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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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 β2/3 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 *GCH1* 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 OPRMI allele [67]. Variable response to remifentanil 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 metha-done 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.

Acknowledgements

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Diatchenko L, Nackley AG, Slade GD, et al. Catechol-*O*-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. Pain 2006; 125:216–224. [PubMed: 16837133]

2. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet 2005; 14:135–143. [PubMed: 15537663]

3. De Gregori M, Diatchenko L, Ingelmo PM, et al. Human genetic variability contributes to postoperative morphine consumption. J Pain 2016;17: 628–636. [PubMed: 26902643]

4. Nackley AG, Tan KS, Fecho K, et al. Catechol-*O*-methyltransferase inhibition increases pain sensitivity through activation of both beta2- and beta3-adrenergic receptors. Pain 2007; 128:199–208. [PubMed: 17084978]

5. Tsao D, Shabalina SA, Gauthier J, et al. Disruptive mRNA folding increases translational efficiency of catechol-*O*-methyltransferase variant. Nucleic Acids Res 2011; 39:6201–6212. [PubMed: 21486747]

6. Nackley AG, Shabalina SA, Tchivileva IE, et al. Human catechol-*O*-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. Science 2006; 314:1930–1933. [PubMed: 17185601]

7. Candiotti KA, Yang Z, Buric D, et al. Catechol-*O*-methyltransferase polymorphisms predict opioid consumption in postoperative pain. Anesth Analg 2014; 119:1194–1200. [PubMed: 25185591]

8. Henker RA, Lewis A, Dai F, et al. The associations between OPRM 1 and COMT genotypes and postoperative pain, opioid use, and opioid-induced sedation. Biol Res Nurs 2013; 15:309–317. [PubMed: 22718527]

9. Sadhasivam S, Chidambaran V, Olbrecht VA, et al. Genetics of pain perception, COMT and postoperative pain management in children. Pharmacogenomics 2014; 15:277–284. [PubMed: 24533707]

10. Fillingim RB, Kaplan L, Staud R, et al. The A118G single nucleotide polymorphism of the μ-opioid receptor gene (OPRM1) is associated with pressure pain sensitivity in humans. J Pain 2005; 6:159–167. [PubMed: 15772909]

11. Janicki PK, Schuler G, Francis D, et al. A genetic association study of the functional A118G polymorphism of the human mu-opioid receptor gene in patients with acute and chronic pain. Anesth Analg 2006; 103:1011–1017. [PubMed: 17000822]

12. Kim H, Neubert JK, San Miguel A, et al. Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. Pain 2004; 109:488–496. [PubMed: 15157710]

13. Tegeder I, Costigan M, Griffin RS, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med 2006; 12:1269–1277. [PubMed: 17057711]

14. Lotsch J, Klepstad P, Doehring A, Dale O. A GTP cyclohydrolase 1 genetic variant delays cancer pain. Pain 2010; 148:103–106. [PubMed: 19959292]

15. Latremoliere A, Costigan M. GCH1, BH4 and pain. Curr Pharm Biotechnol 2011; 12:1728–1741. [PubMed: 21466440]

16. Costigan M, Latremoliere A, Woolf CJ. Analgesia by inhibiting tetrahydrobiopterin synthesis. Curr Opin Pharmacol 2012; 12:92–99. [PubMed: 22178186]

17. Mogil JS, Ritchie J, Smith SB, et al. Melanocortin-1 receptor gene variants affect pain and mu-opioid analgesia in mice and humans. J Med Genet 2005; 42:583–587. [PubMed: 15994880]

18. Kim H, Lee H, Rowan J, et al. Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute postsurgical pain in humans. Mol Pain 2006; 2:24. [PubMed: 16848906]

19. Kim H, Mittal DP, Iadarola MJ, Dionne RA. Genetic predictors for acute experimental cold and heat pain sensitivity in humans. J Med Genet 2006; 43:e40. [PubMed: 16882734]

20. Wolf G, Livshits D, Beilin B, et al. Interleukin-1 signaling is required for induction and maintenance of postoperative incisional pain: genetic and pharmacological studies in mice. Brain Behav Immun 2008; 22: 1072–1077. [PubMed: 18442892]

21. James SK. Chronic postsurgical pain: is there a possible genetic link? Br J Pain 2017; 11:178–185. [PubMed: 29123662]

22. Clarke H, Katz J, Flor H, et al. Genetics of chronic postsurgical pain: a crucial step toward personal pain medicine. Can J Anaesth 2015; 62:294–303. [PubMed: 25471684]

