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META-ANALYSIS

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ABCB1 Gene C3435T Polymorphism and Drug Resistance in Epilepsy: Evidence Based on 8604 Subjects

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The present study aimed to assess the role of C3435T polymorphism in drug-resistance in epilepsy by a meta-analysis.

Material/Methods: Databases were obtained from the Cochrane Library, MEDLINE, EMBASE, PubMed, Science Direct database, CNKI, and Wanfang up to October 2014. All the case-control association studies evaluating the role of ABCB1 C3435T in pharmacoresistance to anti-epileptic drug (AED) were identified. RevMan 5.0 software was utilized to perform quantitative analyses in an allele model (C *vs.* T) and a genotype model (CC *vs.* CT+TT).

Results: From the 189 potential studies, we included 28 articles for the meta-analysis, including 30 independent case-control studies involving 4124 drug-resistant epileptic patients and 4480 epileptic patients for whom drug treatment was effective. We excluded 164 studies because of duplication, lack of genotype data, and non-clinical research. We found that C3435T polymorphism was not significantly associated with drug resistance in epilepsy, either in allele model (C *vs.* T: OR=1.07; 95%CI: 0.95–1.19) or in genotype model (CC *vs.* CT+TT: OR=1.05; 95%CI: 0.89–1.24, P=0.55). Subgroup analyses suggested that in Caucasian populations there are significant differences between resistance group (NR) and control group (R) in both allele model (C *vs.* T: OR=1.09; 95%CI: 1.00–1.18, P=0.05) and genotype model (CC *vs.* CT+TT: OR=1.20; 95%CI: 1.04–1.40, P=0.01). However, we did not find this association in Asian populations.

Conclusions: We conclude that the ABCB1 C3435T polymorphism may be a genetic marker for drug resistance in epilepsy in Caucasian populations.

MeSH Keywords: **Epilepsy, Absence • Meta-Analysis • Polymorphism, Genetic**

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Background

Epilepsy is a common and complex disease characterized by a predisposition to recurrent unprovoked seizures [1]. After treatment with anti-epileptic drugs (AEDs), most epileptic patients respond well to medications. However, about one-third of newly treated patients do not respond adequately to medications, because these patients exhibit drug resistance to AEDs [2]. P-glycoprotein (P-gp) was the first discovered human ABC (the ATP-binding cassette) transporter in drug-resistance ovarian cells several decades ago [3]. P-gp is the expression product of ABCB1 (the ATP-binding cassette, subfamily B, member 1 transporter gene), which is also known as MDR1 (multi-drug resistance gene 1). The ABCB1 gene is highly polymorphic and more than 50 variants reside in the coding region which can possibly cause altered function [4]. The C3435T polymorphism is one of the most common polymorphisms in the ABCB1 gene. Siddiqui et al. [5] first reported that among Caucasians, the C3435T single-nucleotide polymorphism (SNP) of ABCB1 was correlated with drug resistance in epilepsy. Following that study, more than 20 replication studies [6–27] were conducted to evaluate this hypothesis.

In 2010, Haerian et al. [28] performed a meta-analysis and did not find an association between ABCB1 polymorphism and drug resistance in epilepsy. In recent year, several large sample-size and well-designed studies related to this topic have been conducted [29–33]. However, the results remain contradictory. To clarify the association with ABCB1 gene C3435T polymorphism and drug resistance in epilepsy, we performed an updated meta-analysis to further explore the correlations between the ABCB1 C3435T polymorphism and drug resistance in epilepsy.

Material and Methods

Literature screening

We used the keywords "polymorphism", "multi-drug resistance gene 1", "C3435T", "epilepsy", "intractable epilepsy", "anti-epileptic drugs", and "drug-resistant" to search the Cochrane Library, MEDLINE, EMBASE, PubMed, Science Direct database, China National Knowledge Infrastructure (CNKI) database, the China Biomedical Literature (CBM) database, the MedCH international medical abstract database, and Wanfang up to October 2014. These searches were supplemented by retrospective and manual searches of the literature by going to a library to read paper copies of scientific journals. The first report on the relationship between the ABCB1 C3435T polymorphism and drug resistance in epilepsy appeared in 2003, and the end date for the retrieval process was October 31, 2014.

