Neurology Asia 2015; 20(3) : 221 – 227

Lack of association between *ABCC2* polymorphisms and plasma carbamazepine concentrations or pharmacoresistance in Chinese patients with epilepsy

*[1]Zhuo Wan, *[2]Hongmei Meng, [1]Yan Bai, [1]Yi Bai, [1]Yang Dong, [1]Min Liang, [1]Yingjie Guo
*These authors contributed equally to this work.

[1]School of Life Sciences, Jilin University, Changchun; [2]The First Hospital of Jilin University, Changchun, China

Abstract

Multidrug resistance proteins (MRP2, ABCC2) may play a role in drug resistance in epilepsy by limiting gastrointestinal absorption and brain access of antiepileptic drugs (AEDs). We sought to investigate the effects of *ABCC2* polymorphisms on plasma carbamazepine (CBZ) concentrations and pharmacoresistance in Chinese patients with epilepsy. *ABCC2* rs717620, rs2273697, rs3740066 polymorphisms were genotyped by polymerase chain reaction amplification followed by restriction fragment length polymorphism analysis or direct automated DNA sequencing in 80 patients treated with CBZ monotherapy. There were no differences in CBZ maintenance doses or adjusted plasma CBZ concentrations among the *ABCC2* rs717620, rs2273697 and rs3740066 genotypic groups. No associations between all the studied genotypes and haplotypes involving the three SNPs of *ABCC2* and CBZ resistance were observed in this patient cohort. These results suggest that *ABCC2* polymorphisms may not contribute to interindividual variabilities in CBZ daily maintenance doses, plasma concentrations, and treatment efficacy.

INTRODUCTION

Carbamazepine (CBZ) is one of the most frequently prescribed anticonvulsant drugs for the treatment of epileptic seizures. Wide variabilities of CBZ daily maintenance doses, plasma concentrations, and treatment efficacy have been observed among patients treated with this agent.[1] There is evidence that drug efflux transporters may play a role in drug-resistant epilepsy by limiting gastrointestinal absorption and brain access of antiepileptic drugs (AEDs).[2] Therefore, genetic variants of drug transporter genes associated with functional variations in efflux activity may influence CBZ plasma concentration and treatment efficacy.

Drug transporters are members of the membrane transport protein families belonging to either ATP-binding cassette (ABC) or solute-linked carrier super family of proteins. Among them, P-glycoprotein (P-gp), encoded by ABCB1 (or MDR1), is an extensively studied drug efflux transporter in epilepsy.[3,4] Although it remains equivocal whether CBZ is a substrate of P-gp,[3,5] numerous studies have explored the role of *ABCB1* polymorphisms on the drug response in different ethnicities.[6-8]

Recently, multidrug resistance proteins (MRP2, ABCC2), have been shown to mediate CBZ transport.[9] Increased expressions of ABCC2 have been observed in brain tissues of patients with refractory epilepsy.[10,11] It was hypothesized that genetic variations in the *ABCC2* gene would probably affect individual drug responses to CBZ. *ABCC2* rs717620, rs2273697 and rs3740066 are the major functional genetic variants, which have been characterized for their influence on the respective mRNA, protein expression, or oral clearance of drug substrates.[12] Choi *et al*. showed that the combined variation of rs1885301and rs717620 decreased *ABCC2* promoter activity by 39%.[13] Laechelt *et al*. demonstrated both a decrease and an increase in ABCC2 expression or activity with different haplotypic combinations of rs717620, rs2273697 and rs3740066[14], which is supported by functional data showing these *ABCC2* polymorphims affected the clearance of

Address correspondence to: Yingjie Guo, School of Life Sciences, Jilin University, Changchun, 130021, China. Tel: +86-431-85155316; Fax:+86-431-85155316; E-mail: guoyingjie@jlu.edu.cn

mycophenolic acid, methotrexate or irinotecan.[15-17] Recently, Puranik *et al*. reported that the rs2273697 variant was associated with higher CBZ clearance[18], and adverse neurological drug reactions to CBZ[9], but there are some conflicting results in other studies.[19,20]

These conflicting results reinforce the need to check the functional significance of *ABCC2* polymorphisms in different ethnic groups. The present study was performed to evaluate associations of the rs717620, rs2273697 and rs3740066 genotypes of *ABCC2* and their haplotypic combinations with CBZ plasma levels and treatment efficacy in Chinese patients with epilepsy.

