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# The association between *MDR1* C3435T genetic polymorphism and the risk of multidrug-resistant epilepsy in Egyptian children

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## Abstract

**Background:** Epilepsy is a chronic disease affecting about 2% of the population and is considered a serious neurological disease. Despite its good prognosis, 20–30% of epileptic patients were not cured of their seizures even with the many trials of antiepileptic drug (AED) therapy. The resistance mechanism is still unclear, maybe due to the effect of the genetic factors on the bioavailability of the drugs. Consequently, the association between therapy resistance and the presence of a gene called “multidrug resistance 1 (*MDR1*)” had been proposed. Thus, the present study aimed to understand the relationship between the genetic polymorphism of *MDR1*C3435T and the resistance to AEDs.

**Result:** A non-significant association was found between *MDR1* C3435T single-nucleotide polymorphism (SNP) and drug-resistant epilepsy. However, there was statistical significance in the association between the drug type and the genotype distribution, in cases that were maintained on sodium valproate and *MDR1*C3435T genotype.

**Conclusion:** Possible involvement of the *MDR1* gene C 3435T polymorphism with sodium valproate resistance clarifies the importance of genetic variability in response to the drug and may help to find novel genetic therapy for epilepsy, by targeting the biological mechanisms responsible for epilepsy in each specific individual. Future studies with bigger sample sizes and in other racial populations will be necessary.

## Background

Epilepsy is one of the most severe neurological chronic diseases, its types and response to drugs affected by multiple genetic polymorphisms in innate immunity receptors [1]. Despite its excellent prognosis, 20–30% of epileptic children were not cured of seizures, even with the various trials of antiepileptic drug (AED) therapy [2–4]. Even with taking many AEDs, as poly-therapy in epileptic seizures, death still may occur and remained a health threat. Also,

the mechanism of the different drug responses from one patient to another is still unclear, and whether a pharmaco-genomic phenomenon exists needs to be explored [5].

The mechanism of the resistance to therapy is still insufficiently studied. However, some theories for this resistance have been suggested, such as the effect of the drug bioavailability by genetic factors in pharmacoresistant epilepsy. These disorders mainly affect the metabolism of the drug, which affects its efficacy [6–8].

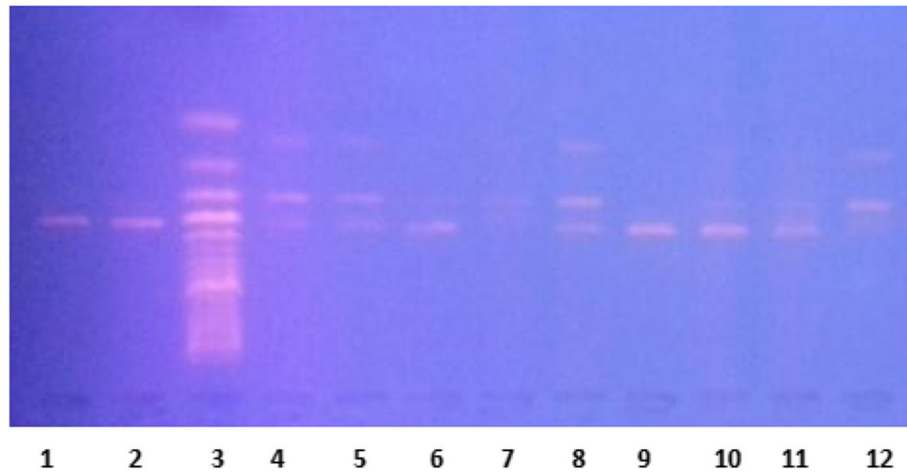
Physicians can predict the long-term outcome of an epileptic patient’s response to the drug by assessing the initial reaction to the drug [9]. Unfortunately, many epileptic children with recurrent epilepsy take many treatments but with no response [2]. Many clinical aspects

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**Fig. 1** Gel electrophoresis images. Lanes 1 and 2: PCR product (206). Lane 3: DNA marker. Lanes 4, 5, and 8: three bands (206 bp, 130 bp, and 76 bp C/T genotype). Lanes 6, 9, 10, and 11: one band (206 bp to T/T genotype). Lane 12: two bands (130,76 bp fragments to the C/C genotype)

are essential for a better understanding of the resistance to epileptic therapy. Some of which include the identification of seizure type, the cause, the onset of epilepsy, the continuation of epilepsy despite treatment, the type of brain lesion, and the number of epileptic fits before the start of treatment [10–12].

