Pharmacogenetics of Opioid Use and Implications for Pain Management

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Background: Opioid analgesics are frequently prescribed to manage acute and chronic pain, but individual differences in opioid response make effective pain control in all patients an elusive goal. Furthermore, the risk of addiction following opioid consumption varies among individual patients. Although many psychosocial factors contribute to an individual's opioid response and risk for addiction, a strong genetic component has also been demonstrated.

Content: Opioids undergo substantial enzymatic modification that can generate metabolites with either increased or decreased opioid activity relative to the parent compound. To elicit their analgesic effect, parent compounds and active metabolites must be transported into the central nervous system where they bind to opioid receptors and inhibit neurotransmission. Inherited genetic variants that alter the function of proteins involved in these processes have been associated with differences in opioid response and risk for addiction. Detection of these variants can help guide opioid selection, inform dosing decisions, or encourage use of a nonopioid analgesic.

Summary: Whereas some genetic variants are clearly associated with differences in opioid response and have been included in consensus clinical practice guidelines, the impact of other variants on opioid response remains unclear. Studies performed to date have generated promising results, but inconsistent findings, reimbursement challenges, and the lack of robust decision support tools have hampered widespread adoption of pharmacogenetic testing to guide pain management treatment decisions. Future work involving the simultaneous evaluation of large numbers of variants and demonstration of a clear clinical benefit provided by pharmacogenetic testing will be required to overcome these obstacles.

IMPACT STATEMENT

Patients seeking care for acute or chronic pain will benefit from the information presented here. A summary of the current benefits and limitations of pharmacogenetic testing in pain management will help guide implementation and future study.

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[3] **Nonstandard abbreviations:** CYP, cytochrome P450; UGT, uridine diphosphate glucuronosyltransferase; ABC, ATP-binding cassette; SNP, single nucleotide polymorphism.

BACKGROUND

An estimated 30% of the US population suffers from chronic pain, making pain relief 1 of the most common reasons for seeking medical care (*1*, *2*). Opioid analgesics are frequently prescribed to manage chronic pain, and in 2012, 289 million opioid prescriptions were written—more than enough for each American adult to receive his or her own bottle (*3*). However, current guidelines for the management of chronic pain have questioned the utility and safety of opioid analgesics because of limited evidence of long-term benefit and the potential for serious adverse events, including nausea, vomiting, dysregulation of the hypothalamic-pituitary-adrenal axis, potentially fatal respiratory depression, and long-term opioid dependence (*4*). Furthermore, long-term use of prescribed opioids is a frequent starting point for many users of illicit substances (*5*).

It is widely acknowledged that individual responses to pain and pain control using opioid analgesics are variable (*6*). Some patients experience complete relief using a standard dose, whereas others require a much higher or lower dose. Some patients receiving opioid treatment become addicted, whereas others do not. Because of these significant interindividual differences, successfully achieving pain control and avoiding adverse events in all patients remains an elusive goal. Although many different factors contribute to the individual pain response, significant research effort has demonstrated a strong genetic component to pain sensitivity and response to opioids (*7*). Many different proteins contribute to an individual's opioid response through their roles in opioid absorption, metabolism, transport, signal transduction, and excretion. Common polymorphisms in genes encoding these proteins can dramatically affect protein expression, catalytic activity, and drug binding affinity.

Pharmacogenetics describes the study of how genetic differences determine drug response by influencing pharmacokinetics (effect of body on drug) and pharmacodynamics (effect of drug on body). This review will focus on the application of pharmacogenetics to the prediction of opioid response to more effectively achieve adequate pain relief while minimizing the risk of overdose and addiction.

CONTENT

Opioids used in pain management

Several natural and synthetic opioids are bound by opioid receptors in the central nervous system, and the downstream effects of this binding interaction determine their classification as weak agonists, strong agonists, mixed agonist-antagonists, or antagonists.

