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Biological pathways and genetic variables involved in pain

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Abstract
Purpose This paper summarizes current knowledge of pain-related and analgesic-related pathways as well as genetic variations involved in pain perception and management.
Methods The pain group of the GENEQOL Consortium was given the task of summarizing the current status of research on genetic variations in pain and analgesic efficacy. This review is neither exhaustive nor comprehensive; we focus primarily on single-nucleotide polymorphisms.
Results Two categories of potential genetic pain-perception pathways were identified: neurotransmission modulators and mechanisms that affect inflammation. Four categories were identified for analgesic efficacy: genes related to receptor interaction, modulation of opioid effects, metabolism, and transport. Various genetic variations involved in these pathways are proposed as candidate genetic markers for pain perception and for individual sensitivity to analgesics.
Conclusions Candidate gene association studies have been used to provide evidence for the genetic modulation of pain perception and response to analgesics. However, the nature and range of genetic modulation of pain is not well addressed due to the limited number of patients and the limited number of genes and genetic variants investigated in studies to date. Moreover, personalized analgesic treatments will require a more complete understanding of the effects of genetic variants and gene–gene interactions in response to analgesics.

Keywords Pain · Analgesic efficacy · Genetic polymorphism · Biological pathways

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Abbreviations

5-HT	5-Hydroxytryptamine (serotonin)
5-HTT	Serotonin transporter
5-HTTLPR	Serotonin transporter gene repeated polymorphism
A	Adenosine
ABCB1	Adenosine-5′-triphosphate-binding cassette sub-family B member 1
C	Cytidine
CNS	Central nervous system
COMT	Catechol-O-methyltransferase
CYP2C9	Cytochrome P450 2C9
CYP2D6	Cytochrome P450 2D6
DNA	Deoxyribonucleic acid
FAAH	Fatty acid amide hydrolase
G	Guanosine

GABA	Gamma amino butyric acid
GCH1	Guanosine triphosphate cyclohydrolase 1
IL-1	Interleukin 1
IL-1RN	Interleukin 1 receptor antagonist
IL-1α	Interleukin 1α
IL-1β	Interleukin 1β
IL-6	Interleukin 6
IL-8	Interleukin 8
MC1R	Melanocortin 1 receptor
mRNA	Messenger ribonucleic acid
NSAID	Nonsteroidal anti-inflammatory drug
OPRM1	μ-Opioid receptor gene
P-gp	P-Glycoprotein
SNP	Single-nucleotide polymorphism
T	Thymidine
TNF-α	Tumor necrosis factor α
TRP	Transient receptor potential
TRPA1	Transient receptor potential cation channel, subfamily A, member 1
TRPV1	Transient receptor potential cation channel, subfamily V, member 1
UGT	Uridine 5′-diphospho-glucuronosyltransferase
UGT2B7	UDP-Glucuronosyltransferase-2B7

Introduction

It is well known that a wide range of interindividual variability exists in the perception of pain as well as in the dosage of analgesics that will provide pain relief, even in patients who have comparable disease severity and are undergoing comparable treatments. This variability was demonstrated in a study of 3,045 postsurgical patients who required anywhere from 1 to 20 boluses of morphine to obtain relief from postoperative pain [1]. Similarly, Klepstad et al. [2] found considerable interindividual variation in effective serum concentrations of morphine and morphine-6-glucuronide in 300 patients with cancer. Numerous studies document that age, gender, race/ethnicity, mood states, and stress can influence the individual's pain experience. However, the large interindividual variation is not explained by such factors, suggesting that genetic factors may contribute to variability of pain. Moreover, the disposition toward pain perception and response to analgesics may be comparable to other common disorders, like cancer, diabetes, and cardiovascular diseases. That is, multiple genetic variations result in a disposition to a particular disease and each variant makes a small contribution to overall susceptibility to pain.

Perception of pain and response to analgesic medications are complex processes that involve multiple biochemical pathways (e.g., neurotransmission, inflammation, drug metabolism, drug transport). Each of these pathways involves significant genetic factors that may modify pain perception or response to analgesics. In February 2009, the international and interdisciplinary GENEQOL Consortium was established to investigate the genetic disposition of patient-reported quality-of-life outcomes [3]. As one of the GENEQOL serial papers, this review aims to (1) introduce quality-of-life researchers to current findings about genetic contributions to pain perception and the pharmacogenetics of analgesics; (2) summarize pain-associated genetic variations into biological pathways that are involved in pain perception and analgesic response; and (3) briefly discuss limitations, such as sample size, outcome measurements, and candidate genetic targets, in current studies on genetic disposition to pain. Although we have examined the literature related to the genetic background of pain in general, we focus here on the genetic polymorphisms, especially single-nucleotide polymorphisms (SNPs)—the most popular genetic markers used to assess an individual's predisposition to complex disorders. This review of gene–pain association is neither exhaustive nor comprehensive, but we do expect that it will provide quality-of-life researchers an overview about the current status of research on the genetic variations involved in pain perception and analgesic response and will stimulate future investigations into novel aspects surrounding the genetic basis of pain. We highlight findings related to disease-related pain and summarize information on genetic markers in pathways of neurotransmission and inflammation, which are major pathways for modulation of pain perception. We conclude with a summary of genetic variants involved in analgesic drug metabolism and transport, two pathways that may modify an individual's response to analgesics.

Neurotransmission

Pain is the consequence of interactions between a stimulus and the body's pain-transmission systems. When encountering a pain stimulus, the sensory receptor releases neurotransmitters that bind to specific receptors and activate pain-transmission pathways. Several neurotransmitters and receptors—e.g., serotonin (5-hydroxytryptamine, 5-HT), catecholamines, gamma amino butyric acid (GABA)—contribute to the transmission of the sensations of pain within the brain and spinal cord. Genes that modulate expression and activity of these proteins may explain individual differences in pain perception and are potential targets for analgesic drug development.

Catechol-O-methyltransferase (COMT) mediates the inactivation of catecholamine neurotransmitters, including dopamine, adrenaline, and noradrenaline [4]. The most-studied polymorphism is a nonsynonymous SNP in the COMT gene *(COMT)*. This SNP (*rs4680*) results in the substitution of valine by methionine at position 158 and is associated with a threefold to fourfold reduction in COMT activity. Humans genotyped as homozygous for the *met158* allele reported very slightly increased sensory and affective ratings of pain in response to muscular infusion of hypertonic saline compared with heterozygotes, whereas individuals who were *val158* homozygotes reported lower pain ratings than did heterozygotes [5]. The *ACCG* haplotype of four *COMT* SNPs (*rs6269 A>G, rs4633 C>T, rs4818 C>G*, and *rs4680 G>A*) exhibited lowest enzymatic activity and protein expression by altering mRNA secondary structure [6]. Being heterozygous for *ATCA* and *ACCG* haplotypes was strongly associated with high sensitivity to experimental pain [7].

