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Investigation of the 1249G>A Genetic Variation of *ABCC2* Drug Transporter Gene in the Turkish Population

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Abstract

Objectives: ATP binding cassette (ABC) transporters are a major superfamily of drug transporters and provide active transport of diverse substrates across cell membranes of several cell types. Genetic variations that affect function in *ABCC2* gene may alter therapeutic outcome and the risk of toxicity to substrate drugs. The goal of the current survey was to ascertain the allele and genotype frequencies of *ABCC2* 1249G>A polymorphism in a Turkish population and to compare the findings obtained with the frequencies of previously reported populations.

Methods: The frequencies of the *ABCC2* 1249G>A gene polymorphism were determined in 101 healthy Turkish individuals using polymerase chain reaction-restriction fragment length polymorphism methods.

Results: The frequencies of GG, GA and AA genotypes were 67.3%, 28.7% and 4.0%, respectively. The frequencies were 81.7% for G allele and 18.3% for A allele. The frequencies of genotypes were in concurrence with Hardy-Weinberg Equilibrium. Significant distinctions were observed in the comparison of the study data with the results of some populations of East and South Asian ancestries.

Conclusions: The current study presents the distribution of genotype and allele frequencies of *ABCC2* 1249G>A polymorphism in the Turkish population. As far as is known, this is the first study about the frequencies of the *ABCC2* 1249G>A polymorphism in the Turkish population. This study may ensure valuable information for evaluating inter-individual differences in drug response, estimating adverse reactions and improving disease management, briefly, it can contribute to pharmacogenetic and epidemiological studies.

Keywords: *ABCC2* 1249G>A, MRP2, V417I polymorphism, drug transporters, Turkish population.

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Türk Popülasyonunda *ABCC2* İlaç Taşıyıcı Genin 1249G>A Genetik Varyasyonunun Araştırılması

Öz

Amaç: ATP bağlayıcı kaset (ABC) taşıyıcıları, ilaç taşıyıcılarının önemli bir süper ailesidir ve farklı hücre tiplerinin hücre zarları boyunca çeşitli substratların aktif taşınmasını sağlar. *ABCC2* genindeki işlevi etkileyen genetik varyasyonlar, terapötik sonucu ve substrat ilaçlara olan toksisite riskini değiştirebilmektedir. Bu araştırmanın amacı, Türk popülasyonunda *ABCC2* 1249G>A gen polimorfizminin alel ve genotip frekanslarını tespit etmek ve elde edilen bulguları daha önce bildirilen popülasyonların sonuçlarıyla karşılaştırmaktı.

Yöntemler: *ABCC2* 1249G>A gen polimorfizminin frekansları 101 sağlıklı Türk bireyinde polimeraz zincir reaksiyon-restriksiyon fragman uzunluk polimorfizmi yöntemleri kullanılarak belirlendi.

Bulgular: GG, GA ve AA genotiplerinin frekansları sırasıyla % 67.3,% 28.7 ve % 4.0 idi. G alelin frekansı % 81.7 ve A alel frekansı % 18.3 idi. Genotip frekansları Hardy-Weinberg dengesi ile uyumludur. Çalışmanın sonuçları, Doğu ve Güney Asya kökenli bazı popülasyonlarının sonuçlarıyla karşılaştırıldığında önemli farklılıklar olduğu gözlenmiştir.

Sonuç: Bu çalışma, Türk popülasyonunda *ABCC2* 1249G>A gen polimorfizminin genotip ve allel frekanslarının dağılımını sunmaktadır. Bilindiği kadarıyla, bu Türk popülasyonunda *ABCC2* 1249G>A polimorfizminin frekansları ile ilgili ilk çalışmadır. Bu çalışma, ilaç yanıtındaki bireyler arası farklılıkları değerlendirmek, advers reaksiyonları tahmin etmek ve hastalık yönetimini iyileştirmek için değerli bilgiler sağlayabilir, kısaca, farmakogenetik ve epidemiyolojik çalışmalara katkı sağlayabilir.

