypoesthesia and hypoalgesia) in the same body area. The co-segregation of the phenotype with the I739V variant confirmed its pathogenicity. Finally, all of our patients showed a good response to pregabalin, a first-line drug for neuropathic pain, in terms of both itch intensity and attack frequency.

Pain and itch reflect 2 different somatosensory modalities that induce different behavioral responses, such as withdrawal to avoid tissue injury and scratching to remove irritants, respectively. These are mediated by primary small DRG or trigeminal ganglion neurons that are highly differentiated by soma sizes, receptor and ion channel expression, receptor fields, and electrophysiological properties [3,16]. Correlation between specific neuron activity and itch sensations in mammals has been widely described [16,19,27,31].

Pruriceptive neurons are a subset of nociceptive neurons whose afferents can elicit itch also in response to pain-inducing chemical, mechanical, and heat stimuli. Mechano-insensitive C-fibers, whose activation by noxious heat and capsaicin induces pain sensation, when activated by histamine, elicit itch sensation [17,19]. Mechano-sensitive A- $\delta$  and C fibers exposed to nonhistaminergic pruritic agents, such as cowhage spicules, induce histamine-independent itch [17,22,23]. Itch induced by pruritic agents such as histamine or cowhage spicule is usually accompanied by slighter and shorter-lasting pricking and burning sensations. Because neurons responsive to pruritic agents can be also activated by painful stimuli, it is uncertain whether their itch mediator function is specific. Recently, a transgenic mouse expressing the transient receptor potential vanilloid type 1 (TRPV1) exclusively in a subset of neurons sensitive to histamine allowed demonstration that capsaicin can evoke itch-related behavior instead of painful sensation [13]. This model, along with others based on silenced transient receptor potential ankyrin 1 and TRPV1 in nociceptors [27], revealed that itch can occur due to the activation of a specific subset of neurons irrespective of the quality of stimuli.

The clinical phenotype of paroxysmal itch in the family described here is different from that previously reported in patients carrying the I739 variant, in whom distal pain and dysautonomia were prominent [9,11,12]. However, 1 of those patients complained of itch at the face, feet, and lower limbs since childhood [9]. Also, in 1 SFN patient of a kindred harboring the L554P variant of *SCN10A* gene, which encodes Na<sub>v</sub>1.8 sodium channel, nocturnal itch was the prominent feature [10]. There is precedent for interfamily differences in the pain phenotype for patients carrying other Na<sub>v</sub>1.7 mutations [8], suggesting that modifier genes, epigenetic factors, or environmental factors may contribute to shaping the precise sensory phenotype in any given family carrying a given Na<sub>v</sub>1.7 mutation.

Notable in the present family was preferential involvement of the proximal arms, trunk, and neck, a pattern usually not seen in peripheral neuropathies. Notable also was the paroxysmal nature

of the symptoms. In terms of both of these features of the clinical phenotype, the present family is similar to the patients with familial episodic pain syndrome caused by gain-of-function TRPA1 mutations [18], which is characterized by episodic pain of the shoulders, upper arms, thorax, abdomen, and cervical spine. It is interesting, in this regard, that TRPA1 is known to be required for some forms of non-histamine-mediated itch [31], and that activity-dependent silencing of fibers expressing TRPA1 with QX-314, which inhibits sodium channels, blocks non-histamine-mediated itch [27]. These observations suggest the possibility of proximal sensory abnormalities (pain in some patients, itch in others) due to hyperexcitability of a subpopulation of sensory neurons, expressing both TRPA1 and Na<sub>v</sub>1.7.

Although the neural circuitry encoding itch in humans remain poorly understood, it is likely that expression and modulation of ion channels in a subset of neurons play key roles [19]. Our observation demonstrates, for the first time, that neuropathic itch can be related to a variant in a gene encoding for a sodium channel subunit involved in the generation of nociception, and suggests that further channels might be involved in other itch phenotypes. The mechanisms underlying the peculiar presentation of itch paroxysms in our family remain unknown, and we cannot exclude the possibility that other gene variants are involved in the pathogenesis of the disorder in the present family. However, our findings widen the spectrum of sodium channel-related painful disorders to include paroxysmal itch, and may provides clues to the pathophysiology of neuropathic itch.

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