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Association between the polymorphisms in the ATP-binding cassette genes *ABCB1* and *ABCC2* and the risk of drug-resistant epilepsy in a Chinese Han population

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ABSTRACT. Epilepsy is a common disease of the nervous system; approximately 20-30% of all patients with epilepsy are reported resistant to antiepileptic drugs. ABCB1 and ABCC2 are members of ATP-binding cassette transporter (ABC) family that is involved in the excretion of antiepileptic drugs. In this case-control study, we have investigated the role of *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 single nucleotide polymorphisms in antiepileptic drug-resistance in patients with epilepsy. A total of 254 patients with epilepsy (104 drug-resistant and 150 drug-responsive) were recruited from the People's Hospital of Wuhan University between March 2013 and April 2014. The correlation between the demographic, clinical, and genotypic characteristics of the patients and risk of drug resistance was statistically analyzed. Patients with drug-resistant epilepsy were more likely to present symptomatic epilepsy ($\chi^2 = 22.29$, $P < 0.001$) compared to those with drug-responsive epilepsy. The TT genotype of the *ABCB1* rs717620 polymorphism was associated with

a higher risk of drug-resistant epilepsy compared to the CC genotype [odds ratio (OR) = 2.97, 95% confidence interval (CI) = 1.11-8.29]. The TT genotype of *ABCB1* rs717620 was also related with an increased risk of drug-resistant epilepsy (OR = 2.64, 95%CI = 1.03-7.13) compared to the CC+CT genotype in the recessive model. Thus, our study suggests that the *ABCC2* rs717620 polymorphism is associated with resistance to antiepileptic drugs in Chinese patients with epilepsy.

Key words: *ABCB1*; *ABCC2*; Polymorphism; Antiepileptic drugs

INTRODUCTION

Epilepsy is a common disease affecting the nervous system; the estimated prevalence and morbidity rates of epilepsy are approximately 2.1-7.8% and 28.8/100,000 in China (Pi et al., 2014; Tang et al., 2014; Zhou et al., 2014). Epilepsy is caused by super-synchronous discharges from the brain neurons, resulting in sudden and repetitive short bursts of central nervous system dysfunction. Epilepsy is treated mainly by pharmaceutical drugs; while these drugs are effective in controlling the symptoms of ~60% epileptic patients, approximately 20-30% of these patients have been shown to be resistant to antiepileptic drugs (Giussani et al., 2016; Huang et al., 2016). Pharmacogenetic factors may play a key role in individualized sensitivity to antiepileptic drugs. Previous studies have identified several genetic factors that are involved in drug resistance in patients with epilepsy, such as *ABCC2*, *SCN1A*, *SCN2A*, *KCNJ10*, *ATP1A2*, and *ATP1A3* (Escalante-Santiago et al., 2014; Ma et al., 2014; Guo et al., 2015; Qu et al., 2015; Wang et al., 2015).

Multidrug transporters play a major role in the drug resistance mechanism. Lazarowski and Czornyj (2011) reported that overexpression of multidrug transporters could result in excessive transport (and hence, elimination) of antiepileptic drugs from the lesions, thereby influencing the on-site concentration and effect of the drug. The ATP-binding cassette (ABC) family is a multidrug transporter family; ABCB1 (P-glycoprotein, P-gp) is an important member of the ABC family that was among the first to be identified (Begley, 2004). High P-gp expression could result in the transfer of lipid-soluble antiepileptic drugs out of the brain tissue, reducing the concentration of antiepileptic drugs in the blood and decreasing their efficacy (Akamine et al., 2012). ABCC2 is another member of the ABC family that is involved in the excretion of antiepileptic drugs (Urry et al., 2009; Subenthiran et al., 2013b). Single nucleotide polymorphisms (SNPs) in *ABCB1* and *ABCC2* could influence the expression and functions of the resultant proteins, and may be associated with drug resistance in patients with epilepsy. Previous studies have reported a correlation between the *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 polymorphisms and drug resistance in patients with epilepsy; however, the results of these studies are inconsistent (Keangpraphun et al., 2015; Li et al., 2015; Yu et al., 2015; Zhou et al., 2015). In this case-control study, the role of *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 SNPs in the resistance to antiepileptic drugs was investigated in patients with epilepsy.