Anahtar kelimeler: *ABCC2* 1249G>A, MRP2, V417I polimorfizmi, ilaç taşıyıcıları, Türk popülasyonu.

INTRODUCTION

Different drug responses may occur when the same drug and dose is taken by different people. Besides environmental and other non-genetic factors, the variants in sequence of genes that encode drug transporters, drug metabolizing enzymes, and drug targets can cause inter-individual difference in drug response[1]. Membrane transporter proteins are a significant determinant of drug response because drug transporters regulate absorption, distribution, excretion of medications by controlling the efflux and influx of medications in cells[2]. Drug transporters are categorized into 2 key superfamilies as the ATP binding cassette (ABC) transporters and the solute carriers (SLC)[3].

The ABC transporters are composed of a great transmembrane protein family binding ATP and using ATP hydrolysis energy to transfer diverse compounds throughout the membrane of cell[4]. In humans, the family of ABC transporters consists of 49 genes, which are separated into 7 different subfamilies, from ABCA through ABCG[5]. The ABCC subfamily contains thirteen members and their members are also mentioned to as multi-drug resistance protein (MRP-ABCC transporters)[4].

MRP2 is a member of the ABC transporter superfamily[6] and also has alternative names as ATP binding cassette subfamily C member 2 (ABCC2) or cMOAT (canalicular multispecific organic anion transporter)[7]. It is expressed in the apical membrane of the liver cells, the apical luminal membrane of epithelial cells of the kidney and small intestine, but also in the apical syncytiotrophoblast membrane of the placenta and in the endothelial cells of the blood-brain barrier[8]. MRP2 is a canalicular multispecific organic anion efflux transporter and affects the biliary excretion and gastrointestinal absorption of a broad range of endogenous compounds and xenobiotic substrates containing numerous clinically used drugs[6]. Typical substrates of the ABCC2 drug transporter are as follows; anticancer drugs

(cisplatin, vincristine, vinblastine, mitoxantrone, methotrexate, irinotecan, etoposide, doxorubicin, camptothecin), antibiotics (ampicillin, cefodizime, ceftriaxone, grepafloxacine, azithromycin), HMG CoA reductase inhibitors (pravastatin), antihypertensive drugs (olmesartan, valsartan), HIV-1 protease inhibitors (saquinavir, ritonavir, nelfinavir, lopinavir, indinavir, cidofovir, adefovir), fluorescent dyes (carboxyfluorescein), and diverse (temocaprilate, valproate, bilirubine, glutathione conjugates, sulfate conjugates, glucuronide conjugates)[4,9,10].

ABCC2 gene encoding MRP2 has been mapped to chromosome 10q24.2 and comprises 32 exons[6,11]. *ABCC2* encodes a protein, which consists of 1545 amino acids and has a molecular weight of 174 kDa[4]. Many single nucleotide polymorphisms (SNPs) have been determined in the *ABCC2* gene. One of the most common SNP polymorphisms is *ABCC2* G1249A polymorphism (rs2273697)[12]. The 1249G>A polymorphism in exon 10 of the *ABCC2* gene leads to an amino acid change from Val to Ile at position 417, present in membrane spanning domain 2 of the protein[11,13]. The G1249A polymorphism can affect the expression of MRP2. It has been reported that the 1249G>A substitution in the *ABCC2* gene was related with gene expression in human liver and that mRNA level was importantly more elevated in the patients with the variant 1249G>A compared to those carrying the wild G allele[14]. Also, the 1249G>A polymorphism was related with an importantly decreased expression of MRP2 mRNA in preterms[15]. The 1249G>A SNP has been suggested to be likely to influence the function of MRP2 in a substrate-specific manner[8].

Genetic polymorphisms might affect the substrate specificity, subcellular localization, expression, and/or intrinsic transport activity of the transporter proteins, and thereby affecting the response and disposition of medication substrates[5]. Thus, genetic variations acting on function in the *ABCC2* gene may alter the toxicity risk and the therapeutic result of substrate drugs[6].

