PAIN® xxx (2014) xxx–xxx

PAIN®

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Bridging the gaps: Special commentary

An *SCN9A* variant, known to cause pain, is now found to cause itch

Itch (also known as pruritus) is transmitted from the skin to the spinal cord by specific subsets of cutaneous sensory neurons that are thought to be distinct from those that mediate nociception [10]. Although we do not yet know all of the factors that trigger itch, it is often caused by a temporary immune response to something irritating in the skin—for instance, a brush with poison ivy. Unfortunately, there are many people for whom itch is a severe, unrelenting condition. Although there are many types of chronic itch, one of the most puzzling is paroxysmal itch, in which individuals experience sudden, intense feelings of itch that can be triggered by seemingly unrelated stimuli, such as heat. Now, the article by Devigili et al in this issue of *Pain* reports the discovery of a rare variant in *SCN9A* (which encodes Nav1.7) in 3 family members with paroxysmal itch. This study is a major breakthrough in our mechanistic understanding of paroxysmal itch, and suggests that drugs that target Nav1.7 have therapeutic potential for the treatment of chronic pruritus.

Nav1.7 is a voltage-gated sodium channel that is expressed in many dorsal root and trigeminal sensory neurons, as well as olfactory sensory neurons and sympathetic neurons. People with rare, recessive loss-of-function variants in *SCN9A* have congenital insensitivity to pain, and report never having experienced pain, even after severe injury [2]. Intriguingly, the loss of function of Nav1.7 also causes anosmia—the inability to smell [11]. However, other sensations, including touch, warm, cold, proprioception, and pressure, are not affected. Whether Nav1.7 is required for itch is not completely clear, as it has not yet been reported whether individuals lacking functional Nav1.7 experience itch. Nevertheless, new evidence suggests that this channel likely plays a key role, as mice treated with monoclonal antibodies that inhibit Nav1.7 show significantly reduced itch behaviors [8].

Dominant, gain-of-function variants in this channel can cause a variety of pain syndromes including paroxysmal extreme pain disorder, inherited erythromylalgia, and small fiber neuropathy [3–5]. However, up to now, there were no reports of Nav1.7 variants that result in neuropathic itch. The study by Devigli et al [1] sets a new precedent. The 3 affected family members described in this article express the 2215A>G variant in *SCN9A* resulting in a single amino acid substitution (I739V) in the Nav1.7 protein. Nav1.7 is normally a slowly inactivating channel, and the I739V variant makes it slower still, thereby causing hyperexcitability in sensory neurons and attacks of itch [7]. For unknown reasons, these attacks typically affect the trunk and distal arms, and can be precipitated by warmth and spicy food, suggesting the possible involvement of TRPV1. Of note, this particular variant has been previously reported in individuals with small fiber neuropathy experiencing paroxysmal pain [6,7]. Why some people expressing this variant develop itch while others experience pain is currently unknown.

There is a substantial interindividual variability with itch perception, likely due, at least in part, to genetic differences among people. Although rare genetic mutations have now been found to cause rare itch conditions, a common polymorphism may contribute to more common forms of itch. Studies of rare pain conditions highlighted *SCN9A* as a candidate gene for susceptibility to other pain conditions and altered pain perception in the general population. Thereafter it was found that a single nucleotide polymorphism in *SCN9A* is associated with increased pain scores in patients with sciatica, phantom limb pain and lumbar disc herniation as well as decreased pain thresholds in healthy volunteers [9]. The discovery in this issue of *Pain* that a variant in *SCN9A* can lead to abnormal itch suggests, by analogy, that alterations in this gene may underlie more common forms of pruritus and may potentially explain individual variability in itchiness.

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☆ DOI of original article: http://dx.doi.org/10.1016/j.pain.2014.05.006

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