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Genetic Basis of Pain Variability: Recent Advances

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Abstract

An estimated 15–50% of the population experiences pain at any given time, at great personal and societal cost. Pain is the most common reason patients seek medical attention, and there is a high degree of individual variability in reporting the incidence and severity of symptoms. Research suggests that pain sensitivity and risk for chronic pain are complex heritable traits of polygenic origin. Animal studies and candidate gene testing in humans have provided some progress in understanding the heritability of pain, but the application of the genome-wide association methodology offers a new tool for further elucidating the genetic contributions to normal pain responding and pain in clinical populations. Although the determination of the genetics of pain is still in its infancy, it is clear that a number of genes play a critical role in determining pain sensitivity or susceptibility to chronic pain. In the present review, the authors provide an update of the most recent findings that associate genetic variation with variability in pain and an overview of the candidate genes with the highest translational potential.

Introduction

Pain, the “unpleasant sensory and emotional experience associated with actual or potential tissue damage…” (IASP Taxonomy; http://www.iasp-pain.org), is a necessary and informative sensory experience which encourages avoidance of danger and recuperative behaviors that promote healing and protection of an injured or diseased area of the body.[1] In pathological conditions, the pain may no longer be useful and may produce more harm than good. Estimates suggest that 15–50% of the population is experiencing pain at any given time.[2, 3] This prevalence is associated with substantial cost, both societal in the form of lost productivity and increased healthcare utilization,[4, 5] as well as personal in the form of increased risk for psychological disorders [6] and reduced relationship satisfaction and greater distress.[7] Because pain is the most commonly reported symptom in clinical settings [4, 5] individual differences in pain reporting could contribute to delayed or ineffective treatment of underlying disease in those with low sensitivity [8] while hypersensitivity could increase an individual’s reporting of pain leading to significant inordinate healthcare utilization, unnecessary personal suffering, and may increase risk for a number of chronic pain conditions.[9, 10, 11]

Though pain is often a normal part of the human condition (with rare exceptions), there is a high degree of inter-individual difference in pain responses and in reporting of pain in the clinical setting.[12] This variability is likely due to the complex interaction of environmental

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and innate factors. For example, socio-economic status and prior history of trauma/stress exposure have both been shown to modulate pain reporting and responding.[13, 14, 15, 16, 17] Heritability estimates based on inbred strains of laboratory mice studies suggest that up to 30–76% of the variance in pain responding is explained by genetic factors.[18, 19, 20] Race and ethnicity have also been shown to explain differences in reports of pain with African-American and non-Caucasian Hispanics typically reporting more pain than Caucasians within the same clinical populations.[21, 22, 23, 24] In addition, gender has been shown to affect pain thresholds as well as pain reporting in a clinical setting with women typically reporting greater pain than men.[25, 26, 27] Even when the variability explained by each of these factors is accounted for, individual differences remain and genetic variation has been shown to explain a significant portion of this remaining variability. While understanding the phenomenon has basic intellectual value, the influence of genetic variation on pain variability is also highly clinically relevant as it may lead to more individualized care for patients and the identification of novel therapeutic targets.

Early research using twin and family studies has established the heritable nature of both experimental and clinical pain.[28, 29] These studies were instrumental in identifying familial trends for pain conditions and rare disorders in which pain responding is significantly altered.[29, 30, 31, 32, 33] Linkage and association studies have pinpointed a number of genes responsible for heritable conditions involving alterations in pain. The hereditary sensory and autonomic neuropathies (HSAN I-V) are a family of such syndromes in which pain perception and responses are significantly reduced or absent due to mutations in single genes (see Table 1).

Individuals diagnosed with HSAN often exhibit progressive injuries to the areas of the body affected (i.e. ulcerations, joint deformities, etc) but do not report discomfort as a result. Other Mendelian heritable conditions are associated with increased pain including erythermalgia, familial hemiplegic migraine, and paroxysmal extreme pain (see Table 1). [45, 46, 54] While these types of pathological conditions add to our overall knowledge regarding pain processing, they do not necessarily give insight into variations within the general population. There is growing evidence that in order to understand the genetics of pain, pain must be considered a complex phenotype or trait resulting from complex polygenic and environmental contributions. Now, more than ever, researchers are focusing on the genetic contribution to normal variation in pain reporting and responding as this may facilitate translation of basic science findings into pain treatment protocols individually tailored to a patient’s pain risk or resilience.

Research into the genetics of pain in humans utilizes a number of methodologies to identify genetic correlates of behavior. Identifying mutations may explain rarer inherited pain syndromes but the application of these findings to variations in the general population has been less fruitful. Twin studies offer an opportunity to evaluate polygenic inheritance. Twin studies and other studies suggest that 30–60% of the variation in chronic pain syndromes may be due to heritable factors.[30, 55, 56, 57] For the purposes of this review, we will primarily focus on findings from human genetic association studies including hypothesis-driven candidate gene studies and genome-wide association studies (GWAS). Recently developed genome-wide arrays allow for the objective unbiased evaluation of the association of human pain phenotypes with single nucleotide polymorphisms (SNPs) across the entire genome including variations in the number of copies of a gene that an individual has (Copy Number Variation, CNV).[58] The current review will highlight the most recently identified genetic factors (2008-present) that confer protection or susceptibility to pain in general and clinic-based populations and which do not show a Mendelian pattern of inheritance.

Genetic correlates of pain: Recent progress

Significant individual variability is observed in both pain threshold and in susceptibility to chronic pain conditions,[59] and a portion of this variation can be explained by variation within specific genes. Single functional SNPs or combinations of SNP alleles that tend to be inherited together (haplotypes) can contribute to increased or decreased susceptibility to pain.[32] One of the most extensively studied pain candidate genes is catechol-O-methyltransferase (*COMT*) known to be involved in the inactivation of dopamine, epinephrine and norepinephrine neurotransmission and associated with variations in experimental and clinical pain behavior.[60, 61] Four SNPs have been identified that may contribute to a haplotype characterized by differences in COMT metabolic enzyme activity that is inversely correlated with alterations in pain perception.[62] Additionally, a single protective haplotype has been related to increased enzymatic activity, decreased pain sensitivity, and reduced risk for temporomandibular joint disorder, a common musculoskeletal pain syndrome. While genomic variation in *COMT* affects RNA stability and protein translation [63, 64] and affects pain through variations in neurotransmitter metabolism, SNPs in the μ-opioid receptor gene (*OPRM1*) alter pain sensitivity through variations in receptor function. Relationships between *OPRM1* and pain sensitivity and efficacy of opioid analgesics have been shown in a number of experimental and clinical populations.[65, 66, 67, 68] Furthermore, recent data show that genetic mutations in *COMT* and *OPRM1* may interact and act synergistically to affect morphine analgesia and side effect burden.[69] Additional evidence comes from the identification of SNPs within the melanocortin 1 receptor gene (*MC1R*) that are associated with pain sensitivity and μ-opioid analgesia in certain populations.[70]

Genes affecting neurotransmitter systems may determine pain phenotypes

Mechanisms of variability related to neurotransmitter systems are of particular clinical relevance due to the number of pharmacological agents already designed to act on them (i.e. agonists and antagonists used for other purposes) (see Table 2).

