Original Article

Phenotypic features of epilepsy due to sodium channelopathies – A single center experience from India

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ABSTRACT

Objectives: Nearly 40% of pediatric epilepsies have a genetic basis. There is significant phenotypic and genotypic heterogeneity, especially in epilepsy syndromes caused by sodium channelopathies. Sodium channel subunit 1A (SCN1A)-related epilepsy represents the archetypical channel-associated gene that has been linked to a wide spectrum of epilepsies of varying severity. Subsequently, other sodium channels have also been implicated in epilepsy and other neurodevelopmental disorders. This study aims to describe the phenotypes in children with sodium channelopathies from a center in Southern India.

Materials and Methods: This is a retrospective, descriptive, and single-center study. Out of 112 children presenting with epilepsy who underwent genetic testing between 2017 and 2021, 23 probands (M: F = 12:11) were identified to have clinically significant sodium channel mutations. Clinical presentation, electroencephalography, and imaging features of these patients were recorded. The utility of genetic test results (e.g., in planning another child, withdrawal of medications, or change in treatment) was also recorded.

Results: Age at onset of seizures ranged from day 4 of life to 3.5 years. Clinical epilepsy syndromes included generalized epilepsy with febrile seizures plus ($n = 3$), Dravet syndrome ($n = 5$), early infantile epileptic encephalopathy ($n = 7$), drug-resistant epilepsy ($n = 5$), and epilepsy with associated movement disorders ($n = 3$). The most common type of seizure was focal with impaired awareness ($n = 18$, 78.2%), followed by myoclonic jerks ($n = 8$, 34.78%), epileptic spasms ($n = 7$, 30.4%), bilateral tonic-clonic seizures/generalized tonic–clonic seizures ($n = 3$, 13%), and atonic seizures ($n = 5$, 23.8%). In addition to epilepsy, other phenotypic features that were discerned were microcephaly ($n = 1$), cerebellar ataxia ($n = 2$), and chorea and dystonia ($n = 1$).

Conclusion: Sodium channelopathies may present with seizure phenotypes that vary in severity. In addition to epilepsy, patients may also have other clinical features such as movement disorders. Early clinical diagnosis may aid in tailoring treatment for the given patient.

Keywords: Pediatric epilepsy, Channelopathy, Sodium channel epilepsy, Dravet syndrome, Generalized epilepsy with febrile seizures plus, Epilepsy genetics

INTRODUCTION

Voltage-gated sodium channels have a vital role in the functioning of neurons. The channel essentially consists of a pore-forming alpha subunit and subsidiary beta-subunit(s).[1] The ion conductance of these channels dictates neuronal functions in many types of neurons. Sodium channel subtypes have unique distributions in the central ($Na_v1.1$, $Na_v1.2$, and $Na_v1.3$ subtypes) and peripheral nervous systems ($Na_v1.6$). Clinical manifestations vary according to the subunit types that harbor mutations.[2] SCN1A-related epilepsy syndromes span a spectrum of phenotypes ranging from benign age-limited epilepsies to devastating neurodevelopmental syndromes such as Dravet syndrome (DS). Various other sodium channel subunits have also been characterized to have a similar spectrum such as SCN1A although a touch more uncommon.

With the advent of whole exome sequencing, knowledge of these rarer phenotypes has evolved significantly. We aimed to study the phenotypic expressions of sodium channel mutations that were identified at our center in this study.

MATERIALS AND METHODS

This was a retrospective study conducted at a tertiary care center in Southern India. The study was approved by the Institutional Ethics Committee.

One hundred and twelve children presenting with epilepsy had undergone genetic testing after informed consent from 2016 to 2021. Genetic testing was done when it was felt to be clinically appropriate by the treating epileptologist. Twenty-three patients were identified to have pathogenic/significant

variants in sodium channel subunits. Clinical findings and treatment details on the number of anti-seizure medications, use of vitamins/steroids, and or other treatment modalities (such as ketogenic diet/surgery) were also documented. Imaging studies were reviewed in all included subjects.