Weak agonists. Weak opioids commonly used in pain management include codeine, hydrocodone, and tramadol. All 3 can be considered "prodrugs" that require transformation by the hepatic cytochrome P450 (CYP)[3] enzyme CYP2D6[4] to the more potent metabolites morphine, hydromorphone, and *o*-desmethyltramadol, respectively (*8*–*10*). In all 3 cases, this increased potency is because of the increased binding affinity of the μ-opioid receptor for the active metabolite than the parent compound. It is important to note that only a small amount (5%–10%) of codeine is converted to morphine, whereas the remainder is glucuronidated to form codeine-6-glucuronide or methylated by CYP3A4 to form inactive norcodeine (Fig. 1) (Table 1). Similarly, the majority of hydrocodone is methylated by CYP3A4 to form the inactive metabolite norhydrocodone. Conversely, tramadol is predominantly metabolized to the active *o*-desmethyltramadol,

[4] Human genes: *CYP2D6*, cytochrome P450 family 2 subfamily D member 6; *CYP2B6*, cytochrome P450 family 2 subfamily B member 6; *CYP3A4*, cytochrome P450 family 3 subfamily A member 4; *COMT*, catechol-*O*-methyltransferase; *ABCB1*, ATP binding cassette subfamily B member 1; *OPRM1*, opioid receptor μ1; *DRD2*, dopamine receptor D2; *ANKK1*, ankyrin repeat and kinase domain containing 1.

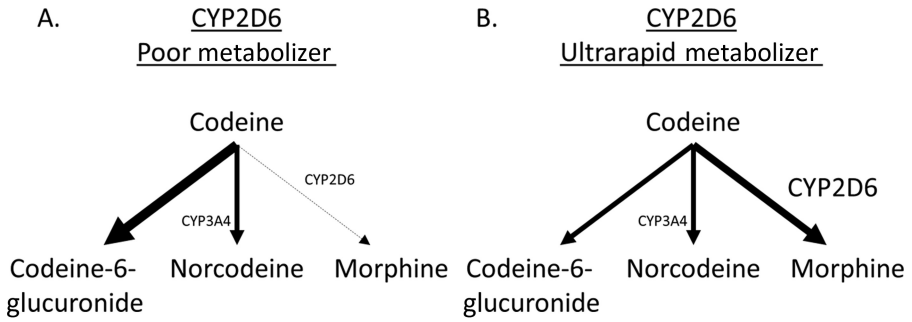

Fig. 1. Effect of CYP2D6 polymorphisms on codeine metabolism.
CYP2D6 poor metabolizers convert relatively little codeine to morphine and require a larger dose for effective analgesia (A). CYP2D6 ultrarapid metabolizers convert relatively large amounts of codeine to morphine and require a smaller dose to avoid respiratory depression (B).

whereas the remainder is converted to inactive *N*-desmethyltramadol via CYP2B6 and CYP3A4.

Strong agonists. Strong opioids include morphine, hydromorphone, oxycodone, oxymorphone, fentanyl, and methadone. Morphine and hydromorphone are both readily absorbed in the gastrointestinal tract when administered orally and undergo extensive first-pass metabolism by hepatic uridine diphosphate glucuronosyltransferase (UGT)2B7, predominantly forming the inactive 3-glucuronide metabolites with a small amount being converted to the active 6-glucuronide metabolites (*11*). Because of this high first-pass effect, oral bioavailability of both morphine and hydromorphone is low (19%–38%) (*12*, *13*).

Fentanyl is a synthetic opioid frequently used during hospital procedures that elicits rapid analgesic effects when given intravenously and demonstrates up to 100-fold greater potency than

Table 1. Summary of the primary and secondary metabolic pathways for commonly prescribed opioids.

Opioid	Primary metabolic pathway	Secondary metabolic pathway(s)
Codeine	Codeine-6-glucuronide via UGT2B7	Norcodeine via CYP3A4
		Morphine via CYP2D6
Hydrocodone	Norhydrocodone via CYP3A4	Hydromorphone via CYP2D6
		Dihydrocodeine via 6-keto-reductase
Tramadol	*O*-Desmethyltramadol via CYP2D6	*N*-Desmethyltramadol via CYP2B6 and CYP3A4
Morphine	Morphine-3-glucuronide via UGT2B7	Morphine-6-glucuronide via UGT2B7
		Normorphine via CYP3A4
Hydromorphone	Hydromorphone-3-glucuronide via UGT2B7	Hydromorphone-6-glucuronide via UGT2B7
Oxycodone	Noroxycodone via CYP3A4	Oxymorphone via CYP2D6
Oxymorphone	Oxymorphone-3-glucuronide via UGT2B7	6-OH-Oxymorphone via unknown enzyme
Fentanyl	Norfentanyl via CYP3A4	Hydroxyfentanyl via unknown enzyme
Methadone	EDDP via CYP2B6	Minor metabolites via CYP3A4, CYP2D6, CYP2C9, CYP2C19
Buprenorphine	Norbuprenorphine via CYP3A4	Buprenorphine-3-glucuronide via UGT2B7
Naltrexone	6β-Naltrexol via dihydrodiol dehydrogenase	2-Hydroxy-3-methoxynaltrexone
Naloxone	Naloxone-3-glucuronide via UGT1A8 and UGT2B7	Minor metabolites

