A NOVEL DUPLICATION ALLELE OF CYP2A6 ENHANCING NICOTINE METABOLISM IN AFRICAN-AMERICAN POPULATION

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Human CYP2A6 is responsible for nicotine metabolism. It can also metabolize pharmaceutical agents such as tegafur, letrozole, valproic acid, and activate some procarcinogens such as 4-methylpinocarcinogen-1-(3-pyridyl)-1-butanone. Genetic polymorphisms in the CYP2A6 gene are associated with large interindividual variability in nicotine metabolism, smoking behavior, and the risk of lung cancer. We encountered an African-American subject possessing CYP2A6*1A, CYP2A6*1D (g.-1013A>G), and CYP2A6*1H (g.-745A>G) alleles, indicating the existence of three copies of the CYP2A6 gene. However, the CYP2A6*1X2 allele reported by Rao et al. (2000) that is created through an unequal crossover with the CYP2A7 gene at intron 8 – exon 9 was not assigned. In the present study, we identified a novel duplication type of CYP2A6 gene that is created through an unequal crossover event with the CYP2A7 gene at 5.4 kb downstream from the stop codon. The novel duplication type of CYP2A6 was found in 6 out of 176 African-Americans, indicating a prevalence of 3.4%, but not found in European-American (n = 187), Korean (n = 209), and Japanese (n = 184) populations. The plasma cotinine/nicotine ratio 2hr after chewing one piece of nicotine gum in subjects having the novel CYP2A6 gene duplication with the CYP2A6*1 allele (10.8 ± 7.0, n = 4) was 1.4 fold higher than that in homozygotes of the wild type (8.0 ± 5.0, n = 87) in African-Americans. Thus, the novel duplicated CYP2A6 allele, which is specific for African-Americans, increases nicotine metabolism and may affect the smoking behavior.

IN VITRO METABOLISM OF DEBRIOSQUINE BY MICROSOMES FROM YEAST CELLS EXPRESSING WILD TYPE CYP2D6, CYP2D19 AND THEIR CHIMERAS

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Human CYP2D6 is the major oxidation enzyme responsible for the metabolism of about 30% of the medicines in current clinical use. Although human CYP2D6 and marmoset CYP2D19 show high homology (91%) at amino acid level, the regio-selectivity of debrisoquine (DB) hydroxylation is extensively different between CYP2D6 and CYP2D19. In this study, the goal was to identify the amino acids responsible for the difference in the DB hydroxylation specificities. Wild-type (WT) CYP2D6, CYP2D19 and their chimera cDNAs were heterologously expressed in yeast cells, and DB 3-, 4-, 5-, 6-, 7- and 8-hydroxylation activities in the microsomal fractions were determined. WT CYP2D6 exhibited high activity of DB 4-hydroxylation, whereas the activity of WT CYP2D19 was 13% or less that of WT CYP2D6. Of six chimeras examined, only chimera containing amino acids 1-122 and 264-497 of CYP2D6 and those 123-263 of CYP2D19 was capable of catalyzing DB 4-hydroxylation comparable to WT CYP2D6. DB 5-, 6- and 7-hydroxylation activities in WT CYP2D19 were higher than those in WT CYP2D6; however, these activities were low in any chimera. These results suggest that the regions of residues 1-122 and 264-497 of CYP2D6 are closely associated with the DB hydroxylation specificities.