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Review Article

The Genetics of Pain: Implications for Perioperative Pain Management

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ABSTRACT

Aim of review: Postoperative pain is one of the most common symptoms in surgical patients. Although numerous measures, such as patient-controlled analgesia and multimodal analgesia, have been developed, postoperative pain treatment is not yet adequate. Human genome analysis allows us to investigate interindividual differences in pain thresholds and pain perception at the genetic level. This article aimed to review important and illustrative results from recent pain genetic studies in this field and to interpret their clinical implications for perioperative pain management.

Method: Literatures were searched via PubMed with the key words of genetics of pain, perioperative pain, cytochrome P450 (CYP450), mu-opioid receptor (MOR)-1, catecholamine-O-methyltransferase (COMT), guanosine triphosphate (GTP) cyclohydrolase 1 (GCH1), interleukin (IL)-1B, SCN9A, CACNG2, transient receptor potential vanilloid-1 (TRPV1) and TRP ankyrin-1 (TRPA1). A few review articles in the relevant fields were also referenced.

Recent findings: There is a growing body of compelling evidence indicating that interindividual differences in pain sensitivity and the predisposition to chronic pain are genetically determined. During the past decade, numerous pain-related genes and their functional polymorphisms have been identified, including CYP450, MOR-1, COMT, GCH1, etc. These functional gene polymorphisms are valuable to perioperative pain management.

Summary: The identification of genetic markers relevant to perioperative pain management may help to predict pain susceptibility, severity, and treatment response in surgical patients. As the foundation for interindividual variability in the experience of postoperative pain, genetic variability will aid anesthesiologists to develop the personalized perioperative pain management strategy.

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Surgery is the most common and predictable source of severe pain (1). Untreated postoperative pain can result in unwanted psychological and physiologic effects that may increase morbidity and mortality, compromise the quality of recovery, and increase the incidence of chronic pain. Although management of postoperative pain has improved tremendously in the last few decades, pain in surgical patients is still undermanaged. A recent survey showed that 30-71% of patients undergoing surgery experience moderate to severe postoperative pain, despite numerous pain management measures (2), suggesting that anesthesiologists still face a great challenge to manage perioperative pain successfully. There are lots of barriers in the perioperative pain management, including analgesic-related side effects, interindividual differences, etc. Perioperative pain management is as much an art as a science and an anesthesiologist must balance the risks and benefits of each modality to customize treatment based on the patient's specific status.

In the past decades, several factors including demographics, psychological variables, quantitative sensory test results, the level of preoperative pain, and the type of surgery, have been identified as predictors of postoperative pain (3-7). These predictors may help anesthesiologists to customize perioperative pain management for surgical patients. On the other hand, the substantial interindividual variability in pain sensitivity, response to analgesics, and susceptibility to chronic pain has been recognized by both anesthesiologists and researchers. Variability in human pain experience appears to be at least partially determined by genetic inheritance. The development and use of genetic testing for specific pain markers may contribute to the personalized perioperative pain management. Recently, human genome analysis has allowed us to investigate interindividual differences in pain thresholds and pain perception at the genetic level (8, 9). Within the next decade, such research is likely to confirm the identity of numerous genetic pain markers that can be incorporated into simple and rapid genetic testing to aid the anesthesiologists in diagnosis, prognosis, risk stratification, and treatment selection.

A critical discovery over the past decade has been the observation of common patterns of interindividual DNA sequence variation throughout the genome. These genetic polymorphisms are fairly evenly distributed and include both coding and noncoding regions. Commonly occurring variations of a single nucleotide locus, termed single nucleotide polymorphisms (SNPs), have served as genetic pain markers for inheritance of specific traits and have been critical to current efforts at developing more personalized pain treatment approaches to deliver health care (Table 1). Increasing number of researchers focus their attention on pharmacogenetics, which studies how genetic variation can affect the pharmacokinetic and/or pharmacodynamic properties of medications (Figure 1). Pharmacokinetic parameters include drug absorption, distribution, metabolism, and excretion (10). Pharmacodynamic variability can be caused by differences in receptor activity, receptor binding affinity, and receptor density (11, 12). As a diagnostic tool, pharmacogenetics has the potential to improve pharmacological pain management by predicting the individual response to a specific substance before initiation of therapy and thus offers hope for successful implementation of individualized treatment in the future (13). This review will characterize the implications of pain genetics for perioperative pain management and highlight recent advances in this field.

Pain-Relevant Functional Polymorphic Genes and Perioperative Pain Management

Cytochrome P450

The cytochrome P450 (CYP450) family of hepatic enzymes metabolizes a wide variety of exogenous and endogenous compounds and is encoded by a superfamily of at least 50 closely related genes (14). There have been 57 enzymes identified in humans and they are divided into family, subfamily, isoenzymes, and allele variants (15). Polymorphic variations in CYP450 enzymes have been extensively studied as a cause of inherited differences in metabolism of various drugs, including a number of analgesic agents.

Due to the study of genetics, patients can be classified by how effectively they metabolize a medication, which is based on how many copies of normal or abnormal alleles they inherited. An

extensive metabolizer (EM) has two normal or "wild type" alleles and is considered "normal". An intermediate metabolizer (IM) has one normal and one reduced allele or two partially deficient alleles. A poor metabolizer (PM) has two mutant alleles leading to a very limited or complete loss of activity, while the ultra-rapid metabolizer (UM) has multiple copies of functional alleles leading to excess activity.

One of the most extensively studied human functional polymorphisms is the debrisoquine/sparteine polymorphism of CYP2D6 (encoding the P450 2D6 enzyme). CYP2D6 is an important metabolic gene associated with the metabolism of many of opioids including codeine, hydrocodone, and tramadol (Table 2). To date, more than 70 different CYP2D6 haplotypes with varying levels of activity have been identified, and sequence variations range from SNPs affecting RNA splice sites to large regional DNA rearrangements (16). Codeine is an inactive compound (a prodrug), metabolized by CYP2D6 into its active form morphine. It has only a weak affinity for the mu- opioid receptor (MOR), which is 300 times less than morphine (17). Therefore, CYP2D6 PMs who are given acetaminophen with codeine are actually being given only acetaminophen, while UM patients may have dangerously high levels of morphine after standard doses (18). About 7-10% of Caucasian population with deficient CYP2D6 activity are insensitive to codeine (17) (Table 2). Hydrocodone displays weak binding capacity for the MOR, but the CYP2D6 enzyme demethylates it into hydromorphone, which then has much stronger MOR binding than hydrocodone (19). Otton et al. (20) found that the activity of CYP2D6 may limit the abuse liability of hydrocodone. Another study showed that 71% of postoperative patients with acute severe pain were PMs for CYP2D6, compared to other metabolizers (21). They also found that PMs of CYP2D6 who were smokers had more pain than the nonsmokers. UMs of CYP2D6 required less morphine in the postoperative period than did any other CYP metabolizer group (22). The synthetic agent tramadol is now extensively used for perioperative pain management and at least partially metabolized by P450 2D6, and interindividual differences in drug efficacy may be partially due to genetically determined variations in P450 2D6 activity (23). Additionally, individuals with decreased P450 2D6 activity have also been shown to possess increased pain sensitivity (Table 1).

