Effect of genetic factors on opioid action
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Purpose of review
Opioid administration is a mainstay of anesthetic practice both for treating acute perioperative pain and for chronic pain syndromes. Growing pharmacogenetic data make it evident that many opiate-related phenomena are influenced by genetics. Genetic variation may significantly affect opiate absorption, distribution, metabolism, excretion and toxicity. We provide a current review of opiate pharmacogenetics.

Recent findings
Gene association studies should ideally be conducted in highly phenotyped populations of homogenous ethnic admixture with identified associations adjusted for patient demographics, risk factors and medications. Patients’ phenotype responses to opiates are the result of a complex interplay between genetic and environmental variables. Although most pharmacogenetic studies to date have assessed the association between individual single nucleotide polymorphisms that exist within selected single gene regions (e.g. opioid receptor mu-1, catechol-O-methyltransferase, cytochrome P450 2D6) and opiate effects, more recent studies have begun to assess the potential influences of gene–gene interactions.

Summary
Knowledge of genetic factors that affect opioid efficacy, metabolism, and side effects have the potential for personalizing both acute and chronic pain management, and for designing more effective opiate pain medications with lower side effect profiles.

Keywords
anesthesia, functional genomics, gene, opiate, opiate receptor, pharmacogenetics

Opioid genetics
Both endogenous (i.e. endorphins, enkephalins, and dynorphins) and exogenous opioids stimulate three receptor types: mu (μ), kappa (κ) and delta (δ). These opioid receptors are encoded by the opioid receptor mu-1 (OPRM1), opioid receptor kappa-1 (OPRK1) and the opioid delta receptor-1 (OPRD1) genes, respectively. In addition to opiate receptor binding, opioid analgesia and side effects may be influenced by genes related to molecular pathways whose primary functions are not pain signaling. Still, these genes may have secondary influences on opioid metabolism, transport and response.

The most common type of human genetic variation is the single nucleotide polymorphism (SNP), which is a ‘point mutation’ for which alternative nucleotide pairings occur at the same chromosomal position in different individuals. These alternate nucleotide pairings are known as alleles of the SNP, with the minor allele referring to the...

Hippocrates stated there is ‘a great difference in the constitution of individuals.’ Despite the truth of his observation it was rarely considered over the next two millennia with the exception of occasional and often erroneous reports of medication responses related to varied external patient characteristics such as skin tone or hair color. Recent advances in molecular biology have enabled researchers to identify associations between individuals’ genetic profiles and drug responses. Pharmacogenetics is the study of inherited differences in drug metabolism and response [1]. Pharmacogenetic research seeks to identify genetic variants that will enable clinicians to tailor therapeutic regimens for individual patients to maximize drug effectiveness while minimizing adverse side effects.

Opiate administration is a mainstay of anesthetic practice for treating acute perioperative pain and chronic pain syndromes. The pharmacokinetics (what a drug does to the body) and pharmacodynamics (what the body does to the drug) of administered opiates are subject to interindividual genetic variations that may explain observed variability in opioid efficacy. Knowledge of genetic factors that affect opioid efficacy, metabolism, and side effects have the potential for personalizing both acute and chronic pain management and for designing more effective opiates with reduced side effect profiles [2*,3].
Opioid receptor \(\mu\)-1 gene

Opioid receptors are G-protein-coupled receptors that are essential targets for opioid analgesia. Although all opioid receptors mediate opiate effects, \(\mu\) receptors have a primary role in analgesia. The \(OPRM1\) gene on chromosome 6q24–25 codes for four \(\mu\) opioid receptor subtypes (MOR-1, MOR-1A, MOR-1X, and MOR-1O) and contains more than 800 SNPs. To date, most studies have focused on the \(OPRM1\) A118G SNP (10–15% minor allele frequency in Caucasians), which results in a substitution of asparagine for aspartate at position 40 of the extracellular N-terminal domain (N40D) of the \(\mu\) receptor [9]. In both cancer and perioperative patients, carriers of the wild-type \(OPRM1\) A118G variant have significantly reduced analgesic requirements for either intravenous morphine or its metabolite morphine-6-glucuronide (M6G) [7**,9–13]. These studies suggested that the \(OPRM1\) A118G SNP could be used to predict and therefore plan adequate opioid dosages for individualized pain treatment and postoperative monitoring [14].

