ABCC2 Polymorphisms and Haplotype are Associated with Drug Resistance in Chinese Epileptic Patients

Jian Qu,¹ Bo-Ting Zhou,^{1,2} Ji-Ye Yin,¹ Xiao-Jing Xu,¹ Ying-Chun Zhao,³ Guang-Hua Lei,⁴ Qiang Tang,⁵ Hong-Hao Zhou¹ & Zhao-Qian Liu¹

¹ Institute of Clinical Pharmacology, Hunan Key Laboratory of Pharmacogenetics, Central South University Xiangya School of Medicine, Changsha, China

² Department of Pharmacy, Xiangya Hospital, Central South University, Changsha, China

³ Laboratories of Functional Genomics and Proteomics, Creighton University Medical Center, Omaha, NE, USA

⁴ Department of Orthopaedics, Xiangya Hospital, Central South University, Changsha, China

⁵ Department of Pharmacy, the Third Hospital of Huaihua City, Huaihua, China

Keywords

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Correspondence

Zhao-Qian Liu, Institute of Clinical Pharmacology, Hunan Key Laboratory of pharmacogenetics, Central South University Xiangya School of Medicine, Changsha, Hunan 410078, China.

Tel: +86-731-84805380;

Fax: +86-731-82354476;

E-mail: liuzhaoqian63@126.com

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The first three authors contributed equally to this work.

SUMMARY

Aims: Some study found that ATP-binding cassette (ABC) efflux transporters play an important role in antiepileptic drug resistance, especially *ABCB1* and *ABCC2*. The aims of this study were to evaluate the relationship between the genetic polymorphisms of *ABCC2* and *ABCB1* and the therapeutic efficacy of antiepileptic drugs (AEDs) in Chinese epileptic patients. **Methods:** *ABCB1* rs1045642 (3435C>T) and *ABCC2* rs717620 (-24C>T), rs3740066 (3972C>T), and rs2273697 (1249G>A) polymorphisms loci in 537 Chinese epilepsy patients (217 drug resistant patients and 320 drug responders) were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). **Results:** *ABCC2* rs717620 -24TT genotype was significantly associated with drug resistant epilepsy (odds ratio [OR] = 4.06 [1.79–9.20], $P = 0.001$). The OR values of *ABCC2* rs717620 -24 CT+TT genotypes and *ABCC2* rs3740066 (3972C>T) CT+TT genotypes were markedly higher in drug resistant patients (OR = 1.57 [1.08–2.29], $P = 0.018$; OR = 1.49 [1.02–2.18], $P = 0.038$, respectively) compared with responsive patients. *ABCC2* rs2273697 (1249G>A) and *ABCB1* rs1045642 (3435C>T) polymorphisms were not associated with drug resistant epilepsy. Linkage disequilibrium (LD) test showed that the *ABCC2* rs717620 were in strong LD with rs2273697 ($D' = 0.694$) and rs3740066 ($D' = 0.699$). The frequencies of haplotypes TGT (*ABCC2* -24C>T/*ABCC2* 1249G>A/*ABCC2* 3972C>T) in resistant patients was significantly higher than those in responsive patients (21.0% vs. 14.2%, $P < 0.05$). **Conclusion:** *ABCC2* -24C>T, 3972C>T polymorphisms and one *ABCC2* haplotype is associated with AED resistance; *ABCC2* 1249G>A and *ABCB1* 3435C>T polymorphisms are not associated with AED resistance in our study. These data suggest that *ABCC2* polymorphisms and haplotype may affect the response of antiepileptic drugs.

Introduction

Epilepsy is a chronic neurological illness, in which abnormal electrical activity in the brain causes involuntary changes in body movement, function, sensation, or behavior [1]. The World Health Organization estimates that epilepsy affects approximately 50 million people worldwide. Now-a-days, we recognize that genetic factors play an even more important role in the pathogenesis of epilepsy and drug efficacy than previously appreciated [1, 2]. Approximately, every second epileptic patient became resistant to the initial drugs [3]. Why so many epileptic patients show resistance against the antiepileptic drugs (AEDs) is not well-understood. Some potential mechanisms have been suggested with regard to the targets and transporters of the drugs. The voltage-gated ion

channels are targets of some AEDs; alternations in the composition and functionality of them may lead to resistance in epileptic patients [4, 5]. The overexpression of ATP-binding cassette (ABC) efflux transporters in the blood-brain barrier (BBB), causing low-drug concentration at their target, may be a potential mechanism [6]. Seizures, exposure to some AEDs such as carbamazepine, and genetic factors may influence the expression of transporters [7–9]. Some ABC transporters such as multidrug resistance 1 (MDR1, p-glycoprotein, *ABCB1*), and a group of multidrug resistance proteins (MRPs, *ABCCs*), have been shown to mediate AEDs in brain [7, 9, 10]. These transporters are expressed in endothelial cells, astrocytes, and neurons of human brain tissues [11]. Therefore, these transporters may influence the efficacy of AEDs.