Table 1. Pain-Relevant Genetic Markers Involved in the Interindividual Variability in Pain Sensitivity, Response to Analgesics and Susceptibility to Chronic Pain in Surgical Patients.

Pain-relevant gene or enzyme	Pain sensitivity	Response to analgesics	Susceptibility to chronic pain
CYP450	Yes	Yes	Unknown
COMT	Yes	Yes	Unknown
MOR-1	Yes	Yes	Yes
GCH1	Yes	Yes	Yes
IL-1B	Yes	Yes	Yes
SCN9A	Yes	Yes	Unknown
CACNG2	Unknown	Unknown	Yes
TRPV1	Yes	Unknown	Unknown
TRPA1	Yes	Yes	Unknown

CYP450, cytochrome P450; COMT, catecholamine-O-methyltransferase; GCH1, GTP cyclohydrolase 1; IL-1B, interleukin 1B; TRPV1, transient receptor potential vanilloid-1; TRPA1, transient receptor potential ankyrin-1.

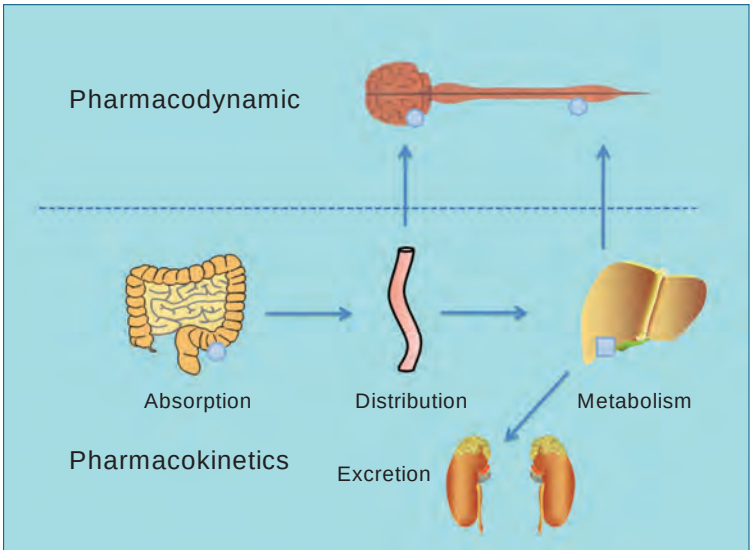

Figure 1. Single Nucleotide Polymorphisms in Multiple Genes Affecting Analgesia in Humans.
○=SNPs at opioid receptor genes (e.g. OPRM1); □=SNPs at CYP (e.g. CYP2D6) and COMT genes
An orally administrated opioid will be absorbed in the gut. Once the opioid is absorbed, it is distributed to various organs (e.g., liver, kidney, peripheral nervous system, and the central nervous system) through the bloodstream. In the liver, opioids are metabolized by enzymes including the CYP family. The kidneys are the primary organs for excretion of opioids. Dashed line separates the pharmacokinetics from the pharmaco-dynamics.
SNP, single nucleotide polymorphism; CYP, cytochrome P450; COMT, catechol-O-methyltransferase.

Table 2. Metabolizer Status by Racial/Ethnic Group.

Gene of enzyme	Drugs metabolized by this enzyme	Phenotype and frequency by groups	Clinical effect
CYP1A2	Anticonvulsants: phenytoin, carbamazepine substrates Antidepressants: clomipramine, fluoxetine, imipramine NSAIDs: acetaminophen, naproxen	PM: Caucasian, 12%	Weak metabolism of enzyme
CYP2C9	Warfarin substratse Phenytoin Angiotensin II blockers: irbesartan, losartan NSAIDs: celecoxib, diclofenac, ibuprofen	PM: Caucasian, 2-6%	Weak metabolism of enzyme
CYP2D6	Analgesics: codeine, dextromethorphan, oxycodone, tramadol substrates	PM: Caucasian, 3-10%; Chinese/Japanese/African American, <2%; UR: Ethiopian, 20% ; Hispanic, 7% ; Scandinavian, 1.5%	Weak metabolism of enzyme; Enhanced metabolism of enzyme substrates

NSAIDs, nonsteroidal anti-inflammatory drugs; PM, poor metabolizer; UR, ultra-rapid.

CYP2C9 (encoding the P450 2C9 enzyme) is another polymorphic gene with at least three different alleles that are prevalent in Caucasian populations. CYP2C9 is responsible for the metabolism of nonsteroidal anti- inflammatory drugs (NSAIDs) (Table 2), and polymorphisms of CYP2C9 may play an important role in the variable efficacy and side effects observed with this class of drugs (24). In particular, the low enzymatic activity of the CYP2C9*3 allele appears to be associated with reduced drug efficacy. Some NSAIDs, including flurbiprofen axetil and parecoxib, are often used for perioperative pain treatment. The identification of CYP2C9 polymorphisms may help anesthesiologists to select suitable analgesics for surgical patients. Interestingly, pharmacogenetic testing has revealed a correlation between NSAIDs- induced gastropathy and an allelic variant of CYP2C9 (25). Although pharmacogenetic testing is not routinely used in clinical decision making, anesthesiologists must be aware of the potential benefits of this testing to manage the surgical patients with pain better, and to improve drug efficacy and safety profile.

Smoking is a potent inducer of CYP1A2 (encoding the P450 1A2 enzyme). Since methadone is also metabolized by CYP1A2, methadone level in a smoker who is stabilized on methadone may increase to a dangerous level with smoking cessation (26, 27). Comparing smokers to nonsmokers, the smokers had higher pain scores and took higher doses of hydrocodone, yet had significantly lower serum levels of hydrocodone (28).

MOR-1

Opioids remain the primary analgesic agent for treating moderate to severe pain after surgery. However, in many cases opioid- related side effects may compromise patients' quality of recovery. Analgesic tolerance also develops frequently with continued use (29, 30). Opioids are characterized as having a relatively narrow therapeutic window, and for most opioids, a balance in dosing is necessary to achieve a therapeutic effect without producing dangerous side effects such as respiratory depression (31). The degree to which individuals experience opioid-induced analgesia and adverse effects is highly variable and difficult to predict (32), which can lead to inadequate pain relief for many individuals as dosing of opioids may be restricted in order to avoid serious adverse events (33).

