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ORIGINAL RESEARCH

Effects of MTHFR and ABCC2 gene polymorphisms on antiepileptic drug responsiveness in Jordanian epileptic patients

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Background: Epilepsy is one of the most common neurological diseases with unclear etiology where its genetic background and treatment regime still need further exploration.
Objectives: This study designed to evaluate the pharmacogenomics of *MTHFR* and *ABCC2* genes, and their association with epilepsy susceptibility among Jordanian population.
Methods: A case-control study was conducted on Jordanian cohort of 296 epileptic patients and 299 healthy individuals. Custom platform array was used to genotype the genetic polymorphisms within *MTHFR* (rs1801133) and *ABCC2 (*rs717620, rs3740066, rs2273697) genes.
Results: This study revealed a significant genetic association of MTHFR rs1801133 polymorphism with susceptibility to generalized in general and generalized tonic-clonic epilepsy (GTCE)(p=0.018 and 0.01, respectively). Regarding *ABCC2* gene, rs717620 was of linkage with generalized and GTCE subtypes (p=0.045 and 0.048, respectively), while rs717620 was associated with poor responder patients (p=0.036) with no linkage of the ABCC2 haplotypes.
Conclusions: MTHFR and ABCC2 polymorphisms showed an association with either epilepsy types in general or subtypes and treatment response among Jordanian population. This study also suggested that these gene polymorphisms have an important role in epilepsy development and drug effectiveness and could be of a great impact in the era of epilepsy diagnosis and treatment.

Keywords: methylenetetrahydrofolate reductase deficiency, epilepsy, pharmacogenetics, tonic- clonic epilepsy, psychotic disorders

Introduction

Epilepsy is one of the most common neurological diseases with a higher prevalence in developing countries.[1–4] It is defined as an unprovoked recurrent seizure due to abnormal recurrent firing from the brain.[5,6] The exact etiology of seizure is still having uncertainty despite the great effort of investigation and analysis. The genetic basis of epilepsy is one of the most ingoing fields in the medical research. Genetic profile studies play a major role in identifying the gene involved in epilepsy development and progression and classifying the disease into different subtypes.[6] Several genetic studies were also conducted on families and twins with epilepsy, suggested that genetic background has an essential role in disease development and progression.[7–10]

Pharmacogenomic studies play a major role in exploring the genetic factors that may influence the responsiveness status of patients to their prescribed medications.[11] Based on previous studies, genetic polymorphisms were found to be implicated in

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pharmacokinetic and pharmacodynamic of antiepileptic drugs (AEDs).[12,13] ATP-binding cassette subfamily C member 2 (*ABCC2*) gene encodes multidrug resistance protein (MRP) which is gaining more attention recently since it has been suggested in different studies and plays a significant role in epilepsy development and its treatment.-[14–18] One possible theory is about its effect on AEDs efflux in the blood-brain barrier, which may decrease the concentration of AEDs at the site of action.[19] MRP protein is found to be associated with multidrug resistance especially in tumor cells, but recently, it found to be associated with resistance to AED treatment.[20–22] The gene encoding 5, 10-methylenetetrahydrofolate reductase (MTHFR) enzyme is known to reduce methylene tetrahydrofolate to methyl tetrahydrofolate.[23] Any defect in this enzyme may increase the level of homocysteine and decrease the level of methionine. Elevated homocysteine level is frequently found in patients with epilepsy (PWE), and it is associated with increased risk of cardiovascular disease in epileptic patients.[24,25] Patients with MTHFR deficiency rapidly develop neurological symptoms such as seizure, stroke, and incoordination.[26] However, early and aggressive treatment can improve the clinical outcome.[27,28]

In this study, the genetic association of *MTHFR* and *ABCC2* gene polymorphisms in PWE was evaluated as a continuation of an extended study to assess the genetic variety of epilepsy and responsiveness to treatment in the Jordanian Arab population.

