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

- 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
  - Antidepressives (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
- 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

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Duplication of functional alleles | Increased function |