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Lack of association of ABCB1 and PXR polymorphisms with response to treatment in epilepsy

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ABSTRACT

It is proposed that overexpression of P-glycoprotein (P-gp), encoded by the ABC subfamily B member 1 (ABCB1) gene, is involved in resistance to antiepileptic drugs (AEDs) in about 30% of patients with epilepsy. Genetic variation and haplotype patterns are population specific which may cause different phenotypes such as response to AEDs. Although several studies examined the link between the common polymorphisms in the ABCB1 gene with resistance to AEDs, the results have been conflicting. This controversy may be caused by the effect of some confounders such as ethnicity and polytherapy. Moreover, expression of the ABCB1 gene is under the control of pregnane X receptor (PXR). Evidence showed that PXR gene contribute to the response to treatment. The aim of this study was to assess the association of ABCB1 and PXR genetic polymorphisms with response to the carbamazepine (CBZ) or sodium valproate (VPA) monotherapy in epilepsy. Genotypes were assessed in 685 Chinese, Indian, and Malay epilepsy patients for ABCB1 (C1236T, G2677T, C3435T) and PXR (G7635A) polymorphisms. No association between these polymorphisms and their haplotypes, and interaction between them, with response to treatment was observed in the overall group or in the Chinese, Indian, and Malay subgroups. Our data showed that these polymorphisms may not contribute to the response to CBZ or VPA monotherapy treatment in epilepsy.

1. Introduction

About one third of epilepsy patients do not respond to antiepileptic drugs (AEDs).[1] Some studies showed that over expression of P-glycoprotein (P-gp) in brain tissue contributes to the resistance to AEDs.[2] P-gp is an efflux transporter that limits the cellular uptake levels of various drugs in intestine, brain, and other tissues.[3] It is encoded by the ABC subfamily B member 1 (ABCB1) transporter gene. The human ABCB1 gene is located at chromosome 7p21, composed of 29 exons (http://www.ncbi.nlm.nih.gov). The C1236T (rs1128503), G2677T/A (rs2032582), and C3435T (rs1045642) loci are the most commonly studied genetic variants in the ABCB1 gene. C1236T and C3435T polymorphisms are synonymous loci which alter the GGC codon to GGT (Gly412Gly) and the ATC codon to ATT (Ile1145Ile), respectively. However, the ABCB1 G2677T/A polymorphism is a non-synonymous locus resulting in amino acid exchanges (Ala893Ser or Ala893Thr). Among these three loci, C3435T polymorphism has received more attention as a critical variant in AEDs resistance.[4–7] Several genetic studies have attempted to link the ABCB1 gene common genetic variants to the resistance to AEDs, but the results have been conflicting. Our meta-analysis involving 6755 Asian and Caucasian patients did not confirm this association in the total study population or in the ethnic subgroups.[8–11] Therefore, it was suggested that controversy between the studies may be caused by the effect of some confounders such as ethnicity and polytherapy.[8]

It is proposed that linkage disequilibrium (LD) of the silent C3435T with other ABCB1 variants in a haplotype block may link with resistance to AEDs.[12] Haplotype and LD patterns are population specific, most probably shaped by evolutionary forces such as natural selection in ancestral populations in various geographical regions. Diversity in the haplotype block structures and LD patterns is high in European and East Asian populations. This diversity may cause crucial changes in the complex interaction of genetic and environmental factors in producing some phenotypes such as susceptibility to disease and response to pharmacological agents.[13–15] Therefore, some studies examined

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