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

Mark D. Baker 1 · Mohammed A. Nassar 2

Received: 28 April 2020 / Revised: 25 May 2020 / Accepted: 10 June 2020 / Published online: 29 June 2020
© The Author(s) 2020

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, NaV1.7 and NaV1.9, play in pain signalling in man. Gain of function mutations in NaV1.7 cause painful conditions while loss of function mutations cause complete insensitivity to pain. Only gain of function mutations have been reported for NaV1.9. However, while most NaV1.9 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,1.7 · Na,1.9

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

1 Blizard Institute, Queen Mary University of London, Whitechapel, London E1 2AT, UK
2 Biomedical Science, University of Sheffield, Firth Court, Western Bank, Sheffield S10 2TN, UK
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 (Na\textsubscript{v}1.7, Na\textsubscript{v}1.8 and Na\textsubscript{v}1.9) meet the above criteria. Not surprisingly, many pharmaceutical companies are developing and testing subunit specific Na\textsubscript{v}1.7, Na\textsubscript{v}1.8 and Na\textsubscript{v}1.9 blockers as analgesics [38, 128].

The three α-subunits differ in their biophysical properties that determine their role in neuronal excitability [104]. The Na\textsubscript{v}1.9 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]. Na\textsubscript{v}1.7 generates a transient Na\textsuperscript{+} 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]. Na\textsubscript{v}1.8 has a relatively depolarised activation voltage (~−20 mV) compared with Na\textsubscript{v}1.7 and Na\textsubscript{v}1.9 [2, 104]; thus, Na\textsubscript{v}1.8 activation comes after and perhaps subsequent to the activation of Na\textsubscript{v}1.9 and Na\textsubscript{v}1.7 channels. Nonetheless, Na\textsubscript{v}1.8’s depolarised inactivation and more rapid recovery from inactivation allow it to contribute to repetitive firing, for example [104]. This review will focus on Na\textsubscript{v}1.9 and Na\textsubscript{v}1.7 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 Na\textsubscript{v}1.7 in pain**

Na\textsubscript{v}1.7 was cloned from PC12 cells in 1997 [118]. At that time, Na\textsubscript{v}1.8 and Na\textsubscript{v}1.3 channels were already under the spotlight and their role in pain was actively being investigated. Na\textsubscript{v}1.8 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 Na\textsubscript{v}1.8 knockout mouse was reported 3 years later and although it showed a pain deficit, its phenotype was compromised by a compensatory up-regulation of Na\textsubscript{v}1.7 [3] with clear functional consequences [3, 89]. However, knockdown of Na\textsubscript{v}1.8 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 Na\textsubscript{v}1.8, the expression pattern of Na\textsubscript{v}1.3 does not suggest it would be a useful drug target. Na\textsubscript{v}1.3 is expressed throughout the nervous system and its expression is highest during embryonic development and decreases postnatally [121]. However, Na\textsubscript{v}1.3 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 Na\textsubscript{v}1.3 do not show any deficits in pain phenotype [92].

Na\textsubscript{v}1.7 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 Na\textsubscript{v}1.7) 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 Na\textsubscript{v}1.7 in most nociceptors [91]. The conditional ablation in nociceptors was achieved using a Cre driver mouse line where Cre is expressed by the Na\textsubscript{v}1.8 promoter [113]. The complete loss of all inflammatory pain and mechanical pressure after ablation of Na\textsubscript{v}1.7 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 Na\textsubscript{v}1.7 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 Na\textsubscript{v}1.7 global KO mice to survive to adulthood [49]. Inducing Na\textsubscript{v}1.7 ablation in adult mice causes pain deficits without detrimental effects [107].

Remarkably, the symptoms of PEM patients complemented the phenotype of the conditional Na\textsubscript{v}1.7 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,
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 Na\textsubscript{1.7}, 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 relief 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 Na\textsubscript{v}1.7 [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 Na\textsubscript{1.7} 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 Na\textsubscript{1.7} 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
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, Na1.7 [10], Na1.8 [44] and Na1.9 [63] channels, have been found in heritable SFN cases.

Characterisation of Na1.7 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. Na1.7 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 Na1.7 in epilepsies**

Although the expression of Na1.7 in the human brain is poorly characterised, there is emerging evidence that Na1.7 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 Na1.7 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 Na1.7 function has no detrimental effect on the brain, altered or increased Na1.7 function does. Therefore, further research is needed to provide insights onto the type of cells that express Na1.7 (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 Na1.7.

