한국인에서의 N-acetyltransferase 2 유전적 다형성

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Genetic Polymorphism of N-acetyltransferase 2 in Korean population

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N-acetylation polymorphism affects the biotransformation of various drugs and carcinogens. Therefore, it is associated with interindividual variation in drug response or toxicity and modulates individual susceptibility to certain cancers. More than twenty N-acetyltransferase 2 (NAT2) alleles have been reported so far. Although genetic polymorphism of NAT2 shows significant ethnic difference, it has not been extensively studied in Koreans. We investigated for NAT2 allelic variability, genotype distributions and correlation with phenotypic activity to understand genetic basis of N-acetylation polymorphism in Korean population.

Total 718 subjects who visited health promotion center, 23 healthy volunteers, and 18 patients with tuberculosis were studied. For genotyping, we performed full sequencing analysis of 870 bp protein-coding region of NAT2 gene and checked nucleotide substitutions by combined use of allele-specific amplification and restriction enzyme digestion. For phenotyping, isoniazid and acetyl-isoniazid concentrations in plasma and urine were measured by high-performance liquid chromatography.

The C282T (30.8%), G590A (20.5%), and G857A (11.4%) were the predominant nucleotide changes. The genotyping method in this study discriminates between all variant NAT2 alleles which share common nucleotide substitutions and 13 alleles including NAT2 *4 (65.7%), *6A (19.6%), and *7B (10.9%) were found. Novel allele *10 with heterozygous G499A substitution was identified. Twenty-one different genotypes were noted and the major genotypes were NAT2 *4 / *4 (42.6%), *4 / *6A (25.2%), and *4 / *7B (14.8%). On the basis of genotype, 313(43.6%) individuals were rapid, 325(45.3%) were intermediate, and 73(10.2%) were slow acetylators. Three groups categorized by genotypes show

significant differences in their acetylation activity. But there was substantial variation within each type and overlap was found between rapid and intermediate type. Concordance rate of genotype and phenotype classification was 90.2% in trimodal model. We could not find any significant differences in genotype distribution or acetylation activity between healthy subjects and patients with tuberculosis.

We accurately determined NAT2 allelic variability, genotype frequency, and the relationship between genotype and phenotype in Korean population. Our results can provide background data for future epidemiological and clinical studies associated with acetylation polymorphism. Also a design of cost-effective genotyping method for searching targeted mutations and prediction or determination of ambiguous alleles and genotypes will be facilitated. Further studies are required to clarify the functional significance of each NAT2 allele.