

Interplay Between SCN1A Genetic Variants, Thyroid Hormone Profile, and Drug Resistance in Children with Epilepsy

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Abstract

Background:

Drug-resistant epilepsy remains a major challenge in pediatric neurology. Genetic factors, particularly *SCN1A* polymorphisms, and endocrine alterations such as thyroid dysfunction may contribute to variability in anti-epileptic drugs (AED) response. However, their combined impact remains incompletely understood.

Objective:

To investigate the relationship between *SCN1A* gene polymorphism, thyroid hormone profile, and anti-epileptic drug resistance in children with epilepsy.

Methods:

This cross-sectional study included 60 pediatric epilepsy patients classified into AED-responsive (n = 30) and AED-resistant (n = 30) groups. Clinical characteristics, seizure patterns, AED regimens, and thyroid hormone levels (TSH and T4) were assessed. *SCN1A* genotyping was performed using molecular techniques. Comparisons between groups were conducted, and correlations between hormonal parameters, seizure frequency, and AED number were analyzed. Receiver operating characteristic (ROC) analysis evaluated the predictive value of *SCN1A* genotype for drug resistance.

Results:

AED-resistant patients had significantly higher seizure frequency and longer disease duration compared to responsive patients ($p < 0.001$ and $p = 0.05$, respectively). Serum TSH levels were significantly elevated in the resistant group (3.36 ± 2.2 vs 2.5 ± 1.4 mIU/L, $p = 0.05$), with a higher prevalence of subclinical hypothyroidism (26.7% vs 3.3%, $p = 0.02$). The *SCN1A* AG genotype was more frequent among resistant patients (66.7% vs 43.3%, $p = 0.05$) and was associated with higher seizure frequency and elevated TSH levels. TSH showed a positive correlation with seizure frequency ($r = 0.59$, $p < 0.001$). ROC analysis demonstrated moderate predictive value of the AG genotype for drug resistance (AUC = 0.67).

Conclusion:

SCN1A polymorphism and thyroid dysfunction are associated with antiepileptic drug resistance in pediatric epilepsy. These findings support a gene–endocrine interaction contributing to seizure refractoriness and highlight the potential value of integrated genetic and hormonal assessment in clinical practice.

Key words

SCN1A polymorphism; Drug-resistant epilepsy; Thyroid dysfunction; Pediatric epilepsy; Antiepileptic drugs; Genetic biomarkers

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Introduction

Approximately, 46 million people all over the world are affected with epilepsy; according to the 2016 Global Burden of Disease Collaborators.¹ Epilepsy is one of the most

prevalent chronic neurological disorders in children, affecting approximately 0.4–1% of the global population and presenting with a wide range of seizure types and severity. Despite advances in pharmacotherapy, about 30% of

children with epilepsy develop drug-resistant epilepsy (DRE), which is defined as the failure to achieve sustained seizure freedom after trials of at least two appropriate antiepileptic drugs (AEDs). DRE is associated with increased disability, psychosocial burden, and higher risk of morbidity and mortality, including sudden unexpected death in epilepsy (SUDEP).^{2,3}

Genetic factors have been increasingly recognized as key determinants of both epileptogenesis and variability in AED response. Among these, the SCN1A gene, located on chromosome 2q24.3, encodes the $\alpha 1$ subunit of the voltage-gated sodium channel (Nav1.1), a major regulator of neuronal excitability. Mutations in SCN1A are well known to cause severe epileptic syndromes such as Dravet syndrome and generalized epilepsy with febrile seizures plus (GEFS+), demonstrating the gene's critical role in seizure pathophysiology.^{4,5}

Beyond rare pathogenic mutations, common single nucleotide polymorphisms (SNPs) in SCN1A have been associated with differential responses to AED therapy. Systematic reviews and recent case-control studies have shown that specific SCN1A polymorphisms (e.g., rs2298771 and rs10167228) are more frequent in drug-resistant patients compared to responders, suggesting that genetic variation in sodium channel encoding genes contributes to pharmacoresistance.⁶

