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MEDICAL REVIEW

Genetic contributions to pain: a review of findings in humans

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Pain represents the major motivating factor for which individuals seek healthcare, and pain responses are characterized by substantial inter-individual differences. Increasing evidence suggests that genetic factors contribute significantly to individual differences in responses to both clinical and experimental pain. The purpose of this review article was to summarize the current literature regarding genetic contributions to pain, highlighting findings relevant to oral pain where available. A brief discussion of methodologic considerations is followed by a review of findings regarding genetic influences on clinical pain. Next, the literature examining genetic contributions to experimental pain responses is presented, emphasizing genetic associations that have been replicated in multiple cohorts. It is hoped that an enhanced understanding of genetic contributions to pain responses will ultimately improve diagnosis and treatment of clinical pain conditions.
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Introduction

Pain represents the most common factor motivating healthcare utilization, accounting for more than 70 million physician office visits annually, and producing more than $100 billion in annual costs in the USA (Turk and Melzack, 2001). Acute and chronic orofacial pain conditions are also highly prevalent. For example, one study found that nearly two-thirds of respondents reported experiencing one or more oral pain symptoms in the last 6 months (Riley and Gilbert, 2001). Other investigators reported that more than half of their sample reported experiencing oral pain over the past 4 weeks (Locker and Grushka, 1987). Also, oral pain is the leading concern for which individuals seek emergent dental care (Rudolph and Brand, 1989; Riley *et al*, 2005). Chronic orofacial pain is most commonly associated temporomandibular disorders (TMD), but also arises from other sources, such as trigeminal neuralgia, burning mouth syndrome (BMS), and intraoral (e.g., dental, mucosal) and idiopathic origins (Agostoni *et al*, 2005). Chronic orofacial pain affects a large proportion of the population, with TMD affecting 5–12% of the population (Lipton *et al*, 1993; LeResche, 1997), women being at greater risk than men (Shinal and Fillingim, 2007). Moreover, persistent orofacial pain is associated with pain in other body areas (Plesh *et al*, 1996; Macfarlane *et al*, 2002), and chronic orofacial pain shares several features with other chronic pain syndromes, including modest associations between symptom severity and physical findings, high rates of healthcare utilization, high interference with daily activities, greater prevalence among women, and significant psychologic distress (Dworkin, 1999; Fillingim and Maixner, 2000; Macfarlane *et al*, 2002). Therefore, it seems plausible that chronic orofacial pain may share risk factors, including genetic predispositions, with other pain conditions. The purpose of this article is to provide an overview of current findings regarding genetic contributions to clinical pain and experimental pain perception, highlighting findings of potential relevance to orofacial pain. We will not be reviewing the substantial literature on genetic contributions to pharmacologic pain treatments, and the interested reader is referred elsewhere for this information (Lotsch *et al*, 2004; Nagashima *et al*, 2007; Stamer and Stuber, 2007). Before discussing specific genetic associations, we will briefly discuss methodologic issues relevant to research on pain genetics. Moreover, we will attempt to place genetics into the broader context of biopsychosocial risk factors for pain.

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Individual differences in pain

The experience of pain is characterized by robust inter-individual differences. In the clinical setting, individual

