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Review Article

Genetic association of SCN1A gene polymorphisms and efficacy of anti-seizure medications

Yusra Abdulqader*, Fatemah Kamel, Rania Magadmi, Haythum Tayeb, Mohammed Bazuhair

Department of Clinical Pharmacology, Faculty of Medicine, King Abdulaziz University, Jeddah 21589, Saudi Arabia

For correspondence:* ***Email:* *yabdulqader0001@stu.kau.edu.sa;* ***Tel:*** *+966-541080510*

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Abstract

Anti-seizure medications (ASMs) are crucial in the management of seizures; however, significant variability in treatment responses exists, even among patients with similar seizure types and clinical histories. Developing an objective biomarker that could consistently predict efficacy of ASMs poses a substantial challenge in transforming the landscape of epilepsy treatment. Currently, healthcare providers tend to rely on trial-and-error methods when selecting ASMs, which constitutes a time-consuming process and may delay the use of alternative non-pharmacological interventions, such as ketogenic diets, epilepsy surgery and neuromodulating therapies. Predicting the efficacy of ASMs through pharmacogenetic studies that explore the relationship between ASMs and genetic variations related to their mechanisms of action offers prognostic insights into treatment responses, potentially leading to improved outcomes. While sodium channel subunit (SCN) genes, along with various ion channels and receptors, have been extensively investigated as therapeutic targets, findings have been inconsistent. This is likely due in part to differences such as variations in defining drug responses, types of ASM combinations used, and the genetic variants tested. Nevertheless, these studies highlight the significant influence of genetic variations on the activity of ASMs and subsequently on predictions for expectable therapeutic responses. Advances in sequencing technologies have resulted in extensive genetic datasets that could enhance the accuracy of ASMs' response predictions. This review examines the pharmacogenetic associations of sodium channel 1A subunit (SCN1A) gene polymorphisms and the efficacy of ASMs in different ethnicities.

Keywords: *Epilepsy, Anti-seizure medications, SCN1A gene, Pharmacogenetics, Drug-resistant epilepsy, Single-nucleotide polymorphisms*

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INTRODUCTION

Epilepsy is a brain condition defined by recurrent and unpredictable disruptions in normal brain function [1]. According to the "World Health Organization 2010 Global Burden of Disease Study", it is recognized as the second most prevalent neurological condition in terms of disability-adjusted life years worldwide [2], contributing approximately 9.9 % to the global burden of neurological diseases [3]. The "International League Against Epilepsy (ILAE)" categorizes seizures and epilepsy into three primary types: focal, generalized, and unknown onset. This classification is based on various factors, including seizure characteristics, electroencephalogram (EEG) findings, imaging results, patient age and potential triggers [4,5].

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Epileptogenesis refers to the transformation of normal brain function resulting from discrepancy in excitatory and inhibitory neuronal activities, ultimately leading to the development of epilepsy [6]. Although the precise mechanisms underlying epileptogenesis remain incompletely understood, multiple contributing factors have been identified, such as structural brain changes, neuroinflammation, neurotransmitter imbalance, metabolic disturbances, environmental triggers and genetic factors [7]. The diagnostic process encompasses a comprehensive assessment that includes a detailed medical history, descriptions of symptoms, patterns of seizure triggers, familial history and a physical examination with a focus on neurological assessment [8]. The goal is to accurately identify the type of seizures, classify the form of epilepsy and develop an effective treatment strategy [9].

Management of epilepsy usually involves a combination of medications, lifestyle modifications and supportive therapies. The specific management approach may vary depending on the individual's seizure type, frequency and underlying cause [9]. Although anti-seizure medications (ASMs) are the primary therapy, they only suppress seizure symptoms but don't cure the basic condition. The purpose of ASM's treatment is to certify the best achievable quality of life by maintaining seizure control with minimal drug side effects. Approximately two-thirds of epileptic patients become seizure-free with ASMs, but the degree of response varies based on factors such as epilepsy types, etiology and the seizure frequency before treatment [9]. Because ASMs typically need to be continued for at least two years, if not for life, the decision to start treatment should consider whether the potential benefit outweighs the risks, as well as the preferences of patients and their families. Treatment is usually initiated once a diagnosis of epilepsy has been confirmed, starting with a single ASM at a low dose that is gradually increased to the minimum effective dose to maintain seizure freedom while minimizing side effects. There is no single ASM ideal for all patients; rather, the choice of ASM should be tailored to the individual characteristics of the patient and the drug itself [9].

Between the 1950s and 2019, more than 21 new ASMs have been introduced [10], providing more options but also complicating the identification of the most suitable drug for specific patients, as each has its advantages and limitations [11]. Most epilepsy treatments consist of ASMs that selectively bind to one or more target molecules, usually ion channels, to achieve therapeutic effects (Figure 1) [12,13]. However, these medications alleviate symptoms in approximately 60 % of patients, with about one-third exhibiting drug resistance [12].

Drug-resistant epilepsy

Drug-resistant epilepsy (DRE) poses significant challenges, like quality of life, limited treatment options, cognitive and psychological issues, and patient compliance with their medications. Interestingly, the mechanisms underlying this resistance remain poorly understood [14]. The International League Against Epilepsy (ILAE) Task Force defined DRE as "the failure of adequate trials of two tolerated, appropriately chosen and used anti-seizure drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" [15]. In these cases, clinicians frequently combine ASMs empirically, considering their molecular mechanisms of action, efficacy and tolerability [10]. The pathogenesis of drug resistance is likely variable and multifactorial, involving different mechanisms that may act simultaneously. Proposed mechanisms of drug resistance are interrelated and encompass disease-related, drug-related and genetic mechanisms [16]. Lin *et al* proposed several hypotheses to explain the pathogenesis of DRE, including the "transporter hypothesis, neuronal network hypothesis, intrinsic severity hypothesis, target hypothesis and gene variant hypothesis" [17]. Many of these hypotheses focus on pharmacokinetic and pharmacodynamic mechanisms related to the physiopathology of epilepsy and potentially linked to pharmaco-resistant epilepsy [14].

Genetic variation is characterized by single-nucleotide polymorphisms (SNPs), which are prevalent in over 1 % of the population and defined as alteration in a single DNA base pair. These alterations influence various regions of genes, including promoters, introns (non-coding regions) and exons (coding regions), which are fundamental to numerous physiological pathways. Such changes impact RNA and protein functions, as well as the efficiency of transcription and translation processes [18]. Consequently, this leads to changes in the protein's amino acid sequence or its expression, subsequently affecting its structure and function [19]. Moreover, these SNPs have the potential to influence gene regulation, protein functionality and various biological mechanisms significantly involved in the development and pathogenesis of epilepsy.