It has been demonstrated that individual differences in opioid requirements have a genetic basis and are related to the polymorphisms in MOR-1gene (34). The MOR-1 gene coding for the MOR was initially cloned in 1993 (35). After gene transcription, alternative mRNA splicing results in multiple receptor subtypes. The mouse analog of the MOR-1 gene, Oprm, contains fourteen separate exons that recombine into at least fifteen different mRNAs and proteins, and the human MOR-1 mRNA appears to undergo a similar degree of alternative splicing. The different receptor variants demonstrate different opiate potency profiles and different rates of cellular internalization after ligand binding. Given that receptor internalization appears to

be associated with the development of opioid tolerance, genetic differences in splicing among individuals could explain at least a part of the large interindividual variation in opioid tolerance observed among different patients.

The MOR is the principle target for most clinically prescribed opioid analgesics, including morphine, buprenorphine and oxycodone (30, 36, 37). Naturally occurring, non-synonymous genetic variants found in the coding region of the gene for MOR, may affect individual opioid response (31, 32). The most prevalent OPRM1 variants are N40D (MOR-N40D, rs1799971) and A6V (MOR-A6V, rs1799971), SNPs in the N-terminal domain of MOR. Knapman et al. (38) found that signaling to adenylyl cyclase and extracellular signal regulated kinase via MOR-A6V is reduced for many opioids and the differences could be of clinical significance. The A6V variant markedly decreased the effect of a number of clinically prescribed opioids including morphine. Since the A6V variant is quite prevalent in some populations, with allelic frequencies of up to 20% (39, 40), understanding how the A6V SNP affects opioid signaling is an important part in predicting individual response to opioids. Although an individual's response to opioids will be influenced by numerous genetic and epigenetic factors, knowledge of the effect of individual MOR genotypes on opioid responses could provide valuable insight into what the most effective form of analgesic therapy might be, particularly in the case of A6V carriers, where opioid efficacy may be significantly diminished.

As morphine is the primary agent for perioperative pain treatment, it is troubled that long-term administration is always associated with the development of tolerance. A preclinical animal study has shown some kind of association between morphine tolerance and selective up-regulation of MOR splice variant mRNAs (41). They assessed the mRNA levels for the various MOR splice variants to determine whether stabilization of morphine tolerance was associated with changes in their levels. They found that mRNA levels of the variants increase as much as 300-fold for selected variants in specific brain regions. This provides strong evidence that the polymorphisms in the human MOR-1 gene may influence the development of morphine tolerance during the period of postoperative morphine analgesia.

There exist several polymorphisms in the human MOR-1 gene and the common A118G polymorphism occurring in a coding region appears to affect receptor binding affinity. Previous studies have shown that genetic variability at position 118 of the human MOR-1 gene altered patients' response to intravenous morphine. Liu and Wang (42) reported a prevalence of 31.3% of the AA (wild type) genotype, 58.3% of the AG genotype, and 10.4% of the GG genotype. Studies showed that patients carrying the GG (homozygous variant) genotype require much higher opioid doses to achieve pain relief (43, 44). Patients carrying the AA genotype required an average dose of 112 mg morphine/24 hours, AG patients required 132 mg morphine/24 hours, and GG patients required 216 mg morphine/24 hours (12). Similar results were obtained that intravenous morphine consumption and pain scores were lowest in AA group (versus AG or GG group) in a population undergoing caesarean section (45). A recent study showed that A118G OPRM1 polymorphism contributes to interindividual variations in the function of neurotransmitters responsive to pain (endogenous opioid and dopamine), as well as their regulation through cognitive-emotional influences in the context of therapeutic expectations, the so-called placebo effect (46). These effects are relevant to human vulnerability to disease processes where these neurotransmitters have a role, such as persistent pain, mood, and substance use disorders, and responses to their treatments. Similarly, another study also reported that A118G polymorphism of MOR-1 gene affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy (47). These studies suggest that identifying the A118G polymorphism of MOR-1 gene in surgical patients may provide beneficial information to modulate the analgesic dosage of opioid for better postoperative pain control.

COMT

There are some controversies surrounding the potential role of catecholamine-O-methyltrans-

ferase (COMT) gene polymorphisms in modulating human pain experience. COMT is an enzyme involved in the metabolic degradation of dopamine, norepinephrine and epinephrine (48). These neurotransmitters are particularly relevant in higher cognitive and emotional processing of human pain experiences. The dopamine and norepinephrine systems also influence opioid behaviors. COMT contains a common functional coding polymorphism rs4680, also known as COMT Val158Met, which substitutes valine with methionine at amino acid position 158, leading to a 3- to 4-fold reduction in the activity of the COMT enzyme. Thus, COMT gene polymorphisms may be involved in the control of pain through indirect regulation of the neurotransmitters and mu- opioid system and contribute to the interindividual variability of pain sensitivity and opioid consumption after surgery.

Evidence regarding the role of COMT gene polymorphisms in pain sensitivity and opioid consumption for chronic pain treatment has been controversial between studies. Zubieta et al. (49) reported that COMT Val158Met may affect the pain susceptibility in human. Individuals with a homozygous Met158 genotype report greater sensory and affective ratings of pain and show a reduced activation of the endogenous opioid system to experimental pain stimuli and a higher regional density of MOR in the brain. Additionally, Rakvåg et al. (50, 51) demonstrated that the rs4680 (Val158Met) polymorphism of the human COMT gene may lead to different opioid consumption in patients with chronic cancer pain. However, Ross et al. (52) and Klepstad et al. (53), showed that rs4680 has no significant association with morphine dose, plasma concentration, and metabolite concentration in cancer pain patients. A meta- analysis showed that the COMT SNP rs4680 is associated with chronic pain only in patients suffering from fibromyalgia or chronic widespread pain (54).

In the presence of acute pain, studies have also yielded conflicting results (55-57). Candiotti et al. (58) demonstrated that the COMT rs4680 SNP is associated with differences in postoperative opioid consumption in patients who underwent a nephrectomy. Deng et al. (59) found that the GA and AA genotype groups of rs4680 require less fentanyl at 48 hours after surgery than the wild type group (GG) in 129 patients undergoing lumbar spine surgery. A recent study has suggested that COMT gene haplotypes are closely associated with postoperative fentanyl dose (60). There were no significant differences in the doses of fentanyl used among patients possessing different SNPs of COMT rs6269, rs4633, rs4818, and rs4680 at 24 and 48 hours after surgery. However, COMT gene haplotypes combined by COMT rs6269, rs4633, rs4818, and rs4680, affected fentanyl consumption significantly, and patients carrying the COMT gene haplotype ACCG consume the most during the first 24 and 48 hours postoperatively. In contrast, Kim et al. (55) reported that there is no association between COMT genetic polymorphism and the interindividual variability in response to acute post-surgical pain in a large sample study. Further studies are needed to clarify the association between COMT rs4680 SNP and pain sensitivity or response to analgesic in the presence of chronic or acute pain.

