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A Review of Genetics in Chronic Pain

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ABSTRACT

Chronic pain impacts up to 50 million Americans yearly, where hundreds of billions of dollars are spent annually treating pain. The burden on health care systems and patients emphasizes our need to further investigate chronic pain. In recent years, the advent of advanced genome sequencing technologies has enabled us to identify variations in genomic regions which might contribute to susceptibility to pain as well as individuals' response to treatment. The purpose of this review is to better understand the complex and multifactorial pathophysiology of chronic pain. A deeper understanding of the genetics of chronic pain could have wide implications in the diagnosis of pain pathologies as well as pain management therapy.

Methods: *This review conducted a literature analysis on the genetics of chronic pain. The PubMed® search engine was used to research key words "chronic pain", "pain management", "pharmacogenomics", "gene therapy", and "individualized medicine". This paper's research focused on investigating studies that conducted hypothesis-free genetic studies and genome-wide association studies (GWAS). Data from our literature search was compiled into this review and analyzed to discuss strengths and weaknesses of the current literature, and to discuss future avenues of research.*

Results: *Many gene loci and mutations were identified as being associated with chronic pain pathologies. Results from pertinent genetic studies as well as online gene databases were compared to one another to isolate significant associations between genetics, pharmacogenomics, and pain management therapy.*

Discussion: *When reviewing the literature searches, we found that although individual studies found significant associations between specific genes and chronic pain pathologies, the results from these studies were unable to be replicated on a larger scale. The genetic data associated with chronic pain has yet to be replicated consistently in different studies on subjects of different ethnicities, geographical distributions, and socioeconomic statuses. Further research into the genetics of chronic pain is needed to make generalizable conclusions and implement them in clinical practice.*

Keywords
Chronic pain, Individualized medicine, Pain genes, Pain management, Pharmacogenomics.

Introduction

Chronic pain is among the most prevalent problems between human health and disease, causing considerable morbidity and mortality and in doing so being a huge cost burden to society and health infrastructure. Chronic pain is defined as pain that lasts or recurs for greater than 3-6 months [1]. Tension headaches, one of the most common forms of chronic pain, affect up to 1.9 billion people worldwide and are the most common symptomatic chronic condition worldwide [2]. In 2016, chronic pain affected an estimated 50 million Americans, and $150 billion USD is spent annually treating pain [3,4]. The current management protocol for chronic pain is highly personalized and offered in a tier-wise manner. Opioids, a very common modality of medical treatment for chronic pain, are associated with high risks of dependence and toxicity. The prevalence and expense of chronic pain, as well as the suboptimal outcomes and risks associated with pain management therapy, emphasize our need to better understand the pathophysiology of chronic pain and develop novel therapies for treatment.

Genome wide association studies (GWAS) have identified multiple susceptibility genetic markers, and since then our understanding of the genetics of pain has deepened significantly. Much information in this area has been obtained by animal studies and, per published literature and databases, genetic variations in more than 350 genes have been reportedly associated with pain perception [5]. Another important contribution of genetics in chronic pain management is pharmacogenomics, which in brief deals with inter-individual genomic variations that cause varying responses to analgesic drugs. This paper centralizes our current knowledge of the genetics of chronic pain, the pharmacogenomics surrounding current pain management therapy, and discusses future avenues of research in this field.

Heritability is a measure of the proportion of disease etiology or disease occurrence which can be attributed to the total sum of genetic variations [6]. Studies performed on monozygotic and dizygotic twins are typically powerful methodology to estimate heritability of a condition. Chronic pain susceptibility is a typical multifactorial disorder resulting from complex interactions between the genome and multiple environmental factors [5]. Genetic studies performed on twins demonstrated relatively early on that the variability of pain responses could be explained by genetics in 20-60% of cases [7,8]. Studies have also shown that chronic pain conditions like irritable bowel syndrome (25%), back and neck pain (35%), and chronic widespread pain and migraines (50%) are largely determined by genetic factors [9].

