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1. CYP2D6 polymorphism and its clinical implications

Martha Sosa Macias and Ismael Lares Asseff
Centro Interdisciplinario de Investigación para el Desarrollo Integral Regional del Instituto Politécnico Nacional- Unidad Durango (CIIDIR-IPN), México

Abstract. CYP2D6 is the most important enzyme in the metabolism of drugs and is responsible for the metabolism of 25% of all drugs currently available on the market. CYP2D6 is not only expressed in liver but also in gut and brain neurons, where endogenous substrates with high turnover have been found. Expression of CYP2D6 is not regulated by any known environmental agents and is not inducible by known hormones, in contrast to other hepatic xenobiotic metabolizing cytochrome P450s. CYP2D6 activity is inherited as a monogenetic trait, and the *CYP2D6* gene appears to be highly polymorphic in humans. The polymorphic alleles may lead to altered activity of the CYP2D6 enzyme causing absent, decreased, or increased metabolism that in turn influences the disposition of about 50% of metabolized drugs. Currently, more than 63 different functional CYP2D6 gene variants have been described. Among them, the most important variants are *CYP2D6*4* (splice defect) and *CYP2D6*5* (gene deletion), whereas the common alleles with severely reduced activity are *CYP2D6*10*, *CYP2D6*17*, and *CYP2D6*41* (splicing defect). *CYP2D6*17* decreases CYP2D6 activity in a substrate-dependent fashion, however

Correspondence/Reprint request: Dr. Martha Sosa-Macías, Laboratory of Pharmacogenomic and Molecular Bio-Medicine, CIIDIR-IPN, Unidad Durango, Sigma S/N, Fracc. 20 de Noviembre II, C.P. 34220, Durango Dgo., Mexico. E-mail: msosam@ipn.mx