METHODS

Patients

Eighty Chinese patients with epilepsy were treated with CBZ monotherapy from the First Hospital of Jilin University in Changchun, China. Patients diagnosed with partial seizures, generalized seizures or mixed seizures. Inclusion criteria for the patients were as follows: (1) Diagnosis of partial or generalized seizures; (2) CBZ monotherapy for a minimum of 1 year; (3) No liver or renal disease. Informed consent was obtained from all participants, and the study complied with the guidelines of the
Medical Ethical Committee of Jilin University School of Medicine.

Carbamazepine quantitation

To ensure that plasma CBZ concentration were in the steady state, peripheral blood was drawn in the early morning before breakfast from each patient after at least one week of continuous treatment with CBZ. CBZ concentrations were quantified in the Inspection Department at the First Hospital of Jilin University, using Carbamazepine Flex Reagent Cartridge (Dade Behring, Inc. Newark, DE). Because of the differences in oral dose taken by the patients, steady-state plasma concentrations of CBZ were adjusted by dose and body weight of each patient.

Definition of drug resistance and response

Drug resistance was defined as no change or less than 50% reduction in seizure frequency for at least one year, up to the date of the last follow-up visit, for patients treated with CBZ monotherapy. Drug response was defined as seizure-free or a 50% or greater reduction in seizure frequency for at least one year, up to the date of the last follow-up visit.

Genotyping

Genomic DNA was extracted from whole blood using SE Blood DNA Kit (Omega Bio-Tek, Inc., Norcross, GA) according to the manufacture's instructions. The *ABCC2* rs717620and rs2273697 polymorphisms were analyzed by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP), as described previously.[21] The *ABCC2* rs3740066 polymorphism was determined by direct automated DNA sequencing after PCR amplification using forward (5'-CTGGGTGACTGATAAGAGGC -3') and reverse (5'- CAAATGATGAAGGCTTAGGG -3') primers.

Statistical analysis

Statistical analysis was performed using the SPSS software(version 16.0; SPSS Inc., IL, USA).The patients' demographic characteristics including age, body weight, CBZ maintenance doses, plasma CBZ concentrations, and adjusted plasma CBZ concentrations with each genetic polymorphism were investigated using one way ANOVA and t-tests. Genotype frequencies were checked with Hardy-Weinberg equilibrium. Haplotype frequencies and linkage disequilibrium between SNP pairs were calculated with the Haploview software (version 4.2). Associations between response to CBZ treatment and *ABCC2* genotypes/ haplotypes were measured as odds ratios (ORs) with 95% confidence intervals (CIs).

RESULTS

A total of 80 patients with epilepsy were recruited for this study and their characteristics are summarized in Table 1. CBZ maintenance doses, plasma concentrations, and adjusted CBZ plasma concentrations of the patients showed a 7.6-, 4.7- and 8.3-fold range, respectively. After one year of CBZ treatment, about one-third of patients were drug resistant.

The genotype or allele frequencies of *ABCC2* rs717620, rs2273697, rs3740066 were analyzed in the 80 patients with epilepsy. The frequencies of rs717620, rs2273697, rs3740066 variant allele were 0.269, 0.206 and 0.231 in the whole patient cohort, respectively. The genotype distributions of *ABCC2* rs2273697, rs3740066, but not rs717620 were in Hardy-Weinberg equilibrium. The linkage

Table 1: Summary of patient demographic

Total number of patients studied	80
Seizure type (partial/generalized/mixed)	52/17/11
Gender (number)	Female:27;Male:53
Age (years)	36.01±16.29
Weight (kg)	63.35±7.69
CBZ maintenance dose (mg/day)	439.38±155.83
CBZ plasma concentration (μg/mL)	7.14±2.25
Adjusted CBZ plasma concentration (μg/mL per mg/kg)	1.10±0.40
CBZ responsiveness /resistance	58/22

CBZ, carbamazepine

Table 2: Effects of the *ABCC2* rs717620, rs2273697, rs3740066 genotypes on carbamazepine (CBZ) maintenance doses, CBZ concentrations and adjusted CBZ concentrations in all studied epileptic patients