Initial observation of the relationship between *ABCB1* 3435C>T and drug resistant epilepsy was followed by a number of studies to evaluate the single nucleotide polymorphism (SNP) as a predictor of AED resistance [12, 13]. However, some studies have conversely suggested no association between *ABCB1* polymorphisms and the response to AEDs [14, 15]. Leschziner et al. studied a cohort of 503 epilepsy patients and found no evidence to support that *ABCB1* common variation influences drug withdrawal outcomes [16]. *ABCC2* is one of the ABC efflux transporters, whose role in human brain tissues is not fully understood due to its low expression in normal brain tissues [17]. But some studies found that the expression of *ABCC2* was upregulated in the brain tissues of epileptic patients [18, 19]. Moreover, in the *ABCC2*-deficient rat model, it is found that *ABCC2* is involved in carbamazepine efficacy [20]. Recently, a study found a significant association between *ABCC2* V417I polymorphism and reduced oral bioavailability of talinolol [21]. Kin et al. found that the *ABCC2* 1249G>A, and *ABCB1* 3435C>T, 1236C>T, 2677G>T/A polymorphisms were not associated with AED resistance in Japanese epileptic patients [22]. The study of Ufer et al. showed that a higher risk of AED failure in *ABCC2* -24T allele carriers is possible due to upregulation of *ABCB1*, but the mechanism is unknown [23].

Overall, whether the polymorphisms of these genes are associated with AED resistance is still not clear. To clarify whether *ABCC2* and *ABCB1* genes are involved in drug resistance epilepsy, we investigated the effects of *ABCB1* rs1045642 and *ABCC2* rs717620, rs3740066, and rs2273697 polymorphisms on AED resistance in Chinese epileptic patients.

Methods and Materials

Subjects

A total of 537 Chinese epileptic patients treated with AEDs (326 males, 211 female, mean age: 16.7 ± 11.7 years) from Xiangya hospital, the Second Xiangya Hospital of Central South University, and Hunan Provincial People's Hospital, were recruited in this study. The patients were diagnosed and classified according to guidelines of the International League against Epilepsy. Exclusion criteria included severe adverse drug reactions, unreliable record of seizure frequency, poor compliance with AEDs, history of alcohol or drug abuse, presence of progressive or degenerative neurological or systemic disorders, and hepatic or renal failure. A standardized questionnaire was administered to collect demographic details and clinical data such as seizure types and frequency, past medical history, AED history, concomitant drug history, and relevant family history. All patients or their parents gave their written consent to participate in the study. The study protocol was approved by the ethics committee of Xiangya School of Medicine and ethics committee of Institute of Clinical Pharmacology of Central South University. A clinical study admission (the registration number: ChiCTR-TCH-0000813) was approved by Chinese Clinical Trial Register. The patients were considered to be drug-responsive if they had not experienced any type of seizures for a minimum of 1 year after receiving AEDs. Drug resistance was defined as having at least four seizures during the previous year

Table 1 PCR-RFLP assays for genotyping of *ABCC2* and *ABCB1* polymorphisms

Gene	SNPs	Primer sequence	Restriction enzyme
ABCC2	rs 717620 (-24C>T)	5'-taaatggttggaagg-3' 5'-gcttttagaccaattgcacatc-3'	Bpi I
	rs2273697 (1249G>A)	5'-gggcaagaagtgtgtggat-3' 5'-acatcaggttcactgtttctccca-3'	Nco I
	rs 3740066 (3972C>T)	5'-atccttggtctgtccttg-3' 5'-aataatcaggttcactgtttctccac-3'	BsiE I
	rs1045642 (3435C>T)	5'-tgtttcagctgcttattgg-3' 5'-aaggcatgtatgttgccctc-3'	Bsp143 I

while trying at least three antiepileptic medications at maximal tolerated doses [16, 22].

Genotyping

Blood samples (5 mL) for genotyping were obtained with EDTA through the venipuncture used for pharmacokinetic monitoring and frozen at -80°C for 24 h. DNA was isolated using phenol-chloroform extraction method. Genotyping was performed using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. The designed primer pairs for *ABCB1* rs1045642 and *ABCC2* rs717620, rs3740066, and rs2273697 loci were summarized in Table 1. Each genotyping was performed in a blinded manner. Automatic sequencing was performed for randomly selected DNA samples from patients.

