Personalized pediatric anesthesia and pain management: problem-based review

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Pharmacogenetics, the genetic influence on the interpersonal variability in drug response, has enabled tailored pharmacotherapy and emerging 'personalized medicine.' Although oncology spearheaded the clinical implementation of personalized medicine, other specialties are rapidly catching up. In anesthesia, classical examples of genetically mediated idiosyncratic reactions have been long known (e.g., malignant hyperthermia and prolonged apnea after succinylcholine). The last two decades have witnessed an expanding body of pharmacogenetic evidence in anesthesia. This review highlights some of the prominent pharmacogenetic associations studied in anesthesia and pain management, with special focus on pediatric anesthesia.

First draft submitted: 9 August 2019; Accepted for publication: 14 October 2019; Published online: 18 December 2019

Keywords: anesthesia • opioids • pain medicine • pediatric anesthesia • personalized medicine • pharmacogenetics

Pharmacogenetics – use of patients' genetic information to guide drug therapy, is emerging as a major component of personalized medicine and targeted interventions. Completion of the human genome project has allowed for an increasing number of drug–gene pairs to be characterized. Over 300 drugs now contain pharmacogenetic information on their labels and nearly 100 drugs have dosing guidelines based on pharmacogenetics. Pharmacogenetics in anesthesia and pain medicine is a growing field with an expanding body of actionable evidence. This review is a hypothetical case-based discussion of the latest evidence in the field of pharmacogenetics in pediatric anesthesia and pain.

Case A

29-year-old Mrs A is an otherwise healthy female who is postoperative day 1 (POD 1) after Cesarean section that was performed due to obstetric reasons. Her male neonate was born at 38 weeks of gestation with Appearance, Pulse, Grimace, Activity and Respiration (APGAR) scores 8/10 and 9/10 at 1 and 5 min, respectively, after birth. He started breast feeding 6 h after birth. On POD 1, the neonate was lethargic and dusky with oxygen saturation of 75% and respiratory rate of 15 breaths/min, and he was gradually becoming bradycardic. He was immediately intubated and mechanically ventilated, and his vital signs returned to normal. A retrospective chart analysis revealed that Mrs A had been receiving postoperative codeine, which was immediately discontinued. The neonate was gradually weaned from the ventilator and eventually extubated later the same day. He was observed in the neonatal intensive care unit for 24 h and then was transferred to the step-down unit. A blood sample was taken from the mother for assessment of opioid levels and genetic testing.

Case B

B is a 5-year-old male with recurrent sore throats impacting his school attendance. He previously had bilateral ear tubes placed. Due to increased clinic visits for sore throats, the pediatrician referred B to the otolaryngologist, recommending an adenotonsillectomy. Mother reported that B snored at night, which she felt impaired his sleep quality and school performance. On the day of surgery, B had a mask induction with sevoflurane. Intravenous access was obtained and he was intubated without difficulty after propofol administration. Intraoperatively, he

Table 1. CYP450 2D6 phenotypes and clinical implications.

Phenotype	Definition	Allele	Activity score	Implications		CPIC recommendation
				Prodrug	Active drug	
PM	Very low to no activity	*3 *4 *5 *6 *9	0	Activation Response	Inactivation Response, toxicity	Avoid codeine. Preferably avoid tramadol, oxy/hydrocodone. Use morphine/non-opioids
IM	Low normal activity	*10 *17 *41	0.5	↓Activation ↓Response	↓Inactivation ↑Response, toxicity	Label-recommended dosing of codeine, tramadol; monitor for response
EM	Wild-type (normal activity)	*1 *2 *33 *35	1–2	↔Activation ↔Response	↔Inactivation ↔Response	Label-recommended dosing of codeine, tramadol
UM	Increased activity	Duplication of functional alleles	>2	Activation Response, toxicity	Inactivation Response	Avoid codeine. Preferably avoid tramadol, oxy/ hydrocodone. Use morphine/non-opioids

CPIC: Clinical Pharmacogenetics Implementation Consortium; EM: Extensive metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer; UM: Ultrarapid metabolizer.

received morphine (100 µg/kg), ondansetron and dexamethasone. Ketorolac was administered at the completion of the case. He was stable in the postanesthesia care unit, where scheduled oral acetaminophen was initiated. He also received two doses of 50 µg/kg morphine. After resuming clear fluid intake and demonstrating adequate pain control, he was discharged home later that day. Scheduled acetaminophen and tramadol were prescribed for home use as necessary. In the early morning of the next day, the mother noticed that B was unresponsive and immediately took him to the emergency department where he was pronounced dead.

Discussion: opioids

The vast majority of pharmacogenetic studies in anesthesia relate to the variation in response to opioid medications. This should be expected, as opioids still comprise the major component of perioperative analgesia and can cause serious life-threatening adverse effects. The US FDA and Clinical Pharmacogenetics Implementation Consortium (CPIC) that have issued genetics-based opioid guidelines and usage warnings. In particular, variability in handling of codeine and tramadol has been well characterized.

Patients A and B described here represent cases of *CYP2D6* polymorphism leading to ultrarapid metabolizer phenotype – culminating in opioid intoxication. Similar cases have been reported in the literature [1,2]. The CYP450 enzyme family is responsible for the Phase I metabolism of many drugs [3]. Many opioids are substrates of CYP450 enzymes for inactivation before they undergo Phase II conjugation and elimination [4]. CYP450 enzymes are also essential for bioactivation of less active prodrugs such as codeine and tramadol to their active metabolites [5].

Codeine is a weak opioid placed in the second step of WHO analgesic ladder for cancer pain. This opioid was commonly used in pediatrics as it is relatively inexpensive and was assumed to be safe. Reports of respiratory depression (RD) and fatalities following codeine administration in children and breast-fed neonates of mothers on codeine have led to questions of its safety [2,6–10]. Codeine itself is a prodrug of its major active metabolite morphine, with a 200-fold lower affinity to µ-opioid receptor (MOR) compared with morphine [11]. About 80% of codeine undergoes Phase II conjugation to inactive glucuronide, which is renally excreted [12]. A smaller portion undergoes *N*-demethylation to form the inactive metabolite norcodeine. Only 5–10% of the administered codeine undergoes *O*-demethylation via *CYP2D6* to form its active metabolite morphine [12].

