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LETTERS

The phenotype of congenital insensitivity to pain due to the $Na_V1.9$ variant p.L811P

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Individuals with congenital insensitivity to pain (CIP) have never felt pain despite possessing an anatomically normal peripheral nervous system and normal intelligence.[1] In 2006/7, biallelic null mutations in the transmembrane voltage-gated sodium channel $Na_V1.7$/*SCN9A* were discovered as a cause of CIP.[2,3] Recently, a new form of CIP was reported in two isolated unrelated cases. Both had recurrent injuries and self-mutilations secondary to feeling no pain, and identical *de novo* heterozygous p.L811P variants in the voltage-gated sodium channel $Na_V1.9$, encoded by *SCN11A*.[4] We have now identified a further case with the identical variant c.2432T>C (p.(L811P)) and report that all have a complex extended phenotype, see Table 1.

The presenting feature in all three was failure to thrive secondary to intestinal dysmotility. Consequent upon this, all had multiple hospital admissions and investigations and two required parenteral nutrition. Abnormal gut peristalsis was found; however, intestinal biopsies were repeatedly normal. All have continuing problems with diarrhoea and/or constipation.

All three have severe pruritus, scratching themselves sufficiently to cause full-thickness skin loss in the cervical area during infancy (see Figure 1). Remarkably this was at the same location as seen in transgenic *Scn11a*-mutant mice.[4] Ulceration and itching may be secondary to hyperhidrosis, as itching only reduced following the use of cyprohepatidine, which lead to a clear reduction in sweating. Hyperhidrosis persisted throughout life, and increased on exertion and raised ambient temperatures. All cried and blushed normally, and none had any abnormal cardiovascular findings nor emotional liability.

Motor milestones were delayed, consequences of a persisting hypotonia and mild muscle weakness. No clinical or significant neurophysiological signs of peripheral neuropathy were observed. Two individuals adopted bizarre dystonia-like postures at the extremes of normal joint positions, awake and asleep.

All have slow wound healing, and patient 3 in particular had *Staphylococci* repeatedly cultured from skin lesions. This apparent selective reduced immunity to staphylococcal infections is also seen in the hereditary autonomic and sensory neuropathy types 4 and 5, caused by biallelic mutations in *NTRK1* and *NGF*, respectively.

No peripheral pain was felt, for example, painless bone fractures and self-amputation of the tongue tip and lips, however, defecation produced significant discomfort. Furthermore, whereas temperature within the normal range could be perceived, variations in temperature such as a gust of cold wind were distinctly unpleasant. These were the only experiences of 'pain' that the individuals describe.

$Na_V1.9$ is strongly expressed in enteric plexus and nociceptor/temperature sensing neurons, which patient biopsies show are present. Therefore the phenotype is mainly caused by nerve dysfunction and not by its absence. The p.L811P variant causes a complex pattern of effects on neuronal subtype activity: it is excitatory in the enteric plexus ($Na_V1.9$ knockout mice have increased intestinal activity[5]), in sweat glands leading to hyperhidrosis and in ano-rectal nociceptors showing these innervations are functioning; but it is inhibitory in most nociceptors and in infective inflammation (which also occur in sensory neuropathies where small unmyelinated nerves are absent). The $Na_V1.9$–CIP phenotype is unique and clearly clinically distinguishable from $Na_V1.7$–CIP, which is accompanied by anosmia but not gastrointestinal motility disturbances or muscle weakness. In contrast to these channelopathies, the *NTRK1*-associated hereditary autonomic and sensory neuropathy type 4 (also termed 'congenital insensitivity to pain with anhidrosis') is characterized by variable degree of intellectual disability and lack of sweat gland innervation, resulting in anhidrosis and recurrent febrile episodes owing to poor thermoregulation. The complex pathophysiological basis of the $Na_V1.9$–CIP is further illustrated by the report of families with a dominant episodic pain syndrome caused by missense SCN11A/$Na_V1.9$ variants and by further missense variants leading to adult onset painful neuropathy.[6,7] All mutations including p.L811P show gain-of-function properties at a channel level and suggest neuron hyperexcitability.[4,6,7] Yet the contrary physiological outcome depending on the variant, that is, increased versus abolished pain perception, remains puzzling. One explanation might be the effect size of the respective mutation on $Na_V1.9$ function that determines the physiological consequences.

This recent insight in human $Na_V1.9$ pathology suggests that channel agonists and antagonists could have multiple therapeutic potentials.

Information regarding the *SCN11A* variant c.2432T>C (p.Leu811-Pro) (NM_014139.2) is available: OMIM Mutation ID 604385.0001 http://omim.org/entry/604385#0001; ClinVar: http://www.ncbi.nlm.nih.gov/clinvar/RCV000074494/

Patient consent had been obtained.