Several studies have also assessed the association between the \(OPRM1\) A118G SNP and postoperative pain control with neuraxially administered opioids (Table 1). Sia et al. [15*] recently assessed the A118G SNP for its association with adequacy of postoperative analgesia after administering 0.1 mg of intrathecal morphine to 588 women of Han Chinese descent who were undergoing cesarean section. The women were assessed postoperatively for interindividual differences in reported pain score, total 24 h dose of self-administered postoperative IV morphine, and incidence of postoperative nausea. Twenty-four hour postoperative total IV morphine administration differed significantly by the A118G genotype \((P = 0.001)\) when comparing the AA homozygous wild-type group (mean dose = 5.9 mg) with the AG heterozygous group (mean dose = 8.0 mg) and GG homozygous group (mean dose = 9.4 mg) [15*]. In contrast, the AA homozygous wild-type group was associated with the

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<td>Sia et al.</td>
<td>A118G</td>
<td>588</td>
<td>Chinese Singaporean women undergoing elective cesarean term delivery</td>
<td>Intrathecal morphine</td>
<td>1) Pain scores</td>
<td>Pain scores and IV morphine requirement lowest in AA group; postoperative nausea highest in AA group</td>
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<td>Hayashida et al.</td>
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<td>138</td>
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<td>Landau et al.</td>
<td>A118G</td>
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<td>Nulliparous women laboring at full term</td>
<td>Continuous spinal–epidural analgesia using intrathecal fentanyl</td>
<td>(ED_{50}) related to intrathecal fentanyl dose with respect to labor analgesia</td>
<td>Reduced intrathecal fentanyl (ED_{50}) in G allele carriers</td>
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**Table 1 Recent studies of \(OPRM1\) gene SNPs and opiate neuraxial analgesia**
highest incidence of nausea (9.6%) compared with the AG heterozygous group (5.6%) and GG homozygous group (1.2%). A second study assessed five tag SNPs within OPRM1 including the A118G SNP in 138 adult Japanese patients undergoing major open abdominal aortic surgery using combined general and epidural anesthesia, followed by continuous postoperative epidural analgesia with 0.25% bupivacaine plus morphine or fentanyl [16]. This study also noted significantly lower 24 h postoperative opioid requirements in the A118G SNP wild-type carriers. A third study by Landau et al. [17] recently assessed the association between the A118G SNP and analgesic efficacy of intrathecal fentanyl in 224 nulliparous laboring women who received combined spinal– epidural for labor analgesia. In contrast to the two previously mentioned studies that found that individuals who were AA carriers required less neuraxial opiates, Landau et al. found that homozygote carriers of the wild-type A118G SNP had a significantly higher intrathecal fentanyl median effective dose (ED₅₀) for labor analgesia (P < 0.001). It is possible that this may reflect a difference in neuraxial responsiveness to morphine versus fentanyl. Together, these findings suggest that larger randomized studies involving preoperative patient screening for the OPRM1 A118G SNP and alternate opioid pain management strategies are warranted.

Several recent studies have sought to elucidate the molecular mechanisms by which the OPRM1 A118G SNP may influence opioid responsiveness. One area of investigation concerns how opioid receptors interact with the hypothalamic–pituitary–adrenal axis regarding release of corticotropin releasing hormones and subsequent release of adrenocorticotropic hormone (ACTH) and cortisol. In a study of 29 healthy individuals who received the µ opioid receptor blocker naloxone versus placebo, individuals with one or two copies of the G allele showed a significantly greater cortisol response to naloxone than did the wild-type homozygotes (P < 0.03) [18]. However, this study needs to be replicated as it was small and contained patients of multiple ethnic backgrounds, a factor that can confound gene association study results when SNP frequencies or phenotypic outcomes vary between the ethnic groups being studied [18].

