ETHNIC DIFFERENCES IN GENETIC POLYMORPHISMS OF CYP3A4 AND CYP3A5

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There are large interindividual differences in CYP3A protein (CYP3A4 and CYP3A5) levels and their catalytic activities in adult liver. In this study, we analyzed CYP3A4 gene using 449 genomic DNAs obtained from Caucasian (150), African American (150), and Japanese (149) subjects to compare the allelic frequency among three races. The CYP3A4*2 and CYP3A4*5 alleles were not detected in any of the three ethnic groups. On the other hand, the CYP3A4*6 allele was detected in a Japanese subject as a heterozygote (CYP3A4*1/*6), although this allele was not detected in any of the Caucasian and African American individuals. In addition, we evaluated a contribution of genetic polymorphisms of CYP3A4 and CYP3A5 to the oxidation of testosterone via CYP3A in a panel of 21 Caucasian and 13 Japanese human livers. Among these liver samples, we found an outlier in Caucasian livers. The activity of this outlier for testosterone 6β-hydroxylation (1.01 nmol/min/mg) was 4-fold higher than those of other Caucasian livers (0.23 ± 0.19 nmol/min/mg). The genotype of this outlier was the homozygote of CYP3A5*1 allele. In contrast, no homozygote of CYP3A5*1 allele was observed in Japanese microsomal samples studied, however, the microsomal sample of Japanese subject showing the lowest activity was from the heterozygote of CYP3A4*6. These results suggest that polymorphic CYP3A5 may contribute to the variation of CYP3A-mediated testosterone 6β-hydroxylation in liver microsomes from Caucasian subjects, while CYP3A4*6, a rare allelic variant of CYP3A4 (0.34% of allelic frequency in a Japanese population), may contribute at least in part to these variation in liver microsomes from Japanese subjects.