Cytochrome P450 Genotyping

Last Literature Review: September 2021 Last Update: November 2023

The cytochrome P450 (CYP) isozymes 2B6, 2C19, 2C8, 2C9, 2D6, 3A4, and 3A5 are involved in the metabolism of many drugs. Variants in the genes that code for these enzymes may influence pharmacokinetics of the respective medications, and therefore may predict or explain nonstandard dose requirements, therapeutic failure, or adverse reactions.

Disease Overview

Treatment Issues

- The actual metabolic phenotype of a drug metabolizing enzyme is subject to drug-drug interactions, clinical factors, and other nongenetic factors.
- 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-gene specific testing (search by test name or number).
- The Clinical Pharmacogenetics Implementation Consortium (CPIC)[1] and the Food and Drug Administration (FDA)[2] have published clinical associations and dosing guidelines involving *CYP* genotypes. Refer to the following list for specific dosing guidelines:
  - Atomoxetine[3] (eg, Strattera)
  - Clopidogrel[4] (eg, Plavix)
  - Efavirenz[5]
  - Opioids (eg, codeine[6], tramadol)
  - Siponimod (eg, Mayzent[7])
  - Nonsteroidal anti-inflammatory drugs[8] (NSAIDs)
  - Ondansetron and Tropisetron[9]
  - Phenytoin[10] (eg, Dilantin)
  - Proton pump inhibitors[11] (eg, omeprazole)
  - Selective serotonin reuptake inhibitors[12] (eg, citalopram)
  - Tacrolimus[13] (eg, Prograf)
  - Tamoxifen[14]
  - Tricyclic antidepressants[15] (eg, amitriptyline)
  - Voriconazole[16]
  - Warfarin[17] (eg, Coumadin)

Genetics

Genes

CYP2B6, *CYP2C19*, *CYP2C8*, *CYP2C9*, *CYP2C* rs12777823, *CYP2D6*, *CYP3A4*, *CYP3A5*

Inheritance

Autosomal codominant

Variants Tested

Variants or groups of variants are classified as “star” (*) alleles, that are associated with predicted enzyme function, based on international consensus nomenclature. However, not all variants on a chromosome/allele are interrogated and assumptions about phase are made, as shown below. More details about

Featured ARUP Testing

Cytochrome P450 Genotyping Panel 3001524

Method: Polymerase Chain Reaction (PCR)/Fluorescence Monitoring/Sequencing

- Assesses genetic variants contributing to risk of abnormal drug metabolism for drugs metabolized by enzymes coded by *CYP2B6*, *CYP2C19*, *CYP2C8*, *CYP2C9*, *CYP2D6*, 2C cluster variant (rs12777823), *CYP3A4*, and *CYP3A5*
- May aid in drug selection and dose planning for many drugs that are either activated or inactivated by one or more CYP450 enzymes. Recommendations may include drug avoidance or nonstandard dosing.

Cytochrome P450 Genotyping Panel, with GeneDose Access 3004255

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- Report may include comprehensive medication guidance based on the genotypes detected and access to GeneDose Live, a cloud-based medication management and risk mitigation tool

nomenclature, allele frequencies and phenotype predictions are available at PharmVar[18] or PharmGKB.[19]

Gene (Transcript)	Alleles	Predicted Allele Function
CYP2B6 (NM_000767)	*CYP2B6*4*: rs2279343, c.785A>G	Increased function
	*CYP2B6*6*: rs3745274, c.516G>T; rs2279343, c.785A>G	Decreased function
	*CYP2B6*7*: rs3745274, c.516G>T; rs2279343, c.785A>G; rs3211371, c.1459C>T	Decreased function
	*CYP2B6*9*: rs3745274, c.516G>T	Decreased function
	*CYP2B6*18*: rs28399499, c.983T>C	No function
	*CYP2B6*22*: rs34223104, c.-82T>C	Increased function
	*CYP2B6*36*: rs34223104, c.-82T>C; rs3745274, c.516G>T; rs2279343, c.785A>G	Decreased function
CYP2C19 (NM_000769)	*CYP2C19*2*: rs4244285, c.681G>A; rs12769205, c.332-23A>G	No function
	*CYP2C19*3*: rs4986893, c.636G>A	No function
	*CYP2C19*4A*: rs28399504, c.1A>G	No function
	*CYP2C19*4B*: rs28399504, c.1A>G, rs12248560, c.-806C>T	No function
	*CYP2C19*5*: rs56337013, c.1297C>T	No function
	*CYP2C19*6*: rs72552267, c.395G>A	No function
	*CYP2C19*7*: rs72558186, c.819+2T>A	No function
	*CYP2C19*8*: rs41291556, c.358T>C	No function
	*CYP2C19*9*: rs17884712, c.431G>A	Decreased function
	*CYP2C19*17*: rs12248560, c.-806C>T	Increased function
	*CYP2C19*35*: rs12769205, c.332-23A>G	No function
CYP2C8 (NM_000770)	*CYP2C8*2*: rs11572103, c.805A>T	Decreased function
	*CYP2C8*3*: rs10509681, c.1196A>G	Decreased function
	*CYP2C8*4*: rs1058930, c.792C>G	Decreased function
CYP2C cluster (NC_000010)	*CYP2C* rs12777823, g.96405502 G>A	Unclassified[a]
CYP2C9 (NM_000771)	*CYP2C9*2*: rs1799853, c.430C>T	Decreased function
	*CYP2C9*3*: rs1057910, c.1075A>C	Decreased function
	*CYP2C9*4*: rs56165452, c.1076T>C	Decreased function
	*CYP2C9*5*: rs28371686, c.1080C>G	Decreased function

[a]The *CYP2C* cluster variant is associated with a decreased warfarin dose requirement in some people of African descent.

