**ARTICLE**

# Sodium channelopathy of peripheral nerve: tightening the genotype-phenotype relationship

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Among proteins involved in neurological disease ion channels are amenable to the most detailed characterisation: patch-clamp methods allow the opening and closing of individual channels to be documented at millisecond resolution in response to precisely delivered stimuli (whether electrical or pharmacological). In theory, therefore, inherited disorders of ion channels should be ideal candidates to link the functional consequences of individual mutations at the molecular level to their clinical manifestations. Disappointingly, it has been difficult to 'explain' the phenotype of many CNS channelopathies: even where disease-associated mutations exert robust effects on ion channel properties studied in vitro, a full account of the occurrence of hemiplegic migraine, seizures, ataxia or paroxysmal dyskinesias remains frustratingly out of reach. More success has been encountered in the muscle channelopathies: myotonic discharges are explained by disruption of the normal membrane-potential stabilising function of mutated chloride channels, or gain-of-function mutations of sodium channels. And if sufficiently severe, impaired inactivation of sodium channels predisposes to persistent depolarisation and inexcitability, accounting for attacks of periodic paralysis. Nevertheless, even among the muscle channelopathies many puzzles remain, not least how mutations that affect voltage-sensing amino acids of sodium or calcium channels lead to hypokalaemic periodic paralysis. In contrast to the patchy success in explaining genotype-phenotype correlations in most CNS and muscle channelopathies, those caused by mutations of the peripheral nerve sodium channel NaV1.7 are showing a remarkable degree of consistency, as illustrated by the elegant study of Han and co-workers in this issue (Han *et al.*, 2009).

NaV1.7, encoded by the gene SCN9A, is expressed in dorsal root ganglion and sympathetic ganglion neurons. Although allocating distinct classes of afferent fibres to different sensory roles remains problematic, the experiments of nature represented by human SCN9A mutations have provided persuasive evidence that NaV1.7 is important for nociception. Three distinct phenotypes have emerged in recent years, with – so far – a striking correspondence with the respective biophysical derangement. Primary erythermalgia (sometimes also known as erythromelalgia) is characterised by burning pain in the periphery exacerbated by high temperatures and associated with redness and oedema of extremities. Underlying mutations, which are typically dominantly inherited, lower the voltage at which channels activate, and therefore act through a gain of function. A second condition, paroxysmal extreme pain disorder (PEPD), is also dominantly inherited, but is characterised instead by episodic proximal pain, most prominent in a sub-mandibular, ocular or perineal distribution (Fertleman *et al*., 2007). Indeed, the alternative term familial rectal pain syndrome draws attention to the severe attacks that often present in early childhood and can lead to secondary constipation. The SCN9A mutations in PEPD also cause a gain in NaV1.7 function, although through impaired inactivation rather than because of a shift in the activation threshold. Although these are distinct disorders, Estacion *et al.* (2008) recently reported overlapping clinical features in a patient with a mutation that both lowered the

threshold of activation and impaired inactivation. The final disorder linked to SCN9A is congenital indifference to pain. This rare recessive disorder, which has so far only been identified in a few consanguineous families, is caused by complete absence of functional Nav1.7 channels and results in total loss of sensitivity to noxious stimuli. Thus a remarkably consistent genotype-phenotype relation is emerging. A lowered voltage threshold for activation presumably leads to spontaneous firing of distal pain fibres, impaired inactivation causes paroxysms of severe pain, and absence of the channel eliminates nociception altogether.

The second type of genotype-phenotype relationship, the one Han *et al.* explore here, is more subtle. That is the link between the severity of the functional change measured in heterologous expression, and the severity of the clinical manifestation, with the age of onset of symptoms as a surrogate marker. Han et al. describe a patient whose symptoms of primary erythermalgia only came on in mid teens, unlike most patients who present in the first decade. The novel mutation, which changes a glutamine residue at position 10 to arginine, is associated with the smallest shift yet reported in the voltage dependence of activation (-5.3 mV). Indeed, this and the I136V mutation reported and studied by Lee *et al.* (2007) and Cheng *et al.* (2008) stand out in that both are associated with a shift less than 6 mV and relatively late onset of symptoms (Table 1).