Oertel et al. [19] found that the presence of the wild-type OPRM1 A118G allele was associated with decreased requirements for alfentanil induced analgesia but was also associated with increased respiratory depression. Four heterozygous and six homozygous carriers of the variant OPRM1 118G allele received a computerized infusion of alfentanil to achieve target effect-site concentrations of 0, 33.33, 66.67 and 100 ng/mL. At each concentration level, analgesia was assessed by means of electrically and chemically induced pain, and respiratory depression was quantified by hypercapnic challenge and breathing frequency. Higher alfentanil concentrations were needed in homozygous carriers than in wild-type individuals (2–4 times) to produce the same degree of analgesia, whereas 10–12 times higher alfentanil concentrations were needed to produce the same degree of respiratory depression. Thus, the OPRM1 A118G SNP affects both analgesic and respiratory depressive effects of opiates.

**Cytochrome P450 2D6 gene**

Many opiates (e.g., codeine, dihydrocodeine, hydrocodone, tramadol) are primarily metabolized by the cytochrome P450 (CYP2D6) enzyme which is encoded by the highly polymorphic CYP2D6 gene. More than 100 alleles within the CYP2D6 gene have been identified, with related genotypes linked to four general phenotypes characterized by differing rates of opiate metabolism: poor metabolizer, intermediate metabolizer, extensive metabolizer, and ultra-rapid metabolizer. Poor metabolizers have two inactive (nonfunctional) alleles of a given variant within the CYP2D6 gene and are therefore at highest risk for opiate analgesic treatment failure (prodrug does not get metabolized quickly enough to active analgesic opiate metabolites) [20]. The poor metabolizer phenotype occurs in 7–10% of Caucasians [9]. Individuals carrying one or two copies of a wild-type (functional) CYP2D6 gene variant are extensive metabolizers (metabolize CYP2D6 substrates normally) and tend to have better analgesic responses to opiates than poor metabolizers. Duplication of the CYP2D6 gene results in the ultra-rapid metabolizer phenotype. Individuals with the ultra-rapid metabolizer phenotype have more than two functional copies of wild-type alleles, resulting in rapid opiate metabolism that can lead to analgesic failure or exaggerated opiate side effects depending upon whether the prodrug or its metabolite is most active [9,21]. However, CYP2D6 activity is not affected by genetics alone. Concurrent administration of medications that are also metabolized by the cytochrome P450 system (drugs that can induce or inhibit CYP2D6 enzyme activity) can imitate genetically mediated alterations in opiate metabolism. For example, paroxetine, amiodarone, cimetidine, and ranitidine are well known CYP2D6 inhibitors. Furthermore, factors such as impaired renal or hepatic metabolism can lead to high plasma levels of active opiate drug, particularly in ultra-rapid metabolizers receiving opiates with an active metabolite. Thus, assessment of CYP2D6 related opiate metabolism phenotypes and associated responses in opiate analgesic action and side effects should seek to take into account both genetic and nongenetic influences on plasma opiate concentrations and related physiologic responses.

CYP2D6 metabolizes tramadol to the analgesic opioid receptor agonist O-desmethyltramadol (O-DT) that has a higher µ opioid receptor affinity and analgesic efficacy
than the tramadol prodrug. Stamer et al. [22] genotyped 174 patients who received IV tramadol for postoperative analgesia after major abdominal surgery. The variability of response to O-DT was closely correlated to CYP2D6 genotypes. Specifically, the poor metabolizer CYP2D6 genotype was associated with poor analgesia in response to tramadol administration, with nonresponse rates to tramadol treatment four-fold higher in poor metabolizer individuals than in individuals with other functional CYP2D6 genotypes (P < 0.001) [22]. Similarly, Foster et al. [20] described a patient who experienced inadequate pain control when multiple different opiates were administered after a T12 vertebral injury. This patient was found to have the CYP2D6 4+/4+ and CYP2C19 1*/2+ genotypes, which correspond to the CYP2D6 poor metabolizer and CYP2C19 extensive metabolizer phenotypes, respectively.