differences manifest themselves such that patients with comparable pathology or disease severity often report dramatically different degrees of pain and disability. Indeed, considerable evidence suggests that measures of disease activity or tissue damage are poor predictors of pain. For example, the majority of individuals who show radiographic evidence of osteoarthritis report no pain (Lawrence *et al*, 2008), and radiographic measures of disease activity among patients with symptomatic osteoarthritis are not strong predictors of the severity of pain and disability (Summers *et al*, 1988; Hagglund *et al*, 1989; Szebenyi *et al*, 2006; Pells *et al*, 2007). Moreover, objective physical findings have limited value in predicting the occurrence or severity of low back pain (Bigos *et al*, 1992; Carragee *et al*, 2005). Similar individual differences emerge in the acute pain setting, as patients undergoing comparable surgical procedures report widely varying amounts of pain (Perkins and Kehlet, 2000; Bisgaard *et al*, 2001; Aubrun *et al*, 2003; Werner *et al*, 2004; Uchiyama *et al*, 2006). Studies of experimental pain modalities also reveal tremendous individual differences in pain perception (Fillingim, 2005). For example, in a recent study of healthy adults, pain intensity ratings ranged from 0 to 100 for an identical cold water stimulus, and ratings of a heat stimulus ranged from 0 to 95.2 (Nielsen *et al*, 2007). Also, a summary index of pain sensitivity created by combining responses to 16 different experimental pain measures ranged from -20 to >30 across the sample of 202 healthy young females (Diatchenko *et al*, 2005). Thus, even in the experimental setting where the research environment and the stimulus characteristics are highly controlled, robust individual differences in pain perception are observed.

Individual differences in pain responses have long been a topic of research (e.g., (Chapman and Jones, 1944; Hardy *et al*, 1952); however, renewed interest in individual differences in pain recently has been ignited due to the genetic revolution. Nonetheless, it is important to remember that inter-individual variability in the experience of pain is mediated by interactions among numerous biopsychosocial factors, including, but certainly not limited to genetic influences. Specifically, dispositional characteristics such as gender, race/ethnicity, personality, and age have been associated with pain responses, as have situational variables, such as mood states, stress, and transient biologic factors (Edwards and Fillingim, 2001; Edwards *et al*, 2001; Gibson and Helme, 2001; Green *et al*, 2003; Fillingim, 2005; Diatchenko *et al*, 2006b). Importantly, these non-genetic factors are thought to interact with genetic influences in altering pain response (Chesler *et al*, 2002; Diatchenko *et al*, 2006b). Therefore, genetic contributions to pain must be considered in the larger biopsychosocial context in which they occur.

Methodologic considerations

Pain phenotypes

Genetic contributions to pain are complicated by the existence of multiple pain phenotypes. For example, one could investigate genetic associations with specific pain conditions (e.g., TMD or low back pain), which themselves can be quite heterogeneous. Alternatively, one might examine a broader category of clinical pain, such as postoperative pain or neuropathic pain, each of which would inevitably include numerous subcategories. When exploring the genetics of clinical pain, it is important to distinguish genetic contributions to the disease process (e.g., 'arthritis' genes involved in joint degradation) from genes involved in pain processing. To isolate the latter, several investigators have utilized experimental pain modalities to characterize genetic associations with pain sensitivity. Heterogeneity reigns even under such well-controlled laboratory conditions, as preclinical evidence as well as association studies in humans suggests that genetic contributions to pain perception vary across experimental pain modalities (Mogil *et al*, 1999; Limer *et al*, 2008). Obviously, the selection of pain phenotype could substantially influence the nature and magnitude of any genetic association.

Approaches to studying genetic contributions

Twin studies are a classic tool to test for a genetic component to a phenotype. Typically, the concordance of a trait in monozygotic twins (MZ) and dizygotic twins (DZ) is calculated (R, intrapair correlations). The influence of environment is considered equal for all of these twin pairs, so a significant increase in concordance in the MZ twins represents a genetic influence. If the MZ concordance is substantially greater than the DZ concordance, the hypothesis that there is a genetic component is supported, and the strength of the heritability can be calculated. However, with complex, multifactorial phenotypes such as pain, sample size requirements for twin studies are quite large, assuming moderate heritability (Risch, 2000). In addition to twin studies to determine heritability, multifactorial traits such as pain can also be studied through family analysis, typically comparing polymorphism genotypes with allele transmission through families. One approach, affected sib-pair analysis, searches for bias of an allele being transmitted to affected offspring from parents (phenotype of parents is irrelevant; the statistics test whether the pairs share alleles more than would be expected at each locus); presence of such a bias indicates that the polymorphism may be genetically associated with that trait. Another approach, the allele-sharing method, analyzes phenotypically well-characterized families with DNA available from at least two affected family members and one or more unaffected members. Both of these non-parametric methods have good sensitivity to detect fairly large genetic effects in complex traits (Tang *et al*, 2008). In addition, a test called the transmission disequilibrium test (TDT) can be implemented for small nuclear families, as a type of genetic association. This can complement the case–control analysis described below, but it is typically more difficult to collect such families and find heterozygosity for the tested markers in the parents. The TDT method was first implemented in pain studies in the study of migraine