Statistical Analysis

The SPSS software package (version 13.0 for Windows; SPSS, Chicago, IL, USA) was used for statistical analysis. Hardy-Weinberg equilibrium was analyzed with χ^2 test or Fisher's Exact test as applicable in the studied sample. Age was compared between responsive and nonresponsive patients with the Student's *t*-test. Sex and other characteristics about patients are compared with χ^2 test. The relationship between various genotypes and responsiveness was examined by binary logistic regression, after adjustment for age, sex, and seizure type. Linkage disequilibrium and haplotypes were analyzed using SHEsis (<http://analysis.bio-x.cn/myAnalysis.php>) [24, 25]. Statistical significance was accepted when $P < 0.05$.

Results

The study population consisted of 320 AED responders (16.4 ± 12.3 years) and 217 resistant patients (17.0 ± 10.7 years). The most commonly used AED is carbamazepine (65.4%), followed by valproic acid (64.6%), oxcarbazepine (27.7%), phenobarbital (20.9%), lamotrigine (17.7%), phenytoinum natricum (15.8%), topiramate (14.0%), and levetiracetam (11.0%; Table 2).

We determined three SNPs in *ABCC2* in 217 drug resistant patients and 320 drug responders (Table 3). The investigated

Table 2 Demographic and clinical characteristics of patients

Parameters	Drug-responsive (320)	Drug-resistant (217)	Total (537)
Sex (%)			
Male	187 (58.4%)	139 (64.1%)	326 (60.7%)
Female	133 (41.6%)	78 (35.9%)	211 (39.3%)
Age (years)	16.4 ± 12.3	17.0 ± 10.7	16.7 ± 11.7
AEDs used in patients (%)			
Carbamazepine	215 (68.1%)	136 (62.7%)	351 (65.4%)
Valproic acid	168 (52.5%)	159 (73.3%)	347 (64.6%)
Phenytoinum	46 (14.4%)	39 (18.0%)	85 (15.8%)
Phenobarbital	54 (16.8%)	68 (31.3%)	112 (20.9%)
Lamotrigine	39 (12.2%)	56 (25.8%)	95 (17.7%)
Levetiracetam	23 (7.20%)	36 (16.6%)	59 (11.0%)
Topiramate	43 (13.4%)	32 (14.7%)	75 (14.0%)
Oxcarbazepine	70 (21.9%)	78 (36%)	148 (27.7%)
Seizure type (%)			
Partial	125 (39.0%)	79 (36.4%)	204 (38.0%)
Generalized	155 (48.4%)	115 (53.0%)	270 (50.3%)
Nonclassifiable	40 (12.6%)	23 (10.6%)	63 (11.7%)
Etiology (%)			
Idiopathic	121 (37.8%)	75 (34.6%)	196 (35.1%)
Symptomatic	85 (26.6%)	64 (29.5%)	149 (31.0%)
Cryptogenetic	114 (35.6%)	78 (35.9%)	192 (33.9%)

SNPs were all in Hardy–Weinberg equilibrium. The OR values in patients with *ABCC2* –24TT genotype or CT+TT genotypes were significantly higher in drug-resistant patients than those in drug responders (OR = 4.06 [1.79–9.20], $P = 0.001$; OR = 1.57 [1.08–2.29], $P < 0.01$). The *ABCC2* rs2273697 (1249G>A) polymorphism was not significantly associated with drug resistance after subjects were adjusted for sex, age, and seizure type. The OR value in patients with *ABCC2* 3972 CT+TT genotypes were also higher in drug-resistant patients than that in drug respon-

Figure 1 The linkage disequilibrium of three SNPs in *ABCC2* in all patients. Linkage disequilibrium between pairs of polymorphisms is shown in diamonds (D-prime), with darker shading indicating greater D-prime.

ders (OR = 1.49 [1.02–2.18], $P = 0.038$). In an independent cohort of young responders and nonresponders, the CT or TT genotypes were overrepresented in nonresponders group (OR = 1.95 [1.11–3.43], $P = 0.020$; OR = 3.30 [1.29–8.40], $P = 0.013$; data not shown). We did not observe any significant differences in *ABCB1* rs1045642 (3435C>T) SNP between drug resistant patients and responders. After adjusted with age, sex, seizure types, the OR values in *ABCB1* 3435TT homozygous and 3435 CT+TT genotypes are 1.04 (0.587–1.85, $P = 0.888$) and 1.02 (0.696–1.48, $P = 0.936$), respectively.