In addition to genetic determinants, thyroid function may influence seizure susceptibility and therapeutic outcomes. Thyroid hormones are essential for central nervous system development and modulation of neuronal excitability, and several studies report that AEDs—particularly traditional agents—can alter thyroid hormone levels, leading to subclinical and overt hypothyroidism in some children with epilepsy.⁷

Despite evidence supporting independent roles of SCN1A polymorphisms and thyroid dysfunction in epilepsy, their combined impact on AED resistance has not been comprehensively examined. Investigating the interplay between genetic variation and endocrine profile may enhance understanding of the mechanisms underlying drug resistance and inform personalized treatment strategies in pediatric epilepsy.

Patients and methods

Study design and setting: This cross-sectional case-control study was conducted at Minia University Children's Hospital, in the Pediatric Neurology Outpatient Clinic, Minia University, Egypt. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Research Ethics Committee. Written informed consent was obtained from the parents or legal guardians of all enrolled participants prior to inclusion.

Participants

A total of 60 children diagnosed with epilepsy were enrolled during the period from [].

The study population included 60 children, aged from [insert age range, e.g., 3–15 years], who were divided into two main groups according to their response to antiepileptic drugs (AEDs):

- **Group I (Drug-Resistant Epilepsy, DRE):** 30 children who met the International League Against Epilepsy (ILAE) criteria for drug-resistant epilepsy (failure of adequate trials of two tolerated, appropriately chosen, and used AED schedules, whether as monotherapies or in combination).
- **Group II (Drug-Responsive Epilepsy):** 30 children whose seizures were well controlled for at least one year on antiepileptic therapy.

Inclusion Criteria

- Children diagnosed with epilepsy according to ILAE criteria.
- Age between [months to 16 ys]
- For the DRE group: failure to achieve sustained seizure control despite adequate antiepileptic therapy.
- For the drug-responsive group: complete seizure control for ≥ 1 year.

Exclusion Criteria

- Children with metabolic, genetic, or structural brain disorders other than epilepsy.
- Those receiving hormonal therapy or drugs affecting endocrine function.
- Chronic systemic illnesses (renal, hepatic, or endocrine diseases).

All cases underwent the following:

Clinical and Demographic Assessment

Demographic and clinical data were collected through structured interviews and medical record review. Collected variables included age, sex, age at seizure onset, seizure type (classified according to the International League Against Epilepsy classification), seizure frequency,

duration of epilepsy, family history of epilepsy, and type and number of antiepileptic drugs used (monotherapy or polytherapy).

Anthropometric Assessment

Weight and height were measured using standardized procedures. Body mass index (BMI) was calculated and expressed as age- and sex-adjusted percentiles based on World Health Organization growth charts. Participants were classified as underweight (< -2 SD), normal (-2 to $+2$ SD), or overweight ($> +2$ SD).

Hormonal Assessment

Venous blood samples were obtained in the morning after an overnight fast. Serum thyroid-stimulating hormone (TSH) and free thyroxine (T4) levels were measured using standardized chemiluminescent immunoassays according to the manufacturer's instructions. Subclinical hypothyroidism was defined as elevated serum TSH with normal free T4 levels.

Genetic Analysis

Genomic DNA was extracted from peripheral blood leukocytes using standard extraction protocols. Genotyping of the SCN1A gene polymorphism was performed using polymerase chain reaction (PCR)-based methods followed by allele discrimination analysis. Genotypes were categorized as AA or AG according to allelic variation.

