Genetics and genomics in postoperative pain and analgesia

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Purpose of review
The review describes recent advances in genetics and genomics of postoperative pain, the association between genetic variants and the efficacy of analgesics, and the role of pharmacogenomics in the selection of appropriate analgesic treatments for postoperative pain.

Recent findings
Recent genetic studies have reported associations of genetic variants in catechol-O-methyltransferase (*COMT*), brain-derived neurotrophic factor (*BDNF*), voltage-gated channel alpha subunit 11 (*SCN11A*) and μ-opioid receptor (*OPRM1*) genes with postoperative pain. The recent pharmacogenetics studies revealed an association of the organic cation transporter 1 (*OCT1*) and ATP-binding cassette C3 (*ABCC3*) polymorphisms with morphine-related adverse effects, an effect of polymorphisms in cytochrome P450 gene *CYP2D6* on the analgesic efficacy of tramadol and no effect of CYP2C8 and CYP2C9 variants on efficacy of piroxicam.

Summary
Genetic variants associate with inter-individual variability in drug responses and they can affect pain sensitivity and intensity of postoperative pain. Despite the recent progress in genetics and genomics of postoperative pain, it is still not possible to precisely predict the patients who are genetically predisposed to have severe postoperative pain or who develop chronic postoperative pain.

Keywords
analgesics, genetic variants, genetics, pharmacogenetics, postoperative pain

INTRODUCTION

Postoperative pain is a major health burden due to increasing prevalence and inadequate efficacy of current treatments [1–4]. All patients undergoing surgery have acute postoperative pain which usually resolves within days to weeks during wound healing. Some patients, however, develop chronic postoperative pain (CPOP), which is usually defined as pain due to surgery lasting for more than 3 months. The severity of acute postoperative pain correlates with the risk of CPOP [5]. Its incidence varies depending on the type of surgery, criteria for pain and duration of follow-up. Fletcher *et al.* [6] have reported an incidence of moderate to severe CPOP of 11.8% at 1 year after surgery whereas Haroutiunian *et al.* [7] reported the incidence of 6–68% for postoperative neuropathic pain depending on the type of surgery. Several risk factors are associated with the development of CPOP such as preoperative pain, type of surgery, perioperative nerve injury, fear of surgery, pain catastrophizing, anxiety, expectation of pain, obesity, young age and sex (female) [8–11]. Single nucleotide polymorphisms (SNPs) of several pain regulating genes have been reported to associate with increased pain sensitivity and higher risk for postoperative pain [12–14].

Pharmacogenetics refers to genetic factors that associate with variation in drug response. The most studied pharmacogenetic effects on analgesics are related to the mutations in the μ-opioid receptor gene (*OPRM1*) [15]. Individuals who are homozygous for the minor allele of the *OPRM1* rs1799971 (118A > G) have been reported to need about 30% more oxycodone to achieve adequate analgesia

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KEY POINTS

- Candidate gene studies have identified genetic variants in several genes that might predispose patients to more severe postoperative pain.
- Genetic variants can modulate the severity of postoperative pain, analgesic efficacy, metabolism, and adverse events of analgesics.
- Pharmacogenetics can improve pain management by predicting the individual response to analgesics prior to therapy and facilitate the development of novel and more effective pain medication for postoperative pain.
- Larger cohorts using standardized analgesia methods are needed for future progress in this field.

compared with the individuals who are homozygous for the major allele [16]. Drugs metabolized by the CYP2D6 isoenzyme are particularly liable for significant variation in efficacy between individuals as the *CYP2D6* gene is highly polymorphic [17]. Codeine is an excellent example. It is a pro-drug that needs to be metabolized to morphine for analgesic efficacy. Due to variation in the activity of CYP2D6, individuals can produce morphine very efficiently (ultrarapid metabolizers) or not at all (poor metabolizers) [18]. Pharmacogenetics may play a role in many other functions relevant to pharmacokinetics, for example in the transporters [19].

In this review, we will discuss the recent advances in genetics and genomics of postoperative pain, the association between genetic variants and the efficacy of analgesics and the important role of pharmacogenomics in the selection of appropriate analgesic treatments for postoperative pain.

