MAYO CLINIC LABORATORIES

Test Definition: 3A5Q

Cytochrome P450 3A5 Genotype, Varies

Overview

Useful For

Aids in optimizing treatment with tacrolimus and other drugs metabolized by cytochrome P450 3A5

Special Instructions

- Informed Consent for Genetic Testing
- Pharmacogenomic Association Tables
- Multiple Genotype Test List
- Informed Consent for Genetic Testing (Spanish)

Method Name

Polymerase Chain Reaction (PCR) With Allelic Discrimination Analysis

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

Testing is available as the single gene assay (this test) and as a part of a psychotropic or focused pharmacogenomics panel.

If multiple pharmacogenomic genotype testing is desired, order PGXQP / Focused Pharmacogenomics Panel, Varies.

If genotype testing for psychotropic medications is desired, order PSYQP / Psychotropic Pharmacogenomics Gene Panel, Varies.

Additional Testing Requirements

In general, most drugs metabolized by CYP3A5 are also metabolized by CYP3A4 and usually to a greater degree than CYP3A5. For this reason, substrates of these 2 enzymes are sometimes listed together in publications and genotyping of both genes might be needed to fully understand the metabolism of these drugs and predict phenotype. If *CYP3A4* genotyping is needed, order 3A4Q / Cytochrome P450 *3A4* Genotype, Varies.

Specimen Required

Multiple genotype tests can be performed on a single specimen after a single extraction. See Multiple Genotype Test List for a list of tests that can be ordered together.

Submit only 1 of the following specimens:

Specimen Type: Whole blood
Container/Tube: Lavender top (EDTA)
Specimen Volume: 3 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**
Specimen Stability Information: Ambient (preferred)/Refrigerated

Specimen Type: Saliva
Patient Preparation: Patient should not eat, drink, smoke, or chew gum 30 minutes prior to collection.
Supplies: Saliva Swab Collection Kit (T786)
Specimen Volume: One swab
Collection Instructions: Collect and send specimen per kit instructions.
Specimen Stability Information: Ambient

Specimen Type: DNA
Container/Tube: 2 mL screw top tube
Specimen Volume: 100 mcL (microliters)
Collection Instructions:
1. The preferred volume is 100 mcL at a concentration of 50 ng/mcL.
2. Include concentration and volume on tube.
Specimen Stability Information: Frozen (preferred) 1 year/Ambient/Refrigerated

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available:
-Informed Consent for Genetic Testing (T576)
-Informed Consent for Genetic Testing-Spanish (T826)
2. If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:
-Neurology Specialty Testing Client Test Request (T732)
-Therapeutics Test Request (T831)

Specimen Minimum Volume

Blood: 0.4 mL
Saliva: 1 swab

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

Clinical & Interpretive

Clinical Information

CYP3A5 is a member of the *CYP3A* family of genes located on chromosome 7. The cytochrome P450 (CYP) 3A subfamily of enzymes responsible for the metabolism of more than 50% of medications that undergo hepatic metabolism and first-pass metabolism in intestinal epithelial cells. The CYP3A5 expression level and enzymatic activity can be modulated by genetic variation. *CYP3A5* allelic frequency depends upon ethnicity. For example, in individuals of European descent the most common allele is the *CYP3A5*3* allele (c.219-237A>G), which results in a splicing defect and absence of enzyme activity. In individuals of African descent, the **1* allele (functional enzyme) is most common. The distribution of *CYP3A5*3* allele frequencies ranges from 0.14 among sub-Saharan Africans to 0.95 in European populations.

CYP3A5 testing is commonly ordered for patients receiving tacrolimus. Tacrolimus is an immunosuppressive calcineurin inhibitor used in transplant recipients. Tacrolimus has a low therapeutic index with a wide range of side effects and large interindividual variability in its pharmacokinetics, particularly in the dose required to reach target trough blood concentrations, thus necessitating routine therapeutic drug monitoring in clinical practice.

Tacrolimus dose requirements are most closely associated with *CYP3A5* genotype even though the drug is metabolized by both CYP3A4 and CYP3A5. According to existing literature and Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, individuals with at least one copy of fully functional *CYP3A5* (ie, **1/*1* and **1/*3*) require a higher dose of tacrolimus to reach the targeted whole blood concentrations than those without a copy of a fully functional *CYP3A5* allele (ie, **3/*3*) (2-5). *CYP3A5* genotyping may predict dose requirements for tacrolimus but does not replace the need for therapeutic monitoring to guide tacrolimus dose adjustments. For a patient with the *CYP3A5*3/*3* genotype, initiating tacrolimus therapy with a standard (normal) dose is recommended. One of the complications in interpreting *CYP3A5* genotyping results and the effect of genotype on drug dosing is the fact that most individuals involved in drug trials have been of European decent. Individuals of European decent are more likely to have the *CYP3A5*3/*3* genotype, which predicts a poor metabolizer phenotype. Dosing requirements were derived from these clinical trials so individuals with 1 or 2 copies of *CYP3A5*1*, will functionally behave as though they have increased activity and may require higher doses of CYP3A5 metabolized drugs.