The *CYP2D6* gene is subject to extensive polymorphism. Over 100 different alleles have been described in various ethno-geographic groups, leading to a wide range of variation in the enzyme activity [13]. For ease of management, four classes have been described depending on the phenotype (Table 1). These include poor metabolizers (PM; 5–10% prevalence), extensive metabolizers (EM), intermediate metabolizers (IM) and ultrarapid metabolizers (UM; 1–2% prevalence) [14,15]. An activity score is assigned to each allele in the diplotype as follows: 0 = nonfunctional, 0.5 = decreased function and 1 = a fully functional allele [16]. PMs show extremely low analgesic response, while UMs have high blood levels of active metabolite leading to potentially fatal RD. This is especially true in pediatric patients where the margin of error is small. Risk factors like prematurity, age (<1-year old), underweight, obstructive sleep apnea (OSA) and developmental delay predispose children to opioid-induced RD [17].

The CPIC assigns levels from A through D for gene/drug combinations and has issued level A recommendations for codeine-*CYP2D6*. This indicates that genetic information should be used to change prescription of the drug [18]. It recommends avoiding codeine use in those with UM and PM phenotypes and suggests use of viable alternatives [19].

Other alternative oral opioids that belong in the second step of WHO pain ladder include tramadol, low-dose oxycodone and hydrocodone. Given that tramadol, oxycodone and hydrocodone are CYP2D6 metabolites, they might not be the viable alternatives to be used in UM or PMs. This means a step down to non-steroidal anti-inflammatory drugs (NSAIDs) or a step up to morphine in those with a PM or UM phenotype.

Tramadol, similar to codeine is a less active prodrug. It has low affinity to MOR but exerts some analgesic action via serotonin and norepinephrine reuptake inhibition [11,20]. While a major portion of tramadol is inactivated by *N*-demethylation, a small portion is converted by CYP2D6 to its active metabolite *O*-desmethyltramadol [21]. As it uses a similar activation pathway as codeine, *CYP2D6* polymorphisms influence tramadol response in a similar manner. The CPIC also assigns level A prescribing recommendations for tramadol [19]. Similarly, the Dutch Pharmacogenetics Working Group guidelines for tramadol states to choose alternative analgesic agents for UM and PM individuals [22]. If that is not feasible, PMs should be monitored for analgesic response and possibly receive an increased dose in case of inadequate analgesia. If an alternative analgesic is not feasible for UMs, tramadol could be started at 40% of the recommended dose with close monitoring for adverse effects.

RD has been reported in children-receiving tramadol [1,23], leading the FDA to issue restrictions on the use of tramadol (as well as codeine) in children [24]. Codeine and tramadol are now contraindicated in patients less than 12 years of age, and less than 18 years of age following adenotonsillectomy. The agency also warns against prescription of codeine and tramadol in children between 12 and 18 years of age with obesity, OSA or severe lung disease. A strengthened warning recommends against breast feeding in mothers taking codeine or tramadol due to the risk of RD in breast-fed infants. Following the FDA warning, codeine was removed from the drug formularies in many pediatric hospitals. A recent review by Fortenberry *et al.* suggested alternating doses of acetaminophen and ibuprofen in most pediatric patients, which could be stepped up to hydrocodone or oxycodone if necessary [25].

Oxycodone and hydrocodone are semisynthetic opioids with intrinsic analgesic activity. They are metabolized through similar pathways as codeine. Oxycodone is *N*-demethylated to the inactive noroxycodone and *O*-demethylated by CYP2D6 to active metabolites oxymorphone and noroxymorphone [26]. Similarly, hydrocodone is metabolized to norhydrocodone and active hydromorphone [4]. The MOR affinities for oxymorphone and hydromorphone are 40- and 10- to 33-fold greater, respectively, than the respective parent drugs [27]. Since the parent drugs are active on their own, *CYP2D6* polymorphisms exert less influence on response to oxycodone and hydrocodone. However, mortality has been reported after oxycodone due to genetic factors [28]. Given that possibility, oxycodone or hydrocodone are not ideal alternatives to codeine (especially when UM or PM status has been established). Oxycodone-*CYP2D6* drug-gene pair holds CPIC level A evidence (genetic information should be used to change prescribing of affected drug), but genetics-based dosing guidelines are not yet available.

Polymorphisms have been described in other CYP450 genes involved in opioid metabolism including *CYP3A4*, *CYP3A5* and *CYP2B6*. *CYP3A4* is the enzyme responsible for *N*-demethylation and inactivation of codeine, oxycodone and hydrocodone [4]. Fentanyl undergoes *N*-dealkylation by *CYP3A4* and *CYP3A5* enzymes. Decreased activity alleles have been described in these enzymes (*CYP3A4**22, *CYP3A5**3) that may increase plasma fentanyl levels, although evidence is inconclusive [29,30]. The *CYP3A4**1G allele has been associated with decreased fentanyl elimination and low fentanyl consumption [31]. On the other hand, the *CYP3A5**1 allele causes greater fentanyl elimination and higher-dose requirements compared with general population [32]. Alfentanil and sufentanil responses are also subject to *CYP3A4* and *CYP3A5* polymorphisms [33,34]. Many other *CYP3A4* and *CYP3A5* polymorphisms have been described, although their mean allelic frequency is extremely low and they lack clinical evidence.

Methadone is inactivated by CYP2B6, and metabolized by other minor pathways through CYP3A4 and CYP2D6 [4,35]. The *CYP2B6**6 allele is associated with low hepatic expression and activity [14]. Homozygotes of this allele may suffer from excessive sedation and QT prolongation after methadone administration. On the other hand, *CYP2B6**4 is associated with increased methadone elimination and low plasma levels [35]. Further research is needed on pharmacogenetics of methadone to develop clinical guidelines.

