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The Effects of *ABCC2* G1249A Polymorphism on the Risk of Resistance to Antiepileptic Drugs: A Meta-Analysis of the Literature

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Aims: The G1249A variant of the multidrug resistance-associated protein 2 (*ABCC2*) gene may be associated with the development of antiepileptic drug (AED) resistance. Although numerous studies have investigated the association between the G1249A variant and the risk of drug resistance in epilepsy, the results of these studies have been inconclusive. To assess the role of G1249A polymorphism in drug resistance in epilepsy, a meta-analysis was performed. *Materials and Methods:* We systematically reviewed relevant studies retrieved by the PubMed and Embase. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated based on the date extracted from the studies to evaluate the strength of association. We also analyzed the heterogeneity and sensitivity of each report and the publication bias of the studies. *Results:* A total of 6 published studies, involving 2213 patients (1100 patients with drug-resistant epilepsy and 1113 controls with drug-responsive epilepsy) were reviewed in the present meta-analysis. The overall results indicated that the variant genotypes were associated with a significantly decreased risk of AED resistance (AA vs. GG: OR = 0.372, 95% CI = 0.182–0.762; recessive model: OR = 0.399, 95% CI = 0.200–0.795) (fixed-effects model). A stratified analysis by ethnicity showed similar findings for Caucasians in an additive model (A vs. G: OR = 0.700, 95% CI = 0.494–0.992). *Conclusions:* The meta-analysis suggests that the *ABCC2* G1249A polymorphism is significantly associated with a decreased risk of AED resistance. However, further functional investigations are warranted to validate the association.

Introduction

Epilepsy is considered to be one of the most common and devastating neurological disorders and is characterized by a predisposition to having recurrent uncontrolled seizures (Annegers *et al.*, 1995; Lakhan *et al.*, 2009). Despite the availability of different antiepileptic drugs (AEDs) for therapy, about 30–40% of patients who begin a therapy do not attain seizure control, making drug resistance a major problem for managing epilepsy and creating a substantial public health burden (Kwan and Brodie, 2000; Elger and Schmidt, 2008). The precise reasons why some epilepsy patients fail to respond appropriately to AEDs remain unclear. However, some evidence suggests that ATP-binding cassette (ABC) efflux transporters in the blood–brain barrier (BBB) may contribute significantly to drug resistance in epilepsy by reducing the penetration of AEDs into the brain. Moreover, genetic variants of drug transporter genes, related to functional variations in efflux activity, may be responsible for the interindividual differences in drug resistance (Tishler *et al.*, 1995; Loscher *et al.*, 2009; Cascorbi, 2010).

The association between the overexpression of efflux transporters and the excess efflux of AEDs across the BBB, along with the resulting drug-resistant epilepsy, has been the focus of recent research. *ABCC2* (also known asMRP2), located at the membrane of endothelial cells of the BBB, is a member of the ABC superfamily. Members of the ABC superfamily are important for the bioavailability of and response to medication in epilepsy. *ABCC2* is also normally expressed in the BBB and may reduce the brain concentration of many AEDs, thereby leading to the AED failure (Sisodiya *et al.*, 2003; Schmidt and Loscher, 2005; Kubota *et al.*, 2006; Remy and Beck, 2006; Lazarowski *et al.*, 2007).

The *ABCC2* gene, localized on chromosome 10q23-24, exhibits various genetic polymorphisms (Ito *et al.*, 2001; Itoda *et al.*, 2002; Suzuki and Sugiyama, 2002); these polymorphisms may influence the function of MRPs, resulting in their functional changes (Rau *et al.*, 2006; de Jong *et al.*, 2007; Haenisch *et al.*, 2007). The G1249A (Val417Ile, rs2273697) polymorphism, which is associated with the substitution of Val with an Ile at position 417, is one of the most common polymorphisms in the *ABCC2* gene, and its role in epilepsy pharmacoresistance has been the focus of recent research (Ito *et al.*, 2001; Obata *et al.*, 2006; Kim *et al.*, 2010).

