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Citation

Groot, J. A. N., Harmsze, A. M., Dongen, E. H. P. A. van, Knibbe, C. A. J., & Oud-Alblas, H. J. B. van. (2025). Pharmacogenetics in perioperative care: understanding the impact of genetic variants on patient management. *Journal Of Clinical Anesthesia*, 108.
doi:10.1016/j.jclinane.2025.112064

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).



Review

Pharmacogenetics in perioperative care: Understanding the impact of genetic variants on patient management

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HIGHLIGHTS

- Drug–gene interactions influence both drug metabolism and receptor sensitivity.
- Most current anesthesia guidelines overlook pharmacogenetic variability.
- Common genetic variants affect analgesia, sedation, and recovery outcomes.
- Pre-emptive genotyping may optimize drug selection and reduce complications.
- Genotype–phenotype relationships are complex and limit predictive accuracy.

ARTICLE INFO

Keywords:

Anesthesia
Perioperative care
Pharmacogenetics
Personalized medicine
Pharmacokinetics
Pharmacodynamics

ABSTRACT

Despite advances in perioperative medicine, variability in patient responses to commonly administered anesthetic and analgesic agents remains a clinical challenge. Genetic factors are increasingly proposed contributors to these interindividual differences, yet much of the supporting evidence remains preliminary, heterogeneous or insufficiently validated. Pharmacogenetics has emerged as a promising field to improve therapeutic precision. However, its clinical application in perioperative care remains limited. This narrative review critically appraises pharmacokinetic and pharmacodynamic drug–gene interactions that influence responses to routinely administered agents. Genetic variations affect multiple aspects of perioperative care, including drug metabolism and receptor sensitivity, pain processing, autonomic function, and susceptibility to complications such as post-operative nausea and vomiting and opioid-induced respiratory depression. A better understanding of drug–gene interactions may help anesthesiologists identify patients with atypical sensitivity or resistance to commonly used agents, as well as those at increased risk for perioperative complications. Integration of pharmacogenetic data into perioperative decision-making may facilitate individualized care, but broader implementation will require replication in diverse cohorts, prospective clinical validation and development of evidence-based guidelines.

1. Introduction

Advances in technology, pharmacology, and understanding of human physiology have significantly improved perioperative outcomes. However, interindividual variability in patient responses to anesthetic and analgesic agents remains a persistent clinical challenge. Interpatient variability can result in inadequate analgesia, adverse drug reactions,

prolonged hospital stays, and increased morbidity, all contributing to rising healthcare costs. Current clinical guidelines, which are largely based on population-level averages, often fail to account for interpatient variability. This highlights the limitations of a “one-dose-fits-all” approach and demonstrates the need for more personalized care.

Precision medicine, which integrates patient-specific characteristics such as age, sex, weight, comorbidities, and genetic factors into clinical

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<https://doi.org/10.1016/j.jclinane.2025.112064>

Received 5 June 2025; Received in revised form 21 October 2025; Accepted 28 October 2025

Available online 1 November 2025

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decision-making, represents a shift toward personalized care. An important component of this approach is the use of pharmacogenetic data to guide treatment. Many drugs commonly associated with adverse drug events (ADEs) are metabolized by enzymes exhibiting substantial genetic variability. These genetic differences can cause significant variability in pharmacokinetics, leading to underdosing, overdosing, or increased drug toxicity. Genetic variants also affect pharmacodynamics by altering receptor sensitivity and signal transduction, influencing drug behavior even when pharmacokinetic profiles are similar [1].

Recent pilot studies, such as the Implementation of Pharmacogenomic Decision Support in Surgery (ImPreSS) trial, have demonstrated the feasibility and practical interest among anesthesiologists in incorporating pharmacogenetics into practice [2]. In this trial, anesthesiologists accessed pharmacogenetic results preemptively in approximately 58 % of surgical cases, suggesting initial clinical interest and potential for broader implementation.

Integrating pharmacogenetic data into perioperative care can help anesthesiologists make more informed decisions about drug selection, dosing, and patient monitoring. This individualized approach may reduce adverse drug events (ADEs), thereby improving clinical outcomes, shortening hospital stays, and decreasing readmission rates. Collectively, these improvements could contribute to more sustainable healthcare spending [3].

This narrative review provides a comprehensive overview of pharmacogenetic interactions in perioperative care, focusing on routinely administered anesthetic and analgesic drugs. We examine how pharmacokinetic, pharmacodynamic, and disease-associated drug-gene interactions contribute to individual variability in clinical outcomes. Finally, we discuss current barriers to the routine implementation of pharmacogenetic data in perioperative practice. For clinical context, Fig. 1 presents a simplified workflow illustrating how pharmacogenetic data can be integrated into clinical decision-making, while Table 1 summarizes clinically actionable pharmacogenetic variants with established evidence-based guidelines.

2. Methods

A narrative review was conducted to assess current evidence regarding pharmacogenetic influences on anesthetic and analgesic management in perioperative care. A comprehensive, non-systematic search of PubMed, MEDLINE, Embase, and the Cochrane Library was performed to identify relevant peer-reviewed literature published in English through May 2025. Search terms included combinations of “pharmacogenetics,” “anesthesia,” “perioperative care,” “analgesia,”

and “drug metabolism,” along with specific gene and drug names including but not limited to CYP2D6, CYP3A4, CYP3A5, CYP2B6, UGT1A9, UGT2B7, SLC22A1 (OCT1), ABCB1, OPRM1, COMT, RYR1, CACNA1S, MC1R, GABRA1, GABRB1, GABRB2, CES2, BDNF, and propofol, fentanyl, morphine, codeine, tramadol, oxycodone, ondansetron, granisetron, succinylcholine, and volatile anesthetics. Clinical pharmacogenetic guidelines from CPIC, DPWG, and the FDA were also reviewed to incorporate current consensus recommendations [78–80].

Inclusion criteria comprised original research articles, systematic reviews, meta-analyses, and authoritative guidelines that addressed drug-gene interactions relevant to commonly used perioperative medications. Priority was given to human studies with clinically interpretable outcomes. Gene-drug pairs were classified according to their primary mechanism of action (pharmacokinetic or pharmacodynamic), with emphasis on allele frequency, phenotypic impact, ethnic variability, and potential for clinical implementation.

Evidence levels were assigned to summarize the degree of clinical confidence in each drug-gene interaction. Evidence was graded as follows: A for high-quality data from multiple randomized or well-designed observational studies, B for moderate evidence with limited or inconsistent findings, and C for preliminary or low-quality data requiring further validation. Grading was based on study design, reproducibility, sample size, and alignment with clinical guidelines from the FDA, CPIC, and DPWG.

This review conforms to the SANRA (Scale for the Assessment of Narrative Review Article) framework by providing a clearly defined objective, structured literature synthesis, and a critical appraisal of evidence. Formal methodological quality scoring and quantitative synthesis were not performed, in line with the narrative nature of the review. The goal is to provide a scientifically grounded overview that informs precision medicine strategies in anesthetic practice.

