

Cytochrome P450 2D6 (CYP2D6) 14 Mutations & Gene Duplication

DETECTS CYP2D6 VARIATIONS INFLUENCING DRUG METABOLISM, WHICH MAY PREDICT RISK FOR ADVERSE DRUG REACTIONS OR REDUCED THERAPEUTIC BENEFIT

Disease Overview

- Pharmacogenetic variation leads to inappropriate concentrations of drugs and their metabolites and may contribute to toxicity and risk for adverse drug reactions or reduced therapeutic benefit.
 - CYP2D6 is an isoenzyme of the P450 superfamily and is responsible for biotransformation (metabolism) of commonly prescribed drugs, including tamoxifen, alpha-blockers, analgesics, anticonvulsants, antidepressants, antidiabetics, antihypertensives, antipsychotics, antitussives, β -receptor blockers, cardioactives, norepinephrine reuptake inhibitors, and stimulants, including methylphenidate.
 - CYP2D6 is involved in the metabolism of up to 25 percent of all clinically used drugs.
 - Four distinguishable phenotypes based on drug-metabolism efficiency are estimated by genotypes. However, actual phenotype depends on the substrate in question and non-genetic factors, particularly co-medications.
 - Ultra rapid metabolizer (UM): more than two copies of functional alleles.
 - Extensive metabolizer (EM): expected (normal) metabolic phenotype, two functional alleles, or one copy each of a functional and a decreased function allele.
 - Intermediate metabolizer (IM): two reduced activity alleles, one copy each of a functional and a non-functional allele, or heterozygous for a non-functional allele and decreased function allele. Based on the specific situation, the phenotype may appear more like a poor metabolizer or more like an extensive metabolizer
 - Poor metabolizer (PM): two non-functional alleles.
 - Detection of *CYP2D6* genetic variants does not replace the need for therapeutic drug or other clinical monitoring.
- Functional alleles associated with normal enzymatic activity: *1 (when no variants are detected), *2 (2850C>T), *2A (promoter mutation -1584C>G).
 - Non-functional alleles associated with lack of enzymatic activity: *3 (2549A>del), *4 (1846G>A), *5 (gene deletion), *6 (1707T>del), *7 (2935A>C), *8 (1758G>T), *12 (124G>A), and *14 (1758G>A).
 - Decreased function alleles associated with impaired enzymatic function (i.e., decreased activity, altered substrate specificity, decreased stability, etc): *9 (2613_2615delAGA), *10 (100C>T), *17 (1023C>T), *29 (1659G>A), and *41 (2988G>A).
 - Increased function alleles are represented by duplicated functional alleles and associated with UM phenotype. Duplication of a non-functional allele will not change the metabolic phenotype, and the phenotypic effects of duplicated decreased functional alleles are unknown.

Indications for Ordering

- Pre-therapeutic identification of individuals who should avoid, or may require unconventional doses of, medications that are substrates of CYP2D6.
- Screening of individuals who have experienced adverse drug reactions or therapeutic failure when exposed to CYP2D6 substrates.
- Screening of individuals with a family history of adverse drug reactions or therapeutic failure when treated with medications metabolized by the CYP2D6 enzyme.

Interpretation

- Negative: No mutations were detected predictive of *1 alleles; genotype is consistent with an extensive metabolizer (normal) phenotype.
- Positive:
 - Genotype is consistent with ultra-rapid metabolizer phenotype; drug dose and selection may be affected.
 - Genotype is consistent with intermediate metabolizer phenotype; potential for adverse drug reactions exists.
 - Genotype is consistent with poor metabolizer phenotype; potential for adverse drug reactions exists.
 - Genotype should be interpreted with clinical information; consultation with a clinical pharmacist is recommended.

Genetics

- Autosomal recessive inheritance for *CYP2D6* sequence variants exists. *CYP2D6* duplications are considered autosomal dominant; however, intermediate phenotypes exist.
- Penetrance is drug dependent.
- There are over 80 recognized *CYP2D6* allelic variants; mutation analysis includes the following 14 common or significant variants:

Limitations

- Rare *CYP2D6* mutations affecting drug metabolism may not be detected.
- Phase and copy number for identified *CYP2D6* mutations may not be determined.
- Mutations in other genes and non-genetic factors that may affect drug metabolism are not detected.
- Rare diagnostic errors can occur due to primer-site mutations.

Methodology

- Multiplex PCR and detection primer extension.
- Greater than 95 percent of pathogenic *CYP2D6* mutations are detected in Caucasians; clinical sensitivity is unknown for other ethnicities.
- Analytical sensitivity and specificity for the mutations detected are >99 percent.

Related Tests

- Cytochrome P450 2C9 (*CYP2C9*) 2 Mutations ([0051103](#))
- Cytochrome P450 2C19 (*CYP2C19*) 10 Mutations ([0051104](#))

References

1. Ingelman-Sundberg M. Human drug metabolizing cytochrome P450 enzymes: properties and polymorphisms. *Naunyn Schmiedebergs Arch Pharmacol* 2004;369(1):89–104.
2. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (*CYP2D6*): clinical consequences, evolutionary aspects, and functional diversity. *Pharmacogenomics J* 2005;5(1):6–13.
3. Zanger UM, Raimundo S, and Eichelbaum M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, and biochemistry. *Naunyn Schmiedebergs Arch Pharmacol* 2004;369(1):23–37.

Test Information

0051232

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For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.