It has recently been suggested that an association may exist between the *ABCC2* G1249A polymorphism and risk of

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resistance to AEDs, but the results from various studies on this association remain inconclusive. Ufer *et al.* (2011) discovered a significant association between the *ABCC2* G1249A polymorphism and drug-resistant epilepsy. However, other studies were unable to replicate this finding (Seo *et al.*, 2008; Kim *et al.*, 2009; Ufer *et al.*, 2009; Kwan *et al.*, 2011; Hilger *et al.*, 2012). In view of the uncertainty surrounding this issue and considering the potential importance of this polymorphism for the response to anticonvulsant medication, we carried out this meta-analysis of all the relevant published literature using different genetic model analyses.

Materials and Methods

Search strategy

We conducted a systematic literature search in the PubMed and Embase databases, attempting to identify all published human studies that had investigated the association between the risk of resistance to AEDs and *ABCC2* G1249A polymorphisms (the last search update was conducted on March 31, 2013). We used the following Boolean search keywords "(*ABCC2* OR Multidrug-resistance protein 2 OR MRP2 OR rs2273697) AND epilepsy." The relevant articles were retrieved with no language restrictions. In addition, the reference lists of all pooled articles were carefully screened for additional eligible publications. Unpublished data and further information were also obtained from the authors. Only the case–control studies in which data were available on the role of *ABCC2* G1249A polymorphism in the risk of resistance to AEDs were selected.

To be included in this meta-analysis, the studies had to (1) be related to AED treatment of patients with epilepsy, (2) have a human case–control design, and (3) have sufficient available data on genotype frequencies for both drug-responsive and drug-resistant patients. Studies were excluded from the analysis if they were (1) not about epilepsy research, (2) not human case–control design, (3) lacking usable data on genotype frequencies, and (4) a duplicate of previous publication.

Data extraction

Two reviewers independently extracted information from all eligible publications that met the inclusion criteria using an extraction template. Any disagreement in the extracted data was resolved by discussion. If a disagreement persisted despite the discussion, a third author was invited to assess those articles. The data extracted from each eligible publication included the following information: the first author's name, the year of publication, the country of origin of the article, the ethnic origin of the studied population (either Caucasian or Asian), the genotyping method, and the genotype and allele distributions for both drug-responsive and drug-resistant patients. We also converted genotype distributions that were reported in percentages to actual numbers and calculated allele frequencies from the corresponding genotype distributions.

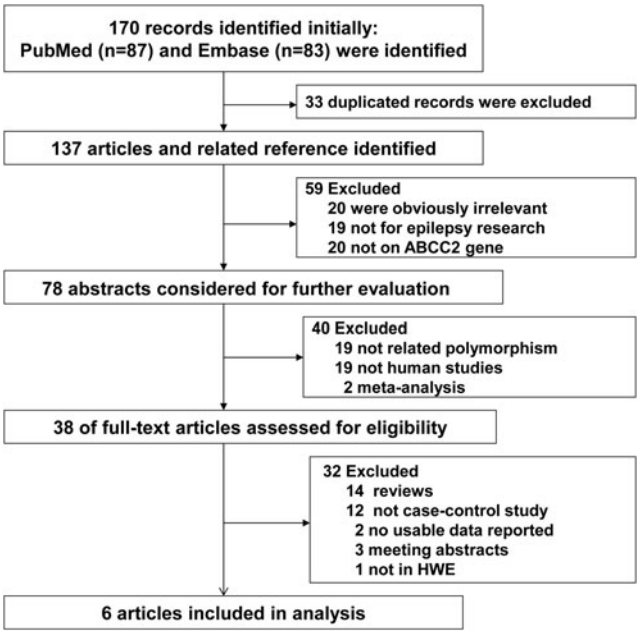

FIG. 1. The selection procedure for included and excluded studies.

Statistical analyses

All statistical analyses were performed using STATA software (version 11; Stata Corporation, College Station, TX). All probability values were two-sided, and *p*-values less than 0.05 were considered statistically significant. We assessed for violations of Hardy–Weinberg equilibrium (HWE) for each study, using a goodness-of-fit test (chi-square or Fisher's exact test). Based on the genotype frequencies in cases and controls, crude odds ratios (ORs) and their 95% confidence intervals (CIs) were employed to assess the strength of the association between the *ABCC2* G1249A polymorphism and the risk of resistance to AEDs in a homozygote comparison (AA vs. GG), a heterozygote comparison (GA vs. GG), and dominant