The genotype and allele frequencies of *ABCC2* 1249G>A gene polymorphism are known to differ among various populations. On the other hand, to my knowledge, no studies have been conducted on *ABCC2* 1249G>A polymorphism in a healthy Turkish population. Therefore, the goal of the current survey was to ascertain the genotype and allele frequencies of *ABCC2* 1249G>A polymorphism in the Turkish population and to compare the findings obtained with the frequencies of previously reported populations, and thus to provide valuable information for pharmacogenetic and epidemiological studies.

METHODS

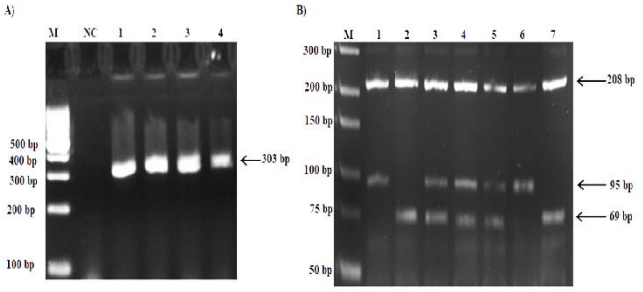
Samples

The DNA samples isolated from the previous study (22/10/2015, protocol no: 2015/317) were included in the current survey. Also, the approval of the Ethics Committee of Mersin University was obtained for the current study (19/02/2020, protocol no: 2020/170). This study was conducted on DNA samples of 101 healthy and unrelated Turkish individuals between the ages of 18 and 65. The study was executed according to Good Clinical Practices and the Helsinki Declaration.

Genotyping

ABCC2 1249G>A gene polymorphism was analyzed as per methods described by Mirakhorli et al.[11] with slight modifications. The 1249G>A polymorphism was determined by polymerase chain reaction (PCR) method using 5'-GGGCAAAGAAGTGTGTGGAT-3' sequence for forward primer and 5'-ACATCAGGTTCACTGTTTCTCCCA-3' sequence for reverse primer. PCR was carried out in a 20-µl reaction mixture which included 10 pmol of each primer, genomic DNA in the range of 300 to 500 ng, 10 x PCR buffer, 0.2 mM each deoxynucleotide triphosphate (Fermentas), 1.50 unit of Taq polymerase (Fermentas), 1.5 mM $MgCl_2$ on MiniAmp Plus Thermal Cycler (Thermo Fisher, USA). The PCR process was as shown: 94 ˚C for 180 sec for initial denaturation, thereafter 35 cycles of 94°C for 20 sec, 56.4 °C for 15 sec, 72 ˚C for 20 sec, followed by a final elongation for 5 min at 72°C. A DNA-free negative control was added to each PCR analysis to ensure that the reagents used did not contain contaminating DNA. PCR products (303 bp) were electrophoresed on a 2 % agarose gel that include ethidium bromide (0.5 µg/ml), which made the products visible. For restriction fragment length polymorphism (RFLP) method, 10 µl of PCR product was cut in 15 minutes at 37°C using FastDigest NcoI

restriction enzyme with the proper buffer in total volume of 20 µl. The wild type genotype (GG) was digested to 208 and 95 bp fragments, the variant genotype (AA) was digested to 208, 69, 26 bp fragments, and the heterozygous genotype (GA) was digested to 208, 95, 69 and 26 bp fragments (Figure 1). The digested fragments were determined using 5% agarose gel with ethidium bromide, and 10% of the samples were reanalyzed at random for quality assurance, that provided 100% concordance.



Electrophoresis pattern of ABCC2 1249G>A polymorphism detected by polymerase chain reaction (PCR) (A) and restriction fragment length polymorphism (RFLP) (B). For A (PCR) part; Lane M: 100 bp DNA ladder,

NC: Negative control, Lane 1-4: PCR product (303 bp). For B (RFLP) part; Lane M: Ultra Low Range DNA Ladder, Lane 1,6: wild type genotype (208, 95 bp), Lane 2,7: mutant genotype (208, 69, 26 bp), Lane 3-5: heterozygous genotype (208, 95, 69, 26 bp).

