Pharmacogenetics Panel for Psychotropics

Content Review: July 2022 Last Update: November 2023

Variation in genes affecting pharmacokinetics and/or pharmacodynamics (pharmacogenetics) may influence medication selection and dose planning.[1] For example, variants in genes that code for metabolizing enzymes (*CYP2B6*, *CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*, and *UGT2B15*) may be associated with altered (slower or faster) metabolism, which would affect the kinetics of medication activation, inactivation, and/or elimination. Other genes may predict the risk of side effects and/or the likelihood of response (*ANKK1*, *COMT*, *DRD2*, *GRIK4*, *HTR2A*, *HTR2C*, *MTHFR*, and *OPRM1*). This panel can provide information that may guide selection and dosing for many prescription medications, including medications relevant to psychiatry such as psychostimulants (eg, ADHD medication), antidepressants, antipsychotics, and anxiolytics. The potential roles of the pharmacogenes included in this test are summarized below.

Featured ARUP Testing

Pharmacogenetics Panel: Psychotropics 3004471

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

Pharmacogenetics Panel: Psychotropics, with GeneDose Access 3006366

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

- Use to assess genetic variants that may inform selection and dosing of common and many other psychotropic medications
- Test is appropriate for individuals with personal or family history of therapeutic failure or adverse events related to psychotropic medications

Refer to the Laboratory Test Directory for additional testing to assess genetic risk of abnormal drug metabolism for specific substrates, including CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4, CYP3A5, and the methylenetetrahydrofolate reductase variant.

Treatment Issues

- Actual metabolic phenotype is subject to interactions related to pharmacogenes, medications, supplements, food, lifestyle choices, clinical factors, as well as genetic and nongenetic factors not identified by this test. This test is intended only to identify targeted pharmacogene variants.
- Therapeutic and clinical monitoring are needed to guide pharmacotherapy for a particular patient. For more information about pharmacogenetic testing and ARUPs test offerings, see the ARUP Consult topic Germline Pharmacogenetics - PGx.
- A table providing known clinical associations between the gene variants detected in this test and several common psychotropic medications can be found here.
- The U.S. Food and Drug Administration (FDA) has published a table[2] characterizing gene-medication associations based on whether current data support therapeutic management decisions, indicate a potential impact on safety or response, or demonstrate a potential impact on pharmacokinetic properties only.
- The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published dosing guidelines for several psychotropic medications such as atomoxetine,[3] selective serotonin reuptake inhibitors[4] (eg, citalopram), and tricyclic antidepressants[5] (eg, amitriptyline). For more detailed information, refer to the CPIC guidelines website.[6]
- The Pharmacogenomics Knowledge Base[7] provides evidence for additional medication-gene associations with relevant clinical associations, medication labeling, and gene-based dosing guidelines.

Testing Considerations

- This panel provides a comprehensive analysis for multiple genes that have strong pharmacogenomic associations with medications used in the treatment of psychiatric disorders, including depression. Specific gene-drug interactions are supported by guidelines from CPIC, Association for Molecular Pathology (AMP), or Dutch Pharmacogenetics Working Group (DPWG) (*CYP2B6*, *CYP2C19*, *CYP2C9*, *CYP2D6*, and *CYP3A4*).
- This panel also provides analysis for multiple genes that have level 3 evidence linking the genes to psychotropic medications according to PharmGKB (*MTHFR*, *CYP3A5*, *DRD2*, *ANKK1*, *GRIK4*, *HTR2A*, *HTR2C*, *UGT2B15*, *COMT*, and *OPRM1*). More details are available in the PharmGKB Levels of Evidence for Selected Medication/Gene Associations table or on the PharmGKB website.[7]
- Some of the genes tested in the psych panel are part of other panels offered by ARUP, and hence there might be instances where some of the alleles reported in the psych panel are not linked to psychotropic medications. Caution must be taken when clinically interpreting these findings relevant to the medications patients are using.
- The test result does not replace the need for therapeutic medication or clinical monitoring.