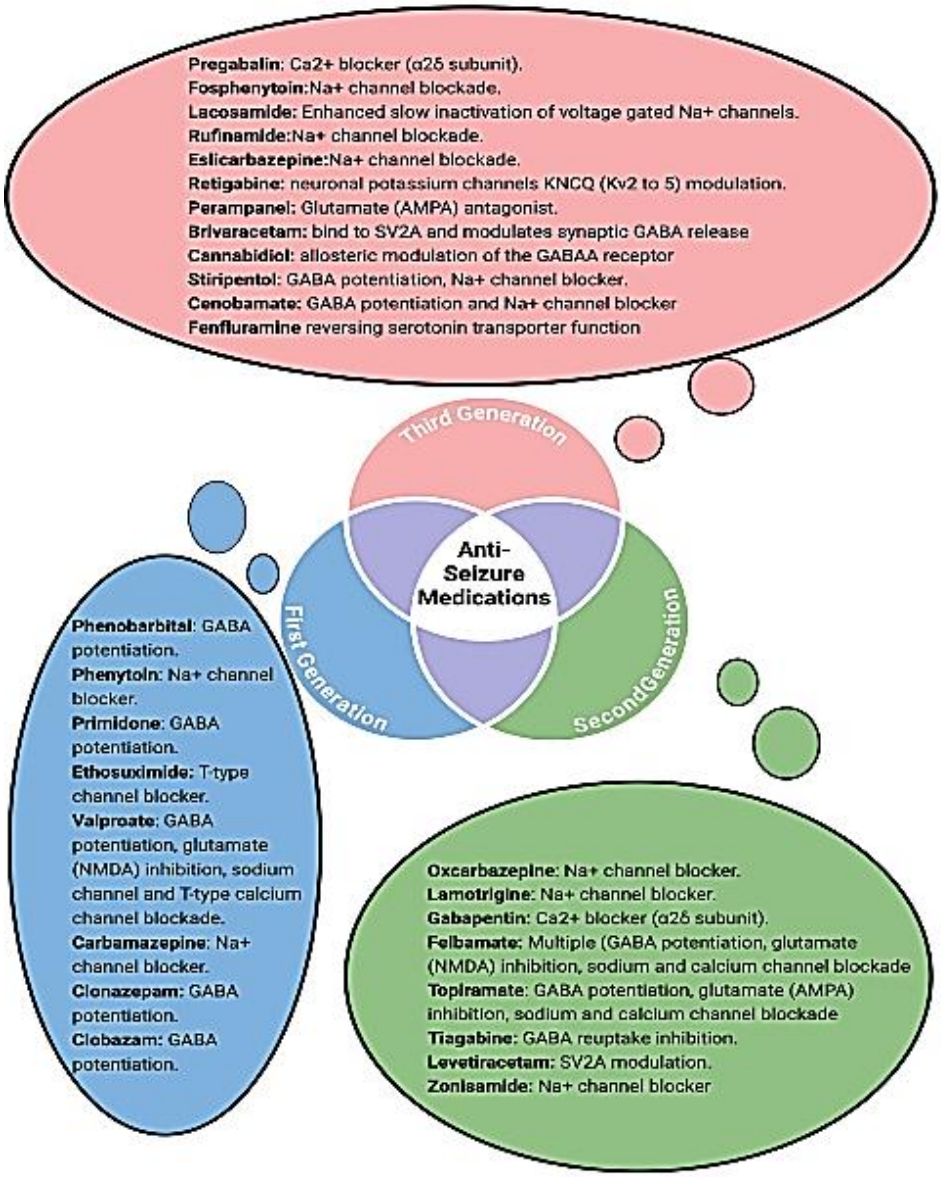

Figure 1: Generation and basic mechanisms of anti-seizure medications

This is particularly relevant given that over half of epilepsy cases are rooted in genetic factors exhibiting complex inheritance patterns. Consequently, SNPs may play a crucial role in determining an individual's vulnerability to epilepsy, contributing to the complex genetic relations underlying this condition [20]. Additionally, SNPs significantly influence the action of medications, thereby impacting DRE [21]. Although the potential risk factors for DRE are well-documented, the reasons behind the varying effectiveness of ASMs in patients with the same epilepsy type or seizure characteristics remain unclear [18].

Genetic factors are likely responsible for variations in the pharmacodynamics (PD) and pharmacokinetics (PK) of the drugs used [19], which may significantly affect drug action, thus contributing to DRE by influencing the pathways through which ASMs exert their effects or by binding to their targets [17,21]. Their effect could influence receptors such as sodium channels (SCN), potassium channels (KCN), GABA receptors, as well as transporters like P-glycoproteins, multidrug resistance-associated protein and some microsomal enzymes, cytochromes P450 enzymes [22].

"Voltage-gated sodium channels (VGSCs)" are major pharmacological targets for many ASMs

[14], as they play a critical role in producing and propagating action potentials in neurons and facilitate the influx of sodium ions down their concentration gradient into the cell [23]. This influx may contribute to the mechanisms underlying epileptogenesis [24]. Consequently, the blockade of SCN within the brain is a principal action through which many ASMs apply their therapeutic outcomes [25] by diminishing the high-frequency firing of sodium ions that characterizes seizure activity [17]. Voltage-gated sodium channels represent significant targets for various ASMs, such as “phenytoin, carbamazepine and lamotrigine”. Additionally, valproic acid influences voltage-gated sodium channels indirectly via the GABAergic system [26].

Structure of voltage-gated sodium channels

Voltage-gated sodium channels are classified as heteromeric integral membrane glycoproteins, consisting of an α-subunit weighing approximately 260 kDa, along with regulatory β-subunits (β1–β4), each around 35 kDa [27]. Each α-subunit is associated with one or more β-subunits to create a functional channel (Figure 2). The α-subunit primarily serves as the voltage sensor and constitutes the pore region of the channel, while β-subunits modulate or enhance the functionality of SCNs [17,20].

α-Subunits

Ten different mammalian α-subunit isoforms have been identified, seven of which are expressed within the nervous system. Isoforms NaV1.1, NaV1.2, NaV1.3 and NaV1.6 are primarily found in the central nervous system, whereas NaV1.7, NaV1.8 and NaV1.9 are predominantly located in the peripheral nervous system [27]. The α-subunit is a large protein composed of 2000 amino acids [28]. Each α-subunit is organized into four homologous domains (DI – DIV), each of which has six transmembrane segments (S1 – S6), which collectively surround the central opening of the channel. Notably, segment 4 (S4) of each domain is rich in positively charged residues and serves as voltage sensor, essential for voltage-dependent activation of the channels, playing a key role in action potentials and changes in graded membrane potential [29]. The inner surface of the pore is formed by segment 6 (S6) from all four domains. Additionally, the hairpin-like loop connecting segments 5 and 6 (S5 – S6) constitutes a narrow, ion-selective filter that regulates ion permeability and selectivity on the extracellular side of the pore [27].

