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ABCB1 C3435T polymorphism and the risk of resistance to antiepileptic drugs in epilepsy: A systematic review and meta-analysis

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ABSTRACT

Objective: The C3435T, a major allelic variant of the ABCB1 gene, is proposed to play a crucial role in drug-resistance in epilepsy. The C/C genotype carriers reportedly are at higher risk of pharmacoresistance to AEDs, but only in some studies. The hypothesis of the C-variant associated risk and resistance to antiepileptic drugs (AEDs) has been hampered by conflicting results from inadequate power in case-control studies. To assess the role of C3435T polymorphism in drug-resistance in epilepsy, a systematic review and meta-analysis was conducted.

Methods: Databases were obtained from the Cochrane Library, MEDLINE, EMBASE, major American and European conference abstracts, and www.google.my for genetic association studies up to February 2010. All the case-control association studies evaluating the role of ABCB1 C3435T in pharmacoresistance to AEDs were identified. The new definition of treatment outcome from International League Against Epilepsy (ILAE) was used for including studies for sub-analysis. To measure the strength of genetic association for the gene variant, the odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using models of both fixed- and random-effects for comparisons of the alleles and genotypes with co-dominant (C/C vs. T/T, C/T vs. T/T), dominant (C/C + C/T vs. T/T), and recessive (C/C vs. C/T + T/T) models in overall and in ethnicity subgroups. The 19 studies were selected for the next sub-analysis based on the new definition of drug-responsiveness and drug-resistance from ILAE. The same analysis was also performed for treatment outcome and ethnicity subgroups.

Results: A total of 22 association studies including 3231 (47.8%) drug-resistant patients and 3524 (52.2%) drug-responsive patients or healthy controls (genotyped for C3435T) were pooled in this meta-analysis. The allelic association of ABCB1 C3435T with risk of drug-resistance was not significant under fixed-effects model, 1.06 (95% CI 0.98–1.14, $p = 0.12$) and random-effects model, 1.10 (0.93–1.30, $p = 0.28$) in overall and in the subgroup analysis by ethnicity. Similar results were also obtained for all genetic models in the stratified analyses by new definition of drug-resistance by ILAE and ethnicity subgroups. There was no publication bias.

Conclusion: We failed to show an association between the ABCB1 C3435T polymorphism and the risk of drug-resistance suggesting a revision in contribution of this polymorphism in the multi-drug transporters hypothesis of pharmacoresistance to AEDs in epilepsy.

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Epilepsy is a complex disease characterized by a predisposition to recurrent unprovoked seizures.¹ Despite treatment with antiepileptic drugs (AEDs), about one-third of newly treated patients do not respond adequately to medications, making pharmacoresistance a major problem in the control of this condition.² Recent studies have investigated the association

between over-expression of efflux transporters and excess efflux of AEDs across the blood-brain barrier (BBB) thereby leading to drug-resistant epilepsy.³ P-glycoprotein (P-gp) was the first discovered human ABC transporter more than 30 years ago in drug-resistance ovarian cells obtained from Chinese hamsters.⁴ P-gp is the most studied protein among the ATP-binding cassette (ABC) efflux transporters. This transmembrane transporter is the product of the ABC subfamily B member 1 transporter (ABCB1) gene, encoded by ABC subfamily B member 1 transporter (ABCB1) gene and located at the endothelial cells of the BBB.⁵ The level of P-

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