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Mechanisms and implications in gene polymorphism mediated diverse reponses to sedatives, analgesics and muscle relaxants

Yan Sun[1,*], Hongyu Zhu[2,*], Elham Esmaeili[3], Xue Tang[3], Zhilin Wu[3]

Department of Anesthesiology, [1]Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology, Wuhan, [2]Linhe District People's Hospital, Bayannur, Inner Mongolia, [3]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

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Corresponding author:
Zhilin Wu, M.D.
Department of Anesthesiology,
Union Hospital, Tongji Medical College,
Huazhong University of Science and
Technology, No. 1277, Jiefang Avenue,
Wuhan 430022, China
Tel: +18963946992
Fax: +86-02785351650
Email: 840916@qq.com; wuzl1977@hust.edu.cn
ORCID: https://orcid.org/0000-0002-9179-1762

*Yan Sun and Hongyu Zhu are contributed equally to this work as co-first authors.

Responses to sedatives, analgesics and muscle relaxants vary among patients under general anesthesia, which could be ascribed to the disparities of clinical characteristics and genetic factors of individuals. Accumulating researches have indicated that gene polymorphisms of the receptors, transporters and metabolizing enzymes associated with anesthetics play a considerable role in their efficacy. However, a systematically summarized study on the mechanisms of gene polymorphisms on pharmacodynamics and pharmacokinetics of anesthetics is still lacking. In this paper, the recent researches on pharmacogenomics of sedatives, analgesics and muscle relaxants are comprehensively reviewed, and the contributions and mechanisms of polymorphisms to the differences of individual efficacy of these drugs are discussed, so as to provide guidance for the formulation of a rational anesthesia regimen for patients with various genotypes.

Keywords: Analgesics; Genetic polymorphism; Hypnotics and sedatives; Individuality; Neuromuscular blocking agents; Pharmacogenetics.

Introduction

Both clinical practices and scientific researches have testified that there are significant individual differences in the efficacy of commonly used sedatives, analgesics and muscle relaxants for general anesthesia. Except for non-genetic factors such as gender, age, liver and renal function [1–7], gene polymorphisms associated with receptors, transporters and metabolizing enzymes play a major role in the disparities of the pharmacodynamics and pharmacokinetics of anesthetics [8]. Genetic factors account for 20–95% of the variation in individual responses to anesthetics [9]. Pharmacogenomics is an available and valuable method to explore the relationship between gene mutations and variability in individual responses to anesthetics. Therapeutic options based on gene polymorphisms could not only improve the outcome of treatments, but also reduce the risk of drug related toxicity and other adverse effects. The purpose of this study is to summarize the mechanisms of genetic polymorphisms in human response differences to commonly used sedatives, analgesics and muscle relaxants, and provide a scientific theoretical basis for the formulation of a rational anesthesia regimen for patients with various genotypes, and ultimately improve the anesthesia quality and avoid the occurrence of potential complications.

Pharmacogenomics of sedatives

Intravenous anesthetics

Propofol, an ultrafast acting intravenous anesthetic agent, is most frequently utilized in induction and maintenance of general anesthesia, as well the sedation for some unpleasant maneuvers of diagnoses and treatments [10,11]. It works mainly by activating gamma-aminobutyric acid (GABA) receptors [12]. Some metabolic enzymes, such as cytochrome P450 2B6 (CYP2B6), cytochrome P450 2C9 (CYP2C9) and UDP-glucuronosyltransferase 1A9 (UGT1A9), are convinced to be involved in the pharmacokinetics of propofol directly or indirectly [13–15]. The sensibility of individuals to propofol is complicated, and it is reflected by various drug consumptions and recovery time required [16,17]. The evidence for a specific association between genetic components and sensibility of propofol in humans remains deficient. Here in this paper CYP2B6 is detailed as an example.

CYP2B6 and propofol

Whether CYP2B6 has an impact on the diverse individual responses to propofol is still controversial. Propofol is initially biotransformed by CYP2B6. Mastrogianni et al. [18] found that the blood propofol distribution at 4 min post-administration in carriers of the T allele was much wider than CYP2B6 c.516G genotypes, which demonstrated CYP2B6 c.516G > T polymorphism was apparently related to the distribution of blood propofol after a single injection. Mourao et al. [19] found that CYP2B6 c.516G > T genetic variant retarded propofol metabolism in 108 healthy adults undergoing total intravenous general anesthesia, resulting in a decrease of approximately 7% in propofol consumption. In addition, a study conducted by Mikstacki et al. [14] further confirmed that polymorphism c.516G > T in the CYP2B6 gene could affect the biotransformation rate of propofol, and CYP2B6 gene might exert a critical role in the optimization of propofol anesthesia. However, some studies were inconsistent with the above results. A pilot study revealed that the mutation of CYP2B6 c.516G > T gene had no significant effect on propofol and were unable to cause obvious individual variability [20]. A prospective study with eighty-three patients enrolled indicated that CYP2B6 gene polymorphism was not an independent factor determining the pharmacokinetics of propofol [21].

