

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](http://www.pharmgkb.org/guideline/PA166124619) (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

- Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP3A5* Genotype and Tacrolimus Dosing. www.pharmgkb.org. Accessed Aug 2017
- MacPhee IA. Pharmacogenetic biomarkers: cytochrome P450 3A5. *Clin Chim Acta*. 2012;413(17-18):1312-1317
- The Human Cytochrome P450 (*CYP*) Allele Nomenclature Database. www.pharmvar.org/htdocs/archive/index_original.htm. Accessed Nov 2017