Sample Size Calculation

The sample size was calculated a priori to ensure adequate power to detect a clinically meaningful association between thyroid function and seizure burden. Assuming a moderate correlation between TSH and seizure frequency ($r = 0.40$), with a two-sided significance level of $\alpha = 0.05$ and 80% power ($1 - \beta = 0.80$), the minimum required sample size was estimated using Fisher's z-transformation:

$$n = \left(\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{0.5 \ln \left(\frac{1+r}{1-r} \right)} \right)^2 + 3$$

Substituting $Z_{1-\alpha/2} = 1.96$, $Z_{1-\beta} = 0.84$, and $r = 0.40$, the required sample size was approximately 47 participants. To strengthen subgroup comparisons and allow genotype-based stratification, the target sample was increased to

60 children, allocated equally into AED-responsive and AED-resistant groups (30 per group)."

Outcome Measures

The primary outcomes were:

1. Association between SCN1A genotype and antiepileptic drug responsiveness
2. Relationship between thyroid hormone levels and seizure frequency

Secondary outcomes included:

- Association between SCN1A genotype and seizure characteristics
- Predictive performance of SCN1A genotype for drug resistance

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 26; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation or median (range), as appropriate. Categorical variables were expressed as frequencies and percentages.

Comparisons between groups were conducted using the Student's *t*-test or Mann-Whitney U test for continuous variables, and the Chi-square or Fisher's exact test for categorical variables. Correlations between hormonal parameters and seizure-related variables were assessed using Pearson or Spearman correlation coefficients, as appropriate.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of SCN1A genotype in predicting antiepileptic drug resistance. A *p* value < 0.05 was considered statistically significant.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Research Ethics Committee. Written informed consent was obtained from parents or legal guardians of all participants prior to enrollment.

Results

A total of 60 pediatric patients with epilepsy were enrolled and classified into AED-responsive ($n = 30$) and AED-resistant ($n = 30$) groups. There were no statistically significant differences between the two groups regarding age, sex distribution, anthropometric measures, or pubertal status (Table 1).

The mean age was 9.5 ± 3.9 years in the AED-responsive group and 11.2 ± 4.6 years in the

AED-resistant group ($p = 0.13$). Male-to-female distribution was comparable between groups ($p = 0.60$). No significant differences were observed in weight, height, or BMI percentiles, indicating comparable nutritional status between groups. Family history of epilepsy was also similar between groups ($p = 0.37$).

Patients in the AED-resistant group had significantly higher seizure frequency compared with the AED-responsive group (4.03 ± 2 vs 1.43 ± 0.82 seizures/month; $p < 0.001$). Seizure duration was also significantly longer among AED-resistant patients (7.45 ± 4.5 vs 5.38 ± 3.7 years; $p = 0.05$). No significant difference was observed in age at seizure onset or seizure type distribution between groups (Table 2).

Regarding treatment patterns, polytherapy was significantly more common in the AED-resistant group (86.7%) compared with the AED-responsive group (40%) ($p < 0.001$). Valproic acid use was significantly higher among AED-resistant patients (83.3% vs 46.7%, $p = 0.003$), whereas the use of other antiepileptic drugs did not differ significantly between groups.

Comparison of thyroid function parameters revealed significantly higher serum TSH levels in the AED-resistant group compared with the AED-responsive group (3.36 ± 2.2 vs 2.5 ± 1.4 mIU/L; $p = 0.05$). In contrast, free T4 levels did not differ significantly between groups ($p = 0.29$). Subclinical hypothyroidism was significantly more prevalent in the AED-resistant group (26.7%) compared with the AED-responsive group (3.3%) ($p = 0.02$) (Table 3).

The distribution of SCN1A genotypes differed significantly between the two groups. The AG genotype was significantly more frequent among AED-resistant patients compared with AED-responsive patients (66.7% vs 43.3%, $p = 0.05$), while the AA genotype was more prevalent in the AED-responsive group (Table 4).

Patients carrying the AG genotype demonstrated significantly higher TSH levels compared with AA genotype carriers (3.74 ± 1.99 vs 1.96 ± 1.27 mIU/L, $p = 0.01$). Although subclinical hypothyroidism was more frequent among AG carriers (21.2% vs 7.4%), this difference did not reach statistical significance.