The extensive biotransformation of propofol is catalyzed through two pathways, glucuronidation by UDP-glucuronosyltransferase family members and hydroxylation by CYP P450 enzymes [22,23]. 4-Hydroxypropofol, a hydroxylated metabolite of propofol, attributes to one-third of the hypnotic activity of propofol [24]. It is reasonable to propose that the highly polymorphic nature of CYP2B6 makes the expression of corresponding hydroxylation enzymes varied, resulting in diverse concentrations of 4-Hydroxypropofol. Indeed, the ratio between glucuronidation and hydroxylation was described recently as being the subject to the interpatient variation [14]. The elimination of propofol is dependent on both metabolism and distribution, which makes the role of CYP2B6 polymorphisms in the efficacy of propofol controversial [25]. However, observing the present research condition, it can be concluded that the alteration in hydroxylation from CYP2B6 polymorphism is responsible for individual variability of propofol metabolism and efficacy.

Volatile anesthetics

Great advances in inhalation anesthesia have been achieved with the introduction of fluorinated anesthetics. In the group of fluorinated compounds, desflurane and sevoflurane are recently deployed as the most representative agents for inhalation anesthesia in clinical practices [26].

MC1R and desflurane

Desflurane is resistant to biotransformation with an extremely low metabolic rate of less than 0.1%. It can be metabolized into trifluoroacetic acid and inorganic fluorine by CYP2E1 [27]. Besides, according to a study on desflurane requirements in different hair colored female volunteers, the demand for desflurane in red-haired persons was significantly higher than in dark-haired persons, which could be traced to the mutation on the melanocortin-1 receptor (MC1R) genotype. DNA analysis revealed that red haired women carried at least one dysfunctional or weakened MC1R allele, and 80% carried two such alleles [28]. Electroencephalogram (EEG) is a reliable tool for evaluating the depth of sedation induced by volatile or intravenous anesthetics [29]. It was observed that gene polymorphisms of MYD88rs6853, BDNFrs6265 and IL-1βrs1143627 might be associated with the individual variability of EEG in desflurane anesthesia [30].

Human MC1R is a major regulator of melanogenic enzymes. It exists in human melanocytes, glial cells, pituitary tissue, and periaqueductal gray matter [28]. Volatile anesthetics produce the effect of sedation by potentiating inhibitory neurotransmitter receptors and suppressing excitatory receptors in the central nervous system [31]. In fact, the anesthesia potency of inhaled anesthetics, such as desflurane, may be mediated via the spinal cord rather than the higher nervous centers [32,33]. Moreover, although mutations of many MC1R alleles do not affect their function, it has been found that MC1R variants V60L, R142H, R151C, R160W,

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D294H make MC1R less effective in intracellular cyclic AMP producing after activation [34]. Though these clues are scattered and are from a small number of studies, they shed light on future researches to more clearly explanation of how MC1R gene polymorphisms induce individual variation in desflurane sensitivity.

MDR1 and sevoflurane

Sevoflurane is another widely used volatile anesthetic, and it is well-tolerated for inhalation induction [35]. The sensitivity of sevoflurane varies among different human groups. Ezri et al. [36] suggested that the minimum alveolar concentration (MAC) for sevoflurane differed in various human ethnicities, which appeared to be related to their genetic makeup. Compared with Caucasian Jews, Oriental Jews had less MAC for sevoflurane, and European Jews had even less. What's more, to ensure an adequate depth of anesthesia and prevent patients from movement during the operation, 24% higher dosage of sevoflurane was required for Jews in Caucasia than in Europe. A study of sevoflurane-remifentanil anesthesia in pediatric tonsillectomy figured out that children bearing multidrug resistant 1 (MDR1) 1236C > T CC genotype received more superior anesthetic effects compared to children with CT + TT genotype, including shorter induction and recovery time, smaller hemodynamic changes at 5 minutes after extubation, better analgesic and sedation effects, as well as less adverse reactions [37].