Gene (Transcript)	Alleles	Predicted Allele Function
	*CYP2C9*6*: rs9332131, c.818del	No function
	*CYP2C9*8*: rs7900194, c.449G>A	Decreased function
	*CYP2C9*11*: rs28371685, c.1003C>T	Decreased function
	*CYP2C9*12*: rs9332239, c.1465C>T	Decreased function
CYP2D6 (M33388 sequence)	*CYP2D6*2*: rs16947, g.2850C>T; rs1135840, g.4180G>C	Functional
	*CYP2D6*2A*: rs1080985, g.-1584C>G; rs16947, g.2850C>T; rs1135840, g.4180G>C	Functional
	*CYP2D6*3*: rs35743686, g.2549del	No function
	*CYP2D6*4*: rs1065852, g.100C>T; rs3892097, g.1846G>A; rs1135840, g.4180G>C	No function
	*CYP2D6*5*: gene deletion	No function
	*CYP2D6*6*: rs5030655, g.1707del; rs1135840, g.4180G>C	No function
	*CYP2D6*7*: rs5030867, g.2935A>C	No function
	*CYP2D6*8*: rs5030865, g.1758G>T; rs16947, g.2850C>T; rs1135840, g.4180G>C	No function
	*CYP2D6*9*: rs5030656, g.2615_2617del	Decreased function
	*CYP2D6*10*: rs1065852, g.100C>T; rs1135840, g.4180G>C	Decreased function
	*CYP2D6*11*: rs1080985, g.-1584C>G; rs201377835, g.883G>C; rs16947, g.2850C>T; rs1135840, g.4180G>C	No function
	*CYP2D6*13*: a CYP2D7-derived exon 1 conversion	No function
	*CYP2D6*14*: rs5030865, g.1758G>A; rs16947, g.2850C>T; rs1135840, g.4180G>C	Decreased function
	*CYP2D6*15*: rs774671100, g.137_138insT	No function
	*CYP2D6*17*: rs28371706, g.1023C>T; rs16947, g.2850C>T; rs1135840, g.4180G>C	Decreased function
	*CYP2D6*29*: rs16947, g.2850C>T; rs59421388, g.3183G>A; rs1135840, g.4180G>C	Decreased function
	*CYP2D6*35*: rs1080985, g.-1584C>G; rs769258, g.31G>A; rs16947, g.2850C>T; rs1135840, g.4180G>C	Functional
	*CYP2D6*36*: a CYP2D6*10 carrying a CYP2D7-derived exon 9 conversion	No function
	*CYP2D6*36-*10*: a *CYP2D6*36* and a *CYP2D6*10* in tandem	Decreased function
	*CYP2D6*40*: rs28371706, g.1023C>T; rs72549356, c.1863_1864ins TTTCGCCCCTTTCGCCCC; rs16947, g.2850C>T; rs1135840, g.4180G>C	No function
	*CYP2D6*41*: rs16947, g.2850C>T; rs28371725, g.2988G>A; rs1135840, g.4180G>C	Decreased function
	*CYP2D6*42*: rs16947, g.2850C>T; rs72549346, g.3260_3261insGT; rs1135840, g.4180G>C	No function

[a]The *CYP2C* cluster variant is associated with a decreased warfarin dose requirement in some people of African descent.

Gene (Transcript)	Alleles	Predicted Allele Function
	*CYP2D6*49*: rs1065852, g.100C>T; rs1135822, g.1611T>A; rs1135840, g.4180G>C	Decreased function
	*CYP2D6*69*: rs1065852, g.100C>T; rs16947, g.2850C>T; rs28371725, g.2988G>A; rs1135840, g4180G>C	No function
	*CYP2D6*114*: rs1065852, g.100C>T; rs5030865, g.1758G>A; rs16947, g.2850C>T; rs1135840, g.4180G>C	No function
	DUP: complete gene duplication	Varies based on the allele that is duplicated
CYP3A4 (NM_017460)	*CYP3A4*1B*: rs2740574, c.-392G>A	Normal function
	*CYP3A4*15*: rs4986907, c.485G>A	Decreased function
	*CYP3A4*22*: rs35599367, c.522-191C>T	Decreased function
CYP3A5 (NM_000777)	*CYP3A5*3*: rs776746, c.219-237A>G	No function
	*CYP3A5*6*: rs10264272, c.624G>A	No function
	*CYP3A5*7*: rs41303343, c.1035dup	No function

[a]The *CYP2C* cluster variant is associated with a decreased warfarin dose requirement in some people of African descent.

Results

- Genetic variant(s) detected: alleles detected are reported. The combination of alleles detected or diplotype is used to predict metabolizer phenotype, and in the case of *CYP2D6*, the activity score. Phenotype predictions are subject to change as the scientific and clinical evidence evolves.
- No variants detected is predictive of **1* functional alleles.
- Functional variants without clinical indication or impact on clinical management may not be reported.

Limitations

- Only the targeted genetic variants will be detected by this panel. Assumptions about phase and content are made to assign alleles.
- Diagnostic errors can occur due to rare sequence variations.
- A combination of the *CYP2D6*5* (gene deletion) and a *CYP2D6* gene duplication cannot be specifically identified; however, this combination is not expected to adversely affect the phenotype prediction.
- Risk of therapeutic failure or adverse reactions with gene substrates may be affected by genetic and nongenetic factors that are not detected by this test. The test result does not replace the need for therapeutic drug or clinical monitoring.
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Related Information

Germline Pharmacogenetics - PGx

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