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PERIPHERAL BLOOD *SCN1A* MRNA EXPRESSION AND ITS ASSOCIATION WITH DEMOGRAPHIC AND CLINICAL CHARACTERISTICS IN IRAQI CHILDREN WITH EPILEPSY: A CASE–CONTROL STUDY

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ABSTRACT

Background: Epilepsy is a very common childhood neurological disorder with varying clinical presentations, partly due to genetic factors. Although the SCN1A gene codes for a subunit of the voltage-gated sodium channel, which is crucial in neuronal excitability, associations between SCN1A mRNA levels in the peripheral blood and childhood epilepsy have been poorly understood. **Objective:** The current study aimed to evaluate peripheral blood SCN1A mRNA expression in children with epilepsy in Iraq and its relationship to the demographic and clinical data of the studied children. **Methods:** Children with epilepsy (n = 70) and apparently healthy controls (n = 30) were selected by convenience sampling from the population of children aged 6 months to 6 years attending the Ibn Sina Teaching Hospital, Mosul, Iraq during November and December, 2025. The expression of SCN1A mRNA was determined in peripheral blood by reverse-transcription quantitative real-time PCR, GAPDH was used as a reference gene and relative expression was calculated by 2-ΔΔCt method. Data were not normally distributed and as such results were reported as medians and interquartile ranges, and groups compared using the Mann–Whitney U test. **Results:** Peripheral blood *SCN1A* mRNA expression was significantly higher in children with epilepsy than in controls (Mann–Whitney U test, $P < 0.001$). The median relative expression was 33.66 (interquartile range 23.84–46.50) in the epilepsy group and 1.08 (interquartile range 0.37–3.99) in the control group, and the fold change by the $2^{-}\Delta\Delta Ct$ method was 35.02. The sex distribution did not differ significantly between the groups ($P = 0.79$). Among children with epilepsy, 56 (80%) had seizure onset at or before one year of age, and relative *SCN1A* expression was negatively correlated with age at seizure onset (Spearman's $\rho = -0.58$, $P < 0.001$). **Conclusion:** Children with epilepsy in this study showed significantly higher peripheral blood *SCN1A* mRNA expression than healthy controls, and expression was inversely associated with age at seizure onset. These findings do not establish diagnostic accuracy or clinical utility; independent validation is required before peripheral *SCN1A* expression can be considered a candidate biomarker.

Keywords: *SCN1A*; mRNA expression; childhood epilepsy; peripheral blood; reverse-transcription quantitative real-time PCR; case–control study.

1. INTRODUCTION

Epilepsy is a frequent neurological disorder that involves an increased risk of having a seizure and the resulting cognitive, psychological and social impairments. Childhood epilepsy is an umbrella term that is applied to a group or syndrome of disorders that may present with a variety of clinical syndromes, causes, outcomes and drugs. In some types of epilepsy, genetic factors are important, particularly if they have early onset of seizures (McTague et al., 2016). Epilepsy also poses a great health problem on a global scale in children (Tu et al., 2025).

The SCN1A gene encodes a sodium channel known as voltage-gated sodium channel NaV1.1 which occurs in a protein that carries and controls electric currents in nerve cells. Pathogenic mutations in SCN1A are present in several other epilepsy phenotypes such as the Dravet syndrome, and other developmental and epileptic encephalopathies (DEEs) (Claes et al., 2001; Marini et al., 2011; Brunklaus et al., 2012; Scheffer and Nabbout, 2019). In general, NaV1.1 channels are expressed in inhibitory (GABAergic) interneurons and the disruption of NaV1.1 channels leads to a decrease in interneuron excitability and loss of excitation–inhibition balance (van Hugte et al., 2023; Catterall, 2018). Experimental studies suggest that seizure mechanisms are related to the dosage and transcriptional regulation of SCN1A, and that SCN1A expression can be used to enhance interneuron function and decrease seizures in animal models (Colasante et al., 2020; Han et al., 2020; Tanenhaus et al., 2022). Non-coding variants are not the only defects that can affect the level of transcripts – e.g., abnormal inclusion of a 'poison exon' and disruption of non-canonical regulatory sequences – and defects have been reported (Carvill et al., 2018; Haigh et al., 2021). A correlation between SCN1A variation with epilepsy has been confirmed, and variations in gene expression could help to explain transcription patterns that lead to the disease.