P-glycoprotein (P-gp), an efflux pump for diverse lipophilic compounds, is encoded by MDR1 [38,39]. Presumedly, gene polymorphisms in MDR1 including 1236C > T may alter the expressions of P-gp and make an impact on the absorption of chemicals into cells. Therefore, the pharmacokinetics and the therapeutic efficacy of some medicines can be influenced by MDR1 gene polymorphisms.

GRIN1 and sevoflurane

Chen et al. [40] have systematically screened the molecular sites that might affect the pharmacological action of sevoflurane. They identified that the N-methyl-D-aspartate receptor NR1 subunit gene (GRIN1) polymorphisms (rs28681971 and rs79901440) were intimately related to the time required for unconsciousness induced by sevoflurane. In more details, individuals with the GRIN1 rs28681971 TT genotype took much less time to achieve the target depth of sevoflurane induced anesthesia than those with the TC genotype. And a longer time was spent to obtain the same sedation depth by individuals with the GRIN1 rs79901440 CT genotype than those with the CC genotype.

Volatile anesthetics exert their efficacy by activating GABA receptors and blocking N-methyl-D-aspartate (NMDA) receptors in the central nervous system [41]. GRIN1 is an essential component of NMDA receptor, which has been confirmed by several molecular cloning studies [42,43]. A functional NMDA receptor is the heteromeric complex consisting of two GRIN1 and two GRIN2 subunits. There is a glycine-binding site in GRIN1 subunit [44]. GRIN1 gene mutations (rs28681971 and rs79901440) may impact on the minimum free energy of the molecular's secondary structure, then disrupt the folding of GRIN1 protein and the function of NMDA receptor [40]. Thus, it is explainable that the action of sevoflurane varies among individuals with mutated GRIN1 genotype. Further cohort study with a larger sample is required to validate these mechanisms.

Pharmacogenomics of opioid analgesics

Adequate analgesia is an indispensable component and the core goal in anesthesia. Dopamine/noradrenalin and endogenous opioids are largely responsible for the activity of the descending pain inhibitory pathways [45]. Analgesics represented by opioids such as fentanyl, sufentanil and remifentanil are used in nearly all surgical procedures [46]. There are obvious individual differences in the efficacy of these opioids, which undoubtedly poses a challenge for effective pain management. In addition to the non-genetic factors, the role of genetic variations in pharmacokinetics of analgesics has attracted extensive attention of researchers in recent years.

Fentanyl

Fentanyl is the first ever synthesized potent lipid-soluble opioid [47]. It has gained popularity for its versatility in numerous acute and chronic pain management, as well as in the induction of general anesthesia and postoperative analgesia. Previous studies have pointed out that metabolic enzymes and transporters play a vital role in the pharmacokinetics of fentanyl. However, the research on the efficacy of fentanyl is affected by multiple factors including discrepancies in races, sample sizes, administration methods etc. The impact of gene polymorphisms on fentanyl requirements is still controversial.

CYP3A4 and fentanyl

MDR1/CYP3A4/OPRM1 gene polymorphisms in Chinese women were identified to influence the consumption of fentanyl during caesarean section and the effect of postoperative intravenous analgesia [48]. The analgesic efficacy of fentanyl is also related to CYP3A4 polymorphisms. Moreover, data from Zhang et al. [49] CYP3A4*1G gene polymorphisms reduced the metabolism of fentanyl, and the level of CYP3A4 mRNA was positively cor-

related with fentanyl metabolism in liver microsomes.

Fentanyl is metabolized by CYP P450 3A4 (CYP3A4) and CYP P450 3A5 (CYP3A5), two major oxidative enzymes in liver [50,51]. CYP3A4∗1G gene polymorphism could attenuate CYP3A activity directly, and reduce the postoperative consumption of fentanyl [52]. However, CYP3A4 polymorphisms may also bring no obvious changes to CYP3A4 activity, while the combination of either the variant alleles of CYP3A4 or CYP3A5∗3 could decrease CYP3A5 activity [49]. Thus CYP gene polymorphism is a possible mechanism for an impaired fentanyl metabolism and different responses to it.