The following table displays the *CYP3A5* variants detected by this assay, the corresponding star allele, and the effect on CYP3A5 enzyme activity:

***CYP3A5* allele**	**cDNA nucleotide change (NM_000777.4)**	**Effect on enzyme activity**
**1*	None (wild type)	Normal activity
**3*	c.219-237A>G	No activity
**6*	c.624G>A	No activity
**7*	c.1035dup	No activity
**8*	c.82C>T	Reduced activity
**9*	c.1009G>A	Reduced activity

Reference Values

An interpretive report will be provided.

Interpretation

An interpretive report will be provided.

The genotype, with associated star alleles, is assigned using standard allelic nomenclature as published by Pharmacogene Variation (PharmVar) Consortium.(1)

For additional information regarding pharmacogenomic genes and their associated drugs, see the Pharmacogenomic Associations Tables in Special Instructions. This resource also includes information regarding enzyme inhibitors and inducers, as well as potential alternate drug choices.

Cautions

Rare variants may be present that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings (phenotype), additional testing could be considered.

Specimens may contain donor DNA if obtained from patients who received non-leukoreduced blood transfusions or allogeneic hematopoietic stem cell transplantation. Results from specimens obtained under these circumstances may not accurately reflect the recipient's genotype. For individuals who have received blood transfusions, the genotype usually reverts to that of the recipient within 6 weeks. For individuals who have received allogeneic hematopoietic stem cell transplantation, a pretransplant DNA specimen is recommended for testing.

CYP3A5 genetic test results in patients who have undergone liver transplantation may not accurately reflect the patient's CYP3A5 status.

This method may not detect all variants that result in altered CYP3A5 activity. Therefore, absence of a detectable variant does not rule out the possibility that a patient has altered CYP3A5 activity due to other *CYP3A5* variants that cannot be detected with this method. Furthermore, when 2 or more variants are identified, the cis-/trans- status (whether the variants are on the same or opposite chromosomes) is not always known.

Drug-drug interactions and drug-metabolite inhibition must be considered.

Drug-metabolite inhibition can occur, resulting in inhibition of CYP3A5 catalytic activity.

Clinical Reference

1. PharmVar: Pharmacogene Variation Consortium. Updated September 26, 2023. Accessed October 25, 2023. Available at www.pharmvar.org/
2. Birdwell KA, Decker B, Barbarino JM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin Pharmacol Ther. 2015;98(1):19-24. doi:10.1002/cpt.113
3. Thervet E, Loriot MA, Barbier S, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. Clin Pharmacol Ther. 2010;87(6):721-726. doi:10.1038/clpt.2010.17
4. Lamba J, Hebert JM, Schuetz EG, Klein TE, Altman RB. PharmGKB summary: very important pharmacogene information for CYP3A5. Pharmacogenet Genomics. 2012;22(7):555-558. doi:10.1097/FPC.0b013e328351d47f
5. Clinical Pharmacogenetics Implementation Consortium (CPIC). Accessed October 25, 2023. https://cpicpgx.org/

Performance

Method Description

Genomic DNA is extracted from whole blood or saliva. Genotyping for *CYP3A5* alleles is performed using a polymerase chain reaction (PCR)-based 5'-nuclease assay. Fluorescently labeled detection probes anneal to the target DNA. PCR is used to amplify the section of DNA that contains the variant. If the detection probe is an exact match to the target DNA, the 5'-nuclease polymerase degrades the probe, the reporter dye is released from the effects of the quencher dye, and a fluorescent signal is detected. Genotypes are assigned based on the allele-specific fluorescent signals that are detected.(Unpublished Mayo method)

PDF Report

No

Day(s) Performed

Monday through Friday

Report Available

3 to 8 days

Specimen Retention Time

Whole blood/Saliva swab: 2 weeks; Extracted DNA: 2 months

Performing Laboratory Location

Rochester

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

81231-CYP3A5

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
3A5Q	CYP3A5 Genotype, V	81140-6

Test Definition: 3A5Q

Cytochrome P450 3A5 Genotype, Varies

Result ID	Test Result Name	Result LOINC® Value
610117	CYP3A5 Genotype	81140-6
610118	CYP3A5 Phenotype	79717-5
610119	Interpretation	69047-9
610120	Additional Information	48767-8
610121	Method	85069-3
610122	Disclaimer	62364-5
610123	Reviewed by	18771-6