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Painful and painless mutations of *SCN9A* and *SCN11A* voltage-gated sodium channels

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Abstract

Chronic pain is a global problem affecting up to 20% of the world's population and has a significant economic, social and personal cost to society. Sensory neurons of the dorsal root ganglia (DRG) detect noxious stimuli and transmit this sensory information to regions of the central nervous system (CNS) where activity is perceived as pain. DRG neurons express multiple voltage-gated sodium channels that underlie their excitability. Research over the last 20 years has provided valuable insights into the critical roles that two channels, Na_v1.7 and Na_v1.9, play in pain signalling in man. Gain of function mutations in Na_v1.7 cause painful conditions while loss of function mutations cause complete insensitivity to pain. Only gain of function mutations have been reported for Na_v1.9. However, while most Na_v1.9 mutations lead to painful conditions, a few are reported to cause insensitivity to pain. The critical roles these channels play in pain along with their low expression in the CNS and heart muscle suggest they are valid targets for novel analgesic drugs.

Keywords Pain · Dorsal root ganglia · Human mutations · Painful conditions · Voltage-gated sodium channels · Na_v1.7 · Na_v1.9

Introduction

Pain is an important warning system to guard against tissue damage and disease. Pathological pain, however, has no warning value and has huge economic, social and personal costs to society. Chronic pain is a global problem affecting up to 20% of the world's population [9, 50]. Sensory neurons of the dorsal root ganglia (DRG) detect painful stimuli and transmit sensory information to regions of the central nervous system (CNS) that perceive pain. DRG neurons are a heterogeneous population of neurons with distinct functional and histochemical properties [53, 77]. The DRG contains neurons responding to a variety

of non-noxious stimuli (such as proprioceptors and low-threshold mechanoreceptors) as well as those responding to noxious stimuli (nociceptors).

Inflammation and nerve injury sensitise DRG neurons and result in decreased pain thresholds and/or intense pain. This can be in part due to increased voltage-gated sodium channel (VGSC) activity resulting in increased excitability of DRG neurons [8, 104]. VGSCs consist of pore-forming α -subunits and auxiliary β -subunits. There are ten cloned α -subunits and 4 β -subunits. The β -subunits modulate the localisation, expression and functional properties of α -subunits [12]. Each α -subunit is composed of four homologous membrane-spanning domains (DI-DIV). Each domain consists of six transmembrane segments (S1-S6) [12]. Different α -subunits have distinct electrophysiological and pharmacological properties [12, 104], and DRG neurons express multiple α -subunits that are essential to their ability to fire action potentials [104].

This review aims to clarify the roles of two VGSC channels expressed selectively, though not exclusively, in primary sensory neurons in pain pathways, and in the light of evidence from genetic mouse models and mutations in man. We discuss the usefulness of these channels as potential drug targets, and suggest that while our present understanding of function has grown more complex, targeting these channels either alone or

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in combination may still provide a strategy for analgesic development, potentially even for chronic use.

VGSC as targets for analgesic drugs

There are two reasons why VGSCs are attractive targets for analgesic drugs. Firstly, VGSCs are required for the firing of action potentials in DRG neurons; therefore, blocking their activity will reduce pain signalling in painful conditions even if they were not the primary or only contributor to increased firing. For example, sensitisation of primary transducing channels, like the transient receptor potential (TRP) channels, is often involved in many forms of pathological pain [11, 90, 105]. This sensitisation will lead to greater generator potentials in sensory nerve terminals. However, since VGSCs are required to initiate an action potential in nerve terminals and to allow conduction into the CNS, an effective VGSC blocker can still cancel out the effect of the sensitised TRP channels in nerve terminals.

Secondly, a few of the VGSC α -subunits expressed in DRG are either exclusive to or enriched in DRG neurons that signal pain, with little expression in other DRG neurons, the CNS, skeletal and heart muscles. Blockers for these subunits would therefore be expected to produce analgesia without detrimental side effects. DRG neurons express many of the cloned α -subunits [104]; however, three subunits ($\text{Na}_v1.7$, $\text{Na}_v1.8$ and $\text{Na}_v1.9$) meet the above criteria. Not surprisingly, many pharmaceutical companies are developing and testing subunit specific $\text{Na}_v1.7$, $\text{Na}_v1.8$ and $\text{Na}_v1.9$ blockers as analgesics [38, 128].

The three α -subunits differ in their biophysical properties that determine their role in neuronal excitability [104]. The $\text{Na}_v1.9$ channel activates over a negative range of membrane potentials close to the resting potential and generates a persistent current. Evidence suggests that it is powerfully regulated by G protein pathways, in a unique way. Therefore, when it is activated, it contributes to setting the resting membrane potentials of neurons expressing it [23]. $\text{Na}_v1.7$ generates a transient Na^+ current, but has a relatively slower rate of inactivation near the resting potential (slow closed-state inactivation) allowing the channel to generate persistent currents and making it a so-called threshold channel [22, 25]. $\text{Na}_v1.8$ has a relatively depolarised activation voltage (~ -20 mV) compared with $\text{Na}_v1.7$ and $\text{Na}_v1.9$ [2, 104]; thus, $\text{Na}_v1.8$ activation comes after and perhaps subsequent to the activation of $\text{Na}_v1.9$ and $\text{Na}_v1.7$ channels. Nonetheless, $\text{Na}_v1.8$'s depolarised inactivation and more rapid recovery from inactivation allow it to contribute to repetitive firing, for example [104]. This review will focus on $\text{Na}_v1.9$ and $\text{Na}_v1.7$ subunits since their biophysical properties allow them both to influence pain thresholds through setting the membrane potential and action potential threshold in DRG neurons.

Role of $\text{Na}_v1.7$ in pain

$\text{Na}_v1.7$ was cloned from PC12 cells in 1997 [118]. At that time, $\text{Na}_v1.8$ and $\text{Na}_v1.3$ channels were already under the spotlight and their role in pain was actively being investigated. $\text{Na}_v1.8$ was cloned in 1996 and its strong expression in medium and small sensory neurons (the sizes of most nociceptors) made it the best and most obvious target for analgesic drug development [2]. The $\text{Na}_v1.8$ knockout mouse was reported 3 years later and although it showed a pain deficit, its phenotype was compromised by a compensatory up-regulation of $\text{Na}_v1.7$ [3] with clear functional consequences [3, 89]. However, knockdown of $\text{Na}_v1.8$ by antisense oligonucleotides in adult rats inhibited neuropathic pain [75, 129]. The difference could be due to the timing of the deletion (embryonic versus adult) or the animal model used (mouse versus rat). In contrast to $\text{Na}_v1.8$, the expression pattern of $\text{Na}_v1.3$ does not suggest it would be a useful drug target. $\text{Na}_v1.3$ is expressed throughout the nervous system and its expression is highest during embryonic development and decreases postnatally [121]. However, $\text{Na}_v1.3$ is the only channel that is re-expressed in DRG following nerve injury and diabetes [122]. This made it a potentially viable target for analgesics. However, mice lacking $\text{Na}_v1.3$ do not show any deficits in pain phenotype [92].

$\text{Na}_v1.7$ became the focus of the pain field in 2004 with the publication of two papers [91, 125]. The first paper identified a mutation in *SCN9A* (the gene coding for $\text{Na}_v1.7$) as the cause for a rare inherited pain condition known as primary erythromelalgia (PEM). PEM symptoms start at early age with episodes of pain in the extremities (usually in the feet) that are triggered by exposure to heat or walking [125]. The second paper reported the complete absence of inflammatory pain in a conditional mouse lacking $\text{Na}_v1.7$ in most nociceptors [91]. The conditional ablation in nociceptors was achieved using a Cre driver mouse line where Cre is expressed by the $\text{Na}_v1.8$ promoter [113]. The complete loss of all inflammatory pain and mechanical pressure after ablation of $\text{Na}_v1.7$ in nociceptors [91] excited the pain field and stimulated drug discovery programmes at several pharmaceutical companies [38, 128]. A conditional mouse was generated because global deletion of $\text{Na}_v1.7$ in mouse proved to be lethal [91]. Global knockout pups were born alive but failed to feed and died within 24 h. Hand feeding and special husbandry arrangements allow $\text{Na}_v1.7$ global KOs to survive to adulthood [49]. Inducing $\text{Na}_v1.7$ ablation in adult mice causes pain deficits without detrimental effects [107].

Remarkably, the symptoms of PEM patients complemented the phenotype of the conditional $\text{Na}_v1.7$ null mice. While pain can be triggered by mechanical pressure on the feet (walking and exercise), conditional null mutants showed a complete loss of pain to mechanical pressure. While PEM patients showed signs of inflammatory pain (heat,

redness and occasionally swelling of the feet), conditional null showed a complete loss of inflammatory pain. This helped support the hypothesis that blocking $\text{Na}_v1.7$ in humans would significantly reduce pain signalling. However, the mouse study raised significant questions. Firstly, is the role of $\text{Na}_v1.7$ in pain signalling in humans as critical as it is in mice, or in other words, would the loss or block of $\text{Na}_v1.7$ in humans lead to the all or none loss of pain seen in mice? Furthermore, if this is the case, then would the loss or block of $\text{Na}_v1.7$ in humans result in lethality (as it did in mice)? These questions were critical for the validity of $\text{Na}_v1.7$ as a drug target. These questions were answered in 2006 when it was reported that a loss of function mutation in *SCN9A* causes complete insensitivity to pain (CIP) [19]. In CIP patients, perception of non-noxious touch and warmth is not affected, whereas perception of noxious heat, pressure and injury pain is completely lost. CIP patients confirmed that $\text{Na}_v1.7$ plays as a critical role in pain signalling in humans as it does in mice. Importantly, loss of $\text{Na}_v1.7$ did not lead to lethality nor any significant disability (CIP patients are anosmic due to the expression of $\text{Na}_v1.7$ in the olfactory epithelia [135]). A second heritable painful condition was mapped to a gain of function mutation in *SCN9A* in the same year (2006). Paroxysmal extreme pain disorder (PEPD, initially known as familial rectal pain), was found to be caused by a gain of function mutation in the $\text{Na}_v1.7$ channel [45]. The four papers between 2004 and 2006 provided very strong evidence that $\text{Na}_v1.7$ is a critical player in pain signalling, catapulting it to the top of the list of analgesic drug targets. Since then, human geneticists have identified scores of mutations causing PEM, PEPD, CIP and small fibre neuropathy (SFN).

Primary Erythromelalgia

Primary erythromelalgia is an autosomal dominant condition caused by a mutation in the *SCN9A* gene. The condition was first mapped to *SCN9A* in 2004 by Yang et al. [125]. The proband suffered from bilateral episodes of burning pain in their hands and feet that started during their childhood and continued throughout their life. During the attacks, the feet and hands became warm and red. The pain episodes were triggered by exercise or exposure to heat. The proband had the nonsense mutation L858H which is located in the second domain, Fig. 1. Characterisation of the channel's biophysical properties showed that the mutation shifted the activation voltage about 12 mV in the hyperpolarising direction resulting in a reduced threshold for channel opening and thus increased excitability [24]. Since the first report, several mutations have been reported that cause PEM, listed in Table 1 in chronological order. Symptoms appear early in life although late onset cases have been reported [16, 21]. All PEM mutations cause similar changes to the biophysical properties of $\text{Na}_v1.7$,

involving a shift of the activation voltage to hyperpolarised potentials [30], and where the magnitude of the shift seems to affect the severity of the symptoms [55]. Furthermore, PEM mutations tend to cluster in domains I and II of the channel protein, Fig. 1.

