Retrogen, Inc.
Solutions for Functional Genomics

CLINICAL DIAGNOSTICS

PHARMACOGENOMICS OVERVIEW

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 for drug metabolism include 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. Within the 50 CYP 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 140 known alleles and allelic frequencies varying greatly between ethnic groups. Many alleles encode enzymes having reduced or no function compared to the wild-type normal 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.

Another factor influencing pharmaceutical outcome is drug-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. 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.

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