GCH1

Within the last decades, several candidate genes have been discovered affecting the pain sensitivity and the risk of chronic pain development in human. One of the most studied genes is the guanosine triphosphate (GTP) cyclohydrolase 1 (GCH1) coding for the enzyme GCH1. GCH1 is the rate-limiting enzyme in tetrahydrobiopterin (BH4) biosynthesis. Multiple studies have strongly implicated that the gene encoding of this enzyme modulates pain sensitivity. A series of animal and human studies have demonstrated that GCH1 is a key modulator of peripheral neuropathic and inflammatory pain. The biosynthesis of BH4 is highly controlled by three main pathways, however, the de novo synthetic pathway has the closest relationship with GCH1. In this pathway, biosynthesis of BH4 proceeds from GTP while the first and rate-limiting step is catalyzed by GCH1, which converts GTP to 7, 8-dihydroneopterin triphosphate. This is subsequently converted to 6-pyruvoyl-tetrahydrobiopterin catalyzed by 6-pyruvoyl-tetrahydrobiopterin synthase (PTPS). The final reaction generates BH4 through reactions catalyzed by sepiapterin reductase (SR) (Figure 2).

After injury or inflammation, GCH1 gene ex-

pression is markedly up-regulated in sensory neurons, accompanied by an increased level of GCH1 protein, GCH1 activity and BH4 biosynthesis (61). This "pain protective" GCH1 haplotype was found in 15% of the studied population, and consisted of 15 SNPs located in several non-coding regions. The decreased pain sensitivity in carriers of the pain protective GCH1 haplotype is thought to be a result of decreased transcription of GCH1, evaluated in ex vivo stimulated leukocytes, leading to reduced GCH1 function and BH4 biosynthesis (62). This pain-protective haplotype may represent a common genetic marker of reduced pain sensitivity in the general population.

Variations in the GCH1 gene not only modulate pain sensitivity, but also pain therapy. It has been demonstrated that carriers of the pain protective GCH1 haplotype showed a shorter pain therapy duration in outpatients with different chronic pain conditions, and a longer interval between cancer diagnosis and initiation of opioid treatment than heterozygous and non-carriers of the pain protective GCH1 haplotype (63, 64). Tegeder et al. (61) suggested that an inhibition of enzymes involved in the biosynthetic pathway of BH4 may produce analgesia. The 2, 4-diamino-6-hydroxypyrimidine (DAHP), the inhibitor of the enzyme GCH1, may markedly decrease BH4 production and reduce pain responses in formalin test and in the complete Freund's adjuvant (CFA) model of inflammatory pain. GCH1 inhibition has also been proposed to improve opioid treatment in cancer pain. Recently, a combination of GCH1 inhibition and morphine was found to increase and prolong the analgesic effects of morphine in a murine model of cancer pain, suggesting a possible co-therapeutic strategy of GCH1 inhibition and opioid treatment in cancer patients (65).

The fact that substantial interindividual variability in pain-related phenotypes within each surgery type cannot be explained by environmental factors alone, suggests that genetic variation may play a role. The identification of GCH1 gene polymorphism is of value for clinical perioperative pain management. Tegeder et al. (61) identified a particular haplotype of the GCH1 gene in humans for the first time and found that the pain protective GCH1 haplotype may attenuate post-surgical pain after lumbar discectomy, as well as pain sensitivity to mechanical stimuli in healthy controls. Preliminary results from a pilot genetic study of patients undergoing surgical treatment for lumbar degenerative disc disease suggested that the T allele at rs998259 of GCH1 may be associated with improvement in numerical rating scale back pain scores and clinical outcomes one year following surgery (66). A recent study about the contribution of GCH1 gene polymorphisms to persistent post herniotomy pain-related functional impairments showed that the A allele of SNP rs3783641, T allele of rs8007267, and AT haplotype may exert a protective effect for GCH1 (67).

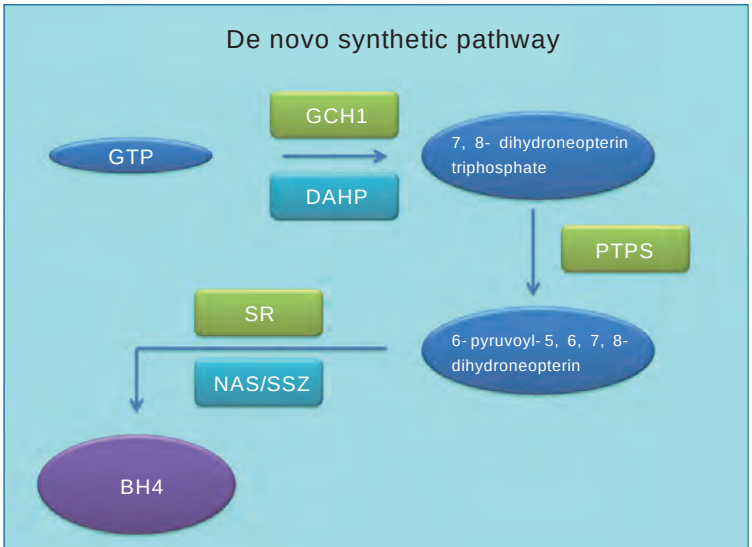

Figure 2. The Biosynthesis and Main Functions of BH4.
One of the three main pathways controls the biosynthesis of BH4: the denovosynthetic pathway. GCH1 is a key factor of BH4 biosynthesis. Inhibitors of the synthetic pathway include DAHP, NAS and SSZ.
GTP, guanosine triphosphate; GCH1, GTP cyclohydrolase 1; PTPS, 6-pyruvoyltetrahydrobiopterin synthase; SR, sepiapterin reductase; DAHP, 2, 4-diamino-6-hydroxypyrimidine; NAS, N-acetylserotonin; SSZ, sulfasalazine.

IL-1B

In previous years, the central role of cytokines in pain and hyperalgesia has been described (68). Proinflammatory cytokines as interleukins (IL) 1, 2, 6, 8, 15, and 18, interferon γ (IFN-γ) and tumor necrosis factor-α (TNF-α) are demonstrated to be involved in the nociceptive transmission, neuropathic pain and analgesics efficacy (69-71). There is a growing body of evidence of the role of IL-1 in pain sensitivity (72), especially IL-1β

(coded by the gene IL-1B). IL-1β is also capable of evoking the production of other proinflammatory cytokines as IFN-γ, TNF-α and IL-6 (73), which can also contribute to pain sensitivity.

SNPs in cytokine genes have been shown to alter their expressions or functions (74, 75). Oliveira et al. (76) conducted a hospital-based study which analyzed 74 Caucasian individuals. The results indicated that genetic variation at IL-1B gene may influence serum levels of IL-1β, with proportional consequences in cancer-related pain. With higher serum levels of IL-1β, patients would be more likely to experience cancer-related pain. Considering this result, the variation at IL-1B gene can be a good predictor for pain perception.