2.1. Pharmacokinetic drug-gene interactions

Cytochrome P450 (CYP450) enzymes play a central role in metabolizing a wide range of endogenous compounds and xenobiotics [4]. CYP450 activity is influenced by both intrinsic and extrinsic factors, including age, body composition, comorbid disease, inflammation, environmental exposures, drug-drug interactions, and inherited polymorphisms. Genetic variants within the CYP450 system can alter enzyme structure, catalytic efficiency, and substrate specificity, thereby influencing drug efficacy, safety, and interindividual variability in anesthetic response [5].

Although genotype provides an estimate of baseline metabolizer

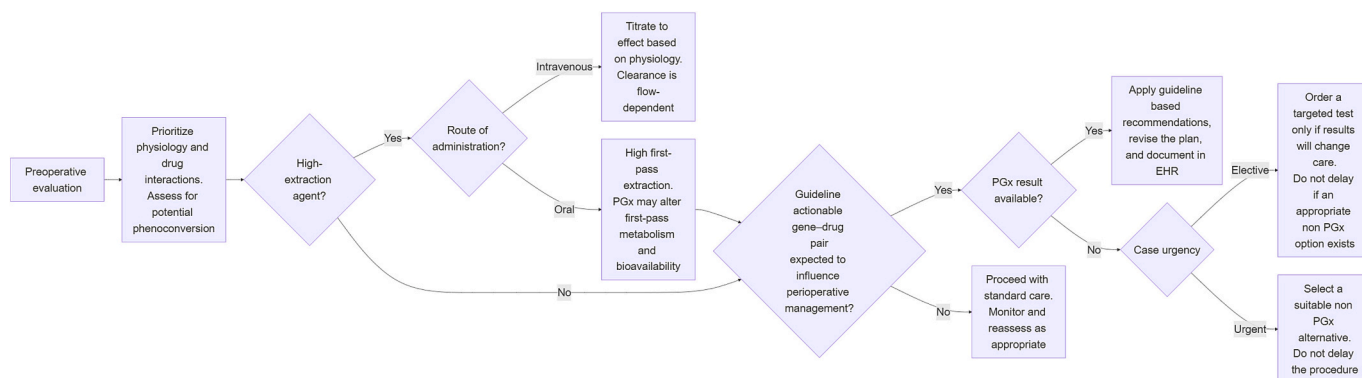


Fig. 1. Simplified perioperative PGx decision pathway. During preoperative evaluation, anesthesiologists first assess potential drug interactions and physiologic factors such as cardiac output, hepatic perfusion, renal function, and inflammation that may transiently alter drug metabolism or response. These factors are prioritized before considering genotype results. PGx testing may be appropriate in selected patients when: (1) a guideline-actionable gene-drug pair is expected to change immediate management, (2) there is a personal or family history of atypical anesthetic or analgesic responses, such as malignant hyperthermia, prolonged neuromuscular blockade, or opioid intolerance, (3) prior postoperative analgesic failure or severe adverse effects, (4) pharmacogenetically relevant comorbidities (e. g., hepatic or renal dysfunction) are present, or (5) the patient belongs to a high-risk or vulnerable population. When testing is indicated, results should be interpreted with clinical decision support or specialist input and documented in the electronic health record (EHR) to support continuity of care.

Table 1

Clinically actionable pharmacogenetic variants with established guidelines (Abbreviations: UM = ultrarapid metabolizer; PM = poor metabolizer; IM = intermediate metabolizer; FDA = U.S. Food and Drug Administration; CPIC = Clinical Pharmacogenetics Implementation Consortium; DPWG = Dutch Pharmacogenetics Working Group; EMHG = European Malignant Hyperthermia Group; MH = malignant hyperthermia).

Drug(s)	Gene	Variant(s)	Recommendation(s)	Guideline(s)	Reference(s)
Succinylcholine, Mivacurium	<i>BCHE</i>	> 75 described (e.g., atypical “A,” silent “S,” fluoride-resistant “F” alleles)	If personal/family history of prolonged paralysis: test dibucaine number or genotype; avoid or plan ventilation	FDA	[30,70,78]
Volatile anesthetics ± Succinylcholine	<i>RYR1</i>	72 EMHG-listed pathogenic variants	Treat as MH-susceptible; avoid triggering agents	FDA, CPIC	[72,75,78,79]
	<i>CACNA1S</i>	p.Arg174Trp, p.Arg1086His	If variant confirmed and RYR1 negative, follow MH precautions	FDA, CPIC	[74,75,78,79]
Codeine	<i>CYP2D6</i>	UM	Risk of morphine overdose; avoid use or reduce dose; use non-CYP2D6 alternative	FDA, CPIC, DPWG	[31,32,78–80]
		PM/IM	Risk of insufficient analgesia; consider alternative opioid or dose adjustment	FDA, CPIC, DPWG	[29,31,78–80]
Tramadol	<i>CYP2D6</i>	UM	Increased M1 levels; reduce dose or use non-CYP2D6 analgesic	FDA, CPIC, DPWG	[31,33,78–80]
		PM/IM	Reduced efficacy; use non-CYP2D6 alternative or increase dose	FDA, CPIC, DPWG	[31,33,78–80]
Ondansetron	<i>CYP2D6</i>	UM	Higher clearance, lower efficacy; use non-CYP2D6 alternative (e.g., granisetron)	CPIC	[42–44]
Opioids (general)	<i>OPRM1</i>	A118G	Anticipate higher opioid requirement for effective analgesia	CPIC	[50,55,79]
	<i>COMT</i>	Val158Met	Increased pain sensitivity. Consider multimodal pain management.	CPIC	[60,61,79]

status, perioperative conditions can acutely modify enzyme function. This discrepancy between predicted and observed metabolism is referred to as phenoconversion, in which the observed phenotype no longer matches the genotype, such as a genotypic normal metabolizer behaving as a poor metabolizer or vice versa. Phenoconversion may occur due to inflammation, concurrent medications, or organ dysfunction that inhibit or induce CYP activity. In clinical practice, it can result from CYP inhibition or induction as well as from perioperative factors such as systemic inflammation, sepsis, hypothermia, or reduced hepatic perfusion during anesthesia or cardiopulmonary bypass, all of which can downregulate multiple CYP isoforms and drug transporters. These dynamic changes can substantially alter anesthetic drug metabolism, leading to prolonged sedation, reduced analgesic efficacy, or unexpected drug accumulation despite an apparently normal genotype.

The extent to which pharmacogenetic variation and enzyme phenoconversion affect drug disposition depends strongly on the hepatic extraction characteristics of the drug. For low-extraction, or capacity-limited, drugs, hepatic clearance is primarily determined by the intrinsic metabolic capacity of the liver. In these cases, CYP phenoconversion or genetic variation that alters enzyme activity can significantly change intrinsic clearance, leading to large differences in systemic clearance and elimination half-life. This represents the clinical scenario in which variation in enzyme function exerts the greatest effect.

In contrast, for high-extraction drugs administered intravenously, clearance is mainly flow limited and approximates hepatic blood flow. Under these conditions, genetic variation and changes in enzyme activity have little influence on clearance unless inhibition is so pronounced that the drug transitions out of the high-extraction category. In this setting, hemodynamic factors such as cardiac output and hepatic perfusion play a greater role in determining clearance than enzyme activity.

For high-extraction drugs administered orally, pharmacogenetic variation or phenoconversion can alter first-pass metabolism, thereby changing bioavailability and systemic exposure. This represents a route-specific effect on first-pass extraction rather than a change in intravenous clearance.

