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Association of SCN1A Polymorphisms (rs2298771 and rs7601520) with Peripheral Blood miR-150 Expression in Iraqi Children with Epilepsy: An Exploratory Case–Control Study

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Abstract

Despite the fact that epilepsy is a widely prevalent neurological disorder that has a significant genetic basis, the interaction between SCN1A polymorphisms and circulating microRNAs has been poorly studied, especially in Middle Eastern populations. The aim of this exploratory case–control study was to explore the distribution of SCN1A polymorphisms (rs2298771 and rs7601520) and relation with peripheral blood miR-150 expression in Iraqi children with epilepsy. A total of 70 children with epilepsy, who had never taken any medication, and 30 healthy controls were recruited. Genotyping was done by polymerase chain reaction (PCR) and Sanger sequencing, and miR-150 expression was determined by reverse transcription quantitative PCR (RT-qPCR) using the 2–ΔCt method. Hardy-Weinberg equilibrium tests were used to assess the genotype distributions at a P value of < 0.05. The genotype frequencies in the control group were in Hardy-Weinberg equilibrium. There were no statistically significant differences in the genotype or allele frequencies of the two SNP (rs2298771 and rs7601520) between the patients and controls. There was a slight up-regulation of miR-150 in patients versus controls (fold change = 1.38) but it was not statistically significant (P = 0.24). Likewise, there was no significant difference in miR-150 expression between any of the genotype groups of both polymorphisms. To our knowledge, this is the first exploratory study in Iraq that investigated both polymorphisms (SCN1A rs2298771 and SCN1A rs7601520) and expression of peripheral blood miR-150 in children with epilepsy. Although no significant associations were found in this cohort, the results can serve as baseline molecular information of the Iraqi pediatric population and may help in designing larger multicenter studies to further explore the possible role of these markers in childhood epilepsy.

Keywords

SCN1A, rs2298771, rs7601520, miR-150, childhood epilepsy.

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Introduction

Epilepsy is prevalent in children and is a huge health problem in clinical, developmental and socio-economic aspects worldwide. Paediatric epilepsy is a significant cause of disability worldwide; although there have been significant advances in the management and diagnosis of paediatric epilepsy, the availability of specialist paediatric epilepsy services is poor in LMICs and this influences outcomes (Xu et al., 2025; Zhang et al., 2025). In addition, about one-third of affected children go on to develop drug-resistant epilepsy, and there is a need to gain a deeper understanding of the molecular mechanisms involved in susceptibility to the disease and progression, as well as to find complementary molecular markers for the characterization of the disease (Zakaria et al., 2025).

Epilepsy in childhood is very heterogeneous, and because of the interplay between genes, environment and development, is very difficult to classify. In recent years, the introduction of molecular genetics and next generation sequencing (NGS) and the discovery of genetic variants pathogenic in a proportion of early onset and developmental epilepsies has led to a change in the diagnosis of childhood epilepsy. In addition to its diagnostic use, the application of molecular diagnosis is also demonstrated to have a potential role in prognosis, precision medicine (Symonds & McTague, 2020; Salinas et al., 2021) and even in the selection of anti-seizure therapy (Krygier et al., 2024). One of the most well studied epilepsy genes, SCN1A encodes the α-subunit of the voltage-gated sodium channel Nav1.1 which is critical for neuronal excitability.

The SCN1A gene has been well described in the literature as a cause of a plethora of epilepsy syndromes, which include Dravet syndrome and genetic epilepsy with febrile seizures plus (GEFS+) with highly variable genotype–phenotype relationship (Scheffer & Nabbout, 2019; Gallagher et al., 2024). But the link between the genetic effects (common polymorphisms) of the gene SCN1A and epilepsy is less well understood. However, a meta-analysis study found no associations between the risk of epilepsy in children and rs2298771 and another systematic review found that some polymorphisms in the SCN1A gene may be associated with drug-resistant epilepsy, but not susceptibility to epilepsy (Zhou et al., 2023; Mohammadi et al., 2025). But, given the findings of these studies, little can be known about the biological importance of the common SCN1A polymorphisms and it is likely that they are populations specific.In addition to the genetic variation, other molecules are also coming to the fore - tiny pieces of RNA, called microRNAs (miRNAs), which are also important post-transcriptional regulators of gene-expression and are also minimally invasive molecules for detection of molecular markers.