**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 nonsense 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 Na1.9 in pain**

Na1.9 (gene name SCN1A) is a tetrodotoxin-resistant (TTX-r), so-called persistent Na+ current, with clear evidence for
The functional expression of 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 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 PEPID-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] |
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 $\text{SCN11A}$ reported in the literature and these have been associated with an elimination of the GTP-$\gamma$-S-upregulated current in primary sensory neurons [94] and a complementary reduction in forms of inflammatory pain following exposure to PGE2 [4]—consistent with a role of Na$_{\text{v}}$1.9 in inflammatory pain in both the skin and gut. A likely role for Na$_{\text{v}}$1.9 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 $\text{SCN11A}$.

### Painful and Painless Na$_{\text{v}}$1.9 Channelopathies

About 20 mutations have been reported for $\text{SCN11A}$, 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 Na$_{\text{v}}$1.9 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, $\text{SCN11A}$ 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 $\text{SCN11A}$-related small fibre neuropathy experience pain, tingling and numbness in their arms and legs. Patients may

![Fig. 2](image-url)
experience diarrhoea which is consistent with expression of Na$_v$1.9 in the gut [130].

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

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

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.
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 Nav1.9 expressing neurons. This prolonged depolarisation causes rapidly gating Na+ channels (e.g. Nav1.7 and Nav1.8) to enter the inactivated state [64]. Since these channels underpin action potential generation and propagation, the depolarizing block of Na1.7 and Na1.8 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 painfull small fibre neuropathy cause smaller shifts, Table 6 [31]. Also of note, SCN11A 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, Na1.9 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, Na1.8 which is expressed in most nociceptors (i.e. in same neurons as Na1.9) 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 Na1.7 and Na1.9 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 Na1,1.7 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 Na1,1.9 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 Na1.8 and Na1.9 in mice does not lead to lethality or any observable detrimental effects. Ablation of Na1.7 in human [19] and in adult mice [107].

| 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] |

**Fig. 4** Topological representation of SCN9A mutations that are linked to epilepsies
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-term administration. The development of specific and effective small molecule inhibitors of Na,1.7 is still elusive, despite efforts by several pharmaceutical companies [38, 71, 128]. The second challenge is the extent of Na,1.7 inhibition required for analgesia in vivo. Given that CIP carriers have normal pain phenotype, an Na,1.7 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,1.7 [87, 97]. Several papers have provided complementary evidence for this hypothesis. The first paper, published in 2001, reported the identification of a novel mutation in SCN9A, S459X, that results in complete insensitivity to pain (CIP) [19]. Since then, numerous other mutations have been identified, as summarized in Table 5.

### Table 5: SCN9A Mutations that Cause CIP

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

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

![Topological representation of SCN9A mutations](image)

![Table 5: SCN9A Mutations that Cause CIP](image)

Fig. 6 a Upregulation of Na,1.9 in an Na,1.8 knockout neuron, following the introduction of 500 μM GTP-γ-S into the cell interior for 12 min. b Upregulation of Na,1.9 using intracellular GTP-γ-S gives rise to changes in the firing properties of Na,1.8 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.

![Fig. 6: Upregulation of Na,1.9](image)
evidence that the loss of Na\textsubscript{v}1.7 reduces the excitability of DRG neurons per se. Deletion of Na\textsubscript{v}1.7 causes an increase in action potential threshold in small-diameter DRG neurons \cite{107}. Deletion of Na\textsubscript{v}1.7 causes a major decrease in DRG neuron responsiveness to the VGSC opener veratridine \cite{89}. Mechanically evoked spiking of C-fibres in the skin-nerve preparation was reduced in Na\textsubscript{v}1.7 KO mice \cite{49}. No changes in the expression of other VGSC channels were reported in the Na\textsubscript{v}1.7 KO mouse to contribute to the observed reduced excitability of DRG \cite{107}. Furthermore, pain deficits in a rat model of Na\textsubscript{v}1.7 deletion were not reversed by the opioid receptor antagonist naloxone \cite{14}. Therefore, although an

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

Fig. 7 Topological representation of SCN11A 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 Na\textsubscript{v}1.7 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 Na\textsubscript{v}1.9 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 (Na\textsubscript{v}1.7, Na\textsubscript{v}1.8 and Na\textsubscript{v}1.9), 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 \cite{88} and provided proof-of-concept data that showed a combination of Na\textsubscript{v}1.7 and Na\textsubscript{v}1.8 blockers produced a reduction in the excitability of DRG neurons close to that measured in Na\textsubscript{v}1.7 KO \cite{89}. Changing the constituents and doses in VGSC blocker combinations may enable clinicians to manage chronic pain safely over the long term.