β-Subunits

The β- β-subunits are also integral membrane proteins, consisting of an extracellular domain (ECD, N-terminal domain), a transmembrane domain, and an intracellular domain (C-terminal domain). These β-subunits are present in excitable and non-excitable cells throughout the nervous system and heart, and they are found in the absence of α-subunit. Each α-subunit interacts with one or more regulatory β-subunits (β1–β4).

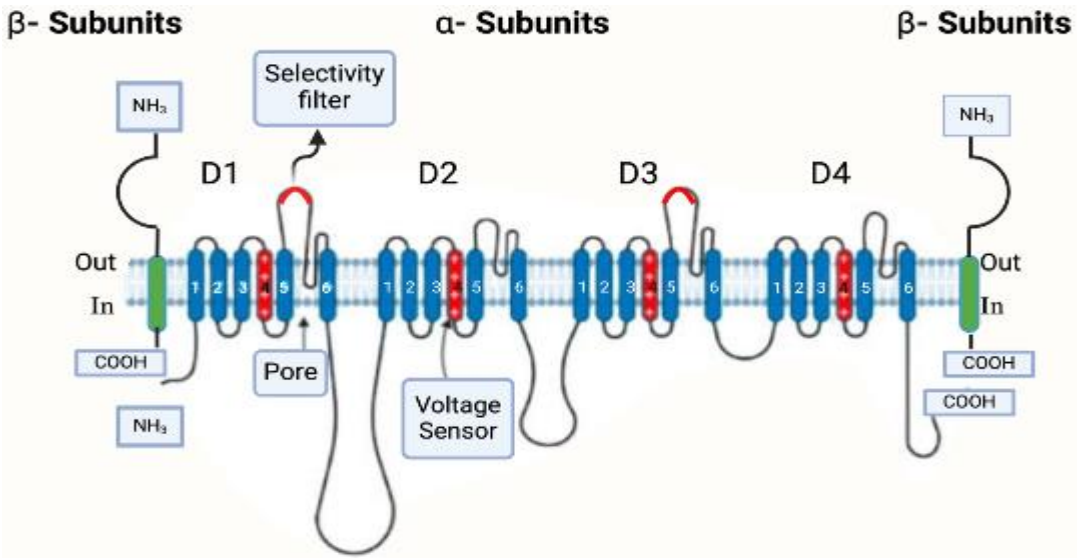

Figure 2: Diagram illustrating sodium channel (α) alpha and (β) beta subunits. Homologous domains (D1–D4); transmembrane segments 1, 2 and 3; segments 4 (red) are the voltage sensors and segments 5 and 6 make up the pore-lining regions; $^{+}H_3N$ represents the N-terminal and CO_2^- the C-terminal

Specifically, a single α-subunit associates with one non-covalently bound β-subunit (either β1 or β3) and one covalently linked β-subunit (either β2 or β4). The β-subunits act as regulatory proteins, serving dual roles as cell adhesion molecules (CAMs) while also modulating the surface expression of VGSC, which enhances sodium channel density and increases cell excitability [27].

Voltage-gated sodium channels are targets for various toxins and medications. There are at least six sites of action for neurotoxins (sites 1 – 6) and one overlapping receptor site for drugs such as class I antiarrhythmic drugs, local anesthetics and related ASMs. This overlapping site is located in the pore's inner cavity and is composed of amino acid residues found in S6 in domains I, III, and IV of the α-subunit [27]. Consequently, mutations in any of these genes significantly disrupt various components of channel function, leading to deviation from normal physiological behavior. This disruption interferes with the structure and biophysical features of the channel, ultimately resulting in channelopathies with potential clinical manifestations, including epilepsy [20,27,30].

Additionally, such polymorphisms may reduce binding affinity at critical residues within the channel's pore, either by decreasing interaction of ASMs with target sites or by altering binding affinity based on the channel's conformation state (rest, active, inactive) [27]. Even minor alterations in the function of sodium channels precipitate epileptic seizures and affect treatment responsiveness. Therefore, genetic variation is crucial in determining individual phenotypic differences related to disease susceptibility and therapeutic response [29]. The majority of mutations in *SCN* genes are concentrated within the *SCN1A* gene, with fewer instances found in *SCN2A*, *SCN8A*, and *SCN1B* [31].

Role of *SCN1A* in pharmacoresistance

The *SCN1A* polymorphisms affect sodium channel gating, rendering them insensitive to drugs blocking sodium channels [32]. Since *SCN1A* is primarily expressed in inhibitory neurons [33], and neuronal excitability is critically governed by interaction of voltage-gated and ligand-gated ion channels, ion channel impairment due to SNPs has emerged as a potential factor contributing to resistance to ASMs [34]. Various studies suggest that drug-resistant patients treated with sodium channel blockers often exhibit specific *SCN1A* genotypes [34].

Therapeutic application of *SCN1A* gene polymorphism and epilepsy pharmacoresistance

A systematic literature search was conducted to highlight a comprehensive understanding of the role of *SCN1A* genetic variants involved in drug efficacy. The methodology included a thorough literature search across multiple databases, including PubMed, Scopus, Web of Science and Google Scholar. The search keywords used were "Drug Resistance Epilepsy" AND "*SCN1A* genetic polymorphisms" OR "*SCN1A* pharmacogenetics" OR "*SCN1A* pharmacogenomics" NOT "Dravet Syndrome" OR "*SCN1A* mutation".

The search focused on studies published in English from any geographic location and included subjects of any ethnicity, with fixed age categories (children < 18 years or adults ≥ 18 years) taking any type of ASMs, and sample size till October 2024. Only studies that examined the *SCN1A* pharmacogenetics related to ASM efficacy and safety were selected to ensure relevance to the review's objectives. Exclusion criteria included articles that had not been accepted, did not specify ethnicity and age, included mixed age groups without specific results for each group, or were not relevant to the response to ASMs. Studies focusing on ribonucleic acid rather than genes, pharmacokinetic studies rather than pharmacodynamics studies, or non-human studies were also excluded. The data collected were synthesized and compared to provide an overview of the progress in ASM pharmacogenetics (Table 1 - 4).

This systematic review was conducted to identify studies examining the association between variation in *SCN1A* gene and efficacy of ASMs across different populations and age groups. The intronic variants rs3812718 and the missense variants rs2298771 are among the most extensively studied polymorphisms. Some studies have shown a significant association between *SCN1A* gene polymorphism and efficacy of ASMs, while others have indicated an association between *SCN1A* gene and the dosage of SCN blocker medications. However, several studies included in this review did not find such a link. This discrepancy may be attributed to multiple reasons including differences in age groups, ethnicity, sample size, and the type of medications used.