In general, for drugs with a high hepatic extraction ratio, patient-specific physiological factors such as age, weight, and cardiac function exert a greater influence on clearance and dosing than genetic variation in metabolic enzymes. However, in conditions associated with reduced cardiac output or impaired liver perfusion, such as heart failure, shock, or hypovolemia, genetic and environmental differences that are usually

of limited importance may become increasingly relevant.

The main pharmacokinetic gene–drug interactions discussed are listed in Table 2, while Fig. 2 illustrates the various genetic mechanisms that influence pharmacokinetic pathways.

2.2. Propofol

Propofol (2,6-diisopropylphenol) is primarily metabolized in the liver through hydroxylation and glucuronidation pathways. Enzymes like CYP2B6, accounting for approximately 20–40 % of its metabolism, and CYP2C9 play central roles in this process [6]. However, because propofol is a high hepatic extraction ratio drug, its clearance is predominantly determined by hepatic blood flow rather than enzyme activity. As a result, factors affecting cardiac output and liver perfusion typically have a more pronounced effect on propofol pharmacokinetics than genetic polymorphisms do.

Nevertheless, genetic variants can still influence an individual's response to propofol by altering both metabolic rates and receptor sensitivities [7]. For instance, natural variants in the *UGT1A9* promoter region have been associated with variations in glucuronidation activity, potentially impacting propofol metabolism [8]. Specific *UGT1A9* variants, such as *UGT1A9-1887 T > G* and *UGT1A9-331C > T*, have been linked to higher dosing requirements and increased clearance of propofol, respectively [9]. The reported minor allele frequencies (MAFs) for these *UGT1A9* variants typically range from 5 to 20 % but can be higher in certain ethnic groups [10]. Similarly, polymorphisms in *CYP2B6*, one of the most variable cytochrome P450 genes, have been studied for their effects on propofol metabolism. The *CYP2B6**6 polymorphism, notably prevalent in Sub-Saharan African populations with an allele frequency of 36.6 %, has been associated with higher plasma propofol levels following bolus administration [11]. Across other ethnic groups, minor allele frequency (MAF) for *CYP2B6**6 can range from 10 to 30 % [10]. However, the clinical significance of these findings may be limited due to small sample sizes and marginal statistical significance when controlling for confounding factors. Moreover, the individual influence of such genetic variants on propofol requirements is estimated to be relatively modest, around 7 % [12]. Recent research has explored integrating genetic information into target-controlled infusion models to better predict infusion rates for maintaining desired target concentrations [13]. However, due to propofol's predominantly flow-dependent clearance, the clinical advantages of personalized dosing models may be limited.

Table 2

Pharmacokinetic drug–gene interactions for commonly used drugs. Evidence grade: A = high-quality evidence from multiple randomized or well-designed observational studies; B = moderate evidence from limited studies or inconsistent results; C = preliminary or low-quality evidence requiring further confirmation (Abbreviations: UM = ultrarapid metabolizer; PM = poor metabolizer; IM = intermediate metabolizer; FDA = U.S. Food and Drug Administration; CPIC = Clinical Pharmacogenetics Implementation Consortium; DPWG = Dutch Pharmacogenetics Working Group; PONV = postoperative nausea and vomiting).

Drug(s)	Gene	Variant Allele(s)	Mechanism of Action	Effect of Variant	Clinical Relevance	Guidelines Available	Quality of evidence	Reference(s)
Succinylcholine, Mivacurium	<i>BCHE</i>	> 75 identified mutations	Reduced pseudocholinesterase activity slowing metabolism	Prolonged paralysis, apnea	High; preoperative testing advised if family/personal history present	Yes (FDA)	A	[30,70,78]
Propofol	<i>CYP2B6</i>	*6 (c.516G > T, rs3745274)	Decreased enzyme activity	Slight increase in plasma concentration	Limited; minor impact outweighed by physiological factors	No	C	[11,12]
	<i>UGT1A9</i>	−188T > G (rs6731242); 331C > T (rs10929303)	Altered glucuronidation activity	Minor increase in clearance	Limited; clinically insignificant compared to physiological variables	No	C	[9]
Fentanyl	<i>CYP3A4</i>	*22 (c.522-191C > T, rs35599367)	Reduced enzyme expression	Slight increase in plasma levels	Limited; rarely necessitates dose adjustments	No	C	[15]
	<i>CYP3A5</i>	*3 (6986 A > G, rs776746)	Decreased enzyme activity	Slight increase in plasma levels	Limited; clinical impact minor compared to physiological factors	No	C	[16]
	<i>ABCB1</i>	1236C > T (rs1128503); 2677G > T/A (rs2032582); 3435C > T (rs1045642)	Altered drug efflux transporter function	Earlier respiratory depression	Moderate; increased monitoring advisable in susceptible patients	No	B	[18,19]
Morphine	<i>UGT2B7</i>	−161C > T (rs7668258); 802C > T (rs7439366)	Altered glucuronidation activity	Slightly reduced active metabolite formation	Limited; minimal clinical impact, typically no dosing changes required	No	C	[24]
	<i>SLC22A1</i>	Arg61Cys (rs12208357); Gly401Ser (rs34130495); Gly465Arg (rs34059508); Met420del (rs72552763)	Reduced transporter function	Increased morphine levels; higher PONV risk (children)	Moderate in pediatrics due to adverse effects; limited in adults	No	B	[25,26]
Codeine	<i>CYP2D6</i>	PM/IM phenotype	Decreased metabolic enzyme activity	Reduced analgesic efficacy	High; alternative analgesics strongly recommended	Yes (FDA, CPIC, DPWG)	A	[29,31,78–80]
		UM phenotype	Increased enzyme activity	Increased toxicity risk	High; strongly advised to avoid codeine	Yes (FDA, CPIC, DPWG)	A	[31,32,78–80]
Tramadol	<i>CYP2D6</i>	PM/IM phenotype	Reduced enzyme activity	Reduced analgesic efficacy	High; alternative analgesics or dosing adjustments recommended	Yes (FDA, CPIC, DPWG)	A	[31,33,78–80]
		UM phenotype	Increased enzyme activity	Increased toxicity risk	High; alternative analgesic or dose reduction recommended	Yes (FDA, CPIC, DPWG)	A	[31,33,78–80]
Ondansetron	<i>CYP2D6</i>	UM phenotype	Increased enzyme activity	Reduced antiemetic efficacy	High; alternative antiemetics recommended	Yes (CPIC)	A	[42–44]

2.3. Fentanyl

Fentanyl exhibits interindividual differences in both pharmacokinetics and dynamics, partially attributable to genetic polymorphisms affecting enzymes like *CYP3A4* and *CYP3A5* [14]. Variants such as *CYP3A4**22 and *CYP3A5**3 have been associated with altered fentanyl plasma concentrations [15,16]. However, similar to propofol, fentanyl is classified as a high hepatic extraction ratio drug, meaning its elimination is more dependent on hepatic blood flow than on enzymatic activity. Therefore, despite genetic variations in hepatic enzymes, their role in

fentanyl metabolism may be relatively minor compared to physiological factors like cardiac output. Studies indicate that polymorphisms in *CYP3A4* and *CYP3A5* have limited impact on fentanyl's pharmacokinetic variability [17]. Additionally, polymorphisms in transporter proteins like *ABCB1* have been explored, revealing some association with clinical outcomes such as respiratory depression [18,19].