Table 1 A comparison of the phenotype of each individual with congenital insensitivity to pain due to SCN11A/$Na_V1.9$ variant p.L811P

Phenotype	*Patient 1*	*Patient 2*	*Patient 3*
Origin	German	Swedish	Scottish
Mutation in *SCN11A*/$Na_V1.9$	p.L811P, de novo	p.L811P, de novo	p.L811P, de novo
Neuro-cutaneous features			
Peripheral pain felt	No	No	No
Self-inflicted injuries	Yes	Yes	Yes
Predilection of skin ulcers to cervical region	Yes	Yes	Yes
Slow healing wounds	Yes	Yes	Yes
Intolerance of moderate cold and moderate heat, but can sense temperature change	Yes	Yes	Yes
Sweats more than expected for ambient temperature or exercise done	Yes	Yes	Yes
Pruritus	Yes	Yes	Yes
Axon flare response	No	No	Yes
Can produce tears, can blush, but can't be tickled	Yes	Yes	Yes
Gastrointestinal features			
Significant problems with failure to thrive secondary to intestinal dysmotility	Yes	Yes	Yes
Diarrhoea	Yes (episodes of diarrhoea/ constipation)	Yes (continuous Imodium therapy)	Yes (during first 1–2 years of life)
Continuing problems with constipation	?	No	Yes
Abdominal discomfort coinciding with constipation	?	Yes	Yes
Perineal discomfort on passing motion or urine	No	Yes	Yes
Episodic abdominal pain (not coinciding with constipation)	No	No	Yes
Rectal pain on defecation (similar to paroxysmal extreme pain disorder due to $Na_V1.7$ mutations)	No	Yes	Yes
Intermittent parenteral nutrition	Yes	Yes	No
Neurodevelopmental profile			
Delayed motor milestones	Yes	Yes	Yes
Intelligence	Normal (born 2002)	Normal (born 2004)	Normal (born 2007)
Emotions, mood, personality	Normal	Normal	Normal
Neurologic features			
Intact sense of smell	Yes	Yes	Yes
Persisting minor hypotonia and muscle weakness	Yes	Yes	Yes
Adopts postures at extremes of joint movement range when awake (giving an appearance similar to dystonia)	Yes	No	Yes
Adopts postures at extremes of joint movement range when asleep	Yes	No	Yes
Standard nerve conduction studies	Normal	Borderline	Normal
Sural nerve biopsy	Normal	Not done	Not done
Musculoskeletal features			
Multiple painless fractures	Yes	Yes	Yes
Charcot-like arthropathy	Yes	Yes	Yes
Pharmacologic features			
Response of pain episodes to carbamazepine (and some other sodium channel blockers, eg, lamotrigine)	Not done	Not done	No
Response of pruritus to standard anti-histamines	Not done	No	No

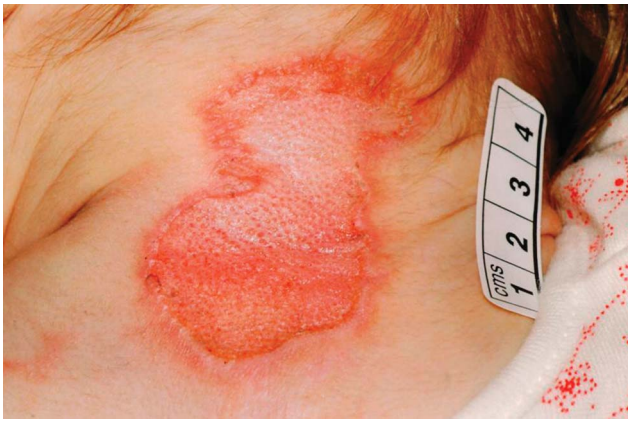

Figure 1 Neck of case 3 with the SCN11A/$Na_V1.9$ mutation p.L811P at the age of 1 year 5 months. A large contiguous healing region is shown. This was caused by the child scratching, mostly while awake. This area was excoriated for 6 months due to intense itching for which hyperhidrosis was a significant contributory factor.

CONFLICT OF INTEREST

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Connexin 26 variant carriers have a better gastrointestinal health: is this the heterozygote advantage?

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Connexin 26 (GJB2) is one of the major factors in human deafness worldwide. On average 1/1000 children is born deaf and the most common GJB2 variant (c.35delG) causes ~40% of cases in Southern Europe. Carriers' frequency for different loss-of-function GJB2 mutations is very high worldwide (up to 3%),[1] suggesting a heterozygous advantage for a global condition or a founder effect.[2] In this light, epidermal thickening in GJB2 carriers[3,4] has been proposed as a possible advantage reducing infections and bacterial invasion through skin.[5,6] Moreover, *in vitro* functional studies demonstrated that the loss-of-functional GJB2 expression provides improved protection against gastrointestinal bacterial pathogens.[7] In particular, enteropathogenic *Escherichia coli* and *Shigella flexneri* may induce a strong selective effect, being the most common causes of diarrhoea. Thus, GJB2 carriers might have an increased resistance to gastrointestinal infectious diseases, as already proposed by Simpson *et al.*[7]

To test this hypothesis, a cross-sectional study involving 203 subjects aged 19–65 years (63% women) was carried out. Subjects (170) were wildtype for the *GJB2* gene, whereas 33 carried one or more variants. The information about diarrhoea episodes and frequency, medical history and covariates (sex and age) was collected. People self-reporting diarrhoea episodes at least once a year were set as cases, whereas the remaining ones were controls (all the subject had similar level of education) (Table 1; Figure 1). Subjects affected by pertinent chronic diseases (Crohn's disease, Intestinal bowel disease and so on) were excluded from the study. Fisher's exact test was performed for case/control proportion in relation to genotype, giving a significant result ($P = 0.007$), with an odds ratio (OR) of 3.21 (95% confidence interval (CI): 1.27–9.24). Although our sample was sex and age homogeneous (Wilcoxon test $P > 0.05$), performing the same analysis separated by sex revealed that females mainly contributed to the finding ($P = 0.0016$). In particular, in our data set women had higher incidence of diarrhoea than men (46% and 36% respectively), and for female GJB2 carriers this proportion dropped to 12.5%, with an OR = 8.33 (95% CI: 1.82–78.03). As regards to the reported frequency per die (range: 0–3), linear regression was applied,