Literature inclusion and exclusion criteria

Literature inclusion criteria

1) Chinese or English publication that addressed the association of the ABCB1 C3435T polymorphism with drug resistance in epilepsy; 2) reported complete data, including the number of examined individuals in the drug-resistant group and the therapeutically effective group, the frequency of the CC, CT, and TT genotypes at the 3435 locus of the ABCB1 gene; 3) the study subjects were epileptic patients who were treated with AEDs.

Exclusion criteria

Studies were excluded if: 1) they were duplicate publications from the same population and the same authors examined in another publication, in which case only the publication with the largest sample size was retained; or 2) they did not contain sufficient quantity or quality of data to analyze.

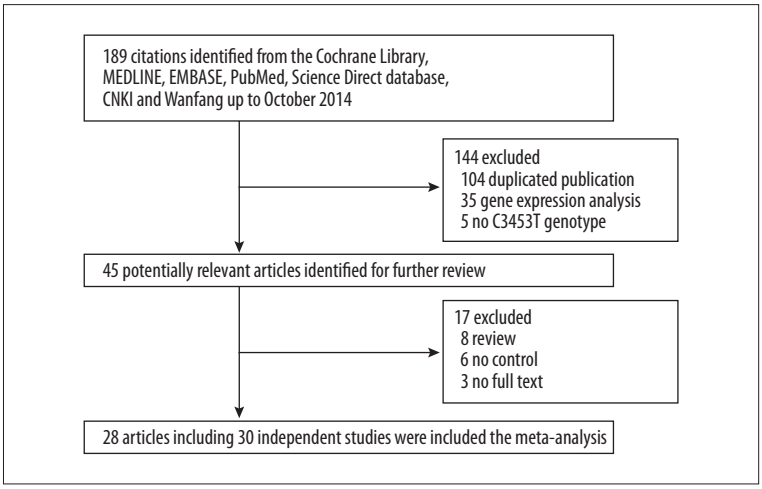

Figure 1. The flow chart of literatures identification.

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Table 1. The characteristics of included studies.

Authors	Publication year	Country	Number of Subjects		NR			R			NR		R	
			NR	R	CC	CT	TT	CC	CT	TT	C	T	C	T
Alpman et al.	2010	Turkey	39	92	6	20	12	26	37	24	32	44	89	85
Haerian et al.	2011	Asian	323	362	109	158	56	110	180	72	376	270	400	324
Szoeke et al.	2009[a]	Australia	64	148	21	27	16	34	67	47	69	59	135	161
Szoeke et al.	2009[b]	Scotland	133	152	20	69	44	34	72	46	109	157	140	164
Szoeke et al.	2009[c]	China	11	34	1	8	2	13	20	1	10	12	46	22
Tan et al.	2004	Australia	401	208	75	193	133	37	115	56	343	459	189	227
Chen L et al.	2007	China	50	164	15	25	10	63	79	22	55	45	205	123
Di Q et al.	2011	China	91	79	44	37	10	32	30	17	125	57	94	64
Dong et al.	2011	China	157	193	64	75	18	82	83	28	203	111	247	139
Hung et al.	2007	China	114	213	40	55	19	39	107	67	135	93	185	241
Kwan et al.	2007	China	221	297	80	104	37	114	161	22	264	178	389	205
Ufer et al.	2009	Germany	188	103	44	85	59	20	46	37	173	203	86	120
Grover et al.	2010	India	87	125	13	44	30	14	55	56	70	104	83	167
Kumaril et al.	2011	India	125	260	12	67	46	42	120	98	91	159	204	316
Takhan et al.	2009	India	94	231	9	52	33	38	104	89	70	118	180	282
Vahab et al.	2009	India	113	54	3	61	49	3	8	43	67	159	14	94
Sayyah et al.	2011	Iran	132	200	34	55	43	32	80	88	123	141	144	256
Shahwan et al.	2007	Ireland	122	233	20	64	38	37	119	77	104	140	193	273
Seo et al.	2006	Japan	126	84	34	58	34	36	34	14	126	126	106	62
Kim et al.	2009	Korea	198	193	73	97	28	81	90	22	243	153	252	134
Emich-Widera et al.	2013	Poland	60	25	9	33	18	1	16	8	51	69	18	32
Emich-Widera et al.	2014	Poland	193	135	19	114	60	21	82	32	152	234	124	146
Sills et al.	2005	Scotland	230	170	41	112	77	32	82	56	194	266	146	194
Sanchez et al.	2010	Spain	111	178	40	49	22	52	81	45	129	93	185	171
Dericiogl et al.	2008	Turkey	89	100	26	34	29	25	49	26	86	92	99	101
Ozgon et al.	2008	Turkey	44	53	13	26	5	16	29	8	52	36	61	45
Saygi et al.	2014	Turkey	59	60	19	26	14	12	30	18	64	54	54	66
Seven et al.	2014	Turkey	69	83	17	30	22	22	38	23	64	74	82	84
Siddiqui et al.	2003	UK	200	115	55	106	39	18	63	34	216	184	99	131
Soranzo et al.	2004	UK	280	136	73	145	62	20	80	36	291	269	120	152