Two suspected hypotheses of drug resistance were proposed. The first hypothesis stated that the change in the target of the drug occurred in the brain, while the second one stated that it occurred in the blood–brain barrier (BBB) by the increased expression of drug efflux [13, 14]. These two changes could be explained by the genetic polymorphisms which altered the pharmacodynamics of epileptic therapy and their associated response [15].

The P-glycoprotein (P-gp) is an energy-dependent efflux pump, which expels many AEDs [13, 16, 17]. This protein is the product of the ATP-binding cassette subfamily B member 1 (*ABCB1*) gene and is also known as the multidrug resistance 1 (*MDR1*) gene [18, 19]. The primary function of P-gp and *MDR1* in the transmembrane transport of epileptic therapy has been illustrated in several pieces of literature [5, 20, 21]. Also, the genetic polymorphism role of the *ABCB1* gene has been

suggested to cause the overexpression of the efflux transporter, P-gp [22].

It was theorized that the drug resistance phenomena (DRE) are influenced by *MDR1*C3435T single-nucleotide polymorphisms (SNPs) (rs1045642) [23–25], where C3435T polymorphism takes place in the transmembrane drug through the alteration of the *MDR1* gene then the P-gp function [21]. The P-gp affects the transportation of multiple drugs through the BBB and the cellular membrane of astrocytes, which illustrates the importance of P-gp in the DRE mechanism [21].

Genetic polymorphisms in the *ABCB1* gene affect the function of *MDR1* gene in both the degree of expression and transport level, which makes it an important factor in pharmaco-resistant epilepsy phenotype [26]. Many SNPs were illustrated in different studies, which change the purpose of this gene [26]. Moreover, *MDR1* inhibitors affect the pharmacokinetics of multiple drugs. A common single-nucleotide polymorphism (SNP) of *ABCB1* is the transition of C base to T base at exon 26 in position 3435 [27–29].

Several studies examined the association between refractory epilepsy and the different SNPs in the

**Table 1** Association between *MDR1* C3435T SNP genotype and multidrug-resistant among epilepsy cases

<i>MDR1</i> C3435T genotype	Drug		$\chi^2$	<i>p</i>	OR (95%CI)
	Resistance, <i>n</i> = 63 (%)	Responsive, <i>n</i> = 43 (%)			
CC(r)	32 (64.0)	18 (36.0)			1
CT	21 (51.2)	20 (48.8)	1.5	0.2	0.6 (0.3–1.4)
TT	10 (66.7)	5 (33.3)	0.04	0.85	1.13 (0.33–3.8)

No statistically significant association was found between drug response or drug resistance, and *MDR1* C3435T genotype distribution among epilepsy cases with 66.7% of TT genotype was detected among cases with drug resistance. The Hardy–Weinberg equation shows a non-statistically significant difference from the gene distribution in the total population

$\chi^2$  chi-square test, OR odds ratio, *p* probability, HW Hardy–Weinberg equilibrium

**Table 2** Distribution of *MDR1* C3435T SNP genotype among the studied groups

<i>MDR1</i> C3435T genotype	Groups		$\chi^2$	<i>p</i>	OR (95%CI)
	Control, <i>n</i> = 100(%)	Cases, <i>n</i> = 106(%)			
CC(r)	56 (56.0)	50 (47.2)			1
CT	34 (34.0)	41 (38.7)	0.988	0.32	1.35 (0.75–2.44)
TT	10 (10.0)	15 (14.2)	0.04	0.85	1.13 (0.33–3.8)
HW	<i>p</i> = 0.169	<i>p</i> = 0.175			

No statistically significant association was found between epileptic cases or control and *MDR1* C3435T genotype distribution

*ABCB1* gene [30, 31]. However, the relationship between the *ABCB1* gene and drug-resistant epilepsy still needs to be confirmed by other studies in different ethnic groups, due to the frequency in gene variation according to the different ethnicity. Thus, the target of this work was to study the relationship between C3435T SNP of the *MDR1* gene and the response to therapy in Egyptian children.

