PROCEEDINGS SRIWIJAYA INTERNATIONAL CONFERENCE ON MEDICAL SCIENCES
VOL. 1, NO 1, Tahun 2026
ISSN: 3124-8098

Pharmacogenomics in Anesthesiology: Tailoring Drug Selection and Dosing

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Abstract

Pharmacogenomics, the study of how genetic variation shapes drug response, is increasingly relevant to anesthesiology, a specialty in which rapid drug administration and narrow safety margins magnify the consequences of interindividual variability. This narrative review synthesizes evidence on pharmacogenomic determinants of anesthetic drug response, drawing on 27 peer-reviewed publications identified through PubMed, Scopus, and Google Scholar (January 2019–September 2025). Variants in CYP2D6, CYP2B6, UGT1A9, OPRM1, BCHE, and RYR1 influence opioid analgesia, antiemetic efficacy, propofol pharmacokinetics, and susceptibility to malignant hyperthermia and prolonged apnea. Clinical translation is most mature for RYR1-based malignant hyperthermia risk stratification, BCHE deficiency screening, and CYP2D6-guided opioid and antiemetic selection; pragmatic trials confirm reduced opioid consumption without compromised analgesia. Reproducibility of weaker associations, limited population diversity, unresolved variants of uncertain significance, and uncertain cost-effectiveness continue to constrain routine implementation. Future progress depends on rapid genotyping, multi-ethnic validation, pediatric-specific evidence, polygenic risk models, and integration into electronic health record–based decision support. Pharmacogenomics is positioned to evolve from a supplementary tool into a central pillar of individualized perioperative care.

Keywords: *Pharmacogenomics, Anesthesiology, Precision medicine, Malignant hyperthermia, CYP2D6*

Abstrak

Farmakogenomik dalam Anestesiologi: Penyesuaian Pemilihan dan Dosis Obat. Farmakogenomik, ilmu yang mempelajari pengaruh variasi genetik terhadap respons obat, semakin relevan dalam anestesiologi, sebuah spesialisasi yang ditandai oleh pemberian obat secara cepat dan margin keamanan yang sempit sehingga memperbesar dampak variabilitas antarindividu. Tinjauan naratif ini merangkum bukti mengenai determinan farmakogenomik pada respons obat anestesi, berdasarkan 27 publikasi terindeks yang diperoleh melalui PubMed, Scopus, dan Google Scholar (Januari 2019–September 2025). Varian pada gen CYP2D6, CYP2B6, UGT1A9, OPRM1, BCHE, dan RYR1 memengaruhi efikasi analgesia opioid, efektivitas antiemetik, farmakokinetik propofol, serta kerentanan terhadap hipertermia maligna dan apnea berkepanjangan. Penerapan klinis paling matang ditemukan pada stratifikasi risiko hipertermia maligna berbasis RYR1, penapisan defisiensi BCHE, serta pemilihan opioid dan antiemetik berbasis genotipe CYP2D6; uji pragmatis menunjukkan penurunan konsumsi opioid tanpa mengurangi efektivitas analgesia. Keterbatasan replikasi pada asosiasi yang lebih lemah, kurangnya keberagaman populasi, variant of uncertain significance (VUS) yang belum terselesaikan, serta ketidakpastian efektivitas biaya masih menjadi kendala implementasi rutin. Kemajuan di masa depan bergantung pada pengujian genetik cepat, validasi multietnik, bukti spesifik pediatrik, model risiko poligenik, serta integrasi ke dalam sistem pendukung keputusan klinis berbasis rekam medis elektronik. Farmakogenomik diproyeksikan berkembang dari alat pendukung menjadi pilar utama perawatan perioperatif yang terindividualisasi.

Kata Kunci: Farmakogenomik, Anestesiologi, Pengobatan presisi, Hipertermia maligna, CYP2D6

Introduction

Pharmacogenomics, the discipline examining how genetic variation affects drug response, is increasingly relevant to anesthesiology, where medications are administered in time-critical, high-risk settings. Polymorphisms in drug-metabolizing enzymes such as CYP2D6, CYP2B6, and UGT1A9, and in receptor proteins such as OPRM1, BCHE, and RYR1, are among the most recognized determinants of variable perioperative drug response.[1,2] CYP2D6 phenotype determines the rate at which prodrugs such as codeine and tramadol are converted to active metabolites: poor metabolizers experience inadequate analgesia, while ultra-rapid metabolizers risk toxic opioid exposure; the same enzyme governs antiemetic response to ondansetron and tropisetron.[1,3] Polymorphisms in OPRM1 alter opioid receptor binding and dose requirements.[2]

