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ABCB1, ABCC2, SCN1A, SCN2A, GABRA1 gene polymorphisms and drug resistant epilepsy in the Chinese Han population

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Drug resistance is common in epilepsy despite multiple available medications. Single nucleotide polymorphisms (SNP) may influence drug efficacy in epilepsy. We therefore aimed to clarify the association between polymorphisms of several controversial SNP loci and drug resistance in Chinese Han epilepsy patients from central China. Among all the 391 recruited subjects, 235 and 156 patients were classified into a drug responsive and resistant group, respectively, according to the definition of drug resistance proposed by the International League Against Epilepsy. The candidate SNP loci, including ATP-binding cassette (ABC) subfamily gene ABCB1 rs2032582 and rs1045642; ABC subfamily gene ABCC2 rs717620 and rs2273697; sodium channel subunit gene SCN1A rs3812718, SCN2A rs2304016; γ-amino butyric acid type A ($GABA_A$) receptor subunit subtype gene GABRA1 rs2279020 were genotyped following the Illumina protocols. There were no significant differences in allelic or genotypic frequencies between the drug responsive and resistant patients. The polymorphisms of the above SNP loci may not be associated with drug resistance of epilepsy in the Chinese Han population.

1. Introduction

Epilepsy is one of the most common chronic neurological disorders afflicting about 50 million people worldwide (Leach and Abassi 2013). About one third of the patients are expected to develop resistance to antiepileptic drugs (AEDs) even when treated with appropriate and adequate pharmacotherapy (Hirose 2013). The pathogenesis underlying AEDs resistance remains unclear so far. Recent studies suggest that single nucleotide polymorphisms (SNP), namely the allelic and genotypic differences of genes involved in the process of AEDs transportation, metabolism or targeting, may play a role in multiple drug resistance of epilepsy (Steinlein 2010).

ABCB1 and ABCC2 genes belonging to the ATP-binding cassette (ABC) gene family were thought to have effects on AEDs resistance in many previous studies. In Caucasian epilepsy patients, the homozygous CC genotype of ABCB1 rs1045642 was remarkably more common in AEDs resistant patients (Siddiqui et al. 2003). In addition, the allele A of rs2032582 in ABCB1 gene was found to have a significant lower proportion in AEDs resistant patients in the Indian population (Kumari et al. 2011). According to the studies by Ufer et al. also in Caucasian patients, the T allele of ABCC2 rs717620 was confirmed to contribute to AEDs resistance while carriers of the heterozygous GA genotype of ABCC2 rs2273697 were significantly more abundant in AEDs responsive patients (Ufer et al. 2009, 2011). As for the Chinese Han population, the TT genotype at locus ABCC2 rs717620 was also verified to be risky for AEDs resistance (Qu et al. 2012). On the other hand, however, some consecutive replication studies did not reach the same conclusions as previously reported (Haerian et al. 2011; Saygi et al. 2014; Sporis et al. 2013).

The studies concerning the voltage-gated sodium channel (VGSC) subunit genes were also notable in the past. The homozygous AA genotype at SCN1A rs3812718 was formerly found to be involved in carbamazepine resistance in Japanese epilepsy patients (Abe et al. 2008). In another study, however, rs3812718 gene polymorphism did not show any association with carbamazepine resistance (Sterjev et al. 2012). In a northern Indian population, rs3812718 polymorphism displayed a relationship with seizure susceptibility but not with AEDs resistance (Kumari et al. 2013). In the Chinese Han population, the A allele of SCN2A rs2304016 and one haplotype containing the A allele were implicated in acquiring increased risk for AEDs resistance (Kwan et al. 2008). Whereas in another cohort study in the Indian and Chinese population, the polymorphisms of rs3812718 and rs2304016 were not supportive of the former findings (Haerian et al. 2013).

