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

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 pharmaco-resistance 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.
Table 1. The characteristics of included studies.

| Authors       | Publication year | Country  | Number of Subjects | 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|
| Szoke et al.  | 2009a            | Australia| 64                | 148 |    | 21 | 27 | 16 | 34 | 67 | 47 |    | 69 | 59 | 135| 161|
| Szoke et al.  | 2009b            | Scotland | 133               | 152 |    | 20 | 69 | 44 | 34 | 72 | 46 |    | 109| 157| 140| 164|
| Szoke et al.  | 2009c            | 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 | 22 | 100| 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|
| Dericioglu 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.
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.

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.

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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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.
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.

**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.
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 enrolment 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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