Statistical Analysis

Allelic and genotypic frequencies were evaluated using genotype counting method. The expected and observed frequencies of *ABCC2* gene were compared using chi-square (X^2) test based on Hardy–Weinberg equilibrium. The data of this study were compared with the frequencies of previously reported populations using X^2 test. Also, comparison of the basic characteristics between the genotypes was done using X^2 test and one-way ANOVA followed by Duncan's multiple-range post hoc test, where appropriate. Statistical analyzes were carried out with IBM SPSS 25.0 computer software for Windows. $p<0.05$, $p<0.01$ and $p<0.001$ were admitted significant as statistical.

RESULTS

ABCC2 G1249A polymorphism was carried out on 101 healthy unrelated individuals. Of the 101 participants, 56 (55% of all participants) were female, 45 (45%) were male. The mean age with standard deviation (SD) of the participants was 27.39 ± 8.54 years, the mean body weight with SD was 70.86 ± 14.27 kg, the mean height with SD was 169.88 ± 8.33 cm and the mean body mass index (BMI) with SD was 24.45 ± 3.96 kg/m^2. There was no important distinction between the genotypes in terms of basic characteristics ($p>0.05$) (Table I).

Table I: Basic characteristics of the individuals included in the study

Basic characteristics	Total	*ABCC2* Genotypes			
		GG	GA	AA	p value
		n (%)			
Gender					
Female	56 (55)	38 (67.9)	18 (32.1)	0 (0.0)	0.064[a]
Male	45 (45)	30 (66.7)	11 (24.4)	4 (8.9)	
		mean±SD			
Age (years)	27.39 ± 8.54	27.84 ± 8.84	26.76 ± 8.24	24.25 ± 5.5	0.646[b]
Body weight (kg)	70.86 ± 14.27	71.74 ±14.24	67.68 ± 14.69	78.0 ± 9.63	0.295[b]
Height (cm)	169.88 ±8.33	169.64 ± 8.22	169.16 ± 8.53	177.75 ± 6.24	0.150[b]
BMI (kg/m^2)	24.45 ± 3.96	24.85 ± 4.13	23.48 ± 3.69	24.67 ± 2.54	0.356[b]

Data were indicated as mean ± standard deviation (mean ± SD). [a]: X^2 test; [b]: One-way ANOVA followed by Duncan's multiple-range post hoc test.

BMI: Body mass index.

The frequencies of GG, GA and AA genotypes were 67.3%, 28.7% and 4.0, respectively, and thus, the frequencies of G and A allele were determined as 81.7% and 18.3%, respectively. The frequencies of genotypes were in concurrence with Hardy-Weinberg equilibrium (X^2=1.65, p>0.05) (Table II).

Table II: The frequencies of *ABCC2* G1249A gene polymorphism in a healthy Turkish population

Genotype	n (Observed)	Genotype frequencies, %	n (Expected)	Allele frequencies, %
GG	68	67.3	67.4	G: 81.7
GA	29	28.7	30.2	A: 18.3
AA	4	4.0	3.4	X^2: 1.65 df = 1; p>0.05
Total	101	100	101	

DISCUSSION

To my knowledge, this is the first exploration to determine the allele and genotype frequencies of the *ABCC2* 1249G>A polymorphism in a healthy Turkish population. The GG, GA and AA genotype frequencies of the *ABCC2* 1249G>A polymorphism were 67.3%, 28.7% and 4.0%, respectively. The frequencies were 81.7% for G allele and 18.3% for A allele.