Materials and methods

Study population and treatment protocol

A pharmacogenetics and case-control study was conducted on Jordanian cohort (595 participants) of 296 PWE and 299 healthy controls. PWE were recruited in the period between 2017 and 2018 from the Neuro-Pediatric Clinic at Queen Rania Al Abdullah Hospital (QRAH). The healthy individuals were recruited from the Blood Bank at the Jordanian Royal Medical Services. All subjects gave their informed consent for inclusion before they participated. The study was conducted in accordance with the Declaration of Helsinki 1975, as revised in 2013, and the protocol was approved by the Ethics Committee at Jordan University of Science and Technology (16/111/2017). According to the last classification by international league against epilepsy, epilepsy has been classified to focal onset and generalized onset. Generalized onset is containing motor, which further classified to tonic-clonic, myoclonic and others.[29,30] PWE were children under 15 years of age, having at least two attacks of seizures within more than 24 hrs apart in the last six months, and receiving antiepileptic treatment for at least three months. Patients were excluded if there was no sufficient medical record, not complaint to the AED, there was non-reliable seizure frequency, had liver disease, was not visiting the clinics regularly, or refused to sign the written consent. Participants should also have normal psychometric development, normal activity in addition to normal neurological examination.

A total of 450 patients were screened with only 350 patients fulfilled the inclusion criteria, but 50 of them were excluded as they were not able to complete the treatment program for clinical reasons or refused to continue the treatment. This cohort was conducted on 300 patients, where four of them were excluded due to a genotyping failure resulted in a final population of 296 PWE. Patients' demographic data were published previously as this study is a continuation of extended study by AL-Eitan et al, that assessed the pharmacogenetics and epilepsy association with different genetic polymorphisms.[31]

Participated patients received antiepileptics for at least two years regarding the standard Practice of the Pediatric Neurology Clinic at the QRAH. Antiepileptic treatment protocol began with 10 mg/kg of valproic acid (VPA) (G.L. Pharma GmbH, Lannach, Austria) for patients diagnosed with generalized seizure or 5 mg/kg daily of carbamazepine (CBZ) (Novartis Pharmaceuticals UK Ltd., Surrey, England) for patients diagnosed with partial seizure. To ensure the dose effectiveness, Seizure was frequency monitored for the first three to four weeks after initiation of the therapy. Patients were given the therapeutic dose by increasing the initial VPA and CBZ doses to 20 and 10 mg/kg, respectively, during follow-up visits in order to minimize seizure frequency.

Outcome measure

Patients were classified according to their AEDs responsiveness to good and poor responders. Patients were considered as a good responder when

> Epilepsy in which the patient receiving the current AED regimen has been seizure-free for a minimum of three times the longest preintervention interseizure interval or 12 months, whichever is longer.[32]

On the other hand, poor responders (ie, resistant) were classified based on the "failure of adequate trials of two tolerated and appropriately chosen and used AED

schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom".[32]

SNP selection and genotyping

Four SNPs were selected from databases such as SNP database of the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/SNP/), Applied Biosystems SNP database (http://www.appliedbiosystems.com), and Ensembl database (http://www.ensembl.org/index.html). For the *ABCC2* gene, rs717620, rs3740066, and rs2273697 were selected and only rs1801133 for the *MTHFR* gene. DNA was extracted from EDTA blood samples by Wizard Genomic DNA Purification Kit (Promega Corporation, Madison, WI, USA) and genotyped by the Australian Genome Research Facility (AGRF) following the manufacturer's recommendation using the MassARRAY (iPLEX GOLD) system (Sequenom, San Diego, CA, USA).

Statistical analysis

Genetic and haplotype association analysis were conducted for the selected SNPs to find out any association if present. Analysis was performed using SNPStats Web Tool (https://www. snpstats.net/start.htm) in addition to Hardy–Weinberg equilibrium values for the genotype distribution and the minor allelic frequency. The Statistical Package for Social Sciences (SPSS) software (v. 22) was also used to conduct all statistical analyses for phenotype–genotype study. *p*-value less than 0.05 was considered to be statistically significant.