headache in a Sardinian population, finding association of the *DRD2* locus (Del *et al*, 1998).

As an alternative to twin and family studies of complex traits, groups of independent patients can be analyzed with genetic association studies. One type of association study, the case–control study, involves collecting phenotype data and DNA samples from patients (cases) and unrelated controls, followed by genotyping of polymorphisms (usually SNPs) of candidate genes. Then, genotype frequencies are compared between cases and controls. Computer programs such as PHASE can be used to generate haplotypes and diplotypes for tightly linked SNPs within a gene, which may prove more informative than the individual SNPs alone. A positive association with a SNP could be due to a functional effect directly based on the polymorphism (e.g., encoding an amino acid substitution), or it could be a surrogate for a functional effect nearby. In some cases, the functional effect may be associated with an entire haplotype (considering alleles in *cis*), such as seen in the catechol-*O*-methyl-transferase (*COMT*) gene (Diatchenko *et al*, 2005). Association studies can also test for genetic associations of SNPs or haplotypes with quantitative traits, either in the general population or within a patient population.

Association studies sometimes are limited to a few SNPs at specific genes. These candidate genes are chosen on the basis of their encoded proteins being involved in (or proposed to be involved in) pathways that are logically expected to affect the phenotype expression. Putative pain candidate genes/pathways have been proposed in reviews by Belfer *et al* (2004) and Diatchenko *et al* (2006b). Genome-wide association studies, on the other hand, obtain genotypes from thousands (or millions, in some systems) of SNPs across the genome in high-throughput platforms (e.g. Illumina, San Diego, CA, USA; Affymetrix 'chips', Santa Clara, CA, USA), typically for hundreds to thousands of subjects. This is an expensive venture, although the per-SNP cost is less than doing a set of individual candidate gene polymorphisms. The high throughput system can also be customized, where one might order chips that have thousands of SNPs from selected candidate genes. This approach yields an enormous amount of data at one time, necessitating appropriate data-handling systems. One complication of genome-wide association studies is that, with thousands of independent tests being performed simultaneously, statistical analysis taking into account the risk of error (false positive by chance) essentially reduces the *P*-value that needs to be met to be considered significant.

Often there are reports of association studies that fail to replicate previous findings (Chanock *et al*, 2007). This could be due to the ancestral background of the cases, as that may affect allele frequencies, and it is also feasible that multiple different pathways are involved in a trait, with some having more impact in certain genetic backgrounds. Further, conflicting results could be due to sample size effects or differences in phenotype ascertainment. It is also possible that analysis of the same data set with different statistical methods may yield conflicting results. Most often this is due to finding significance with rare allele/haplotypes, which would disappear with larger cohorts or analysis of other close SNPs. Ultimately, positively associated SNPs that appear legitimate are the basis for functional studies, to understand why certain gene variants might confer a susceptibility or protective effect for that trait.