23. Hickey OT, Nugent NF, Burke SM, et al. Persistent pain after mastectomy with reconstruction. J Clin Anesth 2011; 23:482–488. [PubMed: 21911195]

24. Lee PJ, Delaney P, Keogh J, et al. Catecholamine-*o*-methyltransferase polymorphisms are associated with postoperative pain intensity. Clin J Pain 2011; 27:93–101. [PubMed: 20842020]

25. Warner SC, van Meurs JB, Schiphof D, et al. Genome-wide association scan of neuropathic pain symptoms post total joint replacement highlights a variant in the protein-kinase C gene. Eur J Hum Genet 2017; 25:446–451. [PubMed: 28051079]

26. Viet CT, Dang D, Ye Y, et al. Demethylating drugs as novel analgesics for cancer pain. Clin Cancer Res 2014; 20:4882–4893. [PubMed: 24963050]

27. Bai G, Wei D, Zou S, et al. Inhibition of class ii histone deacetylases in the spinal cord attenuates inflammatory hyperalgesia. Mol Pain 2010; 6:51. [PubMed: 20822541]

28. Edwards RR. Genetic predictors of acute and chronic pain. Curr Rheumatol Rep 2006; 8:411–417. [PubMed: 17092439]

29. Neville KA, Becker ML, Goldman JL, Kearns GL. Developmental pharmacogenomics. Paediatr Anaesth 2011; 21:255–265. [PubMed: 21320234]

30. Lebe M, Hasenbring MI, Schmieder K, et al. Association of serotonin-1A and - 2A receptor promoter polymorphisms with depressive symptoms, functional recovery, and pain in patients 6 months after lumbar disc surgery. Pain 2013; 154:377–384. [PubMed: 23318131]

31. Diatchenko L, Anderson AD, Slade GD, et al. Three major haplotypes of the beta2 adrenergic receptor define psychological profile, blood pressure, and the risk for development of a common musculoskeletal pain disorder. Am J Med Genet B Neuropsychiatr Genet 2006; 141B:449–462. [PubMed: 16741943]

32. Rowell LN, Mechlin B, Ji E, et al. Asians differ from non-Hispanic whites in experimental pain sensitivity. Eur J Pain 2011; 15:764–771. [PubMed: 21561793]

33. Kim HJ, Yang GS, Greenspan JD, et al. Racial and ethnic differences in experimental pain sensitivity: systematic review and meta-analysis. Pain 2017;158:194–211. [PubMed: 27682208] ■ The meta-analysis reported that African-Americans, Asians and Hispanics had higher pain sensitivity compared with non-Hispanic whites, particularly lower pain tolerance, higher pain ratings and greater temporal summation of pain, which are important in clinical pain management.

34. Sadhasivam S, Chidambaran V, Ngamprasertwong P, et al. Race and unequal burden of perioperative pain and opioid related adverse effects in children. Pediatrics 2012; 129:832–838. [PubMed: 22529273]

35. Sadhasivam S, Krekels EH, Chidambaran V, et al. Morphine clearance in children: does race or genetics matter? J Opioid Manag 2012; 8:217–226. [PubMed: 22941849]

36. Fillingim RB, King CD, Ribeiro-Dasilva MC, et al. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009; 10:447–485. [PubMed: 19411059]

37. Fillingim RB, Maixner W, Amodei N, et al. Gender differences in the responses to noxious stimuli. Pain Forum 1995; 4:209–221.

38. Kapur BM, Lala PK, Shaw JLV. Pharmacogenetics of chronic pain management. Clin Biochem 2014; 47:1169–1187. [PubMed: 24912048]

39. Janicki PK. Pharmacogenomics of pain management. New York, NY: Springer; 2015; 21–31.

40. Owen RP, Sangkuhl K, Klein TE, Altman RB. Cytochrome P450 2D6. Pharmacogenet Genomics 2009; 19:559–562. [PubMed: 19512959]

41. Gasche Y, Daali Y, Fathi M, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 2004; 351:2827–2831. [PubMed: 15625333]

42. Ciszkowski C, Madadi P, Phillips MS, et al. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med 2009; 361:827–828. [PubMed: 19692698]

43. Madadi P, Ross CJD, Hayden MR, et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case–control study. Clin Pharmacol Ther 2009; 85:31–35. [PubMed: 18719619]

44. Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 2006; 368:704. [PubMed: 16920476]

45. Stamer UM, Lehnen K, Höthker F, et al. Impact of CYP2D6 genotype on postoperative tramadol analgesia. Pain 2003; 105:231–238. [PubMed: 14499440]

46. Stamer UM, Musshoff F, Kobilay M, et al. Concentrations of tramadol and *O*-desmethyltramadol enantiomers in different CYP2D6 genotypes. Clin Pharmacol Ther 2007; 82:41–47. [PubMed: 17361124]

47. Stamer UM, Stuber F, Muders T, Musshoff F. Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. Anesth Analg 2008; 107:926–929. [PubMed: 18713907]

48. FDA. FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. 2018; Available from: https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm.■■ The FDA has restricted the use of codeine and tramadol medicines in children as they carry serious risks, including slowed or difficult breathing and death, especially in children less than 12 years and breastfeeding mother (should not be used). In older children, the use of codeine and tramadol should be limited.