**Acknowledgements** MAN is grateful to Yusef Nassar for the proof reading and suggestions on the manuscript.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

**References**

1. Ahn HS, Dib-Hajj SD, Cox JJ, Tyrell L, Elmslie FV, Clarke AA, Drenth JP, Woods CG, Waxman SG (2010) A new Nav1.7 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

2. 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

3. Akopian AN, Soulova V, England S, Okuse K, Ogata N, Ure J, Smith A, Kerr BJ, McMahon SB, Boyce S, Hill R, Stanfia 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

4. Amaya F, Wang H, Costigan M, Allchorne AJ, Hatcher JP, Egerton J, Stein T, Morisset V, Grose D, Gunthorpe MJ, Chessell IP, Tate S, Green PJ, Woolf CJ (2006) The voltage-gated sodium channel Na\textsubscript{v}(1.9) is an effecter of peripheral inflammatory pain hypersensitivity. J Neurosci 26:12852–12860. https://doi.org/10.1523/JNEUROSCI.4015-06.2006

5. Baker MD (2005) Protein kinase C mediates up-regulation of tetrodotoxin-resistant, persistent Na\textsuperscript{+} current in rat and mouse sensory neurons. J Physiol 567:851–867. https://doi.org/10.1113/jphysiol.2005.089771

6. Baker MD, Chandra SY, Ding Y, Waxman SG, Wood JN (2003) GTP-induced tetrodotoxin-resistant Na\textsuperscript{+} current regulates excitability in mouse and rat small diameter sensory neurons. J Physiol 548:373–382. https://doi.org/10.1113/jphysiol.2003.039131

7. Bennett DL, Woods CG (2014) Painful and painless channelopathies. Lancet Neurol 13:587–599. https://doi.org/10.1016/S1474-4422(14)70024-9

8. Beyak MJ, Vanner S (2005) Inflammation-induced hyperexcitability of nociceptive gastrointestinal DRG neurons: the role of voltage-gated ion channels. Neurogastroenterol Motil 17:175–186. https://doi.org/10.1111/j.1365-2982.2004.00596.x

9. Breivik H, Collett B, Ventafredda 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

10. 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/jnns.12071

11. Caterina MJ, Pang Z (2016) TRP channels in skin biology and pathophysiology. Pharmaceuticals (Basel) 9. https://doi.org/10.3390/ph9040077

12. Catterall WA (2017) Forty years of sodium channels: structure, function, pharmacology, and epilepsy. Neuron-Chem Res 42:2495–2504. https://doi.org/10.1007/s11064-017-2314-9

13. Chen L, Efraim P, Carrara J, Zhao P, Dib-Hajj FB, Dib-Hajj SD, Waxman SG (2020) Pharmacological characterization of a rat Nav1.7 loss-of-function model with insensitivity to pain. Pain. https://doi.org/10.1097/j.pain.0000000000001807

14. Cheng X, Dib-Hajj SD, Tyrell L, Te Morsche RH, Drenth JP, Waxman SG (2011) Deletion mutation of sodium channel Na\textsuperscript{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

15. Choi JS, Cheng X, Foster E, Leffler A, Tyrell 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

16. 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

17. Coste B, Osorio N, Padilla F, Crest M, Delmas P (2004) Gating and modulation of presumptive Na\textsubscript{v}1.9 channels in enteric and spinal sensory neurons. Mol Cell Neurosci 26:1263–134. 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, Wraith E, Manor E, Levy J, Woods CG, Parvai 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. Clegg R, Laguda B, Verdehausen 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, Kinalli M (2013) Novel mutations mapping to the fourth sodium channel domain of Nav1.7 result in variable clinical manifestations of primary erythromelalgia. NeuronMolecular 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 131:898–921. https://doi.org/10.1016/j.pain.2007.07.020