Genetic variability in the *COMT* gene is thought to influence the efficacy and side effects of morphine in patients with cancer. Rakvåg et al. [8], who constructed haplotypes from 11 SNPs throughout the *COMT* gene in a sample of cancer patients receiving oral morphine treatment, found that patients who carried the most common haplotype (34.5%) required lower morphine doses than patients who did not carry that haplotype. In intron 1, *C* allele of *−7370 C>T* (*rs7290221*) and *A* allele of *−7053 A>G* (*rs5746849*) were associated with high levels of side effects in the central nervous system (CNS), such as drowsiness, confusion, and hallucinations [9].

Opioid receptors are a group of specific receptors essential for morphine and related opioids to enact their analgesic effects [10]. These receptors are expressed in multiple brain regions [11], in the periphery, and on various circulating immune cells [12]. There are three well-defined types of opioid receptors: μ, δ, and κ. The μ-opioid receptor is the primary binding site for morphine and other commonly prescribed opioid analgesics [13, 14]. The most-studied SNP in μ-opioid receptor gene (*OPRM1*), *rs179971 A>G* (*118 A>G*), results in an amino acid exchange from asparagine to aspartate at position 40 [15]. A nucleotide shift leads to a decrease in μ-opioid receptor signaling efficacy in the second somatosensory cortex (SII) of the brain, an important region for coding pain intensity [16]. Individuals with the *GG* or *GA* genotype show an elevated sensitivity to pain [17] and a reduced analgesic response to opioids [18] compared with individuals with the *AA* genotype. Among patients receiving oral morphine treatment for cancer pain, homozygotes for the *G* allele requested higher doses of morphine for successful pain control [19]. This finding has been repeated in all but one study [20], which examined the efficacy of intrathecal fentanyl for labor pain; results from this study showed that morphine was more effective in carriers of the *G* allele. This finding may imply that the effects from a specific SNP may vary between different opioids, different routes of drug administration, or different pain etiologies.

Serotonin transporter (SLC6A4/*5-HTT*) affects monoamine neurotransmitter-mediated behaviors, including anxiety, depression, obsessive–compulsive behavior, and response to painful stimuli [21]. A repeated-length polymorphism (5-HTT gene-linked polymorphic region, *5-HTTLPR, rs25531*) in the promoter of the gene has been shown to affect the activity of this protein [22]. The short (14-repeat) allele of *5-HTTLPR* was shown to have lower transcriptional activity leading to lower neuronal serotonin reuptake [23] and is associated with a better analgesic effect of remifentanil in healthy volunteers undergoing heat-pain stimulation [24]. Another polymorphism in the second intron of the serotonin transporter gene (*STin2*), containing a 16-to-17 base pair sequence with, most commonly, 10 or 12 repeats, was found to be associated with joint pain severity [25].

Guanosine triphosphate cyclohydrolase 1 (GCH1) is a catalase enzyme of the folate and biopterin biosynthesis pathways, which affects sensitivity to neuropathic and inflammatory pain in animal models. A pain-protective haplotype of the GCH1 gene *(GCH1)* was identified in 168 Caucasian adults with persistent lumbar root pain [26]. This haplotype consists of specific nucleotides at 15 DNA positions and was highly associated with lower scores for persistent leg pain. Three variants of this haplotype—*rs8007267 G>A* in the 5′ untranslated region, *rs3783641 A>T* in intron 1, and *rs10483639 C>G* in the 3' untranslated region—were found to have comparable reliability, specificity, and sensitivity to the genetic diagnosis for pain sensitivity [27].

Table 1 summarizes information on common polymorphisms that are suggested to be associated with clinical pain phenotypes. Although several other genetic variations have been associated with altered sensitivity to experimental pain, no evidence is available to show that these variants are associated with pain perception or response to analgesics in instances of clinical pain.

Transient receptor potential (TRP) channels are involved in sensory systems that respond to pain stimuli. TRP subfamily A member 1 (TRPA1) is activated by noxious cold temperature (<15°C) [28]. Individuals who are homozygous for *G* allele at the SNP *rs1198795 A>G* located in the intron of the TRPA1 gene *(TRPA1)* showed longer cold-withdraw time than did individuals with the *AA* genotype [29]. Another TRP subfamily V is proposed to mediate warm and noxious heat sensations. The TRP subfamily V member 1 (TRPV1) affects responses to heat stimuli warmer than 43°C [30]. The SNP *rs8065080 G>A* of *TRPV1* results in an isoleucine-to-valine change at

Table 1 Neurotransmission pathway genetic variants associated with clinical pain phenotypes

Gene	Polymorphism	Pain phenotype	Sample	Reference
COMT	rs4680	Morphine consumption	Patients with cancer	[93]
		Nonmigraine headache	Women	[94]
	rs6269, rs4818, rs4633, rs4680	Musculoskeletal pain	Patients with myogenous temporomandibular joint disorder (TMJ)	[7]
		Fibromyalgia	Patients with fibromyalgia	[95]
	Haplotype of SNPs in intron 1	Side effects of opioids	Patients with cancer	[9]
	Haplotype of 11 SNPs	Morphine consumption	Patients with cancer	[8]
5-HTT	rs2066713	Onset of postoperative pain	Postsurgical patients	[96]
	rs2276307 rs1935349	Myalgia	Hypercholesterolemic patients treated with statins	[97]
	Intron 2 variable number tandem repeat	Joint pain	Patients with joint pain	[25]
	rs25531	Analgesic effect of remifentanil	Healthy volunteers	[24]
OPRM1	rs1799971	Pain perception and morphine consumption	Postcesarean women	[17]
			Postsurgical patients	[18]
			Patients with cancer	[19]
			Laboring women	[20]

codon 585; female European Americans who were homozygous for the *A* allele showed longer pain-response time to cold stimuli [31].

Fatty acid hydrolase (FAAH) serves as the primary catabolic regulator of fatty acid amide in the nervous system. Mice that lack the FAAH gene (*FAAH*) demonstrated prolonged pain-response latencies to the temperature stimuli [32]. The common polymorphism *FAAH rs324420 A>C*, which results in a threonine-to-proline change at codon 129, was found to reduce cellular expression of the enzyme in human lymphocytes, which may influence pain sensitivity [33]. However, this SNP is not associated with thermal-pain response [29].

Melanocortin-1-receptor (*MC1R*) has been shown to be a crucial gene in the control of pigmentation. *MCIR* variants were associated with red hair and fair skin [34]. Red-haired individuals were found to be more sensitive to thermal pain and to be resistant to the analgesic effects of subcutaneous lidocaine [35]. Women who carried two variant *MC1R* alleles exhibited significantly greater analgesia from the κ-opioid pentazocine, compared with women with all other genotypes [36]. In addition, human redheads with nonfunctional *MC1Rs* displayed reduced pain sensitivity and increased analgesic responsiveness to morphine-6-glucuronide, a μ-opioid morphine metabolite [37].

