Predisposition to epilepsy - Does the ABCB1 gene play a role?

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*

Follow this and additional works at: [https://ir.lib.uwo.ca/paedpub](https://ir.lib.uwo.ca/paedpub)

Citation of this paper:  
Nurmohamed, Laila; Garcia-Bournissen, Facundo; Buono, Russell J.; Shannon, Michael W.; and Finkelstein, Yaron, "Predisposition to epilepsy - Does the ABCB1 gene play a role?" (2010). *Paediatrics Publications*. 1364.  
[https://ir.lib.uwo.ca/paedpub/1364](https://ir.lib.uwo.ca/paedpub/1364)
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.; 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 CC 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...
Table 1. Random effects prevalence of ABCB1 3435 CC versus TT in patients with epilepsy versus nonepileptic subjects (nine studies)

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

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

**Acknowledgments**

In memory of Dr. Michael W. Shannon, a great mentor and clinician, who passed away during the study.

Work partially supported by the SickKids Research Institute Start-Up Fund (YF) and grant R01NS40396 to RJB. Some resources at the Coatesville VAMC were used in production of this manuscript.

**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.

**References**


**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.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting Information supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.