MATERIAL AND METHODS

Subjects

A hospital-based case-control design was employed in this study. A total of 254

patients with epilepsy were recruited from the People's Hospital of Wuhan University between March 2013 and April 2014. Patients conforming to the following criteria were included in this study: Han Chinese, aged between 5 and 80 years, and confirmed to be epileptic based on the diagnostic criteria provided by the International League against Epilepsy in 1981. Patients without serious adverse reactions, poor drug-use adherence, and end-stage liver or kidney diseases were excluded from the study.

All included patients were administered antiepileptic drugs within one year prior to enrollment. Response to antiepileptic drugs was characterized by a lack of epileptic seizures after drug administration. Resistance to antiepileptic drugs was characterized by at least four episodes of epileptic seizure despite receiving at least three types of antiepileptic drugs over a one-year period prior to the study. Based on the effective treatment criteria, 104 patients showed resistance to antiepileptic drugs, whereas 150 patients showed a positive response to antiepileptic drugs.

The clinical variables, including gender, age, use of antiepileptic drugs, body mass index, type of seizures, and etiology of the disease, were collected from the patient medical records. Written informed consent was obtained from all subjects prior to enrollment. The procedures employed in this study were approved by the Ethics Committee of the People's Hospital of Wuhan University.

DNA extraction and genotyping

Peripheral blood (5 mL) was collected from each subject in vacuum tubes containing 5% ethylenediaminetetraacetic acid. DNA was extracted from these samples using the TIANamp Blood DNA kit (Tiangen, Beijing, China) according to the manufacturer instructions. The *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 polymorphisms were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The forward and reverse primer sequences were designed as for PCR analysis as follows: *ABCB1* rs1045642: 5'-TGTTTTCAGCTGCTTFATGG-3' and 5'-AAGGCATGTATGTTGGCCTC-3'; *ABCB1* rs2032582: 5'-CTGGACAAGCACTGAAAGATAAGA-3' and 5'-TGGCTTTGCTAC TTTCTGTAAGTT-3'; *ABCC2* rs2273697: 5'-GGGCAAAGAAGTGTGTGGAT-3' and 5'-AC ATCAGGTTCACTGTTTCTCCCA-3'; and *ABCC2* rs717620: 5'-TAAATGGTTGGGATGAA AGG-3' and 5'-GCTTTAGACCAATTGCACATC-3'.

The amplification was performed in a 20-μL reaction mixture comprising 2 μL 10X PCR Buffer, 1 μL dNTP (2.5 mM), 0.4 μL forward primer (10 μM), 0.4 μL reverse primer (10 μM), 0.2 μL rTaq enzyme (5 U/μL), 1 μL gDNA, and 15 μL ddH_2O. The *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 polymorphisms were amplified as summarized in Table 1. Restriction digestion was performed using a 20-μL digestion mixture comprising 2 μL 10X PCR buffer, 0.5 μL restriction enzyme, and 10 μL PCR amplified mixture, and 7.5 μL ddH_2O. The enzyme-digested products were electrophoresed on an agarose gel.

Statistical analysis

The differences in demographic and clinical variables between patients and controls were analyzed by the Student *t*-test and chi-square test.

Table 1. Restriction enzymes and PCR conditions for the A*BCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 polymorphisms.

