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REVIEW

GENETIC PREDICTORS OF HUMAN CHRONIC PAIN CONDITIONS

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Abstract—Chronic pain conditions are multifactorial disorders with a high frequency in the population. Their pathophysiology is often unclear, and treatment is inefficient. During the last 20 years, genetic linkage analysis and association studies have made considerable strides toward identifying key molecular contributors to the onset and maintenance of chronic pain. Here, we review the genetic variants that have been implicated in chronic pain conditions, divided into the following etiologically-grouped categories: migraine, musculoskeletal pain disorders, neuropathic pain disorders, and visceral pain disorders. In rare familial monogenic pain conditions several strong-effect mutations have been identified. In contrast, the genetic landscape of common chronic pain conditions suggests minor contributions from a large number of single nucleotide polymorphisms representing different functional pathways. A comprehensive survey of up-to-date genetic association results reveals migraine and musculoskeletal pain to be the most investigated chronic pain disorders, in which nearly half of identified genetic variability alters neurotransmission pathways.

Key words: chronic pain conditions, genetic association studies, GWAS, pain genetics, single nucleotide polymorphisms.

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INTRODUCTION

Chronic pain is a persistent maladaptive condition, estimated to affect up to 30% of the world's population (Elzahaf et al., 2012). Given the reported heritability of 16–50% (Hocking et al., 2012; Nielsen et al., 2012), a substantial proportion of the risk of developing a chronic pain condition is driven by genetic background. To date the search for contributing genetic variants has yielded an outline of a centralized pain-processing system, spearheaded by neurotransmitters and their receptors and modulated by myriad other factors, ranging from inflammatory cytokines to growth factors. Although a gestalt understanding is important for conceptualizing chronic pain, genetic studies have shown a cosegregation of distinct pathologies with their putative causal factors at the gene/protein level. Therefore, it will be helpful to present an overview of the current knowledge about genetics of chronic pain separated by etiology, known or hypothesized.

Numerous genetic risk factors have been identified for musculoskeletal, neuropathic, and visceral conditions, as well as migraine. Among these, migraine and musculoskeletal pain disorders have undergone the most extensive investigation in association studies and

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Abbreviations: CWP, chronic widespread pain; FHM, familial hemiplegic migraine; GWAS, genome-wide association studies; OA, osteoarthritis; SNPs, single nucleotide polymorphisms; TMD, temporomandibular disorder; TMJ, temporomandibular joint; VNTR, variable number of tandem repeats.

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have accumulated the highest number of implicated genetic variants (Fig. 1), although many of them await replication (Fig. 2). The list of chronic pain genes (Table 1) is a snapshot of the incredible complexity of the suspected network of molecular interactions. This list includes genes from catecholaminergic, serotonergic, estrogenic, glutamatergic, GABAergic, purinergic and orexinergic pathways; cytokines; growth factors; and proteinases.

The purpose of this review is threefold: (1) provide an overview of the current state of knowledge in human chronic pain genetics, (2) highlight relevant genetic studies and their outcomes for each pathology category, and (3) summarize the genomically-derived mechanisms of molecular pathophysiology for each category.

Genetic variability

The human genome is replete with genetic variants. The majority are germline mutations, passed from parents to offspring. Less common *de novo* mutations are not inherited from parents and occur in offspring only. Examples of *de novo* mutations in sodium channels, Nav1.7, *SCN9A*, and Nav1.9, *SCN11A*, have been described in post-trauma pain perception, congenital insensitivity to pain, and primary erythromelalgia (Klein et al., 2012; Leipold et al., 2013). Somatic mutations acquired during one's lifetime are not passed on to offspring. These mutations have been implicated in cancer but so far have not been associated with chronic pain conditions.

Rare but drastic mutations have been identified as causal in several monogenic familial disorders, in which mutations in a single gene locus result in the onset of the condition. For example, a frameshift mutation, which severely compromises the function of the encoded protein, has been discovered in the TWIK-related spinal cord potassium channel (TRESK) gene, *KCNK18*, and is responsible for familial migraine with aura (Lafrenière et al., 2010). A more common type of causal mutation in rare familial disorders is a nonsynonymous mutation in one nucleotide that leads to an amino acid change of substantial functional effect in the resulting protein. Sodium channels are the best-known example, extensively studied for their role in monogenic conditions such as erythromelalgia, caused by mutations in *SCN9A* (Yang et al., 2004).

Unlike the rare, high-impact mutations described above, common single nucleotide polymorphisms (SNPs), found in >1% of the population, comprise the vast majority of human genetic association studies. These mutations usually have a very minor phenotypic effect and often exert their effect in concert with specific environmental pressures. Rather than directly causing a chronic pain disease, these SNPs modulate susceptibility to it. The minor allele contributes either risk or protection by increasing (conferring gain-of-function on) or decreasing (conferring loss-of-function on) the activity of the resultant protein. Approximately 90% of SNPs are found in introns or intergenic regions, outside of the protein-coding segments of the gene, outlining their regulatory role. SNPs that fall in the exonic, or protein-coding, region may be either non-synonymous, resulting in a different amino acid, or synonymous, not

Condition	# of associations
Migraine	194
Temporomandibular disorder	36
Fibromyalgia	29
Low back pain	20
Visceral pain	11
Cancer pain	11
Postoperative pain	9
Stress-induced chronic pain	7
Diabetic neuropathic pain	2
Trigeminal neuralgia	1

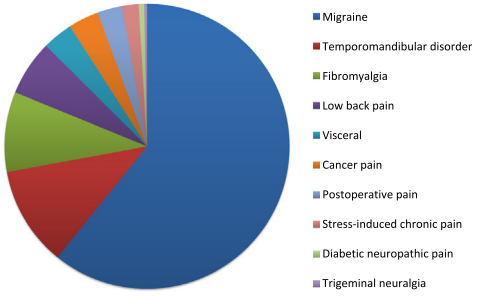

Fig. 1. Chronic pain conditions quantified by the number of genetic association studies. For each condition, the number of published genetic associations is given, including both positive and negative results. Rare Mendelian disorder variants from linkage studies are not included.

Condition	# of citations
Migraine	32
Low back pain	5
Temporomandibular disorder	4
Stress-induced chronic pain	2
Visceral pain	2
Fibromyalgia	2
Postoperative pain	2
Cancer pain	1

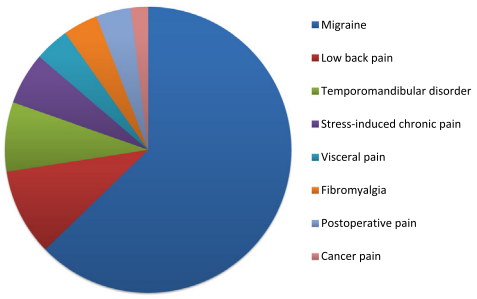

Fig. 2. Chronic pain conditions quantified by the number of genetic loci. Only genes with positive association in a given disorder or group of disorders reported in at least two studies are included, and rare Mendelian disorder variants from linkage studies are not included.