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REVIEW ARTICLE

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A pharmacogenetics approach to pain management

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Abstract

Introduction: Opioid analgesics are widely used as effective analgesics for the treatment of moderate-to-severe pain. However, the analgesic efficacy of opioids is well known to vary widely among individuals, and effective pain treatment is hampered by vast individual differences. Although these differences in opioid requirements have been attributed to various factors, genetic factors are becoming increasingly relevant to the development of genome science.

Aim: This review covers the association between opioid analgesic requirements and particularly gene polymorphisms.

Future perspectives: Personalized pain treatment has begun using prediction formulas based on associated gene polymorphisms. Improvements in personalized pain treatment are expected as scientific knowledge further expands in the future.

KEYWORDS
genetic polymorphisms, opioids, pain, personalized medicine, predictive genetic testing

1 | INTRODUCTION

Pain is an important physiological mechanism by which humans prevent themselves from developing tissue injury. However, excessive pain can markedly increase psychological health problems and decrease health-related quality of life.[1] Therefore, pain should be managed appropriately by analgesics. Opioid analgesics, such as fentanyl and morphine, are widely used as effective analgesics for the treatment of moderate-to-severe pain. In 1986, the World Health Organization proposed a method for the relief of cancer pain.[2] The method can be summarized in five phrases: by mouth, by the clock, by the ladder, for the individual, and with attention to detail. Thus, "for the individual" is a critical principle in pain management, demonstrating that there are no standard doses for opioid drugs. Therefore, opioids should be prescribed with proper doses for individual patients. However, the analgesic efficacy of opioids is well known to vary widely among individuals, thus complicating their effective and safe clinical use.[3,4] Therefore, although the same amount of opioid analgesics may be administered to different patients, it may occasionally cause insufficient analgesia or side effects among some individuals, such as nausea, vomiting, constipation, and respiratory depression.[5] For example, the minimal effective analgesic concentrations (MEACs) of morphine and fentanyl that are required for adequate analgesia vary from 6.3 to 53.6 ng/mL and 0.2 to 2.0 ng/mL, respectively.[6-9] This suggests that the MEAC is five- to tenfold different among individuals. Thus, effective pain treatment is often hampered by significant differences in opioid sensitivity. Empirical methods of administration that are currently performed by trial and error are an imperfect practice that can result in delayed analgesia and possibly overdose (Figure 1).

2 | FACTORS THAT RESULT IN INDIVIDUAL DIFFERENCES

Individual differences have been attributed to environmental, psychological, and genetic factors, including age, gender, patient weight,

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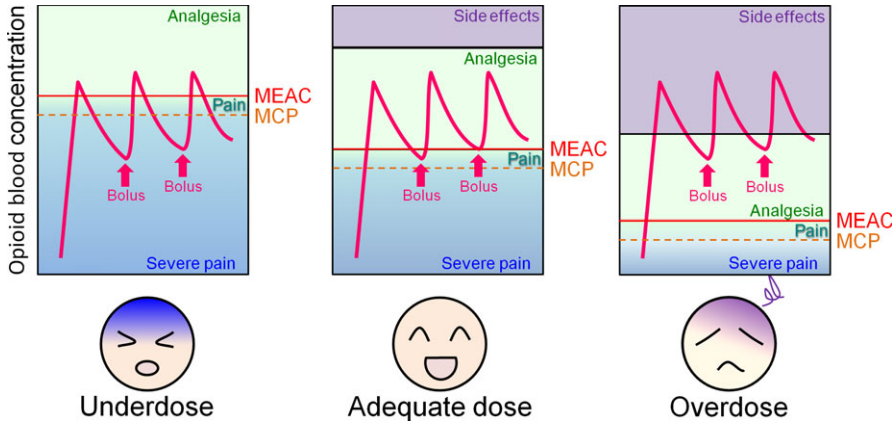