Genetics

Genes

ANKK1, *COMT*, *CYP2B6*, *CYP2C19*, *CYP2C9*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *DRD2*, *GRIK4*, *HTR2A*, *HTR2C*, *MTHFR*, *OPRM1*, *UGT2B15*

Inheritance

Autosomal codominant

Variants Tested

Variant(s) from a reference sequence are detected by targeted genotyping (not full gene sequencing) and by copy number determinations (*CYP2D6* only). Conventional nomenclature for describing the variants and predicting phenotype is applied, when available. For many pharmacogenes, variants are grouped and classified as "star" (*) alleles that are associated with predicted enzyme or protein function, based on international consensus nomenclature. However, not all variants in a gene are tested, and assumptions about phase or diplotype assignments are made. More details about the nomenclature, allele frequencies, and phenotype predictions are available at the PharmVar[7] and PharmGKB[8] websites.

Gene (Transcript) and Brief Summary of Associated Protein Function	Alleles	Predicted Allele Function[a]
ANKK1 (NM_178510) (DRD2 associated) This variant in ANKK1 represents the Taq1A polymorphism that affects the expression of binding sites for dopamine on the D2 receptor and can influence response to psychotropic medications that target the dopaminergic system	rs1800497, c.2137G>A	Drug dependent[b]
COMT (NM_000754) Codes for catechol-o-methyltransferase, an enzyme that metabolizes catecholamines such as dopamine and is involved in response to several medications	rs4680, c.472G>A	Drug dependent[b]
CYP2B6 (NM_000767) Codes for the cytochrome P450 2B6 enzyme, which is involved in metabolism of many medications; impact of the phenotype depends on whether a medication is activated or inactivated by this enzyme	*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) Codes for the cytochrome P450 2C19 enzyme, which is involved in metabolism of many medications; impact of the phenotype depends on whether a medication is activated or inactivated by this enzyme	*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

[a]Predicted allele function based on PharmVar unless otherwise indicated.

[b]See www.pharmgkb.org[7] for allele frequency and other data about these variants.

[c]Genomic coordinates for *CYP2D6* variants are based on reference sequence M33388.

Gene (Transcript) and Brief Summary of Associated Protein Function	Alleles	Predicted Allele Function[a]
	*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
CYP2C9 (NM_000771) Codes for the cytochrome P450 2C9 enzyme, which is involved in metabolism of many medications; impact of the phenotype depends on whether a medication is activated or inactivated by this enzyme	*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
	*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[c] (M33388 sequence) Codes for the cytochrome P450 2D6 enzyme, which is involved in metabolism of many medications; impact of the phenotype depends on whether a medication is activated or inactivated by this enzyme. The test also evaluates copy number variations and can discriminate which allele is affected in most cases that exhibit gene duplication.	*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

[a]Predicted allele function based on PharmVar unless otherwise indicated.

[b]See www.pharmgkb.org[7] for allele frequency and other data about these variants.

[c]Genomic coordinates for *CYP2D6* variants are based on reference sequence M33388.

Gene (Transcript) and Brief Summary of Associated Protein Function	Alleles	Predicted Allele Function[a]
	*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*: rs769258, g.31G>A; rs16947, g.2850C>T; rs1135840, g.4180G>C; rs1080985, g.-1584C>G	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
	*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, g.4180G>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*1A*: rs2740574, c.-392G>A	Normal function

[a]Predicted allele function based on PharmVar unless otherwise indicated.

[b]See www.pharmgkb.org[7] for allele frequency and other data about these variants.

[c]Genomic coordinates for *CYP2D6* variants are based on reference sequence M33388.