Genetic contributions to clinical pain

Twin studies

Several clinical pain conditions have shown familial aggregation, including arthritis, fibromyalgia (FM), irritable bowel syndrome, and migraine and tension-type headache (Kirk *et al*, 2002; Kalantar *et al*, 2003; Arnold *et al*, 2004; Russell *et al*, 2006; Stewart *et al*, 2006). Of course, shared environmental influences, rather than genetics, could explain familial concordance of pain. In more direct tests of the genetic contribution to clinical pain, twin studies pain have reported heritabilities ranging from of 52% to 68% for lower back pain and 35% to 58% for neck pain, strongly supporting a genetic contribution (Macgregor *et al*, 2004). In another study, analysis of 147 MZ and 153 DZ male twin pairs found heritability estimates for back pain variables ranged from 30% to 46% (Battie *et al*, 2007). Twin studies also indicate significant heritability for other pain conditions, including carpal tunnel syndrome (Hakim *et al*, 2002), migraine (Wessman *et al*, 2007), gastro-esophageal reflux disease (Mohammed *et al*, 2003), pelvic pain (Zondervan *et al*, 2005), irritable bowel syndrome (Levy *et al*, 2001; Lembo *et al*, 2007), chronic widespread pain (CWP) (Kato *et al*, 2006), and osteoarthritis (Page *et al*, 2003; Spector and Macgregor, 2004). Notably, both sex and age influenced the heritability of neck pain (Fejer *et al*, 2006a,b), and some evidence suggests that the heritability of chronic pain and psychologic factors, such as anxiety and depression, are mediated by common genetic factors (Reichborn-Kjennerud *et al*, 2002; Lembo *et al*, 2007). Therefore, both demographic and psychosocial factors should be considered in studies of pain genetics.

Limited evidence directly addresses the heritability of orofacial pain. Michalowicz *et al* (2000) examined signs and symptoms of TMD in a group of 146 monozygotic (MZ), 96 dyzygotic (DZ) and 252 twins of unknown zygosity aged 35 years or older. The authors found that 29% of them experienced at least one TMD sign or symptom, approximately one-quarter clenched or ground their teeth, and 8.7% reported history of joint-area pain, with no differences in the concordance of signs or symptoms across MZ compared to DZ twins. The small sample size and low frequency of observed signs and symptoms make it difficult to draw firm conclusions from this study. More recently, Matsuka *et al* (2007) studied signs and symptoms of TMD in 43 MZ and nine DZ adolescent twins in the Japanese population. The authors concluded that MZ twins tended to show higher concordance in jaw pain during mouth opening than DZ twins; however, the difference

was not statistically significant, likely due to the small sample size. Thus, the available data regarding heritability of TMD symptoms are inconclusive.

Candidate gene studies

Association studies using candidate gene approaches have been applied to chronic pain conditions, including TMD and other musculoskeletal pain conditions. Several candidate genes have been examined for association with TMD, including the serotonin transporter (*SLC6A4*), *COMT*, the gene that encodes catechol-*O*-methyltransferase, an enzyme involved in catecholamine metabolism, β2 adrenergic receptor (*ADRB2*) and estrogen receptor alpha. Herken *et al* (2001) examined polymorphisms in the promoter region of the serotonin transporter gene (*SLC6A4*) as well as a variable number of tandem repeats (VNTR) in the second intron among 48 TMD patients and 111 healthy controls. While TMD patients and controls showed similar allele frequencies for the short and long alleles in the promoter region, group differences emerged for VNTR genotype, with more patients being homozygous for the 10-repeat allele and more controls homozygous for the 12-repeat. However, Ojima *et al* (2007) reported a significant association between the serotonin transporter gene polymorphism and TMD, with patients showing greater frequency of the long allele relative to controls in a Japanese population.

