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Laila Nurmohamed
Hospital for Sick Children University of Toronto

Facundo Garcia-Bournissen
Hospital for Sick Children University of Toronto, fgarciab@uwo.ca

Russell J. Buono
Thomas Jefferson University

Michael W. Shannon
Children's Hospital Boston

Yaron Finkelstein
Hospital for Sick Children University of Toronto

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BRIEF COMMUNICATION

Predisposition to epilepsy—Does the *ABCB1* gene play a role?

***Laila Nurmohamed, *†Facundo Garcia-Bournissen, ‡§Russell J. Buono, ¶Michael W. Shannon, and *†¶#Yaron Finkelstein**

***Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; †Divisions of Clinical Pharmacology/Toxicology, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; ‡Neurology, Children's Hospital of Philadelphia, Thomas Jefferson University, Philadelphia, Pennsylvania, U.S.A.; §Research Service, Coatesville Veterans Affairs Medical Center, Coatesville, Pennsylvania, U.S.A.; ¶Clinical Pharmacology Unit, Division of Emergency Medicine, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts, U.S.A.; and #Emergency Medicine, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada**

Summary

We performed a meta-analysis to evaluate the association between *ABCB1 C3435T* polymorphisms and the prevalence of epilepsy, including all relevant human studies (until June 2009), in which patients with or without epilepsy had undergone genotyping for the *ABCB1* gene. Odds ratios (ORs) were calculated using a random effects model. We identified 9 case–control studies that included a total of 3,996 patients (2,454 with epilepsy and 1,542 nonepileptic subjects). No association was found between *ABCB1 C3435T* polymorphisms and the risk of having epilepsy (odds ratio 1.07, 95% confidence interval 0.76–1.51; p = 0.34). *ABCB1* genotyping for epileptic patients is not warranted.

KEY WORDS: MDR1, *ABCB1 C3435T*, Epilepsy, Polymorphism, Meta-analysis.

Epilepsy affects 0.5–2.0% of the general population (Lakhan et al., 2009). It carries significant morbidity and mortality, and has significant implications on society at large. About one-third of patients with epilepsy have poor seizure-control and experience recurrent seizures despite seemingly appropriate therapy (Sills et al., 2005).

It has been recently suggested that polymorphisms of the *ABCB1 C3435T* gene, and more specifically, the *ABCB1 3435CC* genotype, may be associated with a predisposition to develop epilepsy (Hung et al., 2005; Ebid et al., 2007), and can, therefore, identify high-risk groups for the disease. In addition, it has been suggested (Buono et al., 2006) that haplotypes of two markers in the *ABCB1* gene, at positions 1236 and 3435, were associated with epilepsy susceptibility.

The *ABCB1* gene encodes for p-glycoprotein (also known as MDR1), which is expressed in organs and tissues with excretory functions at the blood–tissue barrier, thereby protecting them from xenobiotics. The function of p-glycoprotein can be influenced by polymorphisms in the encoding gene, *ABCB1* (Sills et al., 2005). A synonymous C to T transformation at position 3435 of exon 26 is one common polymorphism of the *ABCB1* gene. This single nucleotide polymorphism (SNP) has been suggested to decrease the expression of the gene, and individuals with the *TT* genotype have decreased MDR1 functional expression compared to the C/C homozygotes (Sills et al., 2005).

The aim of the present study was to investigate whether certain polymorphic alleles of the *ABCB1 C3435T* are more prevalent in epileptic patients versus nonepileptic subjects, and whether this gene may serve as a biomarker for a tendency to develop epilepsy.

Methods

We conducted a systematic review and meta-analysis to address the hypothesis that polymorphisms in the *ABCB1* gene are associated with increased prevalence of epilepsy. We searched MEDLINE and EMBASE to identify all relevant published human case–control or cohort studies that reported the proportion of the *MDR1/ABCB1 C3435T* (rs1045642) [Database of Single Nucleotide Polymorphisms (dbSNP), 2007] genotypes among patients with epilepsy and control (nonepileptic) subjects from January 1966 to June 2009. Relevant articles were retrieved with no language restrictions. The Boolean search strategy ''epilepsy