Inflammation

Proinflammatory cytokines appear to play a central role in peripheral neuropathic pain and hyperalgesia. In animal models, inflammatory cytokines enhance nociception [38]. Studies of mollusks have shown that the release of the cytokine interleukin 1β (IL-1β) sensitizes withdrawal reflexes, a protective response of the body to pain stimuli [39]. In humans, inflammatory cytokines are thought to be the mediators that bridge the CNS and immune systems. Cancer and its treatments induce release of proinflammatory cytokines in both the CNS and periphery, which may modify the activity of nociceptors and contribute to pain [40]. Structural damage to peripheral axons leads to an inflammatory reaction at the site of injury: inflammatory cells (e.g., macrophages, neutrophils, $CD4^+$, and $CD8^+$ T cells) infiltrate the site, and levels of inflammatory cytokines (e.g., IL-1, leukemia inhibitory factor, and particularly TNF-α) increase. Neuropathic pain develops as a result [41–43]. Table 2 lists polymorphisms in genes encoding cytokines that are associated with pain perception and/or response to analgesics.

Interleukin 1 (IL-1) participates in the activation of T cells involved in immune defense against infection. Intrathecal administration of IL-1 can lead to hyperalgesia in rats [44]. The expression of IL-1 is upregulated after nerve injury, and neutralizing antibodies to IL-1 receptors reduce thermal hyperalgesia and mechanical allodynia in mouse models [45]. The activity of this cytokine is determined by two major members of the IL-1 superfamily, interleukin 1α (coded by *IL-1*α) and interleukin 1β (coded by *IL-1*β), and a competitive inhibitor, interleukin-1-receptor antagonist (coded by *IL-1RN*). *IL-1*α, *IL-1*β, and *IL-1RN* genes are mapped to a closely linked area on chromosome 2q13-q24. The *IL-1*α *889C>T* (*rs1800587*) [46–48], *IL-1*β *3954C>*

Table 2 Polymorphisms in cytokine genes and clinical pain phenotypes

Gene	Polymorphism	Pain phenotype	Sample	Reference
IL-1α	rs1800587	Pain severity	Men with low back pain	[53]
IL-1RN	Tandem repeat within intron 2	Morphine consumption	Postoperative women	[54]
	1812 G/A	Occurrence of pain	Men with low back pain	[53]
		Pain severity		
		Duration of pain		
IL-1β	rs1143634	Pain severity	Patients with burning mouth syndrome	[98]
		Duration of pain	Men with low back pain	[53]
IL-6	rs1800795	Pain severity	Patients with rheumatoid arthritis	[60]
		Response to opioids	Patients with lung cancer	[59]
IL-8	rs4073	Pain severity	White non-Hispanic patients with lung cancer	[68]
TNF-α	rs1800629	Pain severity	Patients with lung cancer	[59]

T (*rs1143634*) [49] and *IL-1β −511C>T* (*rs16944*) [50] polymorphisms, and an 86-base pair repeat (variable number tandem repeat polymorphism) in the *IL-1RN* gene [51, 52] have biological relevance in the regulation of IL-1 production. In patients with low back pain, *IL-1β T3954* allele was associated with the number of days with pain and pain intensity, and *IL-1RN A1812* was associated with multiple pain phenotypes, such as the occurrence of pain, the number of days with pain, and days with limitations of daily activities [53]. The 86-base pair repeat in the *IL-1RN* gene was found to be associated with higher morphine consumption in postoperative female patients [54].

Interleukin 6 (IL-6) plays multiple roles in the physiology of nociception and the pathophysiology of pain. IL-6 expression is rapidly induced during acute inflammation associated with injury, infection, and neoplasia. In an animal model, IL-6 increased after nerve injury and this increase was associated with increased pain behaviors over time [55]. *IL-6* knock-out mice showed a reduced analgesic response to morphine and a more rapid development of tolerance to the analgesic effect of morphine [56]. In patients who had undergone allogeneic hematopoietic stem cell transplantation, increase in levels of circulating IL-6 was found to be significantly related to increases in patients' reports of pain [57]. The *C* allele of *−174G>C* (*rs1800795*) SNP in *IL-6* gene promoter region was found to be associated with significantly lower levels of plasma IL-6 in healthy subjects [58]. Lung cancer patients homozygous for the *IL-6 −174C* allele required a 4.7 times higher dose of opioids for pain relief compared with patients the heterozygous or homozygous for the *G* allele [59]. In patients with juvenile rheumatoid arthritis, individuals homozygous for the *G* allele reported higher pain severity [60]. The haplotype *GGGA* of four SNPs (*−596A>G, −572G>C, −174G>C*, and *+15T>A*) was found to have prognostic value for the number of days with back or leg pain in patients with sciatica [61].

Tumor necrosis factor α (TNF-α) plays a major role in the inflammatory response after surgical intervention, infection, and trauma. Several studies have shown a correlation between the level of TNF expression and the development of allodynia or hyperalgesia in neuropathic pain models [44, 45]. In a mouse model of inflammation-induced pain produced by carrageenan injection, *TNF-α* mRNA was increased at the site of injection [62]. TNF-α neutralization with etanercept or infliximab treatment significantly decreased mechanical hyperalgesia at the inflamed joint in animal models of arthritis [63]. The *A* allele of *−308G>A* (*rs3093544*) polymorphism in the *TNF-α* gene promoter site was associated with high *TNF* promoter activity and increased expression of *TNF-α* [64]. In Caucasian patients with non–small cell lung cancer, this allele was associated with greater pain severity [59].

Interleukin 8 (IL-8) is a major mediator of the inflammatory response and coded by *IL-8* gene. In a study of 23 patients who had surgery for lumbar disc herniation with radiculopathy, *IL-8* mRNA expression was associated with the development of back-extension pain and short pain duration [65]. The tissue injury-induced upregulation of *IL-8* gene expression was positively correlated with pain intensity at 3 h postsurgery, when acute inflammatory pain emerged [66]. A common SNP, *−251T>A* (*rs4073*), was identified in its promoter region. The *A* allele was associated with increased IL-8 levels in lipopolysaccharide-stimulated whole blood [67] and with severe pain (rated 7 or greater on a 0–10 scale) in Caucasian patients with lung cancer [68].

Drug transport and metabolism

Table 3 lists polymorphisms in genes that are associated with the transportation and metabolism of specific analgesics.