GENETICS OF POSTOPERATIVE PAIN

Advances in genome-wide association studies (GWAS) have helped to identify the hereditary factors that might predispose patients to postoperative pain [20–22]. Despite the advantage of GWAS studies that are able to genotype thousands of common genetic variants (>1% frequency in population) across the genome [14], the large majority of genetic studies on postoperative pain are still candidate gene studies focusing on individual gene polymorphisms. Emerging next generation sequencing (NGS) technologies enable identification of both common and rare genetic variants [23] but are still to be used for screening of genetic variants in postoperative pain. Recent genetic studies have focused on investigating the association of genetic variants in a limited set of functionally relevant genes with postoperative pain. Variants in catechol-O-methyltransferase (*COMT*), brain-derived neurotrophic factor (*BDNF*), voltage-gated channel alpha subunit 11 (*SCN11A*) and μ-opioid receptor (*OPRM1*) genes have shown evidence of association with postoperative pain.

Mladenovic *et al.* [24▪] investigated the association between *COMT* gene polymorphisms and temporomandibular disorders (TMD), TMD pain and postoperative pain after third molar surgery. The *COMT* SNPs rs6269, rs4633, rs4818 and rs4680 were associated with pain sensitivity and a higher risk to develop TMD which has high incidence in young adults after third molar extraction [25,26]. Targeted genotyping of blood samples from 90 patients with painful TMD and 92 controls was performed for the *COMT* SNPs rs6269, rs4680 and rs165774 revealing an association of AA and AG genotypes with rs165774 (G>A, intron) polymorphism and increased risk of TMD compared with the GG genotype. In addition, the AA genotype for rs6269 polymorphism (A>G, 5'UTR) was associated with lower postoperative TMD pain and acute pain at the dental extraction site. These findings suggest that chronic postoperative TMD pain and acute pain at the extraction site after third moral surgery may be associated with *COMT* rs6269 polymorphism.

Khalil *et al.* [27▪] studied the potential effect of interaction between *COMT* SNPs (rs6269, rs4633, rs4818, and rs4680) with *OPRM1* rs1799971 polymorphism on postoperative pain and opioid consumption in 153 patients after orthopaedic surgery. It was reported that genetic variants of *COMT* can modulate the *OPRM1* gene expression and density in the brain by regulating the level of enkephalin [28,29]. A significant interaction was observed for *OPRM1* and the low pain sensitivity (LPS) haplotype of *COMT*. In patients without the LPS haplotype, carriers of the AA genotype of *OPRM1* were associated with significantly higher postoperative pain scores compared with carriers of the G allele. Patients carrying Met158Met of the *COMT* rs4680 and AG/GG of the *OPRM1* or TT of the *COMT* rs4633 and the AG/GG of *OPRM1* had the highest amount of opioid consumption. These results suggest that interactions of *OPRM1* and *COMT* might contribute to postoperative pain and response to opioids.

Tian *et al.* [30▪▪] analysed the association of 638 polymorphisms in 54 pain-related genes with CPOP in 1152 Chinese surgical patients. The patients carrying the G allele (Val/Met and Val/Val genotypes) for SNP rs6265 (Val66Met) in *BDNF* gene were associated with a higher risk of CPOP compared with the carriers of wild type A allele (Met/Met genotype). The $BDNF^{Met/Met}$ mice were associated with lower mechanical allodynia compared with $BDNF^{Val/Val}$

mice after plantar incision. These results indicate that *BDNF* rs6265 polymorphism may be associated with an increased risk of CPOP.

Sun *et al.* [31▪] examined the association of SNPs in the *SCN11A* gene with postoperative pain sensitivity in 309 Han Chinese female patients after gynaecological laparoscopic surgery. In total, 5 SNPs (rs33985936, rs13080116, rs11720988, rs11709492, and rs11720013) in *SCN11A* were associated with experimental pain sensitivity and minor alleles of rs33985936 and rs13080116 were linked with increased postoperative patient-controlled analgesia consumption of sufentanil and tramadol (13.2% increased PCA for rs33985936 C/T compared to C/C genotype). This finding suggests that *SCN11A* SNPs may associate with postoperative pain after gynaecological surgery.

Werner *et al.* [32] performed a GWAS analysis of neuropathic pain in 613 patients with osteoarthritis (OA) after total joint replacement. The detected variants did not pass the genome-wide significance *P*-value threshold (5×10^{-8}). The strongest association was found for rs887797 variant in protein kinase C alpha (*PRKCA*) previously associated with inflammatory pain [33].

Persson *et al.* [34] studied the association of polymorphisms in 13 candidate pain genes (*ABCB1, COMT, PEBP1, CYP2D6, OPRM1, CYP34A, POMC, MAOB, SCN9A, UGT2B7, SUDS3, TAOK3, VSIG10*) with pain sensitivity after laparoscopic cholecystectomy. Due to the low number of patients ($n = 57$), there were no statistically significant differences after multiple variant analyses based on high and low intensity pain phenotypes for more than 400 SNPs in 13 candidate genes.