Treatment for PEM patients includes avoidance of the conditions that trigger pain (i.e. heat and physical pressure on the feet). Patients typically resort to foot lifting, cooling feet by fans or immersing them in water or iced water to reduce or relieve pain. Although immersion in cold water is effective for mild cases, it can result in ulceration and maceration of foot skin leading to infection [19, 116]. Recently, it has been reported that behavioural therapy reduced dependence on water immersion in PEM patients [67]. There is no consensus on pharmacotherapy. Among effective drugs are non-selective sodium blockers (lignocaine, mexiletine and carbamazepine) [82, 116] which have been shown to inhibit $\text{Na}_v1.7$ [120, 133].

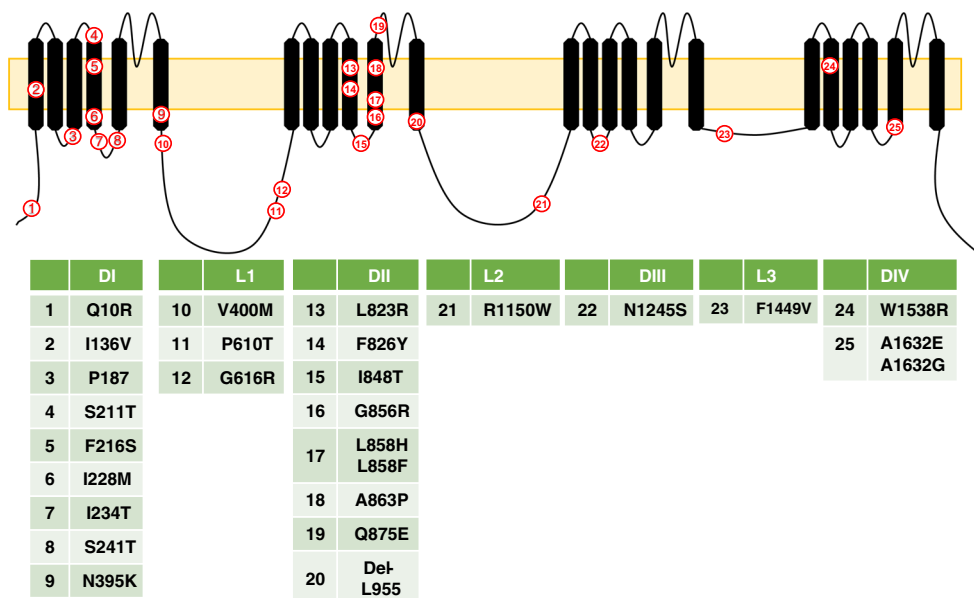
Paroxysmal extreme pain disorder

Paroxysmal extreme pain disorder (PEPD, formerly known as familial rectal pain syndrome), is caused by gain of function mutations in *SCN9A* that alter the biophysical properties of the $\text{Na}_v1.7$ channel [45]. There are several similarities between PEPD and PEM. Both are autosomal dominant conditions with symptoms starting early in childhood (PEPD is observed in infants [17]). PEPD is characterised by episodes of severe burning pain in the rectal, ocular and mandibular areas accompanied by flushing of the skin. Pain in PEPD patients is triggered by otherwise innocuous mechanical stimulation (defecating, chewing and yawning) and warmth of the affected areas. However, functional characterisation of mutant $\text{Na}_v1.7$ channels showed that they have normal activation voltages (unlike PEM mutations). In contrast, PEPD mutations cause a depolarising shift in inactivation voltages with incomplete channel inactivation, leading to a persistent current and increased excitability [7, 45, 119]. Table 2 lists reported *SCN9A* mutations that are found in PEPD patients. PEPD mutations tend to cluster in domains III and IV of the channel protein, Fig. 2. Despite the severity of the pain, PEPD patients responded well to the anti-epileptic drug carbamazepine [117].

Heritable small fibre neuropathy

Small fibre neuropathy (SFN) is caused by damage to thinly myelinated and unmyelinated nerve fibres. SFN is often characterised by late onset, bilateral burning pain to the hands and feet. SFN is also associated with disturbances to autonomic functions like sweating, dryness in the eyes or mouth and

Fig. 1 Topological representation of *SCN9A* mutations that cause PEM. A VGSC α -subunit consists of four homologous domains (DI–DIV). Each domain consists of six transmembrane segments. Three intracellular loops (L1–L2) connect the four domains. Note that most mutations are localised to domains I and II. Structures are not drawn to scale



disturbance to bowel and bladder functions [117]. Autonomic symptoms are not reported in both PEM and PEPD. Diagnosis is usually confirmed by a decrease in intra-epidermal fibre density (IDFD) in skin biopsies. Several conditions can cause SFN, and these include diabetes and autoimmune disease [52, 112]. About 50% of SFN cases are idiopathic, with no obvious aetiology [112]. The dominant pattern of inheritance of SFN in some cases of idiopathic SFN suggested mutations in a single gene [52, 112]. Mutations in the three peripheral VGSCs, $Na_v1.7$ [10], $Na_v1.8$ [44] and $Na_v1.9$ [63] channels, have been found in heritable SFN cases.

Characterisation of $Na_v1.7$ channels in SFN patients, listed in Table 3, showed that they would cause hyperexcitability [43, 62]; however, it is not clear how this leads to a small fibre neuropathy and why it is of late onset. $Na_v1.7$ channel mutations linked to SFN are not localised to a particular region within the channel but many are clustered in the first intracellular loop between domains I and II, Fig. 3. Recently a clinical trial has found lacosamide to be efficacious in reducing pain and well-being of SFN patients with *SCN9A* mutations [27]; however, the effect was linked to subset of *SCN9A* mutations [74].

Role of $Na_v1.7$ in epilepsies

Although the expression of $Na_v1.7$ in the human brain is poorly characterised, there is emerging evidence that $Na_v1.7$ plays some role in modulating excitability in the brain. It is known that CIP patients suffer from the loss of the sense of smell due to expression of $Na_v1.7$ in the olfactory epithelia [135] and a patient with the PEM mutation N1245S displayed high olfactory sensitivity [54]. However, CIP patients are not reported to suffer from brain-related symptoms. Nonetheless,

several papers have recently reported mutations in *SCN9A* in patients with various types of epilepsies, Table 4. These mutations are mostly localised to the DI–DII part of the channel, Fig. 4. The above suggests that while a loss of $Na_v1.7$ function has no detrimental effect on the brain, altered or increased $Na_v1.7$ function does. Therefore, further research is needed to provide insights onto the type of cells that express $Na_v1.7$ (types of neurons? any in glia?) in the brain. Furthermore, knock-in models will help to explore how the mutations cause epilepsy rather than act as modifiers to changes in other genes (e.g. *SCN1A*, *SCN2A* and *SCN3A*). Finally, it is intriguing that a few mutations (e.g. Q10R) cause PEM in some patients, and epilepsy in others. This may suggest that variations in the functional expression of other genes or epigenetic changes influence the biological consequences of mutations in $Na_v1.7$.

Complete insensitivity to pain

Complete insensitivity to pain is characterised by loss of all pain sensations throughout patient's life. *SCN9A* loss of function mutations cause an autosomal recessive CIP [19, 34]. Several mutations have been identified, and most are non-sense mutations causing truncated proteins, Table 5. Most of the mutations are located within domains I and II, Fig. 5. There is recent evidence that the CIP phenotype involves changes to endogenous opioids [87, 97]; however, this was not observed in a rat null model [14].

Role of $Na_v1.9$ in pain

$Na_v1.9$ (gene name *SCN11A*) is a tetrodotoxin-resistant (TTX-r), so-called persistent Na^+ current, with clear evidence for

Table 1 *SCN9A* mutations that cause PEM in order of their publication

Mutation	Notes on effect	Ref
L858H		[125]
I848T		[33, 125]
L858F		[33]
N395K		[33]
F216S		[33]
P610T		[33]
R1150W		[33]
F1449V		[29]
S241T		[86]
A863P		[59]
I136V	Late onset + reduced intradermal fibre density	[78]
A1632E	Causes PEM and PEPD-like symptoms	[39]
Q10R	Late onset	[55]
V400M	Carbamazepine responsive	[46]
L823R	Shifts fast inactivation to more negative potentials, unusual in PEM	[76]
S211P		[40]
I234T	Sitting and heat trigger pain, one of the largest shift in activation voltage.	[1]
G616R		[16]
Del-L955	Large hyperpolarised shift in activation voltage with a large shift in inactivation voltage in the same direction leading to mild symptoms	[15]
I228M		[41]
Q875E	Severe pain	[110]
Q10K		[72]
V1316A		[42, 123]
A1746G		[21]
W1538R	Described as W1550R in [26]	[21]
A1632T		[35]
L245 V	Incomplete fast inactivation but no shift in activation voltage	[37]
A1632G		[126]
G856R	PEM with impaired limb development	[115]
F826Y		[124]
P187L		[131]
N1245S		[54]

functional expression in nociceptive primary sensory neurons in the dorsal root ganglia (DRG) and trigeminal (e.g. [6, 23]), and the *AH* cells of the myenteric plexus in the gut [18, 102]. The human clone (first named as *SCN12A*, 73% identical with rat *SCN11A*) [68] had initial reported expression in the placenta, spleen, small intestine, spinal cord and brain (potentially neurons and glia). In primary sensory neurons, it has been associated with nerve endings in the tooth pulp and cornea using immunohistochemical methods, and evidence suggests it is found distributed along IB4⁺ axons in the sciatic nerve (e.g. [28, 47, 95]); furthermore, the channel have been located to gut afferents [60, 61] and also to the bladder [101] using electrophysiological methods in gene knockout mice.

The functional properties of the channel currents were first identified in Na_v1.8 knockout mouse sensory neurons,

because under these circumstances, the channel generates the only tetrodotoxin-resistant (TTX-r) Na⁺ current [23, 84]. The channel produces a Na⁺ current in sensory neuron cell bodies that has ultra-slow activation and inactivation kinetics. It gives rise to a persistent, non-inactivating current operating over the negative portion of its activation membrane potential range, allowing it to act as a ‘threshold channel’, and to contribute to setting the membrane potential. Its unusual kinetic properties and negative activation range produce ‘plateau potentials’ that amplify applied or transduced sub-threshold depolarisations and massively prolong them in duration (Fig. 6). It is worth noting that Na_v1.9 has activation kinetics that are too slow to directly contribute to impulse firing.