## Method

### Patients

This study is a case-control study involving 106 pediatric patients of The Children Hospital, diagnosed with epilepsy and treated with AEDs, along with 100 healthy non-epileptic children, as the control group (60 males, 40 females) that were chosen based on clinical examination and laboratory investigations, from the same geographical area. Patients were diagnosed and classified according to the guidelines of the International League against Epilepsy (ILAE), which concluded to 63 patients (35 males, 28 females), with a mean age of  $8.58 \pm 4.14$  years, who were resistant to therapy and 43 patients (28 males, 15 females), with a mean age of  $6.83 \pm 4.57$ , who responded to treatment. The exclusion criteria consisted of any significant medical disorders (e.g., hepatic or renal diseases), malignant conditions (e.g., brain tumor), secondary metastasis, history of pseudo-seizures, severe side effects of therapy, and any progressive, degenerative or metabolic brain disorders.

Following the ILAE 2010 definition of drug-resistant epilepsy, as non-successive trials of two or more AEDs, in this study, epileptic children were subtyped into 2 groups: drug-responsive group and drug-resistant epilepsy group. The antiepileptic drug regimens were either administered as mono-therapies or poly-therapies.

### DNA extraction

Three-milliliter samples, of ethylene diamine tetra-acetic acid blood, was obtained from patients and preserved at  $-20^\circ\text{C}$  until relevant analysis was conducted, at the Clinical Pathology Department. DNA extraction from the whole blood was prepared for molecular analysis

using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.

### Genotyping

Extracting DNA and genotyping analysis of *MDR1* gene C 3435T polymorphism (exon 26) by the PCR-RFLP method were performed according to the method described by Seven et al. [32]. PCR amplifications were performed using the following: 100 ng extracted DNA, 1 U of Taq, 1  $\mu\text{M}$  of each primer [F:5'-TTG ATG GCA AAG AAA TAA AGC-3' and R:5'-CTT ACATTAGGC AGT GAC TCG-3'], 1X PCR buffer, 1 mM MgCl<sub>2</sub>, and 0.04 mM dNTPs, where the 1st step was initial denaturation at  $94^\circ\text{C}$  for 4 min; 2nd step 35 cycles each of  $94^\circ\text{C}$  for 30 s,  $56^\circ\text{C}$  for 30 s, and  $72^\circ\text{C}$  for 30 s; and 3rd step final extension at  $72^\circ\text{C}$  for 5 min. The PCR products were digested by restriction endonucleases of Mbolat  $37^\circ\text{C}$  for 3 h and analyzed with 3% agarose gel electrophoresis (Fig. 1).

### Statistical analysis

The gathered data were analyzed using the Statistical Package for the Social Sciences program, version 20.0. Quantitative data were described using the mean, median, and range for nonparametric data after testing normality using the Kolmogorov–Smirnov (K-S) test. Nonparametric data were expressed in median, minimum, and maximum. The normality of data was first tested by the one-sample KS test. The chi-square test was used for comparing categorical variables between the studied groups, while the Kruskal–Wallis test was used for comparing nonparametric continuous variables between more than two studied groups. Also, the Mann–Whitney *U* test was used for comparing nonparametric continuous

**Table 3** *MDR1* C3435T allele distribution between cases and control

Allele	Studied groups		$\chi^2$	<i>p</i> value	OR (95%CI)
	Control, <i>n</i> = 200	Cases, <i>n</i> = 212			
C(r)	146 (73)	141 (66.5)	1.32	0.25	1
T	54 (27)	71 (33.5)			1.4 (0.8–2.3)

No statistically significant association was found between epileptic cases or control and *MDR1* C3435T allele distribution

