

Cytochrome P450 2C9 (CYP2C9) 2 Mutations

DETECTS CYP2C9 VARIATIONS INFLUENCING DRUG METABOLISM, WHICH MAY PREDICT RISK FOR ADVERSE DRUG REACTIONS OR REDUCED THERAPEUTIC BENEFIT

Clinical Background

- Pharmacogenetic variation leads to inappropriate concentrations of drugs and drug metabolites, which may contribute to toxicity and risk of adverse drug reactions, or lack of therapeutic benefit.
- Cytochrome P450 2C9 (CYP2C9) is an isoenzyme of the cytochrome P450 super family and is responsible for the biotransformation (metabolism) and elimination of many commonly prescribed drugs, including anticonvulsants, some antidepressants, hypoglycemics, anticoagulants, antibacterial, the alkylating anticancer prodrugs cyclophosphamide, and some nonsteroidal anti-inflammatory drugs.
- Three 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.
 - Extensive metabolizer (EM): individuals with the expected (normal) metabolic phenotype, associated with two functional alleles or heterozygosity for a decreased function allele.
 - Intermediate metabolizer (IM): individuals with two decreased function alleles or with one functional allele and one non-functional allele.
 - Poor metabolizer (PM): individuals who lack active enzyme and are therefore not expected to metabolize via CYP2C9; associated with two non-functional alleles or one decreased function and one non-functional allele.

Genetics

- Autosomal recessive inheritance.
- Penetrance is unknown but dependant upon enzyme substrate (drug) exposure.
- The *CYP2C9* gene is located on chromosome 10 and consists of nine exons.
- The most common *CYP2C9* allelic variants are *2 (decreased function) and *3 (non-functional).
- *CYP2C9* allele frequencies differ among ethnic groups.
- *CYP2C9* *2: Caucasians: 0.08–0.13; Asians: 0.02–0.06; African-Americans: less than 0.01.
- *CYP2C9* *3: Caucasians: 0.06–0.10; Asians: less than 0.01; African-Americans: 0.01–0.04.

Indications for Ordering

- Pre-therapeutic identification of individuals who should avoid, or may require unconventional doses of, medications that are substrates of CYP2C9.
- Screening for individuals who have experienced adverse drug reactions or therapeutic failure when exposed to medications that are substrates of CYP2C9.
- Screening of individuals with a family history of adverse drug reactions or therapeutic failure when treated with medications metabolized by CYP2C9.

Additional Ordering Notes

CYP2C9 variants are associated with slowed clearance and lower dose requirements for warfarin. To help predict warfarin metabolism, order Warfarin Sensitivity (*CYP2C9* & *VKORC1*) 3 Mutations (ARUP test #0051370).

Interpretation

- Negative: No *CYP2C9* mutations were detected; genotype is consistent with an extensive metabolizer (normal) phenotype.
- Heterozygous *CYP2C9* *2: Genotype is consistent with an extensive metabolizer (normal) phenotype.
- Heterozygous *CYP2C9* *3 or homozygous *CYP2C9* *2/*2: Genotype is consistent with an intermediate metabolizer phenotype; potential for adverse drug reactions exists.
- Homozygous *CYP2C9* *3/*3 or compound heterozygous *CYP2C9* *2/*3: Genotype is consistent with a poor metabolizer phenotype; potential for adverse drug reactions exists.
- Genotype results should be interpreted with clinical information. Consultation with a clinical pharmacy professional is recommended.

Limitations

- *CYP2C9* mutations other than *2 and *3 will not be detected.
- 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.
- The detection of genetic variants does not replace the need for therapeutic drug monitoring or other appropriate clinical monitoring.

Methodology

- Polymerase chain reaction (PCR) and fluorescence monitoring to detect *CYP2C9* *2 (c.430C>T) and *CYP2C9* *3 (c.1075A>C).
- Greater than 90 percent of deleterious *CYP2C9* mutations are detected in Caucasians; clinical sensitivity is unknown in other ethnicities.
- Analytical sensitivity and specificity for the mutations detected are 99 percent.

Related Tests

- Warfarin Sensitivity (*CYP2C9* & *VKORC1*) 3 Mutations ([0051370](#))
- Cytochrome P450 2D6 (*CYP2D6*) 17 Mutations ([0051232](#))
- Cytochrome P450 2C19 (*CYP2C19*) by Tag-IT™ ([0051104](#))

References

1. Goldstein JA and de Morais SM. Biochemistry and molecular biology of the human CYP2C subfamily. *Pharmacogenetics* 1994;6:285–99.
2. Streetman DS, Bertino JS, Jr., and Nafziger AN. Phenotyping of drug-metabolizing enzymes in adults: a review of in-vivo cytochrome P450 phenotyping probes. *Pharmacogenetics* 2000;10(3):187–216.
3. Topic E, Stefanovic M, and Samardzija M. Association between the *CYP2C9* polymorphism and the drug metabolism phenotype. *Clin Chem Lab Med* 2004; 42(1):72–8.

Test Information

0051103

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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.