Intracellular dialysis of the non-hydrolysable GTP analogue, GTP- γ -S, upregulated the Na_v1.9 current with no

Table 2 *SCN9A* mutations that cause PEPD in order of their publication

Mutation	Notes on effect	Ref
R996C		[45]
V1298D		[45]
V1298F		[45]
V1299F		[45]
I1461T		[45]
F1462V		[45]
T1464I		[45]
M1627K		[45]
A1632E	Channel displays properties of PEM and PEPD	[39]
G1607R		[17]
I228M	Produces PEM-like symptoms as well	[41]
R185H		[85]
L1612P		[114]
V1740L	Patients suffer from headache	[66]

changes in current kinetics, recorded in voltage-clamp. It was also found that at a membrane potential of near -60 mV, functional upregulation of the current can cause sensory neurons to fire rhythmically and spontaneously, at low frequency (Fig. 6) [6]. The current could be upregulated following the activation of ATP receptors, deduced to be P2Y, operating through a probable Gq/11 pathway and PKC [5, 6], and such a pathway has later been confirmed to be a contributor to modifying the firing properties of gut afferents.

There are several mouse knockouts of *SCN11A* reported in the literature and these have been associated with an elimination of the GTP- γ -S-upregulated current in primary sensory neurons [94] and a complementary reduction in forms of inflammatory pain following exposure to PGE2 [4] and including the formalin and CFA tests [99]—consistent with a role of $\text{Na}_v1.9$ in inflammatory pain in both the skin and gut. A likely role for $\text{Na}_v1.9$ in the control of normal gut motility, attributable to altered plexus function, seems consistent with the effects of

mutation in human carriers and gain of function is associated with constipation (e.g. [69]). With these facts in mind, it may be possible to understand the defects in pain signalling found in humans with rare, heritable mutations in *SCN11A*.

Painful and painless $\text{Na}_v1.9$ channelopathies

About 20 mutations have been reported for *SCN11A*, Table 6. All follow a dominant inheritance pattern. Most mutations have been confirmed to lead to a gain of function. No loss of function mutations have been reported to date which could be because such mutations cause mild or no effect on pain signalling in humans (given the phenotype of knockout mice, it is very unlikely that human loss of function mutation causes lethality). It is also possible that the loss or reduction of inflammatory pain may mean such individuals are unlikely to have a reason to visit the doctor!

The persistent nature of $\text{Na}_v1.9$ currents and the negative activation voltage dependence make the channel functionally unique. It is proposed to act as a threshold channel in peripheral nociceptors, so gain of function mutations associated with facilitated activation would be expected to give rise to painful neuropathy, because the threshold for action potential generation is reduced. Indeed, *SCN11A* mutations result in two painful conditions, familial episodic pain [65, 80, 93, 130] and painful small fibre neuropathy [48, 57, 63]. In familial episodic pain, painful episodes centre on regions on the arms and legs; in addition, there are age-related decreases of pain, suggesting real age-related changes in gene expression. Painful episodes (lasting 10 s of minutes) are associated with rainy days, cold temperature and commonly also fatigue; some are associated with gut motility symptoms. Further, drugs acting as NSAIDs or anti-pyretics, such as ibuprofen, appear to be able to ameliorate these symptoms. Patients with *SCN11A*-related small fibre neuropathy experience pain, tingling and numbness in their arms and legs. Patients may

Fig. 2 Topological representation of mutations that cause PEPD in the α -subunit of $\text{Na}_v1.7$. Note that most mutations are localised in L3 and domains III and IV. Structures are not drawn to scale

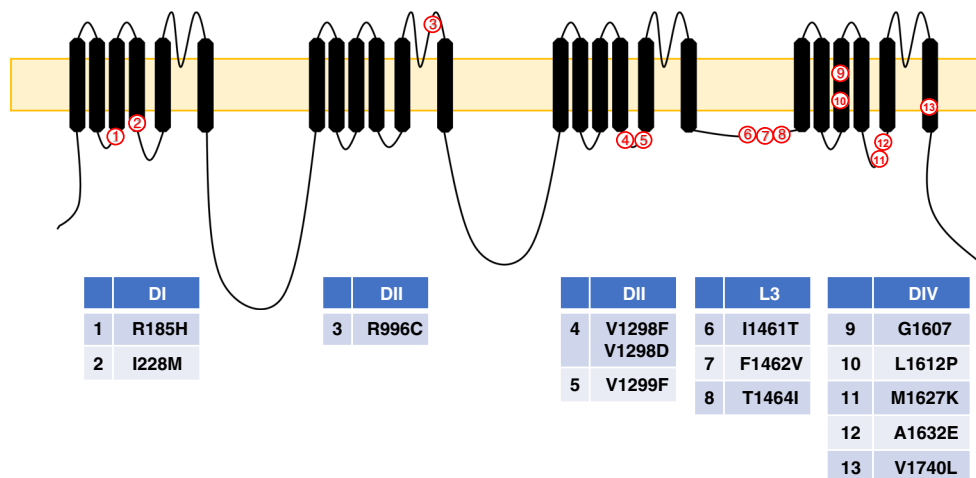


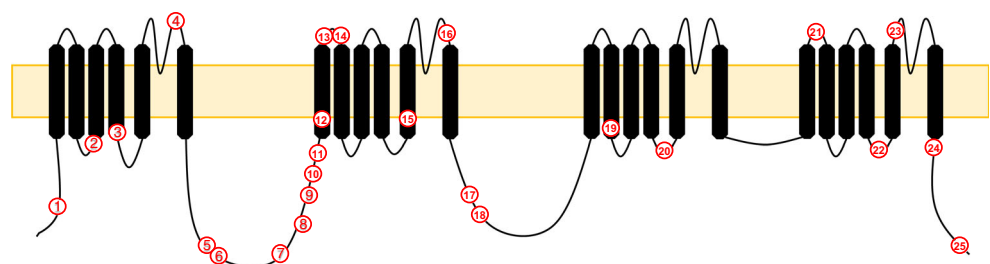
Table 3 Mutations that cause *SCN9A*-linked SFN in order of their publication

Mutation	Notes on effect	Ref
I720K D623N M932L V991L R185H I228M M1532I I739V G856D	Mutations have various impacts on channel properties but all lead to hyperexcitability. Shifts activation voltage to more negative potentials. Shifts fast inactivation to more positive potentials. Causes hyperexcitability.	[43] [62]
K40E N336T V518F E519K T531N A678E F710V W719C I720K P756T M757W Y990C M1230T R1279Q R1620L Y1657S V1754F D1971V	Functional properties uncharacterised	[36]

experience diarrhoea which is consistent with expression of $Na_v1.9$ in the gut [130].

Surprisingly, a few *SCN11A* gain of function mutations cause a complete insensitivity to pain [70, 79, 98]. Several

Fig. 3 Topological representation of *SCN9A* mutations that cause heritable SFN. Most mutations associated with SFN are found clustered around L1. Structures are not drawn to scale



DI		L1		DII		L2		DIII		DIV	
1	K40E	5	V518F	12	I739V	17	Y990C	19	M1230T	21	M1532I
2	R185H	6	E519K	13	P756T	18	V991L	20	R1279Q	22	R1620L
3	I228M	7	T531N	14	M757W					23	Y1657S
4	N336T	8	D623N	15	G856D					24	V1754F
		9	A678E	16	M932L					25	D1971V
		10	F710V								
		11	I720K								

Table 4 Mutations that cause epilepsies in order of their publication

Mutation	Notes on effect	Ref
N641Y	Knock-in mice exhibit significantly reduced thresholds to electrically induced seizures.	[109]
Q10R	From patient with febrile seizures plus	[13]
G327E		[127]
G327E	From twin patients with idiopathic focal epilepsy with Rolandic spikes	[81]
I775M	From patient with febrile seizures	[32]
R429C	From patient with febrile seizures plus	[32]
A442T	From patient with genetic epilepsy with febrile seizures plus	[32]
Y1958C	From patient with genetic epilepsy with febrile seizures plus	[132]

possible explanations for how enhanced channel function leads to reduced neuronal excitability have been suggested [31], although arguments concerning modifications of channel-gating kinetics as the primary cause seem incomplete and are based on voltage-clamp recordings whose interpretation may not be straightforward. It is thought that increased activation/inactivation-gating overlap (or window current) depolarise the $\text{Na}_v1.9$ expressing neurons. This prolonged depolarisation causes rapidly gating Na^+ channels (e.g. $\text{Na}_v1.7$ and $\text{Na}_v1.8$) to enter the inactivated state [64]. Since these channels underpin action potential generation and propagation, the depolarizing block of $\text{Na}_v1.7$ and $\text{Na}_v1.8$ in nerve endings leads to an overall decrease in excitability. It was noted that the mutations that lead to CIP are those that produced the largest shift in the activation threshold of the channel, whereas those that lead to familial episodic pain and painful small fibre neuropathy cause smaller shifts, Table 6 [31]. Also of note, *SCN1A* CIP mutations are all localised to transmembrane segment 6, Fig. 7. However, several issues are difficult to reconcile with the above explanation for the painless phenotype. Firstly, $\text{Na}_v1.9$ is expressed in the IB4^+ subset of neurons and not in all DRG neurons (at least in rodents). Therefore, a depolarising block in this subset of neurons alone is not expected to cause a complete loss of pain. Second, $\text{Na}_v1.8$ which is expressed in most nociceptors (i.e. in same neurons as $\text{Na}_v1.9$) is a channel known to operate at more depolarised membrane potentials and can maintain

excitability, even in the face of a depolarised membrane potential [56, 103, 111, 134].

Concluding remarks

In the past 20 years, mouse models and human genetics have confirmed that $\text{Na}_v1.7$ and $\text{Na}_v1.9$ play critical roles in pain signalling. The link between genotype and phenotype for mutations in both channels is poorly understood. Symptoms manifest in the extremities (mainly in the feet/legs) in most human conditions. In $\text{Na}_v1.7$ channel mutations, there is a link between mutations that cause enhancement of activation to PEM and mutations that cause incomplete inactivation to PEPD. The physiological or microanatomical basis for these associations in terms of nerve ending function is only partly understood. In $\text{Na}_v1.9$ channel mutations, a clear understanding of why most gain of function mutations cause painful conditions while those affecting segment 6 cause insensitivity to pain is also lacking, although insensitivity to pain is hypothesised to be caused by reduced excitability due to a depolarising block [121, 122].