PHARMACOGENETICS OF POSTOPERATIVE PAIN

Pharmacogenetic studies investigate the effect of genetic variants on the efficacy, metabolism and adverse effects of drugs, which might result in heterogeneous individual responses to drugs [35]. As long-term opioid administration after surgery can lead to opioid-induced hyperalgesia [36], pharmacogenetics might improve pain management by predicting the individual response to analgesics prior to the therapy and could help to develop more effective analgesics. Recent pharmacogenetics studies investigated the association of organic cation transporter 1 (*OCT1*) and ATP-binding cassette C3 (*ABCC3*) SNPs with morphine-related adverse effects as well as the effect of polymorphisms in cytochrome P450 genes *CYP2C8, CYP2C9* and *CYP2D6* on the analgesic efficacy of tramadol and piroxicam.

Balyan *et al.* [37▪▪] studied whether the functional polymorphisms in the *OCT1* gene are associated to postoperative morphine-related adverse effects including respiratory depression (RD) and postoperative nausea and vomiting (PONV) in 311 children undergoing tonsillectomy. The OCT1 transporter mediates hepatic uptake of cationic drugs including morphine [38]. It was found that the *OCT1* variant rs12208357 was associated with PONV whereas SNP rs72552763 was associated with RD. Previous studies have linked rs12208357 to decreased OCT1 protein expression [39] and rs72552763 to the increased plasma concentrations of tropisetron, ondansetron and tramadol [40]. This study suggests that genetic variants leading to decreased OCT1 transporter activity and higher morphine plasma levels are associated with a higher incidence of morphine-related RD and PONV.

Chidambaran *et al.* [41▪▪] studied the association between SNPs in the ATP-binding cassette ABCC3 and morphine-induced RD and pharmacokinetics (PK) of morphine in two independent cohorts of children who underwent tonsillectomy ($n = 316$) or adolescents after spine surgery ($n = 67$). The *ABCC3* gene encodes for the liver transporter which plays an important role in morphine metabolism through glucuronidation to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) [42]. Gene-specific analysis of genome-wide genotype data identified 7 intronic SNPs (rs35364174, rs4148412, rs739923, rs733392, rs1978153, rs7216383, rs886493) in the *ABCC3* gene which were significantly associated with prolonged stay in the postoperative anaesthesia care unit (PACU) due to morphine-induced RD. Furthermore, *ABCC3* rs4793665 CC genotype was associated with higher clearance of M3G and M6G compared with CT and TT genotypes in both tonsillectomy and spine surgery subjects. This study suggests that *ABCC3* variants are associated with postoperative RD, prolonged hospital stay and morphine PK, and that children genetically predisposed for higher risk of morphine-related RD could be preoperatively identified in order to use alternative analgesics that are not transported through ABCC3 transporters.

Stamer *et al.* [43▪▪] analysed the effect of loss-of-function polymorphism in the organic cation transporter *OCT1* and variants in *CYP2D6* on the pharmacokinetics and analgesic efficacy of the opioid analgesic tramadol in 205 patients after abdominal or urological surgery. Genetic variants in *CYP2D6* and *OCT1* modulate the pharmacokinetics and analgesic efficacy of tramadol [38,44]. Multiple regression analysis identified that the number of active *OCT1* alleles and *CYP2D6* had a significant impact on tramadol consumption. Furthermore, the loss of

function SNPs in the *OCT1* gene were associated with reduced tramadol consumption and increased plasma concentrations of the active tramadol metabolite (1)O-desmethyltramadol in the patients. These results suggest the importance of genotype-dependent pharmacogenetic dosing of tramadol based on *OCT1* and *CYP2D6* activity.

Bialecka *et al.* [45] addressed the effect of interleukin 6 (*IL-6*) functional polymorphism rs1800795 (G>C) on opioid requirements in OA patients after total hip replacement (THR). Healthy C allele carriers are known to have decreased *IL-6* gene expression and reduced plasma levels of IL-6 compared with the G allele carriers [46] which might be associated with milder inflammation and lower nociceptive stimulation. By genotyping 196 patients after THR for the *IL-6* rs1800795 SNP, it was observed that patients with GG and GC genotypes had significantly increased administration of opioids on days 0, 3 and 4 after THR compared to patients with CC genotype. This indicates that G allele and higher IL-6 levels may predispose OA patients to increased opioid requirements in the early postoperative phase after THR.