Genotype	No. (%)	Age (years)	Weight (kg)	CBZ maintenance dose (mg/kg per day)	CBZ Concentration (μg/ml)	Adjusted CBZ concentration (μg/ml per mg/kg)
rs717620						
CC	39	38.33±17.75	63.49±7.01	7.43±2.64	7.48±2.06	1.10±0.41
CT	39	33.77±14.48	63.46±8.38	6.73±2.82	6.69±2.40	1.09±0.41
TT	2	34.50±24.75	58.50±9.19	6.95±1.06	9.15±0.64	1.35±0.35
CT+TT	41	33.80±14.65	63.22±8.37	6.74±2.75	7.03±2.30	1.10±0.41
P value		0.538	0.857	0.644	0.221	0.860
rs2273697						
GG	48	35.21±16.44	63.33±7.20	7.28±2.74	7.22±2.29	1.10±0.45
GA	31	37.74±16.24	63.32±8.62	6.89±2.62	7.16±2.11	1.13±0.35
AA	1	21.00	65	3.1	2.60	0.80
GA+AA	32	37.22±16.25	63.38±8.49	6.77±2.66	7.02±2.22	1.12±0.35
P value		0.698	0.998	0.406	0.236	0.865
rs3740066						
CC	46	38.59±17.65	62.72±8.46	7.30±2.83	7.23±2.09	1.10±0.43
CT	31	32.84±13.45	64.71±6.40	6.88±2.56	6.97±2.48	1.08±0.39
TT	3	29.33±19.66	59.00±6.56	5.73±2.24	7.50±2.89	1.33±0.25
CT+TT	34	32.53±13.75	64.21±6.53	6.78±2.53	7.02±2.47	1.10±0.38
P value		0.235	0.431	0.668	0.946	0.782

disequilibrium test of three SNPs in *ABCC2* was detected. The D' coefficients between rs717621 and rs2273697, rs717620 and rs3740066, and rs2273697 and rs3740066 were 0.118, 0.881, and 0.310, respectively. Only rs717620 and rs3740066 were in strong linkage disequilibrium.

None of the demographic characteristics was significantly different in any genotypes. No associations between the *ABCC2* rs717620, rs2273697 and rs3740066 genotypes and CBZ maintenance doses or plasma CBZ concentrations were detected (Table 2), even after stratification of the patients on the basis of gender (Table 3). Furthermore, haplotypes of the three SNPs of *ABCC2* were analyzed. The haplotypes composed of *ABCC2* rs717620, rs2273697 and rs3740066 showed no effects on CBZ maintenance dose, plasma CBZ concentrations and adjusted plasma CBZ concentrations (Table 4). Otherwise, there were also no significant differences between *ABCC2* genotypes and haplotypes and CBZ resistance (Table 5).

Table 3: Effects of the *ABCC2* rs717620, rs2273697, rs3740066 genotypes on carbamazepine (CBZ) maintenance doses, CBZ concentrations and adjusted CBZ concentrations in male or female patients with epilepsy

Genotype	Gender	No. (%)	Age (years)	Weight (kg)	CBZ maintenance dose (mg/kg per day)	CBZ Concentration (μg/ml)	Adjusted CBZ concentration (μg/ml per mg/kg)
rs717620							
CC	Male	25	37.68±18.65	66.44±6.56	6.52±2.03	7.55±1.79	1.25±0.42
CT+TT	Male	28	29.82±12.77	66.18±6.95	6.05±2.44	6.58±2.51	1.16±0.41
P value			0.077	0.889	0.453	0.114	0.446
CC	Female	14	39.50±16.64	58.21±4.19	9.04±2.89	7.36±2.54	0.84±0.24
CT+TT	Female	13	42.38±15.22	56.85±7.76	8.23±2.89	7.32±2.14	0.98±0.38
P value			0.643	0.570	0.472	0.970	0.253
rs2273697							
GG	Male	32	31.44±16.03	65.72±6.88	6.58±2.39	7.33±2.40	1.21±0.45
GA+AA	Male	21	36.71±16.21	67.19±6.49	5.81±1.99	6.60±1.92	1.20±0.36
P value			0.249	0.440	0.231	0.247	0.990
GG	Female	16	42.75±15.02	58.56±5.30	8.69±2.92	7.00±2.10	0.88±0.36
GA+AA	Female	11	38.18±15.02	56.09±7.08	8.59±2.91	7.84±2.61	0.95±0.24
P value			0.469	0.309	0.929	0.366	0.579
rs3740066							
CC	Male	26	36.88±18.30	66.96±7.37	6.27±2.24	7.29±1.93	1.28±0.43
CT+TT	Male	27	30.30±13.34	65.67±6.06	6.29±2.30	6.80±2.50	1.14±0.39
P value			0.139	0.487	0.975	0.427	0.221
CC	Female	20	40.80±16.98	57.20±6.42	8.65±3.01	7.16±2.34	0.88±0.30
CT+TT	Female	7	41.14±12.64	58.57±5.32	8.67±2.62	7.87±2.31	0.97±0.37
P value			0.962	0.617	0.984	0.491	0.520