UGT2B7 and fentanyl

As the predominant isozyme of UDP-glucuronosyltransferases, uridine diphosphate-glucuronyltransferase 2B7 (UGT2B7) polymorphism is involved in the biotransformation of multitudinous endobiotics and xenobiotics [53,54]. Fentanyl metabolism is of no exception. Studies revealed that UGT2B7 rs7439366 C allele could enhance the effect of fentanyl, which might be ascribed to the impact of UGT2B7 on fentanyl metabolism [53,55]. Patients with UGT2B7 rs7439366 CT genotype had higher fentanyl sensitivity compared to those with UGT2B7 rs7439366 TT genotype [56].

In humans, UGT2B7 is a uridine diphosphate glucuronic acid transferase with a major role in the disposition of a wide array of small endogenous and exogenous molecules [54,57]. Norfentanyl is the metabolite of fentanyl and has little pharmacological activity [55]. Norfentanyl is reportedly divided into M1, M2, M3, M4, M5, and M7 based on its chemical structure. A portion of norfentanyl is excreted by glucuronidation through urine and bile. The rest norfentanyl is metabolized by glucuronate conjugation, which is dominated by UGT2B7 [57]. Gene polymorphisms of UGT2B7 may alter the activity and function of the enzyme, and affect the metabolism and pharmacokinetics of fentanyl [58].

ABCB1 and fentanyl

Fentanyl is a possible substrate of P-gp which is encoded by adenosine triphosphate binding cassette subfamily B member 1 (ABCB1) [59]. Accordingly, metabolism of fentanyl may also be altered by genetic polymorphisms in ABCB1. Furthermore, there is a positive correlation of single-nucleotide polymorphisms in ABCB1 with respiratory suppression by intravenous fentanyl administration [60]. Horvat et al. [61] observed that less fentanyl was needed for children with ABCB1 rs1045642AA genotype than with AG and GG genotype, which could be explained by decreased expression and activity of P-gp.

A gene-association study has clarified that the analgesic effect of opioids could be influenced by a number of gene polymorphisms including ABCB1 [62]. P-gp encoded by ABCB1 is an integral membranous protein that pumps substrates out of the intracellular compartment [60]. It has been investigated that interindividual differences in P-gp expression and activity is related to ABCB1 polymorphisms [63,64]. Against this background, we hypothesize that ABCB1 polymorphisms could change the substrate disposition of P-gp (fentanyl) and influence its clinical efficacy.

Sufentanil

Sufentanil, a piperidine derivative, is 6–10 times more potent than fentanyl [65]. Sufentanil is now widely used for the induction and maintenance of general anesthesia. In all likelihood, the metabolic mechanism of sufentanil is similar to that of fentanyl.

CYP3A4 and sufentanil

Individual genetic background is also a valuable element for the sensitivity of sufentanil. The high frequency of CYP3A4∗1G variants in Chinese population has been well documented. By oxidizing human liver microsomes, CYP3A4∗1G is believed to be responsible for the metabolism of 45–60% of prescribed drugs including analgesic agents [65–67]. As expected, Zhang et al. [68] proposed that CYP3A4*1G gene polymorphisms resulted in the attenuation of CYP3A activity and the reduction of sufentanil consumption for intraoperative pain management in general anesthesia. The correlation between CYP3A4 gene polymorphisms and the consumption of sufentanil has been further proved by Lv et al. [69]. Polymorphisms of CYP3A4∗1G gene caused significant heterogeneity of the postoperative analgesic effect with sufentanil among various ethnic groups [70].

Like fentanyl, sufentanil is mainly metabolized in liver by CYP3A4, the most important isoform of CYP P450 enzymes [71]. Gene mutations in CYP3A4 theoretically impair its activity and result in individual differences in the metabolism and antinociceptive effects of sufentanil.

Remifentanil

Remifentanil is an ultra-short-acting and powerful synthetic opioid. With its less side effect profile, remifentanil is widely applied in clinical work, especially in the maintenance of general anesthesia [72].

5-HTTLPR and remifentanil

In recent years, accumulating researches on pharmacogenomics of remifentanil have been successively conducted. Gene polymorphisms of serotonin transporter gene (a functional 43 bp inser-

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tion/deletion polymorphism of serotonin transporter gene (5-HTTLPR), rs25531) has been highlighted for the variation of analgesic response to remifentanil [73]. Individuals with 5-HTTLPR low expression genotype responded with more pain relief to remifentanil than individuals with 5-HTTLPR high expression genotype.