Demonstrating altered biophysical properties in a simple heterologous expression system is however limited in its power to explain the occurrence of symptoms, which are presumably due to excessive firing of nociceptors. NaV1.7 is especially suited to amplifying small and slow depolarising stimuli because, unlike many other sodium channels, it undergoes relatively little 'closed state' inactivation, which represents a tendency for sodium channels to become reluctant to open upon slow depolarisation even before they have activated. Because mutations associated with erythermalgia are dominantly inherited, over-expression in small neurons isolated from rat dorsal root ganglion provides a convenient method to examine their effects on firing. Han *et al.* use this method to show that the new Q10R mutation decreases the minimal depolarising current required to obtain action potentials. However, this effect is smaller than that of the I848T mutation associated with a larger shift in activation and earlier onset of symptoms.

Where next? As further spontaneously occurring mutations are identified, it will be important to ask whether the correlation between the degree of alteration in biophysical parameters and phenotypic severity and age of onset holds up. A more daunting challenge is however to understand why mutations that lower the activation threshold and inactivation kinetics are associated with such strikingly different manifestations. The temperature sensitivity of mutant NaV1.7 associated with erythermalgia may provide a clue to why patients often obtain relief from deliberate cooling of their extremities. More widely, however, why are so many channelopathies characterised by paroxysmal symptoms, given that the gene defect is fixed throughout life? Although a positive feedback between muscle depolarisation and extracellular potassium accumulation provides a compelling explanation for attacks of hyperkalaemic periodic paralysis associated with gain-of-function muscle NaV1.4 mutations, the episodic nature of most other channelopathies remains poorly understood. Finally, will the biophysical insights lead to new treatments? As it stands, patients with erythermalgia gain modest benefit from drugs such as carbamazepine that facilitate sodium channel inactivation, although patients with PEPD seem to benefit more. It remains to be determined whether other drugs acting on sodium channels through distinct mechanisms, such as the new antiepileptic agent lacosamide, offer any benefit.

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**Table 1** Shifts in activation, age of onset and amino acid position in SCN9A/NaV1.7

| a.a. position | mean age of onset | V1/2 of activation Mutant | WT | shift in V1/2 | Clinical description | Electrophysiological characterisation |
|---|---|---|---|---|---|---|
| **Q10R** | 14 | -30.0 ± 0.4 mV | -24.7 ± 0.5 mV | -5.3 | Han *et al*., (2009) | Han *et al*., (2009) |
| **I136V** | 9 to 22 | -28.8 ± 0.5 mV | -23.1 ± 0.7 mV | -5.7 | Lee *et al*., (2007) | Cheng *et al*., (2008) |
| **F216S** | <10 | -33.2 ± 1.6 mV | -21.5 ± 1.9 mV | -11.7 | Drenth *et al*., (2001) | Choi *et al*., (2006) |
| **S241T** | <10 | -34.0 ± 1.1 mV | -25.6 ± 0.9 mV | -8.4 | Drenth *et al*., (2005) | Lampert *et al*., (2006) |
| **N395K** | <10 | -28.0 ± 1.1 mV | -20.3 ± 0.8 mV | -7.7 | Drenth *et al*., (2005) | Sheets *et al.*, (2007) |
| **I848T** | <10 | -38.4 ± 1.0 mV | -24.6 ± 1.1 mV | -13.8 | Yang *et al*., (2004) | Cummins *et al*., (2004) |
| **L858H** | 4 to 8 | -37.9 ± 0.9 mV | -24.6 ± 1.1 mV | -13.3 | Yang *et al*., (2004) | Cummins *et al*., (2004) |
| **L858F** | 2 | -37.2 ± 2.1 mV | -28.0 ± 1.8 mV | -9.2 | Han *et al.*, (2006) | Han *et al*., (2006) |
| **A863P** | <5 | -23.6 ± 0.6 mV | -15.9 ± 0.8 mV | -7.7 | Harty *et al*., (2006) | Harty *et al*., (2006) |
| **V872G** | 5 | -30.1 ± 1.8 mV | - 20.8 ± 1.7 mV | -9.3 | Choi *et al.*, (2009) | Choi *et al*., (2009) |
| **F1449V** | 3 | -22.8 ± 1.3 mV | -15.2 ± 1.3 mV | -7.6 | Finley *et al*., (1992) | Dib-Hajj *et al*., (2005) |
| **A1632E** | 3* | -33.3 ± 0.6 mV | -26.2 ± 1.6 mV | -7.1 | Estacion *et al*., (2008) | Estacion *et al*., (2008) |

*symptoms of paroxysmal extreme pain earlier onset