The homozygous GG genotype and G allele of GABRA1 rs2279020 were found to have a predisposition to both epileptic susceptibility and drug resistance in Indians (Kumari et al. 2010). However, the subsequent cohort study in the Indian patients of mesial temporal lobe epilepsy with hippocampal sclerosis (AEDs resistant) and juvenile myoclonic epilepsy (AEDs responsive) had not retained consistent results (Balan et al. 2013).

Based on the reports of previous studies, a list of SNP loci were found to have associations with AEDs resistance, although

Table 1: Demographic and clinical characteristics of epilepsy patients

Characters	AEDs responsive n = 235	AEDs resistance n = 156	OR(95%CI)	*P-value*
Mean age ± SD (years)	22.36 ± 14.10	22.98 ± 11.21	–	0.644
Gender				
Male	144	103	1.228(0.805−1.874)	0.340
Female	91	53		
Number of drugs taken at clinic[a]				
Monotherapy	189(80.4%)	22(14.1%)		
2 drugs in combination	46(19.6%)	122(78.2%)	–	–
3 drugs in combination	0	12(7.7%)		
Seizure types				
Simple partial	6(2.6%)	3(1.9%)	1.276(0.299−5.444)	0.742
Complex partial	62(26.3%)	50(32.0%)	2.508(1.166−3.633)	0.013
Secondarily generalized	93(39.6%)	74(47.4%)	2.030(1.199−3.439)	0.008
Generalized	74(31.5%)	29(18.6%)	reference	–
Age at the onset (years)	14.50 ± 9.66	16.48 ± 13.10	–	0.106
Epilepsy duration(years)	5.90 ± 6.63	8.48 ± 6.94	–	0.001
Initial seizure frequency				
Daily	25(10.6%)	29(18.6%)	reference	–
> 1/week	11(4.7%)	24(15.4%)	1.881(0.771−4.589)	0.165
1-4/month	71(30.2%)	70(44.9%)	0.850(0.453−1.594)	0.612
< 1/month	111(47.2%)	30(19.2%)	0.233(0.119−0.455)	< 0.001
< 1/half a year	17(7.2%)	3(1.9%)	0.152(0.040−0.580)	0.006

OR = odds ratio; CI = confidence interval; [a] The AEDs currently taken by patients at the clinic included carbamazepine, oxcarbazepine, valproate, phenytoin, phenobarbital, topiramate, lamotrigine and levetiracetam.

discrepancies were detected in later consecutive studies. We therefore intended to investigate the association between the polymorphisms of the above SNP loci and AEDs resistance in Chinese Han epilepsy patients for further elucidation.

2. Investigations and results

The patients were classified into an AEDs resistant and responsive group. Genotyping of selected SNP loci was following the Illumina protocols with genotyping call rate >98%. The details of demographics and clinical characteristics of subjects are listed in Table 1. For all the studied controversial SNP loci, we have found no significant differences in allelic and genotypic frequencies between AEDs resistant and responsive patients (Table 2). The genotypic distributions were in accordance with Hardy-Weinberg equilibrium except that in drug responsive patients, the genotypes of rs1045642 in ABCB1 were found to exhibit deviation ($P < 0.05$).

3. Discussion

AEDs resistance in epilepsy is quite complicated and may be caused by many factors, while genetic polymorphisms are believed to be one important factor influencing AEDs efficacy. Over-expression of the multidrug transporter (MDT) gene may bring about lower effective drug concentrations by inducing both excess efflux and reductive uptake of AEDs. P-gp encoded by ABCB1 was initially recognized in resistance to antitumor chemotherapy and its activity in the blood brain barrier (BBB) to reduce the concentrations of AEDs in central nervous system was also considerable in treatment of epilepsy (Lazarowski and Czornyj 2011). MRP2 is another ABC exporter protein encoded by ABCC2 that plays an analogous role in pumping AEDs out of the BBB transmembrane. Both P-gp and MRP2 were detected to be up-regulated in sclerotic hippocampal specimens from AEDs resistant temporal lobe epilepsy patients, indicating that these two proteins may be involved in the therapeutic outcomes of AEDs (Aronica et al. 2004).