Gene polymorphism	Restriction enzyme	Amplification reaction
ABCB1 rs1045642	*Bpi*I	Initial denaturation at 98°C for 5 min; 36 cycles at 98°C for 30 s, 58°C for 30 s, and 72°C for 30 s; and a final extension at 72°C for 5 min
ABCB1 rs2032582	*Nco*I	Initial denaturation at 98°C for 5 min; 36 cycles at 98°C for 30 s, 54°C for 30 s, and 72°C for 30 s; and a final extension at 72°C for 5 min
ABCC2 rs2273697	*Bsi*EI	Initial denaturation at 98°C for 5 min; 36 cycles at 98°C for 30 s, 56°C for 30 s, and 72°C for 30 s; and a final extension at 72°C for 5 min
ABCC2 rs717620	*Bspl*43I	Initial denaturation at 98°C for 5 min; 36 cycles at 98°C for 30 s, 56°C for 30 s, and 72°C for 30 s; and a final extension at 72°C for 5 min

Departure of the *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs71762 polymorphism genotype frequencies from the Hardy-Weinberg equilibrium (HWE) was calculated using the Pearson χ^2 test. The relationships between the *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs71762 polymorphisms and drug-resistant epilepsy were determined by multiple logistic regression analyses and estimated as the odds ratios (ORs) and 95% confidence intervals (CIs). The data was statistically analyzed using SPSS v.16.0 (SPSS Inc., Chicago, IL, USA). Differences with P values <0.05 were considered statistically significant.

RESULTS

The demographic and clinical variables of the investigated subjects are summarized in Table 2. The mean age of patients with drug-resistant and drug-responsive epilepsy was 7.60 ± 15.82 and 7.2 ± 16.14, respectively. Patients with drug-resistant and drug-responsive epilepsy included 61 (58.65%) and 84 (56.00%) males and 43 (41.35%) and 66 (44.00%) females, respectively. Patients with drug-resistant epilepsy were more likely to present symptomatic epilepsy ($\chi^2 = 22.29$, $P < 0.001$) compared to those with drug-responsive epilepsy. We found no significant differences between the age ($t = 0.20$, $P = 0.42$), age at first onset ($t = 1.49$, $P = 0.07$), gender ($\chi^2 = 0.18$, $P = 0.67$), and type of seizures ($\chi^2 = 3.54$, $P = 0.17$) in the two groups.

Table 2. Demographic and clinical variables of epileptic patients.

Variables	Drug-resistant (N = 104)	%	Drug-responsive (N = 150)	%	Chi-square test	P value
Mean age, years	7.60 ± 15.82		7.2 ± 16.14		0.20	0.42
Age at first onset, years	2.15 ± 2.70		2.65 ± 2.58		1.49	0.07
Gender						
Male	61	58.65	84	56.00		
Female	43	41.35	66	44.00	0.18	0.67
Type of seizures						
Simple partial	24	23.08	29	19.33		
Complex partial	26	25.00	26	17.33		
Generalized	54	51.92	95	63.33	3.54	0.17
Etiology						
Idiopathic	49	47.12	114	76.00		
Symptomatic	55	52.88	36	24.00	22.29	< 0.001

The genotypic distributions of the *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 polymorphisms are summarized in Table 3. The CC, CT, and TT genotypes of *ABCC2* rs717620 were significantly different between the drug-responsive and drug-resistant epilepsy groups ($\chi^2 = 6.01$, $P = 0.04$). However, no significant differences were found in the genotypic frequencies of *ABCB1* rs1045642 ($\chi^2 = 1.61$, $P = 0.45$) and rs2032582 ($\chi^2 = 0.22$, $P = 0.90$) and *ABCC2* rs2273697 ($\chi^2 = 0.24$, $P = 0.89$) between the two study groups.

Table 3. Genotype frequencies of *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 polymorphisms.

Genotypes	Drug-resistant (N = 104)	%	Drug-responsive (N = 150)	%	χ^2	P value	χ^2 for HWE		P value	
							Drug-resistant	Drug-responsive	Drug-resistant	Drug-responsive
rs1045642										
CC	43	41.35	61	40.67						
CT	48	46.15	77	51.33						
TT	13	12.50	12	8.00	1.61	0.45	0.005	0.94	3.34	0.07
rs2032582										
GG	35	33.65	54	36.00						
GT/GA	53	50.96	72	48.00						
TT/TA	16	15.38	24	16.00	0.22	0.90	0.31	0.58	< 0.001	1.00
rs2273697										
GG	79	75.96	112	74.67						
GA	23	22.12	36	24.00						
AA	2	1.92	2	1.33	0.24	0.89	0.05	0.83	0.22	0.64
rs717620										
CC	46	44.23	82	54.67						
CT	43	41.35	59	39.33						
TT	15	14.42	9	6.00	6.01	0.04	0.89	0.35	0.14	0.71

HWE, Hardy-Weinberg equilibrium.