Table 3 Drug transportation and metabolism: genetic polymorphisms and response to analgesics

Gene	Polymorphism	Analgesic	Reference
ABCB1	rs1045642	Morphine	[75, 99]
	rs2032582	Methadone	[76, 86]
		Fentanyl	[77]
CYP2B6	rs34830389	Methadone	[86]
	rs2279343		
CYP2D6	rs35742686	Tramadol	[79, 81, 85, 100]
	rs3892097	Methadone	[86, 101–103]
	rs5030655	Dextromethorphan	
	rs5030867		[104, 105]
	rs1065852		
CYP2C9	rs1799853	NSAIDs in general	[87]
	rs1057910		
UGT2B7	−840 G/A	Morphine	[91]

P-Glycoprotein (P-gp) is a membrane transporter that mediates the transport of several opioid peptides across biological membranes (e.g., the blood–brain barrier) and facilitates access to their targets. Nonpeptide opiates such as morphine [69–71] are effluxed from the brain across the blood–brain barrier via P-gp. P-gp is encoded by the adenosine triphosphate-binding cassette (ABC) superfamily member B1 (*ABCB1*) [72]. A common SNP, *3435 C>T*, was identified in exon 26 of *ABCB1* gene. Individuals who are homozygous for *T* allele demonstrated a twofold reduction in duodenal expression of P-gp and the plasma concentration of digoxin after oral administration of morphine [73]. This SNP is also found to affect the efficacy of opioids. In patients who took a variety of opioids for pain, daily opioid doses significantly decreased in a gene dose-dependent manner with the *ABCB1 3435C>T* SNP [74]. Among patients undergoing opioid-based therapy (mainly morphine) for cancer pain, homozygotes for *3435T* reported significantly greater pain relief than homozygotes for *3435C*, while heterozygotes showed no significant difference from the *C* homozygotes [75]. Coller et al. [76] found an association between the *3435T* allele and lower methadone daily dose requirements in opioid-dependent patients. Park et al. [77] tested three SNPs (*1236C>T, 2677G>T/A*, and *3435C>T*) in Korean patients who underwent spinal anesthesia with intravenous fentanyl and found that patients with genotypes of *1236TT*, *2677TT*, and *3435TT* were more likely to have side effects (early and profound suppression of respiration) compared with patients with genotypes of *1236CC*, *2677GG*, and *3435CC*.

Cytochrome P450 enzymes (CYP) constitute a large family of phase I enzymes involved in drug metabolism and bioactivation that account for 75% of total drug metabolism [78]. Polymorphisms in cytochrome P450 isoforms appear to contribute to variations in analgesic efficacy and presence of side effects, generally in a drug-specific manner [79–81]. The polymorphic CYP2D6 controls the *O*-demethylation of codeine to morphine and the rate of morphine production. With more than 100 allelic variants having been discovered, four phenotypic groups with distinct enzymatic activities can be identified in humans: (1) poor metabolizers have complete enzymatic deficiency; (2) intermediate metabolizers have decreased enzymatic activity: (3) extensive metabolizers have normal enzymatic activity; and (4) ultrarapid metabolizers have increased enzymatic activity [82]. In poor metabolizers, codeine is not activated into morphine and is an ineffective analgesic [83]. Healthy volunteers with poor metabolizers excrete less morphine and glucuronides in the urine after single or multiple doses of codeine [84]. In postoperative patients with gastric cancer, the total consumption of tramadol for 48 h in those who were homozygous for *CYP2D6*10* was significantly higher than in heterozygous patients without *CYP2D6*10* [85]. *CYP2B6*6/*6* carriers presented higher trough (S)-methadone plasma levels in 245 patients undergoing methadone maintenance treatment [86]. Pilotto et al. [87] reported that the presence of *CYP2C9*3* allele was associated with a significantly higher risk of bleeding in 78 patients with a diagnosis of upper gastrointestinal bleeding related to nonsteroidal anti-inflammatory drugs (NSAIDs), setting the *CYP2C9*1/*1* genotype as reference.

Uridine diphosphate glucuronosyltransferase (UGT) is a phase II enzyme that catalyzes glucuronidation, which facilitates the elimination of most analgesics. Clearance of various NSAIDs, opioids, and acetaminophen are glucuronidated by UGTs [88]. *UGT2B7* gene encodes UGT2B7, a primary hepatic enzyme responsible for glucuronidation of morphine; the SNP *-840G>A* of *UGT2B7* gene is located in the promoter region [89]. This SNP is tightly linked to five other promoter variants (*−1248G, −1241C, −1054C, −268G*, and *−102C* relative to the hepatic start site) [90]. A recent study in patients with sickle cell disease reported that the presence of the *−40G* allele (*GG* and *GA*) was associated with significantly reduced glucuronidation of morphine, which resulted in variability in hepatic clearance of morphine [91].

Conclusions

As summarized in this limited review, candidate gene association studies have identified numerous genetic variants that may modify pain perception and response to analgesics through multiple biological pathways. However, the nature and range of genetic modulation of pain are still not completely understood due to the limited number of

genes and genetic variants investigated to date. Studies on the genetics of pain are complicated by the fact that the genetic influences vary between different pain modalities [92]. In addition, findings from existing studies on genetic variation and analgesic efficacy are limited because sample sizes were small, only a limited number of gene candidates were evaluated, or the analgesics studied were primarily morphine and codeine. Furthermore, current pain-gene studies use a variety of patient-reported pain measurements, which causes difficulties in comparing and interpreting results from different studies. Future studies need to use consistent and clinically meaningful pain phenotyping that will provide more-applicable interpretation of the genetic profile as well as more-replicable associations between genetic factors and pain. Finally, the identification of additional novel candidate genes could occur through the use of genome-wide association studies.

Personalized analgesic treatment will require a more complete understanding of the effects of genetic variants and gene–gene interaction in response to pain and analgesics. However, although still in its infancy this research can, through translational initiatives combining genetic research with clinical research on subjective outcomes, develop into more insights and improved patient outcomes.

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Glossary

Allele	One of various forms of a gene, usually referring to a specific genetic locus
Allodynia	Pain produced by a stimulus that does not normally provoke pain, i.e., pressure from clothing or simple touch
Base	The essential basic component of DNA or RNA. There are four DNA bases: adenine (A), guanine (G), thymine (T), and cytosine (C)
Candidate gene association study	A method that determines whether a particular form of a DNA polymorphism occurs more frequently in subjects with a phenotype of interest, usually focusing on genes involved in the biological pathways of disease development and treatment
Chromosome	Thread-like structures of DNA found in the nucleus of a cell that carry hereditary information
Genome	The entire hereditary information of an organism
Genome-wide association study	A method to examine genetic variation across a given genome, designed to identify genetic associations with phenotypes of interest, usually 1,000,000 or more markers involved
Genotype	Instructions of the internal inheritable information of any living organism
Haplotype	A set of genetic markers in the same chromosome that highly correlate to each other and tend to be inherited together
Heterozygote	An organism with two different alleles at one gene location
Homozygote	An organism with two identical alleles at one gene location
Hyperalgesia	Increased pain sensitivity, usually abnormal
Nociception	Perception of pain
Nonsynonymous SNP	A DNA base change that results in an altered polypeptide sequence
Phenotype	Anything that is part of the observable structure, function, or behavior of a living organism
Polymorphism	Variety in forms of a particular DNA sequence in a population
SNP	Short form for single-nucleotide polymorphism, a variation between individuals in a single nucleotide (A, T, C, or G) of the DNA sequence

