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TOPICAL REVIEW

Pain channelopathies

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Pain remains a major clinical challenge, severely afflicting around 6% of the population at any one time. Channelopathies that underlie monogenic human pain syndromes are of great clinical relevance, as cell surface ion channels are tractable drug targets. The recent discovery that loss-of-function mutations in the sodium channel Nav1.7 underlie a recessive pain-free state in otherwise normal people is particularly significant. Deletion of channel-encoding genes in mice has also provided insights into mammalian pain mechanisms. Ion channels expressed by immune system cells (e.g. P2X7) have been shown to play a pivotal role in changing pain thresholds, whilst channels involved in sensory transduction (e.g. TRPV1), the regulation of neuronal excitability (potassium channels), action potential propagation (sodium channels) and neurotransmitter release (calcium channels) have all been shown to be potentially selective analgesic drug targets in some animal pain models. Migraine and visceral pain have also been associated with voltage-gated ion channel mutations. Insights into such channelopathies thus provide us with a number of potential targets to control pain.

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Abbreviations FHM, familial hemiplegic migraine; PEPD, paroxysmal extreme pain disorder; TRP channel, transient receptor potential channel.

Introduction

The importance of pain perception as a survival mechanism is undisputed. However, pain syndromes of no physiological utility resulting from chronic inflammatory disease or nerve damage are common and hard to treat. The two major classes of analgesics, non-steroidal anti-inflammatory drugs acting on arachidonic acid metabolism, and opioids acting through endogenous G-protein-coupled receptor systems whilst useful, are often limited by side effects. New drug targets are thus desirable, particularly ion channels that are accessible to circulating drugs and easy to assay in heterologous expression systems. It is striking that the few new treatments for neuropathic or intractable pain act on ion channels. Thus gabapentin/pregabalin acts to lower trafficking and expression of Cav2.1, whilst ziconotide is an N-type calcium channel blocker (Field *et al.* 2006; Rauck *et al.* 2009).

All authors contributed equally to this review.

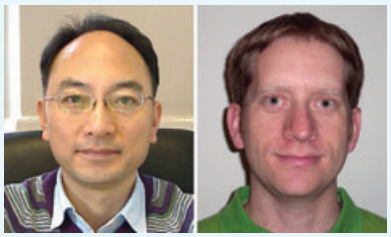

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Table 1. Human pain channelopathies

	Gene	Gene map locus	Channel/pump	Phenotype	Reference
Transduction	*ANKTM1*	8q13	TRPA1	FEPS	(B. Kreymer *et al*. unpublished observations)
Transmission	*SCN9A*	2q24	Nav1.7 sodium channel	IEM	(Yang *et al.* 2004)
	SCN9A	2q24	Nav1.7 sodium channel	PEPD	(Fertleman *et al.* 2006)
	SCN9A	2q24	Nav1.7 sodium channel	CIDP	(Cox *et al.* 2006)
CNS/migraine	*CACNA1A*	19p13	Cav2.1 calcium channel	FHM type I	(Ophoff *et al.* 1996)
	ATP1A2	1q23	α2 subunit, Na^+,K^+-ATPase	FHM type II	(De Fusco *et al.* 2003)
	SCN1A	2q24	Nav1.1 sodium channel	FHM type III	(Dichgans *et al.* 2005)

CIDP, congenital indifference to pain; FEPS, familial episodic pain syndrome; FHM, familial hemiplegic migraine (Type I, II, III); IEM, inherited erythromelalgia (primary erythermalgia); PEPD, paroxysmal extreme pain disorder (familial rectal pain). Online Mendelian Inheritance in Man entry number (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim).

The observation that specialised damage-sensing peripheral neurons are necessary for pain in man and mice focused attention on this first stage of the pain pathway (Indo *et al.* 1996). A number of ion channels selectively expressed in nociceptive neurons have been shown to have a role in pain induction by gene ablation studies, whilst recent rapid advances in human genetics have also identified channels involved in migraine and pain syndromes. The present state of knowledge of channelopathies is schematised in Fig. 1. Table 1 lists known human pain-related channelopathies and Table 2 summarises pain phenotypes associated with channel deletion in mice. References to the syndromes discussed in the text are noted in the two tables. A useful database of pain-related genes identified in transgenic mice has been established by the Mogil group (Lacroix-Fralish & Mogil, 2009). Here we divide pain channelopathies into those that impact on sensory transduction, electrical signalling, neurotransmitter release and central nervous system functions linked to migraines and headache.

