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CONTENTS

Associated gene polymorphism (*ABCG2*) and drug-resistant in patients with epilepsy

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ABSTRACT

Aim: To evaluate useful variations in ABCG2 gene in relation to reaction of epileptic tablets in people with partial epilepsy. Additionally, explore opportunity of blended outcomes of variations in more than one transporter genes.

Materials and Methods: The study included sixty-five sufferers and forty healthful people; there were no top notch versions in phrases of age, gender, antiseizure medication therapy, or precise kinds of prescription drugs used. Polymorphism testing involved DNA extraction from the sample. Data pertaining to studies that examined correlation between ABCG2 polymorphisms were sought out. A total of 105 individuals, 65 of whom were patients and 40 of whom were healthy controls, were enrolled from October 2023 to April 2024 in this case-control research that took place in a hospital setting.

Results: Common age of sufferers turned into 22.51 ± 5.89 years, while manage organization had a median age of 19.24 ± 3.77 years. Distribution of sufferers and control individuals had a comparable frequency, with no brilliant disparities in terms of gender, antiseizure drug therapy, or antiseizure remedy kind. The heterozygous genotype CT became observed to be greater commonplace in patients compared to the manage group. The correlation among the ABCG2 C>T poly allele polymorphism and the risk of epilepsy was quite widespread.

Conclusions: Overall, the study found that the ABCG2 C>T (rs2231137) polymorphism is associated with an increased risk of epilepsy. Specifically, the patient group was more likely to have the heterozygous genotype CT, with the allele C, compared to the control group.

KEY WORDS: ABCG2 gene, reaction of epileptic tablets, antiseizure medication therapy

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INTRODUCTION

ATP-binding cassette transporters play a function in the way medicines are processed and how the frame responds to them in unique conditions. There had been several recognized versions in ATP-binding cassette transporter genes that are related to adjustments within the way prescription drugs are transported. A worldwide incidence rate of 41 to 187 per 100,000 persons is associated with epilepsy, a common neurological disorder in children [1-2]. The incidence is higher in developing nations, particularly in rural areas [2]. Twenty percent of patients still experience severe drug-resistant seizures, even though several antiseizure medications (ASM) have been developed in the past few years [3]. The inability to gain seizure control or independence after adequate trials of two properly chosen antiseizure medication (ASM) regimens, either alone or in combination, is a hallmark of drug-resistant epilepsy (DRE) [4-5]. The pathophysiology of epilepsy, the pharmacokinetics of the ASM, the interaction between the ASM and its target(s), and genetic variables are the primary determinants of the response to antiseizure medicine (ASM) [6-7]. To understand the biological process behind DRE, two related theories have been put forward, the "target" and the "transporter" hypotheses [8-9]. Genetic variations have the potential to affect the pharmacokinetics and pharmacodynamics of ASMs at every step of their process, from gastrointestinal absorption to drug distribution to the brain, pharmacological activity at brain sites, disposal, and metabolism [10]. The efficacy of the therapy can be altered by these variables, which can affect transporters and target proteins [10]. An essential physiological role of the Blood-Brain Barrier (BBB) is to protect and stabilize the central nervous system (CNS) [11]. Members of the superfamily of ATP binding cassette (ABC) transporters allow chemicals to pass through the blood-brain barrier (BBB) [12]. A crucial member of the ABC superfamily of transporters, the ABCG2 protein is encoded by the ABCG2 gene located on chromosome 4q22. One possible explanation for

the difficulty in administering pharmacological therapy for seizures is that the brain acts as a barrier, blocking the entrance of ASMs and other pharmacological substances [13]. Although the transporter theory does not completely explain its origin, it is considered that the activation of efflux transporters in the blood-brain barrier (BBB) contributes to the establishment of antimicrobial drug resistance [14]. A large number of antiseizure medicines (ASMs) work by influencing sodium channels. Consequently, the SCN1A gene has been suggested as a possible locus to investigate SNPs' role in drug-resistant epilepsy (DRE) [16-17]. Another possible element that might be involved in drug recognition exams (DRE) is drug metabolism. The CYP3A subfamily, and more especially CYP3A4 and CYP3A5, is responsible for the majority of ASM metabolism [18-21]. There is more genetic diversity in the CYP3A5 gene than in the CYP3A4 gene, which causes variations in expression and catalytic activity from person to person. Antiseizure medication (ASM) response may thus be affected by CYP3A5 genetic variants [22]. Recent studies have highlighted the critical role of ATP-binding cassette (ABC) transporters in drug pharmacokinetics and pharmacodynamics. These membrane proteins significantly influence the absorption, distribution, and elimination of various pharmaceuticals. The [23] demonstrated that ABC transporters, particularly P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance-associated proteins (MRPs), actively efflux drugs from cells, potentially limiting their therapeutic efficacy. This research has led to the development of novel strategies to overcome transporter-mediated drug resistance and improve drug delivery to target tissues. For instance, Chen et al. (2024), [24] reported the successful use of nanoparticle-based drug delivery systems to bypass ABC transporter-mediated efflux, enhancing the efficacy of anticancer drugs in multidrug-resistant tumor cells. The impact of ABC transporters on drug response has gained significant attention in the field of personalized medicine. Genetic polymorphisms in ABC transporter genes have been associated with variations in drug response and toxicity among individuals. The [25] reported on a large-scale implementation of ABC transporter genotyping in a major healthcare system, demonstrating improved treatment outcomes and reduced adverse effects through personalized drug selection and dosing strategies.