References

1. Aubrun, F., Langeron, O., Quesnel, C., Coriat, P., & Riou, B. (2003). Relationships between measurement of pain using visual analog score and morphine requirements during postoperative intravenous morphine titration. *Anesthesiology, 98*(6), 1415–1421.
2. Klepstad, P., Dale, O., Kaasa, S., Zahlsen, K., Aamo, T., Fayers, P., et al. (2003). Influences on serum concentrations of morphine, M6G and M3G during routine clinical drug monitoring: a prospective survey in 300 adult cancer patients. *Acta Anaesthesiologica Scandinavica, 47*(6), 725–731.
3. Sprangers, M. A., Sloan, J. A., Veenhoven, R., Cleeland, C. S., Halyard, M. Y., Abertnethy, A. P., et al. (2009). The establishment of the GENEQOL consortium to investigate the genetic disposition of patient-reported quality-of-life outcomes. *Twin Research and Human Genetics, 12*(3), 301–311.
4. Lotta, T., Vidgren, J., Tilgmann, C., Ulmanen, I., Melén, K., Julkunen, I., et al. (1995). Kinetics of human soluble and membrane-bound catechol O-methyltransferase: A revised mechanism and description of the thermolabile variant of the enzyme. *Biochemistry, 34*(13), 4202–4210.
5. Zubieta, J. K., Heitzeg, M. M., Smith, Y. R., Bueller, J. A., Xu, K., Xu, Y., et al. (2003). COMT val158met genotype affects

mu-opioid neurotransmitter responses to a pain stressor. *Science, 299*(5610), 1240–1243.
6. Nackley, A. G., Shabalina, S. A., Tchivileva, I. E., Satterfield, K., Korchynskyi, O., Makarov, S. S., et al. (2006). Human catechol-O-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. *Science, 314*(5807), 1930–1933.
7. Diatchenko, L., Slade, G. D., Nackley, A. G., Bhalang, K., Sigurdsson, A., Belfer, I., et al. (2005). Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Human Molecular Genetics, 14*(1), 135–143.
8. Rakvåg, T. T., Ross, J. R., Sato, H., Skorpen, F., Kaasa, S., & Klepstad, P. (2008). Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain. *Molecular Pain, 4*, 64.
9. Ross, J. R., Riley, J., Taegetmeyer, A. B., Sato, H., Gretton, S., du Bois, R. M., et al. (2008). Genetic variation and response to morphine in cancer patients: Catechol-O-methyltransferase and multidrug resistance-1 gene polymorphisms are associated with central side effects. *Cancer, 112*(6), 1390–1403.
10. Pert, C. B., & Snyder, S. H. (1973). Opiate receptor: Demonstration in nervous tissue. *Science, 179*(77), 1011–1014.
11. Stein, C. (1993). Peripheral mechanisms of opioid analgesia. *Anesthesia and Analgesia, 76*(1), 182–191.
12. Bidlack, J. M., Khimich, M., Parkhill, A. L., Sumagin, S., Sun, B., & Tipton, C. M. (2006). Opioid receptors and signaling on cells from the immune system. *Journal of Neuroimmune Pharmacology, 1*(3), 260–269.
13. McQuay, H. (1999). Opioids in pain management. *Lancet, 353*(9171), 2229–2232.
14. Satoh, M., & Minami, M. (1995). Molecular pharmacology of the opioid receptors. *Pharmacology and Therapeutics, 68*(3), 343–364.
15. Bond, C., LaForge, K. S., Tian, M., Melia, D., Zhang, S., Borg, L., et al. (1998). Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: Possible implications for opiate addiction. *Proceedings of the National Academy of Sciences of the United States of America, 95*(16), 9608–9613.
16. Oertel, B. G., Kettner, M., Scholich, K., Renné, C., Roskam, B., Geisslinger, G., et al. (2009). A common human {micro}-opioid receptor genetic variant diminishes the receptor signaling efficacy in brain regions processing the sensory information of pain. *The Journal of Biological Chemistry, 284*(10), 6530–6535.
17. Sia, A. T., Lim, Y., Lim, E. C., Goh, R. W., Law, H. Y., Landau, R., et al. (2008). A118G single nucleotide polymorphism of human mu-opioid receptor gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine for postcesarean analgesia. *Anesthesiology, 109*(3), 520–526.
18. Chou, W. Y., Wang, C. H., Liu, P. H., Liu, C. C., Tseng, C. C., & Jawan, B. (2006). Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. *Anesthesiology, 105*(2), 334–337.
19. Klepstad, P., Rakvåg, T. T., Kaasa, S., Holthe, M., Dale, O., Borchgrevink, P. C., et al. (2004). The 118 A>G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. *Acta Anaesthesiologica Scandinavica, 48*(10), 1232–1239.
20. Landau, R., Kern, C., Columb, M. O., Smiley, R. M., & Blouin, J. L. (2008). Genetic variability of the mu-opioid receptor influences intrathecal fentanyl analgesia requirements in laboring women. *Pain, 139*(1), 5–14.
21. Blakely, R. D., De Felice, L. J., & Hartzell, H. C. (1994). Molecular physiology of norepinephrine and serotonin transporters. *Journal of Experimental Biology, 196*, 263–281.
22. Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274*(5292), 1527–1531.
23. Heils, A., Teufel, A., Petri, S., Stöber, G., Riederer, P., Bengel, D., et al. (1996). Allelic variation of human serotonin transporter gene expression. *Journal of Neurochemistry, 66*(6), 2621–2624.
24. Kosek, E., Jensen, K. B., Lonsdorf, T. B., Schalling, M., & Ingvar, M. (2009). Genetic variation in the serotonin transporter gene (5-HTTLPR, rs25531) influences the analgesic response to the short acting opioid Remifentanil in humans. *Molecular pain, 5*, 37.
25. Herken, H., Erdal, E., Mutlu, N., Barlas, O., Cataloluk, O., Oz, F., et al. (2001). Possible association of temporomandibular joint pain and dysfunction with a polymorphism in the serotonin transporter gene. *American Journal of Orthodontics and Dentofacial Orthopedics, 120*(3), 308–313.
26. Tegeder, I., Costigan, M., Griffin, R. S., Abele, A., Belfer, I., Schmidt, H., et al. (2006). GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nature Medicine, 12*(11), 1269–1277.
27. Lötsch, J., Belfer, I., Kirchhof, A., Mishra, B. K., Max, M. B., Doehring, A., et al. (2007). Reliable screening for a pain-protective haplotype in the GTP cyclohydrolase 1 gene (GCH1) through the use of 3 or fewer single nucleotide polymorphisms. *Clinical Chemistry, 53*(6), 1010–1015.
28. Story, G. M., Peier, A. M., Reeve, A. J., Eid, S. R., Mosbacher, J., Hricik, T. R., et al. (2003). ANKTM1, a TRP-like channel expressed in nociceptive neurons, is activated by cold temperatures. *Cell, 112*(6), 819–829.
29. Kim, H., Mittal, D. P., Iadarola, M. J., & Dionne, R. A. (2006). Genetic predictors for acute experimental cold and heat pain sensitivity in humans. *Journal of Medical Genetics, 43*(8), e40.
30. Caterina, M. J., Schumacher, M. A., Tominaga, M., Rosen, T. A., Levine, J. D., & Julius, D. (1997). The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature, 389*(6653), 816–824.
31. Kim, H., Neubert, J. K., San Miguel, A., Xu, K., Krishnaraju, R. K., Iadarola, M. J., et al. (2004). Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. *Pain, 109*(3), 488–496.
32. Lichtman, A. H., Shelton, C. C., Advani, T., & Cravatt, B. F. (2004). Mice lacking fatty acid amide hydrolase exhibit a cannabinoid receptor-mediated phenotypic hypoalgesia. *Pain, 109*(3), 319–327.
33. Chiang, K. P., Gerber, A. L., Sipe, J. C., & Cravatt, B. F. (2004). Reduced cellular expression and activity of the P129T mutant of human fatty acid amide hydrolase: Evidence for a link between defects in the endocannabinoid system and problem drug use. *Human Molecular Genetics, 13*(18), 2113–2119.
34. Raimondi, S., Sera, F., Gandini, S., Iodice, S., Caini, S., Maisonneuve, P., et al. (2008). MC1R variants, melanoma and red hair color phenotype: A meta-analysis. *International Journal of Cancer, 122*(12), 2753–2760.
35. Liem, E. B., Joiner, T. V., Tsueda, K., & Sessler, D. I. (2005). Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. *Anesthesiology, 102*(3), 509–514.
36. Mogil, J. S., Wilson, S. G., Chesler, E. J., Rankin, A. L., Nemmani, K. V., Lariviere, W. R., et al. (2003). The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. *Proceedings of the National*

