Genome Medicine

MINIREVIEW

Genetic discovery: the prescription for chronic pain

Ming Zheng and Gary Peltz*

Abstract

A recent publication that combined rat gene expression data and a human genetic association study has identified the first genetic risk factor for chronic pain in humans. In four of the five cohorts studied, there was a significant association of an allele within a gene (*KCNS1*) encoding a potassium channel (Kv9.1) with an increased risk for chronic pain. Identification of genetic risk factors for chronic pain could catalyze new advances in this difficult clinical area that has become a major public health problem. Genomic-medicine-based advances for chronic pain could include the development of a mechanism-based classification system for chronic pain, new treatment options, improved methods for treatment selection and targeted prevention strategies for high-risk individuals.

There is tremendous inter-individual variation in the response to painful stimuli. A level of pain that completely incapacitates one individual may cause only a minor annoyance in another. Characterizing the genetic factors affecting susceptibility to chronic pain could lead to novel treatment or prevention strategies, which are desperately needed. A recent paper by Costigan *et al.* [1] presents a bold step toward understanding these differences. The authors performed a multi-dimensional analysis using rat gene expression and human genetic association that identified a new genetic factor affecting susceptibility to chronic pain. This study [1] was initiated by analysis of gene expression changes within rat dorsal root ganglia obtained after nerve damage was induced in three different models of chronic pain. The mRNA for a potassium channel alpha subunit (*Kcns1*) was constitutively expressed in sensory neurons, but was downregulated after three types of nerve injury in these models.

*Correspondence: gpeltz@stanford.edu
Department of Anesthesia, Stanford University School of Medicine, Stanford, CA 94305, USA

Other studies have successfully identified a human genetic susceptibility factor on the basis of a candidate gene emerging from analysis of a rodent model [2]. Costigan and colleagues [1] therefore examined SNP alleles within the human homolog (*KCNS1*) in five independent cohorts (two with chronic low back pain, two after limb amputation and one after mastectomy) that have a high incidence of chronic pain. In four of the five cohorts studied, there was a significant association of the Val allele at a nonsynonymous SNP (rs734784, Val/Ile) with increased risk for chronic pain. For example, homozygous Val/Val individuals had a 2.4-fold increased relative risk of failing to achieve pain improvement 1 year after back surgery. The proportion of individuals without phantom limb pain after leg amputation was 45% in those without the Val allele, but fell to 22% in Val/Val homozygotes. Among healthy volunteers that were subjected to multiple experimental pain stimuli, Val/Val homozygous individuals showed greater sensitivity to the painful stimuli [1].

Although experimental studies demonstrating an allelic effect were not presented, which is a substantial limitation of this study, these results [1] make it likely that *KCNS1* alleles contribute to susceptibility to chronic pain. *KCNS1* encodes the $K_v9.1$ potassium channel subunit. Although KCNS1 by itself does not have potassium channel function when tested in heterologous expression systems, its expression has been shown to modulate the currents formed by other channels [3-5]. Voltage-gated potassium channels have important effects on neuronal function, including altering the resting membrane potential and the shape and frequency of the action potential. Similarly, gain-of-function mutations in the $Na_v1.7$ sodium channel cause syndromes associated with increased pain sensitivity [6,7].

The need for new treatments for chronic pain

Chronic pain has a huge impact on our society, and its treatment is a major driver for the increasing cost of health care. An estimated 76 million people in the US have chronic pain, which costs the US public over $100 billion per year. Approximately 25% of chronic pain is neuropathic (caused by nerve damage), which is characterized by spontaneous pain that is burning or

stabbing in nature. This can develop after limb amputation, mastectomy or lower back injury, or in individuals with a long history of diabetes. Although multiple kinds of treatment can be used, they often have limited efficacy, and chronic pain is often managed by administration of opioids (morphine and related synthetic compounds, including hydrocodone). The increased focus on pain management resulted in a six-fold increase in the per capita sales of prescription opioid medications in the US between 1997 and 2006 [8]. Hydrocodone-acetaminophen is prescribed over 100 million times per year in the US, which is far more than any other medication, including lipid-lowering and blood-pressure-lowering agents [9]. This has led to a dramatic increase in the incidence of opioid misuse, emergency room visits due to opioid analgesic poisoning, and fatal opioid overdose. Prescription opioids have now surpassed marijuana as the drug that is most commonly abused among the newly initiated [10].

