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 (www.pharmgkb.org/guideline/PA166104996)
  - Tricyclic antidepressants (eg, nortriptyline) – refer to CPIC dosing guideline (www.pharmgkb.org/guideline/PA166105006)
  - Selective serotonin reuptake inhibitors (eg, citalopram) – refer to CPIC dosing guideline (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
- Combination of *5 (gene deletion) and gene duplication cannot be specifically identified
  - Combination is not expected to adversely affect the prediction of activity score or phenotype
- 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.pharmvar.org/htdocs/archive/index_original.htm. Accessed Nov 2017

Table 1. Allele Frequencies					
Allele	**African**	**Asian**	**Caucasian**	**Middle Eastern**	**Oceanian**
*CYP2D6*2* or *CYP2D6*2A*	17.6%	21.2%	27.6%	21.7%	1.2%
*CYP2D6*3*	0.2%	0%	1.3%	0.1%	0.2%
*CYP2D6*4*	4.9%	4.6%	18.2%	7.8%	2.5%
*CYP2D6*5*	6.3%	4.3%	2.8%	2.3%	4.3%
*CYP2D6*6*	0.1%	0%	1.0%	0.6%	0%
*CYP2D6*7*	0%	0%	0.1%	0%	0%
*CYP2D6*8*	0%	0%	0%	0%	0%
*CYP2D6*9*	0.3%	0.5%	2.1%	0%	0%
*CYP2D6*10*	5.3%	30.2%	3.0%	3.5%	2.5%
*CYP2D6*12*	0%	0%	0%	0%	0%
*CYP2D6*14*	0.1%	0.4%	0%	0.2%	0%
*CYP2D6*17*	19.0%	0.1%	0.4%	1.6%	0.1%
*CYP2D6*29*	7.7%	0%	0.1%	0.8%	0%
*CYP2D6*36*	0.3%	0.7%	0%	0%	0%
*CYP2D6*41*	9.2%	4.9%	7.9%	19.9%	0.9%
CYP2D6xN (gene duplication)	4.7%	1.6%	2.6%	7.1%	11.8%

Table 2. Variants Detected			
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 *CYP2D7*-derived exon 9 conversion		Nonfunctional
**41*	2988G>A; 2850C>T	rs28371725	Decreased function
Duplication of functional alleles			Increased function