morphine because of its greater ability to cross the blood–brain barrier and access the central nervous system (*14*). Intravenously administered fentanyl is also relatively short-acting, as it is rapidly metabolized by CYP3A4 to norfentanyl. In the outpatient setting, fentanyl is typically administered through transdermal patches, which allow slower release and prolonged analgesic effects.

Methadone is a synthetic opioid with very high oral bioavailability (70%–90%) that is frequently used for the management of chronic pain and opioid addiction (*15*). Methadone also exhibits a long-lasting analgesic effect because of its half-life between 15 h and 60 h. Metabolism of methadone to its inactive metabolite EDDP primarily occurs via CYP2B6, with smaller contributions from other CYP enzymes.

Oxycodone is a synthetic opioid with relatively high bioavailability that is primarily metabolized by CYP3A4 to the inactive noroxycodone, with a smaller amount converted into the more potent oxymorphone by CYP2D6. Oxymorphone is further metabolized by UGT2B7 to the inactive 3-glucuronide.

Partial agonists. Buprenorphine is a partial agonist commonly used in patients seeking treatment for opioid addiction or moderate to severe pain (*16*). Buprenorphine exhibits a prolonged analgesic effect because of its lipophilic nature and its slow dissociation rate from opioid receptors. Despite binding to the μ-opioid receptor with high affinity, buprenorphine possesses low agonist activity, which limits its abuse potential, likelihood of physical dependence, and risk of fatal overdose caused by respiratory depression. However, buprenorphine has been documented to cause respiratory depression and death when administered intravenously or intranasally and combined with other respiratory depressants, including alcohol or benzodiazepines (*17*). Buprenorphine is converted to the inactive norbuprenorphine by CYP3A4, and it undergoes extensive first-pass metabolism when administered orally. As a result, buprenorphine is typically administered through transdermal patches but also may be administered intravenously or intramuscularly. Oral administration of buprenorphine in conjunction with the opioid antagonist naloxone (see below) is commonly used for the treatment of opioid-addicted patients.

Antagonists. Naltrexone and naloxone are full antagonists that bind the opioid receptors with high affinity and block the euphoric and analgesic effects of opioid receptor agonists (*18*). Naltrexone is primarily used for the management of opioid dependence, whereas naloxone (Narcan) is used to manage emergency cases of opioid overdose. Naltrexone is converted to the active metabolite (but weaker antagonist) 6β-naltrexol by dihydrodiol dehydrogenases, and the resulting products are further metabolized by glucuronide conjugation and excreted in urine. Because of the relatively long half-lives of naltrexone (4 h) and 6β-naltrexol (13 h), they produce an extended period of opioid receptor antagonism. By contrast, naloxone exhibits a short half-life of 30 min to 80 min, necessitating repeat administration if extended opioid blockage is required. Metabolism of naloxone occurs primarily through the hepatic production of naloxone-3-glucuronide by UGT1A8 and UGT2B7.

Polymorphisms affecting opioid pharmacokinetics

Most opioids undergo extensive modification by hepatic enzymes that catalyze either modification reactions (phase 1 metabolism) or conjugation reactions (phase 2 metabolism). Phase 1 reactions are typically carried out by CYP enzymes, and phase 2 reactions are catalyzed by UGT enzymes. In some cases, hepatic metabolism reduces the effects of opioids by generating inactive metabolites and facilitating excretion, whereas in others, hepatic metabolism enhances the opioid effect by generating metabolic products with greater potency than the parent compound.