Gene (Transcript) and Brief Summary of Associated Protein Function	Alleles	Predicted Allele Function[a]
Codes for the cytochrome P450 3A4 enzyme, which is involved in metabolism of many medications; impact of the phenotype depends on whether a medication is activated or inactivated by this enzyme		
	*CYP3A4*22*: rs35599367, c.522-191C>T	Decreased function
CYP3A5 (NM_000777) Codes for the cytochrome P450 3A5 enzyme, which is involved in metabolism of many medications; impact of the phenotype depends on whether a medication is activated or inactivated by this enzyme	*CYP3A5*3*: rs776746, c.219-237A>G	No function
	*CYP3A5*6*: rs10264272, c.624G>A	No function
	*CYP3A5*7*: rs41303343, c.1035dup	No function
DRD2 (NM_000795) Codes for the D2 dopamine receptor that is involved in medication dependence and response to psychotropic medications, particularly antipsychotics	rs1799978, c.-585A>G	Drug dependent[b]
GRIK4 (NM_014619) Codes for the ionotropic glutamate receptor also known as AMPA 4, kainate type subunit 4. This receptor is involved in response to psychotropic medications, particularly antidepressants.	rs1954787, c.83-10039T>C	Drug dependent[b]
HTR2A (NM_000621) Codes for a serotonin receptor that is involved in response to many psychotropic medications, including antidepressants and antipsychotics	rs6311, c.-998G>A	Drug dependent[b]
	rs7997012, c.614-2211T>C	Drug dependent[b]
HTR2C (NM_001256760) Codes for a serotonin receptor that is involved in response to psychotropic medications, particularly antipsychotics	rs3813929, c.-850C>T	Drug dependent[b]
MTHFR (NM_005957) Codes for methylenetetrahydrofolate reductase, an enzyme that is involved in folate metabolism and is implicated in response to l-methylfolate supplementation and response to several psychotropic medications, particularly antipsychotics	rs1801131, c.1286A>C	Drug dependent[b]
	rs1801133, c.665C>T	Drug dependent[b]
OPRM1 (NM_000914) Codes for the mu 1 opioid receptor that is involved in response to opioid agonists and antagonists, as well as several other medications	rs1799971, c.118A>G	Drug dependent[b]
UGT2B15 (NM_001076) Codes for UDP glucuronosyl-transferase family 2 member B15 that is involved in metabolism of many medications, such as the anxiolytics oxazepam and lorazepam	rs1902023, c.253T>G	Drug dependent[b]

[a]Predicted allele function based on PharmVar unless otherwise indicated.

[b]See www.pharmgkb.org[7] for allele frequency and other data about these variants.

[c]Genomic coordinates for *CYP2D6* variants are based on reference sequence M33388.

Test Interpretation

Clinical sensitivity is drug and patient dependent.

Analytic sensitivity/specificity is greater than 99%.

Results

- Genetic variant(s) detected: alleles detected are reported. The combination of alleles detected is used to predict phenotype and activity scores, as applicable (eg, *CYP2D6*).
- Phenotype predictions, allele definitions, and associations with specific medications are subject to change as the scientific and clinical evidence evolves.
- When appropriate, results are reported as “star” (*) alleles based on consensus nomenclature. No variants detected is reported as “Negative” and is predictive of *1 functional allele.

- For more information about the association between certain genes and medications, please see the PharmGKB Levels of Evidence for Selected Medication/Gene Associations table.

Limitations

- Only the targeted 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.
- HLA-B*15:02 (an allele that is more common in individuals of Asian descent) and other HLA alleles with pharmacogenetic relevance are not included due to analytical limitations. For additional test options, including testing for HLA-B*15:02 status, refer to the Laboratory Test Directory.

References

1. Hahn M, Müller DJ, Roll SC. Frequencies of genetic polymorphisms of clinically relevant gene-drug pairs in a German psychiatric inpatient population. *Pharmocopsychiatry*. 2021;54(2):81-89.

2. U.S. Department of Health and Human Services, Food and Drug Administration. Table of pharmacogenetic associations. [Updated: May 2022; Accessed: Aug 2022]

3. Brown JT, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium guideline for cytochrome P450 (CYP)2D6 genotype and atomoxetine therapy. *Clin Pharmacol Ther*. 2019;106(1):94-102.

4. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther*. 2015;98(2):127-134.

5. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical Pharmacogenetics Implementation Consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. *Clin Pharmacol Ther*. 2017;102(1):37-44.

6. Clinical Pharmacogenetics Implementation Consortium. CPIC guidelines. [Updated: Mar 2021; Accessed: Oct 2021]

7. Clinical Pharmacogenetics Implementation Consortium, Dutch Pharmacogenetics Working Group, Canadian Pharmacogenomics Network for Drug Safety. PharmGKB. [Accessed: Jul 2022]

8. Pharmacogene Variation Consortium. PharmVar. [Updated: Nov 2020; Accessed: Dec 2020]

Related Information

Cytochrome P450 Genotyping
Methylenetetrahydrofolate Reductase (MTHFR) Testing

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