Polymorphisms within *GCH1,* the gene encoding GTP cyclohydrolase 1, have been shown to form a protective haplotype with reduced sensitivity to both clinical and experimental pain measures. GTP cyclohydrolase 1 is the rate limiting enzyme in tetrahydrobiopterin (BH4) formation, a necessary step in the biosynthesis of serotonin, dopamine, norepinephrine, epinephrine and nitric oxide, all of which have been shown to have a significant role in pain processing. As with *COMT*, it is unclear which of the target neurotransmitters is critically affected and by what mechanism the genetic differences result in an alteration in pain phenotype. A *GCH1* haplotype based on 15 SNPs was shown to contribute to reduced experimental pain sensitivity and to decreased pain persistence after lumbar discectomy in a population of lower back pain (LBP) patients.[11] Moreover, protection from pain following surgery has been linked with one SNP within *GCH1* and a common haplotype confirming previous findings.[80]. A protective haplotype characterized by reduced GCH1 activity and reduced BH4 synthesis has also been associated with decreased pain reporting and decreased need for specialized pain therapy following cancer diagnosis.[72, 73] However, it is important to note that it is not clear whether *GCH1* plays a role in modulating all pain phenotypes. In two separate studies, recurrent acute and chronic pancreatitis and chronic widespread pain (CWP) symptoms showed no relationship with variations in *GCH1*.[74, 81]. Whether the inconsistencies are reflective of a specific role for *GCH1* in certain pain types remains to be fully elucidated. However, other genetic loci that contribute to catecholamine synthesis and transmission have been implicated in a number of pain phenotypes. Most recently, an association has been revealed between polymorphisms of the serotonin transporter gene (*SLC6A4*) and experimental thermal pain thresholds [76] as well as the conditioned [75, 82] and emotional [83] modulation of experimental pain.

Moreover, carriers of the s-allele in the serotonin transporter linked promoter region (5-HTTLPR) within *SLC6A4* show decreased 5-HTT function [84] and an increased risk for the CWP condition fibromyalgia.[85]

Recent data suggest an association between genes encoding for two neurotransmitter receptors, one for serotonin and one for epinephrine, and an increased risk for developing CWP in which pain is the primary symptom of concern (see Table 2). Hocking et al.[77] conducted a prospective study in a community sample to evaluate the risk for CWP. Two SNPs (rs12654778 and rs1042713) within *ADRB2*, which encodes for the beta 2 adrenergic receptor, were associated with risk of CWP. Common functional haplotypes for *ADRB2* were also associated with self-reports of the extent and duration of pain in that population. This confirms an association previously shown between *ADRB2* haplotypes, functional imbalance of beta adrenergic signaling and an increased risk for temporomandibular pain. [86] Recently, the presence of a T allele at a single SNP within *HTR2A*, the gene encoding the serotonin receptor 2A, was also associated with an increased risk of CWP diagnosis [78] and post-surgical pain burden.[79] Taken together with previous data, these findings suggest that genotype differences can result in alterations in neurotransmission, which can in turn contribute to variations in pain reports within normal and clinical populations.

Genetic determinants of ion channel function contribute to pain susceptibility

While alterations in neurotransmission directly affect the messages sent and received by neurons, alterations in ion channels can alter the transmission of messages received by augmenting or decreasing neuronal excitability. Sodium, potassium and calcium channels are known to play a vital role in initiation and propagation of intracellular signals in neurons including primary nociceptors that innervate peripheral tissues and are activated by noxious stimulation to propagate nerve impulses toward the spinal cord.[87] Emerging data offer convergent evidence for the importance of ion channels in both pain sensitivity in normal populations and pathological pain states (see Table 3).

Recent findings suggest a SNP within the *SCN9A* gene that encodes the alpha subunit of the voltage-gated sodium channel $Na_V1.7$ may play a role in determining risk for chronic pain conditions as well as variation in pain responding within normal populations.[92] In a mixed cohort of sciatica, osteoarthritis, pancreatitis, lumbar discectomy and phantom limb pain patients, increased pain was associated with the presence of an A allele at SNP rs6746030 within *SCN9A* (chromosome 2q24) resulting in an amino acid change from arginine to tryptophan at position 1150 of the $Na_v1.7$ voltage-gated sodium channel. This same SNP was associated with decreased thresholds for a composite measure of experimental pain (combined thermal, mechanical, ischemic and temporal summation of thermal stimuli).[88] The subunit encoded by this gene is widely expressed in nociceptors and loss of function alleles have been implicated in congenital autosomal recessive channelopathies characterized by an inability to feel pain (channelopathy associated insensitivity to pain) (see Table 1).[44, 92] Further implicating *SCN9A* in modulation of pain, primary erythermalgia and paroxysmal extreme pain disorder, both disorders characterized by an increase in pain sensitivity, are the result of autosomal dominant mutations shown to facilitate activation of $Na_V1.7$.[88, 93]

Intracellular communication within the nervous system depends on the movement of sodium and potassium ions, and both populations of ion channels have recently been linked with alterations in pain sensitivity. While *SCN9A* has been associated with variations in pain sensitivity, Costigan et al.[94] identified one SNP within *KCNS1*, the gene encoding a voltage-gated potassium channel (subfamily S, member 1), which may play a role in the risk for chronic pain. In this study, five cohorts of lumbar pain, amputation, sciatica, and phantom limb pain patients, and of healthy adults tested for experimental pain, respectively,

showed a significant increase in self-reported pain associated with the SNP rs734784, a missense A to G exonic substitution of *KCNS1* (chromosome 20q12) resulting in a valine in place of isoleucine at residue 488.

Two genes related to calcium channel function have been recently identified for their association with altered pain sensitivity. Individuals homozygous for two minor allele variants within *CACNA2D3* (C/C at SNP 6777055 and A/A at SNP rs1851048), encoding for the alpha 2 delta 3 subunit of voltage dependent calcium channels, exhibit reduced sensitivity to acute noxious heat as well as with lower risk for chronic back pain following surgical intervention for discogenic disease.[90] Providing further evidence for the importance of calcium channel function in determining pain sensitivity, Nissenbaum et al. [91] reported an association between increased susceptibility for pain following full or partial mastectomy and a given haplotype defined by a homozygous AC-C haplotype at three SNPs (rs4820242, rs2284015, and rs2284017) within the *CACNG2* gene that encodes for the gamma 2 subunit (also known as stargazin).[95, 96, 97] This gene product is also intimately involved in the trafficking and function of AMPA receptors and associated ion channels.[96, 97, 98, 99, 100, 101]. In the mouse, the genomic region containing *Cacng2* was linked to self-injury of the hindlimb (autotomy behavior), a measure of neuropathic pain, and the gene was down-regulated in mice in a nerve injury model of sciatic and saphenous nerve transection in mice.[91] Moreover, knockout mice that do not express *Cacng2* exhibited greater autotomy after injury than wild type mice.[91] The precise role that variations in *Cacng2*/*CACNG2* play in the manifestation of these pain behaviors in mice and chronic pain risk in humans remains to be fully defined, but these findings suggest a place for genetic testing in determining treatment plans with a known potential for inducing chronic pain (e.g. surgical procedures, other standard treatments, etc).

