Cytochrome P450 3A5, CYP3A5

Indications for Ordering

• Assess genetic risk of abnormal drug metabolism for drugs metabolized by CYP3A5
• 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 CYP3A5

Test Description

Polymerase chain reaction (PCR)/fluorescence monitoring
• Variant alleles detected – *3, *6

Tests to Consider

Primary test
Cytochrome P450 3A5 Genotyping, CYP3A5, 2 Variants 2012740
• May aid in drug selection and dose planning for drugs metabolized by CYP3A5

Related tests
• Many drugs can be metabolized by alternative cytochrome P450 (CYP) enzymes
• Single gene tests available separately
  ○ Cytochrome P450 2C9, CYP2C9 – 2 Variants 2012766
  ○ Cytochrome P450 2C19, CYP2C19 – 9 Variants 2012769
  ○ Cytochrome P450 2D6 (CYP2D6) 15 Variants and Gene Duplication 2014547
• Panel includes a comprehensive medication guide based on the genotypes detected
  ○ Cytochrome P450 Genotype Panel 2013098
    ● See sample Enhanced Report for panel test
• 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 (search by test name or number)

Disease Overview

Prevalence – allele frequencies differ among ethnic groups
• CYP3A5*3 – Caucasian 92.1%, Middle Eastern 88.1%, Latin American 76.5%, Asian 74.2%, African 29.8%
• CYP3A5*6 – African 17.2%, Latin American 3.7%, Middle Eastern 1.9%, Asian 0.1%, Caucasian 0.1%
• CYP3A5*7 – African 7.7%, Latin American 2.5%, Middle Eastern 0.2%, Asian 0%, Caucasian 0%

Predicted Phenotypes

• Poor metabolizer
  ○ 2 no function alleles
  ○ May result in few to no drug metabolites when the parent drug is a substrate of CYP3A5
• Intermediate metabolizer
  ○ 1 no function allele and 1 functional allele
  ○ May result in lower levels of drug metabolites when the parent drug is a substrate of CYP3A5
• Normal metabolizer
  ○ 2 functional alleles
  ○ Normal levels of drug metabolites when the parent drug is a substrate of CYP3A5

Treatment issues

• CYP3A5 is an isoenzyme involved in the metabolism of ~50% of clinically used drugs, including
  ○ Antibiotics
  ○ Antivirals
  ○ Benzodiazepines
  ○ Immunosuppressants
  ○ Steroids
• Most drug substrates for CYP3A5 are also substrates for other CYP enzymes, particularly CYP3A4
• Some drugs are inactivated by the pathway (eg, tacrolimus)
• Pharmacogenetic variation may lead to inappropriate concentrations of drugs and metabolites, resulting in
  ○ Toxicity and risk for 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 the immunosuppressant drug tacrolimus (eg, Prograf), based on CYP3A5 expressor phenotype, predicted from the CYP3A5 genotype
  ○ CYP3A5 expressors are associated with lower dose-adjusted concentrations of tacrolimus
    ● Typically require higher doses than nonexpressors
  ○ Therapeutic drug monitoring of tacrolimus is recommended to optimize dose
  ○ Refer to CPIC dosing guideline (www.pharmgkb.org/guideline/PA166124619)
Genetics

**Gene** – CYP3A5

**Inheritance** – autosomal codominant

**Penetrance** – drug dependent

**Variants detected**
- *3 (rs776746, c.6986A>G) no function allele
- *6 (rs10264272, c.14690G>A) no function allele
- Variants are numbered according to NG_000004.3 transcript

**Structure/function**
- Human CYP3A enzyme family includes
  - CYP3A4
  - CYP3A5
  - CYP3A7
  - CYP3A43
- Represents ~30% of total CYP content in the human liver
- CYP3A4 metabolic phenotypes are variable but have a unimodal distribution
- Loss of function from genetic associations is rare
- CYP3A5 metabolic phenotypes include normal (extensive), intermediate, and poor metabolizers
  - Also classified as expressors or nonexpressors
  - Nonexpressors are largely explained by the CYP3A5*3 and CYP3A5*6 alleles
- CYP3A7 is expressed in the fetal period
  - After birth, expression shifts to CYP3A4
- CYP3A43 is not known to be involved in drug metabolism

Test Interpretation

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

**Results**
- By report

**Limitations**
- Only the targeted CYP3A5 variants will be detected
- CYP3A5*7 is not analyzed by this test
- Diagnostic errors can occur due to rare sequence variations
- Phenotype predictions for transplant patients may require consideration of genotypes for both donor and recipient
- Risk of therapeutic failure or adverse reactions with CYP3A5 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

**References**