Diatchenko *et al* (2005) examined five SNPs of the *COMT* gene among 202 healthy young women. They constructed three haplotypes, which were termed low pain sensitive (LPS), average pain sensitive (APS), and high pain sensitive (HPS), based on their associations with measures of experimental pain sensitivity. They followed individuals prospectively to determine new onset cases of TMD, and the results indicated that individuals with at least one LPS haplotype were less than half as likely to develop TMD compared to those without any LPS haplotypes. Subsequently, these authors also examined the relationship between three major haplotypes of β2 adrenergic receptor (*ADRB2*) and the risk of developing TMD pain, and found that haplotypes associated with either very low or very high levels of receptor expression were associated with greater risk of TMD (Diatchenko *et al*, 2006a). Moreover, Kang *et al* (2007) examined two estrogen receptor alpha polymorphisms (*Xba*I and *Pvu*II) in a Korean population of patients with temporomandibular joint osteoarthritis (TMJOA). While allele frequencies did not differ for cases *vs* controls, TMJOA patients carrying the PX haplotypes had a significantly higher risk of moderate or severe pain compared to those without the PX haplotypes. This finding suggests that the estrogen receptor alpha polymorphism may be associated with pain susceptibility in TMJOA patients.

Genetic association studies have generally not been conducted for other chronic orofacial pain conditions, with the exception of one investigation of BMS. BMS is a form of chronic orofacial pain characterized by intraoral burning pain, which is most common in older women. A recent study examined the association of the interleukin-1β (*IL-1β*) gene and the serotonin transporter gene (*SLC6A4*) with BMS in a small sample of 30 patients and 31 controls (Guimaraes *et al*, 2006). The short and long alleles of *SLC6A4* showed similar frequencies in patients and controls. However, the minor (T) allele of the +3954 SNP of the IL-1β gene, which is associated with increased production of this proinflammatory cytokine, was significantly more frequent in the BMS patients than in controls. Given the small sample size, replication of these findings would be quite important.

In addition to these association studies of orofacial pain, studies of genetic contributions to other forms of musculoskeletal pain, such as FM and CWP, may be particularly relevant to TMD, given that these pain disorders share several features with TMD, including high levels of psychologic distress, a female predilection, and heightened sensitivity to noxious stimuli (Plesh *et al*, 1996; Macfarlane *et al*, 2002; Diatchenko *et al*, 2006b). Initial studies of FM focused on immunologic contributions through possible linkage analysis with human leukocyte antigen (*HLA*) (Burda *et al*, 1986; Yunus *et al*, 1999). Compared to 869 normal controls, 52 patients with FM showed a statistically significant association with *HLA B58, DR8,* and *DR5* (Burda *et al*, 1986). However, a subsequent study of 40 multicase families showed only a weak linkage of FM with HLA haplotypes (Yunus *et al*, 1999). Based on previous findings of decreased concentrations of serotonin and norepinephrine metabolites in the cerebrospinal fluid of FM patients (Russell *et al*, 1992), several studies have examined genetic polymorphisms in serotonin, dopamine, and catecholamine systems in FM. These studies revealed significant associations with FM of promoter regions of the serotonin (5-HT) transporter gene (*5-HTT*) (Offenbaecher *et al*, 1999) as well as 5-HT2A receptor gene, located on the long arm of chromosome 13 (Bondy *et al*, 1999; Cohen *et al*, 2002). In addition, several gene polymorphisms of serotonin receptor (HTR) subunits, including *HTR3A* and *HTR3B*, have been associated with FM (Frank *et al*, 2004). However, not all studies were able to confirm this association of *5-HTT* gene polymorphism with FM (Gursoy, 2002). Another polymorphism of considerable interest is related to the involvement of the *COMT* gene in FM patients. One study reported significant differences in allele frequencies of a *COMT* SNP (G1947A) among FM patients and controls (Gursoy *et al*, 2003). In a more recent investigation, the association of *COMT* haplotypes with FM was tested in 57 Mexican and 78 Spanish FM patients as well as matched controls. A significant association of *COMT* haplotypes with FM was detected in Spanish patients compared to NC (Vargas-Alarcon *et al*, 2007). In contrast, Mexican patients displayed only a weak association of *COMT* haplotypes with FM. Thus, the role of *COMT* for the pathogenesis of FM is currently unclear, but may be relevant for FM subgroups. In addition, genetic polymorphisms of the D4 dopamine receptor exon III repeat have been associated with FM (Buskila *et al*, 2004). Also, a possible genetic association with FM has been

detected for the *TACR1* gene, which encodes the neurokinin 1 (NK1) receptor, the target for substance P (SP) (Ablin, 2005).