Intravenous agents show similar variability. Propofol pharmacokinetics and pharmacodynamics are shaped by CYP2B6 and UGT1A9 variants, raising the possibility that genotype-guided dosing could reduce delayed emergence or oversedation.[4] Genetic factors also underlie some of the most serious anesthetic complications: malignant hyperthermia, triggered by volatile anesthetics or succinylcholine, arises from pathogenic RYR1 or, less commonly, CACNA1S variants, and updated RYR1 classification has improved risk stratification.[5] BCHE mutations similarly explain prolonged neuromuscular blockade after succinylcholine.[1]

Clinically, pragmatic trials show that CYP2D6-guided opioid prescribing reduces postoperative opioid exposure without compromising analgesia, demonstrating that genotype-informed perioperative care is feasible.[3] Barriers nonetheless persist: limited access to rapid testing, sparse multi-ethnic validation, uncertain cost-effectiveness, and minimal evidence for agents such as ketamine and local anesthetics. This review synthesizes current evidence linking genetic polymorphisms to anesthetic drug response, evaluates the clinical utility of pharmacogenomic testing in perioperative care, and identifies research gaps relevant to broader implementation.

Methods

This narrative review followed general principles of transparent evidence synthesis; formal registration (e.g., PROSPERO) was not pursued given the narrative design. Peer-reviewed articles published between January 2019 and September 2025 were retrieved from PubMed, Scopus, and Google Scholar using combinations of "pharmacogenomics," "pharmacogenetics," "anesthesiology," "anesthesia," "drug response," "dosing," and "precision medicine," combined with Boolean operators and truncation. Eligible sources included original research, systematic reviews, meta-analyses, and clinical practice guidelines addressing genetic determinants of anesthetic drug response; non-peer-reviewed reports, conference abstracts without full text, commentaries, and case reports were excluded. The search yielded 22 PubMed, 280 Google Scholar, and 3 Scopus records; after removing duplicates and applying eligibility criteria, 27 publications were retained for synthesis (Table 1).

Table 1. Search strategy across databases

Database	Search query (combined terms)	Records
PubMed	(pharmacogenomics OR pharmacogenetics) AND (anesthesiology OR anesthesia OR anesthetic agents) AND (drug response OR drug dosing OR precision medicine); 2019–2025	22
Google Scholar	pharmacogenomics AND anesthesia OR anesthesiology AND drug response OR dosing OR precision medicine; since 2019	280
Scopus	TITLE-ABS-KEY(pharmacogenomic* OR pharmacogenetic*) AND TITLE-ABS-KEY(anesthesiology OR anesthesia OR anesthetic*) AND TITLE-ABS-KEY(drug response OR dosing OR precision medicine); PUBYEAR > 2018	3

Results and Discussion

Twenty-seven publications met eligibility criteria, spanning mechanistic, clinical, and implementation aspects of pharmacogenomics in anesthesiology. Findings are organized below into four themes: mechanistic and clinical evidence, diagnostic and therapeutic translation, controversies and limitations, and knowledge gaps and future directions.

Mechanistic and clinical evidence

Pharmacogenomic variability in anesthesiology reflects the interaction between an individual's genetic makeup and the pharmacokinetics and pharmacodynamics of anesthetic agents. The best-characterized example is CYP2D6, which biotransforms codeine into morphine: ultra-rapid metabolizers (multiple CYP2D6 copies) risk dangerously high morphine levels and respiratory depression, while poor metabolizers obtain little analgesic benefit.[6,7] CYP2B6 and UGT1A9 polymorphisms similarly contribute to variable propofol clearance, manifesting as prolonged sedation in some patients and rapid emergence in others.[8] On the pharmacodynamic side, OPRM1 polymorphisms alter mu-opioid receptor binding and analgesic response[9], while RYR1 structural variants lower the threshold for calcium release on exposure to volatile anesthetics or succinylcholine, precipitating malignant hyperthermia, a rare but potentially fatal hypermetabolic crisis.[10]

These mechanisms translate directly into perioperative decision-making. CYP2D6 metabolizer status predicts both analgesic efficacy and risk of opioid toxicity for tramadol, codeine, and oxycodone, allowing clinicians to avoid a trial-and-error approach.[6,11] The same gene shapes antiemetic response: normal and rapid metabolizers often respond poorly to ondansetron and tropisetron, supporting genotype-guided selection of alternative agents such as granisetron for postoperative nausea and vomiting (PONV) prophylaxis.[12] Mutations in butyrylcholinesterase (BCHE) predispose patients to markedly prolonged apnea after succinylcholine or mivacurium, a complication that preoperative recognition can avert by favoring non-depolarizing agents.[13] For RYR1-positive patients, trigger-free total intravenous anesthesia (TIVA), combined with prepared anesthesia machines and ready dantrolene access, mitigates catastrophic risk[14], while pragmatic trials confirm that CYP2D6-guided prescribing reduces opioid consumption while preserving analgesia.[15]

