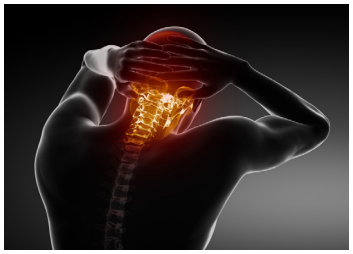
PGxINSIGHT - PAIN MANAGEMENT

INTRODUCTION



Pharmacogenomics is the area of medicine that analyses how the genetic makeup of an individual affects his/her response to drug treatment. Research studies have shown that genetics may account for much of the variability in patients' responses. In many patients, certain drugs do not work as well as expected, whereas in other patients they cause toxic effects, even at lower doses. Much of the variation in drug efficacy and side effects has been shown to be associated with DNA and/or RNA variation between individuals. Relevant polymorphisms have been identified, and tests for many of them are now available in the clinical arena. With the knowledge of a patient's genetic status and the appropriate database, physicians can predict patient response to certain drugs and optimize treatment protocols. Adverse drug reactions can also be minimized as they have a substantial impact on mortality, morbidity and health-care costs. This ushers in the era of "personalized medicine," where drug combinations and dosages are optimized for each individual's unique genetic makeup.

DRUG METABOLISM

It is well understood that differences exist among individuals regarding efficacy and side effects when taking various pharmaceuticals. Such differences can be attributable to genetic variation and drug interactions. It is known that virtually every pathway of drug metabolism, transport, and action is influenced by genetic variation. One of several important gene families responsible includes the cytochrome P450 (CYP) genes. This group encodes enzymes expressed in the liver and mucosal surface of the intestinal tract that play important roles in the biosynthesis and metabolism of endogenous compounds, chemicals, toxins, and medications. Of the more than 50 CYP450 enzymes identified in humans, seven (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) metabolize about 50% of the clinically most important drugs. For example, CYP2D6 is involved in the metabolism of 25% to 30% of all prescribed drugs (over 65 total) including β-blockers, antipsychotics, antidepressants, analgesics, and antiarrythmics, while CYP2C19 is involved in metabolizing 15%. Amitriptyline, clopidogrel, diazepam, and warfarin are examples of substrates metabolized by this enzyme.

The CYP2D6 gene is highly polymorphic, with over 74 known alleles and allelic frequencies varying greatly between ethnic groups (Zhou 2009a). Many alleles encode enzymes having reduced or no function compared to the wild-type enzyme. Individuals can also have gene rearrangements with more than two (duplication) or less than two (deletion) copies of the CYP2D6 gene. Depending on the combination of alleles in an individual, drug-metabolizing phenotypes associated with the CYP2D6 enzyme can vary. Alleles are classified into three functional groups: full (normal), reduced or no function. Patient genotypes are usually categorized into predicted phenotypes. A poor metabolizer (PM) has 2 'no function' alleles leading to limited or loss of activity, an intermediate metabolizer (IM) has 1 'normal (wild-type)' and 1 'reduced' allele or 2 'partially reduced' alleles, an normal (extensive) metabolizer (EM) has 2 'normal' alleles, and the ultra-rapid metabolizer (UM) has excess activity due to duplicate functional alleles.

Drug Class	Drugs	Genes
Antidepressants, SSRIs/SNRI	Citalopram, Escitalopram, Desvenlafaxine, Duloxetine, Mirtazapine, Paroxetine, Sertraline, Venlafaxine, Vortioxetine	CYP2D6, CYP2C19
Antidepressants, Tricyclic	Amitriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline, Trimipramine	CYP2D6, CYP2C19
Antiepileptic	Phenytoin	CYP2C9
Antipsychotics	Aripiprazole, Haloperidol, Iloperidone, Paliperidone, Perphenazine, Pimozide, Risperidone, Thioridazine	CYP2D6, CYP1A2
Anxiety/Insomnia	Diazepam, Clobazam	CYP2C19
Muscle Relaxants	Carisoprodol, Tizanidine	CYP2C19, CYP1A2
Narcotic drug addiction/Pain	Methadone	CYP2B6
Opioids	Codeine, Fentanyl, Hydrocodone, Morphine, Oxycodone, Tramadol	CYP2D6, OPRM1
Other	Bupropion, Naltrexone	COMT, OPRM1
Other Analgesics	Celecoxib, Flurbiprofen, Piroxicam	CYP2C9