The associations between the *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 polymorphisms and risk of drug-resistant epilepsy are summarized in Table 4. Logistic regression analysis indicated that the TT genotype of *ABCB1* rs717620 was associated with a higher risk of drug-resistant epilepsy compared to the CC genotype (OR = 2.97, 95%CI = 1.11-8.29). The TT genotype of *ABCB1* rs717620 was correlated with an increased risk of drug-resistant epilepsy (OR = 2.64, 95%CI = 1.03-7.13) compared to the CC+CT genotype in the recessive model. However, no significant correlation was found between the *ABCB1* rs1045642 and rs2032582 and ABCC2 rs2273697 polymorphisms and risk of drug-resistant epilepsy.

An analysis of the interactions between the demographic and clinical variables (environment) and the *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 polymorphisms revealed that this interaction did not influence the risk of drug-resistant epilepsy.

Table 4. Association between *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 polymorphisms and risk of drug-resistant epilepsy.

Genotypes	Drug-resistant (N = 104)	%	Drug-responsive (N = 150)	%	OR (95% CI)[1]	P value
rs1045642						
Codominant						
CC	43	41.35	61	40.67	1.0 (Ref.)	-
CT	48	46.15	77	51.33	0.88 (0.50-1.56)	0.65
TT	13	12.50	12	8.00	1.54 (0.58-4.07)	0.33
Dominant						
CC	43	41.35	61	40.67	1.0 (Ref.)	-
CT+TT	61	58.65	89	59.33	0.97 (0.57-1.67)	0.91
Recessive						
CC+CT	91	87.5	138	92	1.0 (Ref.)	-
TT	13	12.5	12	8	1.64 (0.66-4.12)	0.24
rs2032582						
Codominant						
GG	35	33.65	54	36.00	1.0 (Ref.)	-
GT/GA	53	50.96	72	48.00	1.14 (0.63-2.06)	0.65
TT/TA	16	15.39	24	16.00	1.03 (0.44-2.35)	0.90
Dominant						
GG	35	33.65	54	36	1.0 (Ref.)	-
GT/GA + TT/TA	69	66.35	96	64	1.11 (0.63-1.95)	0.70
Recessive						
GG + GT/GA	88	84.61	126	84	1.0 (Ref.)	-
TT/TA	69	15.39	96	64	1.03 (0.67-1.59)	0.89
rs2273697						
Codominant						
GG	79	75.96	112	74.67	1.0 (Ref.)	-
GA	23	22.12	36	24.00	0.91 (0.47-1.71)	0.75
AA	2	1.92	2	1.33	1.42 (0.10-19.90)	0.89
Dominant						
GG	79	75.96	112	74.67	1.0 (Ref.)	-
GA + AA	25	24.04	38	25.33	0.93 (0.50-1.73)	0.81
Recessive						
GG + GA	102	98.08	148	98.67	1.0 (Ref.)	-
AA	2	1.92	2	1.33	1.45 (0.10-20.29)	0.71
rs717620						
Codominant						
CC	46	44.23	82	54.67	1.0 (Ref.)	-
CT	43	41.35	59	39.33	1.30 (0.74-2.29)	0.34
TT	15	14.42	9	6.00	2.97 (1.11-8.29)	0.04
Dominant						
CC	46	44.23	82	54.67	1.0 (Ref.)	-
CT + TT	58	55.77	68	45.33	1.52 (0.89-2.60)	0.10
Recessive						
CC + CT	89	85.58	141	94	1.0 (Ref.)	-
TT	15	14.42	9	6	2.64 (1.03-7.13)	0.02

[1]Adjusted for age, sex and etiology. OR = odds ratio; CI = confidence interval.