Table 1: *SCN1A* gene polymorphism and epilepsy pharmacoresistant studies

Ethnicity	Age group	Drug	Sample size	Main findings
Vietnamese [35]	Children (aged 1–15 years) with epilepsy	Various	213	The heterozygous (AG) genotype of rs2298771SNP was significantly associated with DRE, while heterozygous (CT) genotype of rs3812718 was significantly associated with drug response. There was no overall significant association between the rs10188577 polymorphism and DRE.
Greece [36]	Adult age ≥ 18 years diagnosed with focal or generalized seizures	Various	214	The homozygous of G allele of rs3812718 variant was significantly more frequent in the focal onset group compared to generalized onset and focal onset to bilateral tonic–clonic seizures Controls at p=0.034. In contrast, the G allele of the rs2298771 variant was less frequent in focal onset patients compared to generalized onset and focal onset to bilateral tonic–clonic seizures patients. There were no overall significant association between rs2298771 and rs3812718 variants and DRE.
Chinese [37]	Pediatric patient diagnosed with epilepsy	Valproic acid	233	There was a significant association between *SCN1A* rs2298771 and response to monotherapy with valproic acid (VPA), whereas carriers of the TT genotype were more prevalent in the VPA-responsive group, whereas CT and CC genotypes of rs2298771 were significantly associated with VPA resistance. There was no overall significant association between rs10188577 and rs3812718 variants and DRE.
Indian [38]	Adults (mean age 27.30±7.0 years)	Various	100	The heterozygote of AT genotype of rs6732655 was associated with high risk of drug resistance, with an odds ratio of 1.58 compared to AA genotype.
Brazilian [20]	Adults with TLE	Various	120	The heterozygous (AG) genotype carriers of rs2298771 variant were linked with increased risk of TLE and was more frequent in DRE compared to control group. There was no overall significant association between rs3812718 and risk of TLE as well as with DRE.
Chinese Han [39]	children	Valproic acid	114	There was a significant association between carriers of GT genotype of rs1381105 and C allele and heterozygous of (TC) genotype of rs2162600 with VPA resistance at p=0.039, p=0.033 and p=0.049, respectively.

"CBZ: carbamazepine, **CBZD**: carbamazepine-10,11-trans dihydrodiol, **CDR**: concentration-dose ratios, **DRE**: drug-resistance epilepsy, **INCDR**: natural logarithmic CDR, **OR**: odds-ratio, **OXC**: oxcarbazepine, **PHT**: phenytoin, **SCN1A**: sodium channel1A, **SNP**: single-nucleotide polymorphism, **TLE**: temporal lobe epilepsy, **VPA**: valproic acid"

Table 2: SCN1A gene polymorphism and epilepsy pharmacoresistant studies *(contd)*

Ethnicity	Age group	Drug	Sample size	Main findings
Chinese [40]	Children (1 month to 18 years)	Valproic acid	140	The homozygous (AA) genotype carriers of *SCN1*A rs2298771 are linked with increased resistance to VPA in patients with focal epilepsy. There was no significant correlation with VPA efficacy in both subgroups and other SNP genotypes.
Italian [41]	pediatric	Various	120	AC genotype of rs6730344, AA genotype of rs6732655 and AA genotype of rs10167228 were significantly associated with drug resistance with OR = 1.58, 2.25, 1.89, respectively. While AA and AT genotypes of rs1962842 were significantly linked to increased risk of DRE compared with TT genotype, with OR = 3.33
Slovenian [42]	children and adolescents with epilepsy	Various	216	The homozygous (AA) genotype was more frequent in epileptic patients compared to controls, while carriers of homozygous (GG) genotype were less prevalent in epileptic patients compared to controls, with a lower risk of epilepsy. Carriers of G allele tended to have a lower risk of epilepsy and were significantly associated with drug response
Iranian [43]	Children diagnosed as one type of idiopathic refractory epilepsy	Various	34	There was no overall significant difference between the two polymorphisms and DRE in patients with idiopathic refractory epilepsy
Chinese [44]	Adults (mean age 36.20±16.50 years) with epilepsy	Carbamazepine	83	There was no overall association between IVS5-91G > A polymorphism and CBZ maintenance doses or adjusted CBZ concentrations, as well as with carbamazepine resistance.
Ukrainian [45]	Adults mean age 33.6±13.3 yr with epilepsy	Carbamazepine Valproic acid	183	There was a significant association between rs3812718 genotype and CBZ and VPA resistance, CC genotype carriers were more prevalent in CBZ and VPA resistance.
Iranian [46]	children (aged 1.5 to 14 years)	Various	93	There was no significant association between drug-resistant epilepsy.
Chinese [47]	Adult 30.95±15.49 years	Oxcarbazepine	184	A allele and AA genotype carriers of the SCN1A IVS5-91G > A significantly required high maintenance doses of OXC are p=0.007 Corresponding relative ln (concentration-dose ratios) values for SCN1A IVS5-91 variants differed by the genotypic order GG > GA > AA. AA genotype of SCN1A IVS5-91G > A has been significantly linked with lower concentration-dose ratios.

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Table 3: SCN1A gene polymorphism and epilepsy pharmacoresistant studies (*Contd)*

Ethnicity	Age group	Drug	Sample size	Main findings
Kosovar Albanian [48]	Adults aged between 18 – 70 years	Carbamazepine	145	Carriers of *SCN1A* IVS5-91G > A variant were linked with increased risk of epilepsy susceptibility, but there was no impact for SCN1A c.3184A > G SNP. AA genotype carriers of IVS5–91 G > A was linked with increased maintenance dosage, reduced CBZ plasma levels, and increased CBZD to CBZ ratio compared with AG and GG genotype carriers. However, *SCN1A* c.3184A > G SNP was not significantly associated with CBZ clearance. No association was found between SCN1A c.3184A > G SNP and CBZ metabolism.
Chinese [49]	Adults 34.75±15.83	Carbamazepine	166	AG and AA genotype carrier patients of SCN1A IVS5-91G>A significantly need higher CBZ maintenance dose at *p*=0.002 and 0.008, respectively. There was also significant linkage disequilibrium between *SCN1A IVS5-91G > A* and *c.3184A > G* and significantly associated with adjusted maintenance doses and lnCDRs of CBZ. The lnCDR of CBZ differed according to the *SCN1A IVS5-91* genotype in this order: GG > GA > AA. Thus, patients carrying *AA* genotype exhibited a lower lnCDR than those carrying the GG or GA genotype. *p*=0.026 and 0.019, respectively.
Chinese [50]	Children (aged 2 to 18 years) with generalized seizures	Valproic acid	174	The rs10188577 variant was significantly more prevalent in drug-response patients compared to drug-resistant patients at $p = 0.035$.
Chinese [25]	Adults	Carbamazepine	234	Carriers of the variant *SCN1A* IVS5-91G > A significantly required high maintenance dose of CBZ. Also, patients with GA/AA, AA/AA, GA/AG, or AA/AG diplotypes of both SNPs likely required high CBZ maintenance doses. AA and AG haplotype of *SCN1A* IVS5–91 G > A (rs3812718) and c.3184A > G (rs2298771) were significantly associated with maintenance dose of CBZ. Carrier of *SCN1A* IVS5–91 G > A (rs3812718) variant was significantly associated with decreased lnCDRs of CBZ. Also, patients with GA/AA, AA/AA, GA/AG or AA/AG diplotypes were more likely to have lower lnCDRs of CBZ. AA haplotype of *SCN1A* IVS5–91 G > A (rs3812718) and c.3184A > G (rs2298771) was more likely to have lower lnCDRs of CBZ.