ABCB1, also known as P-glycoprotein (P-gp), facilitates ATP-dependent transport of drugs and other substrates across cell membranes [20]. As an efflux pump, *ABCB1* actively reduces intracellular drug concentrations, leading to decreased drug efficacy or drug

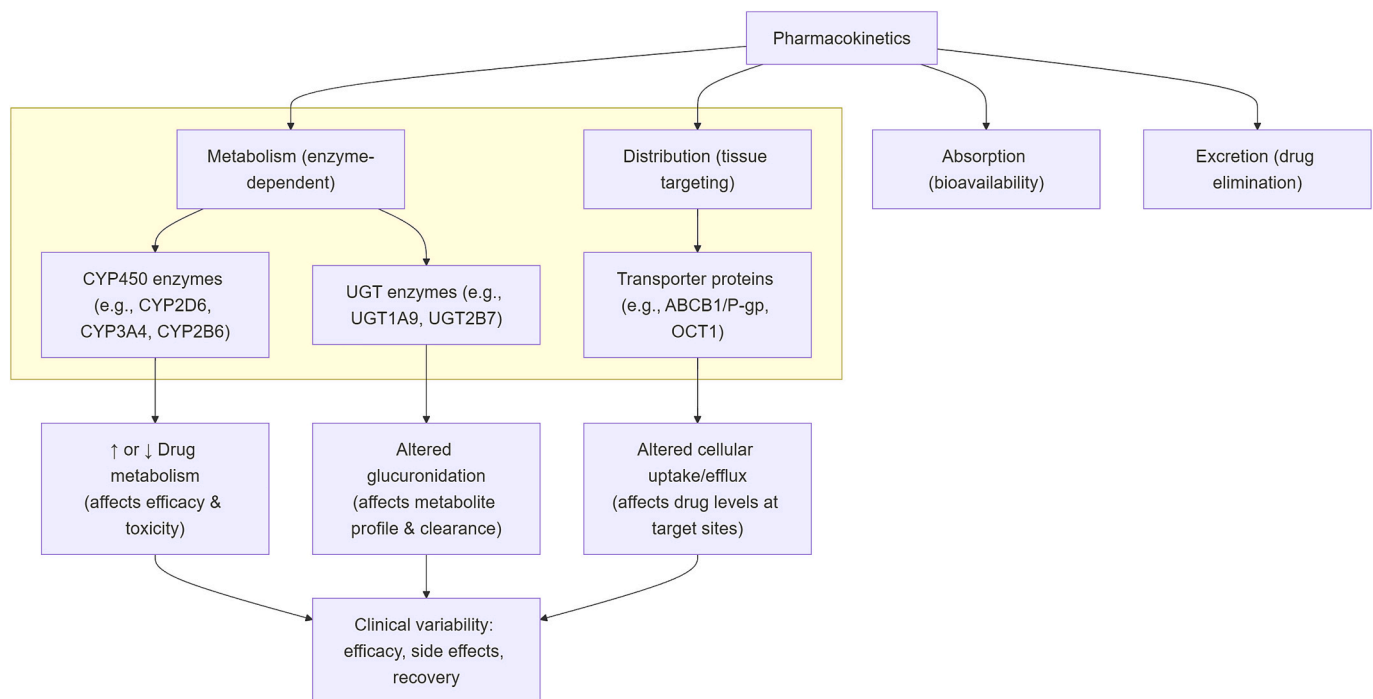


Fig. 2. Schematic representation of key pharmacokinetic processes (absorption, distribution, metabolism, and excretion) and their principal genetic determinants. Polymorphisms in metabolic enzymes (such as CYP450 isoforms and UGTs) and transporter proteins (such as ABCB1/P-gp and OCT1) can influence drug clearance, therapeutic profiles, and toxicity risks. Within the perioperative context, these genotype-dependent effects may be modified by phenoconversion, driven by dynamic physiologic alterations such as changes in hepatic blood flow, cardiac output, or inflammatory state, which can transiently change the functional impact of underlying genetic variation.

resistance [21]. The role of ABCB1 has also been explored in the context of anesthesia. A Korean study showed that carriers of the variant alleles 1236 T, 2677 T/A, and 3435 T exhibited earlier respiratory depression in response to fentanyl compared to patients with the corresponding wild-type or more resistant genotypes [18]. Notably, these three SNPs are common, with variant allele frequencies often ranging between 30 % and 60 %, depending on ethnicity [10]. Supporting these findings, another study demonstrated significant associations between ABCB1 polymorphisms and clinically relevant opioid-induced respiratory depression, resulting in prolonged recovery room stays [19].

2.4. Morphine

Morphine is metabolized by UGT2B7 into morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Although M6G is a potent metabolite, its analgesic effect may be limited by its low concentration. Conversely, the major metabolite M3G, with its neuroexcitatory properties, can lead to side effects including hyperalgesia, allodynia, and postoperative nausea and vomiting [22,23]. Morphine is classified as a medium extraction ratio drug, indicating that mutations affecting glucuronidation activity may influence clinical outcomes. While the common allelic variant *UGT2B7*2* does not appear to significantly affect the metabolism of morphine, data suggest that the *-161C/T* and *802C/T* promoter variants appear to lower M6G/morphine ratios [24]. However, while M6G is more potent than morphine, its concentrations are low by comparison. Therefore, the clinical relevance of genetic variations affecting the M6G/morphine ratio may be limited, as small variances in already low circulating M6G levels might not translate into relevant clinical outcomes.

The organic cation transporter 1 (OCT1), encoded by the *SLC22A1* gene, facilitates the uptake of morphine into liver cells, which is directly related to the extent of its metabolism. Loss-of-function polymorphisms within *SLC22A1*, including *Arg61Cys*, *Cys88Arg*, *Gly401Ser*, *Gly465Arg*, and *Met420del*, have been shown to inhibit OCT1-mediated uptake of

morphine [25]. These polymorphisms exhibit varying frequencies in European populations, with frequencies ranging from approximately 1 % to 15 % [10]. A 2017 study investigated the association between these *SLC22A1* genotypes and morphine-related adverse outcomes in children aged 6–15 years undergoing surgery [26]. Children carrying certain *SLC22A1* polymorphisms required significantly less total morphine (median 0.24 mg/kg) compared to non-carriers (median 0.27 mg/kg; $p = 0.028$). Despite reduced morphine use, these children experienced higher rates of postoperative complications, including postoperative nausea and vomiting (PONV) and respiratory depression, leading to prolonged recovery room stays (>90 min). Specifically, the *Arg61Cys* T allele (rs12208357) was associated with a 2.2-fold increased odds of PONV and a 3.3-fold increased odds of prolonged recovery room stays due to PONV. Meanwhile, homozygous carriers of *Met420del* (rs72552763) had a 9.5-fold increased risk of respiratory depression, resulting in extended hospital stays [26].

Importantly, differences in the prevalence of these polymorphisms across ethnic groups have also been observed. Studies indicate that Caucasian children are more likely to carry these functional variants, whereas African American children predominantly carry the wild-type allele, which may contribute to differential drug response and risk profiles between populations [27].