Variations in cytokine genes are associated with the postoperative acute pain severity and the development of persistent pain following surgery. Persistent pain following breast cancer surgery is a significant clinical problem. Recently, Stephens et al. (77) have evaluated the associations between persistent breast pain following breast cancer surgery and variations in cytokine genes. In this study, associations between previously identified extreme persistent breast pain phenotypes (i.e., no pain vs. severe pain) and SNPs spanning 15 cytokine genes were evaluated. The frequency of 13 SNPs and 3 haplotypes in 7 genes differed significantly between no-pain and severe pain classes. After adjustment for preoperative breast pain and the severity of average postoperative pain, 1 SNP (i.e., IL-1 receptor 2 rs11674595) and 1 haplotype (i.e., IL-10 haplotype A8) were associated with pain group membership. These findings suggested a role for cytokine gene polymorphisms in the development of persistent post-surgical pain.

SCN9A

SCN9A encodes the voltage-gated sodium-channel type IV-α subunit (Nav1.7) and is predominantly expressed in dorsal root ganglion neurons and sympathetic ganglion neurons (78). Some recent genetic studies have identified mutations in SCN9A as contributory in three pain disorders: primary erythermalgia, paroxysmal extreme pain disorder, and congenital indifference to pain (CIP) (79-85). Two very recent studies revealed that patients with mutations in SCN9A develop a partial loss of pain perception (86, 87).

Recently, Duan et al. (88) assessed the association between the 3312G>T SNP (a novle, non-synonymous SNP) in SCN9A and preoperative pain perception as well as postoperative pain. They designed an overall study to explore the association between three different SCN9A SNPs (one identified in Chinese, two in European) and individual baseline pain perception, as well as postoperative pain sensitivity in the general population. The results demonstrated that postoperative patient controlled analgesia (PCA)-pressing frequency and PCA opioid consumption in 48 hours after surgery in patients carrying the 3312Tallele are noticeably lower than those in patients carrying 3312Gallele. The patients carrying the 3312Gallele also have a higher incidence of inadequate postoperative analgesia than those carrying the 3312Tallele. In other words, following a similar surgical stimulus for pain, patients with the 3312Tallele have a lesser degree of postoperative pain experience. Therefore, the identification of the 3312G>T SNP in SCN9A may help improve the management of perioperative pain.

CACNG2 (stargazin gene)

CACNG2 encodes for the γ-2 transmembrane aminomethyl phosphonic acid (AMPA) receptor regulatory protein (TARP) stargazin, known to be intimately involved in the trafficking of glutamatergic AMPA receptors and the modulation of their ion channel function (89-92). AMPA receptors are multimeric assemblies of four subunits, glutamate receptor (GluR)1-4. Changes in GluR1 and GluR2 subunit trafficking, which lead to rapid alterations in the composition of synaptic AMPA receptors, may play an important role in pain hypersensitivity that develops after tissue or nerve injury (93, 94). Guo et al. (95) reported that knockdown of stargazin inhibits the development of incisional pain in a rat model of incisional pain, suggesting that targeting the TARP in the spinal cord could have a potential role in the treatment of postoperative pain. The protein might also be a Ca^{2+} channel subunit. CACNG2 has previously been implicated in epilepsy.

Persistent neuropathic pain following breast

cancer surgery has a higher incidence and is a significant clinical problem (96, 97). Recent study has demonstrated that the susceptibility to chronic neuropathic pain following breast surgery is genetically affected by CACNG2. Nissenbaum et al. (98) analyzed the human homologous CACNG2 in a group of 549 breast cancer patients. Applying standard association analysis, a three-SNP haplotype (rs4820242, rs2284015, and rs2284017) was identified as associated with the tendency to develop neuropathic pain following mastectomy.

Further research is needed to define the specific role played by CACNG2 in neuropathic pain. It is also important to determine why modifications of different Ca^{2+} channel subunits appear to be associated with different chronic pain syndromes. Answers to these questions may help to advance our understanding of pain processing and ultimately pay dividends in terms of the development of better therapeutic options.

TRPV1 and TRPA1

The transient receptor potential vanilloid-1 (TRPV1), is a receptor gated by noxious heat (> 42℃), mechanical distortion, acidosis, capsaicin and various exogenous and endogenous ligands (99). TRPV1 is associated with inflammatory stimuli and nociceptive transmission at both peripheral and spinal cord (100). There exit numerous SNPs in TRPV1 and Carreno et al. (101). have shown that some functional SNPs in TRPV1 gene are associated with the genetic susceptibility to migraine in the Spanish population. As for TRP ankyrin-1 (TRPA1), the receptor that is critical to pain signaling, is identified as mechanosensor that modulates cold and is activated by environmental irritants. TRPA1 has a close relationship with TRPV1 on peripheral and central pain mechanisms (102). It has been demonstrated that some rare naturally SNPs in TRPA1 gene are believed to affect the sensitivity of pain (103). However, it remains unclear whether the SNPs in TRPV1 or TRPA1 gene are involved in the variations in pain sensitivity, treatment response and susceptibility in postoperative pain management. It deserves further investigations in the future.

Concluding Remark

Genetic factors have been recognized as the foundation of interindividual variations in pain sensitivity, treatment response and susceptibility from acute to chronic pain in surgical patients. The functional genetic pain markers mentioned above, including COMT, CACNG2, SCA9A, TRPV1, TRPA1, etc., may provide valuable information for predicting and managing perioperative pain. Further studies are needed to clarify controversies on the association of some gene polymorphisms and postoperative pain and treatment response.

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References

1. Raja SN, Jensen TS. Predicting postoperative pain based on preoperative pain perception: are we doing better than the weatherman? Anesthesiology 2010; 112: 1311-2.
2. Sommer M, de Rijke JM, van Kleef M, Kessels AG, Peters ML, Geurts JW, et al. The prevalence of postoperative pain in a sample of 1490 surgical inpatients. Eur J Anaesthesiol 2008; 25: 267-74.
3. Werner MU, Mjobo HN, Nielsen PR, Rudin A. Prediction of postoperative pain: a systematic review of predictive experimental pain studies. Anesthesiology 2010; 112: 1494-502.
4. Sommer M, de Rijke JM, van Kleef M, Kessels AG, Peters ML, Geurts JW, et al. Predictors of acute postoperative pain after elective surgery. Clin J Pain 2010; 26: 87-94.
5. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. Anesthesiology 2009; 111: 657-77.
6. Lundblad H, Kreicbergs A, Jansson KA. Prediction of persistent pain after total knee replacement for osteoarthritis. J Bone Joint Surg Br 2008; 90: 166-71.
7. Lautenbacher S, Huber C, Baum C, Rossaint R, Hochrein S, Heesen M. Attentional avoidance of negative experiences as predictor of postoperative pain ratings and consumption of analgesics: comparison with other psychological predictors. Pain Med 2011; 12: 645-53.
8. Drenth JP, Waxman SG. Mutations in sodium-channel gene SCN9A cause a spectrum of human genetic pain disorders. J Clin Invest 2007; 117: 3603-9.
9. Vadivelu N, Mitra S, Narayan D. Recent advances in postoperative pain management. Yale J Biol Med 2010; 83: 11-25.
10. Ross JR, Riley J, Quigley C, Welsh KI. Clinical pharmacology and pharmacotherapy of opioid switching in cancer patients. Oncologist 2006; 11: 765-73.
11. Lotsch J, Skarke C, Grosch S, Darimont J, Schmidt H, Geisslinger G. The polymorphism A118G of the human mu-opioid receptor gene decreases the pupil constrictory effect of morphine-6-glucuronide but not that of morphine. Pharmacogenetics 2002; 12: 3-9.
12. Reyes-Gibby CC, Shete S, Rakvag T, Bhat SV, Skorpen F, Bruera E, et al. Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene. Pain 2007; 130: 25-30.
13. Stamer UM, Stuber F. The pharmacogenetics of analgesia. Expert Opin Pharmacother 2007; 8: 2235-45.
14. Oertel B, Lotsch J. Genetic mutations that prevent pain: implications for future pain medication. Pharmacogenomics 2008; 9: 179-94.
15. Linder MW, Valdes R Jr. Fundamentals and applications of pharmacogenetics for the clinical laboratory. Ann Clin Lab Sci 1999; 29: 140-9.
16. Ledesma MC, Agundez JA. Identification of subtypes of CYP2D gene rearrangements among carriers of CYP2D6 gene deletion and duplication. Clin Chem 2005; 51: 939-43.
17. Armstrong SC, Cozza KL. Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, Part II. Psychosomatics 2003; 44: 515-20.