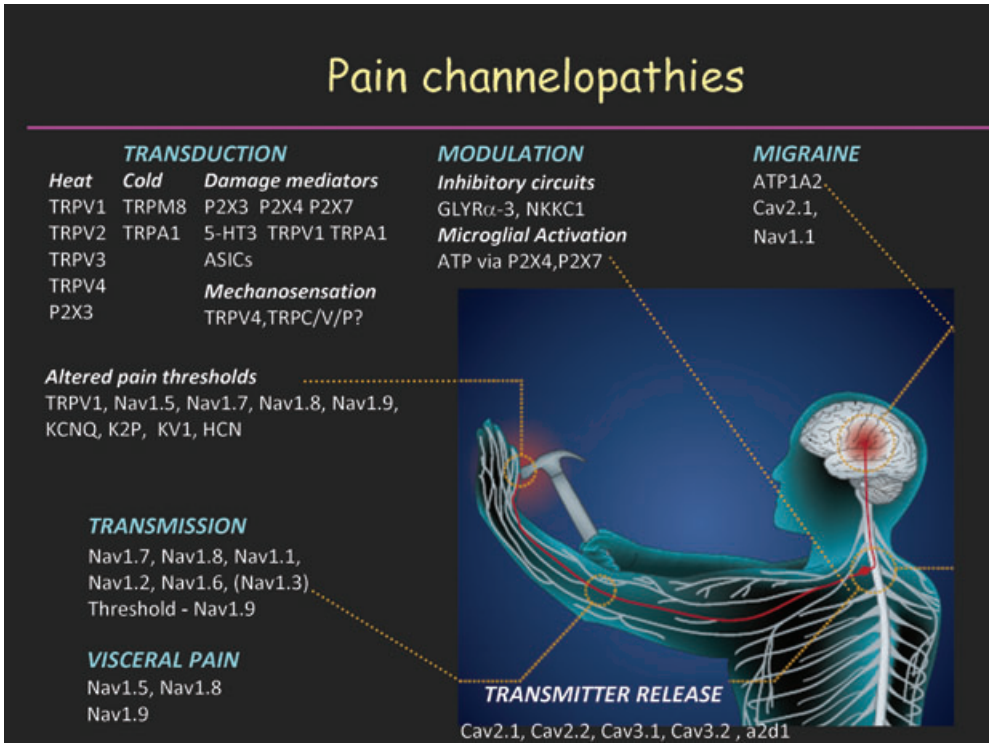

Figure 1
Ion channels associated with pain syndromes identified in transgenic mice and heritable human disorders. Channels are classified by the principal deficits in pain pathways associated with channel dysfunction. Artwork reprinted by permission from Macmillan Publishers Ltd: Poster entitled 'Pain mechanisms' by Stephen McMahon, David Bennett, *Nature Reviews Neuroscience* sponsored by Boehringer Ingelheim, artwork by Kirsten Lee (http://www.nature.com/nrn/poster/pain), © (2007) Nature Publishing Group.