Morphine is the prototypical opioid widely used for acute perioperative pain as well as chronic pain in cancer and non-cancer patients. Morphine undergoes Phase II metabolism via enzymes in the uridine glucuronosyl transferase family, especially UGT2B7 [4]. The major metabolite morphine-3-glucuronide (M3G) has no analgesic activity but has neuroexcitatory effects [36]. The minor metabolite morphine-6-glucuronide (M6G) has similar affinity to MOR as morphine and contributes significantly to its analgesic efficacy. There are also other pathways (UGT1A1 and UGT1A8) involved in formation of M6G [37]. SNPs have been described in *UGT2B7*. SNP 802C>T was demonstrated *in vitro* to decrease transcription of the enzyme, but clinical studies were inconclusive to associate *UGT2B7* polymorphisms with morphine response [38]. A study in the Japanese population demonstrated lower

incidence of adverse effects associated with oral morphine in carriers of the *UGT2B7*2* allele compared with wild-type alleles [39]. Intronic variants in the promoter regions and genetic variability in *UGT1A1* and *UGT1A8* likely cause the difficulty in definitively associating polymorphisms with the morphine response.

Pharmacokinetic variations in opioid response can also be caused by changes in transport proteins such as P-glycoproteins. These include ATP-Binding Cassette family members ABCB1 and ABCC3 – also known as multidrug resistance proteins – and organic cation transport protein 1 (OCT1). ABCB1 is an efflux protein present at the blood–brain barrier and intestinal mucosa. Many opioids including morphine, methadone and fentanyl form substrates of ABCB1 [40]. The *ABCB1* gene is located on chromosome 7. A number of SNPs have been reported with low mean allelic frequencies – the most frequent variants being *3435C>T*, *1236C>T* and *2677G>T/A* [41]. These are in strong linkage disequilibrium, meaning that they are often inherited together and the response resulting from one variant is often influenced by others. Therefore, studying only one variant is often misleading. In the case of *3435C>T*, homozygous T/T genotype is associated with very low expression of the ABCB1 (both intestinal and blood–brain barrier). This results in greater levels of opioids in cerebrospinal fluid with improved analgesia, lower dose requirements and more susceptibility to side effects [42]. While studies relating *3435TT* to opioid dose requirements have been inconsistent, this variant has been associated with increased risk of nausea and vomiting [43]. Children with GA and GG genotypes of *ABCB1* rs9282564 are at higher risk of RD [44]. The ABCC3 protein in hepatocytes serves as an efflux transporter for morphine metabolites M3G and M6G into the blood stream [45]. The *ABCC3* SNP *211C>T* has been associated with decreased expression of the protein [46], and *211C/T* or *211T/T* genotypes result in lower plasma levels of M3G and M6G [47].

The OCT1 is a hepatocyte transport protein responsible for uptake of drugs like morphine. It is coded by *SLC22A1*, a highly polymorphic gene [48]. Loss of function variants of *SLC22A1* (*2, *3, *4, *5 and *6) have been characterized for elimination of morphine and the active metabolite of tramadol (*O*-desmethyl tramadol) [49]. Patients with these polymorphisms show high plasma concentrations of these metabolites [50]. The *SLC22A1* variants are less frequent in African–Americans (AA) compared with Caucasians; therefore, opioid-induced RD is less common in the AA population [47]. Concurrent *SLC22A1* variants and CYP2D6 UM phenotype will compound the problem of RD after codeine administration [51]. Despite the promising scientific premises with the variants affecting transport proteins, strong evidences are still lacking to suggest a clinical implementation.

The genetics of opioid pharmacodynamics are also currently being explored, with special focus on *OPRM1*, *COMT* and *KCNJ6*. The *OPRM1* gene (encoding the MOR) lies on chromosome 6. A polymorphism for *OPRM1*, *118A>G*, leads to reduced MOR signal transduction, increased affinity to endogenous opioids and resistance to exogenously administered opioids [52]. The clinical effects of homozygous state (*118GG*) are unclear, as some studies have demonstrated greater opioid requirements and less opioid-related adverse events, while others have shown no difference in opioid consumption compared with the wild-type allele [30,53]. A meta-analysis revealed a weak association between *OPRM1* variants and lower incidence of opioid adverse events and greater dose requirements [54].

Notably, greater opioid dose requirements do not automatically imply resistance to opioid adverse effects. Genetic variants may have differential effects on opioid requirements and susceptibility to opioid adverse effects [55,56]. Reyes-Gibby *et al.* studied combined effects of *OPRM1* and *COMT* variants in chronic cancer pain patients and found that carriers of the *OPRM1 A118G* and *COMT* Met/Met haplotype required the lowest morphine dose to achieve pain relief [57]. Another study found that heterozygotes for both of the gene variants required significantly lower morphine doses and also experienced lower incidence of opioid adverse events compared with homozygotes [58]. Ruano and Kost [59] described three phenotype classes based on *OPRM1* SNPs in terms of sensitivity to opioids and likelihood of developing opioid dependence. These included: functional *OPRM1* (AA homozygous: 64% frequency), subnormal *OPRM1* (AG heterozygous: 32% frequency) and dysfunctional *OPRM1* (GG homozygous: 4% frequency). Presence of at least one G allele lowers the pain threshold, decreases sensitivity to opioids, increases opioid consumption and increases opioid dependence [59,60]. Similarly, three phenotype classes were described based on *CYP2D6* status: *CYP2D6* functional (neither *CYP2D6* allele is null or ultrarapid: 60% frequency), *CYP2D6* subnormal (one *CYP2D6* allele is null, the other normal: 30% frequency) and *CYP2D6* dysfunctional (both *CYP2D6* alleles are null, or at least one is ultra-rapid: 10% frequency). The authors used functional status of both *CYP2D6* and *OPRM1* and their relative population frequencies to create three categories and nine subcategories of various combinations and recommended clinical action (Figure 1).

The *COMT* gene codes for catechol-O-methyl transferase, which plays an important role in regulating MOR – thus influencing pain perception and opioid response. The *COMT* variant *472G>A* has been linked to reduced COMT activity resulting in greater MOR expression and lower Met-enkephalin concentration. This has clinically

Figure 1. Functional classes for opioid management using CYP2D6 and OPRM1.
Adapted with permission from [59].

been related to lower opioid requirements and fewer opioid side effects. Three functional haplotypes of $472G>A$ have been identified (low, average and high pain sensitivity) [61], but the phenotypical characters of these classes have been inconsistent across studies [62]. The GIRK2 is a downstream signaling effector of MOR. It is coded by the *KCNJ6* gene. Polymorphisms of *KCNJ6* ($1250G>A$ and $1032A>G$) may affect opioid response; however, the evidence is sparse and inconclusive [63]. Polymorphisms of the *OPRD1* gene, coding for delta-opioid receptor, have also been described [64]. Table 2 provides an overview of significant genetic variants relevant to anesthesia providers.