The linkage disequilibrium test of three SNPs in *ABCC2* was shown in Figure 1. Rs717620 and rs2273697 were in strong

Table 3 Genotype frequencies of four SNPs in *ABCC2* and *ABCB1* genes in responsive (n = 302) and resistant patients (n = 217)

Gene	SNP rs#	Drug-resistant (n = 217)	Drug-responder (n = 320)	Odds ratio (95%CI)	P-value
<i>ABCC2</i>	rs717620 (–24C>T)	CC 118 (54.4%)	CC 207 (64.5%)	–	–
		CT 77 (35.5%)	CT 103 (32.2%)	1.32 (0.889–1.97)	0.167
		TT 22 (10.1%)	TT 10 (3.10%)	4.06 (1.79–9.20)	0.001
		CT+TT 99 (45.6%)	CT+TT 113 (35.3%)	1.57 (1.08–2.29)	0.018
	rs227369 (1249G>A)	GG 181 (83.4%)	GG 262 (81.9%)	–	–
		GA 35 (16.1%)	GA 56 (17.5%)	0.915 (0.559–1.50)	0.725
		AA 1 (0.500%)	AA 2 (0.600%)	1.68 (0.147–19.0)	0.679
		GA+AA 36 (16.7%)	GA+AA 62 (18.1%)	0.932 (0.573–1.52)	0.777
	rs3740066 (3972C>T)	CC 123 (56.7%)	CC 200 (62.5%)	–	–
		CT 75 (34.6%)	CT 102 (31.9%)	1.41 (0.943–2.10)	0.094
		TT 19 (8.70%)	TT 18 (5.60%)	1.94 (0.939–4.00)	0.073
		CT+TT 94 (43.3%)	CT+TT 120 (37.5%)	1.49 (1.02–2.18)	0.038
<i>ABCB1</i>	rs1045642 (3435C>T)	CC 81 (37.3%)	CC 116 (36.3%)	–	–
		CT 105 (48.4%)	CT 161 (50.3%)	1.01 (0.683–1.50)	0.967
		TT 31 (14.3%)	TT 43 (13.4%)	1.04 (0.587–1.85)	0.888
		CT+TT 136 (62.7%)	CT+TT 204 (63.9%)	1.02 (0.696–1.48)	0.936

Data has been adjusted for age, sex, and seizure type. Homozygous wild-type patients served as the reference group. OR, odds ratio; CI, confidence interval.

Table 4 Frequencies of haplotypes (>1%) containing all polymorphisms in *ABCC2* in responsive (n = 320) and resistant epileptic patients (n = 217)

Haplotype	Frequency		P-value	
	resistant	responsive	Fisher's P value	Pearson's P value
ABCC2				
CGC	0.600	0.657	0.055	0.055
CGT	0.040	0.065	0.086	0.086
CAC	0.074	0.083	0.591	0.591
TGC	0.064	0.042	0.111	0.111
TGT	0.210	0.142	0.003*	0.003*

Polymorphisms are in the same order as in Table 3. All those frequencies <0.01 will be ignored in analysis.

* $P < 0.05$.

linkage disequilibrium (D' -prime = 0.694) and rs717620 and rs3740066 were also in strong linkage disequilibrium (D' -prime = 0.699). The haplotypes (*ABCC2* -24C>T/*ABCC2* 1249G>A/*ABCC2* 3972C>T) test showed that one haplotype frequency in drug resistant group was different from those in drug responsive group (Table 4). The frequency of haplotype TGT (*ABCC2* -24C>T/*ABCC2* 1249G>A/*ABCC2* 3972C>T) in resistant patients was significantly higher than those in responsive patients (21.0% vs. 14.2%, $P < 0.05$).

Discussion

Despite more and more research on AED resistance, we still know little about the mechanism. One possible reason lays on overexpression of multidrug transporter proteins [26]. As described in one review [27], ABC transporters are considered as one of the hottest topics in epileptology. *ABCB1* was regarded as the first factor influencing AEDs in BBB. Similar to *ABCB1*, *ABCC2* expression was also increased in brain-derived endothelial cells from patients with AED resistance [28].

So in the present study, we investigated three SNPs in *ABCC2* and one SNP in *ABCB1* in 537 responsive or resistant epilepsy patients and found that *ABCC2* -24C>T and 3972C>T polymorphisms are associated with AED resistance (Table 3). But we found no association between polymorphisms of *ABCC2* 1249G>A, *ABCB1* 3435C>T and AED resistance. These data may have some conflicts due to reduced activity of *ABCC2* -24T gene product *ABCC2* protein. In one study, the *ABCC2* -24T construct showed an 18.7% reduced activity *in vitro* because of its lower mRNA levels in normal tissues [29]. Ufer et al. also found the association between -24T allele carriers and AED failure in Caucasian. Moreover, they further found that -24C>T genotype did not affect hippocampal *ABCC2* expression but increased *ABCB1* expression [23]. Despite the expression and functional relevance of *ABCC2* in kidney tissue and other cell lines, its condition in BBB or brain tissue still remains controversial. Increased *ABCC2* mRNA and *ABCC2* protein expression in brain-derived endothelial cells from AED resistant patients have been reported [30, 31]. Therefore, it is possible that tissue dependent differential regulation of *ABCC2* expression induces different conditions in hepatic, BBB, or brain tissue [23].