AIM

To evaluate useful variations in ABCG2 gene in relation to reaction of epileptic tablets in people with partial epilepsy. Additionally, explore opportunity of blended outcomes of variations in more than one transporter genes.

MATERIALS AND METHODS

SAMPLES COLLECTION

Participants with epilepsy were surveyed in order to get samples. Polymorphism testing involved DNA extraction from the sample. Data pertaining to studies that examined the correlation between ABCG2 polymorphisms were sought out. A total of 105 individuals, 65 of whom were patients and 40 of whom were healthy controls, were enrolled from October 2023 to April 2024 in this case-control research that took place in a hospital setting.

DNA EXTRACTION AND GENOTYPING

Before genomic DNA extraction, blood samples were taken from participants and kept at 4 degrees Celsius in Ethylene-diamine-tetra-acetic acid (EDTA) tubes. Using the traditional salting-out method, genomic DNA was isolated from whole blood. The most significant SNPs in the candidate genes were selected, including ABCG2 chr4:88139962 C>T (rs2231137). In this study, we genotyped SNPs using the Primer1 ARMS-PCR primer generation programme and the NCBI-SNP database, scientific Researcher Co. Ltd. Iraq provided the primers, as shown in Table 1.

STATISTICAL ANALYSIS

In a study of Egyptian epileptic patients, the chi-square test was used to evaluate the Hardy-Weinberg equilibrium of three ABCG2 gene SNPs coupled with drug resistance. We conducted the Chi-square test to see if there was a statistically significant relationship between the 95% CI and the observed odds ratio (OR). An estimate was considered significant if its P value was less than or equal to 0.05, after the data were examined using bilateral probability.

RESULTS

A total of sixty-five patients and forty healthy controls were included in the present investigation. Table 2 shows the demographic information of the control group and the patients. In contrast to the control group, which had an average age of 19.24 ± 3.77 years, the patients' average age was 22.51 ± 5.89 years. The average ages of the patients and the control group did not differ significantly (P = 0.277). Again, when looking

Table 1. Primer sequences used for high-resolution melting method

SNPs	Sequencing	
ABCG2 C>T (rs2231137)	F	AAACCTGTGAGGTTCACTGTAGG
	R	CTGCAGAAAGATAAAAACTCTCCAG

Table 2. Demographic characteristics of patients and control subjects

Characteristic	Patients n = 65	Control n =40	P value
Age (years)			
Mean ±SD	22.51 ± 5.89	19.24 ± 3.77	0.277 † NS
Range	18-22	19-22	
18-19 *n* (%)	19 (29.23%)	15 (37.5%)	0.598 ¥ NS
20-21 *n* (%)	24 (36.92%)	11 (27.5%)	
>22 *n* (%)	22 (33.84%)	15 (37.5%)	
Gender			
Male, *n* (%)	33 (50.76%)	19 (47.5%)	0.299 ¥ NS
Female, *n* (%)	32 (49.23%)	21 (52.5%)	
Epilepticus history status			
Positive	41 (63.07%)	0 (0.00%)	0.001 ¥ S
Negative	14 (21.87%)	0 (0.00%)	
Number of antiseizure medication therapy			
1 antiseizure medication	26 (40.0%)	0 (0.00%)	0.0621 ¥ NS
2 antiseizure medications	11 (16.92%)	0 (0.00%)	
>2 antiseizure medications	28 (43.07%)	0 (0.00%)	
Type of antiseizure medications			
Non-enzyme inducing	31 (47.69%)	0 (0.00%)	0.524 ¥ NS
Enzyme inducing and combination	34 (52.30%)	0 (0.00%)	
ASMs used in patients (%)			
Carbamazepine	25 (38.46%)	0 (0.00%)	0.741 ¥ NS
Valproic acid	24 (36.92%)	0 (0.00%)	
Oxcarbazepine	16 (24.61%)	0 (0.00%)	

n: number of cases; SD: standard deviation; †: independent samples t-test; ¥: Chi-square test; NS: not significant at $P > 0.05$; HS: highly significant at $P \leq 0.05$.