Interestingly, more recent studies have found no significant influence of OCT1 genotypes on the pharmacokinetics of morphine in adult surgical patients, suggesting a possible age-dependent effect of these polymorphisms [28]. However, direct comparisons between pediatric and adult populations have not yet been studied in a clinical context.

2.5. Codeine and tramadol

Codeine and tramadol are both metabolized by the polymorphic enzyme CYP2D6, whose enzymatic activity varies widely among individuals, ranging from poor metabolizers (PMs) to ultrarapid metabolizers (UMs). Previous research has shown that the frequency of these

phenotypes differs significantly between populations and sub-populations [29]. PMs have the highest prevalence in Europeans due to the high frequency of the *CYP2D6**4 allele (~10 %) and a lower prevalence in African and Southeast Asian populations. IMs are more frequent in populations where alleles such as *CYP2D6**17 and *CYP2D6**41 are common, including African and Middle Eastern populations. UMs are most common among the Mozabite people (Berbers, North Africa, ~39.5 %), non-Austronesian Melanesians (~21.5 %), and Druze populations in the Middle East (~21.4 %), while their frequency is lower in European populations (~2–3 %) compared to East-African populations (~20–29 %) [29]. Consequently, an increasing number of pharmacogenetic guidelines across different medical specialties have been published to address *CYP2D6* drug–gene interactions [31]. Given the pronounced interindividual variations in *CYP2D6* activity and their implications for drug behavior, prescribing policies for these medications are being reevaluated in light of pharmacogenetic research.

Codeine primarily undergoes *CYP2D6*-mediated *O*-demethylation, resulting in the active metabolite morphine. Among the recognized phenotypes, extensive metabolizers (EMs) exhibit normal *CYP2D6* activity, resulting in efficient conversion of codeine to morphine and thus effective analgesia. In contrast, PMs, characterized by reduced *CYP2D6* activity, may experience reduced conversion to morphine and potentially lower analgesic effects. Intermediate metabolizers (IMs) exhibit partial conversion of codeine to morphine depending on their *CYP2D6* activity. UMs, characterized by increased *CYP2D6* activity, rapidly convert codeine to morphine, which can lead to overdosing and side effects. Previous research indicates that UMs have, on average, 50 % higher plasma morphine concentrations compared to EMs [32]. Given the extensive interindividual variability in *CYP2D6* activity, current guidelines typically advise against using codeine at standard or higher doses in ultrarapid metabolizer (UM) adults because of the risk of excessive morphine formation and resultant toxicity (including respiratory depression). Some pharmacogenetic guidelines or regulatory agencies recommend avoiding codeine altogether in UM patients, especially in children and breastfeeding mothers. In circumstances where codeine is still considered, low doses and close monitoring are suggested. However, for UMs, experts advise using alternative analgesics not dependent on *CYP2D6* activity [31].

The metabolism of tramadol also relies on *CYP2D6*, which converts tramadol into its more potent active metabolite, *O*-desmethyltramadol (M1). Previous research has found that PMs exhibit a slower elimination rate of tramadol, resulting in lower circulating M1 levels and less effective analgesia. Conversely, UMs show elevated M1 concentrations, improving the analgesic response but also increasing the risk of side effects [33]. Therefore, guidelines advise that for tramadol, UMs should receive an alternative drug not significantly metabolized by *CYP2D6* or the dose should be decreased to 40 % of the commonly prescribed dose [31].

2.6. Oxycodone

Oxycodone is primarily metabolized in the liver by *CYP3A4*, which accounts for approximately 50 % of the total metabolism via *N*-demethylation, resulting in the formation of noroxycodone. In parallel, *CYP2D6* facilitates the *O*-demethylation of about 10 % of administered oxycodone, generating the pharmacologically active oxymorphone. Additionally, *CYP2D6* converts noroxycodone into noroxymorphone; however, since noroxymorphone barely crosses the blood–brain barrier, oxycodone and oxymorphone are considered the active components therapeutically [34,35]. While some studies have established a significant relationship between the *CYP2D6* genotype and postoperative opioid consumption, others have reported no differences in post-operative analgesic effects among different *CYP2D6* genotypes [36,37]. Current clinical guidelines, unlike for tramadol and codeine, do not recommend dosage adjustments for oxycodone based on *CYP2D6* genotypes [31]. However, caution is advised in situations where *CYP3A*

inhibition may occur, such as with the concurrent administration of potent *CYP3A* inhibitors like ketoconazole. Inhibition of *CYP3A4* can shift oxycodone metabolism toward *CYP2D6*, making the pharmacokinetics of oxycodone more dependent on the polymorphic *CYP2D6*, potentially resulting in variable efficacy and side effects [38].

2.7. Ondansetron

The cytochrome P450 system is also responsible for the metabolism of most commonly used antiemetics. For instance, ondansetron is predominantly metabolized through hydroxylation by both *CYP3A4* and *CYP2D6*, whereas granisetron is mainly metabolized by *CYP3A4* [39]. Although ondansetron is administered as a racemic mixture of R- and S-enantiomers, its metabolism appears to be enantiomer-specific. A 2011 study examined the relationship between variations in *CYP2D6* and *CYP3A* and plasma concentrations of ondansetron enantiomers [40]. Poor metabolizers (PMs) had notably higher S-ondansetron levels than ultrarapid metabolizers (UMs), whereas R-enantiomer concentrations remained consistent across different *CYP2D6* subcategories. Previous animal studies revealed that both racemic ondansetron and S-ondansetron significantly extended the QTc interval, whereas R-ondansetron did not [41]. The researchers further suggested that S-ondansetron could exhibit greater inhibitory effects on the Bezold–Jarisch reflex. In the context of guiding antiemetic therapy, previous research has shown that patients carrying three copies of *CYP2D6*, consistent with ultrarapid metabolism, have higher ondansetron failure rates compared to other subtypes [42,43]. As a result, the Clinical Pharmacogenetics Implementation Consortium has developed ondansetron therapy guidelines based on genotype. These guidelines recommend standard (ondansetron) treatment for individuals who are extensive metabolizers, while ultrarapid metabolizers (UMs) are advised to use alternative drugs, such as granisetron, which are not primarily metabolized by *CYP2D6* [44].

2.8. Pharmacodynamic drug-gene interactions

Similar to genetic variations that affect drug metabolism, mutations in genes encoding drug receptors and downstream signaling pathways can also lead to altered drug responses. Discussed pharmacodynamic drug–gene interactions are summarized in Table 3, while Fig. 3 illustrates the different mechanisms by which genetic variations can influence drug response.

2.9. GABRA and GABRB

Variations in the genes encoding GABA receptor subunits have been linked to differences in propofol sensitivity. For instance, a recent Chinese study found that individuals carrying the variant G allele of the *GABRA1* rs4263535 gene required a significantly shorter time for their bispectral index (BIS) levels to decrease to 60 following intravenous propofol infusion. In contrast, carriers of the variant T allele of the *GABRB2* rs3816596 gene needed significantly more time for their BIS levels to reach target levels [45]. Additionally, another study showed that the rs4263535 polymorphism in the *GABRA1* gene was associated with both the depth of sedation and the dosage requirements during midazolam-induced sedation, with patients having the A/A wild-type genotype requiring lower doses to achieve desired sedation levels [46]. However, the clinical relevance of these findings may be limited due to relatively small sample sizes and minor differences observed in sedation times and dosage requirements.