**Table 4** Association between *MDR1*C3435T genotype and epilepsy types (generalized and partial)

<i>MDR1</i> C3435T genotype	Epilepsy type		$\chi^2$	<i>p</i>	OR (95%CI)
	Generalized, <i>n</i> = 83 (%)	Partial, <i>n</i> = 23 (%)			
CC(r)	37 (74.0)	13 (26.0)			1
CT	33 (80.5)	8 (19.5)	0.53	0.46	1.4 (0.53–3.9)
TT	13 (86.7)	2 (13.3)	1.04	0.31	2.3 (0.5–11.5)

No statistically significant association was found between epileptic types (generalized and partial) and *MDR1* C3435T genotype distribution

variables between the two studied groups. The Hardy–Weinberg equilibrium was used to compare the frequency of genotype deviation from the general population. The odds ratio was calculated using cross-tabulation through Epi Info. *p* values were < 0.05 and < 0.001 which are considered statistically and highly statistically significant, respectively.

### Result

66.7% of TT genotype was detected among cases with drug resistance, but no statistically significant association was found between drug response and drug resistance and *MDR1* C3435T genotype distribution in epileptic cases. The Hardy–Weinberg equation shows the non-statistical significant difference of the gene distribution within the total population (Table 1). Genotype and allele distributions also show a non-statistically significant difference between the cases and the control groups (Tables 2 and 3). A non-statistically significant association was detected between the types of epilepsy (generalized and partial) and the genotype distribution among epilepsy cases (Table 4; Fig. 2). Similarly, there is no statistically significant association between the types of epilepsy (generalized and partial) and *MDR1*C3435T allele in these studied cases (Table 5). Thus, the types of epilepsy (primary and secondary) have no statistically

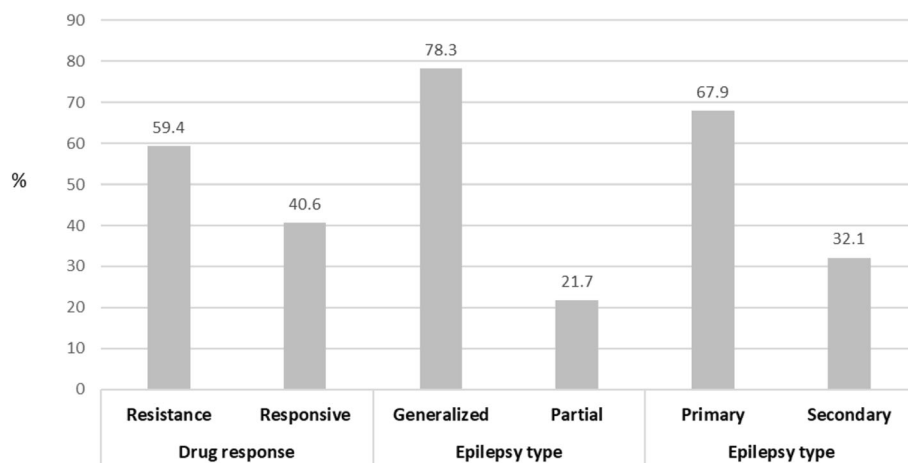
significant association with neither genotype nor allele distribution among epilepsy cases (Tables 6 and 7).

The only statistically significant association found was between the drug type and the genotype distribution, for the cases maintained on sodium valproate and *MDR1* C3435T genotype distribution with 100% of Genotype TT variant, which had resistance followed by CT genotype, then CC (*p* value = 0.04\*). No statistically significant association was found between *MDR1* C3435T genetic polymorphism and many antiepileptic drugs (carbamazepine, levetiracetam, oxcarbamazepine, topiramate, clonazepam, phenytoin, lacosamide, and lamotrigine; *p* value > 0.05) (Table 8).

### Discussion

Epileptic patients mostly show resistance to a wide range of AEDs with different mechanisms of action [33, 34]. The mechanism of drug resistance is explained by increasing drug efflux transporter's expression in BBB, then decreasing the AEDs concentration in the foci of epilepsy [13, 14]. P-gp is defined as an energy-dependent efflux pump that expels many AEDs [13, 16, 17]. Moreover, its production is through *ABCB1*, which is also named *MDR1* [13].