Table 2. Mouse pain channelopathies

	Gene	Gene map locus	Channel	Evidence in knockout mice	Reference
Transduction	*Trpv1*	11 B3	TRPV1	Impaired thermal avoidance. Absence of thermal hyperalgesia.	(Caterina *et al.* 2000)
	Trpv4	5 F	TRPV4	Impaired osmotic, thermal and mechanical hyperalgesia.	(Suzuki *et al.* 2003)
	Trpm8	1 D	TRPM8	Reduced avoidance to cold temperatures but normal response to noxious cold.	(Dhaka *et al.* 2007)
	Trpa1	1 A3	TRPA1	Behavioural deficit in cold hyperalgesia.	(Kwan *et al.* 2006)
	Accn2	15 F1	ASIC 1	Enhanced pain behaviour after formalin injection.	(Staniland & McMahon 2009)
	Accn1	11 B5	ASIC 2	Enhanced pain behaviour after formalin injection.	(Staniland & McMahon 2009)
	Accn3	5 A3	ASIC 3	Lack of chronic hyperalgesia in mice injected with acid.	(Sluka *et al.* 2003)
	P2rx3	2 D	P2X3	Normal acute pain but reduced inflammatory pain	(Souslova *et al.* 2000)
	P2rx4	5 F	P2X4	No major defects in acute pain. Attenuation of pain hypersensitivity to innocuous mechanical stimuli in inflammatory and neuropathic pain.	(Tsuda *et al.* 2009)
	P2rx7	5 F	P2X7	Normal acute pain but complete absence of inflammatory and neuropathic pain	(Chessell *et al.* 2005)
Transmission	*Hcn1*	13 D2.3	HCN1	Reduced behavioural response to cooling.	(Momin *et al.* 2008)
	Scn3a	2 C1.3	Nav1.3	Normal acute, inflammatory and neuropathic pain.	(Nassar *et al.* 2006)
	Scn9a	2 C1.3	Nav1.7	Increased acute mechanical and thermal pain threshold. Inflammatory pain threshold reduced or abolished. No effect on neuropathic pain.	(Nassar *et al.* 2004)
	Scn10a	9 F4	Nav1.8	Diminished response to inflammatory pain. No effect on neuropathic pain.	(Akopian *et al.* 1999)
	Scn11a	9 F3-F4	Nav1.9	Greatly reduced or absent thermal and mechanical inflammatory hyperalgesia. No loss of neuropathic pain hypersensitivity.	(Priest *et al.* 2005)
	Scn2b	9 A5.2	b2	Increased sensitivity to noxious thermal stimuli. Attenuated response to inflammatory pain.	(Lopez-Santiago *et al.* 2006)
	Kcna1	6 F1-F3	Kv1.1	Mice are hyperalgesic.	(Clark & Tempel 1998)
	Kcnd2	6 A2-A3.1	Kv4.2	Mice display enhanced sensitivity to acute thermal and mechanical stimuli.	(Hu *et al.* 2006)
	Kcnj3 and *Kcnj6*	2 C1.1 and 16 C4	Kir3.1 and Kir3.2	Both mice display thermal hyperaglesia and a reduced analgesic response to morphine	(Marker *et al.* 2004)
	Kcnk2	1 H6	K2P2.1	Increased sensitivity to acute pain and display thermal and mechanical hyperalgesia.	(Alloui *et al.* 2006)
	Kcnk3	5 B1	K2P3.1	Enhanced sensitivity to acute thermal pain	(Linden *et al.* 2006)
CNS	*Cacna1a*	8 C3	Cav2.1	Increased mechanical threshold in inflammatory and neuropathic pain.	(Luvisetto *et al.* 2006)
	Cacna1b	2 A2	Cav2.2	Suppressed responses to inflammatory pain. Reduced symptoms of neuropathic pain.	(Saegusa *et al.* 2001)
	Cacna1e	1 G3	Cav2.3	Mice show enhanced morphine analgesia and reduced tolerance in mice.	(Yokoyama *et al.* 2004)
	Cacna1g	11 D	Cav3.1	Neuropathic mice have reduced spontaneous pain and lowered mechanical and thermal hyperalgesia.	(Na *et al.* 2008)
	Cacna1h	17 A3.3	Cav3.2	Endogenous lipoamino acids (anandamide-related molecules) produce strong thermal analgesia that is absent in Cav3.2 mutants.	(Barbara *et al.* 2009)
	Glra3	8 B2	α3 (glycine receptor)	Reduced Complete Freund's Adjuvant (CFA) behaviour.	(Harvey *et al.* 2009)
	Slc12a2	18 D3	NKCC1 Na^+-K^+-Cl^--cotransporter	Mice show increased latency in the tail flick test and reduced capsaicin-evoked pain.	(Laird *et al.* 2004)

