Cytochrome P450 2D6 Genotyping to Predict Metabolic Activation of Tamoxifen

GENETIC VARIANTS OF CYP2D6 *PREDICT POOR METABOLISM AND RISK OF IMPAIRED BENEFIT FROM ADJUVANT TAMOXIFEN THERAPY*

Test Highlights

- Tamoxifen efficacy is largely due to metabolites, such as endoxifen, generated by CYP2D6-mediated reactions.
- *CYP2D6* genotyping detects common mutations associated with little or no enzymatic function.
- Pre-therapeutic testing may identify patients at risk of poor response to adjuvant tamoxifen therapy.

Clinical Background

- Tamoxifen is a potent anti-estrogen drug and is currently the endocrine treatment of choice for the treatment of estrogen receptor (ER)-positive breast cancer.[1]
- Metabolism of tamoxifen mediated by *CYP2D6*[2] generates compounds with up to 100-fold higher potency for binding to estrogen receptors and suppression of breast cancer cell proliferation than parent tamoxifen: 4-hydroxytamoxyphen (4OHtam), 4-hydroxy-N-demethyltamoxifen (4OHNtam), and endoxifen.
- Mutations in the *CYP2D6* gene are associated with altered tamoxifen metabolism.[3,4,5] Patients with impaired *CYP2D6* metabolic capacity do not reach therapeutic concentration of the active metabolite endoxifen and are at an increased risk of breast cancer recurrence compared to women with no known impairment of *CYP2D6*.
- Detection of *CYP2D6* genetic variants does not replace the need for therapeutic drug or other clinical monitoring, and does not prevent drug-drug interactions that may lead to inhibition of *CYP2D6*-mediated metabolism (e.g., SSRI antidepressants).

Disease Overview

- CYP2D6 is an isoenzyme of the cytochrome P450 superfamily and is responsible for biotransformation (metabolism) of many commonly prescribed drugs, including tamoxifen, antiarrhythmics, β-receptor blockers, neuroleptics, antidepressants, and codeine. CYP2D6 is involved in the metabolism of approximately 25 percent of all clinically used drugs.
- Four metabolic phenotypes based on enzymatic function are commonly described. Although the predicted metabolic phenotype is determined by the *CYP2D6* genotype, the actual phenotype depends on the substrate in question and non-genetic factors, such as concomitant medications and hepatic function.
  - Ultra rapid metabolizer (UM)
    - Faster than expected metabolism, yielding a high metabolite:parent ratio.
    - Associated with more than two copies of functional *CYP2D6* genes.
    - Drugs that are metabolized by *CYP2D6* may be inappropriate.
  - Extensive metabolizer (EM)
    - Normal metabolism.
    - Associated with two functional *CYP2D6* genes, or one copy each of a functional and a decreased-function allele.
  - Intermediate metabolizer (IM)
    - Possible impairment in metabolism yielding a moderately low metabolite:parent ratio.
    - Associated with one non-functional allele and either a functional or decreased-function allele, or two decreased-function alleles.
- Poor metabolizer (PM)
  - Two non-functional *CYP2D6* alleles.
- Detection of *CYP2D6* genetic variants does not replace the need for therapeutic drug or other clinical monitoring.

Prevalence

- Percentage of individuals with PM phenotypes resulting from *CYP2D6* alleles producing little or no enzyme: Caucasians and Hispanics (10 percent), African-Americans (2 percent), Asians (<1 percent).
- Approximately 5 percent of Caucasians are predicted to have UM phenotypes.

Genetics

- The inheritance pattern for *CYP2D6* sequence variants is autosomal recessive. *CYP2D6* duplications are considered autosomal dominant; however, intermediate phenotypes exist. Penetrance is unknown but dependent upon enzyme substrate (drug) exposure.
- Over 80 *CYP2D6* mutations have been identified. Mutation analysis includes all common and most rare alleles with known clinical significance.
  - Functional alleles associated with normal enzymatic activity: *1 (when no variants are detected), *2 (2850C>T), *2A (promoter mutation -1584C>G).
  - Non-functional alleles associated with lack of enzymatic activity: *3 (2549A>del), *4 (1846G>A), *5 (gene deletion), *6 (1707T>del), *7 (2935A>C), *8 (1758G>T), *12 (124G>A), and *14 (1758G>A).

500 Chipeta Way, Salt Lake City, UT 84108 | (800) 522-2787 | (801) 583-2787 | www.aruplab.com | www.arupconsult.com
ARUP is an enterprise of the University of Utah and its Department of Pathology.

- Decreased function alleles associated with impaired enzymatic function (decreased activity, altered substrate specificity, decreased stability, etc.): *9 (2613_2615delAAG), *10 (100C>T), *17 (1023C>T), *29 (1659G>A) and *41 (2988G>A).
- Duplication of a functional allele is associated with UM phenotype; duplication of a nonfunctional allele will not change the metabolic phenotype; it is not known how duplications of decreased function alleles may affect the phenotype.

Indication for Ordering

Tamoxifen therapy is indicated or under consideration.

Interpretation

- Negative: No mutations detected that are known to impact tamoxifen efficacy, based on metabolism mediated by *CYP2D6*. Mutations may affect metabolism of drugs other than tamoxifen.
- Positive:
  - Genotype is consistent with intermediate metabolizer phenotype. In the absence of CYP2D6 inhibitors, tamoxifen should be activated by metabolism. However, therapeutic drug monitoring to optimize dose should be considered.
  - Genotype is consistent with poor metabolizer phenotype. Activation of tamoxifen through CYP2D6-mediated metabolism is not expected. Alternate drug selection should be considered.
  - Any genotype that is predicted to affect metabolism should be interpreted with clinical information, particularly co-medications; consultation with a clinical pharmacist is recommended.

Limitations

- Only the targeted *CYP2D6* mutations will be detected.
- Rare diagnostic errors can occur due to primer-site mutations.
- Mutation detection is not a substitute for therapeutic drug monitoring. Non-genetic factors may also affect drug metabolism.

Methodology

- Mutations in the *CYP2D6* gene are assayed by multiplex PCR and detection primer extension. The assay detects 14 mutations (which define 16 *CYP2D6* alleles) in addition to gene duplications.

Allele	Associated Mutation (s)
*1	No mutations detected
*2A	-1584C>G and 2850C>T
*2	2850C>T
*3	2549A>del
*4	1846G>A and 100C>T
*5	Gene deletion
*6	1707T>del
*7	2935A>C
*8	1758G>T
*9	2613_2615delAAG
*10	100C>T
*12	124G>A
*14	1758G>A
*17	2850C>T and 1023C>T
*29	2850C>T and 1659G>A
*41	2850C>T and 2988G>A

- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity varies by ethnicity. Greater than 95 percent of deleterious CYP2D6 mutations are detected for Caucasians.

References

1. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687–717.
2. Desta Z, et al. Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. *J Pharmacol Exp Ther* 2004;310:1062–75.
3. Goetz MP, et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast Cancer Res Treat* 2007;101:113–21.
4. Rae JM, et al. CYP2D6 genotype and tamoxifen response. *Breast Cancer Res* 2005;7:E6.
5. Schroth W, et al. Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. *J Clin Oncol* 2007;25:5187–93.

Test Information

0051232 **Cytochrome P450 2D6 (CYP2D6) 17 Mutations**

For specific collection, transport, and testing information, refer to the ARUP Web site at **www.aruplab.com**.
For information on test selection, ordering, and interpretation, refer to ARUP Consult® at **www.arupconsult.com**.