"CBZ: carbamazepine, **CBZD**: carbamazepine-10,11-trans dihydrodiol, **CDR**: concentration-dose ratios, **DRE**: drug-resistance epilepsy, **INCDR**: natural logarithmic CDR, **OR**: odds-ratio, **OXC**: oxcarbazepine, **PHT**: phenytoin, **SCN1A**: sodium channel1A, **SNP**: single-nucleotide polymorphism, **TLE**: temporal lobe epilepsy, **VPA**: valproic acid"

Table 4: SCN1A gene polymorphism and epilepsy pharmacoresistant studies (*contd)*

Ethnicity	Age group	Drug	Sample size	Main findings
Chinese [51]	Adult (mean age 41.72±0.72)	Phenytoin	269	There was no effect on PHT maintenance dose and lnCDRs in diplotype analysis of both SNPs. Carrier of rs3812718 polymorphism has a significant effect on lnCDR of PHT under adjustment of age, gender and epilepsy classifications.
Egyptian [31]	Children (with non-lesional epilepsy	Various	326	The heterozygous (AG) genotype variant was significantly more frequent in patients with higher seizure frequency and with generalized epileptiform. Also, this heterozygous (AG) genotype variant was associated with topiramate and valproate resistance and was also significantly associated with levetiracetam and carbamazepine response.
Taiwanese [17]	Adult aged >20 years	Phenytoin Carbamazepine Lamotrigine Oxcarbazepine Lacosamide Zonisamide Topiramate Valproic acid	200	There was no association found between all SNPs and drug response for patients taking SCN-ASMs. At *p*=0.0024.
Chinese [52]	aged 2–18 years with epilepsy	Valproic acid	231	There was a significant correlation between TT carriers' genotype and VPA resistance at *p*=0.025 after adjusting the age, body weight, and seizure frequency.
Colombian [53]	Adult	Phenytoin	67	No significant association between SCN1A-IVS5 91G > A (rs3812718) variant and phenytoin resistance.
Japanese [54]	5.1±4.4 years	Valproic acid	77	There was a significant association between homozygous (AA) genotype of rs3812718 and treatment-resistant epilepsy in patients administered VPA.

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Significance of age groups and sample sizes

Age plays a significant role in genetic studies, as many of the reviewed studies (25 studies) have shown its impact on both children and adults. For example, Tang *et al* investigated the association of *SCN1A* SNPs rs2298771, rs3812718, and rs10188577 and drug responsiveness in 213 Vietnamese children with epilepsy (101 drug-responsive, 112 drug-resistant). The study found that the rs2298771 (GA) genotype was significantly associated with DRE, suggesting it could be a risk factor for refractory epilepsy. In contrast, rs3812718 (CT) genotype was significantly associated with drug response [35]. Similarly, Bertok *et al* examined the relation between *SCN1A* Thr1067Ala polymorphism and response to ASMs in 216 Slovenian children and adolescents with epilepsy, identifying a significant relation between *SCN1A* polymorphism and response to the drug [42]. Abo El fotoh *et al* investigated the impact of *SCN1A* c.3184 A/G variant on drug resistance among 130 Egyptian children with epilepsy. The researchers found a significantly higher frequency of AG genotype and G allele in drug-resistant patients compared to those who responded to treatment [32].

In adult studies, Daci *et al* [48] examined the impact of the *SCN1A* gene variant rs3812718 on carbamazepine (CBZ) pharmacokinetics, metabolism and treatment response in epilepsy patients. Carriers of *SCN1A* IVS5-91G > A variant were found to be significantly associated with efficacy of CBZ [48]. Also, Ma *et al* examined the associations between genetic polymorphisms in certain genes (*SCN1A, ABCC2, UGT2B7*) and maintenance doses of the antiepileptic drug, oxcarbazepine, in Han Chinese epilepsy patients. They found a genotypic association between oxcarbazepine dose-response relationship and *SCN1A* IVS5-91G > A variant [47]. Hung *et al* investigated the impact of genetic polymorphisms on the variable dosage and concentrations observed in patients taking CBZ. They found that carriers of the *SCN1A* IVS5-91G > A variant allele tended to require higher CBZ dosages and had lower concentration-to-dose ratios compared to non-carriers [25]. Based on the summarized results, it was shown that the association between *SCN1A* gene polymorphisms and drug-resistant epilepsy differs by age group. In the pediatric population, *SCN1A* SNPs rs2298771 were more prevalent among epileptic patients and significantly associated with ASMs. In contrast, *SCN1A* SNPs rs3812718 was more prevalent in the adult population and significantly associated with SCN blocker ASMs such as carbamazepine and oxcarbazepine. This may be due to distinct pharmacokinetic and pharmacodynamic profiles exhibited by pediatric patients, influenced by several factors such as continuous growth and development. Therefore, adults may show selective resistance to specific ASMs. This highlights the need for treatment approaches to be customized according to the patient's age to optimize therapeutic outcomes [55]. Conducting age-specific study is essential for understanding the impact of genetic factors on drug responses throughout various developmental phases.

The sample size of the studies varied, with some using small sample sizes. For instance, Hosseini and co-workers evaluated the frequency of specific SNPs in *SCN1A* among an Iranian population with idiopathic refractory epilepsy, involving 81 healthy individuals and 34 Iranian patients. Genotyping was performed to determine presence of two SNPs in *SCN1A* (rs2298771, rs7601520) and they showed no statistically significant differences in genotype combination between patient and control groups. This inferred that the selected SNPs in *SCN1A* may not significantly impact efficacy and tolerability of ASMs in the studied Iranian population with idiopathic refractory epilepsy [43]. Similarly, Calderon-Ospina *et al* conducted an observational, prospective cohort study to examine genetic factors influencing response to phenytoin in 67 adult Colombian patients with epilepsy. Results showed that there was no significant association between *SCN1A*-IVS5-91G > A (rs3812718) variant and phenytoin resistance [53].

