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Genetics of perioperative pain management

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Abstract

Purpose of review—The current review will discuss the current literature on genetics of pain and analgesia, with special emphasis on perioperative setting. We will also discuss pharmacogenetics-based management guidelines, current clinical status and future perspectives.

Recent findings—Recent literature suggests that the interindividual variability in pain and postoperative analgesic response is at least in part because of one's genetic make-up. Some of the well characterized polymorphisms that are associated with surgical pain and opioid-related postoperative adverse outcomes are described in catechol-*O*-methyl transferase, CYP2D6 and μ -opioid receptor (OPRM1), ATP-binding cassette subfamily B member 1, *ABCC3*, organic cation transporter 1 genes. Clinical Pharmacogenetics Implementation Consortium has put forth recommendations on CYP2D6 genotype-based opioid selection and dosing. The list of drug–gene pairs studied continue to expand.

Summary—Pharmacogenetic approach marks the dawn of personalized pain medicine both in perioperative and chronic pain settings.

Keywords

analgesia; genetics; opioids; pain; personalized analgesia; pharmacodynamics; pharmacogenomics; pharmacokinetics; postoperative pain; respiratory depression

INTRODUCTION

The past decade has seen tremendous increase in the volume of research on genetics of nociception and analgesia, after the completion of the human genome project. Though genetic factors play a major role in the robust interindividual variability in nociception, the pain experience itself is influenced by a number of other factors such as mood, behavior, expectations, past life experiences, sex and other psychosocial and environmental factors. Understanding the role of genetics is a first and the most essential step toward explaining the disparity in pain threshold and tolerance and in susceptibility to chronic pain, besides explaining interindividual variations in analgesia and adverse outcomes. It also opens up the

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Conflicts of interest

There are no conflicts of interest.

door for exploring the possibility of personalized analgesic interventions to improve surgical pain relief while avoiding adverse effects.

The current review will give an overview of the genetics of nociception, relevant to perioperative pain, chronic postoperative pain and pharmacogenetics of analgesic drugs.

PAIN AND GENOMICS

Nociception involves a number of components including the nociceptors, inflammatory mediators, nociceptive, antinociceptive and pain modulating neuronal pathways and the respective neurotransmitters, ion channels on the neurons, receptors of the neurotransmitters and the second messenger systems to name a few. They serve to transduce, conduct and modulate noxious stimuli. Pain is a subjective, emotional experience, resulting from the complex processing of the noxious stimulus in the pain matrix of the brain. A number of genetic polymorphisms have been described in the above components, resulting in a wide range of variability. Functional pain genomics is the study of genetic basis of pain experience. This includes genetics of nociception, heritable pain conditions like erythromelalgia, congenital insensitivity to pain etc., chronic pain conditions as well as genetic basis of psychological factors that define the pain experience.

Pain perception

Catecholamines like epinephrine, nor-epinephrine and dopamine play a pivotal role in pain transmission and modulation. Catechol-*O*-methyl transferase (COMT) is the enzyme involved in degradation of catecholamines. Decreased activity of COMT results in higher levels of catecholamines, therefore, increased sensitivity to pain [1,2]. Elevated dopamine levels cause a depletion of enkephalins, leading to an upregulation of opioid receptors, causing increased temporal summation and heightened pain sensitivity [3]. Increased levels of epinephrine and the subsequent stimulation of $\beta_2/3$ receptors has also been described [4]. Three haplotypes [low pain sensitivity (LPS), average pain sensitivity and high pain sensitivity (HPS)] have been described based on the four common single nucleotide polymorphisms (SNPs) of the gene coding for COMT [2]. The COMT polymorphisms are found to influence RNA stability and protein translation [5,6]. The LPS phenotype exhibited the highest COMT activity and HPS the lowest. Even a single LPS haplotype has been found to decrease risk of temporomandibular joint disorder [2], postoperative pain and also affect opioid consumption [7,8]. In a study of postoperative pain and opioid consumption in children undergoing adenotonsillectomy, minor allele carriers were found to have significantly greater analgesic requirement compared with homozygotes of major alleles [9].