For ABCB1, the allele change of T to A at rs2032582 in the missense area, may cause substitution of amino acids from Ser to Thr and influence the structures and functions of the P-gp. The synonymous substitution of rs1045642 although without changed amino acid sequence may still influence the three dimensional structure of P-gp. The rs717620 and rs2273697 of ABCC2 are located in UTR-5 and missense regions respectively and both may be quite essential for encoding the functional MRP2 protein. The genotypic proportions of rs1045642 and rs717620 of ABCB1, rs2273697 of ABCB2 of our data were in agreement with a previous study also in the Chinese Han population (Qu et al. 2012). Our outcome of more TT genotypes at rs1045642 in drug resistant patients was consistent with the previous two studies in the Asian populations from HongKong (Kwan et al. 2007) and Japan (Seo et al. 2006) but contrasted with the findings in Caucasian population, which suggesting the higher CC genotype proportion associated with AEDs resistance (Siddiqui et al. 2003). A summary contrasting the studies about ABCB1 rs1045642 polymorphism in different ethnic groups of epilepsy patient is given in Table 3. The Hardy-Weinberg deviation of rs1045642 in drug responsive patients may be caused by hidden stratification or linkage disequilibrium (LD) with other SNP loci because rs1045642 fell within an extensive block of LD spanning from exon 12 to exon 26, or even farther regions (Siddiqui et al. 2003). LD with some other causal but unknown variant located on the same LD-block or a certain haplotype associated with AEDs responsiveness may probably allow the deviation to occur.

Carbamazepine, oxcarbazepine, lamotrigine and phenytoin would suppress the neuronal excitability by blocking effects of VGSCs. It is a reasonable hypothesis that change in the SCN1A and SCN2A genes that encode VGSCs may let the AEDs resistance coming to being. The two SNP loci we studied are both the intron-variants that playing quite complicated roles in gene function such as the alternative splicing of mRNA. The distribution trends of genotypic and allelic frequency of rs3812718

Table 2: Polymorphisms analysis of ABCB1, ABCC2, SCN1A, SCN2A, GABRA1

Genotype and allele	AEDs responsive n = 235	AEDs resistance n = 156	OR(95%CI)	*P-value*
ABCB1, rs2032582				
CC	68(0.292)	48(0.314)	reference	–
AC	112(0.481)	74(0.484)	0.846(0.427−1.675)	0.631
AA	53(0.227)	31(0.203)	0.515(0.206−1.288)	0.156
C	248(0.532)	170(0.556)	0.910 (0.681−1.216)	0.523
A	218(0.468)	136(0.444)		
ABCB1, rs1045642				
CC	79(0.338)	55(0.355)	reference	–
TC	135(0.577)	80(0.516)	1.107(0.524−1.974)	0.961
TT	20(0.085)	20(0.129)	2.622 (0.899−7.646)	0.077
C	293(0.626)	190(0.613)	1.057(0.787−1.421)	0.711
T	175(0.374)	120(0.387)		
ABCC2, rs717620				
CC	136(0.581)	86(0.551)	reference	–
TC	84(0.359)	61(0.391)	1.188(0.763−1.852)	0.446
TT	14(0.060)	9(0.058)	1.108(0.447−2.743)	0.825
C	356(0.761)	233(0.747)	1.078(0.773−1.502)	0.659
T	112(0.239)	79(0.253)		
ABCC2, rs2273697				
GG	204(0.868)	128(0.821)	reference	–
AG	31(0.132)	26(0.167)	1.612(0.882−2.947)	0.121
AA	0(0.000)[a]	2(0.013)[a]	–	–
G	439(0.934)	282(0.904)	1.507(0.892−2.544)	0.123
A	31(0.066)	30(0.096)		
SCN1A, rs3812718				
AA	80(0.342)	46(0.297)	reference	–
AG	112(0.479)	87(0.561)	1.273 (0.796−2.037)	0.314
GG	42(0.179)	22(0.142)	0.748(0.382−1.468)	0.399
A	272(0.581)	179(0.577)	1.016 (0.759−1.358)	0.916
G	196(0.419)	131(0.423)		
SCN2A, rs2304016				
AA	188(0.800)	127(0.814)	reference	–
AG	46(0.196)	28(0.179)	0.988 (0.569−1.715)	0.965
GG	1(0.004)[a]	1(0.006)[a]	–	–
A	422(0.898)	282(0.904)	1.069(0.661−1.729)	0.785
G	48(0.102)	30(0.096)		
GABRA1, rs2279020				
GG	68(0.291)	46(0.295)	reference	–
AG	126(0.538)	87(0.558)	1.149 (0.706−1.870)	0.575
AA	40(0.171)	23(0.147)	1.005 (0.518−1.950)	0.988
G	262(0.560)	179(0.574)	0.945 (0.708−1.262)	0.701
A	206(0.440)	133(0.426)		