Results

Genotypic and allelic distribution

In comparison between healthy controls and epileptic patients, no genetic association exhibited in the studied SNPs of MTHFR (rs1801133), and ABCC2 (rs717620, rs3740066, rs2273697) (Table 1).

Association of MTHFR and ABCC2 SNPs with epilepsy classes andAED responsiveness

Patients were classified into patients with generalized onset epilepsy (GE) and patients with focal onset epilepsy (FE). GE patients showed a statistically significant linkage with MTHFR rs1801133 (p=0.018). ABCC2 rs717620 was also associated with GE as TT was revealed in 2.3% of GE in compare to 0.3% in healthy controls (p=0.045) (Table 2). GE patients were further classified into patients with generalized myoclonic epilepsy (GME), and generalized tonic-clonic epilepsy (GTCE). All the investigated SNPs within both genes were lacked any association in GME patients (Table 3). In GTCE, MTHFR rs1801133 was of a significant relation, as GG was presented in 60.9% of GTCE patients in compare to 46.8% in healthy individuals (p=0.01). In addition, ABCC2 rs717620 was also associated with GTCE patients (p=0.048) (Table 4). On the other hand, scanned polymorphisms were failed to be associated with FE type (Table 5).

Regarding their response to an AED, patients were classified into good responders and poor responders. Studied genes exhibited no relationship with either poor

Table 1 The distributions of *ABCC2* and *MTHFR* SNPs in 296 patients with epilepsy and 299 healthy controls

Gene	SNP ID	Model	Epileptic patients %	Controls %	*p*-value*
MTHFR	rs1801133	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	51.7/38.9/9.5 51.7/48.3 90.5/9.5	46.8/42.5/10.7 46.8/53.2 89.3/10.7	0.49 0.24 0.61
ABCC2	rs717620	CC/CT/TT CC/(CT+TT) (CC+TC)/TT	79.3/19.3/1.4 79.3/20.7 98.6/1.4	79.9/19.7/0.3 79.9/20.1 99.7/0.3	0.37 0.85 0.16
	rs3740066	CC/CT/TT CC/(CT+TT) (CC+CT)/TT	49.1/41.4/9.5 49.1/50.9 90.5/9.5	46/44.3/9.7 46/54 90.3/9.7	0.73 0.44 0.92
	rs2273697	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	58.1/36.8/5.1 58.1/41.9 94.9/5.1	54/40.2/5.7 54/46 94.3/5.7	0.61 0.32 0.72

Note: *Chi–Square Test with p<0.05 is considered significant.

Table 2 The distributions of *ABCC2* and *MTHFR* SNPs in 172 patients with generalized epilepsy (GE) and 299 healthy controls

Gene	SNP ID	Model	GE patients %	Controls %	*p*-value*
MTHFR	rs1801133	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	58.1/33.7/8.1 58.1/41.9 91.9/8.1	46.8/42.5/10.7 46.8/53.2 89.3/10.7	0.06 0.018 0.36
ABCC2	rs717620	CC/CT/TT CC/(CT+TT) (CC+TC)/TT	80.1/17.5/2.3 80.1/19.9 97.7/2.3	79.9/19.7/0.3 79.9/20.1 99.7/0.3	0.12 0.96 0.045
	rs3740066	CC/CT/TT CC/(CT+TT) (CC+CT)/TT	48.8/40.7/10.5 48.8/51.2 89.5/10.5	46/44.3/9.7 46/54 90.3/9.7	0.75 0.55 0.8
	rs2273697	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	57/38.4/4.7 57/43 95.3/4.7	54/40.2/5.7 54/46 94.3/5.7	0.78 0.54 0.61

Note: *Chi-Square Test with *P*<0.05 is considered significant.