Table 1. Characteristics of Eligible Studies Considered in the Meta-Analysis

					Drug-resistant					*Drug-responsive*					
ID	*First author*	*Year*	*Ethnicity*	*Genotyping methods*	*GG*	*GA*	*AA*	*G*	*A*	*GG*	*GA*	*AA*	*G*	*A*	*HWE*
1	Seo (Japan)	2008	Asian	PCR	102	29	2	233	33	104	35	7	243	49	0.087
2	Kim (Korea)	2009	Asian	RT-PCR	162	35	1	359	37	165	27	1	357	29	0.926
3	Ufer (Germany)	2009	Caucasian	PCR-RFLP	66	48	4	180	56	56	37	10	149	57	0.298
4	Ufer (Germany)	2011	Caucasian	PCR	119	48	9	286	66	14	16	2	44	20	0.355
5	Kwan (China)	2011	Asian	Mass array	193	65	0	451	65	255	60	4	570	68	0.825
6	Qu (China)	2012	Asian	PCR-RFLP	181	35	1	397	37	262	56	2	580	60	0.593

PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; HWE, Hardy–Weinberg equilibrium; RT-PCR, reverse transcription PCR.

(AA + GA vs. GG), recessive (AA vs. GA + GG), and additive (A vs. G) genetic model comparisons. In addition, we carried out the stratified analyses by ethnicity for all genetic models. Ethnic groups were either Asian or Caucasian. The between-study heterogeneity was evaluated using the chi-squared-based *Q*-statistic test. When the *p*-value was greater than 0.05 (indicating that the between-study heterogeneity was not significant), the fixed-effects model that was selected (the Mantel–Haenszel method) (Mantel and Haenszel, 1959). For *p*-values < 0.05 in the heterogeneity test, the pooled ORs were analyzed using the random-effects model (the DerSimonian and Laird method) (DerSimonian and Laird, 1986). We also used the I^2 statistic to quantitatively estimate heterogeneity, with I^2 < 25%, 25–75%, and > 75% representing low, moderate and high degrees of inconsistency, respectively (Higgins and Thompson, 2002; Higgins *et al.*, 2003). The significance of the combined OR was determined using the *Z*-test, and *p*-values < 0.05 were considered statistically significant. In addition, we performed sensitivity analyses to evaluate the stability of the results in our meta-analyses through sequentially excluded individual studies. Finally, the Begg's test (Begg and Mazumdar, 1994) and Egger's test (Egger *et al.*, 1997) were also used to statistically assess publication bias (a *p*-value < 0.05 was considered statistically significant).

Results

Characteristics of eligible studies

The selection process is shown in Figure 1. After excluding the duplicated records, a total of 137 articles were identified from the initial search in the PubMed and Embase databases. In this screening process, 20 studies were obviously irrelevant. Thirty-nine studies were excluded because they were not related to epilepsy research (19 studies) or were not associated with *ABCC2* gene (20 articles). Nineteen articles that were not concerned with *ABCC2* G1249A polymorphism were also excluded. Two of the articles were meta-analyses, and 19 of the publications were not human studies. Among the remaining 38 articles, 14 publications were reviews, 3 were meeting abstracts, 12 were not case–control studies, 2 did not present the usable data, and 1 was not in HWE; these studies were also excluded. Finally, a total of 6 published studies, comprising 1113 controls with drug-responsive epilepsy and 1100 patients with drug-resistant epilepsy, concerning G1249A polymorphism in the *ABCC2* gene and the risk of resistance to AEDs were included in our meta-analysis (Seo *et al.*, 2008; Kim *et al.*, 2009; Ufer *et al.*, 2009, 2011; Kwan *et al.*, 2011; Qu *et al.*, 2012). The characteristics of the included studies are listed in Table 1. Among the included publications, two studies included participants of Caucasian descent and four studies included participants of Asian descent. All studies indicated that the distribution of genotypes was consistent with HWE. The genotype frequencies of *ABCC2* G1249A polymorphism were extracted from all eligible studies, and the main results are listed in Table 2.