Reverse-transcription quantitative real-time PCR (RT-qPCR) allows the relative abundance of mRNA to be quantified and can be used to explore the differences in expression of a particular gene between clinical groups. The comparative $2^{-}\Delta\Delta Ct$ method after normalization with an endogenous reference gene is commonly used for this purpose (Bustin et al., 2009; Livak and Schmittgen, 2001). Peripheral blood is a readily available and useful biological specimen for molecular studies, especially in the pediatric population. However, the expression of a gene in circulating blood cells does not necessarily reflect expression in the neurons, nor does it necessarily indicate changes in the abundance of NaV1.1 protein or in the function of NaV1.1 channels (Cai et al., 2010; Sullivan et al., 2006). Therefore, expression of the SCN1A gene in peripheral blood should be considered as a tissue-specific molecular measure, not as a measure of the activity of the neuronal channels. Peripheral blood gene-expression profiles have, however, also been investigated in neurological disorders with careful consideration for appropriate biomarkers (Cai et al., 2010; Min et al., 2022; Sullivan et al., 2006).

The genetic characterization of epilepsy has improved greatly over the past few years, but information regarding the expression of SCN1A mRNA in the peripheral blood of children with epilepsy is still limited, especially in less representative groups. Defining this expression and investigating the link between it and demographic and clinical parameters could yield initial evidence for further studies. But any potential clinical use would need to be interpreted with great care and further investigated.

Hence, this study was designed to compare the peripheral blood SCN1A mRNA expression level between epileptic children of Iraq and apparently healthy ones, and assess the correlation between selected peripheral blood SCN1A mRNA expression levels and the various demographic and clinical parameters such as age of epilepsy onset. This study was not intended to measure diagnostic performance or to prove causation.

2. Materials and Methods

2.1. Study Design, Ethical Approval, and Participants

The study was a case–control study, approved by the Nineveh Health

Directorate, Ministry of Health, Iraq (Decision No. 292 dated 24 November 2025) and conducted in accordance with the ethical principles of the Declaration of Helsinki. All parents/legal guardians have signed informed consent prior to participation.

A total of 100 children (70 with epilepsy and 30 apparently healthy) were included in the study. The participants were selected by a convenience sampling method between November and December 2025 at Ibn Sina Teaching Hospital, in Mosul, Iraq. Children in both groups were between 6 months and 6 years old. An epileptic diagnosis was made by a consultant paediatric neurologist, who examined the child and reviewed the medical records.

Information on demographics and available clinical data were gathered by means of a structured questionnaire and review of medical records. Recorded factors were age, sex and age of seizure onset. Children in the epilepsy group had been newly diagnosed at recruitment and had not received an antiseizure medication prior to blood collection. Age at seizure onset was provided from clinical history and separated from the age at diagnosis.

Children with hematological disease, acute infection, chronic systemic disease or other neurological disorders were excluded. The children in the control group were not known to have epilepsy or recurring seizures. There was no documented formal a priori calculation of sample size; therefore, sample size was not statistically targeted but rather represented the number of eligible participants that were recruited within the collection period of the study.

2.2. Blood Sample Collection and Processing

Approximately 1 mL of peripheral venous blood was collected aseptically from each participant into ethylenediaminetetraacetic acid (EDTA) tubes. A complete blood count was performed before molecular analysis to identify major hematological abnormalities that could affect the interpretation of peripheral blood gene-expression measurements. Peripheral blood leukocytes were isolated and processed for total RNA extraction.

2.3. RNA Extraction and Quality Assessment

Total RNA was isolated from peripheral blood leukocytes using the TransZol Up Plus RNA Kit (TransGen Biotech, China), following the manufacturer's instructions. RNA concentration and purity were assessed using a NanoDrop spectrophotometer. RNA purity was evaluated using the absorbance ratio at 260 and 280 nm (A260/A280), with ratios of 1.8–2.1 considered acceptable for the purposes of this study.

RNA integrity was not formally assessed using electrophoresis or an RNA integrity number (RIN). Consequently, the A260/A280 ratio was used as an indicator of RNA purity and should not be interpreted as direct evidence of RNA integrity.

2.4. Complementary DNA Synthesis

Complementary DNA (cDNA) was synthesized from total RNA using the EasyScript® One-Step gDNA Removal and cDNA Synthesis SuperMix Kit (TransGen Biotech, China), according to the manufacturer's protocol. Each reverse-transcription reaction contained 4 µL of RNA template. The thermal program consisted of incubation at 25°C for 10 minutes, reverse transcription at 42°C for 15 minutes, and enzyme inactivation at 85°C for 5 seconds.