Currently in anesthesia practice, the only opioid drug–gene combinations with actionable guidelines are the CYP2D6 substrate drugs (Figure 2). More randomized controlled trials in this domain are emerging, which is encouraging. Smith *et al.* demonstrated the benefits of CYP2D6 genotype-guided pain management compared with conventional management in patients visiting the pain clinic [65]. The composite pain score was significantly lower in the CYP2D6-guided group, especially for IM/PM patients.

Case C

C is a 7-year-old female who presented on emergency with lower abdominal pain, vomiting, diarrhea and fever. Acute appendicitis was diagnosed, and intravenous fluids and an antibiotic were given in the emergency department. She was transferred to the operating room for emergency laparoscopic appendectomy. Rapid sequence induction was performed, including propofol and succinylcholine followed by tracheal intubation. She was placed on ventilator

Table 2. Overview of genetic variants relevant for anesthesiologists.

Genes associated with anesthesia relevant medications and conditions	Genotypes and clinical implications
Opioids	
CYP450 2D6 (CYP2D6)	PMs – Extremely low analgesic response with codeine, tramadol UMs – Fatal respiratory depression with codeine, tramadol
CYP450 3A4 3A5 (CYP3A4, 3A5)	CYP3A4*22, CYP3A5*3 alleles – decreased elimination, greater plasma fentanyl levels CYP3A4*1G allele – decreased fentanyl elimination and low consumption CYP3A5*1 allele – greater fentanyl elimination and higher dose requirements
CYP450 2B6 (CYP2B6)	CYP2B6*6 allele – homozygotes, excessive sedation and QT prolongation after methadone CYP2B6*4 allele – increased elimination and low plasma levels of methadone
UDP (UGT2B7)	UGT2B7*2 allele – lower incidence of adverse effects with oral morphine
ABC (ABCB1, ABCB3)	ABCB1 SNPs – 3435C>T, homozygous T/T – greater levels of opioids in CSF – 3435TT – increased risk of nausea and vomiting – GA and GG genotypes of rs9282564 are at higher risk of respiratory depression ABCC3 SNPs – 211C>T – decreased expression of the protein – 211C/T or 211T/T genotypes – lower plasma levels of M3G and M6G ABCC3 SNPs – 211C>T – decreased expression of the protein – 211C/T or 211T/T genotypes – lower plasma levels of M3G and M6G
OCT1 hepatocyte transport protein (SLC22A1)	SLC22A1 Loss of function variants (*2, *3, *4, *5, *6) – High plasma concentration of morphine and the active metabolite of tramadol
μ-opioid receptor (OPRM1)	Polymorphism 118A>G – Increased affinity to endogenous opioids – Resistance to exogenously administered opioids
COMT	Polymorphism 472G>A – Lower opioid requirements and fewer opioid side effects
GIRK2 (KCNJ6)	Polymorphisms of KCNJ6 (1250G>A and 1032A>G) – May affect opioid response
Succinylcholine	
BChE gene	BChE deficiency– K variant – 30% reduction in enzyme activity – Fluoride-resistant variant – 60% reduction in enzyme activity – Atypical dibucaine-resistant variant – 70% reduction in enzyme activity – Silent variant – 100% reduction in enzyme activity, may experience up to 3–4 h of apnea after succinylcholine
Malignant hyperthermia	
RYR1	300 genetic variants of RYR1 on chromosome 19 CACNA1S, STAC3 genes influence skeletal muscle calcium metabolism (inconclusive)
PONV	
Variants of genes coding for receptors (5HT _{3A} , B, CHRM3, DRD2)	5HT _{3A} and 5HT _{3B} genes (encoding 5-HT ₃ receptors), CHRM3 gene (encoding M3 muscarinic cholinergic receptor) and DRD2 gene (encoding dopamine D2 receptor)
CYP2D6	UMs – poor response to ondansetron
Transport protein genes (ABCB1, OCT1)	Polymorphisms increase PONV risk CHRM3 (coding for muscarinic cholinergic receptor) and KCNB2 (coding for voltage-gated potassium channel) associated with increased PONV risk
Benzodiazepines	
GABA _A receptor (GABRA1)	GABRA1 gene polymorphisms influence benzodiazepine sensitivity
CYP450 (CYP3A4, 1C9)	Polymorphisms in CYP3A4 affect clearance of midazolam Polymorphisms in CYP2C19 affect clearance of diazepam
Propofol	
UDP (UGT1A9)	Affects propofol glucuronidation
CYP2B6	Affects propofol dose requirements
Etomidate	
GABA _A receptor	Polymorphisms in genes coding for GABA _A receptor influence efficacy

CSF: Cerebrospinal fluid; NSAID: Nonsteroidal anti-inflammatory drug; PM: Poor metabolizer; PONV: Postoperative nausea and vomiting; UM: Ultrarapid metabolizer.

Table 2. Overview of genetic variants relevant for anesthesiologists (cont.).

Genes associated with anesthesia relevant medications and conditions	Genotypes and clinical implications
Ketamine	
<i>CYP2B6</i>	<i>CYP2B6</i> *6 was found to decrease enzyme activity <i>in vitro</i> ; inconclusive clinical evidence
Dexmedetomidine	
Alpha2 adrenergic receptors (<i>ADRA2A</i>)	<i>ADRA2A</i> polymorphism has been linked to variability in response
Inhalational agents	
<i>GSTP1</i>	Variants implicated in sevoflurane-induced hepatotoxicity
GABA _A receptor (<i>GABRA1</i>)	Polymorphisms in genes coding for GABA _A receptor are associated with emergence agitation after sevoflurane
<i>MC1R</i>	Variants in <i>MC1R</i> gene – greater desflurane dose requirements
5,10-methylenetetrahydrofolate reductase	Gene mutation reduces enzyme activity; neurological injury after nitrous oxide exposure
NSAIDs	
<i>CYP450 (CYP2C9)</i>	<ul style="list-style-type: none"> – <i>CYP2C8</i>*3, <i>CYP2C9</i>*2, <i>CYP2C9</i>*3 – decreased activity and clearance of Ibuprofen – <i>CYP2C9</i>*3 decreased function polymorphism – lower pain scores after celecoxib – Maximum plasma concentrations of celecoxib are seen in <i>CYP2C9</i> PMs (homozygous *3/*3)
<i>GSTP1</i>	Polymorphisms – susceptibility to acetaminophen-induced hepatic injury
Local anesthetics	
Sodium channel (<i>SCN9A</i>)	N395K mutation – increased resistance to lidocaine binding on sodium channels
<i>TRPV1</i>	Point mutation – lidocaine resistance
<i>MC1R</i>	Variants in <i>MC1R</i> – reduce lidocaine efficacy
<i>CYP450 (CYP3A4, CYP1A2)</i>	<p><i>CYP3A4</i></p> <ul style="list-style-type: none"> – Not fully mature at birth – Increase toxicity with lidocaine and bupivacaine in infants younger than 6 months <p><i>CYP1A2</i></p> <ul style="list-style-type: none"> – Not fully mature at birth – Increase toxicity with ropivacaine in infants younger than 6 months

