

Association analysis of a polymorphism of MDR1 Gene and refractory temporal lobe epilepsy in a Chinese population

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Background and Objective: Although pharmacoresistance is almost certainly due to several factors, the family of multidrug transporter proteins are likely to play a prominent role in this phenomenon given the often observed broad resistance to all antiepileptic drugs despite their different modes of action. Evidence suggests that the homozygous C-variant, which is associated with higher expression and increased activity of P-gp, is more common in patients with pharmacoresistent epilepsy.¹ In addition, recent studies showed high-degree linkage disequilibrium among C1236T-G2677T-C3435T, homozygous carriers of the CGC haplotype in exons 12, 21 and 26 were found to exhibit higher pharmacoresistance in patients with epilepsy.² We investigated the prevalence of those polymorphisms in a population of China, and the association with pharmacoresistance in temporal lobe epilepsy (TLE).

Methods: The study consisted of 154 outpatients diagnosed with TLE who visited the Hakuai Epilepsy Center in Peking Union Medical College Hospital from December 2000 to Jan 2006. All patients had used several suitable AEDs over 12 consecutive months. We stratified patients for whom average seizure frequencies could be reliably assessed into “Drug-resistant group” (n = 80, mean age at the time of the study was 32.6 ± 8.7 years, mean duration of epilepsy was 15.3 ± 7.5 years) and “Drug-responsive group” (n = 74, mean age at the time of the study was 32.2 ± 9.7 years, mean duration of epilepsy was 9.7 ± 5.7 years) taking the individual average seizure frequency under AED treatment as the best surrogate marker for pharmacoresistance. One hundred and twenty unrelated, matched for age, sex, ethnicity; neurologically normal subjects were also randomly selected as controls. Informed consent for this study was obtained from all subjects. Venous blood was drawn from each individual, and genomic DNA was prepared from whole blood by using a standard proteinase K digestion and phenol-chloroform method. The polymorphisms (exon 12 C1236T, exon 21 G2677T, and exon 26 C3435T) were identified by polymerase chain reaction restriction fragment length followed by restriction digest and detection of restriction products by 3.5% gel electrophoresis.

Results: Compared with drug-responsive patients, drug-resistant patients were more likely to have the C allele than the T allele at exon 26 C3435T ($\chi^2=14.68$, $P\leq 0.001$), and were more likely to have the CC genotype than the TT genotype at exon 26 C3435T ($\chi^2=15.04$, $P<0.001$). Highly significant linkage disequilibrium was shown among exon 12 C1236T, exon 21 G2677T, exon 26 C3435T. Haplotype analysis demonstrated that patients with the CGC were more likely to be drug resistant. In contrast, patients with the TTT haplotype were more likely to be seizure free (all p-values <0.01).

Conclusion: Our study corroborated a previously reported association between the C3435T polymorphism in the human MDR1 gene and drug-resistant epilepsy in a Chinese population.³ And the results showed that the three loci, C1236T, G2677T and C3435T, jointly influenced the treatment response for epileptic patients. These findings suggest that examination of the haplotypes of the three loci could be useful in predicting drug resistance in epilepsy.

References

1. Siddiqui A, Kerb R, Weale ME, *et al.* Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. *N Engl J Med* 2003; 348: 1442–8.

2. Zimprich F, Sunder-Plassman R, Stogmann E, *et al.* Association of an ABCB1 gene haplotype with pharmacoresistance in temporal lobe epilepsy. *Neurology* 2004; 63: 1087-9.
3. Hung CC, Tai JJ, Lin CJ, *et al.* **Complex haplotypic effects of the ABCB1 gene on epilepsy treatment response.** *Pharmacogenomics* 2005; 6(4): 411-7.