Results

One powerful way to gain insight into the genetics of chronic pain is by identifying single genes inherited in a Mendelian manner that result in an abnormality of pain perception or present with pain as a predominant symptom. This group comprises disorders associated with pathogenic variants in one of the genes responsible for pain perception. The knowledge of these conditions is important because these genes are strong candidates for large scale GWAS, which provide valuable insights for understanding pain pathophysiology as well as planning research towards the development of drugs. The most important genes in this group of disorders where abnormal pain perception or body pain are the main presenting features are discussed in Table 1. Table 1 is meant to highlight the most important single gene disorders and is not meant to be exhaustive by any means.

Table 1: Single-gene chronic pain disorders and their associated genes as reported by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [10-22].

Gene(s)	Associated pathology
SCN9A	Congenital insensitivity to pain (CIP), Autosomal recessive hereditary sensory neuropathy type IID (HSN2D), Paroxysmal extreme pain disorder, Familial rectal pain
NGF, KIF1A, SCN11A, RETREG1, DST, SPTLC1, ELP1, PRDM12, ATL3, WNK1, ATL1, SPTLC2, TECPR2, DNMT1	Associated with the group of hereditary sensory and autonomic neuropathies
SEPT9	Hereditary neuralgic amyotrophy (HNA)
TNFRSF1A	Familial periodic fever
MEFV	Familial Mediterranean fever
NTRK1	Congenital insensitivity to pain with anhidrosis
TRPA1, SCN10A, SCN11A	Associated with the group of familial episodic pain syndromes
GLA	X-linked pathology associated with angiokeratoderma as well as heart and kidney failure
TGFB1	Camurati-Engelmann disease
COL9A2, MATN3, SLC26A2, COL9A1, CANT1, COMP and COL9A3	Various types of multiple epiphyseal dysplasia
ATP1A2, SCN1A and CACNA1A	Familial hemiplegic migraine
COL2A1 and TRPV4	Autosomal dominant primary avascular necrosis of the femur

Susceptibility to pain is a complex physiological state, which is determined by multiple genetic and environmental factors. The most common mutations that affect genes are single nucleotide polymorphisms (SNPs), where a single base-pair mutation alters the structure of the resultant protein and thus its activity in the body [22]. Various genomic polymorphisms, mainly SNPs, have been associated with pain perception and the response to injury/inflammation. The prominent genes in which these risk alleles or genetic polymorphisms have been reported are *COMT*, *GCH1*, *OPRM1*, *OPRD1*, *TRPA1*, *KCNA1*, *TRPV1*, *SCN9A*, *KCNS1*, *CACNA2D3*, *FAAH*, *MC1R*, *CYP2D6*, *HLA**, *HTR2A*, *IL1RN*, *TNF*, *SLC6A4*, and *ABCB1* [23]. These risk alleles or genetic polymorphisms are identified by two main approaches — candidate gene-based approach and hypothesis-free GWAS.

Candidate gene-based approaches typically target genes which are already known to be associated with pathophysiology of pain perception, response to injury/inflammation (i.e., post-surgical) or genes which are strongly associated with Mendelian pain conditions as described in Table 1. GWAS, on the other hand, are performed on a larger number of subjects with identified pathology (i.e., with chronic pain) with their matched controls. The presence or absence of SNPs are analyzed for relative abundance or absence in the targeted cohort.

One study by Johnston et al. conducted a GWAS on ~380,000 UK Biobank participants for multisite chronic pain (MCP) [24]. The study found that 76 SNPs at 39 genomic loci had significant associations with MCP. In their study, the sum aggregate of genetic contribution of SNPs was determined to be 10%. Significant genetic correlations were also observed between chronic pain conditions and neuropsychiatric disorders, as well as autoimmune and anthropometric traits like body mass index [25,26]. Similarly, many genetic association studies have been performed for other types of chronic pain conditions like migraine, low back pain, cancer pain, and visceral pain [27]. However, since chronic pain is a complex symptomatology with varied clinical presentations and cohort characteristics, conflicting results for SNPs remain a huge challenge in deciphering these studies.