Polymorphisms in *OPRM1* gene, have been known to alter experimental pain sensitivity by affecting the μ -opioid receptor function [10]. *OPRM1* SNPs also influence postoperative pain [8] and opioid requirements in chronic pain conditions [11]. Sexual dimorphism in heat pain sensitivity secondary to SNPs in *OPRD1* gene coding for δ -opioid receptors has been reported [12].

Guanosine Triphosphate (GTP) cyclohydrolase 1 is the rate limiting enzyme in the synthesis of tetrahydrobiopterin (BH₄), which is an essential cofactor in the formation of pain

modulators like serotonin, dopamine, nor-epinephrine, epinephrine and nitric oxide. Existence of a specific haplotype of *GCHI* gene encoding for GTP cyclohydrolase 1 with lower levels of enzyme activity, has been shown to decrease experimental pain sensitivity and also decrease the levels of pain after lumbar discectomy for radicular lower back pain [13]. The protective haplotype is associated with delayed need for opioid therapy for cancer pain [14]. Research on the role of BH4 blocking drugs as potential analgesics is ongoing [15]. Sulfasalazine decreases levels of BH4 and has been proposed for neuropathic pain [16].

Polymorphisms associated with variation in pain sensitivity have been reported in genes coding for melanocortin 1 receptor (MC1R) [17], transient receptor potential V1 [12], transient receptor potential A1, monoamine oxidase, serotonin transporter (SLC6A4), norepinephrine transporter (SLC6A2) [18] and fatty acid amide hydrolase [19] among others.

Inflammation is an important response to trauma that contributes to pain. Hence it is intuitive that genetic variants in inflammatory mediators result in varying pain perception and analgesia. For instance, IL-1 plays a critical part in postincision pain [20].

Polymorphisms of IL-1 receptor antagonist gene causing a lower concentration of the antagonist, results in higher postoperative opioid consumption [7].

Chronic postsurgical pain

Pain lasting for 3 months or more after surgery is called chronic postsurgical pain (CPSP). This is encountered by 15–30% of the surgical population and may last lifelong in some [21,22]. The role of genetic polymorphisms and epigenetic modifications have been suggested in persistence of pain beyond the duration of tissue healing. For instance, COMT polymorphisms have been associated with development of CPSP [23,24]. A variant of protein kinase C alpha gene (PRKCA) has been reported in patients suffering from neuropathic pain following knee arthroplasty [25]. It is remarkable that PRKCA has been associated with long-term potentiation and synaptic plasticity [21].

Epigenetics and acute to chronic transition of pain

Epigenetics refers to the modification of gene expression under environmental influence, that does not alter the gene sequence itself. DNA methylation and histone deacetylation are some examples. There is evidence suggesting the role of epigenetic modification in the development of CPSP [21]. Drugs targeting epigenetic modifications like zebularine (DNA methyltransferase inhibitor) and valproic acid (histone deacetylase inhibitor) are being studied for pain [26,27].

Psychosocial factors, race and sex

A number of factors, other than genotype *per-se*, moderate the 'gene-pain' relation. For instance, advancing age appears to decrease the influence of pain-specific genotype on actual pain experience, as environmental factors play a greater role with age [28,29]. Psychological factors have a big part to play in pain perception. Polymorphism in serotonin receptor genes 5HTR1A and 5HTR2A have been related to postoperative pain and depression [30]. Haplotype variants ADRB2 gene coding for β_2 -adrenergic receptors have

been related to a number of pain-related psychologic and physiological phenotypes. A certain variant has been related to positive psychological characteristics such as lower levels of anxiety and somatization and lower risk of chronic pain [31].

Experimental pain models indicate unequal burden of pain in different races [32,33]. In a prospective trial of children undergoing tonsillectomy, it was found that African-American children had greater postoperative pain and white children had higher incidence of opioid-related adverse events [34]. Though genetic differences are known to play a role [35], it is not quite clear about the relative contributions of genetic, socioenvironmental factors and past life experiences.

Many studies examining the sex difference in pain point toward greater sensitivity to experimental pain, higher prevalence of chronic pain and higher postoperative pain in women [36,37]. Though a number of factors are known to contribute to this difference, genetic dimorphism plays a major role. The best characterized dimorphism being the *MC1R* gene coding for melanocortin receptor. Certain allelic variants of the *MC1R* significantly improve κ -opioid analgesia in red-haired women compared with the men counterparts [17].