No significant difference in free T4 levels was observed between genotypes (Table 5).

Seizure frequency was significantly higher in patients carrying the AG genotype compared with AA carriers (3.59 ± 2.1 vs 1.68 ± 1.2 seizures/month; $p < 0.001$). However, no statistically significant differences were observed between genotypes regarding seizure type, age at seizure onset, seizure duration, or antiepileptic drug regimen (Table 6).

When stratified by AED responsiveness, AG genotype carriers in the AED-responsive group exhibited significantly higher TSH levels than AA carriers ($p = 0.009$). Among AED-resistant patients, AG genotype carriers showed significantly lower free T4 levels compared with AA carriers ($p = 0.04$). Subclinical hypothyroidism was more frequent among AG carriers in both groups, although the difference was not statistically significant (Table 7).

Correlation analysis revealed a significant positive correlation between serum TSH levels and seizure frequency ($r = 0.59$, $p < 0.001$). No significant correlation was observed between TSH and the number of antiepileptic drugs used. Free T4 levels showed no significant correlations with seizure frequency or drug number (Table 8).

Receiver operating characteristic (ROC) curve analysis demonstrated that the SCN1A AG genotype had a moderate ability to predict AED resistance, with an area under the curve (AUC) of 0.67 (95% CI: 0.52–0.80; $p = 0.05$). Sensitivity and specificity were 66.7% and 56.7%, respectively, with an overall diagnostic accuracy of 61.6% (Table 9).

Table (1) comparison of demographic data between studied groups

	AEDs responsive group, N=30	AEDs resistant group, N=30	P value
Age			
Mean $\pm$ SD	9.5 $\pm$ 3.9	11.2 $\pm$ 4.6	0.13
Range	3-17	2-17	
Gender			
Males	15 (50%)	13 (43.3%)	0.60
Females	15 (50%)	16 (56.7%)	
Weight percentile	2 (6.7%)	6 (20%)	0.19

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< -2SD -2SD to+2SD >+2SD	21 (70%) 7 (23.3%)	15 (50%) 9 (30%)	
Height percentile < -2SD -2SD to+2SD >+2SD	1 (3.3%) 27 (90%) 2 (6.7%)	3 (10%) 25 (83.3%) 2 (6.7%)	0.84
BMI percentile < -2SD -2SD to+2SD >+2SD	2 (6.7%) 21 (70%) 7 (23.3%)	6 (20%) 19 (63.3%) 5 (16.7%)	0.29
Family history Negative Positive	24 (80%) 6 (20%)	21 (70%) 9 (30%)	0.37
Tanner stage Prepubertal Pubertal	12 (40%) 18 (60%)	8 (26.7%) 22 (73.3%)	0.27

Table (2) comparison of seizure character between studied groups

	AEDs responsive group, N=30	AEDs resistant group, N=30	P value
Seizure type			
Tonic	7	1	0.13
Clonic	(23.3%)	(3.3%)	
Tonic clonic	3 (10%)	1	
Myoclonic	17	(3.3%)	
Absence	(56.7%)	23	
	1 (3.3%)	(76.7%)	
	2 (6.7%)	)	
		2	
		(6.7%)	
		3	
		(10%)	
Seizure frequency/month	1.43±0.8	4.03±2	<0.001*
Mean ±SD	2	4 (1-9)	
Median	1 (0.5-3)		
(range)			

First seizure attack (year)	3.75±2.2	3.65±2.4	0.87
Mean ±SD	3.5 (1-9)		
Median (range)		3 (1-8)	
Duration of seizure (years)	5.38±3.7	7.45±4.5	0.05*
Mean ±SD	4.5 (1-16)	8.5 (1-15)	
Median (range)			
Type of AEDs	7	14	0.05*
Topiramate	(23.3%)	(46.7%)	0.003*
Valproic acid	14	)	0.79
Carbamazepine	(46.7%)	25	0.12
Levetiracetam	12 (40%) 11 (36.7%)	(83.3%)) 11 (36.7%)) 17 (56.7%))	
AEDs Monotherapy	18 (60%)	4	<0.001*
Polytherapy	12 (40%)	(13.3%)	
		26 (86.7%))	