The main disadvantage of studies that were conducted with small sample size is that statistically significant results may not be observed unless the authors adjust for age, gender, epilepsy classification and other factors that could affect the significance of final results. However, Nakashima *et al* evaluated the optimal concentration of valproic acid (VPA) for treating epilepsy in 77 Japanese pediatric epileptic patients and found a significant association between (AA) genotype and VPA resistance [54]. While this is informative, it limits the applicability of their finding to other populations and the generalization of the conclusion. In contrast, studies with larger sample sizes are applicable to other populations. For instance, Ghazala *et al* investigated the *SCN1A*-A3184G gene polymorphism among 326 Egyptian children with non-lesional epilepsy (163 drug-resistant and 163 drug-responsive) and 163 healthy controls. It was shown that the AG

genotype was significantly associated with specific ASM use (e.g., topiramate, valproic acid) in the drug-resistant group, and levetiracetam and carbamazepine in the drug-responsive group. The authors suggested that the AG genotype of *SCN1A*-A3184G may serve as a predictor of treatment response, aiding in personalized ASMs selection, though larger studies are needed to validate the findings across different populations [31]. Increasing sample size provides more robust data and increased confidence in findings, as well as increased statistical power to detect significant associations between *SCN1A* polymorphisms and ASM responsiveness. As shown from previous studies, adequate and larger sample sizes are required to validate the results of genetic associations and to provide tailored, personalized treatment approaches.

Significance of ethnicity

The association between *SCN1A* gene polymorphisms, such as rs2298771, rs3812718 and rs10188577, and drug resistance has been observed across different ethnicities. For instance, in the European population, Bertok *et al* examined the association between *SCN1A* Thr1067Ala polymorphism and response to ASMs in 216 Slovenian children and adolescents with epilepsy, identifying a significant association between this polymorphism and drug response. From the results obtained, it was concluded that the homozygote A allele was associated with increased risk of drug resistance [42]. In the Ukrainian population, Oros and co-workers examined the association between genetic polymorphisms in the ABCB1 and *SCN1A* genes and the response to the ASMs, sodium valproate and carbamazepine, in patients with epilepsy. There was a significant association between CC genotype carriers and resistance to CBZ and VPA [45]. Similarly, Daci *et al* evaluated the impact of the *SCN1A* gene variant rs3812718 on CBZ pharmacokinetics, metabolism and treatment response in Kosovar Albanian epilepsy patients. Carriers of the *SCN1A* IVS5-91G > A variant were found to possess significantly lower plasma CBZ levels compared to common allele carriers [48].

In contrast, Calderon-Ospina *et al* examined genetic factors influencing the response to phenytoin in Colombian patients with epilepsy and found no significant association between *SCN1A*-IVS5- 91G > A (rs3812718) variant and phenytoin resistance [53]. Additionally, Katsarou *et al* reported a negative association between two *SCN1A* gene polymorphisms (rs3812718 and rs2298771) and DRE in a cohort of 214 patients with focal or generalized epilepsy in the Greek population [36]. In this analysis, the authors found that the *SCN1A* SNP polymorphism, rs3812718, showed a significant association with SCN blocker like carbamazepine and VPA among the adult European population, while in the pediatric population, rs2298771 SNP was significantly associated with various ASMs.

In the Asian population, Tang *et al* investigated the association of *SCN1A* SNPs rs2298771, rs3812718 and rs10188577 with drug responsiveness in 213 Vietnamese children with epilepsy, finding that the rs2298771 (GA) genotype was significantly associated with DRE, while rs3812718 (CT) genotype was significantly associated with drug response [35]. Similarly, Nakashima *et al* found that the (AA) genotype of rs3812718 variant was associated with VPA resistance in pediatric Japanese patients [54]. In Chinese children, Bao *et al* investigated the impact of genetic variations in the *SCN1A* and *SCN2A* genes on the efficacy of VPA treatment in 233 Chinese children with epilepsy. The results showed that the homozygous TT genotype of *SCN1A* rs2298771 was significantly linked to VPA responsiveness, whereas CT and CC genotype carriers were associated with VPA resistance. Patients with certain variants of these SNPs were more likely to respond positively to VPA monotherapy [37]. Also, Liu *et al* investigated the effects of genetic variations in certain genes on responsiveness to valproic acid (VPA) monotherapy in 140 Chinese children with epilepsy. It was shown that in the subgroup of children with focal seizures, those with *SCN1A* rs2298771 AG genotype had a lower incidence of VPA resistance compared to those with the AA genotype [40].

In addition, Feng *et al* evaluated the associations between genetic polymorphisms and the therapeutic response to sodium valproate (VPA) treatment in children with generalized seizures. The study enrolled 174 children on VPA therapy and analyzed their steady-state plasma VPA concentrations. Seventy-six (76) SNPs related to VPA absorption, metabolism, transport, and target receptors were identified and their impact on seizure reduction were assessed. The results showed the *SCN1A* rs10188577 (T > C) polymorphism was significantly more common in drug-responsive patients compared to drug-resistant patients (p = 0.035) [50]. Moreover, Ma *et al* found that carriers of the A allele of rs3812718 variant in the *SCN1A* gene tended to require higher doses of CBZ but had lower concentration-to-dose ratios compared to non-carriers [49]. Also, they identified a genotypic dose-response relationship

for CBZ with the *SCN1A* IVS5-91G > A variant, where the AA genotype required the highest doses and was significantly linked to lower values (concentration-dose ratios) [47].

Also, Hung *et al* investigated the impact of genetic polymorphisms on dosage variability and concentration levels in patients taking CBZ. It was discovered that carriers of the *SCN1A* IVS5-91G > A variant allele required higher CBZ dosages and had lower concentration-to-dose ratios compared to non-carriers. Moreover, carrier of *SCN1A* IVS5–91 G > A (rs3812718) and c.3184A > G (rs2298771) variants were significantly associated with maintenance dose of CBZ and more likely to have lower lnCDRs of CBZ, but no significant association with phenytoin was observed. However, when adjustments of age, gender and epilepsy classification was done, it was found that carrier of *SCN1A* IVS5–91 G > A (rs3812718) polymorphism had a significant effect on lnCDR of PHT (concentration/ dose) ratio [25,51].

In contrast, Yun *et al* examined the effects of genetic polymorphisms in the *EPHX1*, *SCN1A* and *CYP3A4* genes on CBZ pharmacokinetics and pharmacoresistance in 83 Chinese patients with epilepsy. The *SCN1A* IVS5-91G > A variant did not significantly impact CBZ maintenance doses or adjusted plasma concentrations. Also, there were no associations between the studied genotypes and pharmacoresistance to CBZ in this patient cohort [44]. These findings indicate that in the Asian population, the *SCN1A* rs2298771 and rs3812718 polymorphisms were significantly associated with VPA response in children. In adults, the *SCN1A* rs2298771 variant was associated with CBZ use, while the *SCN1A* rs3812718 variant was associated with sodium channel blockers ASMs like oxcarbazepine, CBZ and phenytoin. However, some studies yielded conflicting results within the same ethnic groups, possibly due to environmental factors affecting drug concentration and therapeutic outcomes.