CSF: Cerebrospinal fluid; NSAID: Nonsteroidal anti-inflammatory drug; PM: Poor metabolizer; PONV: Postoperative nausea and vomiting; UM: Ultrarapid metabolizer.

and given fentanyl and ondansetron. Postoperatively, the anesthesiologist noticed that the patient had no respiratory effort. Peripheral nerve stimulation with train-of-four recorded on a twitch monitor demonstrated decreased twitch with no fade. Blood was drawn for estimation of pseudocholinesterase and the patient was transferred to the intensive care unit to be placed on ventilator. Within 3 h, she began triggering the ventilator. Following extubation within the next hour, she was transferred to the step-down unit.

Discussion: neuromuscular blockers

There are several case reports of prolonged paralysis after succinylcholine due to pseudocholinesterase deficiency [66,67]. Succinylcholine is a rapid, short-acting depolarizing neuromuscular blocker (NMB) that is rapidly hydrolysed in plasma by pseudocholinesterase (also known as butyrylcholinesterase; BChE). Deficiency of BChE is rare and results in prolonged paralysis after exposure to succinylcholine or mivacurium – a non-depolarizing NMB metabolized by BChE. The BChE enzyme is produced in the liver, but present in all cells except erythrocytes [68]. Whole-body levels of BChE exceed that of acetylcholinesterase [69].

The *BChE* gene is located on chromosome 3 and BChE deficiency is inherited as an autosomal recessive trait [68]. Many genetic variants have been described. The wild-type (normal function) variant accounts for 98% of the population; however, about 1.5% of people display the Kalow ('K') variant associated with 30% reduction in enzyme activity [70]. Other variants are extremely rare, including the atypical-dibucaine-resistant variant [71,72], fluoride-resistant variant [73] and silent variant [74] associated with 70, 60 and 100% reductions in BChE activity, respectively. Patients with the silent variant may experience up to 3–4 h of apnea after succinylcholine. The prevalence of the rare silent-type homozygote variant is 1:100,000 [75]. Certain populations like the Inuit Eskimo population and the Vysya population of India have shown prevalence as high as 1:25 [74,75]. The frequency of the Leu307Pro substitution seen in the silent-type BChE deficiency is 4000-fold greater in the Vysya population compared with other populations [74].

Figure 2. Pharmacogenetics guided perioperative management pathway: CYP2D6.

EM: Extensive metabolizers; IM: Intermediate metabolizers; NSAID: Nonsteroidal anti-inflammatory drug; OSA: Obstructive sleep apnea; PM: Poor metabolizer; UM: Ultrarapid metabolizer.

Although genetic testing is available for BChE deficiency, the most commonly used assays include inhibition tests (using dibucaine or fluoride to quantify activity) and plasma cholinesterase levels [71,73]. Acquired causes of BChE deficiency such as hepatic or renal disease, pregnancy, burns and malignancy should be ruled out before lab testing [68]. Drugs and toxins like echothiophate, organophosphates, cyclophosphamide, physostigmine, neostigmine, oral contraceptives and metoclopramide can also inhibit BChE [68]. Treatment with whole blood and fresh frozen plasma have been described for prolonged apnea after succinylcholine administration in BChE deficiency [76,77]. However, patients are typically allowed to recover spontaneously with ventilatory support. BChE deficiency is also associated with poor metabolism of ester group local anesthetics such as chloroprocaine or cocaine, leading to toxicity [78].

Other NMBs such as mivacurium and rocuronium may have prolonged activity due to enzyme deficiencies. Mivacurium is a non-depolarizing muscle relaxant metabolized by BChE. The duration of action may be prolonged from the usual 25–30 min to about 300 min in homozygotes with BChE deficiency [79,80]. Genetic variants in hepatocellular uptake protein OATP1A2 are known to influence biliary elimination of rocuronium [81].

Case D

D is an 8-year-old female who was previously healthy but presented with a supracondylar humeral fracture after falling. She was placed nil per os before surgery. On preanesthetic evaluation, D's father mentioned that his father (D's grandfather) had died after anesthetic exposure. He and his two siblings had been tested for malignant hyperthermia (MH), and his sister (D's aunt) was MH susceptible. He remembers that she was given a 'special kind of anesthetic' for her laparoscopic cholecystectomy, and she had no anesthetic complications. He could not recall any details of the MH testing or the anesthesia that his sister had received. He personally had no anesthetic

exposures, and this was D's first exposure to anesthesia. The anesthesiologist planned an intravenous induction with propofol, laryngeal mask airway, and a total intravenous anesthetic with propofol and remifentanyl. The intraoperative and postoperative periods were uneventful, and D was discharged home after 1 day of observation in the surgical unit.

