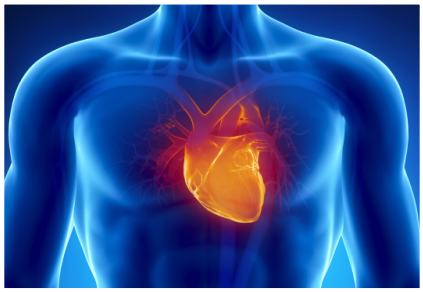
PGxINSIGHT - CARDIOVASCULAR MEDICATIONS

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
Antiarrhythmics	Flecainide, Propafenone, Mexiletine	CYP2D6
Antidiabetics	Glimepiride, Glipizide, Glyburide, Tolbutamide	CYP2C9
Antihyperlipidemic agents	Atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, simvastatin, rosuvastatin	SLCO1B1, CYP3A4, CYP2C9
Antihypertensives	Carvedilol, metoprolol, irbesartan, nebivolol, propranolol, timolol	CYP2D6, CYP2C9
Antiplatelets--Anticoagulants	Clopidogrel, Prasugrel, Ticagrelor, Warfarin	CYP2C19, CYP2C9, VKORC1, CYP3A5

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 - CARDIOVASCULAR DISEASE

Millions of Americans currently take cardiovascular medications to treat or prevent heart disease and many have had problems finding the right drug and dose. Over half of all medications, including the majority of heart disease medications, are metabolized by enzymes in the liver. Gene variation is the main factor determining enzyme levels in the liver. If you have too much of the enzyme, you process the medication too quickly: too little of the enzyme and the medication builds up in your bloodstream, potentially causing adverse reactions or side effects. Without knowing your genetics, your physician may need to go through months of trial-and-error prescribing to find the right drug and dose for you.

Tests offered by Retrogen include the CYP2D6, CYP2C9, CYP2C19, VKORC1, SLCO1B1, CYP3A4, CYP3A5, MTHFR, Factor V Leiden, Factor II, and APOE genes. Variation in the Apolipoprotein E gene is associated with increased risk of hyperlipidemia/atherosclerotic vascular disease. Variation in the Factor II and Factor V Leiden genes is associated with increased thrombosis risk. Genetic variants in the MTHFR gene are associated with increased risk of hyperhomocysteinemia. Variation in the SLCO1B1 gene is associated with increased risk of myopathy. Variation in the VKORC1 gene is associated with increased risk of warfarin sensitivity.

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		
#9002	Cardiovascular Panel	CYP2D6, CYP2C9, CYP2C19, VKORC1, SLCO1B1, CYP3A4, CYP3A5, MTHFR, Factor V Leiden, Factor II, APOE

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