2.5. Quantitative Real-Time PCR

Relative *SCN1A* mRNA expression was measured using reverse-transcription quantitative real-time polymerase chain

reaction (RT-qPCR) on a Rotor-Gene Q instrument (QIAGEN, Germany). The expression of *GAPDH* was used as the endogenous reference for normalization. The target-gene and reference-gene primer sequences and expected amplicon sizes are presented in Table 1.

Each PCR reaction had a final volume of 20 µL and contained 10 µL of 2× TransStart® Top Green qPCR SuperMix, 1 µL of forward primer (10 µM), 1 µL of reverse primer (10 µM), 2 µL of cDNA template, and 6 µL of RNase-free water (Table 2).

The amplification program included denaturation at 94°C for 30 seconds, 40 cycles of denaturation at 94°C for 5 seconds, annealing at 58°C for 15 seconds, and extension at 72°C for 20 seconds. To evaluate the specificity of the amplification products, melting-curve analysis was carried out between 55–95°C (Figure 1).

All samples were run in duplicate and the average of the two technical replicates was used for analysis. Possible genomic DNA contamination was evaluated using a no-reverse-transcription (no-RT) control. No template control (NTC) was not included, however. Formal determination of amplification efficiency was not conducted and validity of GAPDH stability across the groups studied was not formally validated. The relative expression results and the interpretation of these results should take into account the methodological limitations mentioned in these omissions.

Table 1. Primer sequences used for amplification of *SCN1A* and *GAPDH*

Gene	Primer direction	Sequence (5′–3′)	Expected amplicon size
SCN1A	Forward	TCCAAGGATGTGCTATTGAGC	120 bp
SCN1A	Reverse	TTCAACACTGCTGCCAGTTC	120 bp
GAPDH	Forward	GAAATCCCATCACCATCTTCCAGG	200 bp
GAPDH	Reverse	GAGCCCCAGCCTTCTCCATG	200 bp

SCN1A, sodium voltage-gated channel alpha subunit 1; *GAPDH*, glyceraldehyde-3-phosphate dehydrogenase; bp, base pairs.

Table 2. Composition of the RT-qPCR reaction mixture

Component	Volume per reaction
2× TransStart® Top Green qPCR SuperMix	10 µL
Forward primer (10 µM)	1 µL
Reverse primer (10 µM)	1 µL
cDNA template	2 µL
RNase-free water	6 µL
Total reaction volume	**20 µL**

2.6. Relative Gene Expression Analysis

Relative *SCN1A* mRNA expression was normalized to *GAPDH* using the comparative cycle-threshold method (Livak and Schmittgen, 2001). For each sample, ΔCt was calculated as the difference between the Ct value of *SCN1A* and that of *GAPDH*:

$\Delta Ct = Ct(SCN1A) - Ct(GAPDH)$.

Relative expression before calibrator normalization was represented by $2^{-}\Delta Ct$. The comparative ΔΔCt value was calculated by subtracting the mean ΔCt of the control group, used as the calibrator, from the ΔCt of the corresponding sample. Relative fold change was then calculated as $2^{-}\Delta\Delta Ct$.

The $2^{-}\Delta Ct$ values and the $2^{-}\Delta\Delta Ct$-derived fold-change values represent different quantities and were therefore distinguished in reporting the molecular results. The fold change of 35.02 was derived from the $2^{-}\Delta\Delta Ct$ calculation described above and is not a ratio of group medians.

2.7. Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequencies and percentages and compared using Pearson's chi-square test. The distribution of continuous variables was assessed using the Shapiro–Wilk test. Because the relative gene-expression data were not normally distributed, expression values were summarized using medians and interquartile ranges (IQRs). The Mann–Whitney U test was used for comparisons of relative expression between two independent groups. Associations between relative *SCN1A* mRNA expression and age at seizure onset were assessed using Spearman's rank correlation coefficient (ρ). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic and Clinical Characteristics

The study included 100 children: 70 children with epilepsy and 30 apparently healthy controls. All participants were aged 6 months to 6 years. The sex distribution did not differ significantly between the epilepsy and control groups (χ^2 test, $P = 0.79$; Table 3). Among the children with epilepsy, 56 (80.0%) had experienced seizure onset at or before 1 year of age, whereas 14 (20.0%) had seizure onset after 1 year of age.