CYP2D6. CYP2D6 is responsible for the *O*-dealkylation of opioid agonists codeine, oxycodone, hydrocodone, and tramadol to the more potent opioid agonists morphine, oxymorphone, hydromorphone, and *o*-desmethyltramadol, respectively. More than 100 *CYP2D6* alleles have been described, including deletions, duplications, insertions, and point mutations. Some alleles have no impact on CYP2D6 activity, whereas others result in increased or decreased activity. Four CYP2D6 phenotypes have been established: poor metabolizers (activity score of 0), intermediate metabolizers (activity score of 0.5), extensive metabolizers (activity score of 1.0–2.0), and ultrarapid metabolizers (activity score of >2.0). It is recommended that codeine be avoided in CYP2D6 ultrarapid metabolizers because of an increased risk for respiratory depression and in CYP2D6 poor metabolizers because of a lack of efficacy (*19*) (Fig. 1).

Studies evaluating the use of codeine, oxycodone, and tramadol for the management of postoperative pain in adult populations have generally supported these recommendations. In 1 study of 11 women self-administering codeine following hysterectomy, 1 poor metabolizer required 10 times more codeine than the 10 extensive metabolizers and quickly dropped out of the study because of ineffective analgesia (*20*). Subsequent studies have also demonstrated increased tramadol consumption in poor metabolizers relative to extensive or ultrarapid metabolizers (*21*). However, a similar study showed no difference in oxycodone consumption between poor and extensive metabolizers (*22*).

CYP2B6. CYP2B6 is not involved in the metabolism of most opioids, with the notable exception of methadone, a synthetic opioid typically used as substitution therapy for opioid-dependent patients. *CYP2B6* is highly polymorphic with >61 distinct allelic variants. Not surprisingly, specific *CYP2B6* variant alleles have been associated with increased or decreased maintenance dose requirements. The most clinically significant variant allele, *CYP2B6*6*, is commonly found in African, Asian, Hispanic, and white populations and results in markedly reduced hepatic enzyme activity, higher trough plasma concentrations, and lower maintenance dose requirements. Conversely, *CYP2B6*4* has been associated with an increased rate of methadone clearance and lower steady-state plasma concentrations, suggesting an ultrarapid metabolizer phenotype requiring a higher methadone dose for effective pain control and addiction therapy (*23*).

CYP3A4. CYP3A4 is responsible for the *N*-demethylation of opioids such as tramadol, fentanyl, and oxycodone to the inactive metabolites *N*-desmethyltramadol, norfentanyl, and noroxycodone, respectively. CYP3A4 is relatively nonpolymorphic with 41 allelic variants having been described, of which 9 are associated with very modest or nonexistent enzymatic activity in in vitro studies. Many of these variants are exceedingly rare, making their evaluation in a clinical context difficult. However, several in vitro and in vivo studies have demonstrated that the *CYP3A4*1G* variant is associated with a lower rate of fentanyl metabolism and significantly lower consumption relative to patients with wild-type alleles (*24*).

Catechol*-O-*methyltransferase (COMT). COMT catalyzes the metabolism of catecholamine neurotransmitters. As catecholamines are involved in the modulation of pain and catecholamine coadministration can enhance opioid analgesia, *COMT* polymorphisms that affect the rate of catecholamine metabolism have been postulated to play a role in mediating the opioid response (*25*). The most frequently studied variant allele, 472G>A (rs4680), encodes a protein with methionine substituted for the wild-type valine. This substitution results in a 3- to 4-fold reduction in enzymatic activity, but conflicting results have been generated in studies assessing the impact of this variant on pain scores and opioid consumption. Individuals homozygous for the wild-type (GG, Val/Val) allele

required more morphine for the management of cancer pain than heterozygous or homozygous variant (AA, Met/Met) patients (*26*). Somewhat paradoxically, patients homozygous for the variant allele reported higher pain scores but no significant difference in opioid dose requirements for the management of postoperative pain (*27*).