FIGURE 1 Illustration of individual differences in opioid requirements. Although the blood opioid concentration changes similarly after administration (*arrows*) and the difference between the minimal effective analgesic concentration (MEAC) (*solid line*) and maximum concentration with pain (MCP) (*dashed line*) is low among individuals, the clinical response can differ between patients because of five- to tenfold interpatient differences in the MEAC. Therefore, a particular opioid dose that produces satisfactory pain relief in some patients may be either too low (resulting in insufficient analgesia) or too high (resulting in adverse effects) in other patients

ethnic origin, hepatic or renal function, type of surgery, surgical methods, duration of surgery, anxiety, and psychological distress.[10-13] In this section, we describe each of these factors.

2.1 | Environmental factors

Various environmental factors have been reported. Among these, advancing age has been shown to reduce morphine requirements because age has been suggested to blunt peripheral nociceptive function.[11] Additionally, fentanyl use for pain management is more in females than in males.[14]

2.2 | Psychological factors

Many studies have reported associations between depression and pain. The prevalence of pain in depressed cohorts and the prevalence of depression in pain cohorts are higher than the prevalence when these conditions are examined individually.[15] Indeed, the prevalence of pain in depressed patients was approximately 60%, and the intensity of depression was generally higher in patients with greater pain.[16] Thus, psychological distress, such as depressed mood and negative affect, can increase postoperative analgesic consumption. Moreover, patients who undergo emergency surgery may have less preoperative information and time for psychological preparation, resulting in increased requirements for postoperative analgesia.[11]

2.3 | Genetic factors

Recent studies of individual differences in opioid analgesic requirements have demonstrated the significant involvement of genetic factors. The twin study paradigm is one of the few available designs that provide global estimates of genetic and environmental contributions to complex phenotypes, including interindividual differences in drug responses.[17-19] Genetic effects are thought to be responsible for approximately 12%-60% of response variability in opioid treatment in twin studies.[18-20] A twin approach generally provides an excellent opportunity to understand the causes and consequences of epigenetic variations. Although the epigenetic modulation of analgesic receptor targets and drug-metabolizing enzymes may alter the pharmacodynamics and pharmacokinetics of analgesic drugs, respectively,[21] to date, no studies have adopted twin approaches to examine the causal effects of epigenetic variations on interindividual differences in opioid responses.

3 | PHARMACOGENOMICS

Empirical approaches to the effective treatment of pain are currently limited because the initial drug selection, subsequent dosage titrations, and drug additions are made according to only a few patient-specific clinical features.[22] Therefore, pharmacogenetic studies and in vitro companion diagnostic devices (IVD companion diagnostic devices) are being developed. Pharmacogenetics is defined as the use of pharmacogenomic or pharmacogenetic tests in conjunction with drug therapy. The goal of pharmacogenomic research is to offer personalized medicine to improve the efficacy of medications and patient safety by helping predict the risk of adverse outcomes. Translating pharmacogenetics to clinical practice has been challenging in the context of pain therapies because of the inherent complexity of the study of pain that involves subjective and multifactorial pain perception experiences or responses to pain-modulating drugs.[23,24] However, the number of United States Food and Drug Administration (FDA)-approved drug label modifications that contain pharmacogenetic information has significantly increased.[25] Additionally, the Clinical Pharmacogenetics Implementation Consortium published guidelines for codeine, clopidogrel, and tacrolimus dosing based on pharmacogenetics testing.[26-28] An IVD companion diagnostic device provides information that is essential for the safe and effective use of a corresponding therapeutic product. The FDA issued draft guidance for IVD companion diagnostic devices in July, 2011.[29]