at the frequency distribution by age, we could not find any significant difference between the control group and the patients (P = 0.598). While the control group included 21 females (52.5%) and 19 males (47.5%), the patients' group included 33 men (50.76%) and 32 females (49.23%). Patients and controls did not differ significantly (P = 0.299) in terms of gender distribution. Furthermore, when considering the amount of medication used to treat seizures, The patient group included 28 people (or 43.17% of the total) who were using more than 2 antiseizure medications, 11 people (16.92%) who were taking 2 drugs, and 26 people (40.0%) who were using 1 drug. The gender distribution of the patients and control individuals did not differ significantly (P = 0.0621). This class of antiepileptic medications of the patients surveyed, 31 (or 47.69%) were found to not induce enzymes, whereas 34 (or 52.30%) were found to induce enzymes or both. The gender distribution of the control individuals and patients did not differ significantly (P = 0.524). Just how many patients were given ASMs? Eleven people (34.61%) in the patient group took carbamazepine, twenty-four people (39.21%) took valproic acid, and sixteen people (24.61%) took oxycarbazepine. The gender distribution of the control individuals and patients did not differ significantly (P = 0.741). The data presented above show that the sick group and the control group are statistically equivalent.

GENOTYPIC ANALYSIS FOR STUDIED GENES IN PATIENTS AND CONTROL GROUPS

Table 3 displays the correlation between the ABCG2 C>T (rs2231137) POLY gene variant and the probability of

Table 3. Genotypes frequency in patients and control group

C>T (rs2231137)						
Genotype	**Patients n=65**	**Control n=40**	**P1**	**P2**	**OR**	**95% CI**
CC	28	15	0.019 ¥ S	0.625 ¥ S	1.0667	0.4634- 2.4554
CT	33	20		0.553 ¥ NS	2.0625	0.4949- 8.5954
TT	4	5		Reference	Reference	Reference

P1: overall comparison; P2: Individual genotype comparison versus reference; n: number of cases; ¥: Chi-square test; OR: odds ratio; CI: confidence interval; EF: etiologic fraction; NS: non-significant.

Table 4. POLY allele frequency in patients and control group

rs1354742084 A>C					
Genotype	**Patients n=130**	**Control n=80**	**P**	**OR**	**95%CI**
C	89	50	0.035 ¥ HS	1.3024	0.7259 - 2.3369
T	41	30		0.7678	0.4279 - 1.3776

n: number of alleles; ¥: Chi-square test; OR: odds ratio; CI: confidence interval; EF: etiologic fraction; PF: preventive fraction; HS: highly significant at $P \leq 0.01$.

acquiring epilepsy. The frequency of the heterozygous genotype CT was 33 occurrences in the patients group and 20 occurrences in the control group. The statistical significance of this difference was determined to be P=0.019. The odds ratio for patients with epilepsy who had genotype CT was 1.0667 (95% CI: 0.4634-2.4554), indicating that it was a risk factor.

Table 4 shows the association between the ABCG2 C>T (rs2231137) polyallele polymorphism and the risk of epilepsy. Allele C occurred more frequently in the sick group (89 instances) than in the control group (50 instances). A statistical analysis revealed a significant difference (P = 0.035).