ABCB1. The ATP binding cassette (ABC) transporters mediate the translocation of various substances across cellular membranes. The P-glycoprotein efflux transporter, encoded by *ABCB1*, is the most widely studied member of this protein family and, when overexpressed, has been shown to confer multiple drug resistance because of its ability to remove a wide variety of natural and synthetic compounds. *ABCB1* is highly polymorphic with >100 documented single-nucleotide polymorphisms (SNPs), and *ABCB1* mRNA expression can vary up to 200-fold. However, attempts to associate *ABCB1* polymorphisms with opioid response have generated mixed results. Multiple studies evaluating the C3435T and G2677T/A variants in patients receiving morphine, oxycodone, or fentanyl for the management of postoperative pain have shown no difference in pain scores or opioid usage (*28*). In patients receiving opioids for management of cancer pain, patients homozygous for the 3435T allele experienced greater pain relief than heterozygotes or 3435C homozygotes (*29*). Similarly, for the management of nonmalignant chronic pain, the T allele was associated with reduced opioid requirements (*30*). Unfortunately, subsequent studies have not confirmed these findings.

P-glycoprotein has also been implicated as a potential determinant of methadone dose requirements, as individuals homozygous for the 1236T, 2677T, 3435T genotype were more likely to require a higher methadone dose (*31*). Support for this observation was provided by in vitro studies that demonstrated P-glycoprotein variants encoded by the TTT and TAT genotypes were less subject to methadone inhibition (*32*).

Polymorphisms affecting opioid pharmacodynamics

The opioid response is mediated by G protein-coupled receptors (μ, κ, and δ) in the central nervous system that bind endogenous and exogenous opioids with high affinity, resulting in reduced transmission of nerve impulses and inhibited neurotransmitter release (*33*). Similarly, dopamine receptors play important roles in pleasure and reward sensation and novelty-seeking behavior. Significant research effort has been devoted to understanding whether opioid and dopamine receptor polymorphisms help determine an individual's opioid response and risk of addiction.

OPRM1. *OPRM1* encodes the μ-opioid receptor, the main target of abused opioids and compounds used in addiction therapy, including methadone, buprenorphine, naloxone, and naltrexone. *OPRM1* is highly polymorphic, but the most widely studied SNP is A118G, which results in the substitution of aspartate for the wild-type asparagine, reduced mRNA and protein expression, and reduced signaling efficacy. Although no difference in binding affinity for exogenous ligands was observed between the wild-type and variant receptor, the variant receptor showed significantly enhanced binding affinity for the natural ligand β-endorphin (*34*). A large number of studies have demonstrated consistently lower pain scores and opioid requirements in patients homozygous for the wild-type A allele (*7*). However, other studies have contradicted these findings, finding no difference in pain score or opioid consumption, and 1 study controversially demonstrated increased opioid requirements in patients homozygous for the G allele.

In the setting of opioid addiction, at least 13 studies performed in patients with different genetic backgrounds have demonstrated an increased frequency of the A118G variant in heroin-addicted patients relative to nonaddicted controls (*35*). Although other studies have not been able to replicate these findings, a large body of evidence

seems to support a role for the A118G variant as a risk factor in the development of opioid addiction.

DRD2. Dopamine exerts its biological effects through the dopamine receptors *DRD1–5*. *DRD2*, the gene encoding the D2 dopamine receptor, is perhaps the most widely studied in the assessment of opioid addiction risk. The *Taq*IA polymorphism (rs1800497, 2137G>A) is located in the *ANKK1* gene, just downstream of *DRD2*, but gives rise to the *DRD2*A1* allele that has been associated with a reduced number of dopamine binding sites in the brain (*36*). In a study of Han Chinese heroin-addicted patients, individuals with at least 1 copy of the A1 allele consumed twice as much heroin as patients without the A1 allele. The A1 allele was also enriched in the heroin-addicted population relative to the nonaddicted controls (*37*). A subsequent study in white opioid-addicted patients also demonstrated an enriched A1 allele frequency in addicted patients relative to control patients with no history of substance abuse.

Analysis of genetic variants associated with opioid response

Detection of genetic variants associated with drug response consists of 2 main categories: (*a*) identifying genetic variants associated with drug metabolism and (*b*) identifying variants associated with the presence or absence of a drug target. The selection of targeted therapies for cancer patients by detecting somatic variants acquired by the tumor cells is an example of the latter application. In the prediction of opioid response, an example of the former application, genetic variants of interest are germline polymorphisms that alter the absorption, distribution, metabolism, and excretion of the drug and its metabolites. Germline polymorphisms that affect these processes can be detected in DNA isolated from whole blood, buccal swabs, saliva, etc., and thus do not require a disease tissue.