18. Kirchheiner J, Schmidt H, Tzvetkov M, Keulen JT, Lötsch J, Roots I, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J 2007; 7: 257-65.
19. Kaplan HL, Busto UE, Baylon GJ, Cheung SW, Otton SV, Somer G, et al. Inhibition of cytochrome P450 2D6 metabolism of hydrocodone to hydromorphone does not importantly affect abuse liability. J Pharmacol Exp Ther 1997; 281: 103-8.
20. Otton SV, Schadel M, Cheung SW, Kaplan HL, Busto UE, Sellers EM. CYP2D6 phenotype determines the metabolic conversion of hydrocodone to hydromorphone. Clin Pharmacol Ther 1993; 54: 463-72.
21. Yang Z, Yang Z, Arheart KL, Morris R, Zhang Y, Rodriguez Y, et al. CYP2D6 poor metabolizer genotype and smoking predict severe postoperative pain in female patients on arrival to the recovery room. Pain Med 2012; 13: 604-9.
22. Candiotti KA, Yang Z, Rodriguez Y, Crescimone A, Sanchez GC, Takacs P, et al. The impact of CYP2D6 genetic polymorphisms on postoperative morphine consumption. Pain Med 2009; 10: 799-805.
23. Xu J, Zhang XC, Lv XQ, Xu YY, Wang GX, Jiang B, et al. Effect of the cytochrome P450 2D6*10 genotype on the pharmacokinetics of tramadol in post-operative patients. Pharmazie 2014; 69: 138-41.
24. Kirchheiner J, Meineke I, Freytag G, Meisel C, Roots I, Brockmoller J. Enantiospecific effects of cytochrome P450 2C9 amino acid variants on ibuprofen pharmacokinetics and on the inhibition of cyclooxygenases 1 and 2. Clin Pharmacol Ther 2002; 72: 62-75.
25. Gupta A, Zheng L, Ramanujam V, Gallagher J. Novel use of pharmacogenetic testing in the identification of CYP2C9 polymorphisms related to NSAID-induced gastropathy. Pain Med 2015; 16: 866-9.
26. Eich-Hochli D, Oppliger R, Golay KP, Baumann P, Eap CB. Methadone maintenance treatment and St. John's Wort-a case report. Pharmacopsychiatry 2003; 36: 35-7.
27. Wahawisan J, Kolluru S, Nguyen T, Molina C, Speake J. Methadone toxicity due to smoking cessation--a case report on the drug-drug interaction involving cytochrome P450 isoenzyme 1A2. Ann Pharmacother 2011; 45: e34.
28. Ackerman WE 3rd, Ahmad M. Effect of cigarette smoking on serum hydrocodone levels in chronic pain patients. J Ark Med Soc 2007; 104(1): 19-21.
29. Boom M, Niesters M, Sarton E, Aarts L, Smith TW, Dahan A. Non-analgesic effects of opioids: opioid-induced respiratory depression. Curr Pharm Des 2012; 18: 5994-6004.
30. Matthes HW, Maldonado R, Simonin F, Valverde O, Slowe S, Kitchen I, et al. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. Nature 1996; 383: 819-23.
31. Somogyi AA, Barratt DT, Coller JK. Pharmacogenetics of opioids. Clin Pharmacol Ther 2007; 81: 429-44.
32. Lötsch J, Geisslinger G. Are μ-opioid receptor polymorphisms important for clinical opioid therapy? Trends in Molecular Medicine 2005; 11: 82-9.
33. Skorpen F, Laugsand EA, Klepstad P, Kaasa S. Variable response to opioid treatment: any genetic predictors within sight? Palliat Med 2008; 22: 310-27.
34. Crist RC, Berrettini WH. Pharmacogenetics of OPRM1. Pharmacol Biochem Behav 2014; 123: 25-33.
35. Wang JB, Imai Y, Eppler CM, Gregor P, Spivak CE, Uhl GR. mu opiate receptor: cDNA cloning and expression. Proc Natl Acad Sci U S A 1993; 90: 10230-4.
36. Nozaki C, Kamei J. Involvement of mu1-opioid receptor on oxycodone-induced antinociception in diabetic mice. Eur J Pharmacol 2007; 560: 160-2.
37. Virk MS, Arttamangkul S, Birdsong WT, Williams JT. Buprenorphine is a weak partial agonist that inhibits opioid receptor desensitization. J Neurosci 2009; 29: 7341-8.
38. Knapman A, Santiago M, Connor M. The A6V polymorphism of the human mu-opioid receptor negatively impacts signalling of morphine and endogenous opioids in vitro. Br J Pharmacol 2015; 172: 2258-72.
39. Crowley JJ, Oslin DW, Patkar AA, Gottheil E, DeMaria PA Jr, O'Brien CP, et al. A genetic association study of the mu opioid receptor and severe opioid dependence. Psychiatr Genet 2003; 13: 169-73.
40. Kapur S, Sharad S, Singh RA, Gupta AK. A118g polymorphism in mu opioid receptor gene (oprm1): association with opiate addiction in subjects of Indian origin. J Integr Neurosci 2007; 6: 511-22.
41. Xu J, Faskowitz AJ, Rossi GC, Xu M, Lu Z, Pan YX, et al. Stabilization of morphine tolerance with long-term dosing: Association with selective upregulation of mu-opioid receptor splice variant mRNAs. Proc Natl Acad Sci U S A 2015; 112: 279-84.
42. Liu YC, Wang WS. Human mu-opioid receptor gene A118G polymorphism predicts the efficacy of tramadol/acetaminophen combination tablets (ultracet) in oxaliplatin-induced painful neuropathy. Cancer 2012; 118: 1718-25.
43. Zhang Y, Wang D, Johnson AD, Papp AC, Sadee W. Allelic expression imbalance of human mu opioid receptor (OPRM1) caused by variant A118G. J Biol Chem 2005; 280: 32618-24.
44. Chou WY, Yang LC, Lu HF, Ko JY, Wang CH, Lin SH, 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: 787-92.
45. Sia AT, Lim Y, Lim EC, Goh RW, Law HY, Landau R, et al. 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 2008; 109: 520-6.
46. Pecina M, Love T, Stohler CS, Goldman D, Zubieta JK. Effects of the mu opioid receptor polymorphism (OPRM1 A118G) on pain regulation, placebo effects and associated personality trait measures. Neuropsychopharmacology 2015; 40: 957-65.