Calvo *et al.* [47▪] investigated the association between polymorphisms in *CYP2C8* and *CYP2C9* genes with the efficacy of the nonsteroidal anti-inflammatory drug (NSAID) piroxicam during the management of postoperative pain following lower third molar surgery. The elimination half-life of piroxicam is about 45 h [48]. The carriers of the *CYP2C9* mutant allele 3 (1/3 and 3/3 genotypes) were previously reported to have slower metabolism of piroxicam compared with people homozygous for the wild type allele 1 (*CYP2C9* 1/1 genotype) [49] while some SNPs of *CYP2C8* such as *CYP2C8∗3* were reported to decrease the metabolism of NSAIDs [50]. Based on genotyping of 105 volunteers, no differences were found in efficacy of piroxicam and adverse effects between the carriers of normal and slow metabolizing *CYP2C8∗3* and *CYP2C9* alleles after 4 days administrations. These results indicate that piroxicam regulates the inflammation after third molar surgery without influence from CYP genotypes.

Somogyi *et al.* [51▪] studied the contribution of ethnicity-dependent genetic variability in innate immune signalling to morphine consumption during PCA in 598 Han Chinese, 230 Malay and 133 Indian women after elective caesarean section under spinal anaesthesia. The incidence of postoperative pain was significantly higher in Chinese patients with *COMT* rs4680 genotypes which was not observed in Malay and Indian cohorts. Interaction between ethnicity and *OPRM1* variant rs1799971, Toll-like receptor 2 (*TLR2*) variant rs3804100 and *IL-6* variant rs1143634 predicted 9.8% of the variability in morphine consumption in the entire cohort. These findings indicate that innate immune system might contribute to the variability in postoperative morphine requirements in an ethnicity-dependent manner.

Senagore *et al.* [52▪▪] analysed the effect of pharmacogenetics-guided selection of analgesics following major abdominal surgery within an enhanced recovery protocol (ERP). The analgesic protocol was guided based on the assessment of *CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, COMT, OPRM1* and *ABCB1* genes which were part of a diagnostic pain gene panel. The evaluation was performed for 63 patients undergoing open or laparoscopic colorectal and major ventral hernia surgeries and 47 control patients undergoing the same operations while being managed with standard ERP. Pharmacogenomic guidance resulted in modifications of opioid analgesia of the ERP in 80% of the patients and changes in the choice of NSAID in 56% of the patients. These changes resulted in a 50% reduction in opioid consumption and reduced adverse effects compared with standard ERP.

Yuan *et al.* [53] investigated the effect of the pregnane X receptor *PXR∗1B* polymorphisms on CYP3A4 enzyme activity and postoperative consumption of the μ-opioid receptor agonist fentanyl in 287 Han Chinese female patients undergoing abdominal total hysterectomy or myomectomy. PXR is a nuclear receptor which regulates the expression of *CYP3A4* [54], the liver enzyme responsible for the metabolism of fentanyl [55]. There were no significant differences in the consumption of fentanyl 24 h after surgery, pain scores and the enzyme activity of CYP3A4 in Chinese female patients based on the *PXR∗1B* haplotypes which might be due to the low number of patients ($n = 95$) with complete clinical data and information regarding CYP3A enzyme activity.

CONCLUSION

In general, the main predictive factor for postoperative pain is type of surgery [56]. Other major factors include preoperative pain, anxiety and age [8,56]. On an individual basis, genetic variation may play a significant role in pain intensity and treatment outcome. However, despite the recent progress in genetics and genomics of postoperative pain, it is still not possible to predict how much pain a patient will have postoperatively. Future genetic studies should consider recruiting larger patient cohorts with standardized analgesic protocols in order to achieve sufficient statistical power to detect genetic variants associated with postoperative pain. Also,

more advanced methods such as NGS should be utilized to screen for rare genetic variants that can modulate pain. Furthermore, it is encouraged to perform meta-analyses of previous studies and to independently reproduce the findings in different research groups. Utilizing the novel genome-editing technologies such as CRISPR/Cas9 should help to develop new animal models for postoperative pain which can better model the development of postoperative pain in humans. The associations between epigenetic changes and postoperative pain are poorly understood and require more intensive research. The emerging diagnostic pain panels can be used to select more effective analgesic treatments based on genotype-dependent dosing of analgesics. Finally, pharmacogenetics might facilitate the development of novel analgesics for postoperative pain with less adverse effects by taking into account the inter-individual variability in drug responses.

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Conflicts of interest

There are no conflicts of interest.

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