Variant detection can be accomplished using many different techniques and instruments, and we highlight 3 examples of various approaches for this application. For testing that is aimed at detecting low numbers of variants, it is feasible to use real-time PCR and Taqman probe chemistry. This approach allows for the detection of a wild-type and polymorphic variant using 1 PCR reaction containing probes labeled with 2 separate fluorescent dyes for each variant (Fig. 2). These assays can be performed on several different real-time PCR instruments and can be scalable from a single tube to 96-well plates to much higher throughput platforms such as the Thermofisher OpenArray®, which consists of a glass slide with >3000 reaction wells. In other instances, it may be necessary to test samples for numerous variants in a single gene such as *CYP2D6* or for multiple variants in several genes for a more comprehensive evaluation of drug response. It is possible to accomplish such testing for multiple targets and with increased sample throughput using mass spectrometry whereby each sample is subjected to PCR amplification and primer extension and detection using a time-of-flight mass spectrometer (*38*). Finally, for those scenarios in which a comprehensive assessment of either numerous genes or all genes and all possible genetic variants involved in metabolism of a known drug is needed, it is possible to use next-generation sequencing. Next-generation sequencing allows for the scalability in numbers of targets being analyzed as well as in the number of patient samples that are simultaneously sequenced (*39*, *40*). Depending on the chosen assay and platform, data analysis via onboard informatics pipelines or offline pipelines will generate large amounts of genomic data. Variants with clear significance and contribution to phenotype must be identified from the variants of unknown significance that will require more careful interpretation and possible functional evaluation. Regardless of the laboratory approach taken, accurate