Table 3. Demographic and clinical characteristics of the study participants

Characteristic	Epilepsy group (n = 70)	Control group (n = 30)	P-value
Age range	6 months–6 years	6 months–6 years	—
Male, n (%)	37 (52.9%)	15 (50.0%)	0.79*
Female, n (%)	33 (47.1%)	15 (50.0%)	
Seizure onset ≤1 year, n (%)	56 (80.0%)	Not applicable	—
Seizure onset >1 year, n (%)	14 (20.0%)	Not applicable	—

*The P-value refers to the comparison of sex distribution between the epilepsy and control groups. Seizure-onset categories apply only to children with epilepsy.

3.2. Peripheral Blood SCN1A Relative Expression

Peripheral blood *SCN1A* mRNA relative expression was higher in children with epilepsy than in healthy controls. Because the expression data were not normally distributed, the results are presented as medians and interquartile ranges (IQRs). The median relative expression was 33.66 (IQR: 23.84–46.50) in the epilepsy group and 1.08 (IQR: 0.37–3.99) in the control group. The between-group difference was

statistically significant (Mann–Whitney U test, $P < 0.001$; Table 4). Representative amplification curves are shown in Figure 2.

The relative-expression analysis using the $2^{-}\Delta\Delta Ct$ method, with the control group as the calibrator, yielded a fold change of 35.02.

Table 4. Peripheral blood SCN1A mRNA relative expression in children with epilepsy and healthy controls

Parameter	Epilepsy group (n = 70)	Control group (n = 30)	P-value
Median relative expression	33.66	1.08	
25th percentile (Q1)	23.84	0.37	
75th percentile (Q3)	46.50	3.99	
IQR width (Q3 − Q1)	22.66	3.62	
Between-group comparison	—	—	< 0.001
Fold change ($2^{-}\Delta\Delta Ct$)	35.02-fold	Reference group	—

Values are presented as medians and quartiles because the expression data were not normally distributed. The P-value was obtained using the Mann–Whitney U test. The 35.02-fold change is the result of the $2^{-}\Delta\Delta Ct$ analysis and is not calculated by dividing the two group medians.

3.3. Association Between SCN1A Expression and Age at Seizure Onset

Among children with epilepsy, *SCN1A* relative expression was negatively correlated with age at seizure onset (Spearman's $\rho = -0.58$, $P < 0.001$, n = 70; Table 5). This finding indicates that higher expression values tended to be associated with a younger age at seizure onset within the epilepsy group.

Table 5. Correlation between SCN1A relative expression and age at seizure onset

Variables	Statistical test	Correlation coefficient	P-value
SCN1A relative expression and age at seizure onset	Spearman's rank correlation	−0.58	< 0.001

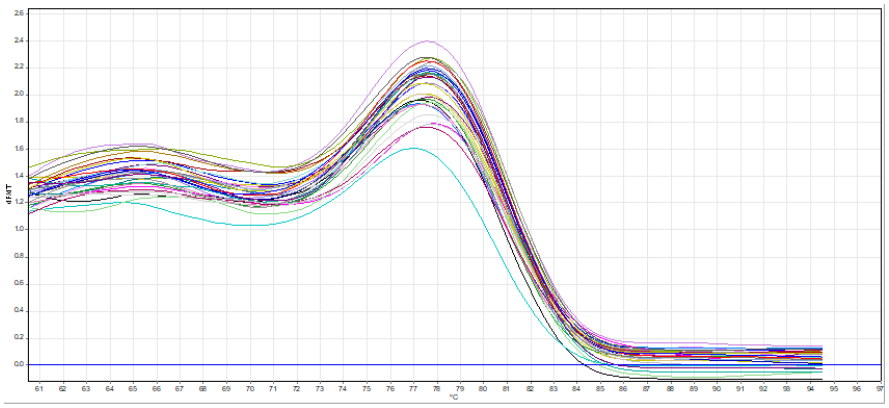

Figure 1. Melting curve analysis demonstrating a single specific melting peak for *SCN1A* and *GAPDH*, confirming amplification specificity without primer-dimer formation.