Meta-analysis results

Table 2 shows the association between *ABCC2* G1249A polymorphism and the risk of drug resistance in epilepsy. Overall, the results indicated that *ABCC2* AA genotype was associated with a significantly decreased risk of AED

Table 2. Total and Stratified Analysis of *ABCC2* G1249A Polymorphism on the Risk of Drug Resistance in Epilepsy

	AA vs. GG			*GA vs. GG*			*A vs. G*			*Recessive model*			*Dominant model*		
Variables	*OR (95% CI)*	p^a	I^2 (%)	*OR (95% CI)*	p^a	I^2 (%)	*OR (95% CI)*	p^a	I^2 (%)	*OR (95% CI)*	p^a	I^2 (%)	*OR (95% CI)*	p^a	I^2 (%)
Total	**0.372 (0.182–0.762)**	0.916	0.0	0.977 (0.704–1.355)[b]	0.046	55.7	0.914 (0.761–1.098)	0.104	45.3	**0.399 (0.200–0.795)**	0.827	0.0	0.976 (0.795–1.199)	0.056	53.6
Ethnicity															
Asian	0.357 (0.123–1.041)	0.731	0.0	1.133 (0.893–1.437)	0.310	16.2	1.010 (0.814–1.252)	0.239	28.9	0.356 (0.123–1.035)	0.726	0.0	1.075 (0.852–1.358)	0.260	25.3
Caucasian	0.388 (0.148–1.013)	0.666	0.0	0.646 (0.212–1.966)[b]	0.021	81.1	**0.700 (0.494–0.992)**	0.206	37.5	0.441 (0.178–1.092)	0.368	0.0	0.699 (0.453–1.078)	0.052	73.5

The results that are in bold type show statistical significance.
[a]*p*-Value of *Q*-test for heterogeneity test.
[b]Random-effects model was used when *p*-value for heterogeneity test < 0.05; otherwise, fixed-effects model was used.
CI, confidence interval; OR, odds ratio.

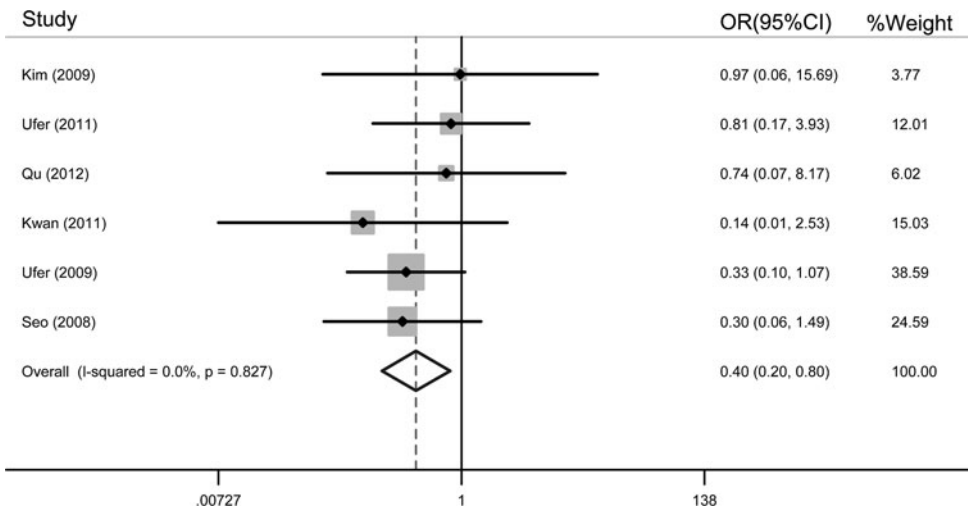

FIG. 2. Overall meta-analysis of the *ABCC2* G1249A polymorphism and the risk of drug resistance in epilepsy in the recessive model (odds ratio [OR] = 0.399, 95% confidence interval [CI] = 0.200–0.795) (the fixed-effects model).

resistance (AA vs. GG: OR = 0.372, 95% CI = 0.182–0.762; recessive model: OR = 0.399, 95% CI = 0.200–0.795) (fixed-effects model). Homozygous carriers of variant allele of the *ABCC2* 1249G > A polymorphism contributed greatly to the response to AEDs. Figure 2 shows the overall meta-analysis of the *ABCC2* G1249A polymorphism and the risk of drug resistance in epilepsy in the recessive model.

In the analysis stratified by ethnicity, being Caucasian was associated with a significantly reduced risk of drug resistance in additive model (A vs. G: OR = 0.700, 95% CI = 0.494–0.992) (fixed-effects model). However, this association was not found among Asians in the additive model (A vs. G: OR = 1.010, 95% CI = 0.814–1.252). In addition, we failed to find any association between the G1249A polymorphism in the *ABCC2* gene and response to anticonvulsant drugs in the other genetic models. Table 2 depicts the results of the other genetic comparisons models.