Table 3 The distributions of *ABCC2* and *MTHFR* SNPs in 57 generalized myoclonic epileptic (GME) patients and 299 healthy controls

Genes	SNP ID	Model	GME patients %	Control %	*p*-value*
MTHFR	rs1801133	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	52.6/40.4/7 52.6/47.4 93/7	46.8/42.5/10.7 46.8/53.2 89.3/10.7	0.58 0.42 0.38
ABCC2	rs717620	CC/CT/TT CC/(CT+TT) (CC+TC)/TT	80.7/17.5/1.8 80.7/19.3 98.2/1.8	79.9/19.7/0.3 79.9/20.1 99.7/0.3	0.51 0.89 0.26
	rs3740066	CC/CT/TT CC/(CT+TT) (CC+CT)/TT	49.1/42.1/8.8 49.1/50.9 91.2/8.8	46/44.3/9.7 46/54 90.3/9.7	0.9 0.66 0.82
	rs2273697	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	66.7/29.8/3.5 66.7/33.3 96.5/3.5	54/40.2/5.7 54/46 94.3/5.7	0.2 0.076 0.47

Note: *Chi-Square Test with *P*<0.05 is considered significant.

or good responders (Table 6) except for the ABCC2 rs717620 that found to be associated with the poor responders' group (p=0.036).

Association of the ABCC2 haplotypes with epilepsy susceptibility and treatment responsiveness

Five haplotypes were found for *ABCC2* gene where CCA and CTG blocks showed significant association with GME susceptibility as their frequency was higher in controls (0.23% vs 0.12%, p=0.0069 and 0.2 vs 0.13, p=0.034, respectively) (Table 7). Regarding patients' response to AED, none of the ABCC2 haplotypes were found to be associated with either poor or good responders (data not shown).

Association between MTHFR and ABCC2 SNPs and the patients' phenotype

Seven clinical characteristics were investigated in relation to the *MTHFR* and *ABCC2* genes including the history of febrile seizure, family history of epilepsy, psychosis, suicidal thoughts or actions, epilepsy syndromes, classification of epilepsy and response to the first drug. None of the aforementioned phenotypes were associated with MTHFR (Table 8). ABCC2 rs3740066 was predominant in individuals with suicidal thoughts or actions (p=0.007) where

Table 4 The distributions of *ABCC2* and *MTHFR* SNPs in 115 generalized tonic-clonic epileptic (GTCE) patients and 299 healthy controls

Genes	SNP ID	Models	GTCE patients %	Control %	*p*-value*
MTHFR	rs1801133	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	60.9/30.4/8.7 60.9/39.1 91.3/8.7	46.8/42.5/10.7 46.8/53.2 89.3/10.7	0.035 0.01 0.54
ABCC2	rs717620	CC/CT/TT CC/(CT+TT) (CC+TC)/TT	79.8/17.5/2.6 79.8/20.2 97.4/2.6	79.9/19.7/0.3 79.9/20.1 99.7/0.3	0.13 0.98 0.048
	rs3740066	CC/CT/TT CC/(CT+TT) (CC+CT)/TT	48.7/40/11.3 48.7/51.3 88.7/11.3	46/44.3/9.7 46/54 90.3/9.7	0.71 0.62 0.64
	rs2273697	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	52.2/42.6/5.2 52.2/47.8 94.8/5.2	54/40.2/5.7 54/46 94.3/5.7	0.9 0.73 0.83

Note: *Chi-Square Test with $P<0.05$ is considered significant.