Disease-related genes play a role in pain responding

Susceptibility to a disease and the pain associated with that disease may have overlapping genetic contributions. On face value alone, it stands to reason that when variation in a gene is associated with an increase in disease severity, one might expect higher pain reporting. However, it is not always the case that disease severity and disease-induced pain go hand-in-hand. In fact, there is often marked variability of pain reports even within a seemingly homogenous population.[59, 65] Two recently identified candidate genes known to be involved in chronic disease processes have specifically been associated with pain as well. One such gene, *CASP-9*, which encodes for caspase-9 known to be involved in programmed cell death, was previously shown to play a role in determining the severity of lumbar discogenic disease (LDD).[102] More recently, a SNP within the promoter region of this gene and known to increase transcriptional activity of the gene has also been shown to increase self-reporting of pain without effects on disease process *per se*.[102] In a population of females diagnosed with endometriosis, a recent study found an increased representation of the C allele at rs4778889 within the *IL16* gene for interleukin 16 compared to normal healthy females (i.e., more C/C homozygotes and T/C heterozygotes than T/T homozygotes were found in this population).[103] This polymorphism shows a further increase in prevalence in the subset of those diagnosed with endometriosis and reporting disease-associated pain compared to those diagnosed but not reporting pain.[103] While the specific role played by these factors in normal variability in pain remains to be determined, the implication is that these genes may contribute independently to augmentation of pain processing and the progression of disease. Moreover, previously identified “pain genes” may affect pain without altering disease process but this does not detract from their inherent importance for clinical practice. In short, though pain and disease may be somewhat related in nature, it is important to address each effectively and genetics may offer a tool for maximizing quality of life by decreasing pain as a separate focus during treatment.

Pain GWAS: Progress and pitfalls

Our understanding of the genetics of human pain is rapidly growing and several recent GWAS have offered a glimpse of what is to come in terms of pinpointing distinct genetic contributions to risk and severity of pain syndromes. One such study revealed a strong relationship between genotype for a SNP in linkage disequilibrium with SNPs for *ZNF429* on chromosome 19 and analgesic use following oral surgery.[104] Two other SNPs were tentatively associated with pain ratings following surgery, but these associations did not reach statistical significance. In this study, the sample size was small (60 females and 52 males) resulting in a lack of statistical power to adequately evaluate multiple genetic associations within the same population.

Oedegard et al.[105] used a much larger sample of approximately 1000 cases to evaluate genetic associations for migraine pain in populations with a diagnosis of bipolar disorder or attention deficit-hyperactivity disorder. In these two populations, a SNP within the previously uncharacterized *KIAA0564* gene region on chromosome 13 was associated with an increased diagnosis of migraine. Comorbid diagnoses are common in GWAS designs, but it should be noted that these comorbidities could contribute to reduced power to detect significant associations or idiosyncratic findings that do not generalize to the overall population. Anttila et al.[106] report a link between the minor allele of rs1835740 on chromosome 8q22.1 and the risk for migraine pain. This study may mark a transition in the human genetics of pain literature in that it is the first to use a powerful design with thousands of both diagnosed migraine cases and appropriate controls. A more recent study employing both a large population based study of approximately 23,000 women with and without migraine and a meta-analysis of two population-based cohorts and a separate cohort of those diagnosed with migraine reported a set of 3 susceptibility loci for common migraine (within which are *TRPM1*, *PRDM16*, and *LRP1*).[107] Polymorphisms in transient receptor protein channels, such as those encoded by *TRPM1,* have been associated with neuropathic pain in a rodent model of peripheral nerve injury [108] and may, therefore, show promise as candidate genes for pain susceptibility across models.

That the first two powerful GWAS focus on migraine is not coincidental and is likely due to several factors, not the least of which are that migraine is extremely common and the main symptom of the disorder is patient reported pain. The clinical populations of interest are expanding as evidenced by preliminary reports from a GWAS by Maixner et al.[109] linking a number of loci to pain symptoms from osteoarthritis. The genome-wide approach to studying human pain is still in its infancy due to the complexities involved with the potentially heterogeneous populations with a given diagnosis, the expense of genotyping samples from large cohorts, and the analysis of data that may not be suited for standard statistical analyses. Even with these caveats, the potential value of clinical pain GWAS are anything but trivial. Using this methodology, it may be possible to identify novel mediators of pain beyond those molecules discussed in the neurobiology literature [110] and/or prioritize among the existing pain targets for further mechanistic studies and drug discovery with data collected specifically in human subjects. Ironically, GWAS may prove useful for improving our understanding of non-genetic contributions to pain by allowing us to accurately extract the variance accounted for by genetic factors. Clinically, GWAS could provide a tool for precise classification of pain syndromes based on shared genetic underpinnings thereby enhancing both diagnosis but also treatment. Understanding the genetic contributions to patient risk for pain, chronic pain susceptibility, and/or the expected efficacy of analgesic therapy would allow for truly individualized patient care.

Significant relationships have been found between pain-related traits, behaviors and candidate genes, but it is important to note that the literature available does not paint a

picture of absolute certainty. While we have focused herein on significant relationships found in association studies, there are numerous studies in which associations between the same genetic targets and pain fail to replicate these significant findings. For example, while certain *COMT* haplotypes have been associated with an increased risk specifically for fibromyalgia,[111] the same relationship was not replicated in chronic widespread pain [78] or in those with pain following dental surgery [112] though the latter association has since been found by others.[113] Moreover, *GCH1* polymorphisms failed to show an association with pain after oral surgery [114] while others have found *GCH1* haplotypes that are associated with pain protection in thermal, mechanical, and ischemic experimental pain as well as following lumbar discectomy.[11]

A number of factors may be at work in these seemingly inconsistent findings. First, the methods used to analyze early genetic associations with complex traits likely resulted in the identification and reporting of spurious relationships.[115] As the field has developed, bioinformatics techniques have evolved that reduce the risk of false positive reports. Aside from the methods used to collect and analyze the data for genetic associations, there are also some basic issues related to the populations used for these studies. There is substantial population variability between studies, defined by differences in demographics as well as differences in diagnoses and pain status. For example, it remains to be seen whether genetic associations that exist for one type of chronic pain, for example chronic post-mastectomy pain, are also true for other types of chronic pain (i.e. lower back pain, cancer pain, phantom limb pain). This may be, at least in part, due to the relatively small number of studies published using genetic association methods to assess human pain that are available for comparisons and hypothesis generation. Moreover, the lack of consistent replication across human studies may be due to inadequate power, population heterogeneity in a single study (i.e. based on differential disease diagnosis, ethnicity, gender, etc) or differences in the method of measurement and reporting of pain across studies.[58, 110]

Importantly, one notable factor that has been somewhat overlooked is the potential for independent genetic associations with specific pain behaviors or pain states. Findings from animal studies [18, 20] would suggest that some specificity of genetic associations with modality or type of pain is expected and human studies have shown non-overlapping genetic associations with different pain modalities.[59] As seen in Figure 1, there is a lack of evidence for specificity of genetic associations with specific types of pain in humans. Experimental pain studies would suggest that pain specific genetic associations are likely, but the translation of these findings to clinical pain has not yet been achieved. For instance, studies combining several cohorts (defined by diagnosis and/or pain outcome) may shed light on common mechanisms involved in multiple pain states but may also fail to show significant genetic associations that are specific to only one of the cohorts in question. This circumstance could result in an artificial narrowing of the candidate gene list for subsequent hypothesis testing, and could lead to overgeneralization and false assumptions in future studies. The challenge at hand, therefore, is how to efficiently increase power in human pain studies to test specificity hypotheses in cohorts that represent different pain populations.