Localized in pre-synaptic neuronal membranes, serotonin transporter (5-HTT) is a key regulator of serotonin metabolism and availability. It terminates synaptic actions by transporting serotonin from the synapse back into the pre-synaptic neuron [74]. 5-HTTLPR is a known polymorphism in 5-HTT promoter region and can influence 5-HTT gene transcription [75]. Although the key role of the rostral ventromedial medulla (RVM) in opioidergic pain regulatory mechanism is well known, a separate serotonergic channel from RVM is also crucial in modulating pain transmission in the dorsal horn of the spinal cord [76]. Several animal studies have demonstrated that serotonin is involved with the clinical analgesia of opioids at the spinal cord level [77,78]. It can be inferred that individual variability in pain responses to opioid may put down to changes in 5-HTT function caused by gene polymorphism 5-HTTLPR.

TMEM8A/SLC9A9 and remifentanil

To comprehensively investigate the genetic factors underlying individual differences in remifentanil demand, a multistage genome-wide association study was carried out in patients who underwent laparoscopic-assisted colectomy. It revealed that rs199670311 of encoding transmembrane protein 8A (TMEM8A) gene and rs4839603 of encoding solute carrier family 9 member A9 (SLC9A9) gene were involved in the sensitivity of remifentanil. Carriers of A and T alleles at rs199670311 and rs4839603 were less sensitive to remifentanil during the operation [79]. To date, there have been no studies on remifentanil sensitivity changes of TMEM8A or SLC9A9 that are caused by gene polymorphisms.

Pharmacogenomics of muscle relaxants

Depolarized muscle relaxants

Succinylcholine has been introduced into anesthesia practice for nearly seventy years, and it remains to be of clinical value in some critical conditions due to its unmatchable property of rapid onset and short duration of action [80]. However, concerns over the safety of succinylcholine still remain today.

BChE and succinylcholine

Butyrylcholinesterase enzyme (BChE) is a hydrolase of succinylcholine. More than sixty BChE gene variations are considered to be responsible for the hydrolysis enzyme dysfunction or instability, which leads to approximately 65% of succinylcholine related apnea [81]. The most frequent mutation in the BChE gene is the Kalow (K) variant [82]. Bretlau et al. [83] found the mean duration of succinylcholine induce muscle relaxation was up to 4 minutes longer in K-variant patients than in wild-type patients. Another study showed that variations in the genetic sequence of BChE, especially BChE * I3E4-14C, BChE * FS126 and BChE * 328D, were closely related to prolonged duration of succinylcholine action [82]. Seven new mutation sites of BChE gene (I373T, G467S, W518R, L184S, V421A, M462I and R577H) were further identified as essential biomarkers for prolonged action of succinylcholine [84].

BChE is a serine hydrolase with the highest concentration in plasma and liver [85]. Earlier reports claimed that genetic variant of BCHE gene impaired the quaternary organization of the tetramer, and decreased the plasma concentration and activity of BChE molecules [86]. Furthermore, it has been found that patients with atypical BChE gene variant are unable to be involved in the normal metabolism of muscle relaxants [87]. Herein, what we may conclude is that BCHE gene polymorphisms appear to be a major factor in various sensitivity to succinylcholine and the occurrence of adverse complications related to it.

Non-depolarized muscle relaxants

The wonderful characteristics of succinylcholine are, however, accompanied by many unpleasant, sometimes serious adverse effects. Studies were carried out to find new fast effective non-depolarization muscle relaxant for rapid sequence induction (RSI) of general anesthesia. Among non-depolarizing muscle relaxants, rocuronium is a good option for achieving RSI [88]. Variations of several key genes, including but not limited to organic anion-transporting polypeptide 1B1 (SLCO1B1), organic anion-transporting polypeptide 1A2 (SLCO1A2), ABCB1 and genetic variants of pregnane X-receptor (NR1I2), have considerable consequences for individual pharmacokenetic differences of rocuronium.

SLCO1B1/SLCO1A2 and rocuronium

Studies found that gene variations in SLCO1B1 and SLCO1A2 could influence the pharmacodynamics of rocuronium. Clinical duration and recovery time were significantly prolonged in patients with SLCO1B1 rs2306283 AG and GG genotypes than in patients with wild-type homozygous genotypes. Similarly, signifi-

cant reduction of rocuronium elimination and the extension of were observed in patients with SLCO1A2-189-188InsA genotype [5,6].