Patients expressing the CYP2D6 ultra-rapid metabolizer genotypes can also have atypical responses to opioid treatment. For example, a 66-year-old man with renal insufficiency and a CYP2D6 ultra-rapid metabolizer genotype underwent surgery for recurring renal carcinoma and developed postoperative respiratory depression while receiving tramadol intravenously via patient controlled analgesia [21]. Similarly, Kircheiner et al. [23] compared carriers of the CYP2D6 ultra-rapid metabolizer and extensive metabolizer genotypes following treatment with tramadol. Patients expressing the CYP2D6 ultra-rapid metabolizer genotype had consistently higher plasma levels of OD-T and better pain control than carriers of the extensive metabolizer genotype; however, carriers of the CYP2D6 ultra-rapid metabolizer genotype had more nausea secondary to tramadol than patients expressing the CYP2D6 extensive metabolizer genotype. In a different study, Kircheiner et al. [24] compared plasma morphine metabolite concentrations and sedation side effects in individuals given codeine (11 carriers of the CYP2D6 ultra-rapid metabolizer genotype and 12 carriers of the extensive metabolizer genotype) and found that ultra-rapid metabolizer individuals had significantly higher plasma morphine concentrations and significantly more sedation than individuals with the extensive metabolizer genotype. Together, these data suggest that patients expressing CYP2D6 ultra-rapid metabolizer genotypes may be at greater risk for opiate-related adverse side effects, and that patients with CYP2D6 genotypes related to the ultra-rapid metabolizer phenotype might benefit from lower dosing of drugs such as tramadol or codeine that are metabolized from prodrug to active metabolite, particularly if patients have renal insufficiency.

ATP-binding cassette sub-family B member-1 gene

Drug transporters are structural proteins involved in opioid absorption, distribution, and elimination. One of the drug transport protein families that play a major role in opiate pharmacokinetics is the ATP binding cassette (ABC) superfamily of efflux transporters. The ABCB1 gene, also referred to as the multidrug resistance-1 (MDR1) gene, is highly polymorphic and encodes P-glycoprotein (P-gp) 170. P-gp 170 is a protein transporter that pumps drugs from intracellular to extracellular domains in various tissues including the central nervous system. P-gp 170 acts as a blood–brain barrier ‘gatekeeper’ that affects both clinical opioid efficacy and safety by regulating opiate accumulation in the central nervous system.

Levran et al. [25**] assessed the association between nine SNPs in the ABCB1 gene and methadone dose requirements in 98 methadone maintained patients and found a significantly higher minor allele frequency for the C1236T coding SNP (rs1128503; odds ratio = 6.67, P = 0.0325 after adjusting for multiple hypothesis testing) in the higher (>150 mg/day) versus lower dose (≤150 mg/day) methadone maintenance groups. Furthermore, individuals who carried two copies of the minor allele for all three assessed ABCB1 coding SNPs (TT-TT-TT; rs1128503, rs2032582, and rs1045642) were five times more likely to be in the high dose methadone maintenance group than individuals carrying any other allele pattern (P = 0.034), and individuals who were heterozygous for all three of these SNPs had an approximately three-fold chance of stabilizing at the ‘lower’ methadone dose than individuals carrying any other allele pattern (P = 0.014). These data suggest that variations within the ABCB1 gene may significantly influence the overall methadone dose required to prevent withdrawal symptoms and relapse in populations being treated for heroin addiction. However, another study found no significant relation between total methadone dosage requirements and ABCB1 haplotypes, suggesting that further studies in larger, well phenotyped patients undergoing heroin recovery are needed to determine the influence of ABCB1 gene variation on total stable methadone dose required to prevent withdrawal and relapse [26].