Table 4: Effects of the *ABCC2* haplotypes on carbamazepine (CBZ) maintenance dose, plasma CBZ concentrations and adjusted plasma CBZ concentrations

Haplotype ABCC2	Frequency	CBZ maintenance dose (mg/kg per day)	CBZ Concentration (µg/ml)	Adjusted CBZ concentration (µg/ml per mg/kg)
CGC	0.562	7.28±2.72	7.22±2.20	1.10±0.42
TGT	0.178	6.89±2.62	7.15±2.47	1.12±0.40
CAC	0.149	6.86±2.72	6.97±2.24	1.09±0.34
TGC	0.035	7.28±2.68	7.23±2.31	1.08±0.39
TAT	0.033	6.94±2.94	6.89±2.79	1.03±0.31
P-value		0.953	0.985	0.993

DISCUSSION

Lack of responsiveness to AEDs constitutes a major clinical problem in epilepsy treatment. This partly contributes to overexpressed efflux transporters at the blood-brain barrier (BBB), which reduces the penetration of AEDs into the brain. Pharmacogenetic research has mainly focused on the *ABCB1* gene, though the role of *ABCB1* variants are still viewed controversially. Recently, ABCC2 has also received attention. ABCC2 transporter is mainly overexpressed in endothelial cells of the BBB, liver, intestine,

Table 5: Genotype and Haplotype frequencies of the *ABCC2* rs717620, rs2273697, rs3740066 polymorphisms in carbamazepine (CBZ)-resistant and CBZ-responsive patients with epilepsy

ABCC2	Frequency		Odds ratio (95% CI)	P value
	CBZ-resistant epilepsy	CBZ-responsive epilepsy		
rs717620	n=22	n=58		
CC	13 (59.09%)	26 (44.83%)	Referent	
CT	9 (40.91%)	30 (51.72%)	0.600 [0.221-1.629]	0.451
TT	0(0.00%)	2 (3.45%)	-	1.000
CT+TT	9 (40.91%)	32 (55.17%)	0.562 [0.208-1.521]	0.319
rs2273697	n=22	n=58		
GG	12 (54.55%)	36 (62.07%)	Referent	
GA	10 (45.45%)	21 (36.21%)	1.429[0.527-3.871]	0.608
AA	0	1 (1.72%)	-	1.000
GA+AA	10 (45.45%)	22 (37.93%)	1.364 [0.505-3.680]	0.613
rs3740066	n=22	n=58		
CC	14 (63.64%)	32 (55.17%)	Referent	
CT	8 (36.36%)	23 (39.66%)	0.795[0.287-2.206]	0.798
TT	0	3 (5.17%)	-	0.548
CT+TT	8 (36.36%)	26 (44.83%)	0.703 [0.256-1.933]	0.615
Haplotypes				
CGC	0.579	0.556	Referent	0.788
CAC	0.192	0.133	0.667 [0.260-1.712]	0.343
TGT	0.140	0.193	1.467 [0.534-4.030]	0.428
TGC	0.030	0.037	1.600 [0.171-14.999]	0.838

kidney, placenta and lungs. Thus *ABCC2* polymorphisms may affect the pharmacokinetics and pharmacodynamics of AEDs. Our study comprehensively assayed the roles of *ABCC2* polymorphisms on plasma CBZ concentrations and drug resistance in Chinese patients with epilepsy.