PHARMACOGENETICS

Pharmacogenetics is the study of genetic variations affecting individual drug response. This includes genetic factors influencing the pharmacokinetics and pharmacodynamics of the drug. Genetic variations can be observed in the metabolism of drugs (pharmacokinetics) or at the site of action of the drug (pharmacodynamics).

Opioids

Polymorphisms have been described in enzymes involved in opioid metabolism, various transporters as well as opioid receptors. Like most other drugs, opioids undergo phase I metabolism mediated by the cytochrome P450 (CYP) family of enzymes. Some of the prodrugs are converted to their active forms and some are inactivated by CYP enzymes. Codeine is a prodrug that undergoes CYP2D6 mediated *O*-demethylation to produce its active form, morphine. There are more than 100 alleles of CYP2D6 described, with varying population frequencies [38,39]. They can be classified into four broad phenotypes: ultrarapid, extensive, intermediate and poor metabolizers [40]. Poor metabolizers show substandard analgesic response to codeine due to low levels of morphine, and ultrarapid metabolizers exhibit excessive and significant adverse events including respiratory depression, in response to codeine. Cases of respiratory depression and death after codeine administration have been reported, especially in children and breast-fed infants of ultrarapid metabolizer mothers taking codeine [41–44].

Tramadol is another CYP2D6 substrate, to form *O*-desmethyl tramadol, which is more active on μ -opioid receptor (MOR) than tramadol. CYP2D6 polymorphism markedly affects the safety and anal-gesic efficacy of tramadol [45,46]. Respiratory depression has been reported in ultrarapid metabolizers after tramadol administration [47].

Reports of mortality after codeine and tramadol has led the food and drug administration (FDA) to issue warnings against the use of tramadol and codeine in all children less than 12 years, children less than 18 years with obstructive sleep apnea (OSA), obesity or chronic lung disease and after adeno-tonsillectomy and also in breast-feeding mothers [48].

Methadone is administered as a racemic mixture of (*R*)-enantiomers and (*S*)-enantiomers, with the (*R*)-accounting for the majority of the opioid effect and the (*S*)-enantiomer responsible for adverse effects [49,50]. CYP2B6 primarily metabolizes methadone to the inactive metabolite 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine. CYP3A4 and CYP2D6 have also been shown to be involved in methadone metabolism. The CYP2B6 gene is highly polymorphic with over 38 variants identified to date [51]. *CYP2B6*6* is the most common and clinically relevant allele, with a markedly reduced hepatic expression and activity [52]. Carriers of this allele, particularly homozygotes exhibit slower elimination increasing risk of overdose after administration [53] (Table 1).

Fentanyl, alfentanil and sufentanil metabolism are subject to genetic variability in the CYP3A system [54,55].

Uridine diphosphate glucuronosyltransferase (UGT) is a phase II enzyme, and morphine is subject to conjugation by UGT2B7. Morphine-3-glucuronide is the major metabolite, and morphine-6-glucuronide is the more active, minor metabolite [56]. Polymorphism in the UGT enzyme and variable response to morphine have been reported [3,57]. ATP-binding cassette subfamily B member 1 (ABCB1), also known as multidrug resistance 1 is an efflux protein that determines the quantity of morphine reaching the central nervous system and binding to MOR. Variable response to morphine has been reported secondary to polymorphisms in *ABCB1* gene and *OPRM1* gene coding for MOR [10,58–60]. Organic cation transporter 1 (OCT1) mediates hepatocellular uptake of morphine [61] (Table 1).

Genetic polymorphisms have been studied in *OCT1* gene. There is evidence of decreased clearance of *O*-desmethyl tramadol in patients with decreased OCT1 activity, leading to higher plasma concentration and improved analgesic efficacy [62].

Nonfunctional variants of melanocortin (*MC1R*) gene, which results in red hair, are associated with sexual dimorphism in κ -opioid analgesia. Red-haired women with certain *MC1R* variants are known to require a lesser dose of pentazocine compared with red-haired men [17,63].

