

Genetic polymorphism of CYP2A6 and nicotine metabolism in humans

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CYP2A6 is a major hepatic member of the CYPs in humans, which metabolizes pharmaceutical agents such as coumarin, (+)-cis-3,5-dimethyl-2-(3-pyridyl) thiazolidin-4-one hydrochloride (SM-12502), methoxyflurane, halothane, losigamone, letrozole, valproic acid, disulfiram, fadrozole, and activates some procarcinogens such as 4-methylnitrosoamino-1-(3-pyridyl)-1-butanone and N-nitrosodiethylamine. Especially, CYP2A6 is a major metabolic enzyme of nicotine. Nicotine is metabolized to cotinine by CYP2A6, and cotinine is further metabolized to trans-3'-hydroxycotinine. Nicotine metabolism is known to show large interindividual differences. Previously, we established a phenotyping method of in vivo nicotine metabolism. The purpose of the present study was to clarify the ethnic differences in nicotine metabolism and CYP2A6 genetic polymorphism in 209 Koreans and 92 Japanese. There were ethnic differences in the allele frequencies of CYP2A6 (*1A, *1B, *4, *5, *7, *8 and *10) between Koreans (45.9, 37.1, 11, 0.5, 3.6, 1.4 and 0.5%, respectively) and Japanese (42.4, 27.7, 20.1, 0, 6.5, 2.2 and 1.1%, respectively). The subjects who possess CYP2A6*1B tended to show higher metabolic ratio than the subjects without the allele. The CYP2A6 enzymatic activity is lost in the subjects homozygous for either CYP2A6*4, CYP2A6*7 or CYP2A6*10, or heterozygous for these alleles in combination. The novel allele was termed CYP2A6*10. The CYP2A6*1X2 allele was found in only one Korean (0.5%) whose nicotine metabolic potency was not very high. The Koreans revealed significantly higher metabolic ratios than the Japanese. The ethnic difference in cotinine formation (Koreans > Japanese) would be due to the difference in the CYP2A6 genetic polymorphism in these populations.