CYP2D6 Polymorphisms and the Impact on Tamoxifen Therapy

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ABSTRACT: The cytochrome P450 2D6 (CYP2D6) is an enzyme known to metabolize a variety of xenobiotics and drugs. Inter-individual variation in the metabolic capacity of this enzyme has been extensively studied and associations with genotype have been established. Genetic polymorphisms have been grouped as nonfunctional, reduced function, functional, and multiplication alleles phenotypically. Individuals carrying these alleles are presumed to correspond to poor, intermediate, extensive, and ultrarapid metabolizers (UM), respectively. Tamoxifen has been shown to be metabolized by CYP2D6 to the more potent metabolite endoxifen. Poor metabolizers (PM) of tamoxifen have lower levels of endoxifen and poorer clinical outcomes as compared to extensive metabolizers (EM). Here, we will provide an overview of the history and application of CYP2D6 pharmacogenetics, and will discuss the clinical implications of recent developments relating to the involvement of CYP2D6 in tamoxifen treatment. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 96:2224–2231, 2007
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INTRODUCTION

The cytochrome P450 2D6 (CYP2D6) is one of many different human cytochrome P450 enzymes that catalyze the bioconversion of xenobiotics. It is estimated that CYP2D6-dependent metabolism occurs for nearly 25% of the common drugs used today.[1] This includes beta-blockers, tricyclic antidepressants, antiarrythmic agents, serotonergic antidepressants, antipsychotic agents, opioids, and anticancer agents.[2] Inter-individual variability in the enzymatic activity of CYP2D6, in part brought on by genetic polymorphisms in the *CYP2D6* gene, has presented a barrier to achieving optimal drug concentrations in patients. Such innate variability in metabolism renders, in the extreme cases, drug plasma concentrations that are either subtherapeutic or toxic. Those drugs that are most affected by these polymorphisms are those in which CYP2D6 represents a significant metabolic pathway in either the clearance or activation of the agent. Activation of the hormonal agent tamoxifen by CYP2D6 is a fundmental metabolic process, as CYP2D6 is primarily responsible for the formation of endoxifen—the most therapeutically active metabolite of tamoxifen. This review provides an overview of the genotypic variations of CYP2D6 and their relationship to phenotype, the data describing the polymorphic

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metabolism of tamoxifen by CYP2D6, and the implications that such research has on tamoxifen therapy.

CYP2D6 HISTORY

As early as the 1970s, researchers noted that the metabolism of certain drugs, such as debrisoquine and spartein, occurred in a polymodal fashion, with distinctly separate distributions when urine metabolite to parent drug ratios were plotted.[3] A decade later it was noted that poor metabolizers (PM) of debrisoquine/spartein had negligible activity of the cytochrome P450 enzyme later called CYP2D6, and that the gene encoding this enzyme was located on human chromosome 22, mapped to 22q13.1.[4–7] Defective alleles in patients with the PM phenotype were then genotyped and shown to correlate with variations in debrisoquine/spartein metabolism.[8] Kagimoto et al.[9] then used the sequenced gene to describe the defective alleles leading to poor metabolism, setting the stage for the identification of genetic polymorphisms associated with differential metabolism of drugs. Today, over 80 allelic variants resulting in effects including nonsynonymous changes, synonymous changes, frameshifts, insertions, deletions, and splicing defects have been described in the literature (see Home Page of the Human Cytochrome P450 (CYP) Allele Nomenclature Committee: http://www.cypalleles.ki.se/).

CYP2D6 PHENOTYPE

CYP2D6 phenotype has traditionally been determined by the use of probe drugs that are proven CYP2D6 substrates. Phenotype can be quantified in terms of metabolic ratio (MR), defined as the concentration of unchanged probe drug divided by the concentration of metabolite at any specified time following administration. Probe drugs such as debrisoquine, spartein, dextromethorphan, bufuralol, and metoprolol have been used due to their specificity as substrates of CYP2D6. CYP2D6 phenotype is conventionally divided in four separate metabolic classes: PM, intermediate metabolizers (IM), extensive metabolizers (EM), and ultrarapid metabolizers (UM). EM are the reference phenotype. For example, the EM MR of spartein falls between 0.15 and 1.2, whereas the IM MR of spartein (i.e., the concentration ratio: spartein/2- and 5-dehydrospartein) is between 1.2 and 20, and the PM MR for spartein is greater than 20.[10–12] More recently, the ultrarapid metabolizer phenotype for CYP2D6 has been characterized. Johansson et al.,[13] defining UM as those individuals that have an MR of 0.01–0.1 for debrisoquine, demonstrated that this phenotype was the result of the CYP2D6 gene amplification.

CYP2D6 GENETICS

There is documented genetic variability of the CYP2D6 gene in the population. As mentioned previously, over 80 different single nucleotide polymorphisms have been identified to date. In general, phenotypic relationship to genotype is derived by performing studies *in vivo*, *ex vivo*, or *in vitro* in recombinant expression systems.[14] In this manner, variant alleles can be associated with normal, reduced, or absent enzyme function. Null or nonfunctional alleles are those that do not encode a functional gene product and thus do not confer functional enzymatic activity. Poor metabolizers are those individuals who are homozygous for nonfunctional alleles.[14–16] UM have three or more copies of functional alleles, conferring increased enzymatic activity *in vivo*.[15] There is some inconsistency in the definition of EM, with some authors defining this group as having two copies of functional genes[15] whereas others also include individuals heterozygous for at least one functional allele.[14,16] Likewise, there are some inconsistencies in the correlation of genotype to phenotype for IM. Some authors group IM to include both those individuals heterozygous with reduced/nonfunctional genotype and those homozygous for reduced function alleles.[14,17] Others describe the IM as having reduced function in only one allele.[15] It should be emphasized that the intermediate phenotype cannot be entirely due to individuals with one functional and one nonfunctional allele as the IM frequency is about 10–15% in the normal European population.[12] If IM phenotype disposition was conferred by the EM/PM heterozygous phenotype alone, the Hardy–Weinberg equilibrium would predict this frequency to be about 35–40% based on observed PM frequency.[14] This is probably due to haploinsufficiency of some heterozygous alleles and not others towards specific substrate drugs. Therefore, before the metabolizing phenotype could be linked to any set of genetic markers, standardization of the reference of genotype to metabolizer