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**UGT1A9 IVS1+399C>T ITSELF LACKS THE EFFECT ON IRINOTECAN PHARMACOKINETICS IN JAPANESE CANCER PATIENTS**

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An anti-cancer drug, irinotecan, is metabolized to an active form SN-38, and then SN-38 is inactivated by glucuronidation with UGT1A1 and UGT1A9. Recently the **UGT1A9 IVS1+399C>T** polymorphism has been reported to increase SN-38 glucuronidation, without strong linkage disequilibrium (LD) with **UGT1A1*6, *28 and *60** in Caucasian or Chinese subjects. By haplotype analysis of **UGT1A9-UGT1A1** in 177 Japanese cancer patients administered irinotecan, we evaluated its role on in vivo SN-38 glucuronidation activity. **UGT1A9 IVS1+399C>T** was detected at an allele frequency of 0.636. This polymorphism was in strong LD with **UGT1A9 -126_-118T>T_R** (*22 allele, D'=0.99) and **UGT1A1 211G>A** (*6, 0.86), and in moderate LD with **UGT1A1 -3279T>G** (*60, 0.55), but not with **UGT1A1 -54_-39A(TA)_TAA>A(TA)_TAA** (*28, 0.25). Haplotype analysis showed that 98% of the **UGT1A9 IVS1+399C** alleles were associated with the low-activity alleles **UGT1A1*6, *28 or *60**. On the other hand, 85% of the T alleles were linked with the **UGT1A1** wild-type allele *I. Although the patients with homozygous **UGT1A9 IVS1+399T** showed a statistically significant increase in the in vivo UGT activity parameter, SN-38 glucuronide/SN-38 AUC ratio (p<0.001) compared with those with homozygous C alleles, this effect was not significant after adjustment for **UGT1A1*6, *28 and *60 genotypes. These results suggest that at least in Japanese, the influence of **UGT1A9 IVS1+399C>T** on SN-38 glucuronidation could be attributable to its inverse linkages with **UGT1A1*6, *28 and *60**.

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**EXPRESSION AND CHARACTERIZATION OF MOUSE UDP-GLUCURONOSYLTRANSFERASE FAMILY 1a (Ugt1a) ISOFORMS USING RECOMBINANT PROTEIN EXPRESSION SYSTEMS**

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UDP-glucuronosyltransferases (UGTs) play an important role in physiological defence system via the metabolism of a broad range of xenobiotic and endogenous compounds. UGT catalyzes the transfer of a glucuronic acid group to a variety of functional groups on the substrates. Among the UGT gene families, the mammalian **UGT1A** locus contain several promoters /first exons that encode each isoforms sharing a common C-terminus encoded by 3' exons 2-5. In contrast to rat and human, although the mouse is an useful animal model for drug metabolism studies, the Ugt1a system from this species is not well understood. In order to characterize mouse Ugt1a isoforms for catalytic properties, we have cloned the major hepatic Ugt1a cDNA (Ugt1a1,1a5,1a6a,1a6b, and 1a9) and constructed in recombinant proteins using mammalian and yeast expression system. The expression of protein level were confirmed by western blot analysis using anti-peptide antibody against C-terminal common region to be highly monospecific for each Ugt1a isoform. Ugt1a1 is highly conserved in all Ugt1a isoform, and showed the glucuronidating activity toward bilirubin. Ugt1a6a and Ugt1a6b are almost identical with several differences of amino acids and catalyzing the glucuronidation of small planar phenols. We are currently analyzing the substrate specificity of glucuronidation in each isoform including Ugt1a5 and Ugt1a9. This mouse Ugt1a expression system would be useful for drug metabolism studies in mouse.