* significant at p value <0.05

Table (3) comparison of hormonal profile between studied groups

	AEDs responsive group, N=30	AEDs resistant group, N=30	P value
TSH			
Mean ±SD	2.5±1.4	3.36±2.2	0.05*
Range	0.5-5.9	0.5-7.6	
T4			
Mean ±SD	1.30±0.1	1.23±0.2	0.29
Range	0.9-1.7	0.8-1.6	
Subclinical hypothyroidism	1 (3.3%)	8 (26.7%)	0.02*

Table (4) comparison of Distribution of the SCN1A genotypes and alleles between the study groups

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	AEDs responsive group, N=30	AEDs resistant group, N=30	P value
SCN1A genotypes			
AG	13 (43.3%)	20 (66.7%)	0.05*
AA	17 (56.7%)	10 (33.3%)	

Table (5) comparison of hormonal profile regarding SCN1A genotypes

	SCN1A genotypes		P value
	AG (N=33)	AA (N=27)	
TSH			0.01*
Mean $\pm$ SD	3.74 $\pm$ 1.99	1.96 $\pm$ 1.27	
Range	0.50–7.60	0.50–4.55	
T4			0.10
Mean $\pm$ SD	1.24 $\pm$ 0.24	1.31 $\pm$ 0.27	
Range	0.80–1.60	0.80–1.70	
Subclinical hypothyroidism	7 (21.2%)	2 (7.4%)	0.13

Table (6) comparison of seizure character regarding SCN1A genotypes

	SCN1A genotypes		P value
	AG (N=33)	AA (N=27)	
Seizure type			0.33
Tonic	2 (6.1%)	6 (22.2%)	
Clonic	3 (9.1%)	1 (3.7%)	
Tonic clonic	24 (72.7%)	16 (59.3%)	
Myoclonic	2 (6.1%)	3 (11.1%)	
Absence	2 (6.1%)	1 (3.7%)	
Seizure frequency/month	3.59 $\pm$ 2.13 (0.5-9)	1.68 $\pm$ 1.2	<0.001*
Mean $\pm$ SD			

Median (range)		1 (0.5-5)	
First seizure attack (year)	3.48 $\pm$ 2.43 (1-9)	3.96 $\pm$ 2.2 (1-8)	0.43
Duration of seizure (years)	7.03 $\pm$ 4.08 (1-14)	5.66 $\pm$ 4.3 (1-16)	0.21
Type of AEDs	13 (39.4%)	8 (29.6%)	0.43
Topiramate	22 (66.7%)	17 (63%)	0.76
Valproic acid	13 (39.4%)	10 (37%)	0.85
Carbamazepine	17 (51.5%)	11 (40.7%)	0.50
Levetiracetam	10 (30.3%)	12 (44.4%)	0.25
AEDs Monotherapy	23 (69.7%)	15 (55.6%)	
Polytherapy			

Table (7) comparison of hormonal profile regarding SCN1A genotypes among responsive and resistant groups

	AEDs responsive group, N=30		P value	AEDs resistant group, N=30		P value
	AG (N=13)	AA (N=17)		AG (N=20)	AA (N=10)	
TSH			0.09*			0.31
Mean $\pm$ SD	3.2 $\pm$ 5	1.9 $\pm$ 5		3.6 $\pm$ 4	2.7 $\pm$ 3	
Range	1.3–3 (1.50–5.9)	1.2–1 (0.50–4.5)		2.1–1 (0.50–6.7)	2.6–1 (0.70–7.6)	

