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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 SNPAlyze 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

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