Catechol-O-methyltransferase (COMT) gene

Catecholamines such as dopamine and norepinephrine are secondarily involved in the modulation of pain and are in part metabolized by the catechol-O-methyltransferase (COMT) enzyme. Thus, variability in the COMT gene on chromosome 22 may contribute to variability in analgesic responses to opioids as well as differences in susceptibility to opioid dependence and addiction. The COMT gene contains a frequent coding SNP (G472A) that codes for a Val158Met substitution that is known to result in reduced COMT enzyme activity. Oosterhuis et al. [27*] found that frequencies of the G472A SNP as well as other novel SNPs identified within the same exon of the COMT gene varied significantly (P = 0.029) between Caucasian
(\(n = 173\)), Hispanic (\(n = 122\)), and African descent (\(n = 100\)) individuals. Oosterhuis et al. [27] assessed the \(COMT\) SNPs in each ethnic stratum for association with a history of opioid dependence and found that the G472A SNP was marginally associated with opioid addiction in Hispanic women (\(P = 0.049\)) and in Hispanic men and women assessed together (\(P = 0.053\)) before adjusting for multiple hypothesis testing. Given the small number of individuals enrolled in three ethnic groups, this study suggests that larger studies may be warranted to assess the associations between \(COMT\) SNPs and opiate addiction. In another study, Rakvag et al. [5] investigated 11 \(COMT\) SNPs in 197 Caucasian patients receiving oral morphine treatment for cancer pain. After multivariate adjustments they found that patients with the most frequent \(COMT\) haplotype involving the 11 genotyped SNPs (34.5% frequency) required lower daily morphine doses than patients with the other \(COMT\) haplotypes. This study suggests that genetic variability within the \(COMT\) gene is significantly associated with morphine efficacy in patients with cancer pain and highlights that haplotypes sometimes are more powerfully predictive of outcomes than individual SNPs [5].

### Joint gene effects

Few studies have attempted to assess the joint effects of variations within two or more gene regions in relation to opioid response (Table 2) [4,6,28,29]. Recently, 145 cancer patients of Italian origin undergoing morphine therapy were genotyped for the \(ABCB1/MDR1\) C3435T and \(OPRM1\) A118G SNPs [28]. Pain relief variability over a 2-month period with morphine therapy was significantly (\(P < 0.0001\)) associated with both polymorphisms. When the two SNPs were considered together, the association between these polymorphisms and pain relief became even more significant (\(P < 0.0001\)). Three groups of morphine responders were related to differing combinations of the \(ABCB1/MDR1\) and \(OPRM1\) SNP genotypes: nonresponders were homozygous for the major allele of the \(MDR1\) SNP and the minor allele of the \(OPRM1\) SNP, whereas strong responders were homozygous for the opposite alleles of the two SNPs. Patients with intermediate genotypes were intermediate responders to morphine therapy [29]. Another study by Reyes-Gibby et al. [6] assessed the joint effects of the \(OPRM1\) A118G and \(COMT\) Val158Met SNPs for predicting