DISCUSSION

In this study, we attempted to evaluate the relationship between the *ABCB1* rs1045642 and rs2032582 and *ABCC2* rs2273697 and rs717620 polymorphisms and risk of drug-resistant epilepsy; the results revealed that the TT genotype of the *ABCC2* rs717620 polymorphism is significantly associated with the risk of drug-resistant epilepsy compared to the wild-type genotype.

Multidrug resistant protein 2, encoded by *ABCC2*, is a multidrug transporter distributed in the blood-brain barrier, endothelial cells, astrocytes, and the surfaces of some neurons (König et al., 2013). Multidrug transporters regulate the two-way transfer balance of drugs in the blood and brain tissues to influence the drug concentration in the brain tissue, thereby influencing its resistance to antiepileptic drugs (Glauser and Pippenger, 2000). Previous studies have indicated that multidrug transporters could influence the efficacy of antiepileptic drugs (Zimprich et al., 2004; Ufer et al., 2009). Therefore, the *ABCC2* expression could influence the mechanism of transport of antiepileptic drugs in the brain tissues (Nies et al., 2004). A SNP is an insertion, deletion, or substitution of nucleic acid bases leading to a polymorphism in the gene sequence (Friedberg, 2003). Genetic polymorphisms can change the structure and quantity of the gene product, ultimately affecting the function of the product. Polymorphisms in *ABCC2* could influence the expression of this protein, therein affecting its response or resistance to antiepileptic drugs.

Several previous studies have reported an association between the *ABCC2* rs2273697 and rs717620 polymorphisms and risk of drug-resistant epilepsy, but with conflicting results (Seo et al., 2008; Kwan et al., 2011; Hilger et al., 2012; Qu et al., 2012; Sporis et al., 2013; Subenthiran et al., 2013a; Escalante-Santiago et al., 2014; Ma et al., 2014). Qu et al. (2012) revealed a significant association between the *ABCC2* rs2273697 and rs717620 polymorphisms and resistance to antiepileptic drugs in Chinese epileptic patients. Subenthiran et al. (2013a) indicated a correlation between the *ABCC2* rs2273697 and rs717620 polymorphisms and resistance to antiepileptic drugs in a study comprising 152 and 162 anti-epileptic drug-responsive and -resistant patients, respectively (Subenthiran et al., 2013a). Ma et al. (2014) reported a possible correlation between the *ABCC2* rs2273697 polymorphism and resistance to antiepileptic drugs in 453 Chinese Han patients with epilepsy. However, other studies have reported that the *ABCC2* rs2273697 and rs717620 polymorphisms were not associated with resistance to antiepileptic drugs (Seo et al., 2008; Kwan et al., 2011; Hilger et al., 2012; Sporis et al., 2013). In this study, we reported a significant correlation between the *ABCC2* rs717620 polymorphism and resistance to antiepileptic drugs. The discrepancies among these results may be attributed to differences in the sample populations and sizes, etiology of epilepsy, and patient selection criteria.

The results of this study are subject to two limitations. First, the patients were selected from a single region in China; therefore, the sample may not be representative of the general population. However, the genotype frequencies of the *ABCB1* and *ABCC2* polymorphisms were in accordance with the HWE, indicating that the samples could be representative of the general population. Second, the sample size was quite small, resulting in low statistical power to compare the differences between groups.

In conclusion, our study suggests that the *ABCC2* rs717620 polymorphism is associated with antiepileptic drug resistance in Chinese patients with epilepsy. Further studies with larger sample sizes and subjects with diverse ethnic backgrounds are required to confirm the mechanism by which the *ABCB1* and *ABCC2* polymorphisms resist antiepileptic drugs.

Conflicts of interest

The authors declare no conflict of interest.

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