Table 5 The distributions of *ABCC2* and *MTHFR* SNPs in 124 focal onset epileptic patients and 299 healthy controls

Genes	SNP ID	Model	PE patients %	Control %	*p*-value*
MTHFR	rs1801133	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	42.7/46/11.3 42.7/57.3 88.7/11.3	46.8/42.5/10.7 46.8/53.2 89.3/10.7	0.74 0.44 0.86
ABCC2	rs717620	CC/CT/TT CC/(CT+TT) (CC+TC)/TT	78.2/21.8/0.0 78.2/21.8 100/0.0	79.9/0.3/79.9 79.9/20.1 99.7/0.3	0.64 0.69 0.4
	rs3740066	CC/CT/TT CC/(CT+TT) (CC+CT)/TT	49.6/42.3/8.1 49.6/50.4 91.9/8.1	46/44.3/9.7 46/54 90.3/9.7	0.75 0.5 0.6
	rs2273697	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	59.7/34.7/5.7 59.7/40.3 94.3/5.7	54/40.2/5.7 54/46 94.3/5.7	0.55 0.29 0.97

Note: *Chi-Square Test with $P<0.05$ is considered significant.

rs2273697 showed an association with the classification of epilepsy (p=0.002) (Table 8).

Discussion

In this study, our Jordanian cohort was used to investigate the genetic association of MTHFR and ABCC2 gene polymorphisms with the susceptibility to develop epilepsy and responsiveness to treatment. rs1801133 SNP within *the MTHFR* gene was found to be associated with epilepsy. The frequency of the rare homogenous genotype of this SNP in healthy controls was 10.7%, which is the highest in the Middle East, as it was reported to be less than 3% in Yemeni people,[33] 7.5% in Turkey,[34] and less than 1% in sub-Saharan Africa,[33] but it is almost consistent with what was reported in Japan (10.2%).[35] The highest percentage was reported in Italian and Hispanics people, which is around 20–25%.[36] Up to date, no data have been published regarding its frequency in Jordanian Arab population.[37] This SNP is known to be associated with multiple neurological diseases such as sensorineural hearing loss,[38] Parkinson disease,[39] Alzheimer disease,[40] and Migraine.[41] In this study, rs1801133 was found to be associated with GE but not with epilepsy in general. However, Wu et al, and Scher et al, revealed an associated of this SNP and epilepsy without mentions any epilepsy subtypes.[42,43] Additionally, rs1801133 was associated specifically with the myoclonic and tonic-clonic subtypes of generalized epilepsy. These findings reflect

Table 6 The distributions of *ABCC2* and *MTHFR* SNPs in 124 good responder, 171 poor responder patients with epilepsy

Genes	SNP ID	Model	Poor responder patients %	Good responder controls %	*p*-value*
MTHFR	rs1801133	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	53.2/36.8/9.9 53.2/46.8 90.1/9.9	50/41.1/8.9 50/50 91.1/8.9	0.75 0.59 0.76
ABCC2	rs717620	CC/TC/TT CC/(TC+TT) (CC+TC)/TT	80.1/17.5/2.3 80.1/19.9 97.7/2.3	78.9/21.1/0 78.9/21.1 100/0	0.089 0.79 0.036
	rs3740066	CC/CT/TT CC/(CT+TT) (CC+CT)/TT	50/40.6/9.4 50/50 90.6/9.4	48.4/42.7/8.9 48.4/51.6 91.1/8.9	0.93 0.78 0.87
	rs2273697	GG/AG/AA GG/(AG+AA) (GG+AG)/AA	57.3/47.4/5.3 94.7/5.3 94/6	58.9/36.3/4.8 95.2/4.8 95.7/4.3	0.96 0.79 0.87

Note: *Chi-Square Test with $P<0.05$ is considered significant.

Table 7 The distributions of *ABCC2* haplotypes and 57 patients with generalized myoclonic epilepsy in compare to 299 healthy controls

Gene	Haplotypes	GMEP (%)	Controls (%)	Odds ratio (95% CI)	*p*-value*
ABCC2	CCG	0.576	0.4411	1.00	–
	CCA	0.1257	0.2313	0.40 (0.20–0.77)	0.0069
	CTG	0.1346	0.2001	0.49 (0.26–0.95)	0.034
	TTG	0.1052	0.0932	0.83 (0.41–1.70)	0.61
	CTA	0.0584	0.0255	1.63 (0.55–4.80)	0.38

Notes: *Chi-Square Test with $P<0.05$ is considered significant. Global haplotype association *p*-value: 0.029.