Because of the enormity of this public health problem, we desperately need new approaches for the prevention or treatment of chronic pain conditions. It is likely that genetic discoveries can lead to new approaches for chronic pain, because genetic discoveries have catalyzed new approaches for related clinical conditions. For example, haplotype-based computational genetic analysis has identified causative genetic factors affecting analgesic medication [11] and inflammatory pain responses [12,13], and it has identified four genes affecting narcotic drug responses [11,14-16] in mice. The latter genetic discovery generated a new treatment strategy for preventing narcotic drug withdrawal symptoms, which was shown to be effective in humans [16]. Moreover, the variable response to multiple classes of analgesic medications among inbred mouse strains was shown to be due to genetic variation within a genetic locus (*Kcnj9*) that also encodes a potassium channel (GIRK3) [11]. Hopefully, characterizing the functional role of *KCNS1* in neuronal responses and pain perception, and the impact of the allelic differences, could lead to new approaches for treatment of chronic pain. Although the tractability of KCNS1 (or other potassium channels) as a therapeutic target remains to be determined, small molecules targeting potassium channels have been produced (reviewed in [17]), and one has attenuated neuropathic pain in animal models [18].

Although the *KCNS1* Val allele explains only a small percentage of the total variance (4.6 to 7.8%) in the chronic pain endpoints in the cohorts studied [1], the identification of an initial genetic factor for chronic pain is an important achievement for two reasons. First, it shows that genetic factors can be identified for this condition, and this study provides a template for subsequent studies. Second, it is likely that a greater percentage of the genetic susceptibility to chronic pain can be explained by combining this genetic factor with other subsequently identified factors. Moreover, pain is a subjective sensory symptom; it is difficult to measure; and there are substantial psychological and emotional components that contribute to the perception of pain [19]. It has recently been found that there are different subtypes of chronic pain, which are distinct from the causative disease (diabetic neuropathy, radicular back pain and so on) [20]. It is likely that genetic factors determine whether a chronic pain syndrome will develop and the specific subtype that emerges after exposure to a triggering cause. Thus, the impact of a single genetic factor could be much larger if a specific pain subtype is examined relative to that measured in a large cohort of individuals with different types of chronic pain.

Genomic medicine for chronic pain

Beyond finding new drug targets, identification of genetic factors affecting susceptibility to chronic pain syndromes could be the lever that drives advances in this difficult clinical area. A genetic risk factor could have a substantial impact on clinical practice because individuals at increased risk for developing a chronic pain syndrome could be identified before a surgical procedure or immediately after a traumatic incident. The genetic information could be used to develop proactive methods for prevention of chronic pain syndromes, enabling interventions to be targeted to the high-risk subset. Because of the great inter-individual variation in the response to painful stimuli and to analgesic drugs, knowledge of genetic risk factors could enable better stratification of chronic pain patients or aid in the selection of the appropriate therapy. Rather than focusing on the disease that is etiologically associated with the chronic pain, genetic stratification would enable mechanism-based treatment selection.

The Costigan *et al*. study [1] is hopefully one of the first of many subsequent genetic studies that could lead to entirely new ways to approach chronic pain syndromes. Clearly, the clinical and research communities have a long way to go before genetically targeted therapies for chronic pain become a reality. However, *KCNS1* (or other channels) could perhaps become the next target for a new class of analgesics that are selectively used in the 20% of the population that are homozygous for the Val alleles of *KCNS1*. The day might soon come when we no longer think of 'chronic pain' as a single clinical entity, but have the tools to characterize the specific 'channelopathy' that underlies the clinical presentation and targeted treatments for each subgroup.

Abbreviations

SNP, single-nucleotide polymorphism.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
GP and MZ wrote the article.

Author information
GP is a professor and MZ is the director of statistical research in the Department of Anesthesia at Stanford University Medical School.

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