Test of heterogeneity

There was significant heterogeneity among the studies in the heterozygote comparison (GA vs. GG: $p_{\text{heterogeneity}} = 0.046$, $I^2 = 55.7\%$), but not in the homozygote comparison (AA vs. GG: $p_{\text{heterogeneity}} = 0.916$, $I^2 = 0.0\%$), the recessive model comparison (AA vs. GA + GG: $p_{\text{heterogeneity}} = 0.848$, $I^2 = 0.0\%$), the additive model comparison (A vs. G: $p_{\text{heterogeneity}} = 0.104$, $I^2 = 45.3\%$), and the dominant model comparison (AA + GA vs. GG: $p_{\text{heterogeneity}} = 0.056$, $I^2 = 53.6\%$). In the analysis by the ethnicity, heterogeneity was not observed for the Asian group in the heterozygote comparison (GA vs. GG: $p_{\text{heterogeneity}} = 0.310$, $I^2 = 16.2\%$). Heterogeneity was observed for the Caucasian group, however (GA vs. GG: $p_{\text{heterogeneity}} = 0.021$, $I^2 = 81.1\%$).

Sensitivity analysis

We performed sensitivity analyses to assess the influence of each individual study on the pooled OR by sequentially removing each eligible study (Fig. 3). The results indicated that the independent study conducted by Ufer *et al.* (2011) made the greatest contribution to the heterogeneity. This heterogeneity was effectively removed by excluding this study from the analysis. In addition, we did not find that any single study influenced the quality of the pooled ORs, suggesting that the results of this meta-analysis were stable and reliable.

Publication bias

The shape of the funnel plot seemed symmetrical, suggesting that there was no obvious publication bias. In addition, the results of Egger's test showed no significant publication bias in this meta-analysis ($t = 0.34$, $p = 0.748$ for AA vs. GA + GG, Figure 4).

Discussion

Epilepsy, which is characterized by its significant morbidity and mortality, affects ~0.5–2.0% of the general population (Annegers *et al.*, 1995; Lakhan *et al.*, 2009). About one in three of patients with epilepsy fails to respond to medication, as a result of the resistance to AEDs, constituting a significant public health challenge (Kwan and Brodie, 2000; Sills *et al.*, 2005; Elger and Schmidt, 2008). Recent studies have confirmed that multidrug resistance-associated protein (*ABCC2*), an important member of the ABC efflux transporters, when overexpressed in

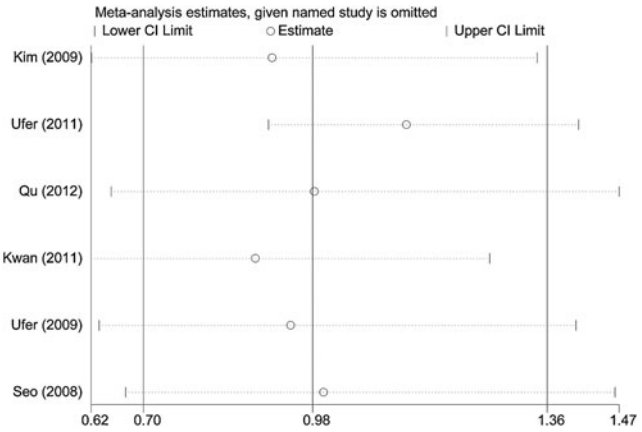

FIG. 3. Results of the cumulative meta-analysis examining the association between the *ABCC2* G1249A polymorphism and the risk of drug resistance in epilepsy in the heterozygote comparison model.