The Human Pain Genetics Database (HPGDB) is a freely accessible, regularly updated database that identifies genomic variants associated with pain phenotypes [28]. Currently, this database describes >1652 variants [accessed on Oct 17th, 2021]. Such databases mapping the genomic markers associated with pain are important to understand the pathophysiology of human pain perception, response to injury/inflammation, and the risk of developing chronic pain conditions. Furthermore, these databases offer potentially enabling novel and informed approaches to identify new treatment targets, tailor personalized treatment regimens, and develop genetically based diagnostic approaches [9]. However, as mentioned earlier, the genomic data explaining chronic pain conditions is still limited. The individual contribution of these SNPs is very small, and the association of many of the identified risk susceptibility alleles needs to be consistently proven in large sample sizes across all ethnic and geographical populations before we can draw any meaningful, generalizable conclusions. Current knowledge of genetic association is quite primitive, and in the absence of a strong family history or a high suspicion of single gene disorders, genetic testing remains for research and academic interest only.

Large-scale omics data like exome or genome sequencing and functional data like protein expression hold promise for the future. Table 2 highlights genes in which mutations have been found to be significantly associated with prominent chronic pain conditions. The data demonstrates that certain chronic pain conditions are associated with variants in more than one gene.

Table 2: Gene polymorphisms and their associated pain pathologies [9,29].

Gene(s)	Associated pathology
SLC6A4, TRPV2, and COMT	Fibromyalgia
OPRM1, COMT, CASP9	Chronic low back pain
SCN9A, HMGB1P46, TLR4, OPRM1	Diabetic peripheral neuropathy
5-HTTLPR	Trigeminal neuralgia
SCN9A	Erythromelalgia
KCNS1, COMT, GCH1, OPRM1, ABCB1	Post operative pain
CACNA2D3,TRPV1, COMT	Migraine
TRPV1, KCNS1, TRPA1	Neuropathic pain
COMT, GCH1, OPRM1, KCNS1, ABCB1	Postoperative pain
SLC6A4, TRPV2, and COMT	Fibromyalgia
OPRM1, COMT, CASP9	Chronic low back pain
SCN9A, HMGB1P46, TLR4, OPRM1	Diabetic peripheral neuropathy

Genomic variants not only account for individual variations in pain perception or response to injury/inflammation, but also partially explain the interindividual difference in responses to pain management therapy. Before the availability of cost-effective genomic testing, typical drug efficacy and adverse reactions were based on population averages. However, the expanding knowledge of genomic variations associated with optimum drug dosage has the potential of converting trial and error-based treatment to personalized, genomically tailored treatment [30]. Pharmacogenetics describes genetic testing that is targeted for variation known to be associated with a particular drug metabolism or mechanism of action, while pharmacogenomics deals with large scale genomic testing geared towards identifying any potential genomic variations, which can affect drug efficacy, potency, or adverse effects [31].

The main class of drugs used to treat chronic pain conditions are nonsteroidal anti-inflammatory drugs (NSAIDS), tricyclic antidepressants (TCAs), anticonvulsants, opioids, muscle relaxants, and serotonin and norepinephrine uptake inhibitors (SNRIs) [32]. Studies show that despite the standardized protocols for chronic pain management, around 20-40% of patients are either non-responders or experience serious adverse drug reactions [29]. This leads to the persistence of pain or nonadherence to treatment.

Individuals can harbor millions of SNPs in their genome of which 1000s may affect genes in drug metabolism pathways. Despite the large number of identifiable SNPs, only some clinically actionable drug-genomic variations have implications for individualized treatment. The genes involved in pharmacodynamic pathways are mainly related to cytochrome P450 (CYP450) enzymes. There are 57 genes coding for different subclasses of enzymes in the CYP450 group. In this group of genes, the *CYP2D6*, *CYP2C19, CYP1A2* and *CYP2C9* genes are of significant importance from a pharmacogenomic perspective [33]. An individual genetic variant is called an "allele" while the sum of genomic variants in any gene is known as a "haplotype" [34]. Based on the predicted composite effects of haplotypes on enzyme function, an individual can be classified as normal, intermediate, poor, rapid, or ultra-rapid metabolizers.