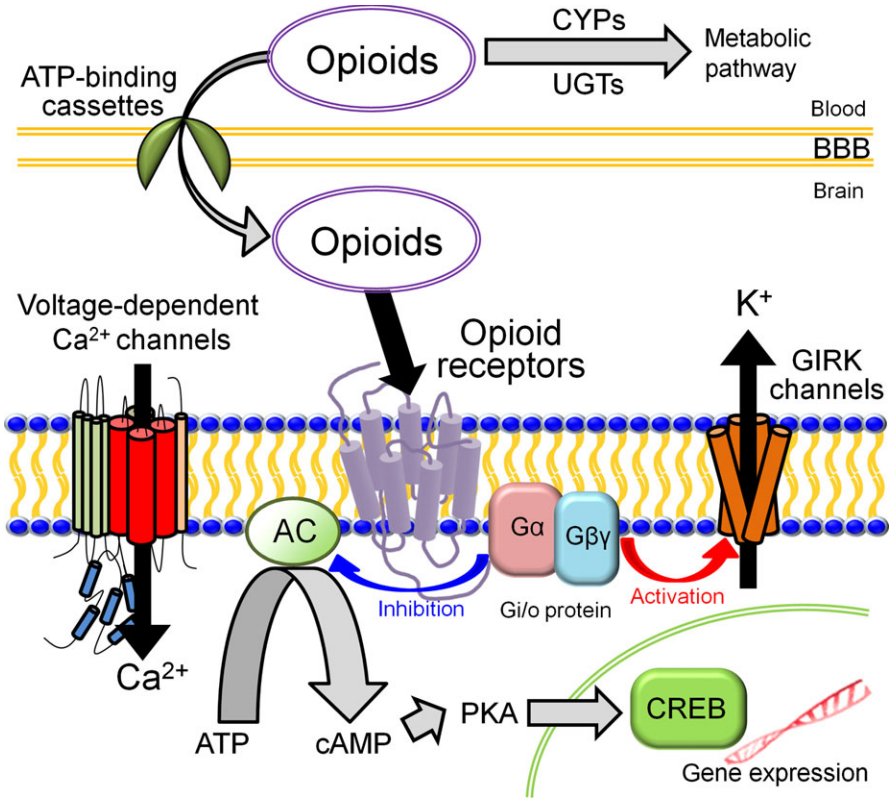

FIGURE 2 Molecules associated with the action of opioid analgesics. The analgesic effects of opioids depend on such factors as opioid peptide receptors, effector molecules, metabolic enzymes, and transporters. The effector molecules are affected by $G_{i/o}$ protein include G protein-activated inwardly rectifying potassium (GIRK) channels, voltage-dependent Ca^{2+} channels, and adenylyl cyclase (AC), which influence the activity of cyclic adenosine monophosphate (cAMP)-responsive element-binding protein (CREB) through the actions of cAMP and protein kinase A. The metabolic enzymes include cytochrome P450 enzymes (CYPs) and UDP-glucuronosyltransferases (UGTs). The transporters include adenosine triphosphate (ATP)-binding cassettes

4 | CANDIDATE GENES THAT PREDICT THE ANALGESIC EFFECT OF OPIOIDS

Opioids exert their effects by binding to opioid peptide receptors ($G_{i/o}$ protein-coupled receptors) and triggering signaling transmission to several effector systems, including the inhibition of adenylyl cyclase, activation of G protein-activated inwardly rectifying potassium (GIRK) channels,[30] and inhibition of voltage-dependent Ca^{2+} channels. Most opioid drugs are metabolized by cytochrome P450 (CYP) enzymes, including CYP2D6, that are glucuronidated by UDP-glucuronosyltransferases (UGTs) and transported between the blood and brain by adenosine triphosphate (ATP)-binding cassette, subfamily B (MDR/TAD), member 1 (ABCB1[31-34]; Figure 2). Many studies have reported associations between gene polymorphisms in these molecules, some of which are described below, and pain/opioid sensitivity (Table 1).

