

Cytochrome P450 2D6, *CYP2D6*

Indications for Ordering

- Assess genetic risk of abnormal drug metabolism for drugs metabolized by CYP2D6
- 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 CYP2D6

Test Description

Polymerase chain reaction (PCR)/fluorescence monitoring

- Variant alleles detected – *2 to *10, *12, *14, *17, *29, *36, *41
- Gene duplication also assessed

Tests to Consider

Primary test

[Cytochrome P450 2D6 \(*CYP2D6*\) 15 Variants and Gene Duplication 2014547](#)

- May aid in drug selection and dose planning for drugs metabolized by CYP2D6

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 3A5 Genotyping, *CYP3A5*, 2 Variants 2012740](#)
- 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
- See Table 1 for allele frequencies

Predicted Phenotypes

- Poor metabolizer
 - 2 no function alleles
 - May result in few to no drug metabolites when the parent drug is a substrate of CYP2D6; activity score prediction is 0 of 2
- Intermediate metabolizer
 - 1 no function allele and 1 decreased function allele
 - May result in lower levels of drug metabolites when the parent drug is a substrate of CYP2D6; activity score prediction is <1 of 2
 - Avoid concomitant use of CYP2D6 inhibitors to prevent conversion of intermediate metabolizer to a poor metabolizer
- Normal metabolizer
 - 2 functional alleles
 - Normal levels of drug metabolites when the parent drug is a substrate of CYP2D6
 - Activity score prediction is 1-2 of 2
 - Avoid concomitant use of CYP2D6 inhibitors to prevent conversion of normal metabolizer to an intermediate or poor metabolizer
- Ultrarapid metabolizer
 - More than 2 copies of functional alleles (gene duplication)
 - May result in higher levels of drug metabolites when the parent drug is a substrate of CYP2D6; activity score prediction is >2

Treatment issues

- CYP2D6 is an isozyme involved in the metabolism of up to 25% of all clinically used drugs, including
 - Antiestrogens (eg, tamoxifen)
 - Alpha blockers
 - Analgesics
 - Anticonvulsives
 - Antidepressants (eg, nortriptyline)
 - Antidiabetics
 - Antihypertensives
 - Antipsychotics
 - Antitussives (eg, codeine)
 - Beta blockers
 - Cardioactives
 - Norepinephrine reuptake inhibitors
 - Stimulants
- Some drugs are
 - Activated by the pathway (eg, codeine)
 - Inactivated by the pathway (eg, nortriptyline)
- 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 and drug/food interactions
 - Clinical factors
 - Other nongenetic factors

Treatment guidelines

- The Clinical Pharmacogenetics Implementation Consortium (CPIC) has published dosing guidelines for *CYP2D6* genotypes and
 - Codeine – refer to [CPIC dosing guideline](http://www.pharmgkb.org/guideline/PA166104996) (www.pharmgkb.org/guideline/PA166104996)
 - Tricyclic antidepressants (eg, nortriptyline) – refer to [CPIC dosing guideline](http://www.pharmgkb.org/guideline/PA166105006) (www.pharmgkb.org/guideline/PA166105006)
 - Selective serotonin reuptake inhibitors (eg, citalopram) – refer to [CPIC dosing guideline](http://www.pharmgkb.org/guideline/PA166127638) (www.pharmgkb.org/guideline/PA166127638)

Genetics

Gene – *CYP2D6*

Inheritance – autosomal codominant

Penetrance – drug dependent

Variants detected – see Table 2

Structure/function – located on chromosome 22

Test Interpretation

Sensitivity/specificity

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

Results

- By report
- No variants detected (negative) – predictive of *1 functional allele and normal enzymatic activity

Limitations

- Only the targeted *CYP2D6* variants will be detected
- Diagnostic errors can occur due to rare sequence variations
- Risk of therapeutic failure or adverse reactions with *CYP2D6* 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

- Bernard S, Neville KA, et al. Interethnic differences in genetic polymorphisms in the U.S. population: clinical implications. *Oncologist*. 2006;11(2):126-135
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and dosing of selective serotonin reuptake inhibitors. www.pharmgkb.org. Accessed Aug 2017
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and codeine therapy. www.pharmgkb.org. Accessed Aug 2017
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* and *CYP2C19* genotypes and dosing of tricyclic antidepressants. www.pharmgkb.org. Accessed Aug 2017
- The Human Cytochrome P450 (CYP) Allele Nomenclature Database. www.cypalleles.ki.se/. Accessed Jun 2017

Allele	African	Asian	Caucasian	Middle Eastern	Oceanian
<i>CYP2D6</i> *2 or <i>CYP2D6</i> *2A	17.6%	21.2%	27.6%	21.7%	1.2%
<i>CYP2D6</i> *3	0.2%	0%	1.3%	0.1%	0.2%
<i>CYP2D6</i> *4	4.9%	4.6%	18.2%	7.8%	2.5%
<i>CYP2D6</i> *5	6.3%	4.3%	2.8%	2.3%	4.3%
<i>CYP2D6</i> *6	0.1%	0%	1.0%	0.6%	0%
<i>CYP2D6</i> *7	0%	0%	0.1%	0%	0%
<i>CYP2D6</i> *8	0%	0%	0%	0%	0%
<i>CYP2D6</i> *9	0.3%	0.5%	2.1%	0%	0%
<i>CYP2D6</i> *10	5.3%	30.2%	3.0%	3.5%	2.5%
<i>CYP2D6</i> *12	0%	0%	0%	0%	0%
<i>CYP2D6</i> *14	0.1%	0.4%	0%	0.2%	0%
<i>CYP2D6</i> *17	19.0%	0.1%	0.4%	1.6%	0.1%
<i>CYP2D6</i> *29	7.7%	0%	0.1%	0.8%	0%
<i>CYP2D6</i> *36	0.3%	0.7%	0%	0%	0%
<i>CYP2D6</i> *41	9.2%	4.9%	7.9%	19.9%	0.9%
<i>CYP2D6</i> xN (gene duplication)	4.7%	1.6%	2.6%	7.1%	11.8%

Allele Designation	Nucleotide Change (Numbered According to M33388 sequence)	Reference Sequence Identifier	Predicted Enzyme Activity
*2	2850C>T	rs16947	Functional (normal)
*2A	-1584C>G; 2850C>T	rs1080985, rs16947	Functional (normal)
*3	2549delA	rs35742686	Nonfunctional
*4	100C>T; 1846G>A	rs3892097	Nonfunctional
*5	Gene deletion		Nonfunctional
*6	1707delT	rs5030655	Nonfunctional
*7	2935A>C	rs5030867	Nonfunctional
*8	1758G>T; 2850C>T	rs5030865	Nonfunctional
*9	2613-5delAGA	rs5030656	Decreased function
*10	100C>T	rs1065852	Decreased function
*12	124G>A; 2850C>T	rs5030862	Nonfunctional
*14	1758G>A; 2850C>T	rs5030865	Nonfunctional
*17	1023C>T; 2850C>T	rs28371706	Decreased function
*29	1659G>A; 2850C>T	rs59421388	Decreased function
*36	*10 carrying a <i>CYP2D7</i> -derived exon 9 conversion		Nonfunctional
*41	2988G>A; 2850C>T	rs28371725	Decreased function
Duplication of functional alleles			Increased function