Sensory transduction

Members of the transient receptor potential (TRP) family of cation channels have been implicated in many aspects of sensation. TRP receptors activated by acid, eicosanoids, heat, cold and possibly mechanical pressure are all expressed in damage-sensing neurons (Bevan & Andersson, 2009). Deleting TRPV1 and TRPV4 lead to inflammatory and mechansensory pain deficits, respectively, in mice (Caterina *et al.* 2000; Suzuki *et al.* 2003), whilst gain-of-function mutations in TRPV4 in man do not lead to enhanced pain but rather to a Charcot Marie tooth syndrome associated with peripheral nerve loss and skeletal abnormalities (Landouré *et al.* 2009). TRPA1 deletion in mice leads to deficits in responses to environmental irritants, and possible effects on cold sensing and mechano-transduction (Kwan *et al.* 2006). In man, a gain-of-function mutation in TRPA1 that leads to enhanced channel activity in response to both endogenous agonists and cold has been linked to paroxysmal pain induced by tiredness (B. Kreymer, F. Lopera, J.J. Cox, A. Momin, F. Rugiero, S. Marsh, G.C. Woods, N.G. Jones, K.J. Paterson, F.R. Fricker, A. Villegas, N. Acosta, N.G. Pineda-Trujillo, J.O. Ramirez, J. Zea, M.W. Burley, G. Bedoya, D.L.H. Bennett, J.N. Wood & A. Ruiz-Linares). No human TRPA1 null mutants have as yet been identified.

Other receptors, including members of the epithelial sodium channel family (EnaC) family, have been implicated in acid sensing, whilst ATP-gated cation channels in sensory neurons (P2X3) and macrophages/microglia also have pronounced pain phenotypes on deletion in mice. P2X3 has been linked to heat-sensing, mechanical allodynia and acute pain deficits (Souslova *et al.* 2000). P2X7 null mice are unable to respond to tissue damage with sensitised pain thresholds (Chessell *et al.* 2005).

Excitability and electrical signalling

Ongoing pain or allodynia associated with nociceptor hyperexcitability seems to be the hallmark of chronic pain syndromes including neuropathic pain (pain caused by nerve damage). Attempts to identify the channels responsible for this over-activity have invoked voltage-gated sodium and potassium channels. Human Nav1.1 mutations have been linked to both epilepsy and migraine (Dichgans *et al.* 2005). Nav1.3 is upregulated in animal models of neuropathic pain, but the deletion of this channel in mice does not lead to pain deficits (Nassar *et al.* 2006). Some human Nav1.5 mutations cause visceral pain (Saito *et al.* 2009). Nav1.8, a marker for nociceptors, plays a critical role in cold pain and inflammatory and mechanical pain in mice, but its role in neuropathic pain is less certain, as gene deletion or even the ablation of neurons expressing Nav1.8 does not seriously diminish neuropathic pain (Zimmermann *et al.* 2007; Abrahamsen *et al.* 2008). Interestingly, a common non-synonymous Nav1.8 single-nucleotide polymorphism (SNP) expressed in human heart is a risk factor for atrial fibrillation and heart attacks (Chambers *et al.* 2010). Nav1.9, a voltage-gated ion channel that is associated with a persistent current, and whose biophysical properties are sensitised by inflammatory mediators seem to be essential for inflammatory pain in mice, but does not play a major role in neuropathic pain (Priest *et al.* 2005). Accessory β-2 subunit deletion also has effects on heat and inflammatory pain perception (Lopez-Santiago *et al.* 2006).

The sodium channel most closely associated with human pain syndromes is the peripheral nervous system channel Nav1.7 encoded by *SCN9A*, which is discussed in the context of erythermalgia in a paper by Estacion *et al.* (2010) in this issue. Gain-of-function mutations that lead to incomplete inactivation result in a paroxysmal pain syndrome (PEPD) which is triggered by mechanical pressure, for example during defecation. The persistent current associated with PEPD mutations seems to account for this phenotype (Fertleman *et al.* 2006). Consistent with such a mechanism, tissue-specific deletion of Nav1.7 in mouse nociceptors was shown to block noxious mechanosensation and attenuate inflammatory, but not neuropathic pain (Nassar *et al.* 2004). In man, a number of groups have described pain-free families with loss-of-function mutations in Nav1.7. Apart from anosmia (Nav1.7 is expressed in olfactory neurons) human Nav1.7 nulls are normal, highlighting this channel as an attractive, potentially side-effect-free, analgesic drug target (Cox *et al.* 2006).

Loss of function of potassium channels involved in determining action potential threshold or repolarisation may cause neurons to become hyperexcitable resulting in increased sensitivity to noxious stimuli and less sensitivity to analgesics. One such family of potassium channels is the Kv7 family (KCNQ) that mediates the M current. Genetic or pharmacological inhibition of M current leads to increased neuronal excitability whereas M channel openers, such as retigabine, suppress action potential firing. Thus it appears that the KCNQ family plays a key role in controlling the excitability of nociceptors and may represent a novel analgesic target.