Many miRNAs are involved in pathways that are associated with epileptogenesis, such as neuroinflammation, oxidative stress, apoptosis, synaptic plasticity and neuronal remodeling (Yousefi et al., 2025). However, plasma miRNA profile of epilepsy has yet to be fully implemented in the clinical setting, mainly because of factors like the type of epilepsy syndrome, age, stage of the disease and biological samples and analytical method (Zakaria et al., 2025). One of these is MiR-150 that has recently been identified as a new miRNA involved in immune/inflammatory processes in neurological diseases. However, while a few studies have suggested that circulating miRNAs might be valuable markers which aid in the biological characterisation of paediatric epilepsy, the findings of these studies have been inconsistent and none of the miRNAs identified has been sufficiently strong to become a marker alone.

Therefore, it is important to interpret the results of the use of miRNAs in recent paediatric studies with caution and perhaps the use of miRNAs in combination (panel) might be more beneficial (Wang et al., 2022; Rzepka-Migut et al., 2025; Gerbatin et al., 2022).Although the importance of genetic variation and the role of circulating miRNAs in epilepsy are increasing, few studies have been conducted to compare both these molecular mechanisms, especially in children from less-represented geographical regions. Furthermore, whether there is an association between common

polymorphisms of SCN1A gene and plasma level of miR-150 has never been studied. A study to investigate polymorphisms in the genes and miRNAs has yet to be performed in children with epilepsy, but a preliminary study was performed in Brazil investigating the role of these polymorphisms in TLE. To our knowledge, there are no investigations that studied the relationship between two polymorphisms (rs2298771 and rs7601520) of SCN1A and expression of miR-150 in peripheral blood of Iraqi children with epilepsy. The lack of this deficiency might be helpful in future studies in this area and information of basic molecule to paediatric population of Iraqis.This is an exploratory case-control study in which the distribution of the polymorphisms (rs2298771 and rs7601520) of the SCN1A gene, and their association with PB miR-150 level was studied in Iraqi children with epilepsy.

Materials and Methods

Study Design and Participants

To explore whether there is any association between SCN1A gene polymorphisms (rs2298771 and rs7601520) with peripheral blood miR-150 expression in Iraqi children with epilepsy, this exploratory case–control study was conducted. The total number of children enrolled was 100 (70 patients with epilepsy and 30 apparently healthy controls). The children were recruited from the Neurology Unit at Ibn Sina Teaching Hospital, Mosul, Iraq, who were consecutive and fulfilled the eligibility criteria. As this is an exploratory study, for which no previous data on expression of the SCN1A gene polymorphisms (rs2298771/rs7601520) and miR-150 in the Iraqi pediatric population is available, no formal a priori power calculation was performed; the sample size represents the number of eligible drug-naïve children who presented consecutively during the study period.Epilepsy diagnosis was made by a consultant Paediatric Neurologist using the International League Against Epilepsy (ILAE) classification and diagnostic criteria.

Children between 6 months and 10 years of age with a definite diagnosis of epilepsy were eligible for this study. To reduce the confounding effect of strongly heritable or monogenic epilepsy syndromes, children with a metabolic disorder, central nervous system infection, congenital neurological abnormality, traumatic brain injury, neurodegenerative disorders, or other major neurological disease, or with a documented family history of epilepsy or seizures in first-degree relatives were excluded. This exclusion criterion limits the generalizability of the results to sporadic (non-familial) pediatric epilepsy and must be taken into account when extrapolating the results to the broader population of childhood epilepsy. The control group was made up of apparently healthy children with no history of epilepsy, recurrent seizures, or other neurological disorders, drawn to give an age-sex distribution similar to that of the patient group. Demographic and clinical data such as age, sex, age at onset of seizures, seizure type and parental consanguinity were obtained from medical records and standardized interviews with parents or legal guardians.

Ethical Approval

This study protocol was approved by the Nineveh Health Directorate/ Ministry of Health (Decision No. 292, 3 December 2025) in Iraq. All the procedures in the study were done in accordance with the ethical principles of Declaration of Helsinki. Informed consent forms were signed by all participants and their parents/legal guardians before they were enrolled.