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T4						
Mean	1.3	1.3	0.9	1.2	1.4	0.
±SD	0 ±	1 ±	0	0 ±	0 ±	04
Range	0.2	0.2		0.2	0.2	*
	4	6		4	6	
	(0.	(0.		(0.	(0.	
	90–	80–		80–	90–	
	1.6	1.7		1.5	1.7	
	0)	0)		0)	0)	
Subclin			0.4			0.
ical	1	0	3	6	2	68
hypoth	(7.	(0		(30	(20	
yroidis	7%	%)		%)	%)	
m	)					

Table (8) correlation of hormonal profile with number of antiepileptic drug among all cases (n=60)

	Number of AEDs		Frequency of seizure per month	
	r	P value	r	P value
TSH	0.22	0.08	0.59	<0.001*
T4	0.08	0.49	0.004	0.97

Table (9) ROC curve analysis for genotype for prediction of AED resistant seizure among all cases (n=60)

	AG genotype
AUC	0.67
95% CI	0.52-0.80
P value	0.05*
Sensitivity	66.7%
Specificity	56.7%
PPV	60.6%
NPV	63%
Total accuracy	61.6%

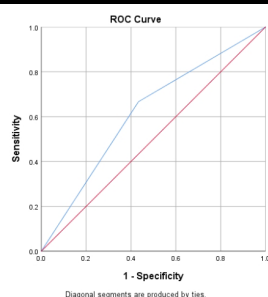


Fig (1) ROC curve analysis for genotype for prediction of AED resistant seizure among all cases

DISCUSSION:

In this study, we examined the relationships among *SCN1A* gene polymorphism, thyroid hormone profile, and antiepileptic drug (AED)

resistance in a pediatric epilepsy cohort. We found that the *SCN1A* AG genotype was significantly associated with AED resistance and higher seizure frequency, and that elevated TSH levels and subclinical hypothyroidism were significantly more common in resistant patients. These findings reflect a complex interplay between genetic predisposition and endocrine dysregulation in determining treatment outcomes in childhood epilepsy.

The present data show a significant predominance of the *SCN1A* AG genotype among AED-resistant children compared to responders ($p = 0.05$), suggesting a genetic contribution to pharmaco-resistance. This aligns with the findings of Mohammadi et al., whose recent systematic review and meta-analysis reported that *SCN1A* polymorphisms are associated with resistance to AED therapy across multiple cohorts, reinforcing the role of sodium channel gene variants in pharmacogenetic susceptibility to drug resistance.²

Similar conclusions were reported by Tang et al., who identified *SCN1A* variants as significant risk factors for drug-resistant epilepsy in a cohort of pediatric patients, highlighting consistency across ethnic and geographical populations.⁽⁵⁾ These data emphasize the importance of voltage-gated sodium channel genes in modulating neuronal excitability and AED responsiveness, which is consistent with the concept that epilepsy is partly an ion-channelopathy.⁸

Our study demonstrated significantly elevated serum TSH levels in the AED-resistant group compared with AED-responsive patients ($p = 0.05$), with a markedly higher prevalence of subclinical hypothyroidism (26.7% vs 3.3%, $p = 0.02$). These findings are consistent with previous reports indicating that chronic AED therapy may affect thyroid hormone homeostasis by altering thyroid hormone metabolism, secretion, or peripheral conversion.^{9, 10}

These results strongly support Han et al. (2019), who demonstrated in 181 pediatric patients that TSH levels were relatively higher at initial testing compared with 2-week follow-up (median 3.97 μ IU/mL vs 2.24 μ IU/mL, $p < 0.0001$), with 30% showing abnormally high TSH levels (>4.2 μ IU/mL).¹¹ Specifically,

Yılmaz et al. observed that most AEDs except levetiracetam are associated with elevations in TSH and reductions in thyroid hormones in pediatric epilepsy patients, suggesting a deleterious endocrine effect of traditional AEDs.¹² Likewise, Amer et al. reported significant effects of traditional AEDs on thyroid profiles, supporting the association between long-term AED use and acquired thyroid dysfunction in children.⁷ These alterations are clinically relevant, as even subclinical hypothyroidism may contribute to fatigue, cognitive slowing, and poor seizure control if unrecognized and untreated.