<table>
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<th>Study</th>
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<tr>
<td>Campa et al.</td>
<td>(ABCB1/MDR1) C3435T and (OPRM1) A118G</td>
<td>145</td>
<td>Italians undergoing chronic morphine therapy</td>
<td>Pain relief over 2 months measured by Numerical Rating Scale and Present Pain Intensity Scale</td>
<td>Pain relief was greater in the (ABCB1/MDR1) TT and (OPRM1) AA groups. When the combined effect of each SNP was assessed, pain relief was significantly greater than each SNP alone</td>
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<tr>
<td>Reyes-Gibby et al.</td>
<td>(OPRM1) A118G and (COMT) Val158Met</td>
<td>207</td>
<td>Caucasian inpatients on a stable morphine dose for more than 3 days prior to study enrollment</td>
<td>Morphine Daily total morphine dose</td>
<td>(OPRM1) AA and (COMT) Met/Met carriers required lower morphine doses. When the combined effect of each SNP was assessed, the morphine requirement was lower than each SNP alone</td>
</tr>
<tr>
<td>Ross et al.</td>
<td>(COMT) and (ABCB1/MDR1) SNPs</td>
<td>228</td>
<td>Cancer patients</td>
<td>Oral morphine</td>
<td>Central side effects (drowsiness, confusion, hallucinations), morphine dose, serum morphine or metabolite</td>
</tr>
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\(COMT\) rs740603 was associated with increased central side effects, whereas \(MDR1\) rs1128503 and \(rs2032882\) were associated with decreased central side effects. There were no associations between genotypes and morphine dose or serum morphine or metabolite concentrations.
morphine dose for cancer pain relief in 207 inpatients. Carriers of the COMT Val/Val and Val/Met genotype required 63 and 23% higher respective daily morphine doses than carriers of the Met/Met genotype \( (P = 0.02) \). Homozygote carriers of the minor allele of the OPRM1 A118G SNP required significantly higher daily morphine doses than homozygotes for the major allele \( (P = 0.012) \). Furthermore, individuals who were homozygous for both the major allele of the OPRM1 A118G SNP and the Met variant of the COMT Val158Met SNP required the lowest daily morphine dose to achieve adequate pain control \( (P < 0.012) \), even after adjusting for demographic and clinical covariates in multivariable analyses. Finally, Ross et al. [4] investigated a possible correlation between morphine-related side effects and COMT and ABCB1/MDR1 gene SNPs in a population of 228 cancer patients. Analysis revealed a significant association between centrally mediated morphine side effects (drowsiness, confusion, hallucinations, nightmares) and genetic variation in the MDR1 and COMT genes. Specifically, the MDR-1 21/2677G and 12/1236G alleles were significantly associated with a decreased level of drowsiness, confusion or hallucination [4]. In contrast, the COMT–4873G SNP allele was significantly associated with increased central side effects. These observed genetic associations with centrally mediated morphine side effects were unrelated to administered morphine or serum morphine or morphine metabolite concentrations. These data suggest that variants in multiple genes may be usefully assessed together to predict opiate response.

Summary

Growing pharmacogenetic data make it evident that many opiate related phenomena have an underlying genetic influence. Genetic variation may significantly affect opiate absorption, distribution, metabolism, excretion and toxicity. Although pharmacogenetics has the potential to increase drug efficacy, prevent drug toxicity, and to eliminate costly and ineffective drug alternatives, many gene–drug associations at present are poorly understood and of unclear clinical significance. Thus, there remains at present a strong need for prospective, sufficiently powered gene association studies conducted and validated in well defined, highly phenotyped populations.

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

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 542).


16 A well designed prospective gene association study of intrathecal morphine administration and subsequent need for intravenous morphine during the 24 h after cesarean section. The study develops a clinical and demographic multi-variable model for predicting need for increased intravenous postoperative morphine dose and then statistically adjusts the observed SNP associations with increased intravenous morphine dose for the clinical model. This study also looks at morphine side effects based on genotype.


Levran O, O’Hara K, Peles E, et al. ABCB1 (MDR1) genetic variants are associated with methadone doses required for effective treatment of heroin dependence. Hum Mol Genet 2008; 17:2219–2227. Provides an example of how gene association studies can be conducted that adjusts for multiple hypothesis testing using permutation analyses and also shows how haplotype analyses can be conducted when assessing multiple single nucleotide polymorphisms that may be inherited together.


Oosterhuis BE, LaForge KS, Proudnikov D, et al. Catechol-O-methyltransferase (COMT) gene variants: possible association of the Val158Met variant with opiate addiction in Hispanic women. Am J Med Genet B Neuropsychiatr Genet 2008; 147B:793–798. An interesting study in that the authors directly sequenced exon IV of the COMT gene and identified five novel coding SNPs in that region (one synonymous and four nonsynonymous). They also assessed differences in frequencies of these four of these newly identified SNPs as well as the previously known G472A coding SNP (also in exon IV) in Caucasian, Hispanic and African-American individuals. The study reported no significant associations between these SNPs and opioid dependence, but the study had limited statistical power to assess for SNP associations in different ethnic strata.