NR – anti-epileptic drug no response (case group); R – effective group (control group). a, b, and c represent independent studies from the same article.

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Table 2. Meta-Analysis of C3435T polymorphism of the ABCB1 gene and drug resistance in epilepsy.

Genetic model	Sample size		Test of association			Test for heterogeneity	
	Case	Control	OR	95%CI	P	P	I^2
Total							
CC *vs.* (CT+TT)	4124	4480	1.05	0.89–1.24	0.55	0.0003	54%
C *vs.* T	8246	8950	1.07	0.95–1.19	0.26	<0.001	64%
Caucasian							
CC *vs.* (CT+TT)	2414	2191	1.20	1.04–1.40	0.01	0.04	42%
C *vs.* T	4826	4372	1.09	1.00–1.18	0.05	0.02	48%
Asian							
CC *vs.* (CT+TT)	1710	2289	0.90	0.70–1.17	0.43	0.002	61%
C *vs.* T	3420	4578	1.03	0.84–1.26	0.77	<0.001	76%

OR – odds ratio, CI – confidence interval, *vs.* – versus.

Data extraction

Data extraction was performed independently by 2 researchers (Li SX and Liu YY), and the extracted data were subsequently verified. The retrieved data included the author names, the date of publication, the nationality of the study population, and the allele and genotype frequency distributions. If genotype frequency distributions were expressed as percentages, then data were entered after converting these percentages into numbers of cases. If allele distributions were not provided, then these distributions were calculated from genotype distributions.

Statistical analysis

Meta-analysis was performed using the RevMan 5.0 software. Cochran's Q test was used for the analysis of heterogeneity between the results of each study. When there was no heterogeneity between studies (I^2<50%), a fixed-effects model was used for the meta-analysis. When there was heterogeneity (I^2>50%), a random-effects model was used for the meta-analysis. The OR and 95% CI of each allele and genotype frequency were calculated for each study. The Hardy-Weinberg equilibrium of the control group was calculated. P<0.05 was considered statistically significant. Sensitivity analysis was conducted using the individual exclusion method. The overall effects were re-assessed and compared with the overall effects prior to exclusion. Begg's test and Egger's test were applied to determine whether there was publication bias in the studies.

Results

Search results and literature

As shown in Figure 1, a total of 189 articles were retrieved after first search in the Cochrane Library, MEDLINE, EMBASE, PubMed, Science Direct database, China National Knowledge Infrastructure (CNKI) database, the China Biomedical Literature (CBM) database, the MedCH international medical abstract database, and Wanfang up to October 2014. Finally, there were 28 articles including 30 independent case-control studies [6–27,29–33] that fulfilled the inclusion criteria. The characteristics of each study are summarized in Table 1. These 30 studies involving 8604 subjects were ultimately analyzed in our meta-analysis. There were 17 studies carried out in Caucasian populations while the other 13 studies were performed in Asian populations. In the subgroup analysis, patients from Hong Kong, China were included in the Asian population, whereas patients from Australia and Scotland were included in the Caucasian population. Therefore, there were effectively a total of 13 studies examining Asian populations and a total of 17 studies that examined Caucasian populations (Table 1).