OPRM1 polymorphism has been studied to influence fentanyl dose requirements after orofacial surgery and intrathecal fentanyl doses for labor analgesia [64–66]. κ -agonist such as buprenorphine may be used instead of a μ -agonist such as morphine in patients with an inactive *OPRM1* allele [67]. Variable response to remifentanyl has been documented secondary to polymorphism in serotonin transporter (5-HTT) [68].

NSAIDs

NSAIDs are predominantly metabolized by the CYP2C9 enzyme system. Poor metabolizers with lower CYP2C9 enzyme activity show decreased clearance and high incidence of

adverse events like gastro-intestinal bleeding [69,70]. The bleeding risk rises several-fold when warfarin, another CYP2C9 substrate is coadministered in these patients [71]. Celecoxib, a cyclo-oxygenase 2 (COX-2) inhibitor is a substrate of CYP2C9 enzyme and high plasma concentrations have been reported in poor metabolizers [72]. FDA has issued drug label suggesting dose reduction or alternative therapy based on CYP2C9 status, considering the high risk of cardiovascular and gastrointestinal side effects in poor metabolizers [73]. For poor metabolizers, treatment with NSAIDs should start at half the lowest recommended dose to avoid adverse cardiovascular and gastrointestinal events [67]. Parecoxib is a prodrug that is converted to its active form valdecoxib by the polymorphic CYP3A enzyme system [39].

NSAIDs act through inhibition of COX-1 and COX-2 enzymes, that are coded by prostaglandinendoperoxide synthase (PTGS) 1 and 2, respectively [74]. Patients with increased expression of PTGS 2 may have better analgesic response to COX-2-specific agents like celecoxib, valdecoxib etc. compared with nonspecific NSAIDs.

Local anesthetics

Regional techniques are a preferred modality of perioperative analgesia, favored for their superior analgesia with minimal adverse effects. Local anesthetics act by blocking sodium channels and mutations in SCN9A channels coding for sodium channels have been shown to demonstrate resistance to lidocaine [75]. Genetic variability has also been associated to risk of local anesthetics toxicity. MC1R variants with decreased lidocaine efficacy has also been described [76].

CLINICAL APPLICATION AND RECOMMENDATIONS

Clinical implementation of pharmacogenetics in pain remains limited due to a number of barriers that include inexperience, accessibility and cost of genetic testing and lack of integration of genetic test results to clinical decision support in electronic medical records. Nevertheless, the slow translation of pharmacogenomics into clinical practice is evident from the fact that the FDA had issued warnings and drug inserts increasingly contain dosing statements based on the patient's genetic makeup.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) has put forth dosing guidelines for a number of drugs, and one of the most prominent examples relevant to pain medicine is CYP2D6 status and dosing of opioids like codeine and tramadol [77] (Table 2). Drug-gene pairs are systematically classified into various CPIC levels based on the strength of evidence. CPIC level 'A' denotes that 'genetic information should be used to change prescribing of affected drug' and level 'B' denotes that 'genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as nongenetically based dosing' [78].

Table 2 shows the CPIC recommendations for codeine and tramadol [77]. Since weak opioids like codeine and tramadol form the second step of the WHO pain management ladder, an alternative therapy in ultrarapid metabolizer or poor metabolizer would constitute a step up to morphine or step down to NSAIDs. A monitored trial of oxycodone and

hydrocodone could be viable alternatives in these patients because, despite being CYP2D6 substrates to a smaller extent, they also have analgesic activity of their own [79]. CPIC guidelines are not yet available for oxycodone, celecoxib and methadone despite CPIC level A or B.

CONCLUSION

As regulatory bodies advocate the use of genetic information in patient management and genetic testing becomes widely available and affordable, the era of personalized perioperative analgesia is on the horizon, especially with growing literature on surgical pain, CPSP and opioid analgesia/adverse effects. A good starting point would be to target the high-risk population [80]. As far as opioids are concerned, high risk population would comprise of small children, breast-feeding women, patients with generally increased risk of respiratory depression such as those with OSA, chronic lung disease, children undergoing adeno-tonsillectomy and ethnic groups with extremely high prevalence of certain polymorphisms and genetic variations. For instance, CYP2D6 ultrarapid metabolizer status is as high as 30% in Ethiopians (compared with ~1% in whites); the Surui Indians of the Amazon are said to have greater than 80% prevalence of homozygous carriers of reduced activity allele of OCT1 [62]. Pharmacogenetics being a science of outliers, genetic testing and reporting of patients at higher risk for an unexpected and significant adverse event to an analgesic in the perioperative period would contribute to the growing body of evidence. Large multicenter randomized controlled trials in perioperative setting, with standardized and sensitive outcome measures are also an essential step toward personalized pain medicine.

