ETHNIC DIFFERENCES IN ALLELE FREQUENCIES OF GENOTYPES IN UGT1A1 AND GLUCURONIDATION ACTIVITY OF A NOVEL SNP 686C>T (P229L)

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UGT1A1 polymorphisms have been reported to be associated with hyperbilirubinemia, neonatal jaundices and toxicity caused by SN-38, an active metabolite of an anticancer drug CPT-11. Ethnic differences in UGT1A1 genetic polymorphisms were investigated among African-Americans, Caucasians and Japanese using genomic DNA obtained separately from 150 individuals from each population. Genotyping of -3279T>G in a transcription regulating region, (TA) repeats (5 – 8) in the TATA box, 211G>A (G71R) and 686C>A (P229Q) in exon 1, and 1941C>G in the 3’ untranslated region in exon 5 was performed by Pyrosequence methods. Eight haplotypes using the first four marker variations were inferred and assigned to individuals. The dominant haplotype in African-Americans was *28 (-3279G;TA7;211G;686C) (0.446) followed by *60 (-3279G;TA6;211G;686C), while that in the Japanese population was *1 (-3279T;TA6;211G;686C) (0.610). Frequencies of haplotypes *1 and *28 were nearly comparable in Caucasians (0.451 and 0.389). The haplotype *6 (-3279T;TA6;211A;686C) was unique in the Japanese, whereas haplotypes *36 and *37 (-3279T;TA5 and TA8;211G;686C) were unique in African-Americans. The allele frequencies of 1941C>G in African-Americans and Caucasians were higher than that in the Japanese. We found a novel SNP 686C>T (P229L) in an African-American individual. The apparent intrinsic clearance of SN-38 by the variant exogenously expressed in COS-1 cells was extremely lower (<5 %) than that by the wild type.

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