Studies have also explored the impact of genetic variations on cardiovascular responses to propofol, particularly changes in mean arterial pressure (MAP). Notably, carriers of the variant C allele of the *GABRA1* polymorphism and the variant T allele of the *GABRB2* experienced a less pronounced decrease in MAP following propofol infusion [45]. A related study examined the factors contributing to hemodynamic instability during anesthesia with propofol and opioids. It found that specific

Table 3

Pharmacodynamic (receptor-level) drug–gene interactions of commonly used drugs.

Drug(s)	Gene	Variant Allele(s)	Mechanism of Action	Effect of Variant	Clinical Relevance	Guidelines Available	Quality of evidence	Reference(s)
Volatile Anesthetics, Succinylcholine	<i>RYR1</i>	72 considered diagnostic	Increased calcium release	Greatly increases malignant hyperthermia (MH) susceptibility	High; genetic screening recommended if family history of MH	Yes (FDA, EMHG, CPIC)	A	[72,75,78,79]
	<i>CACNA1S</i>	2 considered diagnostic: <i>p.Arg174Trp</i> (rs772226819), <i>p.Arg1086His</i> (rs1800559)	Altered voltage sensing, increased calcium influx	Increased but less common risk for MH	High; consider testing if no <i>RYR1</i> mutation identified	Yes (FDA, EMHG, CPIC)	A	[74,75,78,79]
Propofol	<i>GABRA1</i>	rs4263535 (often noted as A > G)	Altered GABA receptor sensitivity	Shorter time to achieve sedation target	Limited; minor sedation effect, no dosing changes required	No	C	[45]
		rs1157122 (often noted as G > C)	Altered cardiovascular response	Smaller reduction in mean arterial pressure	Limited; minimal cardiovascular impact	No	C	[45]
	<i>GABRB2</i>	rs3816596 (often noted as C > T)	Altered GABA receptor sensitivity	Delayed sedation onset with propofol	Limited; minor clinical effect, no adjustments needed	No	C	[45]
		rs76774144 (often noted as C > T)	Altered cardiovascular response	Reduced propofol-induced hypotension	Limited; modest effect, standard care usually sufficient	No	C	[45]
	<i>GABRB1</i>	rs4694846 (CT/CC genotype)	Altered GABA receptor signaling	Higher heart-rate fluctuations	Limited; minor impact, typically no dosing changes required	No	C	[47]
	<i>CES2</i>	rs8192925 (AA genotype)	Altered propofol metabolism	Greater heart-rate variability under anesthesia	Limited; metabolic changes minor, no dosing implications	No	C	[47]
	<i>BDNF</i>	rs2049046 (AA genotype)	Altered neurotrophic signaling	Blood-pressure swings during propofol anesthesia	Limited; manageable within routine care	No	C	[47]
Opioids	<i>GABBR2</i>	rs1167768 (GG genotype)	Altered GABA receptor signaling	Variations in blood pressure after induction	Limited; modest clinical significance, no changes typically needed	No	C	[47]
	<i>OPRM1</i>	<i>c.118 A > G</i> (<i>p. Asn40Asp</i> , rs1799971)	Altered μ -opioid receptor function	Higher pain threshold, increased opioid dose requirement	Moderate; genotype may guide opioid dosing decisions	Yes (CPIC)	B	[50,55,79]
	<i>COMT</i>	<i>c.472G > A</i> (<i>p. Val158Met</i> , rs4680)	Reduced catecholamine metabolism and altered pain modulation	Altered morphine efficacy and increased hyperalgesia with repeated pain exposure	Moderate; potential benefit from genotype-informed analgesia	Yes (CPIC)	B	[60,61,79]
	<i>MC1R</i>	Various loss-of-function mutations	Reduced MC1R activity altering endogenous opioids	Higher anesthetic/opioid requirements	Moderate; important in red-haired patients, awareness advised	No	B	[66,68,69]

Evidence grade: A = high-quality evidence from multiple randomized or well-designed observational studies; B = moderate evidence from limited studies or inconsistent results; C = preliminary or low-quality evidence requiring further confirmation (Abbreviations: MH = malignant hyperthermia; FDA = U.S. Food and Drug Administration; CPIC = Clinical Pharmacogenetics Implementation Consortium).

genetic variants such as the CT/CC genotype of *GABRB1* and the AA genotype of *CES2* were associated with increased heart rate instability. Additionally, the AA genotype of *BDNF* and the GG genotype of *GABBR2* were linked to more pronounced fluctuations in mean arterial pressure [47].

2.10. *OPRM1*

The mu-opioid receptor gene (*OPRM1*) A118G polymorphism has been implicated in modulating pain responses associated with opioid analgesia, substantially contributing to interindividual variability. Allele frequencies of this polymorphism vary widely across different ethnic groups, generally ranging from 10 % to 30 % worldwide [48,49]. Specifically, the minor allele (G) is more prevalent in East Asian

populations, where its frequency can reach between 30 % and 50 %. In contrast, African populations exhibit much lower frequencies of the G allele, typically ranging from 1 % to 5 % [10]. A 2005 post-mortem study discovered that brain tissue from heterozygous individuals demonstrated 1.5 to 2.5 times higher levels of A118G mRNA compared to G118 mRNA [50]. Moreover, experimental studies have found that carriers of the 118G allele exhibit higher pressure pain thresholds than those with the common allele, suggesting a genetic contribution to mechanical pain responses [51]. Research, including genome-wide studies and meta-analyses, links the G allele (A118G) to increased opioid use and a lower risk of postoperative nausea and vomiting (PONV). Specifically, a 2015 Korean study discovered that the A118G polymorphism provided protection against PONV [52], and a Japanese study demonstrated that various *OPRM1* polymorphisms significantly

