



Cytochrome P450 Polymorphisms: Genetic Variation in Drug Metabolism and Therapeutic Response

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DESCRIPTION

Cytochrome P450 polymorphisms are inherited variations in genes that encode enzymes responsible for the metabolism of numerous medicines and endogenous compounds. These enzymes are present mainly in the liver, although several members of the cytochrome P450 family are also found in the intestine and other tissues. Differences in the genetic sequence of these enzymes can change their activity, expression, or stability, leading to variation in the way individuals process medicines. Such differences can influence drug concentration, therapeutic response, duration of action and the likelihood of adverse reactions. The cytochrome P450 family contains many enzymes, but *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP3A4*, *CYP3A5* and *CYP1A2* have particular importance in pharmacology. Each enzyme acts on a different range of chemical compounds, although some medicines can be processed by more than one enzyme. Genetic variants within these genes may result in different metabolic phenotypes, commonly described as poor, intermediate, normal, or ultrarapid metabolizers depending on the enzyme and clinical classification system.

CYP2D6 is one of the most genetically variable members of the family. The *CYP2D6* gene contains numerous alleles with differences in enzymatic function. Some variants result in little or no enzyme activity, while others retain normal function. In some individuals, duplication of functional gene copies can produce increased metabolic capacity. These differences can affect medicines used in areas such as psychiatry, cardiology, pain management and neurology. For a medicine primarily eliminated through *CYP2D6*, reduced enzyme activity may cause the compound to remain in the body for a longer period. Higher exposure can increase the possibility of concentration-related adverse effects. In contrast, increased *CYP2D6* activity may lower the concentration of some medicines and reduce their therapeutic effect. The outcome depends on the chemical properties of the medicine and whether metabolism produces an active or inactive compound.

Prodrugs provide an important example of how enzyme activity can influence treatment. Some medicines require metabolic conversion before they become pharmacologically active. If the responsible enzyme has low activity, less active compound may be generated. Individuals with higher enzyme activity may produce active drug more efficiently. Therefore, the same prescribed dose can result in different biological effects depending on the person's metabolic capacity. *CYP2C19* is another clinically important enzyme with several functional genetic variants. Reduced-function alleles can decrease the metabolism of medicines that depend on this pathway. Some compounds may therefore reach higher concentrations, whereas medicines requiring *CYP2C19*-mediated activation may produce less active product. Clinical guidelines for selected medicines use *CYP2C19* genotype information to assist with medication selection or dosing.

CYP2C9 participates in the metabolism of several commonly prescribed medicines. Genetic variants can decrease enzyme activity and alter the elimination rate of particular compounds. Warfarin is a well-known example in which genetic information involving *CYP2C9*, together with other clinical factors, can influence dose requirements. Genetic variation does not act independently, because age, diet, interacting medicines, liver function and other factors can also affect anticoagulant response. *CYP3A* enzymes contribute substantially to the metabolism of many medicines. *CYP3A4* and *CYP3A5* are expressed in the liver and intestine and process a broad range of pharmaceutical compounds. *CYP3A5* expression differs considerably between individuals because of genetic variation. Some people produce substantial amounts of functional *CYP3A5*, while others have very limited expression. This difference can affect the handling of selected medicines.

Cytochrome P450 activity is influenced by more than inherited Deoxyribonucleic Acid (DNA) variation. Certain medicines can inhibit these enzymes and reduce the metabolism of another

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compound. Other substances can increase enzyme expression and accelerate drug clearance. Food components, smoking, hormonal factors, inflammation, age and liver condition can also influence enzyme activity. These factors can modify the effect associated with a particular genotype. Genetic variants can occur in protein-coding regions as well as regulatory DNA. A coding variant may change an amino acid and alter enzyme structure or catalytic function. A regulatory variant can influence the amount of enzyme produced by a cell. Some genetic changes affect messenger Ribonucleic Acid (RNA) processing or protein stability. The final metabolic phenotype can therefore arise from several molecular mechanisms.

Pharmacogenetic testing can identify selected Cytochrome P450 (CYP) variants through targeted genotyping or DNA

sequencing. Laboratory results may be translated into predicted metabolic categories using established allele definitions and clinical guidelines. Such information can be useful for medicines where a validated relationship exists between genotype, drug exposure and clinical outcome. Genetic information should be interpreted together with the patient's medication list and clinical condition. Population variation is also important because CYP allele frequencies differ among geographical and ancestral groups. A functional allele may be relatively frequent in one population and uncommon in another. Accurate interpretation therefore benefits from databases containing information from diverse populations. This can improve the representation of genetic variation used in pharmacogenetic decision-making.