Discussion: MH

MH is a rare (1 in 15,000 anesthetics in children) [82,83], often fatal, idiopathic reaction to volatile anesthetics and succinylcholine. There have been numerous isolated case reports of both successfully managed as well as fatal instances of MH [84–86]. Exposure to a triggering agent causes sustained opening of ryanodine receptor 1 (RYR1) calcium channels on sarcoplasmic reticulum, resulting in elevated calcium ion release and sustained contraction. Patients display sustained skeletal muscle contraction, ATP depletion, rigidity, excessive heat production and muscle breakdown [87]. About 300 genetic variants of *RYR1* on chromosome 19 have been described, with varying levels of clinical significance [87]. The prevalence of pathogenic *RYR1* variants in MH susceptible individuals documented in various studies varies from 23 to 86% depending on the method used and the population studied [88–92]. Apart from *RYR1*, variants have been described in *CACNA1S*, *STAC3* and other genes that influence skeletal muscle calcium metabolism, however, their causative role in MH is unclear [93,94]. But only about 50% of the MH susceptible individuals carry potentially pathogenic variants in the known MH-associated genes [95].

Recent advancements in technology and cost-effectiveness of next-generation sequencing have enabled genetic testing to be a viable first-line diagnostic test for patients or relatives of patients suspected to have MH [95]. The European Malignant Hyperthermia group has published diagnostic guidelines for MH susceptibility, which includes genetic and functional characterization of relevant *RYR1* and *CACNA1S* variants [96]. But the *in vitro* caffeine-halothane contracture test still remains the gold standard to confirm MH susceptibility, since not all genetic variants have been characterized, [97].

Case E

E is an 11-year-old female presented for dental restoration under general anesthesia, as her dental surgeon felt that it was beyond the scope of what could be done in the office setting. E's surgical history included adenotonsillectomy at 7 years of age and appendectomy at 10 years of age. Her parents recalled that she experienced severe postoperative nausea and vomiting (PONV) following both of the previous surgeries. She also had severe pain – unresponsive to tramadol – after her adenotonsillectomy. An emergency physician had prescribed a different medication that provided good pain relief. They also recalled that a genetic test had been performed during her appendectomy stay, and the doctor had mentioned that E was a 'poor metabolizer'. E's maternal family also had history of PONV. E received a preoperative scopolamine patch, intravenous induction with propofol, endotracheal intubation, total intravenous anesthetic with propofol and remifentanyl, dexamethasone, granisetron and generous intravenous crystalloid administration. Postoperative promethazine was available; she did not require any rescue medication for PONV during her postoperative recovery.

Discussion: antiemetics

PONV is a relatively common anesthetic concern with a general incidence of 30%, which could be as high as 80% in high-risk individuals [98]. PONV risk factors may be patient related (female gender, positive family history, motion sickness) or surgery related (strabismus surgery) or anesthesia related (postoperative opioid use, use of volatile anesthetics). In addition to these factors, certain genetic variants have been described to increase PONV risk. The pathophysiology of PONV involves a number of neural pathways including serotonin (5-hydroxytryptamine 3 receptor; 5-HT₃), dopamine (D2 and D3 receptors), histamine and neurokinin. All of these pathways may be utilized for pharmacological intervention of PONV. Enhanced susceptibility to PONV has been linked to the following genetic variants: polymorphic variants in *5HTR3A* and *5HTR3B* genes (encoding 5-HT₃ receptors), *CHRM3* gene (encoding M3 muscarinic cholinergic receptor) and *DRD2* gene (encoding dopamine D2 receptor) [99–101]. The most commonly used class of drugs for PONV prophylaxis and treatment is the 5-HT₃ receptor antagonist class including ondansetron, granisetron, tropisetron and others. CYP450 enzymes – CYP2D6, CYP3A4 and CYP1A2 – are involved in the metabolism of ondansetron to its inactive metabolites [102], with most activity conferred by CYP2D6. Previous studies have demonstrated that CYP2D6 UMs show a poor response to ondansetron compared with EM or IM phenotypes [103–105]. CPIC guidelines, therefore, recommend granisetron as an alternative to ondansetron for CYP2D6 UMs since granisetron is not a CYP2D6 substrate [105]. Tropisetron

– which is also metabolized by CYP2D6 – would not be a viable alternative to ondansetron [106]. Finally, variable response to 5HT₃ antagonists is also associated with polymorphisms in transport protein genes like *ABCB1* and *OCT1* [107,108]. Other genes identified to be associated with increased PONV risk include *CHRM3* (coding for muscarinic cholinergic receptor) and *KCNB2* (coding for voltage-gated potassium channel) [100,109].

Sedative, hypnotics & volatile agents

Benzodiazepines, acting through GABA_A receptors, are used for anxiolysis and sedation in the perioperative period. A polymorphism in *GABRA1* gene (encoding GABA_A receptor) has been shown to influence benzodiazepine sensitivity [110]. Benzodiazepines are metabolized by CYP450 enzymes; midazolam is hydrolyzed by CYP3A4 and CYP3A5 enzymes, while diazepam is a CYP2C19 substrate. Polymorphisms in CYP enzymes, therefore, can affect their clearance. This has been demonstrated with CYP3A4 for midazolam and CYP2C19 for diazepam [111,112].

Propofol is an intravenous anesthetic agent with substantial variation in interindividual response, and it is mainly eliminated via glucuronidation by UGT1A9. It also undergoes hydroxylation mediated by CYP2B6 and CYP2C9. Polymorphisms of *UGT1A9* have been known to affect propofol glucuronidation [113]. There have been studies on *CYP2B6* variants and their influence on propofol dose requirements, but no conclusive association between genetic factors and the variability in propofol dose or adverse events has been established [114,115]. Since propofol acts via GABA_A receptors, the impact of polymorphisms of *GABRE* (encoding the GABA_A receptor subunit epsilon) have also been investigated, with inconclusive results [116]. The GABA_A receptor is also used by another intravenous anesthetic, etomidate. Polymorphisms in genes coding for GABA_A receptor subunits have been known to influence etomidate efficacy [117]. No published studies, however, have associated genetic factors with etomidate-induced adrenal suppression [83].

Ketamine acts by blocking *N*-methyl-D-aspartate receptors in brain and spinal cord. It is metabolized by CYP2B6 and CYP3A4 [118]. The variant *CYP2B6**6 was found to decrease enzyme activity *in vitro*, but it did not significantly affect metabolism and clearance of low-dose ketamine [119].

Dexmedetomidine is a centrally acting α_2 adrenergic receptor agonist. Dexmedetomidine is metabolized via glucuronidation and CYP2A6 hydroxylation pathways. CYP2A6 variants have shown no association with dexmedetomidine response [120]. On the other hand, *ADRA2A* polymorphism affecting α_2 adrenergic receptors has been linked to variability in dexmedetomidine response [121].

