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Genetic Polymorphisms in Drug Transporters and Regulatory Xenobiotic Receptors in Korean Population

Sang Seop Lee, PhD and Jae-Gook Shin, MD, PhD
Department of Pharmacology and Pharmacogenomics Research Center
Inje University College of Medicine, Busan, Korea

Abstract

Drug transporters play an essential role in the absorption, distribution and elimination of clinical drugs, nutrients and toxicants. The importance of the transporters is exampled by therapeutic failure in cancer chemotherapy that is mainly caused by the overexpression of multidrug resistance (MDR)-related transporters. In addition, the transporters may involve in drug-drug interactions that lead to serious adverse drug responses and some transporters also contribute to inter-individual variation in drug responses. As an effort to understand the mechanism underlying the inter-individual variation of transporters activity, genetic and environmental factors influencing the expression or function of the transporters have extensively explored through last decade. Among them, genetic polymorphism of drug transporter encoding genes has generated much interest since the discovery of functional single nucleotide polymorphisms (SNP) of *MDR1* gene.

Besides drug transporters, xenobiotic receptors also modulate drug disposition by regulating the transcription of drug metabolizing enzymes and drug transporters. Among many xenobiotic receptors, pregnane X receptor (PXR) and constitutive androstane receptor (CAR) are two most well characterized since these receptors show wide substrate specificities and regulate the expression of various enzymes involved in drug disposition. Recently, several functional genetic polymorphisms were reported in PXR coding gene. In the present study, genetic polymorphisms of two drug transporters, MDR1 and BCRP, and two xenobiotic receptors, PXR and CAR, were investigated in Korean population.

1. Genetic polymorphism of Drug Tranporters in Koreans

It has been eagerly tried to investigate the inter-individual variation of drug disposition in genetic bases in order to reveal functional genetic variations for the prediction of drug

responses. Genetic polymorphism of *MDR1* has been intensively studied due to its involvement in pharmacokinetics of many therapeutic drugs. Among the *MDR1* polymorphism, two genetic variations, C3435T in exon 26 and G2677T/A in exon 21, are most well characterized since these SNPs are first discovered functional variations. The association of these SNPs with clinical outcome is still controversial, but there is increasing evidence to show their contribution to altered pharmacokinetics of many drugs. In order to investigate *MDR1* polymorphism in Koreans, we analyzed C3435T and G2677T/A variations by pyrosequencing method in 797 healthy Korean subjects. Allele frequency of C3435T, G2677T and G2677A variations were 38.6%, 38.5% and 17.6%, respectively. Haplotype analysis revealed that three major haplotypes with frequencies higher than 10% are present in the Korean population. Association between each haplotype and drug response should be evaluated.

Breast cancer resistance protein (BCRP), another drug transporter, plays a role in the transport of many anti-cancer agents and the protection from toxicants. Recently, it was known that this gene also shows genetic polymorphism. Genetic variations of *BCRP* gene were explored by direct sequencing method in 50 Korean subjects. Functional variations including V12M, Q126X and Q141K were found in the Koreans. And five novel SNPs were identified, in which two are exonic and three are in promoter region. Recombinant BCRP protein including one nonsynonymous SNP was found to have decreased transporter activity. Haplotype analysis demonstrates that the second, the third, and the fourth frequent haplotypes in the Koreans contain one or more functional allelic variations leading to the altered transporter activity. Contribution of these haplotypes to inter-individual variation of drug response is under our investigation.

2. Genetic polymorphism of Xenobiotic Receptors in Koreans

PXR and CAR play an important role in regulation of the expression of drug transporters as well as drug metabolizing enzymes. Interestingly, the expression level of PXR and CAR shows high inter-individual variation and is in good accordance with the expression level of certain drug metabolizing enzymes such as CYP2A6 and CYP3A4. Previous results suggest that genetic polymorphism of PXR also may contribute to the inter-individual variation of drug disposition. For example, several nonsynonymous mutations in PXR gene result in the change of its transactivation activity that leads to the altered expression of CYP3A4. We explored genetic polymorphism of PXR and CAR genes in 50 healthy

Korean subjects by direct sequencing method. Twenty-one SNPs in PXR gene and nine SNPs in CAR gene were found in the Koreans. Nonsynonymous mutation resulting in amino acid change was not found in both of the genes. Seven SNPs of PXR are positioned within promoter region and the allelic frequency of the SNPs were 0.86-20.69%. Prediction of regulatory sites of PXR promoter region reveals that locations of some SNPs are putative binding sites for heat shock factor, NF-kB, C/EBP or progesterone receptor. Whether these SNPs in the promoter region may cause the change in the expression of PXR remains to be determined. The allelic frequency of many SNPs was found to show ethnic variation between Korean and others. In case of CAR, two SNPs with allelic frequencies of 1.06% and 37.23% reside in the promoter region. Our results demonstrate that functional nonsynonymous SNPs of PXR and CAR are very rare in Koreans and genetic polymorphism of PXR is dependent on ethnicity. Therefore, for better understanding the mechanism of inter-individual variation in the expression of PXR and CAR, the effects of SNPs in the regulatory region should be evaluated.