Meta-analysis results

Analysis of the allele contrast model (C *vs.* T) for the overall population revealed that there was high heterogeneity among the included studies (I^2=64%, P<0.001); therefore, a random-effects model was used to pool the OR values for the frequency of the 3435C allele. The pooled OR value was 1.07 (95% CI: 0.95–1.19, P=0.26) in allele model and 1.05 (95% CI: 0.89–1.24, P=0.55) in genotype model, indicating that the 3435C allele

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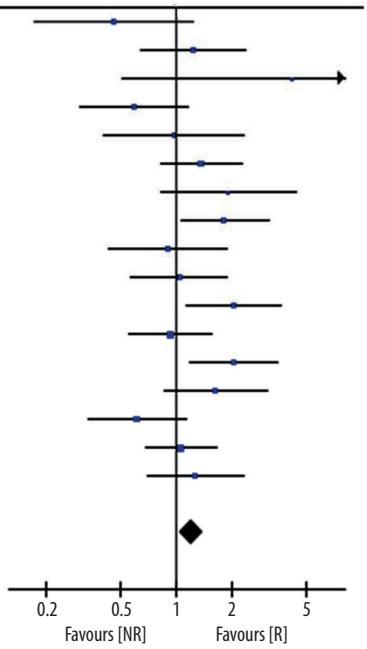
A

Study or subgroup	NR Events	NR Total	R Events	R Total	Weight	Odds ratio M-H, fixed, 95% CI
Alpman et al. 2010	6	6	26	92	4.1%	0.46 [0.17, 1.23]
Dericioglu et al. 2008	26	26	25	100	5.2%	1.24 [0.65, 2.36]
Emich-Widera et al. 2013	9	9	1	25	0.4%	4.24 [0.51, 35.36]
Emich-Widera et al. 2014	19	19	21	135	7.0%	0.59 [0.31, 1.15]
Ozgon et al. 2008	13	13	16	53	3.2%	0.97 [0.40, 2.32]
Sanchez et al. 2010	40	40	52	178	8.0%	1.37 [0.82, 2.28]
Saygi et al. 2014	19	19	12	60	2.5%	1.90 [0.82, 4.38]
Sayyah et al. 2011	34	34	32	200	5.9%	1.82 [1.06, 3.14]
Seven et al. 2014	17	17	22	83	4.7%	0.91 [0.44, 1.89]
Shahwan et al. 2007	20	20	37	233	6.7%	1.04 [0.57, 1.88]
Siddiqui et al. 2003	55	55	18	115	5.2%	2.04 [1.13, 3.69]
Sills et al. 2005	41	41	32	170	9.5%	0.94 [0.56, 1.56]
Soranzo et al. 2004	73	73	20	136	6.2%	2.05 [1.19, 3.53]
Szoeke et al. 2009a	21	21	34	148	4.3%	1.64 [0.86, 3.13]
Szoeke et al. 2009b	20	20	34	152	8.4%	0.61 [0.33, 1.13]
Tan et al. 2004	75	75	37	208	12.4%	1.06 [0.69, 1.64]
Ufer et al. 2009	44	44	20	130	6.2%	1.27 [0.70, 2.30]
Total (95% CI)		**2414**		**2191**	**100.0%**	**1.20 [1.04, 1.40]**
Total events	532		439			

Heterogeneity: Chi^2=27.61, df=18 (P=0.04); I^2=42%
Test for overall effect: Z=2.43 (P=0.01)



B

Study or subgroup	NR Events	NR Total	R Events	R Total	Weight	Odds ratio M-H, fixed, 95% CI
Alpman et al. 2010	32	76	89	174	3.1%	0.69 [0.40, 1.20]
Dericioglu et al. 2008	86	178	99	200	4.7%	0.95 [01.64, 1.43]
Emich-Widera et al. 2013	51	120	19	50	1.4%	1.31 [0.66, 2.60]
Emich-Widera et al. 2014	152	386	124	270	8.7%	0.76 [0.56, 1.05]
Ozgon et al. 2008	52	88	61	106	2.2%	1.07 [0.60, 1.89]
Sanchez et al. 2010	129	222	185	356	5.9%	1.28 [0.91, 1.80]
Saygi et al. 2014	64	118	64	120	2.4%	1.45 [0.87, 2.41]
Sayyah et al. 2011	123	264	144	400	6.0%	1.55 [1.13, 2.13]
Seven et al. 2014	64	138	82	166	3.9%	0.89 [0.56, 1.39]
Shahwan et al. 2007	104	244	193	466	7.5%	1.05 [0.77, 1.44]
Siddiqui et al. 2003	216	400	99	230	5.7%	1.55 [1.12, 2.15]
Sills et al. 2005	194	460	146	340	9.6%	0.97 [0.73, 1.29]
Soranzo et al. 2004	291	560	120	272	7.6%	1.37 [1.02, 1.83]
Szoeke et al. 2009a	69	128	135	296	3.7%	1.39 [0.92, 2.11]
Szoeke et al. 2009b	109	266	140	304	7.6%	0.81 [0.58, 1.13]
Tan et al. 2004	343	802	189	416	14.0%	0.90 [0.71, 1.14]
Ufer et al. 2009	173	376	86	206	5.9%	1.19 [0.84, 1.68]
Total (95% CI)		**4826**		**4372**	**100.0%**	**1.09 [1.00, 1.18]**
Total events	2252		1964			