After Bonferroni's method for multiple testing correction, $P < 0.007$ would be significant; OR = odds ratio; CI = confidence interval. [a] Not analyzed due to low frequency.

and rs2304016 conformed to the previous studies in the Asian population (Kwan et al. 2008), but our findings did not support the associations of SCN1A and SCN2A polymorphisms with AEDs resistance.

γ-Amino butyric acid (GABA) is the most important inhibitory neurotransmitter in the brain. The GABA type A ($GABA_A$) receptor is also an inviting target of AEDs and is confirmed to be associated with AEDs efficacy by its suppression of postsynaptic potentials and reduction of neuronal firing through chloride ion channel (Hines et al. 2012). Multiple AEDs, such as benzodiazepines, phenobarbital, lamotrigine, topiramate and valproate, were believed to enhance the inhibition effects. For polymorphism analysis of GABRA1 that encodes the subunit of $GABA_A$ receptor, the G allele of rs2279020 was notably the major allele according to our data and the genotypic distributions were different from those formerly reported in Indian population, in which G was presented as the minor allele (Kumari et al. 2010; Balan et al. 2013). Our results did not support the association of AEDs resistance with GABRA1 rs2279020.

Except for the ethnic variance, the inconsistent results may be brought about by varied definition of drug resistant epilepsy. Siddiqui et al. (2003) and Seo et al. (2006) defined drug resistance as seizures more than four times a year under more than three appropriate drugs. In the study of Kwan et al. (2007) an average of one seizure or more per month over the previous year despite treatment with two or more AEDs were classified as drug resistance. Moreover, drug resistance was accepted as a less than 50% reduction in seizure frequency in the preceding year in study of Shahwan et al. (2007). We here used the definition proposed by ILAE for classification, which may be hopefully recommended in the future to minimize the differences of recruiting criteria.

It is worth noting that the early onset age and frequent seizures before treatment may be two poor prognostic factors as the data showed in our study. This may be explained by the lack of neuronal plasticity in older patients which may be essential for the development of AEDs resistance. The neuronal loss along with mossy fiber sprouting caused by repeated seizures may on the

Table 3: A comparison of ABCB1 rs1045642 polymorphism analysis in different ethnic groups