In Iranian ethnicity, Hosseini *et al* evaluated the frequency of specific SNPs among individuals with idiopathic refractory epilepsy, involving 81 healthy individuals and 34 Iranian patients. Genotyping was performed to determine the presence of two SNPs in *SCN1A* (rs2298771, rs7601520) and no statistically significant differences in the genotype combination between the patient and control groups was found. The authors suggested that the selected SNPs in *SCN1A* may have an insignificant impact on the efficacy and tolerability of ASMs in the studied Iranian population with idiopathic refractory epilepsy [43]. Similarly, Mousavi *et al* investigated the association between genetic polymorphisms in three genes (*CYP3A5, SCN1A, ABCG2*) and drug-resistant epilepsy in 93 children. Interestingly, no significant associations of *SCN1A* (rs2298771) gene polymorphisms was found [46]. In an Arab population, Abo El Fotoh *et al* investigated the potential impact of genetic *SCN1A* c.3184 A/G variants on drug resistance among 130 Egyptian children with epilepsy. A significantly higher frequency of the AG genotype and G allele in drug-resistant patients compared to those who responded to treatment was observed [32]. In conclusion, *SCN1A*-A3184G gene polymorphism has a significant association with ASMs efficacy in Egyptian population, suggesting that conducting further studies in the Saudi population could yield meaningful insights.

In brief, findings among different ethnicities show variability, indicating that factors such as age group, sample size, power of the study, ASM used during the study, differences in allelic frequencies, other genetic, drug-drug interactions and environmental factors such as lifestyle, dietary habits as well as other comorbidities may influence response to ASMs. Meanwhile, *SCN1A* gene polymorphisms play a role in pharmacoresistance and could serve as useful genetic biomarkers to predict drug response and guide personalized epilepsy treatment.

Significance association between *SCN1A* gene polymorphism and SCN blocker used:

Valproic acid (VPA)

In cases where VPA was used as monotherapy, significant association was observed between five SNPs (rs10188577, rs2298771, rs3812718, rs1381105, rs2162600), establishing VPA efficacy as an ASMs. Regarding the rs3812718 variant, Wang *et al* investigated the association between *SCN1A* gene polymorphism rs3812718 and resistance to VPA in children with epilepsy. The study enrolled 231 children who were exclusively treated with VPA. The authors found that TT genotype of rs3812718 polymorphism was significantly associated with a higher risk of developing VPA resistance (OR = 2.636 and p = 0.033) and this association remained significant even after adjusting for other risk factors (OR = 2.861 and p = 0.025). Conversely, the recessive model (TT vs CT+CC) was associated with a decreased risk of VPA resistance (OR = 0.402). Additionally, a meta-analysis of nine studies supported the link between rs3812718 polymorphism and VPA resistance [52].

In a Japanese study, Nakashima *et al* evaluated the optimal concentration of VPA for treating epilepsy and found that (AA) genotype was associated with VPA resistance in pediatric Japanese patients [54]. Conversely, in a study on the Ukrainian population, Oros *et al* examined the association between genetic polymorphisms in the *ABCB1* and *SCN1A* genes and response to the ASMs, VPA and CBZ, in Ukrainian patients with epilepsy. The researchers showed a significant association between CC genotype carriers and CBZ plus VPA resistance. This suggests that these genetic factors may influence the efficacy and tolerability of these common ASMs [45]. Therefore, carriers of rs3812718 polymorphism may provide evidence for VPA efficacy and protection against resistance. However, some studies provide contrasting result such as findings from the Ukraine study. Further study is therefore required to clarify the impact of rs3812718 variant and VPA response.

Regarding the rs2298771 variant, (AA) genotype carriers have been linked to increased resistant to VPA in patient with focal epilepsy [40], while (TT) genotype was more prevalent in the VPA-responsive group when used as monotherapy [37]. Interestingly, the dominant genotype of rs2298771 variant shows contrasting results. Therefore, further studies are required to confirm the relationship between rs2298771 *SCN1A* gene polymorphism and VPA response. In addition, Lu *et al* found that *SCN1A* gene polymorphisms, such as rs1381105 and rs2162600, had significant association with VPA response. Specifically, in carriers of the (GT) genotype of rs1381105, the C allele and (TC) genotype of rs2162600 were significantly associated with VPA resistance in the pediatric Chinese population [39]. On the other hand, the rs10188577 variant was significantly more prevalent in drug-responsive patients compared to drug-resistant patients and was associated with treatment efficacy in children with generalized seizures on VPA therapy [50]. Thus, the authors suggest conducting linkage disequilibrium in those five *SCN1A* SNPs to find the relation between *SCN1A* gene and VPA efficacy as well as risk factors associated with VPA resistance.

Carbamazepine and oxcarbazepine

With respect to CBZ treatment, two SNPs (rs3812718 and rs2298771) showed a significant association with efficacy of CBZ as an ASM. In a Chinese population, Ma *et al* evaluated the relationship between genetic variations in pharmacokinetic/pharmacodynamic (PK/PD) genes and the dosage and concentration of CBZ. The study involved 166 patients receiving CBZ as monotherapy. Genetic analysis revealed that carriers of A allele of rs3812718 variant in the *SCN1A* gene required higher CBZ doses but had lower concentration-to-dose ratios compared to non-carriers. The authors concluded that the *SCN1A* IVS5-91 G > A gene polymorphism is a potential genetic biomarker linked to the pharmacokinetics of CBZ [49].

In another Chinese study, Hung *et al* investigated the impact of genetic polymorphisms on the variable dosage and concentration levels observed in patients taking CBZ. The study analyzed genetic variants in several genes related to the pharmacokinetics and pharmacodynamics of CBZ in a cohort of 234 epilepsy patients on CBZ monotherapy. It was shown that carriers of the *SCN1A* IVS5-91G > A variant allele tended to require higher CBZ dosages and had lower concentration-to-dose ratios compared to non-carriers. Also, homozygous carriers of these variants also seemed to require higher CBZ doses and had lower concentration-to-dose ratios. Moreover, carriers of *SCN1A* IVS5 – 91 G > A (rs3812718) and c.3184A > G (rs2298771) variants were significantly associated with maintenance dose of CBZ and more likely to have lower lnCDRs of CBZ. The author concluded that these genetic factors are associated with CBZ therapy optimization and could provide useful information for individualizing CBZ treatment in epilepsy patients [25].

Meanwhile, in the Ukrainian population, Oros *et al* showed a significant association between CC genotype carriers of rs3812718 and CBZ and VPA resistance. This suggests that these genetic factors may influence efficacy and tolerability of these common ASMs [45]. Also, in Kosovar Albanian population, Daci *et al* evaluated the impact of genetic variants in *SCN1A* gene rs3812718 on CBZ pharmacokinetics, metabolism and treatment response in epilepsy patients. The authors found that carriers of the *SCN1A* IVS5-91G > A variant had significantly lower plasma CBZ levels compared to common allele carriers. Therefore, it was suggested that CBZ-resistant patients required higher daily doses but also had increased plasma CBZ levels, indicating resistance is not simply due to pharmacokinetics. These results highlight the importance of genetic factors, particularly in the *SCN1A* gene, in influencing CBZ disposition and metabolism, which could impact treatment response in epilepsy patients [48].