The results of this study have been compared with the findings of the previously published studies[3,16,18-24] and of the 1000 Genomes Project[17] as demonstrated in Table III. The frequency of A allele of the *ABCC2* 1249G>A polymorphism was observed to be dominat in South Asian populations, including Indian Telugu in the UK (ITU), Punjabi in Lahore, Pakistan (PJL) and Pakistani when compared to the Turkish population and also the other populations. The A variant allele frequencies in ITU, PJL and Pakistani were 29.4%, 30.7% and 33.1%, respectively. In addition, the frequencies of the A variant allele were found to lower in East Asian populations, including Chinese Dai in Xishuangbanna, China (CDX), Kinh in Ho Chi Minh City, Vietnam (KHV) and Korean when compared to the Turkish population and the other populations. The A variant allele frequencies in CDX, KHV and Korean populations were 4.3%, 6.1% and 8.3%, respectively. Thus, there were statistically important distinctions between the aforementioned populations and the Turkish population. On the other hand, no significant distinctions were between the results obtained in this study and the findings of the other Asian populations with range from 11.0 to 27.0%, including Southern Han Chinese, China (CHS), Japanese in Tokyo, Japan (JPT), Han Chinese in Bejing, China (CHB), Chinese, Japanese, Bengali in Bangladesh (BEB), Sri Lankan Tamil in the UK (STU), Iranian, Jordanian.

Table III: Distribution of genotype and allele frequencies of *ABCC2* G1249A polymorphism in various populations

Ethnicity	Population	Sample size	Genotype frequencies n (%)			Allele frequencies n (%)		References
		n	GG	GA	AA	G	A	
White								
	Turkish	101	68 (67.3)	29 (28.7)	4 (4.0)	165 (81.7)	45 (18.3)	The current study
	Spanish	569	367 (64.5)	184 (32.3)	18 (3.2)	918 (80.7)	220 (19.3)	Boso et al.[16]
	Iberian populations in Spain (IBS)	107	68 (63.6)	33 (30.8)	6 (5.6)	169 (79.0)	45 (21.0)	1000 Genomes Project[17]
	German	374	(62.3)	(33.2)	(4.5)	(78.9)	(21.1)	Haenisch et al.[18]
European	British in England and Scotland (GBR)	91	51 (56.0)	37 (40.7)	3 (3.3)	139 (76.4)	43 (23.6)	1000 Genomes Project[17]
	Finnish in Finland (FIN)	99	70 (70.7)	27 (27.3)	2 (2.0)	167 (84.3)	31 (15.7)	1000 Genomes Project[17]
	Utah Residents with Northern and Western European Ancestry (CEU)	99	57 (57.6)	37 (37.4)	5 (5.0)	151 (76.3)	47 (23.7)	1000 Genomes Project[17]
American	Puerto Rican in Puerto Rico (PUR)	104	69 (66.3)	32 (30.8)	3 (2.9)	170 (81.7)	38 (18.3)	1000 Genomes Project[17]
	Colombian in Medellin, Colombia (CLM)	94	67 (71.3)	25 (26.6)	2 (2.1)	159 (84.6)	29 (15.4)	1000 Genomes Project[17]
	Mexican Ancestry in Los Angeles, California (MXL)	64	46 (71.9)	17 (26.6)	1 (1.6)	109 (85.2)	19 (14.8)	1000 Genomes Project[17]
	Peruvian in Lima, Peru (PEL)	85	62 (72.9)	22 (25.9)	1 (1.2)	146 (85.9)	24 (14.1)	1000 Genomes Project[17]