Translational potential of genetic association studies

The ultimate value in understanding the genetic determinants of pain is to be able to reduce suffering in human populations. While the flow of information from basic and clinical science studies is beginning to increase, there has not been a boon of genetic testing for use in risk assessment and diagnosis of pain in typical healthcare settings. There are, however, a number of genes that seem to have the most translational potential and may represent key tools in diagnosis and treatment of pain in the future. These can be roughly divided into three categories of translational application based on the association between the gene and

pain phenotype: pain facilitating alleles, pain protective alleles, and alleles related to analgesia.

A number of recent associations suggest that certain polymorphisms act to facilitate or increase pain; the most recent genes of interest within this group include *KCNS1*, *SCN9A*, *ADRB2*, *H2TRA*, *CACNG2*, and *IL16* (for details, see above). Genetic association studies indicate that these genes contribute to an increase in pain sensitivity and, in many cases, an increased risk for developing chronic pain conditions. As a result, the combined genotype for an individual at these multiple loci could give insight into risk for pain following treatment in the clinical setting. For example, if a patient were considering the benefits and costs of an elective surgical procedure, their genetic predisposition (or lack thereof) for developing neuropathic pain afterwards could be used as a factor in the decision.

Another family of alleles has been identified as conferring pain protection or a decrease in pain; the most recent candidates in this category include *COMT*, *OPRM1*, *TRPV1, MC1R*, *GCH1*, and *CACNA2D3*. These loci are associated with reductions in pain and/or resiliency to develop chronic pain, thus, they could be of significant clinical importance to guide physicians and patients in determining who might be suitable for more aggressive treatment plans.

Finally, it is important to note that there are several alleles that have been shown to modulate the efficacy of analgesic agents in the treatment of pain. Polymorphisms in *COMT*, *MC1R*, and *OPRM1* have been associated with resistance to the effects of analgesics. Polymorphisms within *COMT* [61, 116, 117] and *OPRM1* [118] result in decreased morphine efficacy while mutations of *MC1R* are associated with a reduction in the analgesic effects of lidocaine administration.[119] Interestingly, other polymorphisms within *OPRM1* are associated with decreased morphine side effect sensitivity, i.e. decreased pupil constriction and decreased respiratory depression. Conversely, polymorphisms within two other genes, *CYP2D6* (encoding for cytochrome P450 enzyme involved in metabolism of opioids) [120] and *ABCB1* (encoding for the P-glycoprotein transporter) [121] have been associated with increased side effects following opioid administration. *COMT* haplotype has recently been associated with the efficacy of the beta-adrenergic antagonist propanolol for pain reduction in patients with temporomandibular disorder (TMD).[122] Interestingly, those with increased risk for chronic pain as a result of s-allele carrier status in the 5-HTTLPR of *SLC6A4* exhibited better analgesic effects following opioid administration. [123] While a risk assessment based on an individual's pain-related genotype is a long-term translational goal, it may be more practical in the short-term to identify those with a genotype suggestive of increased analgesic-resistance and/or increased risk of negative side effects when designing pharmacological pain management plans since these comprise much of the current available arsenal used to fight pain.

References

1. Bolles RC, Fanselow MS. Endorphins and behavior. Annu Rev Psychol. 1982; 33:87–101. [PubMed: 6277239]
2. Crook J, Rideout E, Browne G. The prevalence of pain complaints in a general population. Pain. 1984; 18(3):299–314. [PubMed: 6728496]
3. Jakobsson U. The epidemiology of chronic pain in a general population: results of a survey in southern Sweden. Scand J Rheumatol. 2010; 39(5):421–9. [PubMed: 20476853]
4. Cordell WH, Keene KK, Giles BK, et al. The high prevalence of pain in emergency medical care. Am J Emerg Med. 2002; 20(3):165–9. [PubMed: 11992334]
5. Tanabe P, Buschmann M. A prospective study of ED pain management practices and the patient's perspective. J Emerg Nurs. 1999; 25(3):171–7. [PubMed: 10346837]

6. Fishbain DA, Cutler RB, Rosomoff HL, et al. Do antidepressants have an analgesic effect in psychogenic pain and somatoform pain disorder? A meta-analysis. Psychosom Med. 1998; 60(4): 503–9. [PubMed: 9710298]
7. Saarijarvi S, Rytokoski U, Karppi SL. Marital satisfaction and distress in chronic low-back pain patients and their spouses. Clin J Pain. 1990; 6(2):148–52. [PubMed: 2152010]
8. Sheifer SE, Gersh BJ, Yanez ND 3rd, et al. Prevalence, predisposing factors, and prognosis of clinically unrecognized myocardial infarction in the elderly. J Am Coll Cardiol. 2000; 35(1):119–26. [PubMed: 10636269]
9. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet. 2005; 14(1):135–43. [PubMed: 15537663]
10. Kasch H, Qerama E, Bach FW, et al. Reduced cold pressor pain tolerance in non-recovered whiplash patients: a 1-year prospective study. Eur J Pain. 2005; 9(5):561–9. [PubMed: 16139185]
11. Tegeder I, Costigan M, Griffin RS, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med. 2006; 12(11):1269–77. [PubMed: 17057711]
12. Lacroix-Fralish ML, Mogil JS. Progress in genetic studies of pain and analgesia. Annu Rev Pharmacol Toxicol. 2009; 49:97–121. [PubMed: 18834308]
13. Dorner TE, Muckenhuber J, Stronegger WJ, et al. The impact of socio-economic status on pain and the perception of disability due to pain. Eur J Pain. 2011; 15(1):103–9. [PubMed: 20558096]
14. Spertus IL, Burns J, Glenn B, et al. Gender differences in associations between trauma history and adjustment among chronic pain patients. Pain. 1999; 82(1):97–102. [PubMed: 10422665]
15. Walker E, Katon W, Harrop-Griffiths J, et al. Relationship of chronic pelvic pain to psychiatric diagnoses and childhood sexual abuse. Am J Psychiatry. 1988; 145(1):75–80. [PubMed: 3337296]
16. Walker EA, Katon WJ, Neraas K, et al. Dissociation in women with chronic pelvic pain. Am J Psychiatry. 1992; 149(4):534–7. [PubMed: 1554041]
17. Walker EA, Katon WJ, Roy-Byrne PP, et al. Histories of sexual victimization in patients with irritable bowel syndrome or inflammatory bowel disease. Am J Psychiatry. 1993; 150(10):1502–6. [PubMed: 8379554]
18. Mogil JS, Wilson SG, Bon K, et al. Heritability of nociception II. ‘Types’ of nociception revealed by genetic correlation analysis. Pain. 1999; 80(1–2):83–93. [PubMed: 10204720]
19. Mogil JS, Wilson SG, Bon K, et al. Heritability of nociception I: responses of 11 inbred mouse strains on 12 measures of nociception. Pain. 1999; 80(1–2):67–82. [PubMed: 10204719]
20. Lariviere WR, Wilson SG, Laughlin TM, et al. Heritability of nociception. III. Genetic relationships among commonly used assays of nociception and hypersensitivity. Pain. 2002; 97(1–2):75–86. [PubMed: 12031781]
21. Breitbart W, McDonald MV, Rosenfeld B, et al. Pain in ambulatory AIDS patients. I: Pain characteristics and medical correlates. Pain. 1996; 68(2–3):315–21. [PubMed: 9121820]
22. Creamer P, Lethbridge-Cejku M, Hochberg MC. Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures. J Rheumatol. 1999; 26(8):1785–92. [PubMed: 10451078]
23. Faucett J, Gordon N, Levine J. Differences in postoperative pain severity among four ethnic groups. J Pain Symptom Manage. 1994; 9(6):383–9. [PubMed: 7963791]
24. Sherwood G, McNeill JA, Hernandex L, et al. A multinational study of pain management among Hispanics: an evidence-based approach. J Res Nursing. 2005; 10(4):403–23.
25. Fillingim RB. Sex, gender, and pain: women and men really are different. Curr Rev Pain. 2000; 4(1):24–30. [PubMed: 10998712]
26. Fillingim RB, King CD, Ribeiro-Dasilva MC, et al. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain. 2009; 10(5):447–85. [PubMed: 19411059]
27. Keefe FJ, Lefebvre JC, Egert JR, et al. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain. 2000; 87(3):325–34. [PubMed: 10963912]