In the case of oxcarbazepine used as monotherapy, rs3812718 was significantly associated with efficacy of oxcarbazepine. The associations between genetic polymorphisms in (*SCN1A, ABCC2, UGT2B7*) and the maintenance doses of the oxcarbazepine in Han Chinese epilepsy patients were examined by Ma *et al* [47]. They found that there was a genotypic dose-response relationship for the *SCN1A* IVS5-91G > A variant, with the AA genotype requiring the highest doses and was significantly linked to lower values (concentration-dose ratios). The authors concluded that these genetic polymorphisms are associated with oxcarbazepine dosing requirements and could be useful for personalizing oxcarbazepine therapy in epilepsy patients [47]. Overall, this study highlights the potential of pharmacogenomics in guiding individualized drug dosing for ASMs like oxcarbazepine. Thus, these findings highlight the potential clinical relevance of pharmacogenesis in optimizing ASM therapy. The results provide insights into the genetic underpinnings of variable drug response in this patient population. Therefore, the authors suggested that any patient that have A allelic variants of *SCN1A* polymorphisms of both SNPs (rs3812718 and rs2298771) may need a higher dose of carbamazepine and oxcarbazepine or could become more resistant to these ASMs.

Phenytoin

In phenytoin monotherapy, a significant association with one SNPs (rs3812718) regarding the efficacy of phenytoin was observed. For the rs3812718 variant, *Hung et al* investigated the association between genetic variants in several genes and the dosage, concentration and concentration-dose ratio of the phenytoin in Han Chinese patients. The study analyzed 11 genetic polymorphisms across 6 candidate genes in 269 epilepsy patients on phenytoin monotherapy. It was reported that being carriers of this polymorphism produced a significant effect on lnCDR of phenytoin (concentration/ dose) ratio under adjustment of age, gender and epilepsy classifications in a multivariate analysis [1]. In contrast, a Colombian study by Calderon-Ospina *et al* examined the genetic factors that may influence the response to phenytoin in a group of Colombian patients with epilepsy. The study found no significant association between *SCN1A*-IVS5- 91G > A (rs3812718) variant and phenytoin resistance. However, there was a trend towards higher rates of seizure freedom on phenytoin therapy (p = 0.07), although this was not statically significant [53].

These findings suggest that *SCN1A* genetic variants may influence the pharmacodynamic of sodium channel-blocking antiseizure drugs like phenytoin. This could be due to possible binding sites and the affinity of phenytoin to *SCN1A* receptor, as well as other genes affecting phenytoin metabolism. Therefore, polygenic analysis provides valuable information in guiding phenytoin therapy, highlighting the importance of considering genetic factors that influence an individual's response to this commonly used ASM.

Risk of gene variant and susceptibility of epilepsy

In Greek ethnicity, Katsarou *et al* examined the association between two common *SCN1A* gene variants, rs3812718 and rs2298771, and different types of ASMs in a sample of 214 individuals. The results showed that compared to individuals with focal onset seizures, those with A allele-containing genotypes of rs3812718 and rs2298771 were more likely to have generalized onset seizures and focal to bilateral tonic-clonic seizures, with a higher frequency in these patients [36]. Similarly, in Kosovar Albanian, Daci *et al* found that carriers of the *SCN1A* IVS5-91G > A variant were associated with increased susceptibility to epilepsy [48]. These findings suggest that the A allele of *SCN1A* rs3812718 variant may increase the risk of epilepsy, especially generalized onset, while G allele may be present in patients with focal onset seizures which support the role of *SCN1A* genetic factors in contributing to the variable clinical presentation of epilepsy.

Furthermore, regarding the *SCN1A* rs2298771 variants, Bertok *et al* investigated the association between the *SCN1A* Thr1067Ala polymorphism and epilepsy risk in Slovenian population. The results showed that carriers of the *SCN1A* c.3184A>G/p. Thr1067Ala G allele had a lower risk of developing epilepsy [42]. In the Brazilian population, Buainain *et al* found that carriers of the rs2298771 variant were significantly frequent among temporal lobe epilepsy patients with the AG and GG genotypes compared to AA genotype [20]. However, in the Egyptian population, Abo El Fotoh *et al* and Ghazala *et al* found that the AG genotype was significantly associated with higher seizure frequency, more generalized EEG abnormalities, earlier age of seizure onset and was more frequent among epileptic patients [31,32]. These findings suggest that carriers of G allele of *SCN1A* rs2298771 variant may be more prevalent in patients with TLE and generalized epilepsy, while carriers of

the A allele may be more susceptible to an increased risk of epilepsy.

Overall, the A allele of both *SCN1A* SNPs variants (rs3812718 and rs2298771) is associated with an increased risk of epilepsy. Thus, there may be a potential association between the investigated *SCN1A* polymorphisms and heightened epilepsy risk. If *SCN1A* pharmacogenomic analysis were conducted routinely, it could significantly enhance the overall management of patients with epilepsy. Such analysis would allow for the early identification of high-risk individuals for drug resistance, facilitate more individualized treatment choices, optimize therapy and potentially reduce the time required to achieve seizure control, thereby improving patients' quality of life. Given the complexity of genetic factors involved in drug resistance and the pressing need for further studies, it is crucial to deepen the understanding of the relationship between gene variations and the effectiveness of ASMs.

CONCLUDING REMARKS

Epilepsy is a major global health problem, with over thirty to forty percent of patients experiencing drug resistance. This review provides a comprehensive understanding of the impact of *SCN1A* genetic variation on drug efficacy. These analyses indicates that rs3812718 polymorphism in *SCN1A* gene is frequently associated with drug-resistant epilepsy across various studied populations. Additionally, other loci with *SCN1A*, such as rs2298771 and rs10188577, also influence how individuals respond to ASMs. These findings highlight the importance of utilizing genetic markers for personalized approaches to managing epilepsy. Understanding how different *SCN1A* variants affect the efficacy of specific ASMs — through alterations in the structure and function of sodium channels — empower healthcare providers to make informed decisions about the most appropriate anticonvulsant for each patient.

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Conflict of interest

No conflict of interest is associated with the work.

Contribution of authors

All authors contributed significantly to this work. Prof. Fatemah Kamel, Dr. Rania Magadmi, and Dr. Yusra Abdulqader were responsible for conceptualization and design of the study. Dr. Yusra Abdulqader and Dr. Rania Magadmi conducted the literature review and analysis while Dr. Rania Magadmi, Prof. Haythum Tayeb and Dr. Mohammed Bazuhair contributed to drafting and revising the manuscript. All authors approved the final version and agree to be accountable for the content of the work.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

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