Heterogeneity: Chi^2=30.60, df=16 (P=0.02); I^2=48%
Test for overall effect: Z=1.94 (P=0.05)

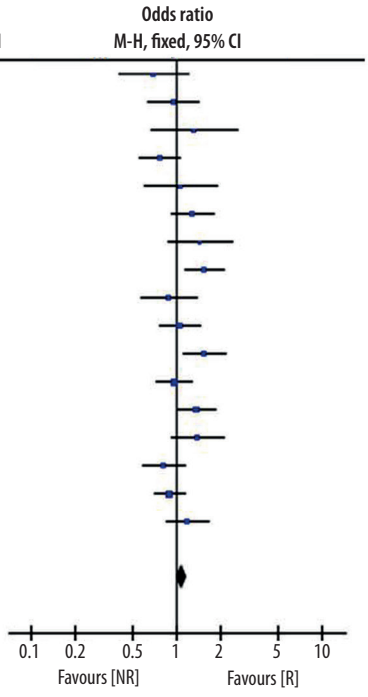


Figure 2. Forest plot of C3435T polymorphism of the ABCB1 gene and drug resistance in epilepsy in Caucasian population, the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95%CI. (**A**) C *vs.* T; (**B**) CC *vs.* CT+TT.

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was not significantly correlated with drug resistance in epilepsy (Table 2). Subgroup analyses were performed in accordance with the race of the study subjects There was significant heterogeneity among the studies examining Asian populations (I^2=–76%, P<0.001); therefore, a random-effects model was used to pool OR values, producing a pooled OR value of 1.03 (95% CI: 0.84–1.26, P=–0.77) in allele model and 0.90 (95% CI: 0.70–1.17, P=–0.43) in genotype model (Table 2). There was no heterogeneity among studies examining Caucasian populations (I^2=42%, P=0.04); therefore a fixed-effects model was utilized to merge the OR values. We found in Caucasian populations there are significant differences between resistance group and control group in both allele model (C *vs.* T: OR=1.07; 95%CI: 0.95–1.19) and in genotype model (CC *vs.* CT+TT: OR=1.05; 95%CI: 0.89–1.24, P=0.55, Table 2 and Figure 2).

Quality analyses of the included studies

Sensitivity analysis

We deleted 1 study from the overall pooled analysis each time to check the influence of the removed data set on the overall ORs. The pooled ORs and 95% CIs were not significantly altered when any part of the study was omitted, which indicated that this study exhibited relatively good stability.

Analysis of publication bias

Funnel plot and Egger's test were performed to assess the publication bias of the literatures. Symmetrical funnel plots were obtained in the SNP tested in all of the models. Egger's test further confirmed the absence of publication bias in this meta-analysis (P>0.05) (Figure 3). Similarly, additional analyses of the studies included in the examined genetic models and subgroups revealed no significant publication bias, indicating that the study results were relatively creditable.