We found no associations of the *ABCC2* rs717620, rs2273697 and rs3740066 genotypes and CBZ maintenance doses, plasma CBZ concentrations and drug resistance in Chinese patients with epilepsy, consistent with two previous reports in Asian populations.[19,20] The results were in contrast to those of a previous study in Caucasian populations that indicated the association between the rs2273697 genotype and CBZ clearance.[18] Another study in Korean populations demonstrated that rs2273697 variant reduced transport activity of CBZ across the cell membrane, resulting in more frequent adverse drug reactions.[9]

Discrepancies in the results of different studies may be attributed to several limitations. First, it remains equivocal whether CBZ is a substrate of ABCC2. Kim *et al*. showed that CBZ is a substrate of ABCC2.[9] In contrast, another report failed to show any role of ABCC2 in the transport of AEDs including CBZ.[22] Second, definition of seizure control may affect drug responsiveness and thereby have an effect on association studies data. Drug response is generally defined as seizure freedom for at least 1 year. In our study, drug response was defined as seizure-free or a 50% or greater reduction in seizure frequency for at least one year, up to the date of the last follow-up visit, which were also adopted in a study of Irish patients with epilepsy.[23] It is difficult to compare results across studies. There needs to be a consensus on the definition of drug resistance in epilepsy as described by Kwan *et al*.[24,] so that results from different studies can be easily compared. Third, there is the question of potential differences in the genetic background of the studied population. In the study, only rs717620 and rs3740066 in the studied three SNPs of *ABCC2* were in strong linkage disequilibrium, consistent with a previous report in Chinese populations.[25] However, another study in Japanese populations showed a strong linkage disequilibrium between rs2273697 and rs3740066.[26] In Caucasian populations, there was linkage disequilibrium between rs717620and rs3740066; rs717620 and rs2273697; rs2273697 and rs3740066.[27] Therefore, the differences in the linkage disequilibrium pattern for linkage between rs717620, rs2273697, and rs3740066 in different ethnic group may result in different treatment efficacy. Fourth, the other SNPs in *ABCC2* gene or epigenetic factors may affect the CBZ metabolism and drug response. Fifth, the sample size of our study may not be large enough to render sufficient power to detect a significant association.

In conclusion, we failed to find any significant associations between the *ABCC2* rs717620, rs2273697 and rs3740066 genotypes, haplotypes and CBZ maintenance dose and plasma CBZ concentrations in Chinese patients with epilepsy. Furthermore, there were no significant associations between all the studied genotypes and haplotypes involving the three SNPs of *ABCC2* and CBZ resistance. Our study suggests that genetic polymorphisms in *ABCC2* gene may not be significant predictors of plasma CBZ concentration or drug response in patients with epilepsy. A study with a larger cohort of patients is warranted.

DISCLOSURE

Conflict of interest: None

REFERENCES

1. Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia* 2001; 42(10): 1255-60.
2. Löscher W, Klotz U, Zimprich F, *et al*. The clinical impact of pharmacogenetics on the treatment of epilepsy. *Epilepsia* 2009; 50(1): 1-23.
3. Potschka H, Fedrowitz M, Löscher W. P-glycoprotein and multidrug resistance-associated protein are involved in the regulation of extracellular levels of the major antiepileptic drug carbamazepine in the brain. *Neuroreport* 2001; 12(16): 3557-60.
4. Potschka H, Fedrowitz M, Löscher W. Multidrug resistance protein MRP2 contributes to blood-brain barrie function and restricts antiepileptic drug activity. *J Pharmacol Exp Ther* 2003; 306(1): 124-31.
5. Luna-Tortós C, Fedrowitz M, Löscher W. Several major antiepileptic drugs are substrates for human P-glycoprotein. *Neuropharmacology* 2008; 55(8): 1364-75.
6. Seo T, Ishitsu T, Ueda N, *et al*. ABCB1 polymorphisms influence the response to antiepileptic drugs in Japanese epilepsy patients. *Pharmacogenomics* 2006; 7(4): 551-61.
7. Ozgon G O, Bebek N, Gul G, *et al*. Association of MDR1 (C3435T) polymorphism and resistance to carbamazepine in epileptic patients from Turkey. *Eur Neurol* 2007; 59(1-2): 67-70.
8. Simon C, Stieger B, Kullak-Ublick GA, *et al*. Intestinal expression of cytochrome P450 enzymes and ABC transporters and carbamazepine and phenytoin disposition. *Acta Neurol Scand* 2007; 115(4): 232-42.
9. Kim W J, Lee J H, Yi J, *et al*. A nonsynonymous variation in MRP2/ABCC2 is associated with