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Address correspondence to Yaron Finkelstein, M.D., Clinical Pharmacology Unit, Division of Emergency Medicine, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts, U.S.A. or Divisions of Clinical Pharmacology and Toxicology, Emergency Medicine, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada. E-mail:yaron.finkelstein@childrens.harvard.edu or yaron.finkelstein@sickkids.ca

and (MDR1 or ABCB1 or C3435T or p-glycoprotein)'' was used. Once all relevant articles were compiled, their reference lists were reviewed manually by an experienced researcher for additional sources. In addition, we searched Web of Knowledge and Scopus conference proceedings, using a similar search strategy, in order to retrieve all relevant unpublished studies and scientific meeting abstracts. Two experienced investigators acted as reviewers, independently selecting studies for inclusion in the meta-analysis based on the inclusion criteria described and a standardized checklist. For all relevant sources, data were extracted from the results section and placed into contingency tables. Prevalence of homozygous *ABCB1 3435CC* was compared to prevalence of homozygous *ABCB1 3435TT* (Siddiqui et al., 2003). The extracted data were entered into Cochrane's Review Manager Software (version 4.1; Cochrane Collaboration, Oxford, United Kingdom). Individual and summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a random effects model (Bournissen et al., 2009). Included studies were tested for heterogeneity using the chi-square test and the I^2. Publication bias was assessed by visual inspection of the funnel plot (effect size vs. study size). To test the robustness of our findings, we also performed a cumulative meta-analysis (Bournissen et al., 2009), by sequentially adding studies to the meta-analysis in chronological order, using a random effects model. Publication bias was assessed by visual inspection of the funnel plot (effect size vs. study size).

Results

We identified nine relevant studies; all were observational case–control studies that reported on *ABCB1 C3435T* allele frequencies in epileptic versus nonepileptic subjects (Table 1). A total of 3,996 subjects were included in the nine studies, including 2,454 patients with epilepsy and 1,542 nonepileptic subjects.

We found no statistical significance between the prevalence of the homozygous *ABCB1 3435CC* genotype compared to the homozygous *ABCB1 3435TT* genotype in epileptic versus nonepileptic patients (OR 1.07, 95% CI 0.76 – 1.51; Fig. 1). The cumulative meta-analysis indicates that as early as 2006, with the publication of the third study, we would have identified no association between the *ABCB1* polymorphism and the risk to develop epilepsy (supplementary Fig. S1).

The included studies reported genetic data from various geographic areas including four from Europe, two from Turkey (Dericioglu et al., 2008; Ozgon et al., 2008), one from the United Kingdom (Siddiqui et al., 2003), and one from Germany (Ufer et al., 2009). Three studies were performed in East Asia: Taiwan (Hung et al., 2005), Korea (Kim et al., 2006), and China (Kwan et al., 2007); one study was performed in Egypt (Ebid et al., 2007) and one in India (Lakhan et al., 2009). Data on genotypes from additional markers in the *ABCB1* gene were not prevalent in the literature to allow haplotype analysis.

Table 1. Random effects prevalence of *ABCB1 3435 CC* versus *TT* in patients with epilepsy versus nonepileptic subjects (nine studies)

	OR	Lower 95%	Upper 95%
Siddiqui et al. (2003)	1.27	0.74	2.18
Hung et al. (2005)	1.90	1.22	2.98
Kim et al. (2006)	0.68	0.38	1.20
Ebid et al. (2007)	2.46	0.95	6.32
Kwan et al. (2007)	0.90	0.51	1.58
Dericioglu et al. (2008)	0.93	0.43	2.00
Ozgon et al. (2008)	2.05	0.95	4.42
Lakhan et al. (2009)	0.53	0.28	0.99
Ufer et al. (2009)	0.71	0.44	1.16

Summary OR 1.07, 95% CI 0.76–1.51).
CI, confidence interval. OR, odds ratio.

Discussion

This meta-analysis of observational studies, which included 3,996 patients, failed to show an association between *ABCB1 C3435T* genotypes and predisposition to epilepsy.