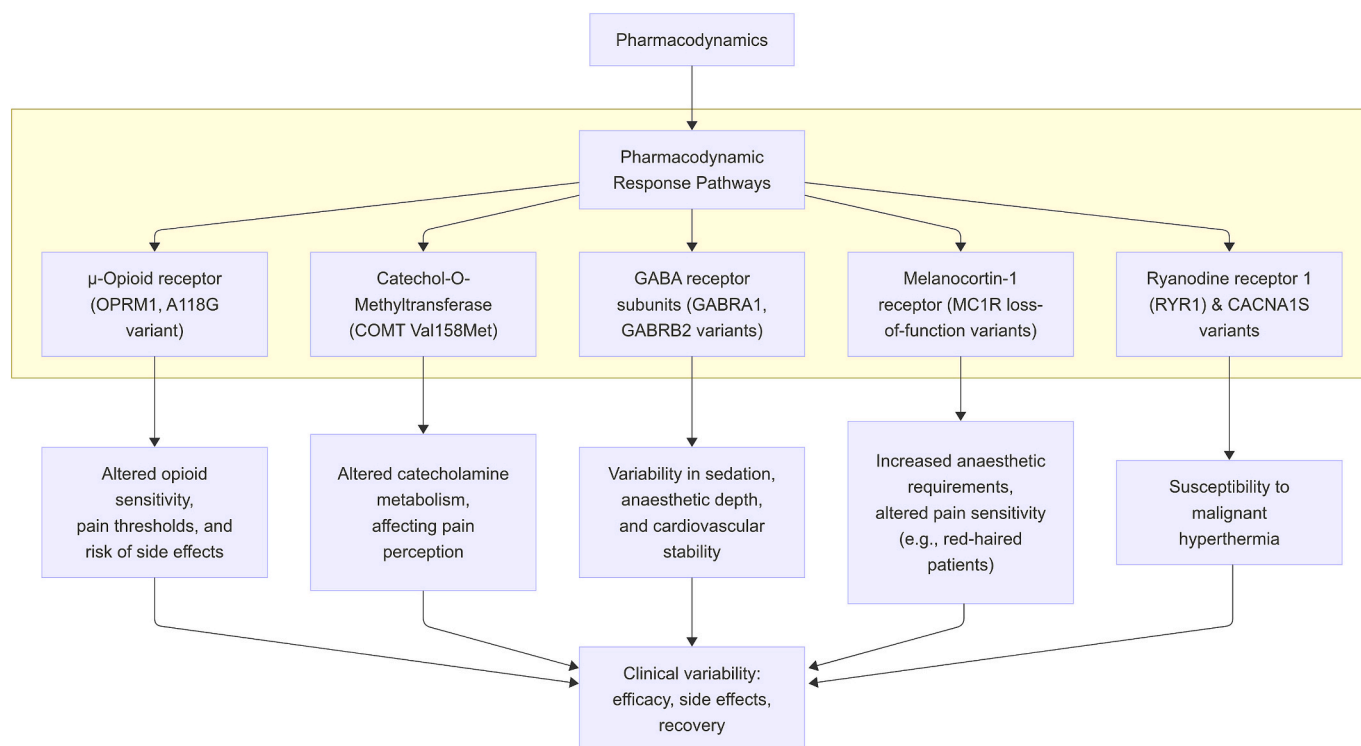


Fig. 3. Schematic representation of pharmacodynamic pathways and associated genetic variants that modulate anesthetic and analgesic responses. Variations in *OPRM1*, *COMT*, *GABA* receptor subunits, *MC1R*, and *RYR1/CACNA1S* can alter analgesic sensitivity, anesthetic depth, and susceptibility to adverse events such as malignant hyperthermia. Within the perioperative context, these genotype-dependent effects are further modulated by physiologic and pharmacologic factors which may transiently change the functional impact of underlying genetic variation.

reduced the severity of PONV related to general anesthesia and opioid administration [53]. Furthermore, the clinical implications of *OPRM1* polymorphisms extend beyond direct pain perception, as demonstrated by research examining associations with various neurotransmitter systems, personality traits, and placebo responses [54]. Interestingly, *A118G* carriers displayed diminished baseline μ -opioid receptor availability in regions crucial for pain and affective regulation. While the polymorphism did not influence pain-induced endogenous opioid release, it affected the dopamine response, with AA homozygotes exhibiting a muted response within the nucleus accumbens to painful stimuli [54]. In therapeutic settings, this polymorphism may impact treatment efficacy, as carriers of the variant G allele showed reduced placebo-induced μ -opioid system activation in the anterior insula, amygdala, nucleus accumbens, thalamus, and brainstem, with lower dopamine D2/3 activation in the nucleus accumbens post-placebo administration [54]. Meta-analyses further underscore the clinical relevance of the *OPRM1 A118G* polymorphism, revealing that G-allele carriers require higher opioid doses postoperatively, suggesting that the polymorphism may drive variability in opioid response [55]. Additionally, the *A118G* polymorphism has been linked to opioid dependence. Therefore, understanding and accounting for different *OPRM1* polymorphisms may help anesthesiologists identify at-risk patients who could benefit from alternative, non-opioid pain management strategies.

2.11. *COMT*

COMT (catechol-O-methyltransferase) is a gene that encodes the *COMT* enzyme, involved in the metabolism of catecholamine neurotransmitters such as dopamine, norepinephrine, and epinephrine. The enzyme is expressed throughout the body, with particularly high expression in the liver and nervous system. *COMT* polymorphisms have been associated with a range of phenotypes, including several psychiatric conditions, substance use disorders, and neurological disorders

such as Parkinson's disease [56,57]. Increasing evidence indicates that *COMT* polymorphisms can impact pain sensation. One notable variant, *Val158Met*, involves a substitution from valine to methionine at position 158 of the *COMT* protein, resulting in a three- to four-fold reduction in enzyme activity [58,59]. The Met allele occurs in roughly 25–30 % of Caucasians, with even higher frequencies reported in some East Asian groups [10]. A 2003 study found that carriers of the *Met158* allele demonstrated diminished responses to pain within the regional μ -opioid system and experienced higher sensory and affective ratings of pain, while those homozygous for the *Val158* allele exhibited opposite effects [60]. Subsequent research involving 102 surgical patients undergoing lower abdominal surgery showed that heterozygous patients required significantly less morphine for postoperative pain management and experienced fewer side effects, such as nausea and sedation, than non-carriers of the variant allele [61]. Specifically, patients with combined *OPRM1 A118G* and *COMT G194A* polymorphisms required an average of 51.9 mg of morphine over 48 h, significantly less than the 71.6 mg required by patients homozygous for *OPRM1 A118* [61]. Additionally, only 18 % of these heterozygous patients needed antiemetic treatment, compared to 37 % in the homozygous wild-type group, indicating a reduction in side effects like nausea and sedation [61]. Furthermore, a study on Caucasian cancer patients revealed that those with the Val/Val genotype needed significantly higher morphine doses for adequate pain management than carriers of the Val/Met and Met/Met genotypes [62]. A 2013 study provided additional evidence of the increased pain sensitivity in Met/Met patients compared with Val/Met and Val/Val patients undergoing morphine treatment after cardiac surgery [63]. A more recent 2020 investigation assessed the impact of *COMT* polymorphisms on acute, chronic, and experimental thermal pain in cardiac surgery patients, using a randomization protocol between fentanyl and remifentanyl. It was found that patients in the fentanyl group with a high-pain sensitivity haplotype of *COMT* required less postoperative morphine than those with an average-pain sensitivity haplotype [64]. In

this study, the *COMT* haplotype was not associated with postoperative morphine consumption for patients who received remifentanyl. In contrast, another investigation involving 43 healthy participants examined the influence of the *Val158Met* polymorphism on pain sensitivity and remifentanyl-induced hyperalgesia [65]. Despite no initial differences in pain ratings across different genotypes, results indicated that homozygous carriers of the *Met158* allele reported significantly more pain following repeated painful stimuli after the administration of remifentanyl. The authors suggest that the *COMT* polymorphism may more prominently affect individuals with an already compromised inhibitory system, such as those suffering from chronic pain.

2.12. *MC1R* Gene variants

Red hair is a phenotype resulting from mutations in the melanocortin-1 receptor (*MC1R*) gene, which affects skin and hair pigmentation. These *MC1R* variants not only influence pigmentation but also have been associated with altered pain sensitivity and opioid analgesic requirements [66]. Studies have shown that individuals with red hair may exhibit increased sensitivity to thermal pain and may require higher doses of anesthetics like desflurane [67]. The *MC1R* gene is involved in the regulation of the endogenous opioid system, and mutations can lead to decreased efficacy of certain analgesics. In mouse models, *MC1R*-deficient mice displayed altered responses to pain and opioids, suggesting a link between *MC1R* function and nociception [66]. The mechanism is thought to involve an imbalance in the melanocortin and opioid receptor systems. Reduced *MC1R* activity may lead to lower levels of melanocyte-stimulating hormone (MSH), which in turn affects the modulation of pain through opioid pathways. This can result in altered analgesic responses, necessitating dose adjustments for effective pain management in red-haired individuals [68,69].