Nonetheless, available evidence confirms a critical role for both channels in pain earning them a position in the list of potential drug targets. Ablation of $\text{Na}_v1.8$ and $\text{Na}_v1.9$ in mice does not lead to lethality or any observable detrimental effects. Ablation of $\text{Na}_v1.7$ in human [19] and in adult mice [107]

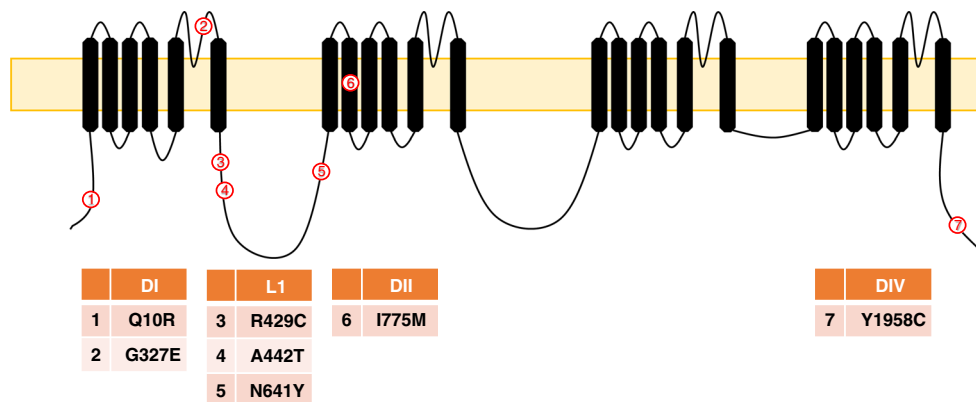
Fig. 4 Topological representation of *SCN9A* mutations that are linked to epilepsies

Table 5 *SCN9A* mutations that cause complete insensitivity to pain (CIP) in order of their publication

Mutation	Ref
S459X	[19]
I767X	[19]
W897X	[19]
R277X	[51]
Y328X	[51]
E693X	[51]
Splice junction mutation intron 23-24	
R830X	[51]
F1200L fs	[51]
R1488X	[51]
K1659X	[51]
I1235L fs	
W1689X	[51]
R523X	[73]
R896Q	[20]
K370Q	[108]
G375A fs	
E919X	[96]
M1190X	[106]
G1822 fs	[100]
R896G	[83]
Q369X	

does not lead to lethality. Reassuringly, there are no reported respiratory or behavioural abnormalities as a result of the absence of any one of these three channels in mouse and human. Yet important challenges for VGSC blockers in chronic pain remain, developing subunit-specific blockers being the first. This is important considering that VGSC blockers would need to be administered regularly to treat chronic pain and perhaps at higher doses for breakthrough pain, when pain is severe. Therefore, VGSC blockers would need to be safe for long-

Fig. 5 Topological representation of *SCN9A* mutations that cause CIP. Mutations associated with CIP are widely distributed throughout the α -subunit

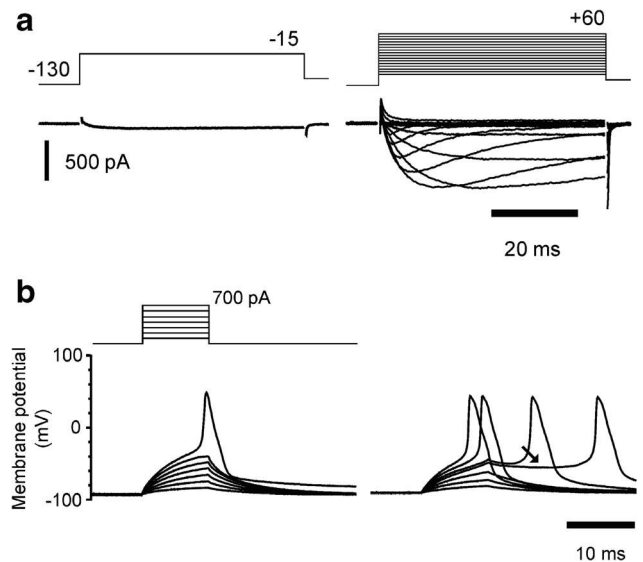
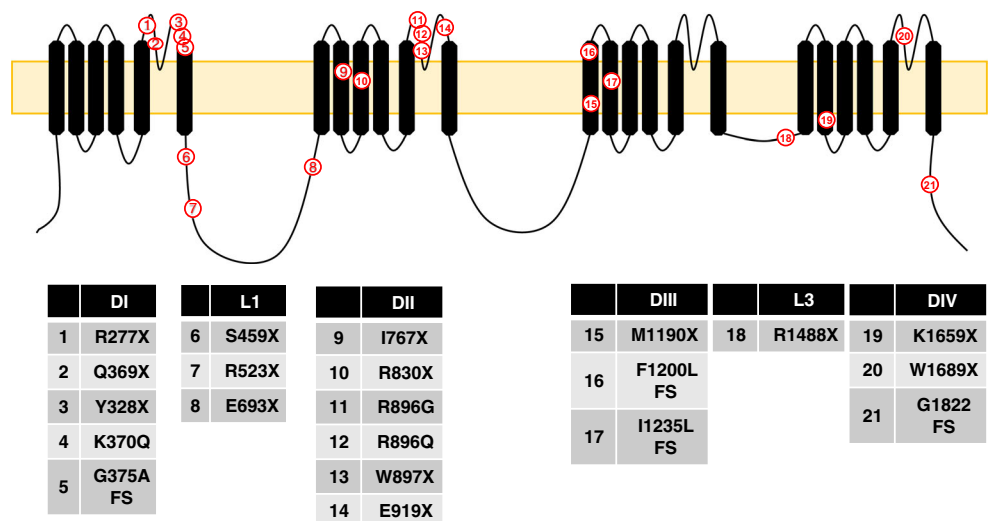


Fig. 6 **a** Upregulation of $Na_v1.9$ in an $Na_v1.8$ knockout neuron, following the introduction of 500 μ M GTP- γ -S into the cell interior for 12 min. **b** Upregulation of $Na_v1.9$ using intracellular GTP- γ -S gives rise to changes in the firing properties of $Na_v1.8$ knockout neuron, with reductions in current and voltage threshold, recorded from a holding potential of -90 mV. The upregulated current gives rise to plateau potentials (arrow). Reproduced from [6], with permission

term administration. The development of specific and effective small molecule inhibitors of $Na_v1.7$ is still elusive, despite efforts by several pharmaceutical companies [38, 71, 128]. The second challenge is the extent of $Na_v1.7$ inhibition required for analgesia in vivo. Given that CIP carriers have normal pain phenotype, an $Na_v1.7$ blocker may need to reduce channel activity to a level well below 50% to produce analgesia.

The contribution of the endogenous opioid system to the phenotype of the *SCN9A* CIP raises the question of whether the CIP phenotype is a direct consequence of the loss of $Na_v1.7$ [87, 97]. Several papers have provided complementary

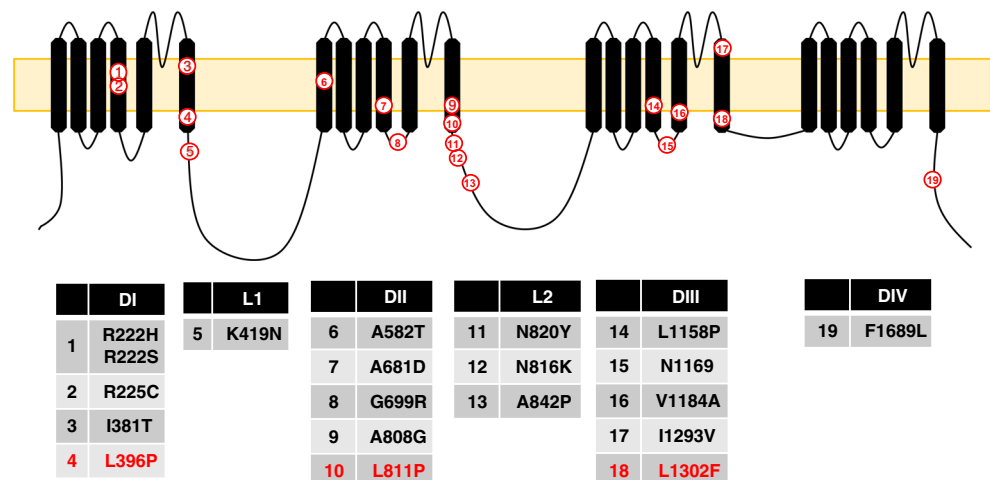
Table 6 *SCN1IA* mutations that cause painful and painless human conditions. Mutations causing painless condition are associated with big shifts in either their activation or inactivation voltages

Mutation	Notes on effect	Ref
L811P	CIP	[79]
R225C	Episodic pain	[130]
A808G	Increase current density	
I381T	No effect on activation and inactivation voltages Painful neuropathy	[63]
K419N	I381T: activation voltage shifted by -6.7 mV	
A582T	L1158P: activation voltage shifted by -6.9 mV	
A681D		
A842P		
L1158P		
F1689L		
G699R	Painful neuropathy	[57]
V1184A	Activation voltage shifted by -10.1 mV Episodic pain	[80]
R222S	Activation voltage shifted by -17 mV Episodic pain	[93]
R222H		
R222H	Episodic pain	[58]
L1302F	Activation voltage shifted by -6.4 mV CIP	[98]
N1169S	PEM-like pain	[131]
I1293V		
L396P	CIP	[70]
L1302F	Deactivation voltage shifted by -22.8 mV CIP	[64]
N820Y	Painful neuropathy	[48]
N816K	Episodic pain	[65]

evidence that the loss of $Na_v1.7$ reduces the excitability of DRG neurons per se. Deletion of $Na_v1.7$ causes an increase in action potential threshold in small-diameter DRG neurons [107]. Deletion of $Na_v1.7$ causes a major decrease in DRG neuron responsiveness to the VGSC opener veratridine [89]. Mechanically evoked spiking of C-fibres in the skin-nerve

preparation was reduced in $Na_v1.7$ KO mice [49]. No changes in the expression of other VGSC channels were reported in the $Na_v1.7$ KO mouse to contribute to the observed reduced excitability of DRG [107]. Furthermore, pain deficits in a rat model of $Na_v1.7$ deletion were not reversed by the opioid receptor antagonist naloxone [14]. Therefore, although an

Fig. 7 Topological representation of *SCN1IA* mutations. Notice that all CIP causing mutations (red) are located in the transmembrane segment 6



increase in spinal cord opioid synthesis would reduce signal transmission at the first synapse in CIP patients, the loss of $\text{Na}_v1.7$ has a profound effect on the excitability of DRG neurons (i.e. expected to affect the initiation of the pain signal in the periphery).

The lack of reported $\text{Na}_v1.9$ loss of function mutations may indicate that its loss does not lead to a major phenotype in humans, or at least does not make people go to the doctor, raising doubts as to whether a blocker would lead to a major analgesic effect. Finally, considering that nociceptors express at least two of the peripheral VGSC subunits ($\text{Na}_v1.7$, $\text{Na}_v1.8$ and $\text{Na}_v1.9$), an effective analgesic strategy may ultimately result from a combination of blockers against these subunits to have additive and synergistic effects on nociceptors. The effectiveness of various drug combinations to reduce neuronal excitability can only be measured in DRG neurons because they express the target VGSCs at biologically relevant levels. Equally important, for the evaluation of any drug combination, is the potential effects on non-nociceptors as well as nociceptors. We recently described a relevant assay [88] and provided proof-of-concept data that showed a combination of $\text{Na}_v1.7$ and $\text{Na}_v1.8$ blockers produced a reduction in the excitability of DRG neurons close to that measured in $\text{Na}_v1.7$ KO [89]. Changing the constituents and doses in VGSC blocker combinations may enable clinicians to manage chronic pain safely over the long term.