28. MacGregor AJ, Andrew T, Sambrook PN, et al. Structural, psychological, and genetic influences on low back and neck pain: a study of adult female twins. Arthritis Rheum. 2004; 51(2):160–7. [PubMed: 15077255]
29. Turk DC, Flor H, Rudy TE. Pain and families. I. Etiology, maintenance, and psychosocial impact. Pain. 1987; 30(1):3–27. [PubMed: 3614978]
30. Arguelles LM, Afari N, Buchwald DS, et al. A twin study of posttraumatic stress disorder symptoms and chronic widespread pain. Pain. 2006; 124(1–2):150–7. [PubMed: 16701954]
31. Fejer R, Hartvigsen J, Kyvik KO. Heritability of neck pain: a population-based study of 33,794 Danish twins. Rheumatology (Oxford). 2006; 45(5):589–94. [PubMed: 16332950]
32. Foulkes T, Wood JN. Pain genes. PLoS Genet. 2008; 4(7):e1000086. [PubMed: 18654615]
33. Norbury TA, MacGregor AJ, Urwin J, et al. Heritability of responses to painful stimuli in women: a classical twin study. Brain. 2007; 130(Pt 11):3041–9. [PubMed: 17932101]
34. Bejaoui K, Wu C, Scheffler MD, et al. SPTLC1 is mutated in hereditary sensory neuropathy, type 1. Nat Genet. 2001; 27(3):261–2. [PubMed: 11242106]
35. Auer-Grumbach M. Hereditary sensory neuropathy type I. Orphanet J Rare Dis. 2008; 3:7. [PubMed: 18348718]
36. Guelly C, Zhu PP, Leonardis L, et al. Targeted high-throughput sequencing identifies mutations in atlastin-1 as a cause of hereditary sensory neuropathy type I. Am J Hum Genet. 2011; 88(1):99–105. [PubMed: 21194679]
37. Klein CJ, Botuyan MV, Wu Y, et al. Mutations in DNMT1 cause hereditary sensory neuropathy with dementia and hearing loss. Nat Genet. 2011; 43(6):595–600. [PubMed: 21532572]
38. Lafreniere RG, MacDonald ML, Dube MP, et al. Identification of a novel gene (HSN2) causing hereditary sensory and autonomic neuropathy type II through the Study of Canadian Genetic Isolates. Am J Hum Genet. 2004; 74(5):1064–73. [PubMed: 15060842]
39. Kurth I, Pamminger T, Hennings JC, et al. Mutations in FAM134B, encoding a newly identified Golgi protein, cause severe sensory and autonomic neuropathy. Nat Genet. 2009; 41(11):1179–81. [PubMed: 19838196]
40. Slaugenhaupt SA, Blumenfeld A, Gill SP, et al. Tissue-specific expression of a splicing mutation in the IKBKAP gene causes familial dysautonomia. Am J Hum Genet. 2001; 68(3):598–605. [PubMed: 11179008]
41. Indo Y, Tsuruta M, Hayashida Y, et al. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet. 1996; 13(4):485–8. [PubMed: 8696348]
42. Einarsdottir E, Carlsson A, Minde J, et al. A mutation in the nerve growth factor beta gene (NGFB) causes loss of pain perception. Hum Mol Genet. 2004; 13(8):799–805. [PubMed: 14976160]
43. Minde J, Toolanen G, Andersson T, et al. Familial insensitivity to pain (HSAN V) and a mutation in the NGFB gene. A neurophysiological and pathological study. Muscle Nerve. 2004; 30(6):752–60. [PubMed: 15468048]
44. Drenth JP, Waxman SG. Mutations in sodium-channel gene SCN9A cause a spectrum of human genetic pain disorders. J Clin Invest. 2007; 117(12):3603–9. [PubMed: 18060017]
45. Yang Y, Wang Y, Li S, et al. Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. J Med Genet. 2004; 41(3):171–4. [PubMed: 14985375]
46. Fertleman CR, Baker MD, Parker KA, et al. SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. Neuron. 2006; 52(5): 767–74. [PubMed: 17145499]
47. Fertleman CR, Ferrie CD, Aicardi J, et al. Paroxysmal extreme pain disorder (previously familial rectal pain syndrome). Neurology. 2007; 69(6):586–95. [PubMed: 17679678]
48. Kraus RL, Sinnegger MJ, Glossmann H, et al. Familial hemiplegic migraine mutations change alpha1A Ca2+ channel kinetics. J Biol Chem. 1998; 273(10):5586–90. [PubMed: 9488686]
49. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. Cell. 1996; 87(3):543–52. [PubMed: 8898206]