neurological adverse drug reactions of carbamazepine in patients with epilepsy. *Pharmacogenet Genomics* 2010; 20(4): 249-56.
10. Aronica E, Gorter J A, Ramkema M, *et al*. Expression and cellular distribution of multidrug resistance–related proteins in the hippocampus of patients with mesial temporal lobe epilepsy. *Epilepsia* 2004; 45(5): 441-51.
11. Dombrowski S M, Desai S Y, Marroni M, et al. Overexpression of multiple drug resistance genes in endothelial cells from patients with refractory epilepsy. *Epilepsia* 2001; 42(12):1501-6.
12. Grover S, Gourie-Devi M, Bala K, *et al*. Genetic association analysis of transporters identifies ABCC2 loci for seizure control in women with epilepsy on first-line antiepileptic drugs. *Pharmacogenet Genomics* 2012; 22(6): 447-65.
13. Choi J H, Ahn B M, Yi J, *et al*. MRP2 haplotypes confer differential susceptibility to toxic liver injury. *Pharmacogenet Genomics* 2007; 17(6): 403-15.
14. Laechelt S, Turrini E, Ruehmkorf A, *et al*. Impact of ABCC2 haplotypes on transcriptional and posttranscriptional gene regulation and function. *Pharmacogenomics J* 2011; 11(1): 25-34.
15. Jong F A, Scott-Horton T J, Kroetz D L, *et al*. Irinotecan-induced diarrhea: Functional significance of the polymorphic ABCC2 transporter protein. *Clin Pharmacol Ther* 2007; 81(1): 42-9.
16. Naesens M, Kuypers D R J, Verbeke K, *et al*. Multidrug resistance protein 2 genetic polymorphisms influence mycophenolic acid exposure in renal allograft recipients. *Transplantation* 2006; 82(8):1074-84.
17. Rau T, Erney B, Göres R, *et al*. High-dose methotrexate in pediatric acute lymphoblastic leukemia: Impact of ABCC2 polymorphisms on plasma concentrations. *Clin Pharmacol Ther* 2006; 80(5): 468-76.
18. Puranik Y G, Birnbaum A K, Marino S E, *et al*. Association of carbamazepine major metabolism and transport pathway gene polymorphisms and pharmacokinetics in patients with epilepsy. *Pharmacogenomics* 2013; 14(1): 35-45.
19. Subenthiran S, Abdullah N R, Joseph J P, *et al*. Linkage disequilibrium between polymorphisms of ABCB1 and ABCC2 to predict the treatment outcome of Malaysians with complex partial seizures on treatment with carbamazepine mono-therapy at the Kuala Lumpur Hospital. *PloS one* 2013; 8(5): e64827.
20. Hung C C, Chang W L, Ho J L, *et al*. Association of polymorphisms in EPHX1, UGT2B7, ABCB1, ABCC2, SCN1A and SCN2A genes with carbamazepine therapy optimization. *Pharmacogenomics* 2012; 13(2): 159-69.
21. Qu J, Zhou B T, Yin J Y, *et al*. ABCC2 polymorphisms and haplotype are associated with drug resistance in Chinese epileptic patients. *CNS Neuroscience & Therapeutics* 2012; 18(8):647-51.
22. Luna-Tortós C, Fedrowitz M, Löscher W. Evaluation of transport of common antiepileptic drugs by human multidrug resistance-associated proteins (MRP1, 2 and 5) that are overexpressed in pharmacoresistant epilepsy. *Neuropharmacology* 2010; 58(7): 1019-32.
23. Shahwan A, Murphy K, Doherty C, *et al*. The controversial association of ABCB1 polymorphisms in refractory epilepsy: an analysis of multiple SNPs in an Irish population. *Epilepsy Res* 2007; 73(2): 192-8.
24. Kwan P, Arzimanoglou A, Berg A T, *et al*. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010; 51(6):1069-77.
25. Kwan P, Wong V, Ng P W, *et al*. Gene-wide tagging study of the association between ABCC2, ABCC5 and ABCG2 genetic polymorphisms and multidrug resistance in epilepsy. *Pharmacogenomics* 2011; 12(3):319-25.
26. Seo T, Ishitsu T, Oniki K, *et al*. ABCC2 haplotype is not associated with drug-resistant epilepsy. *J Pharm Pharmacol* 2008; 60(5): 631-5.
27. Hilger E, Reinthaler E M, Stogmann E, *et al*. Lack of association between ABCC2 gene variants and treatment response in epilepsy. *Pharmacogenomics* 2012; 13(2):185-90.