The *Shaker*-like (Kv1) class of voltage-gated delayed rectifier K^+ channels and inwardly rectifying potassium channels (Kir3.1 and 3.2) play a central role in nociceptive pathways, and help to mediate the analgesic effects of morphine. Null mutant animals for all three channels show a reduced or blunted response to morphine analgesia. Furthermore, Kv1.1 null mutants have significantly shorter latencies to heat pain and increased responses to formalin injection whilst morphine analgesia is blunted (Clark & Tempel, 1998).

The K2p2.1 channel (TREK-1) is a member of the 2P-domain K^+ channel (K_{2P}) family. Mice with a disrupted TREK-1 gene are more sensitive to painful heat sensation near the threshold between noxious warmth and painful heat. Furthermore, knockout mice display increased thermal and mechanical hyperalgesia in conditions of inflammation (Alloui *et al.* 2006). HCN channels have also been implicated in neuropathic pain through studies of null mutant mice (Momin *et al.* 2008).

Neurotransmitter release

Although channelopathies suggest that nociceptor-associated voltage-gated ion channels are the most promising analgesic drug targets, deficits in calcium channels and their auxiliary subunits associated with neurotransmitter release have also been found to be associated with defective pain pathways. Engineered mutation in the coding sequence of accessory subunit $\alpha 2\delta 1$ prevents binding of the drug gabapentin, used widely in the treatment of neuropathic pain, with loss of its analgesic efficacy (Field *et al.* 2006). $\alpha 2\delta 1$ enhances trafficking of Cav2.1 involved in neurotransmitter release (Hendrich *et al.* 2008). $\alpha 2\delta 1$ null mice exist but have not been tested for pain deficits.

Cav2.1 null mutant mice show a number of deficits in pain pathways depending on their age (Luvisetto *et al.* 2006). Young null mutants display a reduced number of writhes in response to acetic acid I.P. injection and a reduced tail flick latency. Heterozygous adult mutant mice demonstrate a reduced licking time during the phase 2 of the formalin test and a reduced mechanical allodynia in response to chronic constriction injury of the sciatic nerve These differential effects of Cav2.1 deletion are likely to be explained by the widespread expression of this protein in dorsal root ganglion, spinal cord and rostral ventromedial medulla and by the fact that Cav2.1 controls the release of both excitatory and inhibitory transmitters.

Cav2.2 null mice (Saegusa *et al.* 2002) have lowered inflammatory and neuropathic pain as demonstrated by phase 2 of the formalin test and spinal nerve ligation models, respectively. In addition, this deletion causes differential response to general anaesthetic agents (Takei *et al.* 2003).

Cav2.3 deletion in mice highlights the importance of this protein in supra-spinal morphine analgesia and tolerance (Yokoyama *et al.* 2004). Cav2.3 null mice display enhanced analgesia following systemic or I.C.V. morphine injection or endogenous opioid release elicited by stress. These mice are resistant to morphine tolerance, making Cav2.3 an attractive drug target, although the therapeutic window of Cav2.3 blockers is made narrow by the hyperglycaemic phenotype of Cav2.3 mutants (Matsuda *et al.* 2001).

Ca^{2+} channel α subunits underlying low-voltage-activated neuronal T-type currents also play an important role in pain pathways. For instance Cav3.1$^{-/-}$ mice show reduced spontaneous pain responses, increased paw withdrawal threshold in response to mechanical stimulation and attenuated thermal hyperalgesia following L5 spinal nerve ligation (Na *et al.* 2008).

Studies of Cav3.2$^{-/-}$ mice relate mainly to the channel's prominent role in cardiac and endothelial tissues. Nevertheless, knock-down of Cav3.2 revealed its importance in both acute and chronic pain conditions (Bourinet *et al.* 2005). Furthermore Barbara *et al.* (2009) using Cav3.2$^{-/-}$ mice demonstrated that Cav3.2 subunits are major targets of endogenous lipoamino acids, anandamide-related molecules that produce strong thermal analgesia, and that this analgesia is lost in Cav3.2 mutants.