TABLE 1 Summary of candidate genes related to predicting the analgesic effect of opioids

Gene	Related polymorphism	Subjects	Related phenotype	Reference
OPRM1	rs1799971 (A118G)	Patients undergoing total knee arthroplasty	Analgesic response to morphine for acute postoperative pain relief	Wang et al [37]
		Female patients undergoing abdominal total hysterectomy		Chou et al[38]
		Mice possessing the equivalent substitution		Chou et al[39]
OPRM1	rs9384179 (IVS3 + A8449G)	Patients undergoing sagittal split ramus osteotomy	Fentanyl requirements for postoperative analgesia	Fukuda et al[40]
CREB1	rs2952768	Patients undergoing sagittal split ramus osteotomy	Fentanyl requirements for postoperative analgesia	Nishizawa et al[44]
GIRK2 (KCNJ6)	rs2835859	Patients undergoing sagittal split ramus osteotomy	Fentanyl requirements for postoperative analgesia	Nishizawa et al[48]
CACNA1E	rs3845446	Patients undergoing sagittal split ramus osteotomy	Fentanyl requirements for postoperative analgesia	Ide et al[14]
		Patients undergoing laparoscopic colectomy	Fentanyl requirements for postoperative analgesia	Amano et al[52]

4.1 | *OPRM1*

Opioids exert their pharmacological actions through three types of opioid receptors, designated μ, κ, and δ.[35] Among these three receptors, morphine and fentanyl particularly interact with μ-opioid receptors (MOPs). MOPs are essential for the analgesic effects of most clinically effective opioid drugs. Genetic variations in the human MOP gene (*OPRM1*) that alter the expression of MOPs can affect opioid efficacy. To date, more than 250 single nucleotide polymorphisms (SNPs) have been identified in the human *OPRM1* gene.[36] The A118G polymorphism (rs1799971) has been the most extensively studied polymorphism because of its clinical associations with opioid responses. This SNP is located in exon 1 and leads to an amino acid substitution that alters the N-linked glycosylation sites on the receptor. Several clinical studies have shown that subjects with the G118 allele presented a reduction in the analgesic response to morphine for acute postoperative pain relief.[37-39] For example, in Japanese patients who underwent sagittal split ramus osteotomy, the analgesic effects of fentanyl were related to genotypes of the *OPRM1* gene. Subjects with the G allele of the *OPRM1* A118G SNP were less sensitive to fentanyl. Additionally, subjects with the G allele of the IVS3 + A8449G SNP (rs9384179), representing the complete disequilibrium block, including the 3′ untranslated region (UTR) of the *OPRM1* gene, required less fentanyl for postoperative analgesia.[40]

4.2 | *CREB1*

The inhibition of adenylyl cyclase inhibits the production of cyclic adenosine monophosphate (cAMP), thus decreasing the active form of protein kinase A, phosphorylating cAMP-responsive element-binding protein (CREB), decreasing various gene expression in the nucleus, and subsequently affecting analgesia.[41] Indeed, the administration of cAMP intracerebrally or intravenously antagonized morphine analgesia, and all of the major behavioral effects of morphine, including analgesia, were attenuated in mice that lacked adenylyl cyclase 5.[42,43] A recent study found that higher *CREB1* mRNA expression levels in subjects with the C/C genotype in the rs2952768 SNP may result in elevated CREB function and decreased sensitivity to the rewarding effects of opioids, resulting in greater postoperative opioid analgesic requirements.[44]

4.3 | *GIRK2*

GIRK channels are expressed in many tissues and activated by several $G_{i/o}$ protein-coupled receptors, such as opioid receptors, and thus are known to be involved in the modulation of opioid-induced analgesia.[45] Several studies that used knockout mice showed that opioid-induced GIRK channel activation, co-expressed with opioid receptors, inhibited nociceptive transmission and thus opioid-induced analgesia.[46,47] Recently, an association was found between opioid analgesic sensitivity and the rs2835859 SNP in the *GIRK2* (*KCNJ6*) gene, in which carriers of the C allele of this SNP required less analgesics compared with noncarriers after painful cosmetic surgery.[48]