Table III: continued

Ethnicity	Population	Sample size	Genotype frequencies n (%)			Allele frequencies n (%)		References
		n	GG	GA	AA	G	A	
Asians								
South Asian	Pakistani*	68	34 (50.0)	23 (33.8)	11 (16.2)	91 (66.9)	45 (33.1)	Afsar et al.[19]
	Punjabi in Lahore, Pakistan (PJL)*	96	50 (52.1)	33 (34.4)	13 (13.5)	133 (69.3)	59 (30.7)	1000 Genomes Project[17]
	Indian Telugu in the UK (ITU)*	102	48 (47.1)	48 (47.1)	6 (5.9)	144 (70.6)	60 (29.4)	1000 Genomes Project[17]
	Sri Lankan Tamil in the UK (STU)	102	56 (54.6)	41 (40.2)	5 (4.9)	153 (75.0)	51 (25.0)	1000 Genomes Project[17]
	Bengali in Bangladesh (BEB)	86	49 (57.0)	35 (40.7)	2 (2.3)	133 (77.3)	39 (22.7)	1000 Genomes Project[17]
East Asian	Chinese	80	48 (60.0)	31 (38.8)	1 (1.2)	127 (79.4)	33 (20.6)	Wan et al.[3]
	Han Chinese in Bejing, China (CHB)	103	79 (76.7)	20 (19.4)	4 (3.9)	178 (86.4)	28 (13.6)	1000 Genomes Project[17]
	Japanese	67	50 (74.6)	16 (23.9)	1 (1.5)	116 (86.6)	18 (13.4)	Fujite et al.[20]
	Japanese in Tokyo, Japan (JPT)	104	80 (76.9)	22 (21.2)	2 (1.9)	182 (87.5)	26 (12.5)	1000 Genomes Project[17]
	Chinese	116	91 (78.4)	23 (19.7)	2 (1.7)	205 (88.4)	27 (11.6)	Shen et al.[21]
	Southern Han Chinese, China (CHS)	105	82 (78.1)	23 (21.9)	0 (0.0)	187 (89.0)	23 (11.0)	1000 Genomes Project[17]
	Korean**	204	173 (84.8)	28 (13.7)	3 (1.5)	374 (91.7)	34 (8.3) [a]	Choi et al.[22]
	Kinh in Ho Chi Minh City, Vietnam (KHV)**	99	87 (87.9)	12 (12.1)	0 (0.0)	186 (93.9)	12 (6.1)	1000 Genomes Project[17]
	Chinese Dai in Xishuangbanna, China (CDX)***	93	85 (91.4)	8 (8.6)	0 (0.0)	178 (95.7)	8 (4.3)	1000 Genomes Project[17]
West Asian	Iranian	65	35 (53.8)	25 (38.5)	5 (7.7)	95 (73.0)	35 (27.0)	Sharifi et al.[23]
	Jordanian	437	256 (58.6)	151 (34.5)	30 (6.9)	663 (75.9)	211(24.1) [a]	Al-Eitan et al.[24]
Black								
African	Yoruba in Ibadan, Nigeria (YRI)	108	62 (57.4)	41 (38.0)	5 (4.6)	165 (76.4)	51 (23.6)	1000 Genomes Project[17]
	African Caribbeans in Barbados (ACB)	96	59 (61.5)	34 (35.4)	3 (3.1)	152 (79.2)	40 (20.8)	1000 Genomes Project[17]
	Esan in Nigeria (ESN)	99	66 (66.7)	28 (28.3)	5 (5.1)	160 (80.8)	38 (19.2)	1000 Genomes Project[17]
	Luhya in Webuye, Kenya (LWK)	99	64 (64.6)	32 (32.3)	3 (3.0)	160 (80.8)	38 (19.2)	1000 Genomes Project[17]
	African Ancestry in Southwest USA (ASW)	61	48 (78.7)	11 (18.0)	2 (3.3)	107 (87.7)	15 (12.3)	1000 Genomes Project[17]

Differences in the frequencies were evaluated using X^2 test. n total number of subjects. [a]: Data were obtained from the results of the articles.

*Significant at *p<0.05, **p <0.01 and *** p<0.001 when compared to the findings of the present study.*

Additionally, the A allele frequency of the *ABCC2* 1249G>A polymorphism in the Turkish population was similar to those reported for White ancestry with range from 14.1 to 23.7%, including German, Spanish, Iberian populations in Spain (IBS), British in England and Scotland (GBR), Finnish in Finland (FIN), Utah Residents with Northern and Western European Ancestry (CEU), Puerto Rican in Puerto Rico (PUR), Colombian in Medellin, Colombia (CLM), Mexican Ancestry in Los Angeles, California (MXL), Peruvian in Lima, Peru (PEL) ($p>0.05$). Similarly, there were no significant distinctions between the Turkish population and Black ancestry with range of 12.3 to 23.6% allelic frequencies, including Yoruba in Ibadan, Nigeria (YRI), African Caribbeans in Barbados (ACB), Esan in Nigeria (ESN), Luhya in Webuye, Kenya (LWK), African Ancestry in Southwest USA (ASW) ($p>0.05$).