Genetic contributions to experimental pain responses

The literature described above suggests potentially important genetic contributions to clinical pain conditions, including orofacial pain. Most of the significant associations are with candidate genes that encode proteins involved in the processing of painful stimuli, that is, they seem to represent 'pain sensitivity genes' rather than genes associated with an underlying disease process. A more direct approach to determining whether genes predict pain sensitivity is to examine their associations with experimental pain responses. This line of investigation may be of particular relevance for idiopathic pain disorders, such as TMD and FM, as these conditions are characterized by enhanced sensitivity to experimentally induced pain. Indeed, heightened pain sensitivity, which is at least partially determined by genetic factors, has been postulated as a risk factor for future development of chronic pain (Diatchenko *et al*, 2005, 2006b; Edwards, 2005).

Twin studies

A handful of twin studies has examined the heritability of experimental pain sensitivity in humans. In the first such study, pressure pain threshold on the forehead was assessed in 269 monozygotic twin pairs and 340 dizygotic twin pairs, and the findings indicated only 10% heritability (Macgregor *et al*, 1997). However, as noted previously, sample size requirements are substantial for twin studies of multifactorial traits with modest heritability, such as pain perception. Moreover, these investigators tested twin pairs together, which may have mitigated genetic influences by artificially enhancing environmental contributions. Two more recent twin studies have examined additional laboratory pain phenotypes. In a study of 53 MZ and 39 DZ Norwegian twin pairs, Nielsen *et al* (2007) reported significant heritability for sensitivity to both cold pain (60% heritability) and heat pain (26% heritability). Recently, another study involving 98 pairs of female twins (51 MZ and 47 DZ) reported significant heritability estimates ranging from 22% to 55% for several experimental pain measures, including responses to heat pain and chemically induced pain (Norbury *et al*, 2007). Thus, human twin studies on balance suggest significant heritability for experimental pain responses.

Candidate gene studies

A more common approach to investigating genetic influences on pain perception has been to conduct association studies between specific candidate genes and responses to experimentally induced pain. Several genes have been examined for associations with various experimental pain phenotypes, as shown in Table 1. As with many genetic association studies (Hirschhorn *et al*, 2002; Lohmueller *et al*, 2003; Ioannidis, 2007), non-replication of findings has been the rule rather than the exception; therefore, we will focus primarily on the candidate genes for which associations have been performed across multiple cohorts [for additional reviews see (Diatchenko *et al*, 2007; Edwards, 2006; Limer *et al*, 2008; Lotsch and Geisslinger, 2007)]. One commonly studied candidate gene is *COMT*. One SNP of this gene (met158val) involves the substitution of valine for methionine, which results in lower enzymatic activity due to thermal instability of the enzyme. Zubieta *et al* (2003) reported that *val* homozygotes showed lower pain sensitivity and significantly greater brain μ-opioid receptor activation in response to experimental muscle pain, which was induced via injection of hypertonic saline into the masseter muscle. However, this SNP was not associated with ratings of cold pain in a subsequent study (Kim *et al*, 2006). As described above in their prospective study of TMD, Diatchenko *et al* (2005) examined associations between *COMT* haplotypes and an index of experimental pain sensitivity created by summing across several stimulus modalities, including heat, pressure and ischemic pain. *COMT* haplotypes were associated with overall pain sensitivity, and the haplotype that was characterized by low pain sensitivity also conferred protection against subsequent development of TMD.