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References

- Ahn HS, Dib-Hajj SD, Cox JJ, Tyrrell L, Elmslie FV, Clarke AA, Drenth JP, Woods CG, Waxman SG (2010) A new $\text{Nav}1.7$ sodium channel mutation I234T in a child with severe pain. *Eur J Pain* 14:944–950. <https://doi.org/10.1016/j.ejpain.2010.03.007>
- Akopian AN, Sivilotti L, Wood JN (1996) A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. *Nature* 379:257–262. <https://doi.org/10.1038/379257a0>
- Akopian AN, Souslova V, England S, Okuse K, Ogata N, Ure J, Smith A, Kerr BJ, McMahon SB, Boyce S, Hill R, Stanfa LC, Dickenson AH, Wood JN (1999) The tetrodotoxin-resistant sodium channel SNS has a specialized function in pain pathways. *Nat Neurosci* 2:541–548. <https://doi.org/10.1038/9195>
- Amaya F, Wang H, Costigan M, Allchorne AJ, Hatcher JP, Egerton J, Stean T, Morisset V, Grose D, Gunthorpe MJ, Chessell IP, Tate S, Green PJ, Woolf CJ (2006) The voltage-gated sodium channel $\text{Na}(v)1.9$ is an effector of peripheral inflammatory pain hypersensitivity. *J Neurosci* 26:12852–12860. <https://doi.org/10.1523/JNEUROSCI.4015-06.2006>
- Baker MD (2005) Protein kinase C mediates up-regulation of tetrodotoxin-resistant, persistent Na^+ current in rat and mouse sensory neurones. *J Physiol* 567:851–867. <https://doi.org/10.1113/jphysiol.2005.089771>
- Baker MD, Chandra SY, Ding Y, Waxman SG, Wood JN (2003) GTP-induced tetrodotoxin-resistant Na^+ current regulates excitability in mouse and rat small diameter sensory neurones. *J Physiol* 548:373–382. <https://doi.org/10.1113/jphysiol.2003.039131>
- Bennett DL, Woods CG (2014) Painful and painless channelopathies. *Lancet Neurol* 13:587–599. [https://doi.org/10.1016/S1474-4422\(14\)70024-9](https://doi.org/10.1016/S1474-4422(14)70024-9)
- Beyak MJ, Vanner S (2005) Inflammation-induced hyperexcitability of nociceptive gastrointestinal DRG neurones: the role of voltage-gated ion channels. *Neurogastroenterol Motil* 17:175–186. <https://doi.org/10.1111/j.1365-2982.2004.00596.x>
- Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D (2006) Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 10:287–333. <https://doi.org/10.1016/j.ejpain.2005.06.009>
- Brouwer BA, Merkies IS, Gerrits MM, Waxman SG, Hoeijmakers JG, Faber CG (2014) Painful neuropathies: the emerging role of sodium channelopathies. *J Peripher Nerv Syst* 19:53–65. <https://doi.org/10.1111/jns.12071>
- Caterina MJ, Pang Z (2016) TRP channels in skin biology and pathophysiology. *Pharmaceuticals (Basel)* 9. <https://doi.org/10.3390/ph9040077>
- Catterall WA (2017) Forty years of sodium channels: structure, function, pharmacology, and epilepsy. *Neurochem Res* 42:2495–2504. <https://doi.org/10.1007/s11064-017-2314-9>
- Cen Z, Lou Y, Guo Y, Wang J, Feng J (2017) Q10R mutation in SCN9A gene is associated with generalized epilepsy with febrile seizures plus. *Seizure* 50:186–188. <https://doi.org/10.1016/j.seizure.2017.06.023>
- Chen L, Effraim P, Carrara J, Zhao P, Dib-Hajj FB, Dib-Hajj SD, Waxman SG (2020) Pharmacological characterization of a rat $\text{Nav}1.7$ loss-of-function model with insensitivity to pain. *Pain*. <https://doi.org/10.1097/j.pain.0000000000001807>
- Cheng X, Dib-Hajj SD, Tyrrell L, Te Morsche RH, Drenth JP, Waxman SG (2011) Deletion mutation of sodium channel $\text{Na}(V)1.7$ in inherited erythromelalgia: enhanced slow inactivation modulates dorsal root ganglion neuron hyperexcitability. *Brain* 134:1972–1986. <https://doi.org/10.1093/brain/awr143>
- Choi JS, Cheng X, Foster E, Leffler A, Tyrrell L, Te Morsche RH, Eastman EM, Jansen HJ, Huehne K, Nau C, Dib-Hajj SD, Drenth JP, Waxman SG (2010) Alternative splicing may contribute to time-dependent manifestation of inherited erythromelalgia. *Brain* 133:1823–1835. <https://doi.org/10.1093/brain/awq114>
- Choi JS, Boralevi F, Brissaud O, Sanchez-Martin J, Te Morsche RH, Dib-Hajj SD, Drenth JP, Waxman SG (2011) Paroxysmal extreme pain disorder: a molecular lesion of peripheral neurons. *Nat Rev Neurol* 7:51–55. <https://doi.org/10.1038/nrneurol.2010.162>
- Coste B, Osorio N, Padilla F, Crest M, Delmas P (2004) Gating and modulation of presumptive $\text{NaV}1.9$ channels in enteric and spinal sensory neurons. *Mol Cell Neurosci* 26:123–134. <https://doi.org/10.1016/j.mcn.2004.01.015>

19. Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, Springell K, Karbani G, Jafri H, Mannan J, Raashid Y, Al-Gazali L, Hamamy H, Valente EM, Gorman S, Williams R, McHale DP, Wood JN, Gribble FM, Woods CG (2006) An SCN9A channelopathy causes congenital inability to experience pain. *Nature* 444:894–898. <https://doi.org/10.1038/nature05413>
20. Cox JJ, Sheynin J, Shorer Z, Reimann F, Nicholas AK, Zubovic L, Baralle M, Wraige E, Manor E, Levy J, Woods CG, Parvari R (2010) Congenital insensitivity to pain: novel SCN9A missense and in-frame deletion mutations. *Hum Mutat* 31:E1670–E1686. <https://doi.org/10.1002/humu.21325>
21. Cregg R, Laguda B, Werdehausen R, Cox JJ, Linley JE, Ramirez JD, Bodi I, Markiewicz M, Howell KJ, Chen YC, Agnew K, Houlden H, Lunn MP, Bennett DL, Wood JN, Kinali M (2013) Novel mutations mapping to the fourth sodium channel domain of Nav1.7 result in variable clinical manifestations of primary erythromelalgia. *NeuroMolecular Med* 15:265–278. <https://doi.org/10.1007/s12017-012-8216-8>
22. Cummins TR, Howe JR, Waxman SG (1998) Slow closed-state inactivation: a novel mechanism underlying ramp currents in cells expressing the hNE/PN1 sodium channel. *J Neurosci* 18:9607–9619
23. Cummins TR, Dib-Hajj SD, Black JA, Akopian AN, Wood JN, Waxman SG (1999) A novel persistent tetrodotoxin-resistant sodium current in SNS-null and wild-type small primary sensory neurons. *J Neurosci* 19:RC43
24. Cummins TR, Dib-Hajj SD, Waxman SG (2004) Electrophysiological properties of mutant Nav1.7 sodium channels in a painful inherited neuropathy. *J Neurosci* 24:8232–8236. <https://doi.org/10.1523/JNEUROSCI.2695-04.2004>
25. Cummins TR, Sheets PL, Waxman SG (2007) The roles of sodium channels in nociception: implications for mechanisms of pain. *Pain* 131:243–257. <https://doi.org/10.1016/j.pain.2007.07.026>
26. Dabby R, Sadeh M, Gilad R, Lampi Y, Cohen S, Inbar S, Leshinsky-Silver E (2011) Chronic non-paroxysmal neuropathic pain—novel phenotype of mutation in the sodium channel SCN9A gene. *J Neurol Sci* 301:90–92. <https://doi.org/10.1016/j.jns.2010.10.006>
27. de Greef BTA, Hoeijmakers JGJ, Geerts M, Oakes M, Church TJE, Waxman SG, Dib-Hajj SD, Faber CG, Merkies ISJ (2019) Lacosamide in patients with Nav1.7 mutations-related small fibre neuropathy: a randomized controlled trial. *Brain* 142:263–275. <https://doi.org/10.1093/brain/awy329>
28. Dib-Hajj S, Black JA, Cummins TR, Waxman SG (2002) Na_v1.9: a sodium channel with unique properties. *Trends Neurosci* 25:253–259. [https://doi.org/10.1016/s0166-2236\(02\)02150-1](https://doi.org/10.1016/s0166-2236(02)02150-1)
29. Dib-Hajj SD, Rush AM, Cummins TR, Hisama FM, Novella S, Tyrrell L, Marshall L, Waxman SG (2005) Gain-of-function mutation in Nav1.7 in familial erythromelalgia induces bursting of sensory neurons. *Brain* 128:1847–1854. <https://doi.org/10.1093/brain/awh514>
30. Dib-Hajj SD, Cummins TR, Black JA, Waxman SG (2007) From genes to pain: Na_v 1.7 and human pain disorders. *Trends Neurosci* 30:555–563. <https://doi.org/10.1016/j.tins.2007.08.004>
31. Dib-Hajj SD, Black JA, Waxman SG (2015) NaV1.9: a sodium channel linked to human pain. *Nat Rev Neurosci* 16:511–519. <https://doi.org/10.1038/nrn3977>
32. Ding J, Zhang JW, Guo YX, Zhang YX, Chen ZH, Zhai QX (2019) Novel mutations in SCN9A occurring with fever-associated seizures or epilepsy. *Seizure* 71:214–218. <https://doi.org/10.1016/j.seizure.2019.06.005>
33. Drenth JP, te Morsche RH, Guillet G, Taieb A, Kirby RL, Jansen JB (2005) SCN9A mutations define primary erythromelalgia as a neuropathic disorder of voltage gated sodium channels. *J Invest Dermatol* 124:1333–1338. <https://doi.org/10.1111/j.0022-202X.2005.23737.x>
34. Drissi I, Woods WA, Woods CG (2020) Understanding the genetic basis of congenital insensitivity to pain. *Br Med Bull*. <https://doi.org/10.1093/bmb/ldaa003>
35. Eberhardt M, Nakajima J, Klinger AB, Neacsu C, Huhne K, O'Reilly AO, Kist AM, Lampe AK, Fischer K, Gibson J, Nau C, Winterpacht A, Lampert A (2014) Inherited pain: sodium channel Nav1.7 A1632T mutation causes erythromelalgia due to a shift of fast inactivation. *J Biol Chem* 289:1971–1980. <https://doi.org/10.1074/jbc.M113.502211>
36. Eijkenboom I, Sopacua M, Hoeijmakers JGJ, de Greef BTA, Lindsey P, Almomani R, Marchi M, Vanoevelen J, Smeets HJM, Waxman SG, Lauria G, Merkies ISJ, Faber CG, Gerrits MM (2019) Yield of peripheral sodium channels gene screening in pure small fibre neuropathy. *J Neurol Neurosurg Psychiatry* 90:342–352. <https://doi.org/10.1136/jnnp-2018-319042>
37. Emery EC, Habib AM, Cox JJ, Nicholas AK, Gribble FM, Woods CG, Reimann F (2015) Novel SCN9A mutations underlying extreme pain phenotypes: unexpected electrophysiological and clinical phenotype correlations. *J Neurosci* 35:7674–7681. <https://doi.org/10.1523/JNEUROSCI.3935-14.2015>
38. Emery EC, Luiz AP, Wood JN (2016) Nav1.7 and other voltage-gated sodium channels as drug targets for pain relief. *Expert Opin Ther Targets* 20:975–983. <https://doi.org/10.1517/14728222.2016.1162295>
39. Estacion M, Dib-Hajj SD, Benke PJ, Te Morsche RH, Eastman EM, Macala LJ, Drenth JP, Waxman SG (2008) NaV1.7 gain-of-function mutations as a continuum: A1632E displays physiological changes associated with erythromelalgia and paroxysmal extreme pain disorder mutations and produces symptoms of both disorders. *J Neurosci* 28:11079–11088. <https://doi.org/10.1523/JNEUROSCI.3443-08.2008>
40. Estacion M, Choi JS, Eastman EM, Lin Z, Li Y, Tyrrell L, Yang Y, Dib-Hajj SD, Waxman SG (2010) Can robots patch-clamp as well as humans? Characterization of a novel sodium channel mutation. *J Physiol* 588:1915–1927. <https://doi.org/10.1113/jphysiol.2009.186114>
41. Estacion M, Han C, Choi JS, Hoeijmakers JG, Lauria G, Drenth JP, Gerrits MM, Dib-Hajj SD, Faber CG, Merkies IS, Waxman SG (2011) Intra- and interfamily phenotypic diversity in pain syndromes associated with a gain-of-function variant of NaV1.7. *Mol Pain* 7:92. <https://doi.org/10.1186/1744-8069-7-92>
42. Estacion M, Yang Y, Dib-Hajj SD, Tyrrell L, Lin Z, Yang Y, Waxman SG (2013) A new Nav1.7 mutation in an erythromelalgia patient. *Biochem Biophys Res Commun* 432:99–104. <https://doi.org/10.1016/j.bbrc.2013.01.079>
43. Faber CG, Hoeijmakers JG, Ahn HS, Cheng X, Han C, Choi JS, Estacion M, Lauria G, Vanhoutte EK, Gerrits MM, Dib-Hajj S, Drenth JP, Waxman SG, Merkies IS (2012) Gain of function Nav1.7 mutations in idiopathic small fiber neuropathy. *Ann Neurol* 71:26–39. <https://doi.org/10.1002/ana.22485>
44. Faber CG, Lauria G, Merkies IS, Cheng X, Han C, Ahn HS, Persson AK, Hoeijmakers JG, Gerrits MM, Pierro T, Lombardi R, Kapetis D, Dib-Hajj SD, Waxman SG (2012) Gain-of-function Nav1.8 mutations in painful neuropathy. *Proc Natl Acad Sci U S A* 109:19444–19449. <https://doi.org/10.1073/pnas.1216080109>
45. Fertleman CR, Baker MD, Parker KA, Moffatt S, Elmslie FV, Abrahamsen B, Ostman J, Klugbauer N, Wood JN, Gardiner RM, Rees M (2006) SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. *Neuron* 52:767–774. <https://doi.org/10.1016/j.neuron.2006.10.006>
46. Fischer TZ, Gilmore ES, Estacion M, Eastman E, Taylor S, Melanson M, Dib-Hajj SD, Waxman SG (2009) A novel Nav1.7 mutation producing carbamazepine-responsive