Blood Sample Collection

Peripheral venous blood of each participant was aseptically collected in sterile EDTA tubes (5 mL) and sent in cold-chain to the Molecular Biology Laboratory. Aliquots of each sample were used for genomic DNA extraction and total RNA isolation and analyzed immediately if possible or stored at –80°C.

Genomic DNA Extraction

Peripheral whole blood (PWB) was obtained for extraction of genomic DNA with the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany). DNA concentration and purity were determined by NanoDrop spectrophotometer (Thermo Fisher Scientific, Wilmington, DE, USA) and accepted DNA

samples were kept at −20°C and later used for PCR amplification.

Total RNA Extraction and cDNA Synthesis

Total RNA (also small RNA) was isolated using miRNeasy Mini Kit (QIAGEN) and cDNA was synthesized using miScript II RT Kit (QIAGEN) as per the manufacturer's instructions. The purity of the RNA was checked using NanoDrop and the values of A260/A280 were accepted to be in the range of 1.8-2.1. The cDNA was kept at −20°C for later qPCR analysis.

Quantification of Peripheral Blood miR-150 Expression

The expression level of miR-150 in peripheral blood was determined by quantitative real-time PCR (qRT-PCR) using the Rotor-Gene Q Real-Time PCR System (QIAGEN), following a PCR program designed by the manufacturer, and the miScript SYBR Green PCR Kit in combination with the miScript Primer Assay for human miR-150 (QIAGEN). The endogenous control gene was the U6 small nuclear RNA (U6 snRNA). The relative miR-150 expression was determined by using the comparative 2−ΔCt method (ΔCt = Ct miR-150 − Ct U6 snRNA). No-template controls were performed to check for contamination in each of the runs.

Genotyping of SCN1A Polymorphisms

Two SCN1A polymorphisms, rs2298771 (G/A) and rs7601520 (C/T), were genotyped by PCR and then bidirectional Sanger sequencing was performed using an ABI 3500 Genetic Analyzer (Applied Biosystems). The chromatograms were analyzed and compared using BioEdit software and all genotype determinations were double checked.

Statistical Analysis

IBM SPSS Statistics version 26.0 was used for statistical analyses. The Shapiro–Wilk test was used to determine normality of data distribution, continuous variables are expressed as mean ± SD, and categorical variables as absolute numbers and percentages. As the data was not normally distributed, the Mann–Whitney U test was used to compare relative miR-150 expression between patients and controls and the Kruskal–Wallis test was used to compare the relative expression of miR-150 among the different genotype groups of SCN1A. The chi-square or Fisher's exact test was used to compare the genotype and allele frequencies as appropriate. Most common homozygous genotype was used as a reference for odds ratio (95% CI) calculations. Chi-squared goodness-of-fit tests were used to test for Hardy–Weinberg equilibrium in controls. All tests were two-tailed and P values of < 0.05 were deemed significant. No corrections for multiple comparisons were made considering the limited number of a priori comparisons; this is a study limitation.

Results and Discussion

Demographic and clinical characteristics

Demographic and clinical data of the study population are presented in Table 1.

Table 1. Demographic and clinical characteristics of the study population.

Characteristic	Patients (n = 70)	Controls (n = 30)
Age (years), mean ± SD	3.9 ± 2.1	4.2 ± 1.8
Male, n (%)	39 (55.7)	15 (50.0)
Female, n (%)	31 (44.3)	15 (50.0)
Age at seizure onset (months), mean ± SD	14.7 ± 9.2	—
Generalized tonic–clonic seizures, n (%)	61 (87.1)	—
Other seizure types, n (%)	9 (12.9)	—
Drug-naïve patients, n (%)	70 (100.0)	—
Family history of epilepsy, n (%)a	0 (0.0)	0 (0.0)

a Family history of epilepsy or seizures in first-degree relatives was an exclusion criterion for both groups.

Patient and control group were alike and there was no significant difference in demographic factors such as age and sex. None of the children with epilepsy had received a diagnosis before blood was collected, and were therefore drug naïve at the time of study, thereby reducing the potential effect of anti-seizure medications on the circulating molecular markers. This design helps to confirm the peripheral miRNA data, as the miRNA profile in circulation can be altered by a treatment and/or developmental changes. The relatively moderate sample size and unequal case–control ratio should be taken into account, however, when interpreting subtle molecular associations.