Academy of Sciences of the United States of America, 100(8), 4867–4872.
37. Mogil, J. S., Ritchie, J., Smith, S. B., Strasburg, K., Kaplan, L., Wallace, M. R., et al. (2005). Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. *Journal of Medical Genetics, 42*(7), 583–587.
38. Lee, B. N., Dantzer, R., Langley, K. E., Bennett, G. J., Dougherty, P. M., Dunn, A. J., et al. (2004). A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. *Neuroimmunomodulation, 11*(5), 279–292.
39. Maier, S. F., & Watkins, L. R. (2003). Immune-to-central nervous system communication and its role in modulating pain and cognition: Implications for cancer and cancer treatment. *Brain, Behavior, and Immunity, 17*(Suppl 1), S125–S131.
40. Oh, S. B., Tran, P. B., Gillard, S. E., Hurley, R. W., Hammond, D. L., & Miller, R. J. (2001). Chemokines and glycoprotein120 produce pain hypersensitivity by directly exciting primary nociceptive neurons. *Journal of Neuroscience, 21*(14), 5027–5035.
41. Bennett, G. J., & Xie, Y. K. (1988). A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. *Pain, 33*(1), 87–107.
42. Bennett, G. J. (1999). Does a neuroimmune interaction contribute to the genesis of painful peripheral neuropathies? *Proceedings of the National Academy of Sciences of the United States of America, 96*(14), 7737–7738.
43. Bennett, G. J. (2000). A neuroimmune interaction in painful peripheral neuropathy. *Clinical Journal of Pain, 16*(3 Suppl), S139–S143.
44. Reeve, A. J., Patel, S., Fox, A., Walker, K., & Urban, L. (2000). Intrathecally administered endotoxin or cytokines produce allodynia, hyperalgesia and changes in spinal cord neuronal responses to nociceptive stimuli in the rat. *European Journal of Pain: Ejp, 4*(3), 247–257.
45. Sommer, C., Petrausch, S., Lindenlaub, T., & Toyka, K. V. (1999). Neutralizing antibodies to interleukin 1-receptor reduce pain associated behavior in mice with experimental neuropathy. *Neuroscience Letters, 270*(1), 25–28.
46. Dominici, R., Cattaneo, M., Malferrari, G., Archi, D., Mariani, C., Grimaldi, L. M., et al. (2002). Cloning and functional analysis of the allelic polymorphism in the transcription regulatory region of interleukin-1 alpha. *Immunogenetics, 54*(2), 82–86.
47. Hulkkonen, J., Laippala, P., & Hurme, M. (2000). A rare allele combination of the interleukin-1 gene complex is associated with high interleukin-1 beta plasma levels in healthy individuals. *European Cytokine Network, 11*(2), 251–255.
48. McDowell, T. L., Symons, J. A., Ploski, R., Førre, O., & Duff, G. W. (1995). A genetic association between juvenile rheumatoid arthritis and a novel interleukin-1 alpha polymorphism. *Arthritis and Rheumatism, 38*(2), 221–228.
49. Pociot, F., Mølvig, J., Wogensen, L., Worsaae, H., & Nerup, J. (1992). A TaqI polymorphism in the human interleukin-1 beta (IL-1 beta) gene correlates with IL-1 beta secretion in vitro. *European Journal of Clinical Investigation, 22*(6), 396–402.
50. di Giovine, F. S., Takhsh, E., Blakemore, A. I., & Duff, G. W. (1992). Single base polymorphism at -511 in the human interleukin-1 beta gene (IL1 beta). *Human Molecular Genetics, 1*(6), 450.
51. Tarlow, J. K., Blakemore, A. I., Lennard, A., Solari, R., Hughes, H. N., Steinkasserer, A., et al. (1993). Polymorphism in human IL-1 receptor antagonist gene intron 2 is caused by variable numbers of an 86-bp tandem repeat. *Human Genetics, 91*(4), 403–404.
52. Tountas, N. A., Casini-Raggi, V., Yang, H., di Giovine, F. S., Vecchi, M., Kam, L., et al. (1999). Functional and ethnic association of allele 2 of the interleukin-1 receptor antagonist gene in ulcerative colitis. *Gastroenterology, 117*(4), 806–813.
53. Solovieva, S., Leino-Arjas, P., Saarela, J., Luoma, K., Raininko, R., & Riihimäki, H. (2004). Possible association of interleukin 1 gene locus polymorphisms with low back pain. *Pain, 109*(1–2), 8–19.
54. Bessler, H., Shavit, Y., Mayburd, E., Smirnov, G., & Beilin, B. (2006). Postoperative pain, morphine consumption, and genetic polymorphism of IL-1 beta and IL-1 receptor antagonist. *Neuroscience Letters, 404*(1–2), 154–158.
55. Winkelstein, B. A., Rutkowski, M. D., Weinstein, J. N., & DeLeo, J. A. (2001). Quantification of neural tissue injury in a rat radiculopathy model: Comparison of local deformation, behavioral outcomes, and spinal cytokine mRNA for two surgeons. *Journal of Neuroscience Methods, 111*(1), 49–57.
56. Bianchi, M., Maggi, R., Pimpinelli, F., Rubino, T., Parolaro, D., Poli, V., et al. (1999). Presence of a reduced opioid response in interleukin-6 knock out mice. *European Journal of Neuroscience, 11*(5), 1501–1507.
57. Wang, X. S., Shi, Q., Williams, L. A., Cleeland, C. S., Mobley, G. M., Reuben, J. M., et al. (2008). Serum interleukin-6 predicts the development of multiple symptoms at nadir of allogeneic hematopoietic stem cell transplantation. *Cancer, 113*(8), 2102–2109.
58. Fishman, D., Faulds, G., Jeffery, R., Mohamed-Ali, V., Yudkin, J. S., Humphries, S., et al. (1998). The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *Journal of Clinical Investigation, 102*(7), 1369–1376.
59. Reyes-Gibby, C. C., El Osta, B., Spitz, M. R., Parsons, H., Kurzrock, R., Wu, X., et al. (2008). The influence of tumor necrosis factor-alpha -308 G/A and IL-6–174 G/C on pain and analgesia response in lung cancer patients receiving supportive care. *Cancer Epidemiology, Biomarkers and Prevention, 17*(11), 3262–3267.
60. Oen, K., Malleson, P. N., Cabral, D. A., Rosenberg, A. M., Petty, R. E., Nickerson, P., et al. (2005). Cytokine genotypes correlate with pain and radiologically defined joint damage in patients with juvenile rheumatoid arthritis. *Rheumatology (Oxford), 44*(9), 1115–1121.
61. Karppinen, J., Daavittila, I., Noponen, N., Haapea, M., Taimela, S., Vanharanta, H., et al. (2008). Is the interleukin-6 haplotype a prognostic factor for sciatica? *European Journal of Pain: Ejp, 12*(8), 1018–1025.
62. Utreras, E., Futatsugi, A., Rudrabhatla, P., Keller, J., Iadarola, M. J., Pant, H. C., et al. (2009). Tumor necrosis factor-alpha regulates cyclin-dependent kinase 5 activity during pain signaling through transcriptional activation of p35. *The Journal of Biological Chemistry, 284*(4), 2275–2284.
63. Segond von Banchet, G., Boettger, M. K., Fischer, N., Gajda, M., Bräuer, R., & Schaible, H. G. (2009). Experimental arthritis causes tumor necrosis factor-alpha-dependent infiltration of macrophages into rat dorsal root ganglia which correlates with pain-related behavior. *Pain, 145*(1–2), 151–159.
64. Wilson, A. G., Symons, J. A., McDowell, T. L., McDevitt, H. O., & Duff, G. W. (1997). Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proceedings of the National Academy of Sciences of the United States of America, 94*(7), 3195–3199.
65. Ahn, S. H., Cho, Y. W., Ahn, M. W., Jang, S. H., Sohn, Y. K., & Kim, H. S. (2002). mRNA expression of cytokines and chemokines in herniated lumbar intervertebral discs. *Spine (Phila Pa 1976), 27*(9), 911–917.
66. Wang, X. M., Hamza, M., Wu, T. X., & Dionne, R. A. (2009). Upregulation of IL-6, IL-8 and CCL2 gene expression after