- erythromelalgia. *Ann Neurol* 65:733–741. <https://doi.org/10.1002/ana.21678>
47. Fjell J, Hjelmstrom P, Hormuzdiar W, Milenkovic M, Aglieco F, Tyrrell L, Dib-Hajj S, Waxman SG, Black JA (2000) Localization of the tetrodotoxin-resistant sodium channel NaN in nociceptors. *Neuroreport* 11:199–202. <https://doi.org/10.1097/00001756-200001170-00039>
 48. Ginanneschi F, Rubegni A, Moro F, Volpi N, Santorelli FM, Rossi A (2019) SCN11A variant as possible pain generator in sensory axonal neuropathy. *Neurol Sci* 40:1295–1297. <https://doi.org/10.1007/s10072-019-3703-4>
 49. Gingras J, Smith S, Matson DJ, Johnson D, Nye K, Couture L, Feric E, Yin R, Moyer BD, Peterson ML, Rottman JB, Beiler RJ, Malmberg AB, McDonough SI (2014) Global Nav1.7 knockout mice recapitulate the phenotype of human congenital indifference to pain. *PLoS One* 9:e105895. <https://doi.org/10.1371/journal.pone.0105895>
 50. Goldberg DS, McGee SJ (2011) Pain as a global public health priority. *BMC Public Health* 11:770. <https://doi.org/10.1186/1471-2458-11-770>
 51. Goldberg YP, MacFarlane J, MacDonald ML, Thompson J, Dube MP, Mattice M, Fraser R, Young C, Hossain S, Pape T, Payne B, Radomski C, Donaldson G, Ives E, Cox J, Younghusband HB, Green R, Duff A, Boltshauser E, Grinspan GA, Dimon JH, Sibley BG, Andria G, Toscano E, Kerdraon J, Bowsher D, Pimstone SN, Samuels ME, Sherrington R, Hayden MR (2007) Loss-of-function mutations in the Nav1.7 gene underlie congenital indifference to pain in multiple human populations. *Clin Genet* 71:311–319. <https://doi.org/10.1111/j.1399-0004.2007.00790.x>
 52. Gwathmey KG, Pearson KT (2019) Diagnosis and management of sensory polyneuropathy. *BMJ* 365:l1108. <https://doi.org/10.1136/bmj.l1108>
 53. Haberberger RV, Barry C, Dominguez N, Matusica D (2019) Human dorsal root ganglia. *Front Cell Neurosci* 13:271. <https://doi.org/10.3389/fncel.2019.00271>
 54. Haehner A, Hummel T, Heintz W, Krueger S, Meinhardt M, Whitcroft KL, Sabatowski R, Gossrau G (2018) Mutation in Nav 1.7 causes high olfactory sensitivity. *Eur J Pain* 22:1767–1773. <https://doi.org/10.1002/ejp.1272>
 55. Han C, Dib-Hajj SD, Lin Z, Li Y, Eastman EM, Tyrrell L, Cao X, Yang Y, Waxman SG (2009) Early- and late-onset inherited erythromelalgia: genotype-phenotype correlation. *Brain* 132:1711–1722. <https://doi.org/10.1093/brain/awp078>
 56. Han C, Hoeijmakers JG, Liu S, Gerrits MM, te Morsche RH, Lauria G, Dib-Hajj SD, Drenth JP, Faber CG, Merkies IS, Waxman SG (2012) Functional profiles of SCN9A variants in dorsal root ganglion neurons and superior cervical ganglion neurons correlate with autonomic symptoms in small fibre neuropathy. *Brain* 135:2613–2628. <https://doi.org/10.1093/brain/aww187>
 57. Han C, Yang Y, de Greef BT, Hoeijmakers JG, Gerrits MM, Verhamme C, Qu J, Lauria G, Merkies IS, Faber CG, Dib-Hajj SD, Waxman SG (2015) The domain II S4-S5 linker in Nav1.9: a missense mutation enhances activation, impairs fast inactivation, and produces human painful neuropathy. *NeuroMolecular Med* 17:158–169. <https://doi.org/10.1007/s12017-015-8347-9>
 58. Han C, Yang Y, Te Morsche RH, Drenth JP, Politei JM, Waxman SG, Dib-Hajj SD (2017) Familial gain-of-function Nav1.9 mutation in a painful channelopathy. *J Neurol Neurosurg Psychiatry* 88:233–240. <https://doi.org/10.1136/jnnp-2016-313804>
 59. Harty TP, Dib-Hajj SD, Tyrrell L, Blackman R, Hisama FM, Rose JB, Waxman SG (2006) Na(V)1.7 mutant A863P in erythromelalgia: effects of altered activation and steady-state inactivation on excitability of nociceptive dorsal root ganglion neurons. *J Neurosci* 26:12566–12575. <https://doi.org/10.1523/JNEUROSCI.3424-06.2006>
 60. Hockley JR, Boundouki G, Cibert-Goton V, McGuire C, Yip PK, Chan C, Tranter M, Wood JN, Nassar MA, Blackshaw LA, Aziz Q, Michael GJ, Baker MD, Winchester WJ, Knowles CH, Bulmer DC (2014) Multiple roles for Nav1.9 in the activation of visceral afferents by noxious inflammatory, mechanical, and human disease-derived stimuli. *Pain* 155:1962–1975. <https://doi.org/10.1016/j.pain.2014.06.015>
 61. Hockley JR, Tranter MM, McGuire C, Boundouki G, Cibert-Goton V, Thaha MA, Blackshaw LA, Michael GJ, Baker MD, Knowles CH, Winchester WJ, Bulmer DC (2016) P2Y receptors sensitize mouse and human colonic nociceptors. *J Neurosci* 36:2364–2376. <https://doi.org/10.1523/JNEUROSCI.3369-15.2016>
 62. Hoeijmakers JG, Han C, Merkies IS, Macala LJ, Lauria G, Gerrits MM, Dib-Hajj SD, Faber CG, Waxman SG (2012) Small nerve fibres, small hands and small feet: a new syndrome of pain, dysautonomia and acromesomelia in a kindred with a novel Nav1.7 mutation. *Brain* 135:345–358. <https://doi.org/10.1093/brain/awr349>
 63. Huang J, Han C, Estacion M, Vasylyev D, Hoeijmakers JG, Gerrits MM, Tyrrell L, Lauria G, Faber CG, Dib-Hajj SD, Merkies IS, Waxman SG, Group PS (2014) Gain-of-function mutations in sodium channel Na(v)1.9 in painful neuropathy. *Brain* 137:1627–1642. <https://doi.org/10.1093/brain/awu079>
 64. Huang J, Vanoye CG, Cutts A, Goldberg YP, Dib-Hajj SD, Cohen CJ, Waxman SG, George AL Jr (2017) Sodium channel Nav1.9 mutations associated with insensitivity to pain dampen neuronal excitability. *J Clin Invest* 127:2805–2814. <https://doi.org/10.1172/JCI92373>
 65. Huang J, Estacion M, Zhao P, Dib-Hajj FB, Schulman B, Abicht A, Kurth I, Brockmann K, Waxman SG, Dib-Hajj SD (2019) A novel gain-of-function Nav1.9 mutation in a child with episodic pain. *Front Neurosci* 13:918. <https://doi.org/10.3389/fnins.2019.00918>
 66. Imai N, Miyake N, Saito Y, Kobayashi E, Ikawa M, Manaka S, Shiina M, Ogata K, Matsumoto N (2015) Short-lasting unilateral neuralgiform headache attacks with ipsilateral facial flushing is a new variant of paroxysmal extreme pain disorder. *J Headache Pain* 16:519. <https://doi.org/10.1186/s10194-015-0519-3>
 67. Ito M, Yamaguchi S, Omine T, Miyagi T, Arakaki O, Yamamoto YI, Takahashi K (2019) Behavioral therapy ceased cold water immersion dependence in a patient with familial erythromelalgia caused by SCN9A mutation. *JAAD Case Rep* 5:806–808. <https://doi.org/10.1016/j.jcdr.2019.07.007>
 68. Jeong SY, Goto J, Hashida H, Suzuki T, Ogata K, Masuda N, Hirai M, Isahara K, Uchiyama Y, Kanazawa I (2000) Identification of a novel human voltage-gated sodium channel alpha subunit gene, SCN12A. *Biochem Biophys Res Commun* 267:262–270. <https://doi.org/10.1006/bbrc.1999.1916>
 69. Kabata R, Okuda H, Noguchi A, Kondo D, Fujiwara M, Hata K, Kato Y, Ishikawa K, Tanaka M, Sekine Y, Hishikawa N, Mizukami T, Ito J, Akasaka M, Sakurai K, Yoshida T, Minoura H, Hayashi T, Inoshita K, Matsuyama M, Kinjo N, Cao Y, Inoue S, Kobayashi H, Harada KH, Youssefian S, Takahashi T, Koizumi A (2018) Familial episodic limb pain in kindreds with novel Nav1.9 mutations. *PLoS One* 13:e0208516. <https://doi.org/10.1371/journal.pone.0208516>
 70. King MK, Leipold E, Goehringer JM, Kurth I, Challman TD (2017) Pain insensitivity: distal S6-segment mutations in Nav1.9 emerge as critical hotspot. *Neurogenetics* 18:179–181. <https://doi.org/10.1007/s10048-017-0513-9>
 71. Kingwell K (2019) Nav1.7 withholds its pain potential. *Nat Rev Drug Discov*. <https://doi.org/10.1038/d41573-019-00065-0>
 72. Klein CJ, Wu Y, Kilfoyle DH, Sandroni P, Davis MD, Gavrilova RH, Low PA, Dyck PJ (2013) Infrequent SCN9A mutations in congenital insensitivity to pain and erythromelalgia. *J Neurol*