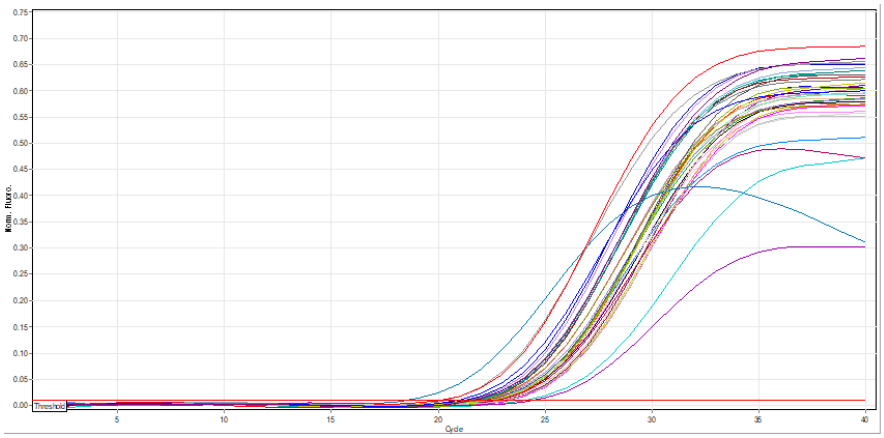

Figure 2. Representative amplification curves obtained during RT-qPCR analysis of *SCN1A* expression.

4. Discussion

In this case–control study, peripheral blood *SCN1A* mRNA expression was higher in children with epilepsy than in apparently healthy controls. The difference was statistically significant, and the $2^{-}\Delta\Delta Ct$ analysis yielded a 35.02-fold change relative to the control group. These findings suggest that altered peripheral blood *SCN1A* expression may be associated with childhood epilepsy in the studied population. However, the results should be interpreted as an association rather than evidence of a causal relationship.

The *SCN1A* gene encodes the voltage-gated sodium channel α-subunit NaV1.1, which contributes to neuronal excitability, particularly in inhibitory GABAergic interneurons (Catterall, 2018; van Hugte et al., 2023). Although changes in *SCN1A* expression are biologically relevant to epilepsy research, the present study measured mRNA in peripheral blood leukocytes. Therefore, the expression differences observed do not necessarily represent changes in expression in the brain, abundance of NaV1.1 protein or function of the channels or neuronal excitability. These results were not directly evaluated. The increase in peripheral transcription level may instead reflect molecular responses to disease as abundance of mRNA is regulated at multiple layers of transcription and post-transcription and not necessarily correlated with protein abundance or channel activity (Haigh et al., 2021). There is also a major difference in the way blood is expressed and central nervous system (Cai et al., 2010; Sullivan et al., 2006) is expressed, which limits the ability to extrapolate results from the periphery to the central nervous system (CNS).

The marked difference in expression of peripheral blood between the groups is interesting, but is not yet known what clinical implications this may have. This study was not designed to establish a threshold for diagnosis or test the performance of clinical classifications; it was only a comparison of expressions among children with epilepsy and controls. No receiver operating characteristic curve, sensitivity nor specificity and no independent validation were done. Based on these results, therefore, the expression of SCN1A in the peripheral blood cannot be considered to be a definitive diagnostic biomarker. However, expression profiles from peripheral blood can provide additional information regarding molecular changes associated with disease but should be used with caution (Cai et al., 2010; Min et al., 2022; Sullivan et al., 2006); transcriptomic measures can also be used to measure molecular changes that are not measured by a DNA sequence-based approach. Experimental studies

demonstrating positive modulation or restoration in models of Dravet syndrome confirm the biological relevance of the dose of SCN1A, but do not validate peripheral expression as a biomarker.

Negative correlation of SCN1A expression with age at onset of seizures implies that increased expression may have been more likely to have been observed in children with earlier age at onset of seizures. This association could warrant further investigation, but does not indicate that changes in expression came before or were a contributor to an earlier onset of seizures. This correlation was seen within the epilepsy group and should be viewed with caution due to the sample size and the clinical heterogeneity which could arise in a group of children with epilepsy. The direction of the association is consistent with the known association of mutations in SCN1A and early onset epilepsy (early childhood) (Brunklaus et al., 2012; Brunklaus et al., 2022; Clatot et al., 2023; Scheffer and Nabbout, 2019).