49. Crettol S, Deglon JJ, Besson J, et al. Methadone enantiomer plasma levels, CYP2B6, CYP2C19, and CYP2C9 genotypes, and response to treatment. Clin Pharmacol Ther 2005; 78:593–604. [PubMed: 16338275]

50. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet 2002; 41:1153–1193. [PubMed: 12405865]

51. PharmVar Ver 2.0 (7 2018) Pharmacogene variation consortium; Available from: https://www.pharmvar.org/.

52. Zanger UM, Klein K. Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance. Front Genet 2013; 4:24. [PubMed: 23467454]

53. Kharasch ED, Regina KJ, Blood J, Friedel C. Methadone pharmacogenetics: CYP2B6 polymorphisms determine plasma concentrations, clearance, and metabolism. Anesthesiology 2015; 123:1142–1153. [PubMed: 26389554]

54. Zhang H, Chen M, Wang X, Yu S. Patients with CYP3A4*1G genetic polymorphism consumed significantly lower amount of sufentanil in general anesthesia during lung resection. Medicine (Baltimore) 2017; 96:e6013. [PubMed: 28121959]

55. Kharasch ED, Walker A, Isoherranen N, et al. Influence of CYP3A5 genotype on the pharmacokinetics and pharmacodynamics of the cytochrome P4503A probes alfentanil and midazolam. Clin Pharmacol Ther 2007; 82:410–426. [PubMed: 17554244]

56. De Gregori S, De Gregori M, Ranzani GN, et al. Morphine metabolism, transport and brain disposition. Metab Brain Dis 2012; 27:1–5. [PubMed: 22193538]

57. Matic M, Norman E, Rane A, et al. Effect of UGT2B7 −900G>A (−842G>A; rs7438135) on morphine glucuronidation in preterm newborns: results from a pilot cohort. Pharmacogenomics 2014; 15:1589–1597. [PubMed: 25340733]

58. Fujita K, Ando Y, Yamamoto W, et al. Association of UGT2B7 and ABCB1 genotypes with morphine-induced adverse drug reactions in Japanese patients with cancer. Cancer Chemother Pharmacol 2010; 65:251–258. [PubMed: 19466410]

59. Sadhasivam S, Chidambaran V, Zhang X, et al. Opioid-induced respiratory depression: ABCB1 transporter pharmacogenetics. Pharmacogenomics J 2015; 15:119–126. [PubMed: 25311385]

60. Hayashida M, Nagashima M, Satoh Y, et al. Analgesic requirements after major abdominal surgery are associated with OPRM1 gene polymorphism genotype and haplotype. Pharmacogenomics 2008; 9:1605–1616. [PubMed: 19018716]

61. Tzvetkov MV, dos Santos Pereira JN, Meineke I, et al. Morphine is a substrate of the organic cation transporter OCT1 and polymorphisms in OCT1 gene affect morphine pharmacokinetics after codeine administration. Biochem Pharmacol 2013; 86:666–678. [PubMed: 23835420]

62. Tzvetkov MV. OCT1 pharmacogenetics in pain management: is a clinical application within reach? Pharmacogenomics 2017; 18:1515–1523. [PubMed: 29061087]

63. Mogil JS, Wilson SG, Chesler EJ, et al. The melanocortin-1 receptor gene mediates female-specific mechanisms of analgesia in mice and humans. Proc Natl Acad Sci U S A 2003; 100:4867–4872. [PubMed: 12663858]

64. Landau R, Kern C, Columb MO, et al. Genetic variability of the mu-opioid receptor influences intrathecal fentanyl analgesia requirements in laboring women. Pain 2008; 139:5–14. [PubMed: 18403122]

65. Fukuda K, Hayashida M, Ide S, et al. Association between OPRM1 gene polymorphisms and fentanyl sensitivity in patients undergoing painful cosmetic surgery. Pain 2009; 147:194–201. [PubMed: 19783098]

66. Hwang IC, Park JY, Myung SK, et al. OPRM1 A118G gene variant and postoperative opioid requirement: a systematic review and meta-analysis. Anesthesiology 2014; 121:825–834. [PubMed: 25102313]