- Neurosurg Psychiatry 84:386–391. <https://doi.org/10.1136/jnnp-2012-303719>
73. Kurban M, Wajid M, Shimomura Y, Christiano AM (2010) A nonsense mutation in the SCN9A gene in congenital insensitivity to pain. *Dermatology* 221:179–183. <https://doi.org/10.1159/000314692>
 74. Labau JIR, Estacion M, Tanaka BS, de Greef BTA, Hoeijmakers JGJ, Geerts M, Gerrits MM, Smeets HJM, Faber CG, Merkies ISJ, Lauria G, Dib-Hajj SD, Waxman SG (2020) Differential effect of lacosamide on Nav1.7 variants from responsive and non-responsive patients with small fibre neuropathy. *Brain* 143:771–782. <https://doi.org/10.1093/brain/awaa016>
 75. Lai J, Gold MS, Kim CS, Bian D, Ossipov MH, Hunter JC, Porreca F (2002) Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, Nav1.8. *Pain* 95:143–152. [https://doi.org/10.1016/s0304-3959\(01\)00391-8](https://doi.org/10.1016/s0304-3959(01)00391-8)
 76. Lampert A, Dib-Hajj SD, Eastman EM, Tyrrell L, Lin Z, Yang Y, Waxman SG (2009) Erythromelalgia mutation L823R shifts activation and inactivation of threshold sodium channel Nav1.7 to hyperpolarized potentials. *Biochem Biophys Res Commun* 390:319–324. <https://doi.org/10.1016/j.bbrc.2009.09.121>
 77. Lawson SN (2002) Phenotype and function of somatic primary afferent nociceptive neurons with C-, delta- or alpha/beta-fibres. *Exp Physiol* 87:239–244. <https://doi.org/10.1113/eph8702350>
 78. Lee MJ, Yu HS, Hsieh ST, Stephenson DA, Lu CJ, Yang CC (2007) Characterization of a familial case with primary erythromelalgia from Taiwan. *J Neurol* 254:210–214. <https://doi.org/10.1007/s00415-006-0328-3>
 79. Leipold E, Liebmann L, Korenke GC, Heinrich T, Giesselmann S, Baets J, Ebbinghaus M, Goral RO, Stodberg T, Hennings JC, Bergmann M, Altmüller J, Thiele H, Wetzel A, Nurnberg P, Timmerman V, De Jonghe P, Blum R, Schaible HG, Weis J, Heinemann SH, Hubner CA, Kurth I (2013) A de novo gain-of-function mutation in SCN11A causes loss of pain perception. *Nat Genet* 45:1399–1404. <https://doi.org/10.1038/ng.2767>
 80. Leipold E, Hanson-Kahn A, Frick M, Gong P, Bernstein JA, Voigt M, Katona I, Oliver Goral R, Altmüller J, Nurnberg P, Weis J, Hubner CA, Heinemann SH, Kurth I (2015) Cold-aggravated pain in humans caused by a hyperactive Nav1.9 channel mutant. *Nat Commun* 6:10049. <https://doi.org/10.1038/ncomms10049>
 81. Liu Z, Ye X, Qiao P, Luo W, Wu Y, He Y, Gao P (2019) G327E mutation in SCN9A gene causes idiopathic focal epilepsy with Rolandic spikes: a case report of twin sisters. *Neurol Sci* 40:1457–1460. <https://doi.org/10.1007/s10072-019-03752-3>
 82. Mann N, King T, Murphy R (2019) Review of primary and secondary erythromelalgia. *Clin Exp Dermatol* 44:477–482. <https://doi.org/10.1111/ced.13891>
 83. Marchi M, Provitera V, Nolano M, Romano M, Maccora S, D'Amato I, Salvi E, Gerrits M, Santoro L, Lauria G (2018) A novel SCN9A splicing mutation in a compound heterozygous girl with congenital insensitivity to pain, hyposmia and hypogeusia. *J Peripher Nerv Syst* 23:202–206. <https://doi.org/10.1111/jns.12280>
 84. Maruyama H, Yamamoto M, Matsutomi T, Zheng T, Nakata Y, Wood JN, Ogata N (2004) Electrophysiological characterization of the tetrodotoxin-resistant Na⁺ channel, Na(v)1.9, in mouse dorsal root ganglion neurons. *Pflugers Arch* 449:76–87. <https://doi.org/10.1007/s00424-004-1315-0>
 85. Meglic A, Perkovic-Benedik M, Trebusak Podkrajsek K, Bertok S (2014) Painful micturition in a small child: an unusual clinical picture of paroxysmal extreme pain disorder. *Pediatr Nephrol* 29:1643–1646. <https://doi.org/10.1007/s00467-014-2819-2>
 86. Michiels JJ, te Morsche RH, Jansen JB, Drenth JP (2005) Autosomal dominant erythromelalgia associated with a novel mutation in the voltage-gated sodium channel alpha subunit Nav1.7. *Arch Neurol* 62:1587–1590. <https://doi.org/10.1001/archneur.62.10.1587>
 87. Minett MS, Pereira V, Sikandar S, Matsuyama A, Lolignier S, Kanellopoulos AH, Mancini F, Iannetti GD, Bogdanov YD, Santana-Varela S, Millet Q, Baskozos G, MacAllister R, Cox JJ, Zhao J, Wood JN (2015) Endogenous opioids contribute to insensitivity to pain in humans and mice lacking sodium channel Nav1.7. *Nat Commun* 6:8967. <https://doi.org/10.1038/ncomms9967>
 88. Mohammed ZA, Doran C, Grundy D, Nassar MA (2017) Veratridine produces distinct calcium response profiles in mouse dorsal root ganglia neurons. *Sci Rep* 7:45221. <https://doi.org/10.1038/srep45221>
 89. Mohammed ZA, Kaloyanova K, Nassar MA (2020) An unbiased and efficient assessment of excitability of sensory neurons for analgesic drug discovery. *Pain*. 161:1100–1108. <https://doi.org/10.1097/j.pain.0000000000001802>
 90. Moore C, Gupta R, Jordt SE, Chen Y, Liedtke WB (2018) Regulation of pain and itch by TRP channels. *Neurosci Bull* 34:120–142. <https://doi.org/10.1007/s12264-017-0200-8>
 91. Nassar MA, Stirling LC, Forlani G, Baker MD, Matthews EA, Dickenson AH, Wood JN (2004) Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and inflammatory pain. *Proc Natl Acad Sci U S A* 101:12706–12711. <https://doi.org/10.1073/pnas.0404915101>
 92. Nassar MA, Baker MD, Levato A, Ingram R, Mallucci G, McMahon SB, Wood JN (2006) Nerve injury induces robust allodynia and ectopic discharges in Nav1.3 null mutant mice. *Mol Pain* 2:33. <https://doi.org/10.1186/1744-8069-2-33>
 93. Okuda H, Noguchi A, Kobayashi H, Kondo D, Harada KH, Youssefian S, Shioi H, Kabata R, Domon Y, Kubota K, Kitano Y, Takayama Y, Hitomi T, Ohno K, Saito Y, Asano T, Tomiyama M, Takahashi T, Koizumi A (2016) Infantile pain episodes associated with novel Nav1.9 mutations in familial episodic pain syndrome in Japanese families. *PLoS One* 11:e0154827. <https://doi.org/10.1371/journal.pone.0154827>
 94. Ostman JA, Nassar MA, Wood JN, Baker MD (2008) GTP up-regulated persistent Na⁺ current and enhanced nociceptor excitability require Nav1.9. *J Physiol* 586:1077–1087. <https://doi.org/10.1113/jphysiol.2007.147942>
 95. Padilla F, Couble ML, Coste B, Maingret F, Clerc N, Crest M, Ritter AM, Magloire H, Delmas P (2007) Expression and localization of the Nav1.9 sodium channel in enteric neurons and in trigeminal sensory endings: implication for intestinal reflex function and orofacial pain. *Mol Cell Neurosci* 35:138–152. <https://doi.org/10.1016/j.mcn.2007.02.008>
 96. Peddareddygarri LR, Oberoi K, Grewal RP (2014) Congenital insensitivity to pain: a case report and review of the literature. *Case Rep Neurol Med* 2014:141953–141954. <https://doi.org/10.1155/2014/141953>
 97. Pereira V, Millet Q, Aramburu J, Lopez-Rodriguez C, Gaveriaux-Ruff C, Wood JN (2018) Analgesia linked to Nav1.7 loss of function requires micro- and delta-opioid receptors. *Wellcome Open Res* 3:101. <https://doi.org/10.12688/wellcomeopenres.14687.1>
 98. Phatarakijvirund V, Mumm S, McAlister WH, Novack DV, Wenkert D, Clements KL, Whyte MP (2016) Congenital insensitivity to pain: fracturing without apparent skeletal pathobiology caused by an autosomal dominant, second mutation in SCN11A encoding voltage-gated sodium channel 1.9. *Bone* 84:289–298. <https://doi.org/10.1016/j.bone.2015.11.022>
 99. Priest BT, Murphy BA, LINDIA JA, Diaz C, Abbadi C, Ritter AM, Liberator P, Iyer LM, Kash SF, Kohler MG, Kaczorowski GJ, MacIntyre DE, Martin WJ (2005) Contribution of the