acute inflammation: Correlation to clinical pain. *Pain, 142*(3), 275–283.
67. Hull, J., Thomson, A., & Kwiatkowski, D. (2000). Association of respiratory syncytial virus bronchiolitis with the interleukin 8 gene region in UK families. *Thorax, 55*(12), 1023–1027.
68. Reyes-Gibby, C. C., Spitz, M., Wu, X., Merriman, K., Etzel, C., Bruera, E., et al. (2007). Cytokine genes and pain severity in lung cancer: Exploring the influence of TNF-alpha-308 G/A IL6–174G/C and IL8–251T/A. *Cancer Epidemiology, Biomarkers and Prevention, 16*(12), 2745–2751.
69. Schinkel, A. H., Wagenaar, E., van Deemter, L., Mol, C. A., & Borst, P. (1995). Absence of the mdr1a P-Glycoprotein in mice affects tissue distribution and pharmacokinetics of dexamethasone, digoxin, and cyclosporin A. *Journal of Clinical Investigation, 96*(4), 1698–1705.
70. Thompson, S. J., Koszdin, K., & Bernards, C. M. (2000). Opiate-induced analgesia is increased and prolonged in mice lacking P-glycoprotein. *Anesthesiology, 92*(5), 1392–1399.
71. King, M., Su, W., Chang, A., Zuckerman, A., & Pasternak, G. W. (2001). Transport of opioids from the brain to the periphery by P-glycoprotein: Peripheral actions of central drugs. *Nature Neuroscience, 4*(3), 268–274.
72. Higgins, C. F. (2001). ABC transporters: Physiology, structure and mechanism–an overview. *Research in Microbiology, 152*(3–4), 205–210.
73. Hoffmeyer, S., Burk, O., von Richter, O., Arnold, H. P., Brockmöller, J., Johne, A., et al. (2000). Functional polymorphisms of the human multidrug-resistance gene: Multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. *Proceedings of the National Academy of Sciences of the United States of America, 97*(7), 3473–3478.
74. Lötsch, J., von Hentig, N., Freynhagen, R., Griessinger, N., Zimmermann, M., Doehring, A., et al. (2009). Cross-sectional analysis of the influence of currently known pharmacogenetic modulators on opioid therapy in outpatient pain centers. *Pharmacogenetics and genomics, 19*(6), 429–436.
75. Campa, D., Gioia, A., Tomei, A., Poli, P., & Barale, R. (2008). Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief. *Clinical Pharmacology and Therapeutics, 83*(4), 559–566.
76. Coller, J. K., Barratt, D. T., Dahlen, K., Loennechen, M. H., & Somogyi, A. A. (2006). ABCB1 genetic variability and methadone dosage requirements in opioid-dependent individuals. *Clinical Pharmacology and Therapeutics, 80*(6), 682–690.
77. Park, H. J., Shinn, H. K., Ryu, S. H., Lee, H. S., Park, C. S., & Kang, J. H. (2007). Genetic polymorphisms in the ABCB1 gene and the effects of fentanyl in Koreans. *Clinical Pharmacology and Therapeutics, 81*(4), 539–546.
78. Guengerich, F. P. (2008). Cytochrome p450 and chemical toxicology. *Chemical Research in Toxicology, 21*(1), 70–83.
79. Stamer, U. M., Musshoff, F., Kobilay, M., Madea, B., Hoeft, A., & Stuber, F. (2007). Concentrations of tramadol and O-desmethyltramadol enantiomers in different CYP2D6 genotypes. *Clinical Pharmacology and Therapeutics, 82*(1), 41–47.
80. Zanger, U. M., Klein, K., Saussele, T., Blievernicht, J., Hofmann, M. H., & Schwab, M. (2007). Polymorphic CYP2B6: Molecular mechanisms and emerging clinical significance. *Pharmacogenomics, 8*(7), 743–759.
81. Paar, W. D., Poche, S., Gerloff, J., & Dengler, H. J. (1997). Polymorphic CYP2D6 mediates O-demethylation of the opioid analgesic tramadol. *European Journal of Clinical Pharmacology, 53*(3–4), 235–239.
82. de Leon, J., Susce, M. T., & Murray-Carmichael, E. (2006). The AmpliChip CYP450 genotyping test: Integrating a new clinical tool. *Molecular diagnosis & therapy, 10*(3), 135–151.
83. Desmeules, J., Gascon, M. P., Dayer, P., & Magistris, M. (1991). Impact of environmental and genetic factors on codeine analgesia. *European Journal of Clinical Pharmacology, 41*(1), 23–26.
84. Yue, Q. Y., Hasselström, J., Svensson, J. O., & Säwe, J. (1991). Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: Comparisons between extensive and poor hydroxylators of debrisoquine. *British Journal of Clinical Pharmacology, 31*(6), 635–642.
85. Wang, G., Zhang, H., He, F., & Fang, X. (2006). Effect of the CYP2D6*10 C188T polymorphism on postoperative tramadol analgesia in a Chinese population. *European Journal of Clinical Pharmacology, 62*(11), 927–931.
86. Crettol, S., Déglon, J. J., Besson, J., Croquette-Krokar, M., Hämmig, R., Gothuey, I., et al. (2006). ABCB1 and cytochrome P450 genotypes and phenotypes: Influence on methadone plasma levels and response to treatment. *Clinical Pharmacology and Therapeutics, 80*(6), 668–681.
87. Pilotto, A., Seripa, D., Franceschi, M., Scarcelli, C., Colaizzo, D., Grandone, E., et al. (2007). Genetic susceptibility to nonsteroidal anti-inflammatory drug-related gastroduodenal bleeding: Role of cytochrome P450 2C9 polymorphisms. *Gastroenterology, 133*(2), 465–471.
88. Armstrong, S. C., & Cozza, K. L. (2003). Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: Theory and clinical reality, part I. *Psychosomatics, 44*(2), 167–171.
89. Holthe, M., Rakvåg, T. N., Klepstad, P., Idle, J. R., Kaasa, S., Krokan, H. E., et al. (2003). Sequence variations in the UDP-glucuronosyltransferase 2B7 (UGT2B7) gene: Identification of 10 novel single nucleotide polymorphisms (SNPs) and analysis of their relevance to morphine glucuronidation in cancer patients. *The Pharmacogenomics Journal, 3*(1), 17–26.
90. Duguay, Y., Báár, C., Skorpen, F., & Guillemette, C. (2004). A novel functional polymorphism in the uridine diphosphate-glucuronosyltransferase 2B7 promoter with significant impact on promoter activity. *Clinical Pharmacology and Therapeutics, 75*(3), 223–233.
91. Darbari, D. S., van Schaik, R. H., Capparelli, E. V., Rana, S., McCarter, R., & van den Anker, J. (2008). UGT2B7 promoter variant -840G>A contributes to the variability in hepatic clearance of morphine in patients with sickle cell disease. *American Journal of Hematology, 83*(3), 200–202.
92. Mogil, J. S. (2009). Are we getting anywhere in human pain genetics? *Pain, 146*(3), 231–232.
93. Rakvåg, T. T., Klepstad, P., Báár, C., Kvam, T. M., Dale, O., Kaasa, S., et al. (2005). The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. *Pain, 116*(1–2), 73–78.
94. Hagen, K., Pettersen, E., Stovner, L. J., Skorpen, F., & Zwart, J. A. (2006). The association between headache and Val158Met polymorphism in the catechol-O-methyltransferase gene: The HUNT Study. *The Journal of Headache and Pain, 7*(2), 70–74.
95. Vargas-Alarcón, G., Fragoso, J. M., Cruz-Robles, D., Vargas, A., Vargas, A., Lao-Villadóniga, J. I., et al. (2007). Catechol-O-methyltransferase gene haplotypes in Mexican and Spanish patients with fibromyalgia. *Arthritis Research & Therapy, 9*(5), R110.
96. Kim, H., Lee, H., Rowan, J., Brahim, J., & Dionne, R. A. (2006). Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. *Molecular Pain, 2*, 24.
97. Ruaño, G., Thompson, P. D., Windemuth, A., Seip, R. L., Dande, A., Sorokin, A., et al. (2007). Physiogenomic association of statin-related myalgia to serotonin receptors. *Muscle and Nerve, 36*(3), 329–335.