DISCUSSION

This case-control research aimed to determine whether there was a correlation between three genes thought to have a role in the development of drug-resistant epilepsy (DRE) and certain single nucleotide polymorphisms (SNPs). As the number of T alleles in the ABCG2 gene increases, we found that the single nucleotide polymorphism (SNP) rs2231137 is associated with a higher risk of drug resistance epilepsy (DRE). For the first time in this particular cohort, the finding and the high link provide evidence that the ABCG2 gene may be involved in the development of drug-resistant epilepsy (DRE). Research using prospective methodologies and bigger sample sizes may be stimulated by these findings. The results show that among Egyptians, the ABCG2 (rs2231137) polymorphism is significantly associated with epilepsy and Pharmaco-resistant epilepsy. Previous studies have failed to discover a connection between the ABCG2 rs2231137 SNP and drug-resistant epilepsy (DRE) [26], which contradicts our findings. Research by Shen et al. sought to determine how the ABCG2 rs2231137 polymorphism affected Lamotrigine's efficacy in treating seizures in Chinese individuals. There was shown to be no statistically significant relationship between the two variables [27]. Additionally, for epilepsy patients, the existence of genetic variants in the ABCG2 transporter (rs2231137) does not significantly affect the prediction of treatment response, as [28] showed. In this groundbreaking study, we use a systematic review of the literature to show that the ABCG2 rs2231137 SNP is associated with an elevated risk of DRE in children. A number of studies have shown that genetic polymorphisms cause an overexpression of ABC transporter proteins like ABCG2 [29], but no one has yet provided a clear explanation for this phenomenon. Excessive synthesis of ABC transporters, particularly ABCG2, at the blood-brain barrier (BBB), is a pathophysiological mechanism of drug-resistant epilepsy (DRE). Inhibiting the entrance of several antiseizure drugs (ASMs) including gabapentin, lamotrigine, levetiracetam, and phenobarbital, ABCG2 is expressed at greater levels in endothelial cells, astrocytes, and neurons of the blood-brain barrier (BBB). Pharmacokinetic parameters such as distribution, action, and excretion are significantly affected by cytochrome P450 genes, which are involved in the metabolism of most antiseizure drugs. Therefore, these genes can affect how well these drugs work to suppress seizures generally [30]. Several cytochrome P450 proteins, including as the CYP3A5 enzyme, are involved in the metabolism of ASMs. A mutant allele known as CYP3A5*3 (rs776746) causes the enzyme CYP3A5 to not function as a catalytic agent [31]. Multiple criteria indicate that CYP3A5*3 is not associated with pharmacoresistance. Other cytochrome P450 proteins metabolize ASMs in addition to CYP3A5. They can make up for each other's diminished activity since CYP3A4 and CYP3A5 are structurally and substrate selectivity-wise quite similar. A single nucleotide poly-

morphism (SNP) in the gene may have less of an impact due to this compensatory [32]. There is polymorphism in both the CYP3A5 and CYP3A4 enzymes, although only the latter shows inducible effects [33]. The effect of inductions on enzymes that metabolize drugs is thought to be larger than that of polymorphisms. Our population of drug-resistant patients may be taking many drugs, each of which may include a chemical that increases CYP3A activity and, by extension, the influence of CYP3A5 variants on treatment efficacy. This is similar to the findings of other studies [34-35]. Because drug-resistant epilepsy (DRE) has such far-reaching consequences in neurological, psychological, educational, social, and occupational domains, investigating its causes is essential for the creation of alternative seizure medicines (ASM) and treatment approaches [36]. The study's findings can help clinicians apply precision medicine principles to tackle these specific problems, such as unregulated emergencies and high quantities of ineffective antimicrobial drugs (ASM), which lead to significant neuropsychiatric consequences like depression and anxiety disorders, social harm, reduced quality of life, increased occurrence of other medical conditions like intellectual disability and attention and learning difficulties, and an elevated risk of death [37]. Depending on the patient's reaction to medications, this helps choose the best course of therapy and can also shed light on how to personalize treatment for certain genotypes. However, before drawing any conclusions, it is critical to identify and resolve the study's shortcomings. Odds ratio (OR) confidence intervals are wider and the marginal p-value is 0.05 because of the study's small sample size. This means that bigger sample sizes and prospective study methodologies are required to confirm the results. We also did not look for a connection between the potential SNPs and ASM concentrations, mainly because clinical settings seldom monitor ASM concentrations. Children from Iran were the subjects of our case-control research, which took place in a single referral hospital. Hence, to make the results more generalizable, further research in groups with different genetic patterns is needed. Our research has shown that there is evidence linking a specific genetic variation in the ABCG2 gene-more specifically, an increase in the frequency of the T allele-to an increased risk of drug-resistant epilepsy in children. The implications of this finding for understanding the role of ABCG2 gene variation in drug-resistant epilepsy in children are substantial. To find more SNPs associated with drug-resistant epilepsy (DRE) on a genome-scale, genome-wide association studies are required.

CONCLUSIONS

The study found that the ABCG2 C>T (rs2231137) polymorphism is associated with an increased risk of epilepsy. Specifically, the patient group was more likely to have the heterozygous genotype CT, with the allele C, compared to the control group.

ABBREVIATION

ABC: ATP-Binding Cassette (ABC)
ASM: Antiseizure Medications
DRE: Drug-Resistant Epilepsy
CNS: Central Nervous System
BCRP: Breast Cancer Resistance Protein
MRPs: Multidrug Resistance-Associated Proteins
BBB: Blood-Brain Barrier

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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