일반연제

Modulation of the Inducibility by Intron-1 Binding Proteins (In1BPs) in Human *CYP1A2*1C* and *CYP1A2*1F* Genetic Polymorphism

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Single nucleotide polymorphisms (SNPs) of human *CYP1A2* gene have been studied well in several ethnic groups. Particularly, gene polymorphisms of G-3858A (G-2964A, *CYP1A2*1C*) in 5'-flanking region and/or A-164C (A734C, *CYP1A2*1F*) in intron 1 region of the human *CYP1A2* gene were confirmed to be associated with high enzyme activity and inducibility in smokers. Furthermore, the genetic linkage between *CYP1A2*1C* and *CYP1A2*1F* variants has been suggested in some ethnic populations. However, there were no known regulatory factors affecting the activity and/or inducibility, particularly in *CYP1A2*1F* intron mutation site. Here, 137 Korean unrelated healthy volunteers aged 21~33 years (23.1±1.9, 82 nonsmokers and 55 regular smokers) were phenotyped for CYP1A2 by HPLC analysis of urinary caffeine metabolites [(1,7U+1,7X)1,3,7X], and genotyped by PCR-RFLP analysis with their genomic DNAs. The frequencies of the *CYP1A2*1C* and *CYP1A2*1F* alleles were 0.219 and 0.646, respectively, similar to the values determined in other ethnic populations. Seven genotypes were identified with respect to the both variant alleles. In total subjects and smokers, the log activity was normally distributed (W=0.9818, p=0.064 and W=0.9634, p=0.093, respectively). As expected, the mean CYP1A2 activity (metabolic ratio=MR) of smokers (MR=19.45±8.57, ranged from 5.0 to 39.58) was significantly higher (p=0.0002) than that of nonsmokers (13.93±6.26, ranged from 2.41 to 29.53). Among the examined nonsmokers, no significant differences in CYP1A2 activity were evaluated between the genotypes. However, the CYP1A2 inducibility in smokers affected by both *CYP1A2*1C* and *CYP1A2*1F* alleles, not either. The subjects with G^{-3858}/A^{-164} haplo-genotype showed a higher inducibility than those with G^{-3858}/C^{-164} or A^{-3858}/A^{-164} haplo-genotype. In addition, EMSA test for *CYP1A2*1F* allele specific site was clearly distinguished by intron 1 binding proteins (In1BPs) between A^{-164} and C^{-164} alleles without stimulation of 3-MC or TCDD, showing no effects of In1BPs on the basal CYP1A2 activity. After stimulation with 3-MC or TCDD, however, the binding capacities of In1BPs modulated only in C^{-164} allele sequence or equally in both sequences of A^{-164} and C^{-164} alleles. These results indicate that regulatory factors like In1BPs are specifically distributed in *CYP1A2* intron 1 sequences and suggest that interactions between *CYP1A2*1C* and *CYP1A2*1F* alleles can be modulated CYP1A2 inducibility.