Table 8 The distributions of *p*-value in *ABCC2* and *MTHFR* SNPs and the clinical characteristics in 296 epileptic patients

Clinical characteristic	*MTHFR*	*ABCC2*		
	rs2273697	rs3740066	rs717620	rs1801133
	GG vs AG vs AA	CC vs CT vs TT	CC vs CT vs TT	GG vs AG vs AA
History of febrile seizure	0.606	0.983	0.818	0.128
Family history of epilepsy	0.102	0.069	0.447	0.385
Psychosis	0.102	0.955	0.448	0.743
Suicidal thoughts or actions	0.921	0.926	0.007	0.970
Epilepsy syndromes	0.844	0.865	0.533	0.363
Classification of epilepsy	0.087	0.845	0.056	0.002
Response to first drug[a]	0.151	0.476	0.125	0.078

Notes: [a]Antiepileptic treatment protocol began with 10 mg/kg of valproic acid (VPA) for patients diagnosed with generalized seizure or 5 mg/kg daily of carbamazepine (CBZ) for patients diagnosed with partial seizure. Chi-Square Test with $P<0.05$ is considered significant.

the strong relation between MTHFR rs1801133 and epilepsy subclasses and highlight the importance of subdividing patients according to the disease subtypes.

None of the studied SNPs within *the ABCC2* gene were associated with epilepsy in general. Nevertheless, the association of ABCC2 rs717620 with GE and GTCE was reported in this work for the first time. However, previous studies were focused on the genetic association with patients' responsiveness to AED treatment, there is no adequate data that are available regarding the susceptibility to epilepsy in general or epilepsy subclasses.[44–47] One of the largest meta-analysis studies performed by Grover and Kukreti explored

eight reports with more than 2,500 patients, rs717620 was found to be a predictor for the poor response with no association observed in the other SNPs.[46] This is consistent with our finding where rs717620 was the only associated SNP with the poor response status. This finding may have more application in the future, and this gene polymorphism may become a marker for poor responders, since the personalization of treatment is gaining more global attention.

Regarding ABCC2 haplotypes, very limited studies have been done to assess its association with epilepsy susceptibility. This study is one of few studies that found five haplotypes for *ABCC2* gene with GME in a linkage to CCA and CTG, which is to the best of our knowledge was not reported in the literatures before. Qu et al, are one of the first people who find five haplotypes for *ABCC2* gene, and their study showed a significant association between TGT and drug resistance.[48] Moreover, Ufer et al, found four haplotypes for *ABCC2* gene with multiple associations to drugs response in the Caucasian population.[49] In concordance with our study, several studies did not find any association for the ABCC2 haplotypes with drug response, despite the difference in the ethnic background.[50–52]

Finally, MTHFR rs180113 and ABCC2 rs717620 were found to be associated with GE and GTCE in Jordanian population. Moreover, five haplotypes for *ABCC2* gene were found in this study with only CCA and CTG haplotypes were associated with GME subtype. Future studies should be directed to find the relation between genetic variations and epilepsy susceptibility and treatment response. This will lead to a promising result that expected to have a great implication in disease diagnosis and treatment in the near future.

Abbreviation list

AED, Antiepileptic drug; MTHFR, methylenetetrahydrofolate reductase; ABCC2, ATP-binding cassette subfamily C member 2; MRP, Multidrug resistance protein; BBB, Blood-brain barrier; GE, Generalized onset epilepsy; FE, Focal onset epilepsy; GME, Generalized myoclonic epilepsy; GTCE, Generalized tonic-clonic epilepsy; PWE, Patients with epilepsy.

Ethics approval and informed consent

All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and the Declaration of Helsinki with an IRB no. (16/111/2017)

Data availability

The datasets generated and analyzed during the current study are not publicly available. The consent from participants did not cover data sharing but are available from the corresponding author on reasonable request.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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