Population	First Author	Number of patients			Seizure Types	Findings	Year
		Responsive	Resistant	Healthy			
British	Siddiqui	110	187	200	Various	More CC genotypes in drug resistant patients	2003
Australians	Tan	208	401	–	Various	Lack of associations	2004
Middle European	Zimprich	–	193	226	TLE	More homozygous carriers of the CGC haplotype in drug resistant patients	2004
Japan	Seo	84	126	–	Various	More T allele and TT genotypes in drug resistant patients	2005
Korean	Kim	108	63	–	Various	Lack of associations	2006
Chinese Han(HK)	Kwan	297	221	179	Various	More TT genotypes in drug resistant patients	2007
Irish	Shahwan	242	198	–	Various	Lack of associations	2007
Indian	Lakhan	231	94	101	Various	Lack of associations	2008
Turkish	Dericioglu	–	89	100	Partial	Lack of associations	2008
Spanish	Sanchez	178	111	–	Various	Lower risk of drug resistance with TT genotypes in adults	2010
Chinese Han(Western)	Dong	193	157	368	Various	Lack of associations	2011
Macedonians	Sterjev	94	68	–	Various	Enriched T allele in CBZ-responsive patients with higher maintenance doses	2012
Poles	Emich-Widera	25	60	100	Various	Lack of associations	2013

TLE = Temporal lobe epilepsy; CBZ = Carbamazepine

other hand contribute to drug resistance (Mohanraj and Brodie 2013).

According to our study, the polymorphisms of the above discussed SNP loci are not associated with AEDs resistance of epilepsy in Chinese Han population. The drug resistance in epilepsy is quite complicated and cannot be explained by only one or two factors. It may still be quite important to conduct multicenter studies on a large-scale by using the consensus definition of drug resistant epilepsy for consolidation and explore new findings in the foreseeable future.

4. Experimental

4.1. Subjects

All patients were recruited from the Department of Neurology, Xiangya Hospital, Central South University, in the central area of China from March, 2011 to November, 2013. The patients were classified according to the consensus definition of AEDs resistance proposed by International League Against Epilepsy (ILAE). The failure of continuous seizure freedom after adequate treatment of two tolerated and appropriately used AEDs (monotherapies or in combination) may be defined as drug resistant, while drug responsiveness may be considered as complete seizure freedom for a minimum of three times the longest interseizure interval before treatment, or one year (the longer) (Kwan P, et al. 2010). Among the total recruited 391 patients, 235 were classified into AEDs responsive group and the other 156 were classified into AEDs resistant group. The study protocol was approved by the Ethics Committee of Xiangya Hospital. All patients were informed about the study with written consent before evaluation. Patients would be excluded if one of the followings occurred: (a) undefined drug responsiveness; (b) alcohol or drug abuse; (c) poor compliance with AEDs, severe adverse drug reaction, unreliable seizure records, pseudoseizures; (d) brain tumor, vascular malformation, severe traumatic lesions; (e) severe systemic diseases.

4.2. SNP loci selection and genotyping

The controversial SNP loci including rs2032582 and rs1045642 of ABCB1, rs717620 and rs2273697 of ABCC2, rs3812718 of SCN1A, rs2304016 of SCN2A and rs2279020 of GABRA1 were selected for polymorphism analysis. Peripheral venous blood of each patient (5 ml) was collected at the clinic and the genomic DNA was extracted following phenol-chloroform methodology. Genomic DNA was then quantified by NanoDrop 2000c (Thermo Scientific, Waltham, MA, USA). Genomic DNA of each subject (250 ng) was used for genotyping of the selected gene SNP loci through the BeadChip scanning and GoldenGate assay following the Illumina (Illumina,Inc., San Diego, CA, USA) protocols on the custom panel. All these SNP loci had an Illumina SNP score of > 0.6 as the prerequisite for genotyping. Genotype callings were made using llllmina BeadScan and GenomeStudio softwares.

4.3. Statistical analysis

SPSS software package version 21.0 (SPSS, Inc., Chicago, IL, USA) was used in the statistical works. The genotypic distributions, seizure types and frequencies between two groups were analyzed using the binary logistic regression. The differences in age, epilepsy onset and duration were valued using the independent samples t-test meanwhile differences in sex, allelic frequencies and Hardy-Weinberg equilibrium were assessed using chi-square test. Bonferroni's method was used for multiple testing correction. $P < 0.05$ would be significant in all aspects.

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