47. Chou WY, Wang CH, Liu PH, Liu CC, Tseng CC, Jawan B. Human opioid receptor A118G polymorphism affects intravenous patient-controlled analgesia morphine consumption after total abdominal hysterectomy. Anesthesiology 2006; 105: 334-7.
48. Mannisto PT, Kaakkola S. Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. Pharmacol Rev 1999; 51: 593-628.
49. Zubieta JK, Heitzeg MM, Smith YR, Bueller JA, Xu K, Xu Y, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science 2003; 299: 1240-3.
50. Rakvåg TT, Klepstad P, Baar C, Kvam T-M, Dale O, Kaasa S, et al. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain 2005; 116: 73-8.
51. Rakvåg TT, Ross JR, Sato H, Skorpen F, Kaasa S, Klepstad P. Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain. Mol Pain 2008; 4: 64.
52. Ross JR, Riley J, Taegetmeyer AB, Sato H, Gretton S, du Bois RM, et al. 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 2008; 112: 1390-403.
53. Klepstad P, Fladvad T, Skorpen F, Bjordal K, Caraceni A, Dale O, et al. Influence from genetic variability on opioid use for cancer pain: a European genetic association study of 2294 cancer pain patients. Pain 2011; 152(5): 1139-45.
54. Tammimaki A, Mannisto PT. Catechol-O-methyltransferase gene polymorphism and chronic human pain: a systematic review and meta-analysis. Pharmacogenet Genomics 2012; 22: 673-91.
55. Kim H, Lee H, Rowan J, Brahim J, Dionne RA. Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. Mol Pain 2006; 2:24.
56. Henker RA, Lewis A, Dai F, Lariviere WR, Meng L, Gruen GS, et al. The associations between OPRM 1 and COMT genotypes and postoperative pain, opioid use, and opioid-induced sedation. Biol Res Nurs 2013; 15: 309-17.
57. Kolesnikov Y, Gabovits B, Levin A, Voiko E, Veske A. Combined catechol-O-methyltransferase and mu-opioid receptor gene polymorphisms affect morphine postoperative analgesia and central side effects. Anesth Analg 2011; 112: 448-53.
58. Candiotti KA, Yang Z, Buric D, Arheart K, Zhang Y, Rodriguez Y, et al. Catechol-o-methyltransferase polymorphisms predict opioid consumption in postoperative pain. Anesth Analg 2014; 119: 1194-200.
59. Deng J, Wu XZ, Li M, Chen GZ, Song HT. Effects of COMT G472A genetic polymorphism on postoperative analgesia with fentanyl (in Chinese). Chinese J Anesthesiol 2011; 31(9): 1039-41.
60. Zhang F, Tong J, Hu J, Zhang H, Ouyang W, Huang D, et al. COMT Gene Haplotypes Are Closely Associated with Postoperative Fentanyl Dose in Patients. Anesth Analg 2015; 120: 933-40.
61. Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 2006; 12: 1269-77.
62. Tegeder I, Adolph J, Schmidt H, Woolf CJ, Geisslinger G, Lotsch J. Reduced hyperalgesia in homozygous carriers of a GTP cyclohydrolase 1 haplotype. Eur J Pain 2008; 12: 1069-77.
63. Doehring A, Freynhagen R, Griessinger N, Zimmermann M, Sittl R, Hentig 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: 781-5.
64. Lotsch J, Klepstad P, Doehring A, Dale O. A GTP cyclohydrolase 1 genetic variant delays cancer pain. Pain 2010; 148: 103-6.
65. Pickert G, Myrczek T, Ruckert S, Weigert A, Haussler A, Ferreiros N, et al. Inhibition of GTP cyclohydrolase reduces cancer pain in mice and enhances analgesic effects of morphine. J Mol Med (Berl) 2012; 90: 1473-86.
66. Kim DH, Dai F, Belfer I, Banco RJ, Martha JF, Tighiouart H, 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: 1909-14.
67. Belfer I, Dai F, Kehlet H, Finelli P, Qin L, Bittner R, et al. Association of functional variations in COMT and GCH1 genes with postherniotomy pain and related impairment. Pain 2015; 156: 273-9.
68. Shi Q, Cleeland CS, Klepstad P, Miaskowski C, Pedersen NL, GeneQOL Consortium. Biological pathways and genetic variables involved in pain. Qual Life Res 2010; 19: 1407-17.
69. Hutchinson MR, Coats BD, Lewis SS, Zhang Y, Sprunger DB, Rezvani N, et al. Proinflammatory cytokines oppose opioid-induced acute and chronic analgesia. Brain Behav Immun 2008; 22: 1178-89.
70. Kawasaki Y, Xu ZZ, Wang X, Park JY, Zhuang ZY, Tan PH, et al. Distinct roles of matrix metalloproteases in the early- and late-phase development of neuropathic pain. Nat Med 2008; 14: 331-6.
71. Albulescu R, Codrici E, Popescu ID, Mihai S, Necula LG, Petrescu D, et al. Cytokine patterns in brain tumour progression. Mediators Inflamm 2013; 2013: 979748.
72. Gabay E, Wolf G, Shavit Y, Yirmiya R, Tal M. Chronic blockade of interleukin-1 (IL-1) prevents and attenuates neuropathic pain behavior and spontaneous ectopic neuronal activity following nerve injury. Eur J Pain 2011; 15: 242-8.
73. Mika J, Zychowska M, Popiolek-Barczyk K, Rojewska E, Przewlocka B. Importance of glial activation in neuropathic pain. Eur J Pharmacol 2013; 716: 106-19.
74. Qian N, Chen X, Han S, Qiang F, Jin G, Zhou X, et al. Circulating IL-1beta levels, polymorphisms of IL-1B, and risk of cervical cancer in Chinese women. J Cancer Res Clin Oncol 2010; 136: 709-16.
75. Lacruz-Guzman D, Torres-Moreno D, Pedrero F, Romero-Cara P, Garcia-Tercero I, Trujillo-Santos J, et al. Influence of polymorphisms and TNF and IL1beta serum concentration on the infliximab response in