- tetrodotoxin-resistant voltage-gated sodium channel Nav1.9 to sensory transmission and nociceptive behavior. *Proc Natl Acad Sci U S A* 102:9382–9387. <https://doi.org/10.1073/pnas.0501549102>
100. Rajasekharan S, Martens L, Domingues L, Cauwels R (2017) SCN9A channelopathy associated autosomal recessive congenital indifference to pain. A case report. *Eur J Paediatr Dent* 18:66–68. <https://doi.org/10.23804/ejpd.2017.18.01.14>
 101. Ritter AM, Martin WJ, Thormeloe KS (2009) The voltage-gated sodium channel Nav1.9 is required for inflammation-based urinary bladder dysfunction. *Neurosci Lett* 452:28–32. <https://doi.org/10.1016/j.neulet.2008.12.051>
 102. Rugiero F, Mistry M, Sage D, Black JA, Waxman SG, Crest M, Clerc N, Delmas P, Gola M (2003) Selective expression of a persistent tetrodotoxin-resistant Na⁺ current and Nav1.9 subunit in myenteric sensory neurons. *J Neurosci* 23:2715–2725
 103. Rush AM, Dib-Hajj SD, Liu S, Cummins TR, Black JA, Waxman SG (2006) A single sodium channel mutation produces hyper- or hypoeexcitability in different types of neurons. *Proc Natl Acad Sci U S A* 103:8245–8250. <https://doi.org/10.1073/pnas.0602813103>
 104. Rush AM, Cummins TR, Waxman SG (2007) Multiple sodium channels and their roles in electrogenesis within dorsal root ganglion neurons. *J Physiol* 579:1–14. <https://doi.org/10.1113/jphysiol.2006.121483>
 105. Sadler KE, Stucky CL (2019) Neuronal transient receptor potential (TRP) channels and noxious sensory detection in sickle cell disease. *Neurosci Lett* 694:184–191. <https://doi.org/10.1016/j.neulet.2018.11.056>
 106. Sawal HA, Harripaul R, Mikhailov A, Dad R, Ayub M, Jawad Hassan M, Vincent JB (2016) Biallelic truncating SCN9A mutation identified in four families with congenital insensitivity to pain from Pakistan. *Clin Genet* 90:563–565. <https://doi.org/10.1111/cge.12860>
 107. Shields SD, Deng L, Reese RM, Dourado M, Tao J, Foreman O, Chang JH, Hackos DH (2018) Insensitivity to pain upon adult-onset deletion of Nav1.7 or its blockade with selective inhibitors. *J Neurosci* 38:10180–10201. <https://doi.org/10.1523/JNEUROSCI.1049-18.2018>
 108. Shorer Z, Wajsbrot E, Liran TH, Levy J, Parvari R (2014) A novel mutation in SCN9A in a child with congenital insensitivity to pain. *Pediatr Neurol* 50:73–76. <https://doi.org/10.1016/j.pediatrneurol.2013.09.007>
 109. Singh NA, Pappas C, Dahle EJ, Claes LR, Pruess TH, De Jonghe P, Thompson J, Dixon M, Gumett C, Peiffer A, White HS, Filloux F, Leppert MF (2009) A role of SCN9A in human epilepsies, as a cause of febrile seizures and as a potential modifier of Dravet syndrome. *PLoS Genet* 5:e1000649. <https://doi.org/10.1371/journal.pgen.1000649>
 110. Skeik N, Rooke TW, Davis MD, Davis DM, Kalsi H, Kurth I, Richardson RC (2012) Severe case and literature review of primary erythromelalgia: novel SCN9A gene mutation. *Vasc Med* 17:44–49. <https://doi.org/10.1177/1358863X11422584>
 111. Snape A, Pittaway JF, Baker MD (2010) Excitability parameters and sensitivity to anemone toxin ATX-II in rat small diameter primary sensory neurones discriminated by Griffonia simplicifolia isolectin IB4. *J Physiol* 588:125–137. <https://doi.org/10.1113/jphysiol.2009.181107>
 112. Sopacua M, Hoeijmakers JGJ, Merkies ISJ, Lauria G, Waxman SG, Faber CG (2019) Small-fiber neuropathy: expanding the clinical pain universe. *J Peripher Nerv Syst* 24:19–33. <https://doi.org/10.1111/jns.12298>
 113. Stirling LC, Forlani G, Baker MD, Wood JN, Matthews EA, Dickenson AH, Nassar MA (2005) Nociceptor-specific gene deletion using heterozygous Nav1.8-Cre recombinase mice. *Pain* 113:27–36. <https://doi.org/10.1016/j.pain.2004.08.015>
 114. Suter MR, Bhuiyan ZA, Laedermann CJ, Kuntzer T, Schaller M, Stauffacher MW, Roulet E, Abriel H, Decosterd I, Wider C (2015) p.L1612P, a novel voltage-gated sodium channel Nav1.7 mutation inducing a cold sensitive paroxysmal extreme pain disorder. *Anesthesiology* 122:414–423. <https://doi.org/10.1097/ALN.0000000000000476>
 115. Tanaka BS, Nguyen PT, Zhou EY, Yang Y, Yarov-Yarovoy V, Dib-Hajj SD, Waxman SG (2017) Gain-of-function mutation of a voltage-gated sodium channel Nav1.7 associated with peripheral pain and impaired limb development. *J Biol Chem* 292:9262–9272. <https://doi.org/10.1074/jbc.M117.778779>
 116. Tham SW, Giles M (2018) Current pain management strategies for patients with erythromelalgia: a critical review. *J Pain Res* 11:1689–1698. <https://doi.org/10.2147/JPR.S154462>
 117. Themistocleous AC, Ramirez JD, Serra J, Bennett DL (2014) The clinical approach to small fibre neuropathy and painful channelopathy. *Pract Neurol* 14:368–379. <https://doi.org/10.1136/practneurol-2013-000758>
 118. Toledo-Aral JJ, Moss BL, He ZJ, Koszowski AG, Whisenand T, Levinson SR, Wolf JJ, Silos-Santiago I, Halebouga S, Mandel G (1997) Identification of PN1, a predominant voltage-dependent sodium channel expressed principally in peripheral neurons. *Proc Natl Acad Sci U S A* 94:1527–1532. <https://doi.org/10.1073/pnas.94.4.1527>
 119. Vetter I, Deuis JR, Mueller A, Israel MR, Starobova H, Zhang A, Rash LD, Mobli M (2017) Nav1.7 as a pain target—from gene to pharmacology. *Pharmacol Ther* 172:73–100. <https://doi.org/10.1016/j.pharmthera.2016.11.015>
 120. Wang Y, Mi J, Lu K, Lu Y, Wang K (2015) Comparison of gating properties and use-dependent block of Nav1.5 and Nav1.7 channels by anti-arrhythmics mexiletine and lidocaine. *PLoS One* 10:e0128653. <https://doi.org/10.1371/journal.pone.0128653>
 121. Waxman SG, Kocsis JD, Black JA (1994) Type III sodium channel mRNA is expressed in embryonic but not adult spinal sensory neurons, and is reexpressed following axotomy. *J Neurophysiol* 72:466–470. <https://doi.org/10.1152/jn.1994.72.1.466>
 122. Waxman SG, Dib-Hajj S, Cummins TR, Black JA (1999) Sodium channels and pain. *Proc Natl Acad Sci U S A* 96:7635–7639. <https://doi.org/10.1073/pnas.96.14.7635>
 123. Wu MT, Huang PY, Yen CT, Chen CC, Lee MJ (2013) A novel SCN9A mutation responsible for primary erythromelalgia and is resistant to the treatment of sodium channel blockers. *PLoS One* 8:e55212. <https://doi.org/10.1371/journal.pone.0055212>
 124. Wu B, Zhang Y, Tang H, Yang M, Long H, Shi G, Tang J, Shi X (2017) A novel SCN9A mutation (F826Y) in primary erythromelalgia alters the excitability of Nav1.7. *Curr Mol Med* 17:450–457. <https://doi.org/10.2174/1566524017666171009105029>
 125. Yang Y, Wang Y, Li S, Xu Z, Li H, Ma L, Fan J, Bu D, Liu B, Fan Z, Wu G, Jin J, Ding B, Zhu X, Shen Y (2004) Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythromelalgia. *J Med Genet* 41:171–174. <https://doi.org/10.1136/jmg.2003.012153>
 126. Yang Y, Huang J, Mis MA, Estacion M, Macala L, Shah P, Schulman BR, Horton DB, Dib-Hajj SD, Waxman SG (2016) Nav1.7-A1632G mutation from a family with inherited erythromelalgia: enhanced firing of dorsal root ganglia neurons evoked by thermal stimuli. *J Neurosci* 36:7511–7522. <https://doi.org/10.1523/JNEUROSCI.0462-16.2016>
 127. Yang C, Hua Y, Zhang W, Xu J, Xu L, Gao F, Jiang P (2018) Variable epilepsy phenotypes associated with heterozygous mutation in the SCN9A gene: report of two cases. *Neurol Sci* 39:1113–1115. <https://doi.org/10.1007/s10072-018-3300-y>
 128. Yekkirala AS, Roberson DP, Bean BP, Woolf CJ (2017) Breaking barriers to novel analgesic drug development. *Nat Rev Drug Discov* 16:545–564. <https://doi.org/10.1038/nrd.2017.87>

129. Yu YQ, Zhao F, Guan SM, Chen J (2011) Antisense-mediated knockdown of Na(V)1.8, but not Na(V)1.9, generates inhibitory effects on complete Freund's adjuvant-induced inflammatory pain in rat. *PLoS One* 6:e19865. <https://doi.org/10.1371/journal.pone.0019865>
130. Zhang XY, Wen J, Yang W, Wang C, Gao L, Zheng LH, Wang T, Ran K, Li Y, Li X, Xu M, Luo J, Feng S, Ma X, Ma H, Chai Z, Zhou Z, Yao J, Zhang X, Liu JY (2013) Gain-of-function mutations in SCN11A cause familial episodic pain. *Am J Hum Genet* 93:957–966. <https://doi.org/10.1016/j.ajhg.2013.09.016>
131. Zhang Z, Schmelz M, Segerdahl M, Quiding H, Centerholt C, Jureus A, Carr TH, Whiteley J, Salter H, Kvernebo MS, Orstavik K, Helas T, Kleggetveit IP, Lunden LK, Jorum E (2014) Exonic mutations in SCN9A (Nav1.7) are found in a minority of patients with erythromelalgia. *Scand J Pain* 5:217–225. <https://doi.org/10.1016/j.sjpain.2014.09.002>
132. Zhang T, Chen M, Zhu A, Zhang X, Fang T (2020) Novel mutation of SCN9A gene causing generalized epilepsy with febrile seizures plus in a Chinese family. *Neurol Sci*. <https://doi.org/10.1007/s10072-020-04284-x>
133. Zhao F, Li X, Jin L, Zhang F, Inoue M, Yu B, Cao Z (2016) Development of a rapid throughput assay for identification of hNav1.7 antagonist using unique efficacious sodium channel agonist, antillatoxin. *Mar Drugs* 14. <https://doi.org/10.3390/md14020036>
134. Zimmermann K, Leffler A, Babes A, Cendan CM, Carr RW, Kobayashi J, Nau C, Wood JN, Reeh PW (2007) Sensory neuron sodium channel Nav1.8 is essential for pain at low temperatures. *Nature* 447:855–858. <https://doi.org/10.1038/nature05880>
135. Zufall F, Pyrski M, Weiss J, Leinders-Zufall T (2012) Link between pain and olfaction in an inherited sodium channelopathy. *Arch Neurol* 69:1119–1123. <https://doi.org/10.1001/archneurol.2012.21>

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