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/fluorescence monitoring
- Variant alleles detected – *2-10, *12, *14, *17, *29, *41
- Gene duplication also assessed

Tests to Consider

Primary test

Cytochrome P450 2D6 (*CYP2D6*) 14 Variants and Gene Duplication 0051232
- 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
- Additional genotyping tests are available for *CYP2C9* (2012766), *CYP2C19* (2012769), and *CYP3A5* (2012740) as single gene tests or in a panel (2013098)
  - Panel includes a comprehensive medication guide based on the genotypes detected
- 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

Disease Overview

Prevalence

- Poor metabolizer phenotype (caused by two no-function *CYP2D6* alleles)
  - Caucasians and Hispanics – 10%
  - African Americans – 2%
  - Asians – 1%
- Intermediate metabolizer phenotype (caused by one no-function *CYP2D6* allele with a reduced function *CYP2D6* allele) occurs in 2-11%
- Ultra-rapid metabolizer phenotype (caused by duplication of functional *CYP2D6* alleles) occurs in 1-2%, but is observed more commonly in Ethiopians and Saudi Arabian populations

Treatment issues

- CYP2D6 is an isozyme involved in the metabolism of up to 25% of all clinically used drugs, including
  - Antiestrogens (eg, tamoxifen)
  - Antitussives (eg, codeine)
  - Anticonvulsants
  - Antidepressants (eg, SSRIs)
  - Antihypertensives
  - Beta receptor blockers
  - Stimulants (eg, methylphenidate)
  - Cardioactives
- 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 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, amitriptyline) – 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

Structure/function – located on chromosome 22

Test Interpretation

Sensitivity/specificity

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

Results

- By report
- No variants detected – predictive of *1 functional alleles

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
- It is not always possible to identify which allele is duplicated when a *CYP2D6* duplication is 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	No function
*4	1846G>A	rs3892097	No function
*5	Gene deletion		No function
*6	1707delT	rs5030655	No function
*7	2935A>C	rs5030867	No function
*8	1758G>T	rs5030865	No function
*9	2613-5delAGA	rs5030656	Decreased function
*10	100C>T	rs1065852	Decreased function
*12	124G>A	rs5030862	No function
*14	1758G>A	rs5030865	No function
*17	1023C>T	rs28371706	Decreased function
*29	1659G>A	rs59421388	Decreased function
*41	2988G>A	rs28371725	Decreased function
Duplication of functional alleles			Increased function

References

- Bernard S, Neville KA, et al. Interethnic differences in genetic polymorphisms in the U.S. Population: clinical implications. The Oncologist. 2006;11(2):126-135
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors, available along with the 2015 supplement and other relevant resources at www.pharmgkb.org
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and codeine therapy, available along with the 2014 supplement and other relevant resources at www.pharmgkb.org
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants, available along with the 2013 supplement and other relevant resources at www.pharmgkb.org
- The human cytochrome P450 (CYP) allele nomenclature database, available at www.cypalleles.ki.se/