67. Ko TM, Wong CS, Wu JY, Chen YT. Pharmacogenomics for personalized pain medicine. Acta Anaesthesiol Taiwan 2016; 54:24–30. [PubMed: 26976339]

68. Kosek E, Jensen KB, Lonsdorf TB, et al. Genetic variation in the serotonin transporter gene (5-HTTLPR, rs25531) influences the analgesic response to the short acting opioid remifentanil in humans. Mol Pain 2009; 5:37. [PubMed: 19570226]

69. Carbonell N, Verstuyft C, Massard J, et al. CYP2C9*3 loss-of-function allele is associated with acute upper gastrointestinal bleeding related to the use of NSAIDs other than aspirin. Clin Pharmacol Ther 2010; 87:693–698. [PubMed: 20445534]

70. Pilotto A, Seripa D, Franceschi M, et al. Genetic susceptibility to nonsteroidal anti-inflammatory drug-related gastroduodenal bleeding: role of cytochrome P450 2C9 polymorphisms. Gastroenterology 2007; 133:465–471. [PubMed: 17681167]

71. Visser LE, van Schaik RHN, van Vliet M, et al. Allelic variants of cytochrome P450 2C9 modify the interaction between nonsteroidal anti-inflammatory drugs and coumarin anticoagulants. Clin Pharmacol Ther 2005; 77:479–485. [PubMed: 15961979]

72. Kirchheiner J, Stormer E, Meisel C, et al. Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. Pharmacogenetics 2003; 13:473–480. [PubMed: 12893985]

73. FDA. Table of pharmacogenomic biomarkers in drug labeling. 2018 Available from: https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm.

74. Lee Y, Kim H, Wu T, et al. Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. Clin Pharmacol Ther 2006; 79:407–418. [PubMed: 16678543]

75. Sheets PL, Jackson JO, Waxman SG, et al. A Nav1.7 channel mutation associated with hereditary erythromelalgia contributes to neuronal hyperexcitability and displays reduced lidocaine sensitivity. J Physiol 2007; 581:1019–1031. [PubMed: 17430993]

76. Liem EB, Joiner TV, Tsueda K, Sessler DI. Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. Anesthesiology 2005; 102:509–514. [PubMed: 15731586]

77. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical pharmacogenetics implementation consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther 2014; 95:376–382. [PubMed: 24458010]

78. CPIC. Assignment of CPIC levels for genes/drugs. 2018; Available from: https://cpicpgx.org/prioritization/.

79. Smith DM, Weitzel KW, Cavallari LH, et al. Clinical application of pharmacogenetics in pain management. Per Med 2018; 15:117–126. [PubMed: 29714124] ■ Clinical recommendations exist to guide opioid treatment based on CYP2D6 genotype for codeine, tramadol, oxycodone and hydrocodone. Limited evidence supports the use of genetic data to guide chronic pain with TCAs and celecoxib.

80. Gammal RS, Crews KR, Haidar CE, et al. Pharmacogenetics for safe codeine use in sickle cell disease. Pediatrics 2016; 138:pii: e20153479. doi:10.1542/peds.2015-3479. [PubMed: 27335380] ■■ The study describes the implementation of CYP2D6 genotype-based codeine prescribing in electronic health record to prevent adverse drug events with interruptive alerts in patients with high-risk CYP2D6 status.

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	UGT2B7	−161C>T and 802C>T	Decreased morphine levels and morphine-6-glucuronide ratios in adults; no effect in children
	ABCB1	Multiple SNPs including GG and GA genotypes of rs9282564	Increased analgesic effect. Increased risk for postoperative respiratory depression in children
	ABCC3	rs4148412 AA and rs4973665 CC genotypes	Increased liver formation clearance of morphine metabolites and associated transport and morphine- related postoperative respiratory depression in children
	FAAH	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
	OCT1	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
	COMT	Multiple SNPs including 472G>A (rs4680)	Decreased morphine requirements, pain scores and postoperative analgesic interventions
	OPRM1	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	CYP3A4		
	OPRM1	118A>G (rs1799971)	Decreased fentanyl requirements with G allele Decreased ED50 of intrathecal fentanyl with G allele
Remifentanil	5-HTT	rs25531	Better analgesia with low 5-HTT expression
Hydromorphone	CYP2C9		
	CYP3A4		
	CYP3A5		
Methadone	UGT1A3		
	CYP2B6	*6	Slow metabolizer phenotype
	CYP3A4		
	ABCB1		
	OPRM1		

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

Drug	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.