We also find that *ABCC2* 3972 CT>TT genotypes are associated with drug resistance. In another study, it is found that the silent SNP 3972C>T is strongly linked to -24C>T, which is associated with a decreased function of the transporter [32]. In our study, we also investigated the linkage disequilibrium and found strong link between 3972C>T and -24C>T ($D' = 0.699$, Figure 1). Although 3972C>T is a synonymous SNP, we think that it might still have significant function to affect the absorption or excretion of its substrates. One study reported the *in vivo* association of c.3972C>T variant with increased area under the concentration-time curve of irinotecan and its metabolites [33], revealed the functional relevance of this variant for bioavailability of drugs and toxins.

Haenisch et al. observed a significant association of the 1249G>A polymorphism with reduced oral bioavailability of talinolol, presumably as a result of increased *ABCC2* activity [21]. But another study showed that 4171-*ABCC2* (c.1249A) variant indicated reduced carbamazepine transporter activity compared with 417V-*ABCC2* (c.1249G). Interestingly, they found that the 1249G>A showed an association with adverse drug reaction but not with drug efficacy in central nervous system [34]. In this study, we found that there is no association between *ABCC2* 1249G>A polymorphism and AED resistance.

Currently, there are various studies focusing on the relationship between *ABCB1* 3435C>T polymorphism and AED efficacy, but the results have been inconclusive. In some studies, the results were positive [12, 13], but in others, results were negative [15, 16]. Moreover, in some meta-analyses about *ABCB1* 3435C>T, the results were also negative [15, 35]. In a meta-analysis of 23 studies (7,067 patients), no significant association of *ABCB1* alleles, genotypes or haplotypes with the response to treatment was found in the overall population or in each ethnicity subgroup [35]. In a functional study on the polymorphism in the cortex and hippocampus of drug-resistant patients, no association was detected between 3435C>T and 2677G>T/A polymorphisms and *ABCB1* mRNA expression levels [36]. In our study, we did not find any association between 3435C>T polymorphism and AED efficacy either (Table 3).

Now-a-days, more and more studies focused not only on the simple one SNP but also on the haplotypes. We therefore analyzed the haplotypes of the three SNPs. For the first time, we found that there were five haplotypes (>1%), and one haplotype was associated with AED resistance (Table 4). *ABCC2* TGT haplotype frequency is higher in resistant group than in responsive group. Think about of three SNPs' function, 4171-*ABCC2* (c.1249A) variant indicated reduced carbamazepine transporter activity compared with 417V-*ABCC2* (c.1249G); the silent SNP 3972C>T is strongly linked to -24C>T, which is associated with a decreased function of the transporter. We can see that the TGT haplotype really further reduce the transporters activity.

As far as we know, this is the first report about some association between *ABCC2* haplotype and AED efficacy. Patrick Kwan et al. studied a total of 25 tagging SNPs from *ABCC2*, *ABCC5*, and *ABCG2* genes. However, no haplotypes were over 1% frequency, which included all SNPs of the genes associated with drug resistance [37]. Haerian et al. studied *ABCB1* haplotypes on five loci and there were no positive results either [38]. Although so many studies

have been launched on the relationship between ABC transporters and AED resistance, the overall results are inconsistent.

Epilepsy is a complicated disease and most patients were treated with AEDs of varying doses and kinds, making the drug-resistance mechanism extremely complex. Moreover, there is no precise phenotype or definition of drug resistance. Another unfavorable factor for our study is that the study population is limited and modest effects of other SNPs on drug resistance can not be excluded. All these factors contributed to the limitation of our results. Further studies with larger sample size on more related SNPs in different candidate genes are needed to confirm the positive results.

In conclusion, our data revealed that *ABCC2* -24TT or CT+TT genotypes, *ABCC2* 3972 CT+TT genotypes, and one *ABCC2* haplotype is obviously associated with drug resistance in epileptic patients. However, the *ABCC2* 1249G>A polymorphism and

ABCB1 3435C>T polymorphism are not associated with this process.

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Conflict of Interest

The authors declare no conflict of interest.

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