50. Kors EE, Melberg A, Vanmolkot KR, et al. Childhood epilepsy, familial hemiplegic migraine, cerebellar ataxia, and a new CACNA1A mutation. Neurology. 2004; 63(6):1136–7. [PubMed: 15452324]
51. Todt U, Dichgans M, Jurkat-Rott K, et al. Rare missense variants in ATP1A2 in families with clustering of common forms of migraine. Hum Mutat. 2005; 26(4):315–21. [PubMed: 16110494]
52. Segall L, Mezzetti A, Scanzano R, et al. Alterations in the alpha2 isoform of Na,K-ATPase associated with familial hemiplegic migraine type 2. Proc Natl Acad Sci U S A. 2005; 102(31): 11106–11. [PubMed: 16037212]
53. Dichgans M, Freilinger T, Eckstein G, et al. Mutation in the neuronal voltage-gated sodium channel SCN1A in familial hemiplegic migraine. Lancet. 2005; 366(9483):371–7. [PubMed: 16054936]
54. Joutel A, Bousser MG, Biousse V, et al. A gene for familial hemiplegic migraine maps to chromosome 19. Nat Genet. 1993; 5(1):40–5. [PubMed: 8220421]
55. Hakim AJ, Cherkas L, El Zayat S, et al. The genetic contribution to carpal tunnel syndrome in women: a twin study. Arthritis Rheum. 2002; 47(3):275–9. [PubMed: 12115157]
56. Zondervan KT, Cardon LR, Kennedy SH, et al. Multivariate genetic analysis of chronic pelvic pain and associated phenotypes. Behav Genet. 2005; 35(2):177–88. [PubMed: 15685430]
57. Battie MC, Videman T, Carragee EJ. Re: Virtanen IM, Karppinen J, Taimela S, et al. Occupational and genetic risk factors associated with intervertebral disc disease. Spine 2007;32:1129–34. Spine (Phila Pa 1976). 2007; 32(25):2926. author reply -7. [PubMed: 18246021]
58. Kim H, Clark D, Dionne RA. Genetic contributions to clinical pain and analgesia: avoiding pitfalls in genetic research. J Pain. 2009; 10(7):663–93. [PubMed: 19559388]
59. Nielsen CS, Price DD, Vassend O, et al. Characterizing individual differences in heat-pain sensitivity. Pain. 2005; 119(1–3):65–74. [PubMed: 16298065]
60. Andersen S, Skorpen F. Variation in the COMT gene: implications for pain perception and pain treatment. Pharmacogenomics. 2009; 10(4):669–84. [PubMed: 19374521]
61. Belfer I, Segall S. COMT genetic variants and pain. Drugs Today (Barc). 2011; 47(6):457–67. [PubMed: 21695287]
62. Diatchenko L, Nackley AG, Slade GD, et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. Pain. 2006; 125(3):216–24. [PubMed: 16837133]
63. Tsao D, Shabalina SA, Gauthier J, et al. Disruptive mRNA folding increases translational efficiency of catechol-O-methyltransferase variant. Nucleic Acids Res. 2011
64. Nackley AG, Shabalina SA, Tchivileva IE, et al. Human catechol-O-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. Science. 2006; 314(5807): 1930–3. [PubMed: 17185601]
65. Fillingim RB, Kaplan L, Staud R, et al. The A118G single nucleotide polymorphism of the mu-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. J Pain. 2005; 6(3):159–67. [PubMed: 15772909]
66. Lotsch J, Geisslinger G. Current evidence for a genetic modulation of the response to analgesics. Pain. 2006; 121(1–2):1–5. [PubMed: 16472919]
67. Romberg RR, Olofsen E, Bijl H, et al. Polymorphism of mu-opioid receptor gene (OPRM1:c. 118A>G) does not protect against opioid-induced respiratory depression despite reduced analgesic response. Anesthesiology. 2005; 102(3):522–30. [PubMed: 15731588]
68. Wu WD, Wang Y, Fang YM, et al. Polymorphism of the micro-opioid receptor gene (OPRM1 118A>G) affects fentanyl-induced analgesia during anesthesia and recovery. Mol Diagn Ther. 2009; 13(5):331–7. [PubMed: 19791836]
69. Kolesnikov Y, Gabovits B, Levin A, et al. Combined catechol-O-methyltransferase and mu-opioid receptor gene polymorphisms affect morphine postoperative analgesia and central side effects. Anesth Analg. 2011; 112(2):448–53. [PubMed: 21127283]
70. Mogil JS, Ritchie J, Smith SB, et al. Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. J Med Genet. 2005; 42(7):583–7. [PubMed: 15994880]

71. Kim DH, Dai F, Belfer I, et al. Polymorphic variation of the guanosine triphosphate cyclohydrolase 1 gene predicts outcome in patients undergoing surgical treatment for lumbar degenerative disc disease. Spine (Phila Pa 1976). 2010; 35(21):1909–14. [PubMed: 20838263]
72. Doehring A, Freynhagen R, Griessinger N, et al. Cross-sectional assessment of the consequences of a GTP cyclohydrolase 1 haplotype for specialized tertiary outpatient pain care. Clin J Pain. 2009; 25(9):781–5. [PubMed: 19851158]
73. Lotsch J, Klepstad P, Doehring A, et al. A GTP cyclohydrolase 1 genetic variant delays cancer pain. Pain. 2010; 148(1):103–6. [PubMed: 19959292]
74. Holliday KL, Nicholl BI, Macfarlane GJ, et al. Do genetic predictors of pain sensitivity associate with persistent widespread pain? Mol Pain. 2009; 5:56. [PubMed: 19775452]
75. Lindstedt F, Berrebi J, Greayer E, et al. Conditioned pain modulation is associated with common polymorphisms in the serotonin transporter gene. PLoS One. 2011; 6(3):e18252. [PubMed: 21464942]
76. Lindstedt F, Lonsdorf TB, Schalling M, et al. Perception of thermal pain and the thermal grill illusion is associated with polymorphisms in the serotonin transporter gene. PLoS One. 2011; 6(3):e17752. [PubMed: 21423614]
77. Hocking LJ, Smith BH, Jones GT, et al. Genetic variation in the beta2-adrenergic receptor but not catecholamine-O-methyltransferase predisposes to chronic pain: results from the 1958 British Birth Cohort Study. Pain. 2010; 149(1):143–51. [PubMed: 20167428]
78. Nicholl BI, Holliday KL, Macfarlane GJ, et al. Association of HTR2A polymorphisms with chronic widespread pain and the extent of musculoskeletal pain: results from two population-based cohorts. Arthritis Rheum. 2011; 63(3):810–8. [PubMed: 21305503]
79. Aoki J, Hayashida M, Tagami M, et al. Association between 5-hydroxytryptamine 2A receptor gene polymorphism and postoperative analgesic requirements after major abdominal surgery. Neurosci Lett. 2011; 479(1):40–3. [PubMed: 20478362]
80. Kim DH, Dai F, Belfer I, et al. Polymorphic variation of the guanosine triphosphate cyclohydrolase 1 gene predicts outcome in patients undergoing surgical treatment for lumbar degenerative disc disease. Spine. 2010; 35(21):1909–14. [PubMed: 20838263]
81. Lazarev M, Lamb J, Barmada MM, et al. Does the pain-protective GTP cyclohydrolase haplotype significantly alter the pattern or severity of pain in humans with chronic pancreatitis? Mol Pain. 2008; 4:58. [PubMed: 19014702]
82. Treister R, Pud D, Ebstein RP, et al. Association between polymorphisms in serotonin and dopamine-related genes and endogenous pain modulation. J Pain. 2011; 12(8):875–83. [PubMed: 21719351]
83. Palit S, Sheaff RJ, France CR, et al. Serotonin transporter gene (*5-HTTLPR*) polymorphisms are associated with emotional modulation of pain but not emotional modulation of spinal nociception. Biol Psychol. 2011; 86(3):360–9. [PubMed: 21291949]
84. Lesch KP, Bengel D, Heils A, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science. 1996; 274(5292):1527–31. [PubMed: 8929413]
85. Buskila D, Neumann L. Genetics of fibromyalgia. Curr Pain Headache Rep. 2005; 9(5):313–5. [PubMed: 16157058]
86. Diatchenko L, Anderson AD, Slade GD, et al. Three major haplotypes of the beta2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. Am J Med Genet B Neuropsychiatr Genet. 2006; 141B(5):449–62. [PubMed: 16741943]
87. Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. Nat Med. 2010; 16(11): 1248–57. [PubMed: 20948530]
88. Reimann F, Cox JJ, Belfer I, et al. Pain perception is altered by a nucleotide polymorphism in SCN9A. Proc Natl Acad Sci U S A. 2010; 107(11):5148–53. [PubMed: 20212137]
89. Costigan M, Belfer I, Griffin RS, et al. Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. Brain. 2010; 133(9):2519–27. [PubMed: 20724292]

