Genetic variations of voltage-sensitive sodium channel gene SCN1A in Korean epilepsy patients

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Background and Objective: Voltage-sensitive sodium channels are targets for classic anti-epileptic drugs (AED) such as phenytoin and carbamazepine. A common genetic polymorphism of an α-subunit of the sodium channel, namely SCN1A, may be associated with altered drug responses to AED.1 Furthermore, it is likely that rare nonsynonymous mutations of SCN1A have been related to pathogenesis of severe myoclonic epilepsy of infancy or generalized epilepsy with febrile seizure plus.2 In the present study, we systematically investigated the genetic variations of SCN1A gene in 53 Korean patients with epilepsy.

Methods: Molecular analysis was carried out on genomic DNA extracted from whole blood of 53 Korean epilepsy patients. All exons and its flanking regions of SCN1A gene were amplified by polymerase chain reaction and sequenced by an automated sequencer. Linkage disequilibrium (LD) and haplotype analysis were performed using SNPAllyze software.

Results: Thirty four single nucleotide polymorphisms (SNP) were identified in 53 Korean patients. All SNPs except one intronic SNP exhibited Hardy-Weinberg Equilibrium. Fifteen SNPs were located in 5’ flanking region, 16 in introns, and 3 in exons. Of 3 exonic SNPs, 2 SNPs were non-synonymous SNPs that were T1056A and M1812T. SCN1A M1812T variant was found for the first time in one Korean. The frequency of the other T1056A variant was 7.8% in 53 subjects. This frequency was significantly lower than those of Japanese (25.0%) and Chinese (24.4%) revealed by HapMap project. The frequency of known functional intronic SNP relating to the dosages of phenytoin and carbamazepine, SCN1A IVS5-91, was 48.1% in the Koreans. Prediction of putative transcription factor binding to promoter SNPs showed that some variants might produce transcription factor binding sites to hepatocyte nuclear factor-1α (HNF-1α, GATA-1, interferon-simulated gene factor-3 (ISGF-3) or nervous system-specific octamer-binding transcription factor (N-oct3). Pairwise LD analysis showed the presence of strong LD among frequent SNPs, suggesting limited numbers of SCN1A SNPs might be used for genetic analysis in further association studies.

Conclusion: The genetic variations of SCN1A gene are systematically investigated for the first time in Koreans. Our findings including SCN1A haplotype profile, frequency of functional SNP, and novel non-synonymous variant can be useful for the clinical studies such as AED pharmacogenetics and genetic association studies in epilepsy in Korean population.

References