Diagnostic, prognostic, and therapeutic translation

Diagnosis of malignant hyperthermia has shifted from muscle contracture testing toward molecular testing for RYR1 or CACNA1S variants, which now provides a definitive diagnosis in many cases.[14,16] Risk-prediction algorithms combining OPRM1 and COMT genotype with clinical phenotype show promise for forecasting opioid requirements[17], and pharmacogenetic risk scores for PONV susceptibility are under development.[12] Prognostically, patients with altered opioid receptor sensitivity or antiemetic resistance face longer recovery and higher costs[18], while RYR1 carriers require lifelong counseling and family screening.[14]

Therapeutically, CPIC guidelines already provide genotype-based dosing recommendations for ondansetron and tropisetron according to CYP2D6 phenotype[19], and accumulating evidence supports future genotype-guided propofol titration.[8] For perioperative pain, distinguishing poor, intermediate, normal, and ultra-rapid CYP2D6 metabolizers – together with OPRM1-informed receptor sensitivity – allows clinicians to individualize opioid regimens and reduce consumption while preserving analgesia.[9,20] For RYR1/CACNA1S carriers, avoidance of triggering agents alongside dantrolene readiness remains the most mature model of pharmacogenomic translation into anesthetic practice.[14] Preoperative testing and counseling are recommended for first-degree relatives of patients with malignant hyperthermia or BCHE deficiency, both of which follow predictable inheritance patterns[14], although counseling must also address variants of unknown significance (VUS) that complicate perioperative planning.[21]

Controversies and limitations

Despite this progress, the clinical utility of pharmacogenomic testing beyond CYP2D6-guided therapy and malignant hyperthermia screening remains contested: associations involving OPRM1 and COMT are inconsistent across studies, with some reports linking OPRM1 A118G to altered opioid requirements and others failing to replicate this finding.[9,17,22,23] The timing and scope of testing are similarly debated – preemptive panels require infrastructure and upfront investment, while point-of-care testing is constrained by turnaround time – and most validation studies remain concentrated in European-ancestry cohorts, limiting generalizability to genomically diverse populations such as Indonesia's.[24] VUS interpretation, particularly in RYR1, remains incompletely resolved despite ongoing reclassification efforts.[21] Finally, because anesthetic drugs are typically administered acutely rather than chronically, pharmacogenomics is sometimes regarded as less relevant than in oncology or cardiology; this view understates the catastrophic potential of single-exposure events such as malignant hyperthermia or prolonged apnea.[13,14]

Cost, turnaround time, and infrastructure gaps further constrain widespread preoperative testing[25], and limited clinician familiarity with pharmacogenomics, together with the absence of integrated decision-support tools, hinders routine use.[21,26]

Knowledge gaps and future directions

Several gaps merit attention. Evidence is strongest for opioids, antiemetics, and malignant hyperthermia but remains sparse for local anesthetics, ketamine, benzodiazepines, and newer sedatives. Pediatric pharmacogenomics is underexplored despite known interactions between developmental pharmacokinetics and genotype.[27] Large prospective studies validating genotype-guided management across diverse populations are scarce, economic evaluations of testing are limited[25], and integration of pharmacogenomic data into electronic health records (EHR) and clinical decision support remains patchy.[26]

Future progress will likely depend on several developments: large multi-ethnic studies to confirm associations and reduce health disparities[24]; polygenic risk scores to improve prediction of PONV, analgesic requirements, and anesthetic recovery[12,17]; rapid, lower-cost genetic testing technologies suitable for time-critical perioperative settings; extension of pharmacogenomic evidence into pediatric anesthesiology, with precision dosing algorithms for propofol, ketamine, and local anesthetics[4,8,27]; and EHR-embedded decision-support tools that allow anesthesiologists to interpret genomic results efficiently during urgent procedures.[26] Realizing these advances will also require structured education and training for anesthesiologists, genetic counselors, and perioperative teams to support confident interpretation and application of genomic data.[25]

Conclusions

Pharmacogenomics has emerged as an essential lens for understanding variability in anesthetic drug response: genetic variants in CYP2D6, CYP2B6, UGT1A9, OPRM1, RYR1, and BCHE shape analgesic effectiveness, antiemetic responsiveness, anesthetic clearance, and the risk of serious complications such as malignant hyperthermia and prolonged apnea. Clinically, RYR1 testing already guides malignant hyperthermia prevention, BCHE genotyping anticipates prolonged apnea after specific muscle relaxants, and CYP2D6 profiling supports safer opioid and antiemetic selection, together allowing anesthesiologists to reduce adverse drug reactions and personalize perioperative care. Over the next decade, broader multi-ethnic evidence generation, rapid and affordable genotyping, and integration of genomic data into electronic health record–based decision support will be critical to moving pharmacogenomics from a supplementary tool toward a central pillar of precision anesthetic practice.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

The authors thank colleagues at the Department of Medical Biology, Faculty of Medicine, Universitas Sriwijaya, for their support during the preparation of this review.

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