Another factor influencing pharmaceutical outcome is drug interaction. For example, enzymes act by metabolizing specific substrates, that is, drugs, herbs, foods, or other molecules. Drug metabolism depends not only upon which enzymes are present in an individual, but also how different enzymes, compounds, and drugs interact with each other. A drug interaction occurs when one substance affects the activity of another when both are administered together. This interaction may determine whether a drug is safely eliminated from the body or converted into a toxic byproduct. Certain compounds called inhibitors reduce or block the ability of an enzyme to metabolize its substrate, while inducers increase the metabolic activity of an enzyme. Moderate to strong CYP2D6 inhibitors include bupropion (wellbutrin), fluoxetine (Prozac), quinidine (Quinidex) and paroxetine (Paxil). The herb St John's wort has been shown to cause multiple drug interactions through induction of the cytochrome P450 enzymes CYP3A4 and CYP2C9, and CYP1A2.

Retrogen, Inc.
Solutions for Functional Genomics

CLINICAL DIAGNOSTICS

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PHARMACOGENOMIC TESTS OFFERED BY RETROGEN - PAIN MANAGEMENT

Opioids are widely used for the management of moderate to severe pain; however, the efficacy of specific opioids can vary dramatically among individuals. Such variation can be attributed to alterations in opioid metabolism, which can cause the drug or metabolite to leave the body too rapidly or remain in the body too long. Such variation may make dosage optimization a significant challenge for clinicians. Allelic variation in the CYP2D6 and CYP2C19 genes result in markedly increased or decreased drug metabolism, leading to wide variability in clinical outcome. For example, codeine is metabolized by CYP2D6 to the biologically more active drug, morphine. Certain genetic variants in the CYP2D6 gene can result in rapid metabolism of codeine and an exaggerated clinical response, while other variations can result in poor metabolism, little conversion to morphine, and a blunted therapeutic response. Methadone is metabolized mainly by CYP2B6 and is also a substrate for the transporter P-gp. Inhibitors or inducers of CYP2B6 and P-gp are likely to affect its disposition. Individuals with reduced CYP2B6 activity, i.e. poor metabolizers, may require lower doses than normal metabolizers. It is estimated that 1-3% of Caucasians and 13-23% of Asians have the CYP2C19*2 or *3 variant resulting in poor metabolizer status. Recent studies have indicated that genetic testing for variations in CYP2D6 and CYP2C19 may improve pain management, decrease drug toxicity, and reduce adverse drug interactions. Strong inducers of CYP2C19 and CYP3A4/5 include rifampin, carbamazepine, St John's Wort and artemisinin and can influence drug treatment.

Tests offered by Retrogen include the include CYP2D6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP1A2, CYP2B6, OPRM1, COMT genes. Some of the impacted medications include carvedilol, codeine, dexlansoprazole, esomeprazole, hydrocodone, oxycodone, amitriptyline, clomipramine, duloxetine, lansoprazole, mirtazapine, paliperidone, paroxetine, pimozide, and piroxicam.

TESTING METHODOLOGY - POLYMERASE CHAIN REACTION AND SANGER SEQUENCING

Most of the DNA variations, found in genes that impact drug response, are single nucleotide polymorphisms (SNPs) and small (<5 bp) deletions. These are assayed using the polymerase chain reaction carried out on patient genomic DNA following by bidirectional dideoxy sequencing and capillary electrophoresis.

MULTIPLEX LIGATION-DEPENDENT PROBE AMPLIFICATION (MLPA)

Germline copy number changes of CYP2D6 are common due to the presence of repeated sequences around the gene. CYP2D6 gene deletions resulting in a poor metabolizer phenotype are known as CYP2D6*5. CYP2D6 gene duplications resulting in ultrarapid metabolism of certain drugs are also common. The "MLPA P128-B2 Cytochrome P450 probemix kit" from MRC-Holland is used for the detection of copy number changes of CYP2D6.

Available Tests

#9001	Pain Management Panel	CYP2D6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP1A2, CYP2B6, OPRM1, COMT

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Retrogen, Inc. 6645 Nancy Ridge Dr. San Diego, CA 92121
(800) RETROGEN (858) 455-8411 www.retrogen.com
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