Genetic factors, such as SNP in the *ABCB1* gene, have a role in the overexpression of efflux transporters through the increase of P-gp [22]. The association



**Fig. 2** Epilepsy type and drug response among the studied cases

**Table 5** Association between *MDR1* C3435T allele and epilepsy types (generalized and partial)

Allele	Epilepsy type		$\chi^2$	<i>p</i> value	OR (95%CI)
	Generalized, <i>n</i> = 166(%)	Partial, <i>n</i> = 46(%)			
C(r)	107 (64.46)	34 (73.9)	1.45	0.22	1
T	59 (35.54)	12 (26.1)			1.56 (0.75–3.24)

No statistically significant association was found between epileptic types (generalized and partial) and *MDR1* C3435T allele distribution

between refractory epilepsy and genetic polymorphism in the *ABCB1* gene has been documented by several studies at variable positions of nucleotides (e.g., T1236C, C3435T, and G2677T in exons 12, 27, and 21, respectively) [5, 20, 26, 30, 33, 35–38]. However, the results have to be confirmed by further studies and identified in a review of meta-analyses [7, 39, 40].

Thus, this study focused on the association between the C3435T SNP, either genotype or allele, of the *MDR1* gene and epileptic children on either drug-responsive or drug-resistant therapy and revealed the lack of association between them.

The association between drug-resistant epilepsy and C3435T SNP of *ABCB1* gene has been investigated in many studies [22] and confirmed its existence in many variable ethnicities, especially after the first study which reported the more frequent C/C genotype at position 3435 in drug-resistant epilepsy patients [5, 30, 33, 34]. Conversely, a different association (T/T genotype frequency in drug-resistant rather than drug-responsive children) has been reported in a non-Caucasian study [41], as well as the study by Seo et al., which supported the latter results [42].

However, many studies have reported no significant association between *MDR1* C3435T polymorphism and drug-resistance epilepsy, which was consistent with our present study [26, 35]. Also, Alpman et al. studied this relationship in pediatric patients with DRE (*n* = 39) and a control group (*n* = 92) and found no significant relationship between the CC3435/GG2677 SNP and the multidrug resistance therapy. Moreover, Alpman et al. concluded that it may affect the efficacy of administered drugs in cases of drug-resistant epilepsy [43]. Similarly, the

**Table 7** Association between *MDR1* C3435T allele and epilepsy type (primary and secondary)

Allele	Epilepsy type		$\chi^2$	<i>p</i> value	OR (95%CI)
	Primary, <i>n</i> = 144 (%)	Secondary, <i>n</i> = 68 (%)			
C(r)	98 (68.1)	43 (63.2)	0.48	0.49	1
T	46 (31.9)	25 (36.8)			1.24 (0.68–2.27)

No statistically significant association was found between epileptic types (primary and secondary) and *MDR1* C3435T allele distribution

study concerning Korean patients by Kim et al. resulted in the same insignificant association [44].

Our study reported a statistically significant association between the drug type and the genotype distribution for the cases maintained on sodium valproate and *MDR1*C3435T genotype distribution, with 100% of genotype TT variant resistant, followed by CT genotype and CC (*p* value = 0.04\*). This association may be explained by the relationship of this genotype with voltage-gated sodium channels, T-type calcium channel, and/or GABA-A receptor actions in epilepsy, which is unlike Haerian et al., who found no association between C3435T SNP and haplotypes with VPA response in epileptic children in Malaysia [8]. Alternatively, Siddiqui et al. found an increase in 3435CC genotype frequency in DRE patients who were taking valproic acid [5]. The relationship between Toll-like receptor (TLR4) SNPs and resistance to various AEDs such as Na valproate, carbamazepine, clonazepam, phenytoin, and topiramate was examined by Abdelsalam et al., except for rs11536858 with clonazepam, no association was identified between the SNPs tested and drug resistance [1].