Ion channels and migraine

Migraine is a severe, disabling headache affecting about 18% of women and 6% of men (Kors *et al.* 2002). The aetiology of the disease involves multiple interacting genetic and environmental determinants. Recent genetic findings identified mutations in ionchannels and transporters (Cav2.1, $\alpha 2$ subunit Na^+,K^+-ATPase and Nav1.1) in familial hemiplegic migraine (FHM) (Ophoff *et al.* 1996; De Fusco *et al.* 2003; Dichgans *et al.* 2005). FHM is a rare and genetically heterogeneous autosomal dominant subtype of migraine. The first FHM gene, *CACNA1A* (FHM1) encodes the pore-forming $\alpha 1$ subunit of neuronal Cav2.1 (P/Q-type) voltage-gated calcium channels which is widely expressed in the central nervous system. All the 21 FHM1 mutations are missense mutations of conserved amino acids in important functional regions including the pore lining and the voltage sensors. These FHM1 mutations have a broad range of clinical features including hemiplegic migraine, cerebellar ataxia and epilepsy (de Vries *et al.* 2009). The second FHM gene, *ATP1A2* encodes the $\alpha 2$ subunit of the Na^+,K^+-ATPase, which is a P-type ion pump that utilizes the energy of ATP to actively transport Na^+ ions out of and K^+ ions into the cell. There are now over 30 FHM2 mutations most of which are associated with FHM without additional clinical symptoms, although some of them show cerebellar problems, childhood convulsions, epilepsy and mental retardation (Pietrobon, 2007). The third FHM gene *SCN1A* (FHM3) is also a well-known epilepsy gene with over 100 truncating and missense mutations that are associated with childhood epilepsy. Five FHM3 mutations have been identified that all change amino acid residues (Pietrobon, 2007).

Several FHM transgenic mice models have been generated to study the pathogenesis of migraine (Bergerot *et al.* 2006). Transgenic *Cacna1a*-null mutant mice develop

a rapid progressive ataxia and dystonia before dying about 3–4 weeks after birth (Jun *et al.* 1999; Fletcher *et al.* 2001). Total calcium current density in cerebellar cells was decreased by 70%. P/Q-type currents were abolished and appeared partly compensated for by N- and L-type current (Bergerot *et al.* 2006). The *Cacna1a* knock-in mouse carrying the human FHM1 mutation R192Q, previously identified in patients with pure FHM was generated in 2004 (van den Maagdenberg *et al.* 2004), shows no obvious phenotype. However, multiple gain-of-function effects were found, including increased Cav2.1 current density in cerebellar neurons and, in the intact animal, a reduced threshold and increased velocity of cortical spreading depression. FHM2 *ATP1A2*-null mutants, have been generated. However, they die after birth because of spontaneous respiratory failure. Heterozygous *ATP1A2* knock-out mice showed increased fear and anxiety behaviour, probably resulting from neuronal hyperactivity in the amygdala and piriform cortex (James *et al.* 1999; Ikeda *et al.* 2003; Bergerot *et al.* 2006).

Migraine is a complex genetic disorder and the aetiology is still unclear (Goadsby, 2007). Genetic and functional studies in FHM have identified a key role for disturbed ion transport. However, gene identification in common, multifactorial migraine has been largely unsuccessful (de Vries *et al.* 2009). New linkage studies using alternative phenotyping methods and large-scale genome-wide association studies (GWAS) may provide more insights into this disorder.

Future perspectives

GWAS of populations with different pain thresholds and further identification of recessive monogenic pain syndromes associated with channel mutations are all likely to provide useful insights into pain pathways. Recent studies have associated ion channel function with previously uncharacterised hydrophobic proteins (Yang *et al.* 2008), suggesting that our knowledge of ion channels is by no means complete. Trafficking deficits and aberrant interactions with auxiliary proteins are also potential mechanisms of channel dysregulation. Whilst mapping and sequencing strategies have focused on exons, the importance of microRNAs in human pathology is clear, and channel dysregulation through mutations in non-coding sequences are likely to exist (Abelson *et al.* 2005). Thus pain-related channelopathies are likely to provide fruitful analgesic drug targets in the future, and remain a fascinating source of insight into the mechanisms of pain pathways.

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