Another candidate gene that has been associated with experimental pain responses is the μ-opioid receptor gene (*OPRM1*), which has been previously suggested as a promising candidate gene for pain sensitivity (Uhl *et al*, 1999). A common SNP (A118G), which produces an amino acid change from an asparagine residue to an aspartatic residue in amino acid position 40, has shown functional effects. The aspartic acid form (from the G allele) showed higher binding affinity for β-endorphin *in vitro* in one study (Bond *et al*, 1998), though this was not replicated in another study (Beyer *et al*, 2004), and the G allele confers lower mRNA expression and protein yield (Zhang *et al*, 2005). The G allele has been associated with significantly higher pressure pain thresholds compared to the major allele (Fillingim *et al*, 2005), especially for males. Subsequently, it was shown that pain-related evoked potential responses were lower among individuals with at least one G allele compared to those carrying two A alleles (Lotsch *et al*, 2006). Thus, two studies using vastly different experimental pain models suggest that the rare allele is associated with reduced pain sensitivity; however, one other study was unable to test the association of *OPRM1* genotype with experimental pain responses as they failed to detect the 118G allele in their population (Compton *et al*, 2003). Interestingly, the frequency of the G allele was significantly lower among chronic pain patients compared to a postsurgical patient population (Janicki *et al*, 2006), suggesting a possible association with presence of chronic pain.

Recently, a group of investigators employed a translational approach to exploring a novel genetic marker associated with pain sensitivity (Tegeder *et al*, 2006). Based on preclinical data from rodent models of neuropathic and inflammatory pain, they discovered

Table 1 Summary of associations studies linking specific candidate genes with experimental pain perception

Candidate gene		*Pain measures*	*Sample size*	*Findings*
COMT				
Zubieta *et al*, 2003	val158met	Hypertonic saline in masseter muscle; brain μ-opioid receptor binding	18 healthy adults	val158met SNP: val/val Ss showed greater μ-opioid activation & lower pain responses than met/met Ss
Diatchenko *et al*, 2005	Haplotypes	Summed z-score across multiple pain measures	202 healthy females	Haplotypes: haplotypes constructed from 4 SNPs. LPS (low pain sensitive) haplotype associated with lower pain sensitivity compared to HPS (high pain sensitive) haplotype
Diatchenko *et al*, 2006c	Haplotypes & val158met	Heat, pressure, ischemic pain	202 healthy females	Haplotypes: Lower heat pain sensitivity for LPS *vs* HPS haplotype; val158met SNP lower temporal summation of heat pain for met/met *vs* val/val; no associations with pressure & ischemic pain
Kim *et al*, 2004	val158met	Heat pain, cold pain	384 healthy adults	No association with *COMT val158met*
Kim *et al*, 2006	rs6269 SNP	Heat pain, cold pain	368 healthy European American adults	In females, *COMT* SNP (rs6269) was associated with cold pain ratings
OPRM1				
Fillingim *et al*, 2005	*OPRM1* (A118G)	Heat pain, pressure pain, ischemic pain	167 healthy adults	G allele associated with higher pressure threshold *vs* two A alleles; sex X genotype interaction emerged for heat pain ratings, as G allele was associated with lower ratings in men, but higher ratings in women
Lotsch *et al*, 2006	*OPRM1* (A118G)	Event-related potential (ERP) response to Intranasal CO_2	45 healthy adults	N1 ERP response to CO_2 was lower in carriers of the rare (G) allele
GCH1				
Tegeder *et al*, 2006	*GCH1* (haplotype)	Thermal, pressure, ischemic pain	547 healthy adults	Significant association of haplotype with pressure pain thresholds
Tegeder *et al*, 2008	*GCH1* (haplotype)	Pressure pain, mechanical hyperalgesia after skin inflammation and capsaicin	32 healthy adults	Pain protective haplotypes associated with reduced hyperalgesia
Kim and Dionne, 2007	*GCH1* (haplotype)	Cold pain, heat pain	735 healthy adults	No significant associations
TRPV1				
Kim *et al*, 2004	2 SNPs (met315ile & ile585val)	Heat pain, cold pain	384 healthy adults	Among white females only, *TRPV1 val585* homozygotes showed higher cold pain tolerance compared to heterozygotes or *ile585* homozygotes
Kim *et al*, 2006	Multiple haplotypes	Heat pain, cold pain	368 healthy European American adults	No associations
OPRD1				
Kim *et al*, 2004	2 SNPs (phe27cys & T307C)	Heat pain, cold pain	384 healthy adults	Among males only, *OPRD1 Phe27Cys* heterozygotes reported lower heat pain ratings than either homozygous group
Kim *et al*, 2006	Multiple haplotypes	Heat pain, cold pain	368 healthy European American adults	No associations
Additional genes				
(Mogil *et al*, 2005)	*MC1R* (multiple SNPs)	Electrical pain	47 healthy adults	Ss with two or more variant alleles across 3 SNPs had significantly higher electrical pain tolerance than those with 0 or 1 variant alleles
Kim *et al*, 2006	*TRPA1, TRPM8, FAAH* (haplotypes)	Heat pain, cold pain	368 healthy European American adults	In females, a *TRPA1* SNP (rs11988795) was associated with cold pain tolerance. In males, 2 *FAAH* SNPs (rs932816 and rs4141964) were associated with cold pain responses. No associations with *TRPM8*