The variation in results may be due to ethnic differences and many limitations that should be considered during the interpretation phase (e.g., environmental factors, types of seizures, AEDs types, dosage) [45]. Moreover, the variant definition of the classification of the drug-resistant patients may have also caused the difference in the results.

## Conclusion

No significant relationship was found between *MDR1*C3435T single-nucleotide polymorphism and the drug-resistant

**Table 6** Association between *MDR1* C3435T SNP and epilepsy types (primary and secondary)

<i>MDR1</i> C3435T genotype	Total cases, <i>n</i> = 106	Epilepsy type		$\chi^2$	<i>p</i>	OR (95%CI)
		Primary, <i>n</i> = 72 (%)	Secondary, <i>n</i> = 34 (%)			
CC(r)	50	35 (48.6)	15 (30.0)			1
CT	41	28 (38.9)	13 (31.7)	0.03	0.86	0.92 (0.38–2.26)
TT	15	9 (12.5)	6 (40.0)	0.53	0.5	0.6 (0.2–2.1)

No statistically significant association was found between epileptic types (primary and secondary) and *MDR1* C3435T genotype distribution

**Table 8** Relation between MDR1 C3435T SNP and epilepsy drugs used

Drug	MDR1 C3435T genotype			$\chi^2$	p
	CC, n = 50 (%)	CT, n = 41 (%)	TT, n = 15 (%)		
Sodium valproate	41 (82.0)	39 (95.1)	15 (100)	6.2	0.04*
Carbamazepine	11 (22.0)	8 (19.5)	3 (20.0)	0.09	0.95
Levetiracetam	28 (56.0)	23 (56.1)	10 (66.7)	0.59	0.74
Oxcarbamazepine	8 (16.0)	5 (12.2)	3 (20.0)	0.58	0.74
Topiramate	19 (38.0)	12 (29.3)	5 (33.3)	0.77	0.68
Clonazepam	6 (12.0)	5 (12.2)	4 (26.7)	2.3	0.32
Phenytoin	4 (8.0)	0 (0.0)	0 (0.0)	4.7	0.1
Lacosamide	1 (2.0)	0 (0.0)	0 (0.0)	1.1	0.57
Lamotrigine	1 (2.0)	2 (4.9)	1 (6.7)	0.92	0.63

The only statistically significant association between drug type and genotype distribution for the cases maintained on sodium valproate and MDR1 C3435T genotype distribution with 100% of genotype TT variant had resistance followed by CT genotype and CC (value = 0.04\*). Non-statistically significant association was found between MDR1 C3435T genetic polymorphism and many antiepileptic drugs (carbamazepine, levetiracetam, oxcarbamazepine, topiramate, clonazepam, phenytoin, lacosamide, and lamotrigine); p value > 0.05

epileptic patients. The only statistically significant association between drug type and genotype distribution was for the cases maintained on sodium valproate and MDR1 C3435T genotype distribution. Possible involvement of MDR1 gene C 3435T polymorphism with sodium valproate resistance clarifies the importance of genetic variability in response to the drug and may help in finding novel genetic therapy for epilepsy by targeting the biological mechanisms responsible for epilepsy in each specific individual. Future studies with bigger sample sizes in other racial populations will be necessary.

#### Abbreviations

AEDs: Antiepileptic drugs; MDR1: Multidrug resistance 1; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism; SNP: Single-nucleotide polymorphism; P-gp: P-glycoprotein; ABCB1 gene: ATP-binding cassette subfamily B member 1; ILAE: International League Against Epilepsy; TLR4: Toll-like receptor

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#### Authors' contributions

DS performed the examination of the patient and collection of the samples. MA wrote the paper and analyzed and interpreted the patient data regarding the disease. HM made the statistical analysis of the data. NT participate in writing. All authors read and approved the final manuscript.

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#### Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

#### Declarations

##### Ethics approval and consent to participate

This study was approved by the ethics committee of the Faculty of Medicine - Mansoura University [Institutional Research Board (IRB) of Faculty of Medicine - Mansoura University], with approval number [R.20.04.807]. The patient's parent provided written consent.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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