Currently used volatile agents like sevoflurane and desflurane are primarily eliminated unchanged through the lungs, although a minor portion is hepatically metabolized by CYP450 enzymes [122]. Certain variants of *GSTP1* gene (encoding glutathione S-transferase) have been implicated in sevoflurane-induced hepatotoxicity – an extremely rare complication with sevoflurane [123]. Inhalational anesthetic agents act via a different site on the GABA_A receptor, and polymorphisms in GABA receptor genes are associated with emergence agitation after sevoflurane administration [124]. Variants in *MC1R* gene (encoding the melanocortin-1 receptor) have been implicated in greater desflurane dose requirements [125].

Nitrous oxide is uncommonly used now; however, this agent can inhibit vitamin B₁₂-dependent enzymes such as methionine synthase through oxidation of cobalt. In one case report, an infant sustained neurological injury and death after nitrous oxide exposure [126]. Postmortem examination revealed a mutation in the gene coding for 5, 10-methylenetetrahydrofolate reductase with decreased enzyme activity [127]. Exposure to nitrous oxide in addition to this enzyme deficiency resulted in fatal neurological injury.

NSAIDs & acetaminophen

Nonselective cyclooxygenase (COX) inhibitors (e.g., diclofenac and ibuprofen) undergo CYP450 enzyme-mediated Phase I metabolism followed by hepatic glucuronide conjugation. Polymorphisms *CYP2C8**3, *CYP2C9**2 and *CYP2C9**3 are associated with decreased activity and lower ibuprofen clearance [128]. A higher incidence of gastric bleeding has also been shown in carriers of *CYP2C9**3 [129].

Celecoxib is a COX-2 selective inhibitor metabolized by CYP2C9 [130]. The decreased function polymorphism *CYP2C9**3 is associated with lower pain scores after celecoxib administration [131]. Maximum plasma concentrations are seen in CYP2C9 PMs (homozygous *3/*3) compared with EMs (*1/*1) or IMs (heterozygous *1/*3) [132]. The drug label for celecoxib includes an FDA-issued warning for use in CYP2C9 PMs – recommending reducing the dose by 50% or using an alternate drug [133].

Acetaminophen is the most commonly used analgesic agent. It undergoes CYP450-mediated oxidation in the liver to form the reactive metabolite *N*-acetyl para-benzoquinone imine (NAPQI) [134]. CYP3A4, CYP1A2 and

CYP2E1 are the main enzymes involved [135]. NAPQI undergoes glutathione conjugation [134], and depletion of glutathione leads to accumulation of toxic NAPQI and oxidative injury to hepatocytes [136]. Polymorphisms causing decreased activity of glutathione transferase can cause susceptibility to acetaminophen induced hepatic injury [137]. Other acetaminophen metabolic pathways include glucuronidation and sulfation, to some extent [134]. Glucuronidation is absent in fetal livers and newborns, where acetaminophen is mainly eliminated via sulfation [138].

Local anesthetics

Local anesthetics act by blocking sodium channels, and variants in sodium channel genes may reduce the activity of these agents. The N395K mutation on *SCN9A* gene has been shown to increase resistance to lidocaine binding on Nav1.7 channels [139]. Sodium channel mutations have also been implicated in local anesthetic cardiac toxicity. Lidocaine also acts on the TRPA1 and TRPV1 vanilloid receptors [140]. A TRPV1 point mutation led to lidocaine resistance in mice [140]. There is also evidence that variants in *MC1R* (encoding melanocortin-1 receptor) reduce lidocaine efficacy [141]. Lidocaine and bupivacaine are metabolized by CYP3A4, and ropivacaine is metabolized by CYP1A2. These enzymes are not fully mature at birth [142], and this may help to explain the increased toxicity of amide local anesthetics in infants younger than 6 months.

Challenges & implications for pharmacogenetics research in pediatric anesthesia

As our discussion reveals, pharmacogenetics research has been heterogenous with inconsistent results across studies. Pharmacogenetics is a science of outliers [143] attempting to study the thin tails on each side of the bell-shaped curve. Therefore, sample size has a significant impact on the results, and large enough study population and robust study design are of paramount importance. The allelic frequency of polymorphisms can significantly vary across ethnicities, meaning that results can vary based on ethnicity of the chosen study population. The substantial linkage disequilibrium of multiple SNPs on a gene (both exonic as well as intronic regions) could lead to false conclusions when only one variant is closely examined (candidate gene approach). Gene–gene interactions (e.g., *CYP2D6* UM and Loss of function *OCT1*) could also modify responses. Studies on interaction between *COMT* and *OPRM1* variants provide another good example for gene–gene interaction [144]. Concurrent medications (enzyme inducers or inhibitors) can further complicate the picture. For instance, strong CYP2D6 inhibitors like fluoxetine, paroxetine and bupropion may mimic a PM phenotype irrespective of the *CYP2D6* allele [27].

Developmental pharmacogenetics, or the dynamic variation in gene expression and the resulting enzyme activity at various stages of development is another important consideration in pediatric anesthesia. For example, the predominant prenatal CYP enzyme is CYP2C19, but this transitions to CYP2C9 after birth. Levels of CYP2C9 are similar to adults between 1 and 6 months or after puberty, but exceed adult levels at 3–10 years of age [145,146]. Adult levels of CYP2C19 are reached at 10 years of age [147]. Similarly, CYP2D6 activity is about 1–5% of the adult levels at birth and adult levels are seen at about 10 years of age [148]. Thus, all neonates, especially less than 2 weeks of age, essentially belong to the PM phenotype. A similar phenomenon is observed with CYP2E1 and CYP3A4 [149–151]. UGT2B7 is negligible in fetal liver and it takes over 6 months to reach adult activity [152,153].