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■ of special interest

■ ■ of outstanding interest

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KEY POINTS

- Pain is a complex subjective phenomenon with a wide range of variability.
- Genetic variations play important part in a person's pain experience and response to perioperative analgesic therapy.
- Pharmacogenetics of perioperative analgesics (especially opioids) may explain ineffective analgesia in some while excessive adverse events in others.
- Understanding genetic contributions to interindividual variability will help tailor perioperative pain management and optimize outcomes.

Table 1.

Perioperative opioids and genetic variations associated with clinical outcomes

Substrate	Gene	Functionally important allelic variant(s)	Effects associated with variant allele(s)
Morphine	<i>UGT2B7</i>	- 161C>T and 802C>T	Decreased morphine levels and morphine-6-glucuronide ratios in adults; no effect in children
	<i>ABCB1</i>	Multiple SNPs including GG and GA genotypes of rs9282564	Increased analgesic effect. Increased risk for postoperative respiratory depression in children
	<i>ABCC3</i>	rs4148412 AA and rs4973665 CC genotypes	Increased liver formation clearance of morphine metabolites and associated transport and morphine-related postoperative respiratory depression in children
	<i>FAAH</i>	Multiple SNPs including rs324420	High risk for morphine-induced respiratory depression and PONV in children; decreased hypercarbic ventilator response and impending respiratory depression in pediatric postoperative setting
	<i>OCT1</i>	Multiple SNPs including rs12208357 and rs72552763 GAT deletion	Impaired liver uptake of morphine; increased risks of morphine-related PONV and respiratory depression leading to prolonged PACU stay
	<i>COMT</i>	Multiple SNPs including 472G>A (rs4680)	Decreased morphine requirements, pain scores and postoperative analgesic interventions
	<i>OPRM1</i>	118A>G (rs1799971)	Higher pain scores and increased opioid requirements in patients with G allele; AA genotype with higher risk of postoperative respiratory depression in children
Fentanyl	<i>CYP3A4</i>		
	<i>OPRM1</i>	118A>G (rs1799971)	Decreased fentanyl requirements with G allele Decreased ED50 of intrathecal fentanyl with G allele
Remifentanyl	<i>5-HTT</i>	rs25531	Better analgesia with low 5-HTT expression
Hydromorphone	<i>CYP2C9</i>		
	<i>CYP3A4</i>		
	<i>CYP3A5</i>		
Methadone	<i>UGT1A3</i>		
	<i>CYP2B6</i>	*6	Slow metabolizer phenotype
	<i>CYP3A4</i>		
	<i>ABCB1</i>		
	<i>OPRM1</i>		

PONV, postoperative nausea and vomiting; SNP, single nucleotide polymorphism

Table 2.

Clinical Pharmacogenetics Implementation Consortium recommendations

Drug	Gene involved	CPIC level	Phenotype	Recommendation
Codeine Tramadol	CYP2D6	A	UM	Avoid codeine due to increased risk of toxicity. Tramadol, hydrocodone and oxycodone are also metabolized by CYP2D6 and are not good substitutes. Alternatives not affected by CYP2D6 phenotype include morphine and nonopioids
			EM	Label recommended dosing of codeine and tramadol
			IM	Label recommended dosing of codeine and tramadol; monitor for response. If no response, consider alternative like morphine or nonopioid
			PM	Avoid codeine due to risk of ineffective analgesia. Tramadol, hydrocodone and oxycodone are also metabolized by CYP2D6 and are not good substitutes. Alternatives not affected by CYP2D6 phenotype include morphine and nonopioids
	Gene involved	CPIC level		
Oxycodone	CYP2D6	A		
Methadone	CYP2B6	B		
Celecoxib	CYP2C9	B		

CPIC, Clinical Pharmacogenetics Implementation Consortium; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.