

Cytochrome P450 2C19 (CYP2C19) 9 Mutations

FOR DETECTION OF CYP2C19 MUTATIONS AFFECTING DRUG METABOLISM

Clinical Background

- Cytochrome P450 2C19 (CYP2C19) is an isoenzyme of the cytochrome P450 super family that metabolizes and eliminates common prescription drugs, including anti-convulsants, anti-depressants, proton pump inhibitors, and antithrombotics (clopidogrel/Plavix®), as well as chemotherapy, anti-malaria, and anti-ulcer drugs.
- 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.
- Metabolizer phenotypes can be predicted by the CYP2C19 genotype.
- The clinical impact of the CYP2C19 genotype is influenced by whether a drug is activated (e.g., clopidogrel, tamoxifen) or inactivated (e.g., amitriptyline, escitalopram) by CYP2C19, involvement of other metabolic pathways, and other non-genetic factors (e.g., concomitant medications).

Epidemiology

- CYP2C19 mutation frequency is dependent on ethnicity. The most common mutations are represented by the *2 and *3 alleles.
- The *2 allele is found in approximately 30% of Asians and 15% of Caucasians and African-Americans.
- The *3 allele is present in approximately 8% of Asians and is rare (less than 1%) in Caucasians and African-Americans.
- A poor metabolizer phenotype (caused by two non-functional CYP2C19 alleles) is present in 4% of Caucasians, 5% of African-Americans, and up to 25% of Asians.

Genetics

- The CYP2C19 gene has nine exons and is located on chromosome 10.
- Inheritance is autosomal recessive.
- Penetrance is drug-dependant.

Indications for Ordering

- Pre-therapeutic testing to identify individuals who should avoid, or may require unconventional doses of medications metabolized by CYP2C19. Common examples include:
 - Clopidogrel (Plavix®): Carriers of CYP2C19 *2 or *3 alleles have been shown to respond poorly to standard doses due to reduced metabolic activation of the drug. An alternate drug or dose escalation, coupled with monitoring of platelet function, should be considered.
 - Amitriptyline (Elavil®) and escitalopram (Lexapro®): Carriers of CYP2C19 *2 or *3 alleles may exhibit higher plasma

concentrations of the parent drug and slower clearance. Carriers of CYP2C19*17 may exhibit lower plasma concentrations and higher clearance. Therapeutic drug monitoring should be considered to optimize dosing.

- Tamoxifen (Nolvadex®): Carriers of CYP2C19 *17 have been shown to produce higher concentrations of the active metabolite endoxifen and experience decreased breast cancer recurrence when treated with tamoxifen. Decrease function alleles (e.g., CYP2C19 *9) are not expected to affect response to tamoxifen.
- For individuals with a personal or a family history of adverse drug reactions to medications metabolized by CYP2C19.

Interpretation

- If no CYP2C19 mutations are detected, this suggests *1 alleles and normal enzymatic activity.
- If one decreased function or one non-functional CYP2C19 mutation is detected, intermediate-to-normal CYP2C19 enzymatic activity is predicted.
- If two decreased function alleles, or one decreased function and one non-functional allele are detected, intermediate CYP2C19 enzymatic activity is predicted.
- If two non-functional mutations are present on opposite alleles, this predicts low CYP2C19 enzymatic activity and a poor metabolizer phenotype.
- Heterozygosity or homozygosity for the increased function *17 allele is associated with increased CYP2C19 activity and an ultra-rapid metabolizer phenotype.
- Genotype results should be interpreted in the context of the individual clinical situation. Consultation with a clinical pharmacy professional is recommended.

Methodology

- Polymerase chain reaction (PCR) followed by detection primer extension.
- Mutations tested include:

Allele Designation	Nucleotide Change	Mutation Effect	Predicted Enzyme Activity
*2	c.681 G>A	Splicing defect	Non-functional
*3	c.636 G>A	New stop codon	Non-functional
*4	c.1 A>G	Loss of initiation codon	Non-functional

Allele Designation	Nucleotide Change	Mutation Effect	Predicted Enzyme Activity
*5	c.1297C>T	R433W	Non-functional
*6	c.395G>A	R132Q	Non-functional
*7	IVS5+2T>A	Splicing defect	Non-functional
*8	c.358T>C	W120R	Non-functional
*9	c.431G>A	R114H	Decreased function
*10	c.680C>T	P227L	Decreased function
*17	c.991A>G	Increased gene transcription	Increased function

- Clinical sensitivity is estimated at 99% and 87% for Asians and Caucasians, respectively; sensitivity is unknown in other ethnicities.
- Analytical sensitivity and specificity are 99%.

Limitations

- *CYP2C19* mutations, other than those listed above, are not evaluated by this assay.
- Mutations in other genes associated with drug metabolism or drug response will not be detected.

- Drug metabolism may be affected by non-genetic factors.
- Mutation detection is not a substitute for therapeutic drug or clinical monitoring.
- Rare diagnostic errors may occur due to primer-site mutations.

Related Tests

- Cytochrome P450 2C9 (*CYP2C9*) 2 Mutations ([0051103](#))
- Cytochrome P450 2D6 (*CYP2D6*) 14 Mutations & Gene Duplication ([0051232](#))

References

1. Goldstein JA and de Morais SM. Biochemistry and molecular biology of the human CYP2C subfamily. *Pharmacogenetics* 1994;6:285–299.
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. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). <http://medicine.iupui.edu/clinpharm/ddis/table.asp>. (accessed on August 9, 2010).
4. Mega JL, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009;360(4):354–362.
5. Simon T, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360(4):363–375.

Test Information

0051104 Cytochrome P450 2C19 (*CYP2C19*) 9 Mutations

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

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