The present study reveals a significant association between *SCN1A* genotype and thyroid profile, with AG genotype carriers exhibiting elevated TSH levels compared to AA carriers ($p = 0.01$). While the mechanistic link between sodium channel variants and thyroid axis dysregulation remains to be fully elucidated, this observation may reflect shared regulatory pathways at the level of neuronal excitability and hypothalamic-pituitary axis feedback. AED polytherapy, more common in resistant cases, has also been linked with thyroid dysfunction, possibly amplifying these effects when combined with underlying genetic susceptibility.⁹

Importantly, our data show a positive correlation between TSH levels and seizure frequency ($r = 0.59$, $p < 0.001$), indicating that thyroid dysfunction may not only be secondary to AED effects or genetic predisposition but could also contribute to seizure burden. This bidirectional relationship suggests that thyroid hormone abnormalities may be a modifiable factor in managing difficult-to-control epilepsy. The combined assessment of *SCN1A* genotype and thyroid hormone profile may aid in early identification of children at higher risk for AED resistance. Although genetic testing alone has moderate predictive value ($AUC = 0.67$), integrating genetic markers with endocrinological evaluation could improve individualized treatment strategies.

Routine thyroid monitoring in children with poorly controlled epilepsy, particularly those on polytherapy or with genotypes associated with pharmacoresistance, may be clinically indicated. Early detection and management of thyroid dysfunction may help mitigate its

potential contribution to seizure refractoriness and overall disease burden.

Our findings corroborate earlier observations of AED-associated thyroid hormone alterations and genotype–drug response associations. For example, Li et al. noted that sodium channel gene variants, including *SCN1A*, are implicated in drug response phenotypes, although results can vary across populations.⁸ Similarly, cohort studies report that traditional AEDs such as valproate and carbamazepine have more pronounced effects on TSH and thyroid profiles than newer agents like levetiracetam, which show minimal thyroid impact.¹³

Strengths and Limitations

A major strength of this study is the combined evaluation of genetic, hormonal, and clinical seizure data in a well-characterized pediatric cohort. However, our sample size, while sufficient to detect medium effect sizes, may limit the generalizability of some subgroup analyses. The cross-sectional design precludes establishment of temporal causality between thyroid changes and seizure evolution, suggesting a need for longitudinal studies. Additionally, further research is warranted to clarify mechanistic pathways underlying gene–endocrine–drug response interactions.

Conclusion

This study demonstrates that *SCN1A* polymorphism and thyroid dysfunction are significantly associated with AED resistance in pediatric epilepsy. Elevated TSH and increased subclinical hypothyroidism, alongside genetic susceptibility, underscore the multifactorial nature of pharmacoresistance. Integrated genetic and endocrine profiling may enhance personalized therapeutic approaches and clinical outcomes in children with epilepsy.

Recommendations

- Routine thyroid function screening should be considered in children with epilepsy, particularly in those with poor seizure control or receiving polytherapy, due to the strong association between thyroid dysfunction and drug resistance.
- Early genetic screening for *SCN1A* polymorphisms may help identify patients at higher risk of antiepileptic drug resistance and guide individualized treatment strategies.
- Integrated multidisciplinary management, involving neurology and

endocrinology, is recommended for children with refractory epilepsy to optimize seizure control and overall outcomes.

- Close monitoring of patients on long-term or multiple AEDs, especially valproic acid-based regimens, is advised to detect early endocrine disturbances.
- Future research should focus on large, multicenter and longitudinal studies to clarify causal relationships and explore gene-hormone interactions in epilepsy.

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