Several researchers have focused on the potential role of the *ABCB1* gene in drug resistance to anticonvulsant therapy (Siddiqui et al., 2003; Hung et al., 2005; Sills et al., 2005; Kim et al., 2006; Kwan et al., 2007), a serious problem associated with increased morbidity and mortality from epilepsy. The *ABCB1* gene encodes for p-glycoprotein, which is expressed in organs with excretory functions at the blood–tissue barrier. P-Glycoprotein operates as a multidrug efflux pump, extruding xenobiotics from mammalian brain tissue, and acting as a natural defence mechanism (Dericioglu et al., 2008). It has been speculated that polymorphisms in the *ABCB1* gene, specifically the *3435CC* genotype, are associated with drug resistance to anticonvulsants (Siddiqui et al., 2003), and may provide a biologically plausible explanation for this common phenomenon. However, subsequent studies have provided conflicting results and failed to replicate the original findings. In addition, concerns have been raised in multiple studies that results may depend on ethnic background of study subjects. To address these questions, we recently performed a meta-analysis (Bournissen et al., 2009) of all relevant studies (n = 3,371 patients: 1,646 with drug-resistant epilepsy and 1,725 with drug-responsive epilepsy) and showed that the polymorphisms at the *ABCB1 C3435T* gene are not associated with anticonvulsant drug resistance. These results remained stable when we stratified patients by ethnicity.

Previous authors who suggested that an association between the *ABCB1* gene and the development of epilepsy (as opposed to drug resistance) may exist (Hung et al., 2005; Buono et al., 2006; Ebid et al., 2007) have not

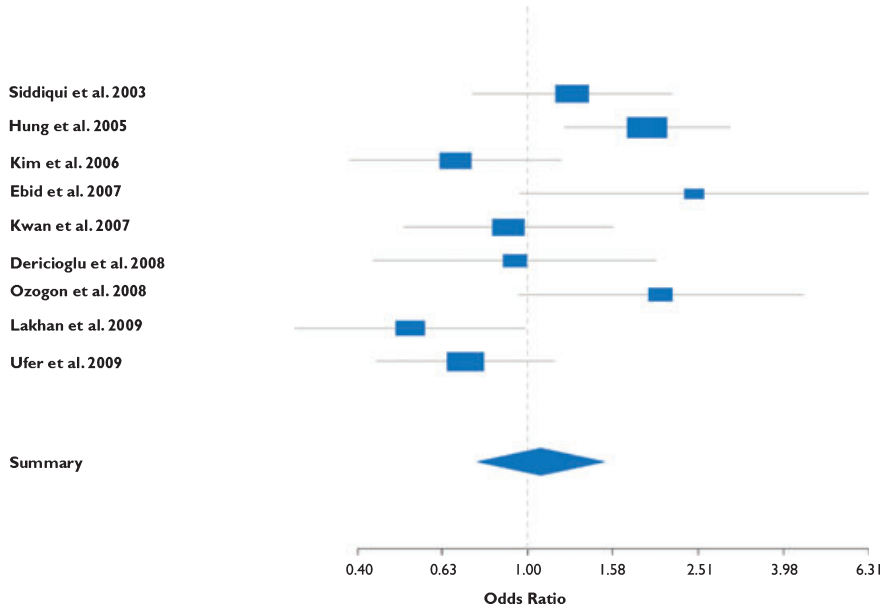

Figure 1.
Prevalence (OR) of *ABCB1 3435 CC* versus *TT* genotypes in patients with epilepsy versus nonepileptic subjects.
Epilepsia © ILAE

provided a biologically plausible or a mechanistic explanation for their hypothesis.

We did not perform a subanalysis of subjects by ethnic background, as we deemed it unnecessary, since only a single study (Hung et al., 2005) clearly supported an association between the *ABCB1 3435CC* genotype and an increased risk for epilepsy.

This meta-analysis provides further evidence that although the *ABCB1* gene has been highly investigated and plays many important roles, it is unlikely that the polymorphism at 3435 plays a major role in the development of epilepsy or in drug resistance to anticonvulsants. It is, therefore, not recommended that patients be tested for the *C3435T* polymorphisms of the *ABCB1* gene in this context, as such testing is unlikely to yield any information that would be useful in the diagnosis, management, or prognosis of epilepsy. It remains to be determined whether haplotypes in the *ABCB1* gene play a role in epilepsy susceptibility or anticonvulsant drug resistance.

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Disclosure

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The manuscript details the opinions of the authors and in no way represents the official views of the US Department of Veteran Affairs or any other US government agency.

None of the authors has potential conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Cumulative meta-analysis of *ABCB1 3435 CC* versus *TT* genotypes.

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