A NOVEL POLYMORPHISM OF HUMAN CYP2A6 GENE, CYP2A6*17, HAS AN AMINO ACID SUBSTITUTION (V365M) THAT DECREASES THE ENZYMATIC ACTIVITY IN VITRO AND IN VIVO

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CYP2A6 metabolizes several drugs such as valproic acid, halothane and tegafur. This enzyme especially metabolizes nicotine to cotinine. With CYP2A6 gene analysis, we found a novel allele, CYP2A6*17 with 4 SNPs (A51G, G1779A, G5065A, and C5717T) in the exons. Among the SNPs, a SNP of G5065A (G1093A on cDNA) in exon 7 caused an amino acid change of V365M. We established a genotyping method for CYP2A6*17 by PCR-RFLP. The allele frequencies of CYP2A6*17 were 10.1% and 0.5% in African-Americans and Caucasians, respectively. In contrast, CYP2A6*17 allele was not found in Japanese and Koreans. To examine the effects of the amino acid change in the CYP2A6*17 allele on the enzymatic activity, we expressed a wild type or variant (G1093A) CYP2A6 together with NADPH-cytochrome P450 reductase in Escherichia coli. The intrinsic clearance values for coumarin 7-hydroxylation (0.60 ± 0.10 µl/min/pmol CYP) and nicotine C-oxidation (23.0 ± 5.6 nl/min/pmol CYP) by the variant were decreased by approximately 60% and 40% compared with the wild type (1.03 ± 0.17 µl/min/pmol CYP and 57.7 ± 16.3 nl/min/pmol CYP), respectively. Furthermore, the cotinine/nicotine ratios after chewing one piece of nicotine gum as an index of in vivo nicotine metabolism were significantly (P < 0.05) decreased in heterozygotes of the CYP2A6*17 allele (5.4 ± 2.7, n = 12) compared with homozygotes of the wild type (11.5 ± 10.5, n = 37). We clarified that the metabolic potency is diminished in subjects with the CYP2A6*17 allele.