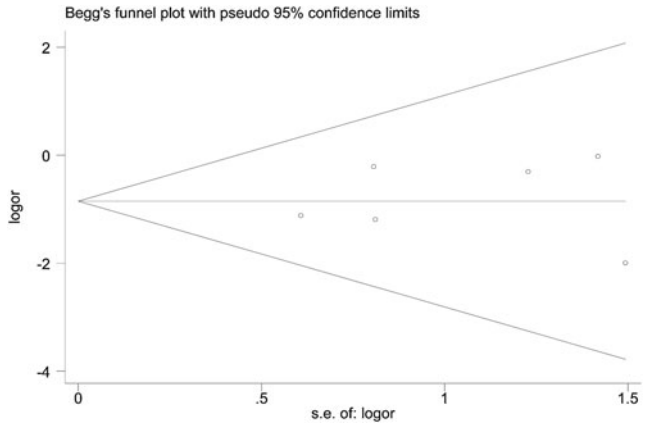

FIG. 4. Funnel plot to determine publication bias of the meta-analysis of the association between the G1249A variant and the risk of drug resistance in epilepsy in the recessive model.

the BBB in patients with epilepsy, could limit the penetration of AEDs into the brain and reduce the intracellular accumulation of the drug, leading to pharmacoresistance in epileptics (Dombrowski *et al.*, 2001; Sisodiya *et al.*, 2003; Schmidt and Loscher, 2005; Kubota *et al.*, 2006; Remy and Beck, 2006; Lazarowski *et al.*, 2007; Szakacs *et al.*, 2008).

Single-nucleotide polymorphisms (SNPs) are extremely common sources of human genetic variation, and pharmacogenetic studies have revealed that such miniscule variation in genome sequence could influenced the drug disposition and pharmacokinetics, thereby affecting individual response to treatment (Sun *et al.*, 2010). Recent studies have identified numerous polymorphisms of the *ABCC2* gene. The G1249A variant, a G to A base change that causes a substitution of isoleucine for valine at position 417 in the *ABCC2* gene, has been suggested to influence ABCC2 function (Ito *et al.*, 2001; Itoda *et al.*, 2002; Suzuki and Sugiyama, 2002). Kim *et al.* (2010) confirmed that this polymorphism reduced the *ABCC2* transportation of carbamazepine, one of the most commonly used first-line drugs in epilepsy. In addition, research has demonstrated that the functional effects of the combination of other SNPs in the haplotypes could lead to an alteration of MRP protein expression. Thus, the gene–gene interactions might play an important role in the functional alteration of the MRP protein (Laechelt *et al.*, 2011; Grover *et al.*, 2012).

Overall, this research is a systematic review to evaluate the association between G1249A polymorphism in the *ABCC2* gene and the risk of developing drug resistance in epilepsy. Our meta-analysis of eligible case–control studies, comprising a total of 2213 patients (1100 patients with drug-resistant epilepsy and 1113 patients with drug-responsive epilepsy), indicated that *ABCC2* G1429A polymorphism was associated with a significant decreased risk of drug resistance in epilepsy in a homozygote comparison (AA vs. GG) and a recessive genetic model comparison (AA vs. GA+GG). A stratified analysis by ethnicity reviewed a similar association for Caucasians but not for Asians in additive comparison model, suggesting that this polymorphism plays different roles in populations with different genetic backgrounds and from different living environments. However, we failed to draw a clear conclusion using other genetic effects models.

In addition, the Egger's test and funnel plot suggested that there was no publication bias for the association between this polymorphism and drug resistance risk in epilepsy in this meta-analysis.

There may be limitations to the results of this meta-analysis. First, the number of published studies in our meta-analysis was insufficient, and the studies with small samples may not have had enough statistical power for evaluating the association. Second, the complex gene–gene or gene–environment interactions, as well as the different polymorphism of the same gene, may contribute to response to AEDs among epileptics. Third, heterogeneity between the included studies, which might affect the results of the meta-analysis, was detected in the heterozygote comparison model. Despite these limitations, our meta-analysis maintains some validity. First, a systematic review of the relationship between *ABCC2* G1249A polymorphism and response to AEDs has more statistical powerful compared with any single study. Moreover, the studies that enrolled in our meta-analysis statistical strictly met the selection criteria set. Furthermore, no publication bias was shown, indicating that there was no bias among the pooled results.

In summary, our meta-analysis showed that the *ABCC2* G1249A polymorphism is significantly associated with decreased risk of resistance to AEDs through a homozygote comparison and a recessive genetic comparison model. This association was also present in the Caucasian subpopulation. However, additional well-designed functional studies, particularly studies investigating gene–gene and gene–environment interactions, need to be conducted, to further understand the association between *ABCC2* polymorphism and the risk of drug resistance in epilepsy.

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Author Disclosure Statement

The authors declare they have no conflicts of interest.

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