For the main classes of drugs used in chronic pain treatment, the Clinical Pharmacogenetics Implementation Consortium (CPIC) provides specific recommendations of dose treatment according to *CYP2D6* and *CYP2C19* "metabolizer phenotypes" [35]. Theoretically, if metabolism results in the conversion of a drug into a more active molecule, then ultra-rapid and rapid metabolizers have the potential to experience serious adverse reactions due to increased bioavailability of active molecules. On the contrary, if a particular enzyme converts an active drug into an inactive or less active molecule, the efficacy of a particular drug is expected to be lower in ultra-rapid or rapid metabolizers [36]. Apart from *CYP2D6* and *CYP2C19*, other important genes which are reportedly associated with individual variations in drug response are *HLA**, *COMT*, *UGT2B7*, *ABCB1*, *ABCC3* and *SLC22A* [29]. The relationship of individual genomic haplotypes with recommended drug dosages is beyond the scope of this review. Recommendations by the CPIC and Dutch Pharmacogenetics Working Group are freely available for detailed information [37]. In short, specific recommendations based on pharmacogenomic findings are available for TCAs (amitriptyline, nortriptyline), carbamazepine, oxcarbazepine, venlafaxine, and opioids (tramadol, oxycodone, morphine, codeine) [29]. Individuals positive for the *HLA-A*31:01* allele are at significantly higher risk for hypersensitivity reactions to carbamazepine and the CPIC recommends using alternate therapy [38]. For codeine, poor metabolizers are at risk of insufficient analgesic response and ultrarapid metabolizers (both due to *CYP2D6* gene haplotypes) are at high risk of toxicity [39]. In both these situations, CPIC recommends the use of alternate classes of drugs, which are not metabolized by the *CYP2D6* gene.

Another important point to discuss is reactive versus preemptive pharmacogenomic testing. Reactive testing is performed when an individual is not responding to a "standard" treatment protocol, while preemptive testing is performed beforehand [40]. Since these genetic markers are, germline (present in all cells of the body and fixed for life), the test does not need to be repeated, and if that individual ever needs a drug for pain management, pre-existing data guides the optimal drug dosage. The utility of preemptive testing can be significant in reducing serious adverse reactions or reaching a therapeutic dose rapidly. There is positive preliminary data on reducing the need of hospitalization in suboptimal dosage of opioids, leading to better patient outcomes in cancer related chronic pain [41].

Genetic data obtained from testing laboratories sometimes may appear confusing to clinicians who are not familiar with the genetic reports format [42]. A cross-disciplinary approach with discussion between laboratory scientists, clinical geneticists, pharmacists, and clinicians may help provide optimal treatment options and thus outcomes for patients. Importantly, clinicians need to be aware that genetic variations contribute only partially to the variability of drug responses. Other non-genetic factors like age, gender, ethnicity, and clinical course of the disease, drug-drug interactions and several unknown factors contribute to susceptibility to pain pathologies as well as variations in treatment response [43].

A new discovery that shows much promise for pain management therapy is CRISPR, a technology that allows us to alter gene expression by targeting specific gene sequences. A 2021 study conducted by Moreno et al. used CRISPR to target key genes involved in the pathogenesis of chronic pain [44]. The study focused on the *SCN9A* gene which codes for the $Na_V1.7$ ion channel. Researchers initially attempted to downregulate $Na_V1.7$ activity at the protein level by using small molecules and antibodies against the sodium channel. This attempt did not yield therapeutic results because the small molecules had many off-target interactions, and thus patients experienced many side effects. However, when using a modified CRISPR-Cas9 system with a repressor protein, they were able to successfully downregulate *SCN9A* gene expression on a genetic level. Importantly, this subsequent attempt yielded no off-target effects, and a strong desired analgesic effect was achieved. Mice that were pre-treated with this CRISPR-Cas9 system were found to be more tolerant to subsequent painful stimuli, and mice who already suffered from chronic pain experienced increases in pain tolerance [45]. The analgesic effect lasted for up to 44 weeks for some subjects in this experiment. Additionally, these mice became more tolerant to pain but no changes in other sensations were identified. This experiment not only exemplifies CRISPR's superiority to generic medications, but it shows that gene therapy can be used as both a preventative and therapeutic measure, thus maximizing its medical potential.

Discussion

To conclude, though the estimated heritability of chronic pain is up to 50-60%, the present available data from genetic association studies only explains up to 10% of these genetic components, with hundreds of small risk-contributing polymorphisms in many genes. A strong suspicion of diagnosis needs to be kept for single gene disorders where diagnosis, prognosis, and treatment regimens may differ from other more common polygenic and multifactorial types of chronic pain. Pharmacogenetics and pharmacogenomics have the potential to modify and tailor personalized drug treatment based on genetic markers and drug response.

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