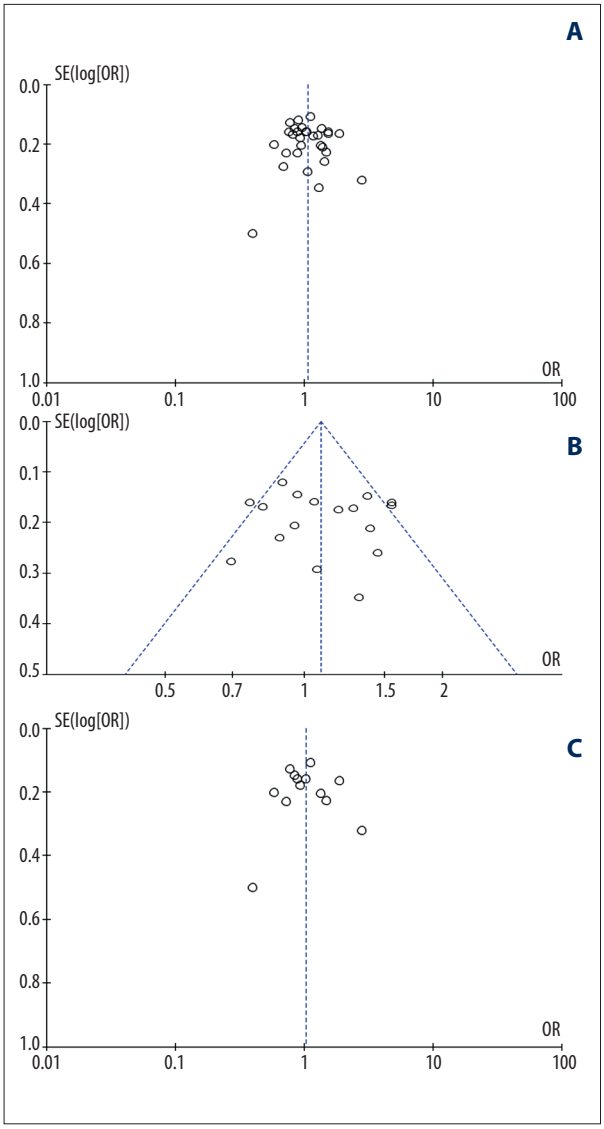

Figure 3. Begg's funnel plot for publication bias tests. Each point represents a separate study for the indicated association. Log or represents natural logarithm of OR. Vertical line represents the mean effects size. (**A**) In total; (**B**) in Caucasian population; (**C**) in Asian population.

Discussion

In the present study, we found that the C3435T polymorphism was associated with AEDs in Caucasian populations. This meta-analysis collected 28 publications addressing the relationship between the ABCB1 C3435T polymorphism and drug resistance in epilepsy. However, the results were contradictory. The C3435T polymorphism of ABCB1 gene was the first single-nucleotide polymorphism that was reported to be associated with drug resistance in epileptic patients [6]. In this report, the CC genotype of this polymorphism was found to be significantly higher in patients with drug-resistant epilepsy, whereas the TT genotype was significantly lower in the same group [6]. However, several studies failed to confirm the association between the C3435T polymorphism and drug-resistant epilepsy. In this meta-analysis, only 6 studies produced positive results [6–11], and in the remaining 24 studies no correlation was found between the C3435T polymorphism and drug resistance in epilepsy. Meta-analysis results showed no statistically significant correlation between the ABCB1 C3435T polymorphism and drug resistance in epilepsy in analyses of either the allele model or genetic model in the total population. Furthermore, subgroup analyses organized in accordance with subjects' racial groups (Asian or Caucasian) revealed positive correlations between this polymorphism and drug resistance in epilepsy in Caucasian populations but not in Asian populations.

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In the present study, we found significant heterogeneity among each study, primarily because of 3 factors. 1) The specific pathogenic gene *loci* that cause differences in ABCB1 function remain unclear; and 2) various included studies involved different uses of AEDs. For instance, certain included studies involved AED monotherapies, whereas others included investigations with combination therapies. Among the currently known AEDs, phenytoin, levetiracetam, lamotrigine, and phenobarbital are all transported by P-gp in the human body. In contrast, valproic acid is not transported by P-gp; thus, if valproic acid was administered to many of the examined patients, it may be difficult to accurately determine whether the ABCB1 C3435T polymorphism is truly correlated with drug resistance in epilepsy. 3) Currently, there is no universally accepted definition of drug resistance in epilepsy. Siddiqui et al. [6] defined drug resistance in epilepsy as the occurrence of at least 4 seizures during the year prior to a subject's enrollment despite the use of at least 3 appropriately selected AEDs at these drugs' maximum tolerated doses. Because different researchers used different criteria, certain patients who would have been classified into the therapeutically effective group by the aforementioned definition were instead classified into the drug resistance group in certain studies. This difference in patient categorization is also an important reason for the different results of various studies.

Conclusions

The current meta-analysis only confirmed the existence of significant correlations between this polymorphism and drug resistance in epilepsy in Caucasian populations. However, our results should be verified by a case-control study with larger sample size.

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