Pharmacogenetics: The Molecular Genetics of *CYP2D6* Dependent Drug Metabolism

J Y Y Wong,*PhD, E S Seah,**MBBS, E J D Lee,***FAMS, M Med (Int Med), PhD

Abstract

***Introduction**: Genetic variation of drug metabolising enzymes has been recognised as one of the major causes of the inter-individual variability to drug response. The vast majority of drugs are degraded via a small number of metabolic pathways, mainly by microsomal P-450 enzymes localised in the liver and, to a minor extent, in the small intestine. Of these,* **CYP3A4** *is the isozyme involved in the metabolism of most of the clinically useful drugs (50%). This is followed by* **CYP2D6** *(20%),* **CYP2C9** *and* **CYP2C19** *(15%). In addition, minor pathways are catalysed by* **CYP2E1, CYP1A2, CYP2A6** *and unidentified P-450s. Almost 40% of human P-450 dependent drug metabolism is carried out by genetically polymorphic enzymes. Polymorphisms generated by mutations in the genes for these enzymes cause quantitatively or qualitatively altered enzyme expression or activity through multiple molecular mechanisms. While* **CYP3A4** *genetic polymorphisms are just beginning to be unraveled, extensive studies on the* **CYP2D6** *gene over the last decade have identified at least 53 alleles. Of these, more than 20 of them are known to significantly alter the metabolism of* **CYP2D6** *substrates. Methods: This article reviews the information derived from various studies over the past decade and explains the molecular basis of functional differences in* **CYP2D6** *variants, especially with respect to inter-ethnic differences and their clinical implications. Results:* **CYP2D6** *activity ranges from complete absence to ultra-rapid metabolism. Large inter-individual and inter-ethnic variability exists in the activity of the enzyme, and consequently in the disposition of drugs undergoing oxidative metabolism. Conclusions: Pharmacokinetic differences resulting from these polymorphisms show potentially important clinical consequences.*

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* *Research Fellow*
NUS Drug Study Centre
** *Postgraduate Student*
*** *Head*
Department of Pharmacology
National University of Singapore
Address for Reprints: Dr J Y Y Wong, NUS Drug Study Centre, Faculty of Medicine, Lower Kent Ridge Road, Singapore 119074.