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Thymidylate Synthase (TYMS) and Dihydropyrimidine Dehydrogenase (DPYD) Polymorphisms in the Korean Population: for Prediction of 5-fluorouracil-associated Toxicity

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Background: The important cellular proteins for 5- Fluorouracil (5FU) are the major target enzyme, thymidylate synthase (TS) and the rate limiting enzyme in the degradation pathway, dihydropyrimidine dehydrogenase (DPD). A serious problem found in 5-FU based chemotherapy has been reported to be in part due to polymorphisms in the thymidylate synthase (TYMS) and dihydropyrimidine dehydrogenase (DPYD) genes. Therefore, we examined the type and frequency of polymorphisms in the TYMS and DPYD genes in 100 healthy Korean individuals and compared these findings with 21 colorectal cancer patients who had severe toxicity reaction to 5-FU.

Methods: Genotyping analysis of the promotor enhancer region (TSER) and the 3'-untranslated region (3'-UTR) of the TYMS gene, as well as haplotype analysis were conducted in all 121 study participants.

Results: For the TSER and the 3'-UTR of the TYMS gene, similar genotypes and allele frequencies were observed in controls and patients. For the haplotype analysis of the single nucleotide polymorphism (SNP) G>C at the 12th nucleotide of the second repeat of 3R allele of the TSER, different haplotype frequencies were noted in comparisons between the two groups; in addition, 3RC-del 6bp was significantly associated with severe toxicity to 5-FU. Extensive polymorphisms in the DPYD gene were observed and four polymorphisms were related to the known DPYD allelic variants or allelic variants altering protein structure, of which the most common polymorphism was A1627G, observed in 20.5% of all alleles. The A496G allele and a novel C1774T allele were identified in two patients. None of the individuals with the DPYD*2A allele causing exon 14 skipping were identified in the study group.

Conclusions: These findings suggest that there may be an important relationship between the TYMS haplotypes examined and the presence of 5-FU toxicity. The novel variant in the DPYD gene, identified in this study, should be further investigated to confirm its functional significance. A large sample is required before DPYD or TYMS genotyping could be used for individualized treatment of patients with colorectal cancer.