Circulating miR-150 expression

The relative miR-150 expression in peripheral blood was determined using the Comparative 2−ΔCt method, and is shown in Table 2.

Table 2. Relative peripheral blood miR-150 expression in children with epilepsy and healthy controls.

Group	Relative miR-150 expression (2−ΔCt), mean ± SD	Fold change	P-value
Patients (n = 70)	0.6010 ± 0.790	1.38	0.24
Controls (n = 30)	0.4340 ± 0.370	Reference	—

There was a trend towards the expression of miR-150 being higher in the epilepsy children than the controls but this was not significant. All these data indicate that, as a single biomarker, circulating miR-150 might not be optimal for discrimination in the present cohort. There are previous studies that indicate miR-150 might have a role in inflammatory response and neuronal processes, which are indications of Epilepsy. Small extracellular vesicles derived miR-150-3p is a candidate diagnostic for children with epilepsy as it was found to be up-regulated by Wang et al. (2022).

Some differences exist between their results and the current results; however, methodological differences could be playing a part as extracellular vesicle derived miRNAs may be an enriched and stable molecular fraction compared to the peripheral blood RNA. Additionally, the fluctuations in the studies regarding circulating miRNAs could be due to the method used for normalization (Zakaria et al., 2025; Rzepka-Migut et al., 2025) and the type of the specimen and the conditions of preanalysis.Although the difference was not significant, it is possible that miR-150 does play a role in epilepsy as in this present study. Instead, it suggests that the expression pattern of it might vary in different conditions such as disease heterogeneity, inflammatory condition and technical aspects of quantifying miRNAs. Therefore, miR-150 is yet to be a validated biomarker.

Association of SCN1A polymorphisms with epilepsy susceptibility

Table 3 and 4 shows the distribution of two genotypes - SCN1A rs2298771 and SCN1A rs7601520 respectively.

Table 3. Genotype distribution of the SCN1A rs2298771 (G/A) polymorphism in children with epilepsy and healthy controls.

Genotype	Patients n (%)	Controls n (%)	OR (95% CI)	P-value*
GG	28 (40.0)	12 (40.0)	Reference	—
GA	28 (40.0)	10 (33.3)	1.20 (0.45–3.23)	0.80
AA	14 (20.0)	8 (26.7)	0.75 (0.25–2.26)	0.78

Overall genotype comparison: χ^2 test, P = 0.72. Odds ratios were calculated using the GG genotype as the reference. Hardy–Weinberg equilibrium in controls: χ^2 = 3.096, P = 0.078

Table 4. Genotype distribution of the SCN1A rs7601520 (C/T) polymorphism in children with epilepsy and healthy controls.

Genotype	Patients n (%)	Controls n (%)	OR (95% CI)	P-value*
CC	25 (35.7)	8 (26.7)	Reference	—
CT	34 (48.6)	14 (46.7)	0.78 (0.28–2.13)	0.80
TT	11 (15.7)	8 (26.7)	0.44 (0.13–1.48)	0.22

**Overall genotype comparison: χ^2 test, P = 0.39. Odds ratios were calculated using the CC genotype as the reference. Hardy–Weinberg equilibrium in controls: χ^2 = 0.133, P = 0.715*

In the present population of children none of these polymorphisms was associated with susceptibility to epilepsy. The findings are confirmed by previous studies, which in general found that there is a lack of big single gene influences with regard to the risk of epilepsy. But a systematic review and meta-analysis conducted by Mohammadi et al. (2025) didn't provide any clear results on the relationship between the common polymorphisms of the SCN1A gene and susceptibility of epilepsy in different populations. Similarly, Katsarou et al. (2024) showed that an association between epilepsy in general and the rs2298771 does not necessarily have to be true but with clinical phenotypes. However, studies by the researchers recently suggested that it was not the incidence of epilepsy, but the epilepsy phenotype that was important as far as the rs2298771 and response to treatment is concerned. But Tang et al. (2024), Bao et al. (2024) and Zhu et al. (2023) have also reported common variants of SCN1A to be associated with response to antiseizure medications (ASM), suggesting that common variants of SCN1A may be modifiers of clinical outcome rather than susceptibility determinants. This lack of association (as observed in the current study) would therefore have biological plausibility as the severe epilepsy syndromes have more commonly been associated with the presence of rare pathogenic variants of SCN1A and common polymorphisms are likely to have a lesser role as a regulator. The fact that the association is lacking is not an argument that the general idea of susceptibility to epilepsy being the product of multiple interacting processes (development, environment and genes) is wrong - just that in this instance it is not a common variant.