SLCO1B1 is a kind of membrane transporter predominantly expressed at the basolateral membrane of hepatocytes. It plays a critical role in the hepatic uptake and clearance of numerous ectogenous and endogenous compounds [89]. A possible mechanism was that gene variant might weaken the transport function of SLCO1B1, which decreased the elimination rate of rocuronium in liver. SLCO1A2 is another important member of the membrane SLC proteins family. It is expressed in a substantial number of organs and determines the drug disposition [90]. The clearance of rocuronium is reported to be mediated by SLCO1A2 dependent hepatocellular uptake and biliary excretion [91]. We speculate the activity of OATP1A2 transporter could be changed due to polymorphisms, which appears to contribute to individual differences in sensitivity to rocuronium.

ABCB1 and rocuronium

The role of ABCB1 gene polymorphisms in the response to rocuronium has been well explored. The duration of rocuronium in ABCB1 rs1128503 CT and CC genotype patients were significantly shorter compared to patients in TT genotype, and the recovery time of rocuronium was significantly shorter in ABCB1 rs1128503 CC genotype patients than in CT and TT genotype patients [5]. Similarly, Qi et al. [4] conducted a study on ABCB1 gene polymorphisms in Chinese people. They found that genetic variants ABCB1 rs12720464 and rs1055302 were the vital factors contributing to the individual variability on muscle relaxation recovery.

Transporter P-gp encoded by ABCB1 has a broad spectrum of substrates including rocuronium, which can be transported by P-gp from hepatocytes to gallbladder [92]. Highly polymorphic ABCB1 gene is associated with structural and functional alterations of P-gp [93]. Moreover, ABCB1 rs1045642 C>T gene mutation could cause P-gp transporter dysfunction and interfere with the absorption and excretion mechanisms of rocuronium [94]. Accordingly, abnormal P-gp is likely to influence the biotransformation of rocuronium.

NR1I2 and rocuronium

Recent findings indicated NR1I2 gene variant might be another major contributor to the variability in rocuronium responses. The clinical duration of rocuronium were extended in NR1I2 rs2472677 and rs6785049 genotypes patients [95]. Existing results of clinical trials are too few, and the association between NR1I2 polymorphisms and individual differences of rocuronium deserves further investigation.

Pregnane X receptor encoded by NR1I2 gene is a member of the nuclear hormone receptors family [96]. It has been well documented that nuclear receptors serve as key transcription regulators to modulate the expression of enzymes and transporters which are involved in the degradation of some drugs [97,98]. Judging this background, the mutation of NR1I2 can change the activities of various transporters (ABCB1, OATP1B1, OATP1A2) and metabolizing enzymes (CYP3A4, CYP2C19, UGT1A1) that are involved in the elimination of rocuronium in vivo.

An individualized anesthesia scheme based on the patient's unique characteristics is essential to the successful operation performing and the early recovery after surgery. These characteristics include not only the clinical features such as the patient's age, gender, height, weight, et al., but also the profound genetic features. For instance, malignant hyperthermia induced by muscle relaxants and volatile anesthetics results in a high incidence of mortality. By gene analysis, patients who are susceptible to the disease can be identified. Use of opioids can cause severe nausea and vomiting, or delayed respiratory inhibition. With pharmacogenomics, those patients who are of high risk to opioids induced adverse effects can be detected. Therefore, more effective anesthesia and analgesia regimen can be made and a variety of adverse complications that are detrimental to patients' health both in the short and long term can be prevented. Over the years, studies on pharmacogenomics of narcotics are relatively few. Nevertheless, the limited findings from these researches are quite helpful and illuminating for individualizing drug administration, improving the efficacy and avoiding serious adverse effects. With the unique genetic background of an individual, a tailored anesthesia scheme could be made, which can maximize beneficial effects, minimize side effects, and relieve financial burden. We believe gene information is expected to become a part of the electronic medical record in the near future, which will be especially useful for personalized anesthesia practicing.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the cur-

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rent study are available in the PubMed.

Author Contributions

Yan Sun (Conceptualization; Validation; Writing – original draft; Writing – review & editing)
Hongyu Zhu (Validation; Writing – original draft)
Elham Esmaeili (Conceptualization; Validation)
Xue Tang (Validation)
Zhilin Wu (Validation; Writing – review & editing)

ORCID

Yan Sun, https://orcid.org/0000-0002-8614-2645
Hongyu Zhu, https://orcid.org/0000-0002-8444-8835
Elham Esmaeili, https://orcid.org/0000-0002-9677-4195
Xue Tang, https://orcid.org/0000-0002-9280-4887
Zhilin Wu, https://orcid.org/0000-0002-9179-1762

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