90. Neely GG, Hess A, Costigan M, et al. A genome-wide Drosophila screen for heat nociception identifies alpha2delta3 as an evolutionarily conserved pain gene. Cell. 2010; 143(4):628–38. [PubMed: 21074052]
91. Nissenbaum J, Devor M, Seltzer Z, et al. Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2. Genome Res. 2010; 20(9):1180–90. [PubMed: 20688780]
92. Cox JJ, Sheynin J, Shorer Z, et al. Congenital insensitivity to pain: novel SCN9A missense and in-frame deletion mutations. Hum Mutat. 2010; 31(9):E1670–86. [PubMed: 20635406]
93. Dib-Hajj SD, Yang Y, Waxman SG. Genetics and molecular pathophysiology of Na(v)1. 7-related pain syndromes. Adv Genet. 2008; 63:85–110. [PubMed: 19185186]
94. Costigan M, Belfer I, Griffin RS, et al. Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. Brain. 2010; 133(9):2519–27. [PubMed: 20724292]
95. Kang MG, Chen CC, Felix R, et al. Biochemical and biophysical evidence for gamma 2 subunit association with neuronal voltage-activated Ca2+ channels. J Biol Chem. 2001; 276(35):32917–24. [PubMed: 11441000]
96. Sandoval A, Andrade A, Beedle AM, et al. Inhibition of recombinant N-type Ca(V) channels by the gamma 2 subunit involves unfolded protein response (UPR)-dependent and UPR-independent mechanisms. J Neurosci. 2007; 27(12):3317–27. [PubMed: 17376992]
97. Tselnicker I, Tsemakhovich VA, Dessauer CW, et al. Stargazin modulates neuronal voltage-dependent Ca(2+) channel Ca(v)2. 2 by a Gbetagamma-dependent mechanism. J Biol Chem. 2010; 285(27):20462–71. [PubMed: 20435886]
98. Bats C, Groc L, Choquet D. The interaction between Stargazin and PSD-95 regulates AMPA receptor surface trafficking. Neuron. 2007; 53(5):719–34. [PubMed: 17329211]
99. Cokic B, Stein V. Stargazin modulates AMPA receptor antagonism. Neuropharmacology. 2008; 54(7):1062–70. [PubMed: 18378265]
100. Milstein AD, Nicoll RA. TARP modulation of synaptic AMPA receptor trafficking and gating depends on multiple intracellular domains. Proc Natl Acad Sci U S A. 2009; 106(27):11348–51. [PubMed: 19549880]
101. Priel A, Kolleker A, Ayalon G, et al. Stargazin reduces desensitization and slows deactivation of the AMPA-type glutamate receptors. J Neurosci. 2005; 25(10):2682–6. [PubMed: 15758178]
102. Guo TM, Liu M, Zhang YG, et al. Association between Caspase-9 promoter region polymorphisms and discogenic low back pain. Connect Tissue Res. 2011; 52(2):133–8. [PubMed: 21091209]
103. Gan XL, Lin YH, Zhang Y, et al. Association of an interleukin-16 gene polymorphism with the risk and pain phenotype of endometriosis. DNA Cell Biol. 2010; 29(11):663–7. [PubMed: 20662556]
104. Kim H, Ramsay E, Lee H, et al. Genome-wide association study of acute post-surgical pain in humans. Pharmacogenomics. 2009; 10(2):171–9. [PubMed: 19207018]
105. Oedegaard KJ, Greenwood TA, Johansson S, et al. A genome-wide association study of bipolar disorder and comorbid migraine. Genes Brain Behav. 2010; 9(7):673–80. [PubMed: 20528957]
106. Anttila V, Stefansson H, Kallela M, et al. Genome-wide association study of migraine implicates a common susceptibility variant on 8q22. 1. Nat Genet. 2010; 42(10):869–73. [PubMed: 20802479]
107. Chasman DI, Schurks M, Anttila V, et al. Genome-wide association study reveals three susceptibility loci for common migraine in the general population. Nat Genet. 2011; 43(7):695–8. [PubMed: 21666692]
108. Staaf S, Oerther S, Lucas G, et al. Differential regulation of TRP channels in a rat model of neuropathic pain. Pain. 2009; 144(1–2):187–99. [PubMed: 19446956]
109. Maixner, W.; Smith, SB.; Bhangale, T., et al. Initial identification of genetic variants associated with painful osteoarthritis - results from a community based genome-wide association study [abstract]. 13th World Congress, International Association for the Study of Pain; Montreal, Quebec, Canada. 2010; 2010.
110. Belfer I, Wu T, Kingman A, et al. Candidate gene studies of human pain mechanisms: methods for optimizing choice of polymorphisms and sample size. Anesthesiology. 2004; 100(6):1562–72. [PubMed: 15166579]

111. Vargas-Alarcon G, Fragoso JM, Cruz-Robles D, et al. Catechol-O-methyltransferase gene haplotypes in Mexican and Spanish patients with fibromyalgia. Arthritis Res Ther. 2007; 9(5):R110. [PubMed: 17961261]

112. Kim H, Lee H, Rowan J, et al. Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. Mol Pain. 2006; 2:24. [PubMed: 16848906]

113. Lee PJ, Delaney P, Keogh J, et al. Catecholamine-o-methyltransferase polymorphisms are associated with postoperative pain intensity. Clin J Pain. 2011; 27(2):93–101. [PubMed: 20842020]

114. Kim H, Dionne RA. Lack of influence of GTP cyclohydrolase gene (GCH1) variations on pain sensitivity in humans. Mol Pain. 2007; 3:6. [PubMed: 17343757]

115. Campbell H, Rudan I. Interpretation of genetic association studies in complex disease. Pharmacogenomics J. 2002; 2(6):349–60. [PubMed: 12629506]

116. Rakvag TT, Klepstad P, Baar C, et al. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain. 2005; 116(1–2):73–8. [PubMed: 15927391]

117. Rakvag TT, Ross JR, Sato H, et al. Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain. Mol Pain. 2008; 4:64. [PubMed: 19094200]

118. Chou WY, Yang LC, Lu HF, et al. Association of mu-opioid receptor gene polymorphism (A118G) with variations in morphine consumption for analgesia after total knee arthroplasty. Acta Anaesthesiol Scand. 2006; 50(7):787–92. [PubMed: 16879459]

119. Liem EB, Joiner TV, Tsueda K, et al. Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. Anesthesiology. 2005; 102(3):509–14. [PubMed: 15731586]

120. Samer CF, Daali Y, Wagner M, et al. The effects of CYP2D6 and CYP3A activities on the pharmacokinetics of immediate release oxycodone. Br J Pharmacol. 2010; 160(4):907–18. [PubMed: 20590587]

121. Park HJ, Shinn HK, Ryu SH, et al. Genetic polymorphisms in the ABCB1 gene and the effects of fentanyl in Koreans. Clin Pharmacol Ther. 2007; 81(4):539–46. [PubMed: 17192767]