26. Dubby R, Sadeh M, Gilad R, Lampl Y, Cohen S, Inbar S, Lesinsky-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 Groot BTA, Hoeijmakers JGI, Geerts M, Oakes M, Church TJ, 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+ Nav1.9: a sodium channel with unique properties. Trends Neurosci 25:253–259. 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/lda003

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, Sopuca M, Hoeijmakers JGI, de Groot BTA, Lindsey P, Almornani 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 novel 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, Vanhouette 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, Kapetsi 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 TZE, Gilmore ES, Estacion M, Eastman E, Taylor S, Melanson M, Dib-Hajj SD, Waxman SG (2009) A novel Nav1.7 mutation producing carbamazepine-responsive
Neurosurg Psychiatry 84:386–391. https://doi.org/10.1136/jnp-2012-033719

73. Kurbau, 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. Labar, Jürgen, Estacion M, Tanaka BS, de Groot BTA, Hoeijmakers JGJ, de Greef BTA, Hoier-Madsen M, Takazawa T, Oostra BA, Oostra BA, Nap JP, Van Zijl MP, Willemsen CJ (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, Jun, Gold MS, Kim CS, Pian 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

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 neurones with C-, adelta- or alpaha/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, Kerenke GC, Heinrich T, Giesselmann S, Baets J, Dib-Hajj SD, Eastman EM, Tyrrell L, Lin Z, Yang Y, Waxman SG (2009) Erythromelalgia mutation in SCN9A gene causes idiopathic focal epilepsy with sensitation to pain in humans and mice lacking sodium channel Nav1.7. Nat Commun 6:8967. https://doi.org/10.1038/ncomms9967

80. Leipold E, Liebmann L, Gong P, Bernstein JA, Voigt M, Katona I, Oliver Goral R, Altmuller J, Nurnberg P, Timmerman V, De Jonghe P, Blum R, Schaible HG, Weis J, Hennings JC, 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 449:76–107. https://doi.org/10.1007/s00424-004-1315-0

81. Liu Z, Ye X, Qiao P, Luo W, Wu Y, He Y, Gao P (2019) G327E mutation in SCN9A gene causes loss of pain perception. Nat Genet 45:1399–1404. https://doi.org/10.1038/ng.2767

82. Mahmood 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.000000000001802

83. 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/10.1166/nnb.12264.10-0200-8

84. Nassar MA, Stirling LC, Fortiani 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

85. Porreca F (2002) Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, Nav1.7. Pflugers Arch 472:865–880
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, Thornele 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, Ritter AM, Martin WJ, Thorneloe KS (2009) The voltage-gated sodium channel expressed principally in peripheral neurons. J Neurosci 23:2715–2725

103. Rush AM, Dib-Hajij SD, Liu S, Cummings TR, Black JA, Waxman SG (2006) A single sodium channel mutation produces hyper- or hypoexcitability 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 electrogensis 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 nosoxisc 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 F, Leppert MF (2009) A role of SCN9A in human epilepsies, as a mutation in SCN9A channelopathy associated autosomal recessive congenital indifference to pain. Eur J Paediatr Dent 18:66–71. https://doi.org/10.23804/ejpd.2017.18.01.14

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.1050-18.2018

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, Gummett 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. Vase Med 17:44–49. https://doi.org/10.1111/j.1538-686X.2011.022584

111. Snape A, Pittaway JF, Baker MD (2010) Excitability parameters and sensitivity to anemone toxin AXH-II in rat small diameter primary sensory neurones discriminated by Griffonia simplicifolia isoslectin IB4. J Physiol 586:125–137. https://doi.org/10.1113/jphysiol.2009.181107

112. Sopacua M, Hoeijmakers JGI, 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, Kutner T, Schaller M, Stauffacher MW, Roulet E, Abrief 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 YE, Yang Y, Yarov-Yarovoy V, Dib-Hajij 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/10.1113/jnci.12000758

118. Toledo-Aral JI, Moss BL, He ZJ, Koszowski AG, Whisendan T, Levinson SR, Wolf JJ, Silos-Santiago I, Halegoua 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, Deus JR, Mueller A, Israel MR, Starobova H, Zhang W, 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-arrrhythmics 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/10.1111/j.1365-2724.1994.tb12146.x

122. Waxman SG, Dib-Hajij 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/10.1016/j.disc.2016.11.015

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, Shah P, Macala L, 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, 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

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.