4.4 | *CACNA1E*

Voltage-activated Ca^{2+} channels (VACCs) mediate Ca^{2+} entry into cells in response to membrane depolarization and play a crucial role in the nervous system by controlling membrane excitability and calcium signaling.[49] $Ca_v2.3$ VACCs are reported to be distributed throughout the central and peripheral nervous systems, including pain pathways. $Ca_v2.3$ knockout mice have been reported to present functional deficits in pain perception.[50,51] Thus, $Ca_v2.3$ (R-type) VACCs have been especially thought to play critical roles in pain pathways. In Japanese patients who underwent sagittal split ramus osteotomy, the analgesic effects of fentanyl were related to genotype of the *CACNA1E* gene. Subjects with the minor G allele of the rs3845446 A/G SNP required less fentanyl for adequate postoperative pain control after painful cosmetic surgery,[14] although those with the same allele reportedly required greater fentanyl after laparoscopic colectomy.[52]

5 | PERSONALIZED PAIN TREATMENT

Although various factors that are related to individual differences in opioid sensitivity have been identified, a prediction model that calculates appropriate opioid analgesic requirements has not yet been established. Therefore, we sought to construct prediction formulas for individual opioid analgesic requirements based on genetic polymorphisms and clinical data using patients in pain management with opioid drugs.[53] Constructing prediction formulas based on data from patients with cancer pain is difficult because the mechanism, severity, and nature of cancer pain can differ substantially between patients.[54] Thus, we investigated patients who underwent mandibular sagittal split ramus osteotomy, which is highly standardized at our institute with regard to surgical procedures, the duration of surgery, and the skill of the surgeons. Because these patients are usually young and healthy and expected to experience similar levels of pain after surgery, they may be ideal for evaluating the analgesic effects of opioids.[39] Stepwise multiple linear regression analysis was performed to construct prediction formulas and predict postoperative fentanyl requirements based on parameters that may affect the analgesic efficacy of fentanyl (eg, age, gender, height, weight, pain perception latency [PPL], and genotype data for five SNPs that have been reported to be strongly associated with opioid requirements in patients who underwent mandibular sagittal split ramus osteotomy with postoperative pain). These analyses showed that four SNPs (ie, rs2952768, rs2835859, rs9384179, and rs11959113 around the adrenoceptor β2, surface gene [*ADRB2*]), PPL, and weight were retained as independent predictors of 24-h postoperative fentanyl use, and two SNPs (ie, rs2952768 and rs3845446) and weight were retained as independent predictors of perioperative fentanyl use. The multiple-regression equations were the following:

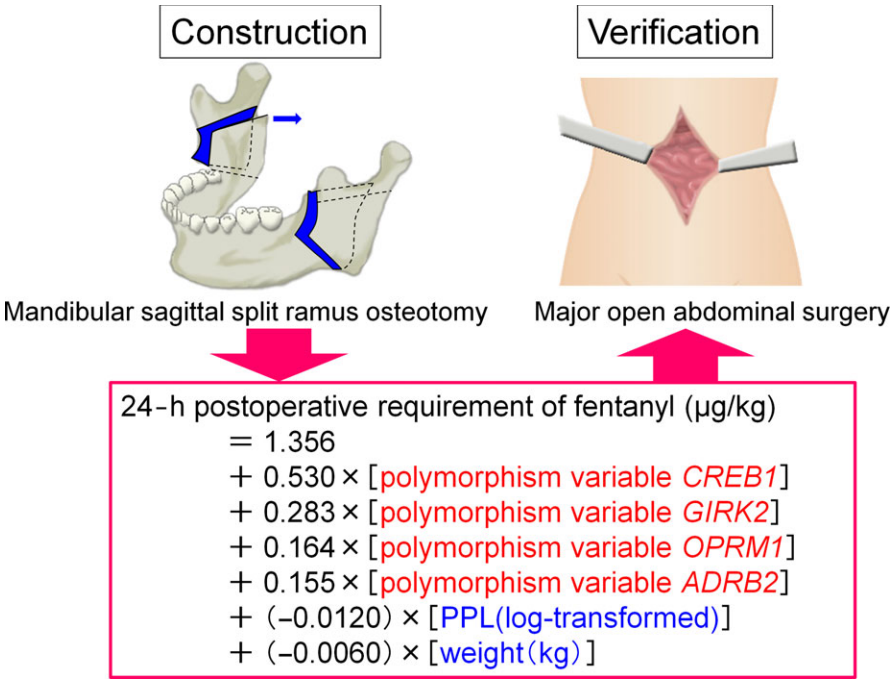

FIGURE 3 Construction and verification of prediction formula for individual opioid analgesics requirements. We constructed a prediction formula for individual opioid analgesic requirements during the first 24-h postoperative period using patients who underwent mandibular sagittal split ramus osteotomy and validated the utility of the formula in another type of surgery, major abdominal surgery

Predicted value of 24-h postoperative fentanyl requirements (μg/kg; log-transformed) = 1.356 + 0.530 × (SNP variable for *CREB1)* + 0.283 × (SNP variable for *GIRK2)* + 0.164 × (SNP variable for SNP variable for *OPRM1)* + 0.155 × (SNP variable for *ADRB2)* + (−0.0120) × (PPL [log-transformed]) + (−0.0060) × (weight [kg])

Predicted value of perioperative fentanyl requirements (μg/kg; log-transformed) = 2.749 + 0.221 × (SNP variable for *CREB1)* + 0.109 × (SNP variable for *CACNA1E)* + (−0.011) × (weight [kg])

We also validated the utility of the prediction formulas in patients who underwent major open abdominal surgery and found that these prediction formulas may be useful for other types of surgery (Figure 3). Using the prediction formulas and patients' genetic polymorphisms and clinical data, better analgesia could be provided to individual patients.

6 | FUTURE PROSPECTS

Although the precision of our prediction formula for individual opioid analgesic requirements appears to be relatively low, such algorithms are expected to be improved in further studies. For example, genetic factors that are involved in metabolic enzymes and transporters may improve the accuracy of the prediction formulas in the future. Indeed, polymorphisms of the *UGT2B7* gene, which encodes one of the UGT subtypes, has recently been reported to be associated with the analgesic effects of fentanyl in the cold pressor-induced pain test,[55] which could also lead to improvement of the accuracy of the prediction formulas. Additionally, the onset of adverse effects (eg, nausea, vomiting, and constipation) may also be a useful and interesting outcome because such effects can cause some patients to stop requesting analgesics despite not actually achieving full analgesia. Gene polymorphisms have also been found to be related to various side effects of other drugs. For example, HLA-A*3101 was present in 60.7% (37/61) of patients with carbamazepine-induced cutaneous adverse drug reactions (cADRs) but in only 12.5% (47/376) of carbamazepine-tolerant controls (odds ratio = 10.8, 95% confidence interval: 5.9-19.6, $P = 3.64 \times 10^{-15}$), implying that this allele has 60.7% sensitivity and 87.5% specificity when we apply HLA-A*3101 as a risk predictor for carbamazepine-induced cADRs.[56] In the future, we expect that more effective personalized pain treatment may be achieved by taking side effects into account.

7 | CONCLUSION

The studies that were presented in this review have shown that individual differences in opioid analgesic requirements are very large, and various factors (eg, genetic factors) are involved in such differences. Although more research is needed, better pain treatment may be provided to patients who suffer from postoperative pain using prediction formulas based on pharmacogenetics research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest for this article. [Correction added on 5 March 2018, after first online publication: The word, 'The', has been added to the start of the conflict of interest statement.]

AUTHOR CONTRIBUTIONS

KY, DN, SI, and KI conceived and designed the contents. KY, DN, SI, TI, KF, and KI wrote the paper.

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