an enzyme (GT cyclohydrolase, or GCH) involved in nociceptive sensitivity and injury-induced hyperalgesia. These findings were translated into humans when a haplotype of the *GCH1* gene was found to predict lower levels of persistent pain following lumbar surgery for disc herniation. This pain protective haplotype was associated with lower sensitivity to experimentally induced pain in two separate cohorts of healthy individuals. In a more recent study, these investigators demonstrated that the pain protective haplotype was associated with decreased hyperalgesia following local inflammation or sensitization (Tegeder *et al*, 2008). In contrast to these findings, another group of investigators failed to show an association between *GCH1* haplotype and heat or cold pain ratings, probably due to use of different pain models as well as differences in haplotypic structure across populations (Kim and Dionne, 2007).

Another gene that has been examined in two studies is the transient receptor potential vanilloid receptor gene (*TRPV1*), which encodes the capsaicin-heat receptor. Kim *et al* (2004) initially reported an association of the *ile585val* SNP with cold pain ratings, but only among females; however, a subsequent study by these investigators did not find any associations of *TRPV1* with cold or heat pain (Kim *et al*, 2006). Similarly, these investigators initially reported an association of *OPRD1*, the delta-opioid receptor gene, with heat pain ratings among males only (Kim *et al*, 2004), but showed no associations with this gene in a subsequent report (Kim *et al*, 2006).

Conclusions

Pain is a complex human trait sculpted by multiple biologic and psychologic systems, each of which involves the influence of numerous proteins throughout the peripheral and central nervous systems, whose effects can be substantially affected by environmental exposures. Therefore, it is inevitable that multiple genes, each with a small individual effect, interact among themselves and with a variety of environmental factors, to influence pain sensitivity and the expression of chronic pain conditions. Twin studies have demonstrated that genetic influences account for approximately 50% of the variance in chronic pain, and the existing data for experimental pain responses show comparable heritability estimates. Moreover, candidate gene association studies have identified multiple genes that may contribute to clinical and experimental pain. Several studies have shown that polymorphisms in genes affecting the function of both catecholaminergic and serotonergic systems may be associated with chronic pain disorders, such as FM and TMD. Candidate gene studies have also linked multiple genes to experimental pain responses, and several of these candidate gene associations have held up in replication studies (e.g. *COMT, OPRM1*, *GCH1*). However, which genes contribute explain the greatest proportion of variance in clinical and experimental pain responses is currently unknown, and the direct functional effects of specific polymorphisms have generally not been elucidated. Better understanding of pain-related genetic influences will provide important insights into pain mechanisms and may identify new targets for pharmacologic and other therapies.

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Author contributions

All authors contributed to the preparation of this article.

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