In short, research to uncover clinically actionable pharmacogenetic interactions requires a ‘birds-eye view’ – considering all influential variables. Solutions to this problem include ‘genome-wide association studies’ and the ‘gene-signature’ approach. In a study by Biesiada *et al.* [154], the researchers examined multiple SNPs of a panel of genes including *ABCB1*, *COMT*, *OPRM1*, *FAAH*, *UGT2B7*, *ADRB2*, *GCH1*, *TRPA1*, *DRD2*, *ANKK1*, *MC1R* along with other demographic factors like sex, race, age and OSA to create a predictive model for morphine-induced RD. They were able to identify a low RD risk cluster and high RD risk cluster, with a number of subclusters under them, forming a continuum of gradually increasing RD risk. The relative risk for RD frequency was significantly higher (up to nearly fourfold difference) in the high-risk cluster versus the low-risk cluster. Thus, risk stratification using a model that takes into account all genetic and non-genetic factors is a vital step in the right direction. Validating genotype–phenotype associations is also important, as this will impact the decision-making process of drug and dose selection to improve clinical practice safety and efficiency. Proteomic, transcriptomic and metabolomic information should be integrated with genetic discoveries and bioinformatics [83]. Much work in this field remains to be done – starting from gathering evidence. Incorporation of these models into machine-learning algorithms and clinical decision support tools will ultimately lead the treating clinician to implement ‘personalized medicine’ in routine clinical practice.

Future directions

Knowledge of genetic influences on drug response is rapidly expanding. Clinical guidelines for select actionable drug–gene pairs are being released by organizations like the CPIC (<https://cpicpgx.org/guidelines/>), the Dutch Pharmacogenetics Working Group (www.knmp.nl/), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS; <http://cpnds.ubc.ca/>) and the European Medicines Agency-Pharmacogenomics Working Party (EMA-PgWP; www.ema.europa.eu/en). Online databases like the Pharmacogenetics Knowledge Base (PharmGKB) serve as an integrated source of pharmacogenetic information from a multitude of sources (www.pharmgkb.org/). Despite this growing knowledge base on the pharmacogenetics of anesthetic medications, actionable drug–gene pairs still remain very few and clinical implementation may be challenging.

The NIH-funded Implementing GeNomics In pracTice (IGNITE) working group supports the development and investigation of genomic medicine practice models to enhance implementation into routine clinical practice [155]. The IGNITE group promotes multicenter collaboration with the ultimate goal of advancing pharmacogenetic practice. As economic constraints are an important barrier, IGNITE aims to provide evidence to support reimbursement for testing and broaden clinical implementation.

A recently published multisite investigation of clinical implementation of CYP2D6 genotyping to guide drug therapy described various roadblocks including lack of stakeholder support, gene complexity and phenotype assignment [156]. Implementation is also hampered by limited provider awareness of the resource availability and the clinical actionability of the knowledge [157]. Technical issues include difficulty in including information in electronic health records due to the complexity of the genetic information, variable phenotype assignment and drug–drug–gene interaction causing phenoconversion. Logistical issues like limited availability of personnel and support staff and difficulty in building a sustainable reimbursement model pose a challenge to implementation. At the time of writing, a large multicentric prospective randomized controlled trial is underway (Indiana Genomics Implementation; an Opportunity for the Underserved; INGENious) [158] to assess implementation of pharmacogenetics guided therapy with a planned sample size of 6000 participants. This would provide insight into the cost and clinical outcome benefits of integrating pharmacogenetics into clinical practice. Eadon *et al.* have described a model for the formation of a pharmacogenomics consultation service at a safety-net hospital serving low-income, uninsured and vulnerable population, addressing concerns of adjudication, credentialing and funding [159].

Conclusion

Our knowledge of pharmacogenetics related to anesthetic agents is expanding. Widespread acceptance of personalized medicine is on the horizon. As we accumulate evidence from large studies on clinical implementation, we will learn how to overcome challenges to integration and produce actionable clinical pharmacogenetic guidelines for anesthetic drugs.

Financial & competing interests disclosure

Funding support was provided by the Department of Anesthesia, Indiana University School of Medicine, Indianapolis, IN, USA and NIH R01 HD089458 (Principal Investigator: S Sadhasivam) and R21 HD094311 (Principal Investigator: S Sadhasivam). The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Pharmacogenetics in anesthesia & analgesia

- An expanding knowledge base in pharmacogenetics has paved way for personalized medicine in the field of anesthesia and pain medicine.
- Recent clinical research on genetic variations in opioid response has led to the characterization of a number of drug–gene pairs, the most actionable among them being *CYP2D6* polymorphism affecting responses of codeine and tramadol.
- The Clinical Pharmacogenetics Implementation Consortium has published guidelines for opioid therapy including avoiding codeine and tramadol, and possibly avoiding hydrocodone and oxycodone for optimal efficacy and safety in those with poor metabolizer and ultrarapid metabolizer *CYP2D6* phenotypes respectfully.
- *OPRM1* polymorphism affecting opioid analgesia and adverse effects have also been well studied and is being actionable.
- Pseudocholinesterase deficiency causing prolonged apnea after succinylcholine is a rare, but well-recognized pharmacogenetic disorder. High-risk populations with greater prevalence of pseudocholinesterase deficiency have been identified.
- Malignant hyperthermia (MH) is a rare, fatal, genetically mediated reaction to inhaled anesthetics and succinylcholine. MH susceptibility variants have been identified in genes like *RYR1*, *CACNA1S*, *STAC3* that are involved in skeletal muscle calcium metabolism. As the penetrance with the known variants are low and there may be a number of other uncharacterized variants, currently skeletal muscle biopsy and caffeine-halothane contracture test is still the gold standard to identify MH susceptible individuals.
- Genetic variants causing increased risk for postoperative nausea and vomiting have been identified. *CYP2D6* ultrarapid metabolizers have been shown to respond poorly to ondansetron therapy.
- *CYP2C9* polymorphism has been shown to influence nonsteroidal anti-inflammatory drug metabolism, certain variants have been shown to increase the risk of nonsteroidal anti-inflammatory drug-related adverse events.
- Genetic variants influencing response to sedative, hypnotics and local anesthetics have been documented. But the evidence is inconclusive.

Future directions

- Future direction includes large multicenter studies with robust methodology, using multi-gene signature, genome wide association approaches, inclusion of proteomic, transcriptomic, metabolomic information and randomized trials to analyze the cost–effectiveness, identify and address road blocks for clinical implementation.
- Machine learning and clinical decision support tools integrated with electronic health records are essential for analysis of complex genetic data and personalizing drug therapy to have a broader impact.

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