Genetic variations influence or do not influence drug response based on their impact on protein activity and the relevance of such proteins in the pathway of the medication, and the frequencies of these genetic variations vary from population to population, thus the clinical significance of a certain variation differs among populations[16]. The frequencies of *ABCC2* 1249G>A polymorphism differ from population to population. Therefore, the clinical significance of this polymorphism varies inter- and intra-population.

Ranganathan et al.[25] investigated the impact of methotrexate (MTX) transporter gene polymorphisms on toxicity of MTX in African American and Caucasian American patients with rheumatoid arthritis, and it was reported that the *ABCC2* 1249G>A variant was related with gastrointestinal toxicity in African-American patients ($p=0.009$). Sharifi et al.[23] evaluated the relationship between 1249G>A, 3972C>T and -24C>T polymorphisms of *ABCC2* gene and serum levels of MTX and its toxic side effects in 65 childhood acute lymphoblastic leukemia patients and reported that patients with the 1249A allele had an increment ratio of gastrointestinal toxicity (odds ratio [OR]=3.47; 95% confidence Interval [CI]=1.04-11.57; $p=0.05$).

In the study by Izzedine et al.[13], a significant allelic relationship was observed between the renal proximal tubulopathy induced by tenofovir disoproxil fumarate and the G1249A polymorphism (OR=6.11; 95%CI=1.19–31.15; $p<0.02$). Furthermore, Nishijima et al.[26] declared that there was an important association between tenofovir-induced kidney tubular dysfunction and the 1249AA genotype of *ABCC2* (adjusted OR=16.21; 95% CI=1.630–161.1; $p=0.017$).

ABCC2 plays a role in the transportation of antiepileptic drugs[27]. One of the most frequently prescribed antiepileptic drugs is carbamazepine (CBZ)[28]. Genetic polymorphisms of the *ABCC2* gene might influence individual drug responses to CBZ[27]. Kim et al.[27] declared that the *ABCC2* 1249G>A polymorphism indicated a potent relationship with the neurological adverse drug reactions induced by CBZ ($p=0.005$) and reported that the existence of A allele at the *ABCC2* G1249A locus was an independent determinant of central nervous system-related adverse drug reactions induced by CBZ. Ufer et al.[29] reported that among those who responded to and did not respond to first-line antiepileptic therapy, the subjects with the G1249A variant were more common among responders. Also, it was declared that the effect of the G1249A polymorphism was more marked among 64 patients with childhood epilepsy that received CBZ or oxcarbazepine ($p=0.005$) and that the *ABCC2* 1249G>A was related with better response in these patients. Also, the rs2273697 variant was reported to be importantly related with the altered CBZ clearance[28]. In contrast, Wan et al.[3] examined the impacts of *ABCC2* polymorphisms on plasma CBZ concentrations

and pharmacoresistance in 80 epileptic patients from China, and it was reported that there were no distinctions in adjusted plasma concentrations or maintenance doses of CBZ among the genotypic groups of rs2273697. In addition, Qu et al.[30] evaluated the impacts of the genetic variations in the *ABCC2* gene on the therapeutic effectiveness of antiepileptic drugs in a group of patients with epilepsy from China, and it was concluded that *ABCC2* rs2273697 polymorphism was not related with drug resistant epilepsy.

Genetic polymorphisms are affected by ethnic differences and thus their frequencies vary from population to population[31]. Furthermore, genetic polymorphisms may alter pharmacodynamic and pharmacokinetics of various medicines, and therefore may give rise to intra- and inter-population variations in drug safety, drug efficacy and drug toxicity.

CONCLUSIONS

The current study presents the distribution of frequencies of *ABCC2* 1249G>A polymorphism in the Turkish population and the comparison of the findings obtained with the results of previously reported populations. This study may ensure beneficial information to evaluate inter-individual difference in response to drug, predict the possibility of adverse effects during treatment with its substrates in patients and improve disease management, briefly, it may help to develop pharmacogenetic studies and contribute to epidemiological studies.

Ethics Committee Approval: The study was conducted in accordance with the approval of the Ethics Committee of Mersin University (19/02/2020, protocol no: 2020/170).

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

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