Crohn's disease and ulcerative colitis. Eur J Clin Pharmacol 2013; 69: 431-8.
76. Oliveira A, Dinis- Oliveira RJ, Nogueira A, Gonçalves F, Silva P, Vieira C, et al. Interleukin- 1β genotype and circulating levels in cancer patients: Metastatic status and pain perception. Clinical Biochemistry 2014; 47: 1209-13.
77. Stephens K, Cooper BA, West C, Paul SM, Baggott CR, Merriman JD, et al. Associations between cytokine gene variations and severe persistent breast pain in women following breast cancer surgery. J Pain 2014; 15: 169-80.
78. Rush AM, Dib- Hajj SD, Liu S, Cummins TR, Black JA, Waxman SG. A single sodium channel mutation produces hyper- or hypoexcitability in different types of neurons. Proc Natl Acad Sci U S A 2006; 103: 8245-50.
79. Zhang LL, Lin ZM, Ma ZH, Xu Z, Yang YL, Yang Y. Mutation hotspots of SCN9A in primary erythermalgia. Br J Dermatol 2007; 156: 767-9.
80. Cox JJ, Reimann F, Nicholas AK, Thornton G, Roberts E, Springell K, et al. An SCN9A channelopathy causes congenital inability to experience pain. Nature 2006; 444: 894-8.
81. Ahmad S, Dahllund L, Eriksson AB, Hellgren D, Karlsson U, Lund PE, et al. A stop codon mutation in SCN9A causes lack of pain sensation. Hum Mol Genet 2007; 16: 2114-21.
82. Cox JJ, Sheynin J, Shorer Z, Reimann F, Nicholas AK, Zubovic L, et al. Congenital insensitivity to pain: novel SCN9A missense and in- frame deletion mutations. Hum Mutat 2010; 31: E1670-86.
83. Ahn HS, Dib-Hajj SD, Cox JJ, Tyrrell L, Elmslie FV, Clarke AA, et al. A new Nav1.7 sodium channel mutation I234T in a child with severe pain. Eur J Pain 2010; 14: 944-50.
84. Lampert A, Dib-Hajj SD, Eastman EM, Tyrrell L, Lin Z, Yang Y, et al. Erythromelalgia mutation L823R shifts activation and inactivation of threshold sodium channel Nav1.7 to hyperpolarized potentials. Biochem Biophys Res Commun 2009; 390: 319-24.
85. Skeik N, Rooke TW, Davis MD, Davis DM, Kalsi H, Kurth I, et al. Severe case and literature review of primary erythromelalgia: novel SCN9A gene mutation. Vasc Med 2012l; 17: 44-9.
86. Staud R, Price DD, Janicke D, Andrade E, Hadjipanayis AG, Eaton WT, et al. Two novel mutations of SCN9A (Nav1.7) are associated with partial congenital insensitivity to pain. Eur J Pain 2011; 15: 223-30.
87. Yuan R, Zhang X, Deng Q, Si D, Wu Y, Gao F, et al. Two novel SCN9A gene heterozygous mutations may cause partial deletion of pain perception. Pain Med 2011; 12: 1510-4.
88. Duan G, Xiang G, Zhang X, Yuan R, Zhan H, Qi D. A single-nucleotide polymorphism in SCN9A may decrease postoperative pain sensitivity in the general population. Anesthesiology 2013; 118: 436-42.
89. Priel A, Kolleker A, Ayalon G, Gillor M, Osten P, Stern- Bach Y. Stargazin reduces desensitization and slows deactivation of the AMPA-type glutamate receptors. J Neurosci 2005; 25: 2682-6.
90. Bats C, Groc L, Choquet D. The interaction between Stargazin and PSD- 95 regulates AMPA receptor surface trafficking. Neuron 2007; 53: 719-34.
91. Cokic B, Stein V. Stargazin modulates AMPA receptor antagonism. Neuropharmacology 2008; 54: 1062-70.
92. 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: 11348-51.
93. Wang W, Petralia RS, Takamiya K, Xia J, Li YQ, Huganir RL, et al. Preserved acute pain and impaired neuropathic pain in mice lacking protein interacting with C Kinase 1. Mol Pain 2011; 7: 11.
94. Choi JI, Svensson CI, Koehrn FJ, Bhuskute A, Sorkin LS. Peripheral inflammation induces tumor necrosis factor dependent AMPA receptor trafficking and Akt phosphorylation in spinal cord in addition to pain behavior. Pain 2010; 149: 243-53.
95. Guo R, Zhao Y, Zhang M, Wang Y, Shi R, Liu Y, et al. Down- regulation of Stargazin inhibits the enhanced surface delivery of alpha-amino-3-hydroxy-5-methyl- 4- isoxazole propionate receptor GluR1 subunit in rat dorsal horn and ameliorates postoperative pain. Anesthesiology 2014; 121: 609-19.
96. Fieldsen D, Wood S. Dealing with phantom limb pain after amputation. Nurs Times 2011; 107: 21-3.
97. Steegers MA, Wolters B, Evers AW, Strobbe L, Wilder-Smith OH. Effect of axillary lymph node dissection on prevalence and intensity of chronic and phantom pain after breast cancer surgery. J Pain 2008; 9: 813-822.
98. Nissenbaum J, Devor M, Seltzer Z, Gebauer M, Michaelis M, Tal M, et al. Susceptibility to chronic pain following nerve injury is genetically affected by CACNG2. Genome Res 2010; 20: 1180-90.
99. Holzer P. Transient receptor potential (TRP) channels as drug targets for diseases of the digestive system. Pharmacol Ther 2011; 131: 142-70.
100. Palazzo E, Luongo L, de Novellis V, Berrino L, Rossi F, Maione S. Moving towards supraspinal TRPV1 receptors for chronic pain relief. Mol Pain 2010; 6: 66.
101. Carreno O, Corominas R, Fernandez-Morales J, Camina M, Sobrido MJ, Fernandez-Fernandez JM, et al. SNP variants within the vanilloid TRPV1 and TRPV3 receptor genes are associated with migraine in the Spanish population. Am J Med Genet B Neuropsychiatr Genet 2012; 159b: 94-103.
102. Wei H, Koivisto A, Saarnilehto M, Chapman H, Kuokkanen K, Hao B, et al. Spinal transient receptor potential ankyrin 1 channel contributes to central pain hypersensitivity in various pathophysiological conditions in the rat. Pain 2011; 152: 582-91.
103. Morgan K, Sadofsky LR, Crow C, Morice AH. Human TRPM8 and TRPA1 pain channels, including a gene variant with increased sensitivity to agonists (TRPA1 R797T), exhibit differential regulation by SRC-tyrosine kinase inhibitor. Biosci Rep 2014; 34(4).