The Genetics of Pain: Implications for Perioperative Pain Management

Meng-Meng Bao¹, Fang Xie¹, Xue-Yang Li¹, Yun Yue¹, Yun Guan², and Yun Wang¹

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) cyclodrolase 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.
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>
<thead>
<tr>
<th>Pain-relevant gene or enzyme</th>
<th>Pain sensitivity</th>
<th>Response to analgesics</th>
<th>Susceptibility to chronic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP450</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>COMT</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>MOR-1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>GCH1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>IL-1B</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>SCN9A</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>CACNG2</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes</td>
</tr>
<tr>
<td>TRPV1</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>TRPA1</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

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.
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.

It has been demonstrated that individual differences in opioid requirements have a genetic basis and are related to the polymorphisms in MOR-1 gene (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

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

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

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.

Figure 2. The Biosynthesis and Main Functions of BH4.
One of the three main pathways controls the biosynthesis of BH4: the de novo synthetic 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-acetylseryotonin; SSZ, sulfasalazine.
(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 novel, 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°C), 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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