Most children in the epilepsy group had experienced seizure onset at or before 1 year of age. This finding describes the distribution of age at onset in the recruited sample; it does not establish that early onset is associated with increased expression unless a separate, appropriately analyzed comparison between onset categories supports that conclusion. Age at seizure onset should also be distinguished from age at recruitment and age at diagnosis. All participants were aged 6 months to 6 years at recruitment, whereas age at onset was obtained from clinical history.

The sex distribution did not differ significantly between the epilepsy and control groups, which suggests that sex is unlikely to explain the between-group difference in expression. Sex has not been described as a major source of clinical heterogeneity in *SCN1A*-related epilepsies (Mei et al., 2019; Scheffer and Nabbout, 2019). Differences in expression according to sex within the epilepsy group are not reported here and should be examined in larger studies.

When interpreting the results some points need to be considered. First, GAPDH was employed as sole reference gene which did not come to any conclusion by being formally validated as being stable within the study population. The use of a single reference gene without a thorough stability analysis can lead to a certain level of uncertainty in the expression difference calculated, whereas relative quantification requires the use of a reference gene. The stability of the reference genes should be assessed in future studies in addition to the selection of multiple validated reference genes.

Secondly, the purity of RNA was determined by spectrophotometry, but not integrity by electrophoresis or RNA integrity metric. Moreover, there was no amplification efficiency calculated and no no-template control was included. A no-RT control was used. These information can be helpful when assessing the quality of the assays and will be taken into account when interpreting quantitative PCR results. Future studies should have a more thorough quality-control plan in accordance with the recommended guidelines for reporting quantitative PCR (Bustin et al., 2009).

Third, 70 children with epilepsy and 30 controls were recruited from a single center. There was no a priori power analysis conducted in advance and the different group sizes might make the findings less precise and generalisable. This case–control design further does not show a temporal relationship or a cause and effect. Furthermore, the study did not include an independent validation cohort, did not measure the protein level and did not carry out any functional channel assays or sequencing of SCN1A. SCN1A-associated epilepsies can result from coding variants, splice-altering variants, and regulatory abnormalities (Carvill et al., 2018; Haigh et al., 2021; Scheffer and Nabbout, 2019), which sequencing could help to identify.

The study offers an initial indication of peripheral blood SCN1A mRNA expression being associated with childhood epilepsy in this Iraqi population, despite these limitations. Further exploration of peripheral gene expression changes in pediatric epilepsy is recommended and larger and more diverse cohorts, reference genes validated for use in the relevant tissue, and extensive quantitative PCR quality controls and replication should be utilized in future studies. Additionally, further research is needed to determine if peripheral expression levels offer clinically meaningful information beyond the traditional clinical assessment, and whether peripheral mRNA levels are representative of neuronal function of channels. Moreover, future studies should report the seizure types and epilepsy classification, using the ILAE classification system (Fisher et al., 2017).

4.1. Study Limitations

There are a number of limitations of this study. The sample size was relatively small, group sizes were unequal (70 and 30), and participants were recruited from a single center (no information provided on formal a priori sample-size calculation). This case-control study does not allow for causality to be determined and clinical characterization was limited as seizure type, electroencephalography (EEG) findings and suspected etiology were not recorded. Integrity of RNA was not tested, efficiency of amplification was not calculated and the stability of the single reference gene, GAPDH, was not formally validated. No-template control was not performed, but a no-reverse-transcription (no-RT) control was done. Sequencing, protein analysis, functional channel assays and independent validation cohort were not performed on the study. Last, mRNA expression in the peripheral blood is not the same as that or function in neuronal tissue.

5. Conclusion

Epileptic children in this study had significantly elevated expression of peripheral blood SCN1A mRNA compared to healthy controls. There was a negative correlation between age at onset of seizures and expression. These results suggest that in this sample there is an association between peripheral blood SCN1A expression and childhood epilepsy. The study is, however, of a single center design, has a small number of samples, and has limitations of quality control in quantitative PCR, so it is recommended that it be validated in multicenter larger cohorts before any potential clinical application can be considered.

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Conflict of Interest

The authors have declared that there is no conflict of interest that could be construed to influence the work reported in this paper.

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None.

Ethics Statement

The Nineveh Health Directorate, Ministry of Health, Iraq, approved this study (Decision No. 292 on 24 November 2025), and it was carried out in accordance with the ethical principles of the Declaration of Helsinki. Written consent was obtained from all parents/legal guardians prior to the enrollment of their child.

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