2.13. Neuromuscular blockade

Pseudocholinesterase deficiency, along with malignant hyperthermia, is among the earliest well-documented pharmacogenetic phenomena in anesthesia. Choline esters are metabolized by acetylcholinesterase (AChE) in neurons and PChE, also known as butyrylcholinesterase (BChE), in plasma. PChE metabolizes drugs like succinylcholine, mivacurium, and ester-type local anesthetics. The dibucaine number (DN) measures PChE activity inhibition by dibucaine. Normal DN values are >80, intermediate values (40–70) indicate heterozygosity, and values <30 are atypical. Over 98 % of the population carries the “usual” (U) allele, showing normal enzyme activity and typical drug responses. However, carriers of variant alleles can experience prolonged apnea and paralysis after succinylcholine administration. Among over 75 BChE gene variations, the most common is the Kalow allele, present in 20–30 % of Caucasians [10,30,70]. It reduces enzyme activity by ~30 %, causing mild paralysis prolongation. In clinical practice, however, these individuals are often lumped under “normal” or “usual” phenotypes if the reduction in enzyme activity does not approach the degree seen with the atypical or silent alleles. The Atypical (A, 209 A > G) allele, with a 1–2 % frequency, reduces enzyme activity by 60–70 %. Homozygotes (~1 in 3500) may experience apnea and paralysis lasting over two hours after succinylcholine or mivacurium use. Rare alleles include the Silent (S) allele, reducing enzyme activity to 0–2 %, causing apnea lasting over four hours in homozygotes (~1 in 100,000), and the Fluoride-resistant (F) allele, reducing activity by ~60 %, affecting ~1 in 150,000 individuals [70]. Current guidelines recommend testing only for individuals with a personal or family history of prolonged paralysis after succinylcholine or mivacurium administration. Despite clear connections between *BChE* gene variations and prolonged muscle relaxation, diagnostic approaches still primarily rely on the dibucaine number to assess PChE activity rather than on genetic sequencing. This underscores the ongoing importance of phenotypic assays, particularly given the variability in how genetic variants

translate to clinical outcomes.

2.14. Malignant hyperthermia

Malignant hyperthermia (MH) is a rare but potentially fatal condition characterized by a hypermetabolic response to volatile anesthetics and succinylcholine, leading to muscle rigidity, hyperthermia, acidosis, and ultimately multi-organ failure. When not identified preoperatively, rapid recognition and intervention are essential to reduce mortality. The prevalence of MH is estimated between 1 in 10,000 and 1 in 250,000 administered anesthetics, occurring more frequently in males than females at a male-to-female ratio of 2:1 [71,73]. Young people are more often affected; the mean age is 18.3 years, and 52.1 % of reactions occur in children under 15 [72,73].

MH is inherited in an autosomal dominant manner; individuals with one mutant *RYR1* allele have a 50 % chance of passing it to their offspring. Genetic variations in *RYR1* and *CACNA1S*, which govern calcium homeostasis and excitation–contraction coupling in skeletal muscle, underlie most cases of MH. *RYR1* encodes the sarcoplasmic-reticulum calcium-release channel central to calcium-induced calcium release (CICR); pathogenic variants are also associated with other skeletal-muscle disorders [77]. *CACNA1S* encodes the $\alpha 1$ -subunit of the dihydropyridine receptor (DHPR) that triggers *RYR1*-mediated CICR; pathogenic variants can therefore precipitate MH [74].

To date, more than 1000 *RYR1* sequence variants have been reported, yet only 72 fulfill the European Malignant Hyperthermia Group (EMHG) diagnostic criteria, accounting for ~70–80 % of MH-susceptible families [75]. Only two *CACNA1S* variants—*p.Arg1086His* and *p.Arg174Trp*—are currently accepted as diagnostic, together explaining approximately 1 % of genetically confirmed MH cases [75,76]. Unfortunately, discordance between *RYR1* mutations and MH remains a significant issue in genetic diagnosis [77]. This discrepancy is attributed to factors like variants of unknown significance, variable expression, false positives, variants causing weak contractures, and genetic alterations resulting in *RYR1* gene silencing. Therefore, genetic testing is currently reserved for individuals with a personal or family history of MH.

3. Discussion

Although some polymorphisms have been confirmed as clinically significant and actionable, many remain under investigation or lack sufficient evidence to support routine clinical use. In addition to financial and logistical challenges, additional factors continue to limit the integration of pharmacogenetic data into practice.

First, while growing evidence suggests genetic polymorphisms can influence anesthetic responses, genotype information currently supplements, rather than replaces, traditional clinical decision-making. Genotype alone rarely provides a comprehensive explanation for observed variability in patient outcomes. Many genotype–phenotype relationships are inherently multifactorial, with patient-specific factors such as age, sex, body weight, comorbidities, and concurrent medications often playing equally or more significant roles compared to any single genetic marker, including instances of phenoconversion.

Additionally, epigenetic modifications, gene–environment interactions, and polygenic influences may substantially affect how individual gene variants manifest clinically. Complex biological factors such as incomplete penetrance, real-time fluctuations in gene expression, and compensatory biochemical mechanisms further complicate direct genotype–phenotype correlations. Although an in-depth discussion of these underlying biological processes falls beyond the clinical focus of this review, clinicians must remain aware of potential confounding factors when interpreting genetic data within a clinical context.

Second, although numerous studies correlate specific genetic variants with anesthetic responses or adverse events, many suffer from limitations such as small sample sizes, narrow gene targets, and inconsistent replication of findings. Discrepant findings typically result from

underpowered designs and inadequate diversity in patient populations, making broad generalizations difficult. Future research should prioritize larger, multiethnic, high-quality trials to establish more definitive evidence.

4. Conclusion

Increasing evidence shows that common genetic variants can affect perioperative outcomes. However, routine perioperative genotyping remains limited by both insufficient evidence and the multifactorial character of genotype-phenotype relationships. Ongoing research continues to identify new genetic variants while improving our understanding of those already known. However, larger and more well-structured trials are needed to identify which variants consistently drive meaningful and reproducible changes in perioperative care. Once more comprehensive data and evidence-based guidelines become available, genetic testing may eventually become a standard component of perioperative care. Until then, anesthesiologists should interpret genetic data with caution and in conjunction with a comprehensive patient assessment.

Ethics and consent

Ethical approval and informed consent were not required for this narrative review.

CRediT authorship contribution statement

Jan Albert Nicolaas Groot: Writing – review & editing, Writing – original draft, Conceptualization. **Ankie Maxelante Harmsze:** Writing – review & editing. **Eric Hendricus Paulus Adrianus van Dongen:** Writing – review & editing. **Catherijne Anette Jantine Knibbe:** Writing – review & editing. **Helena Johanna Blussé van Oud-Alblas:** Writing – review & editing.

Funding

No funding was received for the preparation or publication of this article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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