일반연제 1

C-1584G Polymorphism in Cytochrome P450 2D6 Promoter Is Not a Sole Determinant of Decreased Activity of CYP2D6*41 *in Vivo*

Sang Seop Lee, Hyun-Ju Jung, Hye-Eun Jung, Jae-Gook Shin

Department of Pharmacology and Pharmacogenomics Research Center,
Inje University College of Medicine, Busan, Korea

Cytochrome P450 2D6 (CYP2D6) is well known to have genetic polymorphism with 44 allelic variations registered to CYP allele nomenclature committee. Among them, CYP2D6*2A and CYP2D6*41 have difference only in 5'-flanking region of CYP2D6 gene with C-1584G mutation in CYP2D6*2A. A previous study suggested that C-1584G mutation in CYP2D6*2A is associated with higher activity of CYP2D6 in vivo than CYP2D6*41. Ninty eight Korean subjects were genotyped at −1584 locus for discrimination between CYP2D6*2 and CYP2D6*41. One and seven subjects were homozygous and heterozygous CYP2D6*41, respectively. From a clinical trial using dextromethorphan as a probe drug, Cyp2D6*41, but not CYP2D6*2, showed a tendency to decrease CYP2D6 activity in vivo. In order to investigate the regulatory role of C-1584G mutation, we cloned 1.8kb-long promoter regions of CYP2D6*2A and CYP2D6*1 type. When the two promoters with either C-1584 or G-1584 were located upstream of luciferase reporter gene, the luciferase activities showed no difference as anticipated from no enzymatic difference between CYP2D6*2A and CYP2D6*1A. To test if single mutation of C-1584G has any regulatory role in CYP2D6 expression, C-1584G mutation was introduced into C-1584 promoter by site-directed mutagenesis. When comparing luciferase activity driven from two promoters different only at −1584 locus, there was no difference. Electro-mobility shift assay revealed that −1584 region could not bind to any transcription factors. These results suggest that C-1584G variant by itself is not functional in the regulation of CYP2D6 expression and C-1584G variant in CYP2D6*2A allele may be not a functional SNP responsible for increase of CYP2D6 activity. Considering that there exist several SNPs tightly linked to C-1584G variant shown in CYP2D6*2A (A-1235G, C-740T, and G-678A), it is likely that there might be unknown functional SNP(s) outside 1.8kb 5'-flanking region of CYP2D6 gene.