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CASE REPORT

Lack of association between C3435T nucleotide MDR1 genetic polymorphism and multidrug-resistant epilepsy

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Summary The variability of P-glycoprotein expression in individuals is linked to a C3435T polymorphism of the multidrug-resistance 1 (MDR1) gene, and the CC genotype at the C3435T polymorphism was reported to be associated with multidrug resistance in epilepsy patients. Since population frequencies of polymorphic genes depend on ethnic specificity, we investigated functional significance of the C3435T polymorphism of the MDR1 gene in Korean epilepsy patients. One hundred and eight patients with drug-responsive epilepsy, 63 patients with drug-resistant epilepsy, and 219 control migraine subjects were studied, but the analysis for C3435T allele showed no significant association between the CC genotype and the multidrug-resistant epilepsy. We suggest that influence of the C3435T polymorphism in the multidrug-resistant epilepsy may not be significant in Korean populations and further investigations in various ethnic populations would be necessary to clarify the effect of C3435T polymorphism on the mutidrug resistance in epilepsy patients.
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Introduction

Resistance to antiepileptic drugs (AEDs) affects approximately 30% of patients with epilepsy. In addition to potential causes of apparent resistance such as poor drug compliance or suboptimal dosing, several clinical features like early seizure onset, length of seizure history before treatment, or several pathologic characteristics such as hippocampal sclerosis and severe brain injury have been associated with a high rate of drug resistance.[1]

Progress in epilepsy research has shown that genetic variations can affect responsiveness to AEDs. The multidrug-resistance 1 (MDR1) gene product P-glycoprotein is of particular interest, and was first identified in cancer cells as a protein responsible for resistance to many drugs.[2] P-glycoprotein is expressed in normal tissues, where it performs a defensive role against potentially toxic substances in intestinal cells, renal proximal tubule cells, and in the endothelial cells of the brain capillary endothelium.[3] MDR1 is highly polymorphic and the 'apparently silent' C3435T polymorphism in exon 26 has been correlated with the expression of P-glycoprotein.

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People homozygous for the C allele have on average substantially higher P-glycoprotein expressions than those homozygous for the T allele.[4] With regards to epilepsy treatment, P-glycoprotein can transport many AEDs of different action mechanisms,[5] and the increased expression of P-glycoprotein was found in the brain specimens of those with intractable epilepsy.[6,7] Recently, it has been documented that patients with drug-resistant epilepsy are more likely to have the CC genotype at the C3435T polymorphism than those with drug-responsive epilepsy,[8] and several conflicting reports[9–11] have been published regarding confirmation of the previous report.

Population frequencies of many polymorphic genes of pharmacogenetic interest depend on ethnic specificity. Association of these genes with inter-individual differences in drug effectiveness and drug toxicity may also depend on the ethnic characteristics of a population.[12] Since the C3435T polymorphism has been detected in various ethnic populations with considerable ethnic variation in frequency,[13] we studied the allele frequencies of the C3435T polymorphism with drug-responsive or drug-resistant epilepsy.

Methods

Subjects

Patients were consecutively recruited through the epilepsy clinic at Seoul National University Hospital. Drug-resistant or drug-responsive epilepsy were determined according to the following criteria. Drug resistance was defined as the occurrence of at least four seizures over the year before recruitment with trials of more than three antiepileptic medications at maximal tolerated doses, which were established by the occurrence of clinical side effects at supramaximal doses.

Drug responsiveness was defined as complete seizure freedom for at least an year, up to the date of the last follow-up visit. Control subjects were individuals with migraine without a history of epilepsy. All epilepsy and control patients were ethnically homogeneous Koreans. We analyzed 108 patients with drug-responsive epilepsy, 63 patients with drug-resistant epilepsy, and 219 control patients. The demographic characteristics of subjects are listed in Table 1.

Table 1 Characteristics of patients

Variable	Drug-responsive epilepsy (N = 108)	Drug-resistant epilepsy (N = 63)
Sex		
Male	66	31
Female	42	32
Age (year)		
Mean ± S.D.	32.9 ± 9.6	34.1 ± 9.0
Range	17–56	18–64

Identification of MDR1 polymorphisms

Blood samples (5 ml) were collected in EDTA vacutainer tubes for DNA extraction and MDR1 genotyping. Purified genomic DNA was extracted from peripheral blood leukocytes using the phenol–chloroform extraction method. Genotyping was conducted using an ABI 7700 sequence Detection System, or "Taqman"™ assay (Applied Biosystems). Polymerase chain reaction (PCR) primers and probes were designed using Primer Express™ software (Applied Biosystems). Assay design and conditions were based on the allelic discrimination protocol supplied by Applied Biosystems. The cDNA 3435C allele probe was labeled on the 5′ end with the FAM receptor dye and contained the following nucleotide sequence 5′-CAAGATCCATCCCGACC-3′. The cDNA 3435T allele probe was labeled on the 5′ end with the VIC receptor dye and contained the following nucleotide sequence 5′-CAAGATCCATTCCGACC-3′. Forward and reverse primers were used to amplify the region surrounding the C3435T polymorphism. The nucleotide sequence of the forward primer was 5′-TCTTCTTTGCTCCTCCATTGC-3′ and of the reverse primer was 5′-TGAGCTGCGGTTTCTCTTCA-3′. PCR reactions were performed in a reaction volume 15.0 μl using the hot-start format. The reaction components were as follows: 2X Taqman Universal PCR Master Mix, 600 nM of each primer, 100 nM of each probe, and 20 ng of genomic DNA. PCRs were run on a Perkin Elmer GenAmp® 9700 thermocycler using the 9600 mode under the following conditions: 50 °C for 2 min (AmpErase® UNG activation), 95 °C for 10 min (AmpliTaq Gold Activation), followed by 50 cycles of 92 °C for 15 s (denaturation) and 60 °C for 1 min (annealing/extension). Samples that could not be scored were repeated. Unreadable results on the second run were scored as undetermined (n = 17: 11 cases, 6 controls). We repeated the "Taqman"™ assay on 10% of the samples.

Results

Demographic characteristics showed that the male to female sex ratio in the drug-responsive group was higher than in the drug-resistant group, but this result failed to achieve statistical significance (p = 0.130 by χ^2 test). There was no age difference between the drug-responsive and drug-resistant groups.

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