Relationship between SCN1A polymorphisms and miR-150 expression

The association of SCN1A genotypes with circulating miR-150 expression is presented in Tables 5 and 6.

Table 5. Association between SCN1A rs2298771 (G/A) genotypes and relative miR-150 expression in children with epilepsy (n = 70).

Genotype	n (%)	Relative miR-150 expression (2−ΔCt), mean ± SD	Overall P-value†
GG	28 (40.0)	0.666 ± 1.026	
GA	28 (40.0)	0.538 ± 0.478	
AA	14 (20.0)	0.585 ± 0.438	0.97

†Overall P-value calculated using the Kruskal–Wallis test

Table 6. Association between SCN1A rs7601520 (C/T) genotypes and relative miR-150 expression in children with epilepsy (n = 70).

Genotype	n (%)	Relative miR-150 expression (2−ΔCt), mean ± SD	Overall P-value†
CC	25 (35.7)	0.385 ± 0.172	
CT	34 (48.6)	0.586 ± 0.476	
TT	11 (15.7)	1.154 ± 1.845	0.40

There was no significant difference between the two miR-150 genotype groups for either of the two genotypes: rs2298771 and rs7601520.Knowledge of the direct role of common SCN1A variants in regulating the expression of circulating miRNAs is still limited. Previous research has mainly focused on the link between SCN1A polymorphisms and epilepsy susceptibility, seizure types, and antiseizure medication (ASM) response, while limited attention has been given to the modulation of miRNAs.

Given the lack of an association between the genotype and the expression in the current study, it is likely that other mechanisms (such as neuro-inflammatory pathways, immune responses, epigenetic regulation and polygenetic interactions) regulate the levels of circulating miR-150.Findings from observed subgroups should be interpreted with caution due to a decrease in statistical power in moderate-sized cohorts with genotype-based subgroup analyses. Thus, small regulatory effects cannot be excluded and larger studies incorporating genomic, transcriptomic and epigenetic approaches are required to elucidate the association between SCN1A variation and the circulating miRNA profiles.

Study significance and limitations

In the present study, SCN1A polymorphisms and the expression of miR-150 in peripheral blood were evaluated in newly diagnosed, untreated Iraqi children with epilepsy. The results provide initial data on the association of common underlying genetic polymorphisms with circulating miRNA regulation in paediatric epilepsy.One of the limitations of the study has a relatively small sample size and the total peripheral blood used for miR-150 analysis in the single-center study.

Further, the lack of children with a family history of epilepsy could reduce generalizability. The results of these studies must now be confirmed by larger multicenter studies that use standardized normalization methods. Taken together, the findings are compatible with a multifactorial nature of epilepsy, and point to a potential circulating miR-150 as a possible biomarker, while the polymorphisms in SCN1A genes (rs2298771 and rs7601520) are not

likely to be major independent susceptibility markers in this cohort.

Conclusions

The aim of this exploratory case-control study was to assess the association of SCN1A polymorphisms (rs2298771 and rs7601520) and peripheral blood miR-150 expression in Iraqi children with epilepsy. There was a non-significant increase in the miR-150 in patients. Likewise, no significant association was found between either of the SCN1A polymorphisms and susceptibility to epilepsy or differential expression of miR-150.These findings suggest that the common SCN1A variants studied are unlikely to be major determinants of susceptibility to epilepsy or of circulating levels of miR-150 in this population. Given the exploratory design and the sample size, small genetic and/or regulatory effects cannot be excluded. The study provides preliminary molecular evidence from Iraqi children with epilepsy regarding the correlation between SCN1A variation and the levels of circulating miR-150 and it calls upon more studies to be done on larger groups and standardized miRNA procedures, combined genomic strategies.

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Conflict of Interest

The authors declare no conflict of interest.

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