Cytochrome P450 2C19, *CYP2C19*

Indications for Ordering

- Assess genetic risk of abnormal drug metabolism for drugs metabolized by CYP2C19
- Investigate genetic causes that might contribute to a personal or family history of an adverse drug event or therapeutic failure involving a drug metabolized by CYP2C19

Test Description

Polymerase chain reaction/fluorescence monitoring
- Variant alleles detected – *2-4, *6-10, *17

Tests to Consider

Primary test

Cytochrome P450 2C19, *CYP2C19* – 9 Variants 2012769
- May aid in drug selection and dose planning for drugs metabolized by CYP2C19

Related tests
- Many drugs can be metabolized by alternative cytochrome P450 (CYP) enzymes
- Additional genotyping tests are available for *CYP2C9* (2012766), *CYP2D6* (0051232), and *CYP3A5* (2012740) as single gene tests or in a panel (2013098)
  - Panel includes a comprehensive medication guide based on the genotypes detected
- Therapeutic drug monitoring and/or metabolic ratios may be useful for evaluating the pharmacokinetics of a particular drug, for a particular patient
  - See the ARUP Laboratory Test Directory (www.aruplab.com/) for a list of available drug-specific testing

Disease Overview

Prevalence – allele frequencies differ among ethnic groups
- Most common no function alleles are *2 and *3
  - *CYP2C19**2 – Oceanian 54.9%, South Asian 34.4%, African American 18.3%, Caucasian 14.6%, Middle Eastern 13.2%
  - *CYP2C19**3 – Oceanian 13.9%, East Asian 8.5%, Middle Eastern 2.6%, Caucasian 0.6%, African American 0.3%
  - *CYP2C19**17 – Caucasian 21.5%, African American 19.4%, South Asian 16.5%, Oceanian 2.5%
- Poor metabolizer phenotype (caused by two no function *CYP2C19* alleles) occurs in 2-15%
- Intermediate metabolizer phenotype (caused by one no function *CYP2C19* allele with a functional or *17 allele) occurs in 18-45%
- Rapid metabolizer (caused by the *CYP2C19**17 with a functional allele) and ultra-rapid metabolizer phenotypes (caused by two *17 alleles) occurs in 5-30%

Treatment issues
- CYP2C19 is an isoenzyme involved in the metabolism of many clinically used drugs, including
  - Antidepressants
  - Antimalarials
  - Clopidogrel
  - Diazepam
  - Phenytoin
  - Proton pump inhibitors
  - R-warfarin
  - Tamoxifen
- Some drugs are
  - Activated by the pathway (eg, clopidogrel)
  - Inactivated by the pathway (eg, amitriptyline, escitalopram)
- Pharmacogenetic variation may lead to inappropriate concentrations of drugs and metabolites resulting in
  - Toxicity and risk of adverse drug reactions
  - Lack of therapeutic benefit
- Actual metabolic phenotype is subject to
  - Drug/drug interactions
  - Clinical factors
  - Other nongenetic factors

Treatment guidelines
- The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published dosing guidelines for *CYP2C19* genotypes and
  - Clopidogrel (eg, Plavix)–refer to CPIC dosing guideline (https://www.pharmgkb.org/guideline/PA166104948)
  - Tricyclic antidepressants (eg, amitriptyline)–refer to CPIC dosing guideline (https://www.pharmgkb.org/guideline/PA166105006)
  - Selective serotonin reuptake inhibitors (eg, citalopram)–refer to CPIC dosing guideline (https://www.pharmgkb.org/guideline/PA166127638)

Genetics

Gene – *CYP2C19*

Inheritance – autosomal codominant

Penetrance – drug dependent

Variants detected – see table

Structure/function – located on chromosome 10

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – drug dependent
- Analytical sensitivity/specificity – >99%

Results

- By report

Limitations

- Only the targeted *CYP2C19* variants will be detected
- Diagnostic errors can occur due to rare sequence variations
- Risk of therapeutic failure or adverse reactions with CYP2C19 substrates may be affected by genetic and nongenetic factors that are not detected by this test
  This result does not replace the need for therapeutic drug or clinical monitoring

Allele Designation	Nucleotide Change (NM_000769)	Reference Sequence Identifier	Variant Effect	Predicted Enzyme Activity
*2	c.681G>A	rs4244285	Splicing defect	No function
*3	c.636G>A	rs4986893	Creates stop codon	No function
*4	c.1A>G	rs28399504	Loss of initiation codon	No function
*6	c.395G>A	rs72552267	R132Q	No function
*7	c.891+2T>A	rs72558186	Splicing defect	No function
*8	c.358T>C	rs41291556	W120R	No function
*9	c.431G>A	rs17884712	R114H	Decreased function
*10	c.680C>T	rs6413438	P227L	Decreased function
*17	c.-806C>T	rs12248560	Increased gene transcription	Increased function

References

- Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update, the 2013 supplement and other relevant resources at www.pharmgkb.org
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors, available along with the 2015 supplement and other relevant resources at www.pharmgkb.org
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants, available along with the 2013 supplement and other relevant resources at www.pharmgkb.org
- The human cytochrome P450 (CYP) allele nomenclature database, available at www.cypalleles.ki.se/