122. Tchivileva IE, Lim PF, Smith SB, et al. Effect of catechol-O-methyltransferase polymorphism on response to propranolol therapy in chronic musculoskeletal pain: a randomized, double-blind, placebo-controlled, crossover pilot study. Pharmacogenet Genomics. 2010; 20(4):239–48. [PubMed: 20216107]

123. Kosek E, Jensen KB, Lonsdorf TB, et al. Genetic variation in the serotonin transporter gene (5-HTTLPR, rs25531) influences the analgesic response to the short acting opioid Remifentanil in humans. Mol Pain. 2009; 5:37. [PubMed: 19570226]

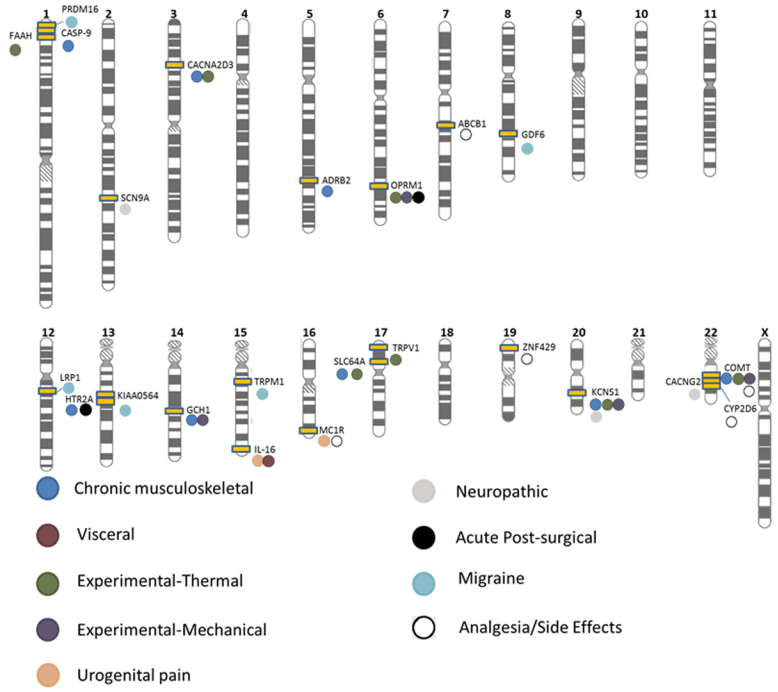

Figure 1.

Chromosome mapping of genes implicated in human pain variability. A summary of the reviewed genes implicated in pain facilitation, pain protection, and/or analgesic effects have been mapped to their approximate locations in the genome. Colored circles indicate significant associations with pain or analgesic effects (see legend above).

Table 1

Mendelian heritable pain conditions

Pain Syndrome*	Gene Affected	Transmission	Gene Product Effect	Phenotype	References
HSAN-I**	A: *SPTLC1*	Dominant	Disrupted sphingolipid synthesis	Pain and heat loss	[34, 35]
	C: *SPTLC2*	Dominant	Disrupted sphingolipid synthesis	Sensory loss	[35]
	D: *ATL1*	Dominant	Reduced GTPase activity; disrupted sensory neuron function	Sensory loss	[36]
	E: *DNMT1*	Dominant	Disrupted DNA methylation resulting in neurodegeneration	Sensory loss; hearing loss; early onset dementia	[37]
HSAN-II (Morvan's disease)	*HSN2*	Recessive	Disrupted transmission of sensory signals	Loss of sensation	[38]
	B: *FAM134B*	Recessive	Alterations of cis-Golgi protein; neuronal apoptosis	Sensory loss	[39]
HSAN-III (Familial dysautonomia or Riley-Day Syndrome)	*IKBKAP*	Recessive	Reduced transcription of IKAP	No pain sensation	[40]
HSAN-IV (Congenital Insensitivity to Pain with Anhydrosis, CIPA)	*NTRK1*	Recessive	Reduced NTR activity/impaired neuronal differentiation	Congenital insensitivity to pain with anhydrosis	[41]
HSAN-V (CIPA)	*NGFB*	Recessive	Loss of functional TrKA receptor	Congenital insensitivity to pain with partial anhydrosis	[42] [43]
Channelopathy-associated insensitivity to pain	*SCN9A*	Recessive	Loss of function in $Na_V1.7$ channel	Congenital insensitivity to pain without anhidrosis	[44]
Erythermalgia	*SCN9A*	Dominant	Decreased threshold in $Na_V1.7$ channel	Chronic inflammation/burning pain	[45]
Paroxysmal Extreme Pain (PEPD)	*SCN9A*	Dominant	Impaired $Na_V1.7$ channel inactivation	Mandibular, ocular, and rectal pain	[46, 47]
FHM-I	*CACNA1A*	Dominant	Increased Ca^{2+} channel activation at negative potentials	Migraine (with or without aura/hemiparesis) and cerebellar degeneration	[48, 49] [50]
FHM-II	*ATP1A2*	Dominant	Loss of function/reduced Na^+/K^+ ATPase activity	Migraine (with or without aura/hemiparesis)	[51, 52]
FHM-III	*SCN1A*	Dominant	Loss of $Na_V1.1$ channel subunit; neuronal hyperexcitability	Migraine (with or without aura/hemiparesis)	[53]

*HSAN, hereditary sensory and autonomic neuropathy (Types I-V); PEPD – Paroxysmal Extreme Pain Disorder; FHM - Familial Hemiplegic Migraine (Types I-III).

**also referred to as hereditary sensory radicular neuropathy, ulcero-mutilating neuropathy, thevenard syndrome, familial trophoneurosis, *mal perforant du pied,* familial syringomyelia, and Charcot-Marie-Tooth type 2B syndrome (sub-type 1C only).

Table 2

Pain-related genes associated with neurotransmitter systems

Gene Name	Neurotransmitter System Affected	Phenotype	References
GCH1	Serotonin, Dopamine, Norepinephrine, Epinephrine, Nitric Oxide (all via BH4)	↓ Sensitivity to Experimental Pain ↓ Post-surgical pain (lumbar discectomy)	[11, 71, 72, 73, 74]
SLC6A4	Serotonin	↑ Risk for CWP ↑ Facilitation of Experimental Pain	[75, 76]
ADRB2	Epinephrine	↑ Risk for CWP	[77]
HTR2A	Serotonin	↑ Risk for CWP ↑ Post-surgical pain	[78, 79]

Table 3

Pain-related genes associated with ion channel function

Gene Name	Channel Type Affected	Phenotype	References
SCN9A	Voltage gated Na^+ channels	↑Chronic pain in mixed cohort (sciatica, osteoarthritis, pancreatitis, lumbar discectomy, and phantom limb) ↑ Sensitivity for experimental pain	[88]
KCNS1	Voltage gated K^+ channels	↑ Chronic pain in 5 cohorts (sciatica, lumbar pain, amputation, phantom limb) ↑ Sensitivity for experimental pain	[89]
CACNA2D3	Voltage gated Ca^{2+} channels	↓ Sensitivity to thermal Pain ↓ Chronic post-surgical pain (discogenic disease)	[90]
CACNG2	Voltage gated Ca^{2+} channels	↑Chronic post-surgical pain (post-mastectomy)	[91]