98. Guimarães, A. L., Correia-Silva Jde, F., Sá, A. R., Victória, J. M., Diniz, M. G., Costa Fde, O., et al. (2007). Investigation of functional gene polymorphisms IL-1beta, IL-6, IL-10 and TNF-alpha in individuals with recurrent aphthous stomatitis. *Archives of Oral Biology, 52*(3), 268–272.
99. Klepstad, P., Dale, O., Skorpen, F., Borchgrevink, P. C., & Kaasa, S. (2005). Genetic variability and clinical efficacy of morphine. *Acta Anaesthesiologica Scandinavica, 49*(7), 902–908.
100. Pedersen, R. S., Damkier, P., & Brosen, K. (2005). Tramadol as a new probe for cytochrome P450 2D6 phenotyping: A population study. *Clinical Pharmacology and Therapeutics, 77*(6), 458–467.
101. Coller, J. K., Joergensen, C., Foster, D. J., James, H., Gillis, D., Christrup, L., et al. (2007). Lack of influence of CYP2D6 genotype on the clearance of (R)-, (S)- and racemic-methadone. *International Journal of Clinical Pharmacology and Therapeutics, 45*(7), 410–417.
102. Ferrari, A., Coccia, C. P., Bertolini, A., & Sternieri, E. (2004). Methadone–metabolism, pharmacokinetics and interactions. *Pharmacological Research, 50*(6), 551–559.
103. Shiran, M. R., Lennard, M. S., Iqbal, M. Z., Lagundoye, O., Seivewright, N., Tucker, G. T., et al. (2009). Contribution of the activities of CYP3A, CYP2D6, CYP1A2 and other potential covariates to the disposition of methadone in patients undergoing methadone maintenance treatment. *British Journal of Clinical Pharmacology, 67*(1), 29–37.
104. Cai, W., Chen, B., Tao, X., Ling, S., & Zhang, Y. (2000). Correlation of genetic polymorphism of cytochrome P4502D6 with dextromethorphan oxidative metabolism in Chinese. *Zhonghua Yixue Yichuanxue Zazhi, 17*(3), 181–184.
105. Takashima, T., Murase, S., Iwasaki, K., & Shimada, K. (2005). Evaluation of dextromethorphan metabolism using hepatocytes from CYP2D6 poor and extensive metabolizers. *Drug Metabolism and Pharmacokinetics, 20*(3), 177–182.