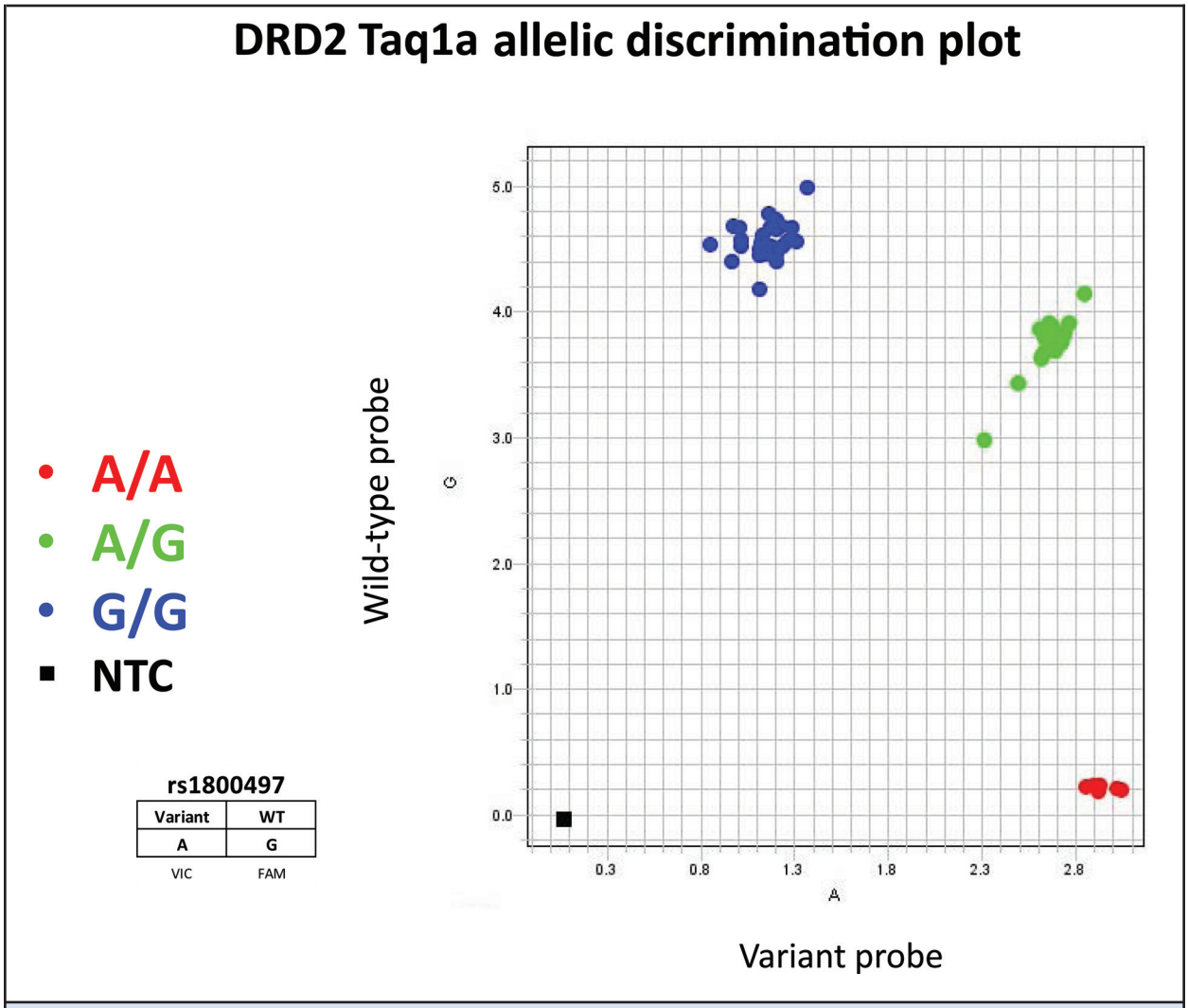

Fig. 2. Application of PCR and Taqman probe chemistry to the detection of a single wild-type/polymorphic variant pair affecting DRD2 expression.
In this assay, the Taqman chemistry of wild-type and variant-specific sequence probes labeled with reporter and quencher dyes is used to discriminate normal from variant gene sequences. Fluorescence signal from the wild-type probe is shown on the *x* axis, and variant probe is seen on the *y* axis. Scatter plot clusters indicate individuals who are homozygous wild-type (blue), heterozygous (green), and homozygous variant (red).

result annotation and curation are critical to the clinical interpretation of genomic variant results.

Implementation challenges

Pharmacogenetic testing for pain management has demonstrated the potential to improve therapeutic outcomes; however, several challenges must be overcome. First, the Centers for Medicare and Medicaid Services has argued that a conclusive benefit has not been demonstrated for many gene–drug interactions. Reimbursement is allowed for only a select number of well-defined clinical scenarios, and institutions must determine whether improved patient outcomes justify the performance of

nonreimbursable testing. Second, many clinicians have limited experience with the interpretation of pharmacogenetic test results, often leading to underutilization and misinterpretation. Extensive decision support tools are required to ensure test results are interpreted and acted upon correctly.

SUMMARY

It is clear that individuals respond to opioids differently and genetic factors likely play a key role in defining this variable response. Polymorphisms in the *CYP2D6*, *OPRM1*, and *DRD2* genes have been most closely associated with increased opioid requirements and risk for addiction, but these findings are inconsistent and frequently difficult to reproduce. This lack of reproducibility can be attributed to many confounding factors, including age, sex, type of pain, method of opioid administration, and genetic background. As SNP allele ratios vary substantially between ethnic groups, it is not surprising that observations made in a particular ethnic population are not replicated in individuals with a different genetic makeup. Furthermore, most studies performed to date have investigated the role of a handful of SNPs in determining the opioid response, but it is becoming increasingly clear that many genes collectively define an individual's response to opioids. Future studies must include substantially increased sample sizes, interrogation of hundreds of SNPs, and complex statistical analyses able to identify meaningful correlations while eliminating confounding factors.

Despite these challenges, findings of current studies associating polymorphisms with differences in opioid response are promising. It is hoped that future studies that include a large number of SNPs in genes defining both pharmacokinetic and pharmacodynamic parameters will someday lead to the personalization of opioid therapy to maximize the analgesic effect while minimizing the risk of adverse events.

Additional Content on this Topic

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Maja Matic, Saskia N. de Wildt, Dick Tibboel, and Ron H.N. van Schaik. Clin Chem 2017;63:1204–13

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Nigel J. Clarke. Clin Chem 2015;62:70–6

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