Electrophysiological data in the form of electroencephalography (EEGs) were reviewed for background (normal/slow/asymmetric) and sleep transients. Interictal discharges were qualified based on standard International Federation for Clinical Neurophysiology (IFCN) definitions. Pertinent details from exome sequencing reports such as type of variation (missense, non-sense, deletion, duplication, frameshift, and insertions), zygosity, *in silico* predictions, and their classification according to the American College of Medical Genetics were gathered.

RESULTS

Clinical and genotype

Both sexes were equally affected (M: F = 12:11). The mean age at onset was 10.4 ± 12 months (range: 0.03–4 years, median 6 months). Fever/vaccine-induced seizures were observed in 10 probands (43.4%). Family history of epilepsy in first-degree relatives was noted in two probands. Focal seizures with impaired awareness ($n = 18$, 78.2%) were the most common phenotype, followed by myoclonic jerks ($n = 8$, 34.78%) and infantile spasms ($n = 7$, 30.4%). In addition, focal to bilateral tonic–clonic seizures/generalized tonic–clonic seizures ($n = 3$, 13%) and atonic seizures ($n = 5$, 23.8%) were also observed. Multiple semiologies were present in 73.9% of the cohort ($n = 17$). Epileptic encephalopathies (EEs) such as early infantile forms ($n = 5$, 38%), West syndrome ($n = 2$, 9.5%), Lennox-Gastaut syndrome ($n = 1$, 4.7%), and DS constituted the most common presentations ($n = 5$, 38%) of SCN1A variants. Other phenotypic features observed were microcephaly ($n = 1$), cerebellar ataxia in two subjects, and chorea-dystonia in one proband. Developmental abnormalities were present in 18 children. Three probands with generalized epilepsy with febrile seizures plus (GEFS+), and P15 and 22 with refractory focal epilepsy had normal development. In our study, all variants were found in a heterozygous state that the most common subunit with mutations was SCN1A ($n = 13$, 56.52%), followed by SCN2A ($n = 6$, 28.5%). Mutation in SCN8A was detected in two probands (8.6%) and SCN1B in one (4.7%). Among the probands with SCN1A mutations, eight (61%) carried reported pathogenic variants and the remaining were novel. Four probands were identified to have non-sense variants, among which one was a novel variant. Most of the mutations were missense ($n = 9$). Details of mutations and patient characteristics are shown in Table 1, Figures 1 and 2. Five probands with SCN1A had DS and four had drug-resistant focal seizures. Three children had a GEFS+-like phenotype and one had early infantile EE.

Two patients (one with DS and the other with EIEE) shared the same mutation in SCN1A. Phenotypic heterogeneity was also noted in SCN2A. Two probands carrying the same variant presented with different phenotypes. One presented with a drug-resistant focal epilepsy while the other developed early infantile EE akin to Ohtahara syndrome. All patients carrying SCN2A variants had severe phenotypes and adverse neurodevelopmental profiles.

EEG and imaging features

Background slowing was evident in all patients with DS and EE. Epileptiform discharges were multifocal in 4 subjects (17.4%) and generalized discharges were identified in up to 57% ($n = 12$). Classical hypsarrhythmia pattern was not identified in any of the subjects with West Syndrome/Early infantile epileptic encephalopathy (WS/EIEE).

Magnetic resonance imaging (MRI) was available for all patients and was normal in 60% of subjects ($n = 14$). Non-specific periventricular white matter changes ($n = 6$, 28.5%), cerebral ($n = 1$)/cerebellar ($n = 1$), and atrophy ($n = 6$, 28.5%) were the commonly detected abnormalities. Central tegmental tract hyperintensity was noted in one proband. No malformations of cortical development were detected. A clinical example is shown in Figure 3.

Treatment and clinical implications

Four patients were administered sodium channel blockers for variable durations (carbamazepine = 3 and lamotrigine = 1) before genetic testing. Among them, one proband with DS harboring a frameshift mutation in SCN1A had a drastic increase in the frequency of seizures necessitating the stoppage of treatment. The other two probands did not have worthwhile seizure reduction. The most common ASMs used in this cohort were levetiracetam and valproate. Two patients with DS were also administered stiripentol which resulted in a slight improvement in seizure frequency. Worsening of seizure frequency (tonic spasms) was noted with vigabatrin in one proband with SCN1A mutation R853Q.

Four out of 21 patients were administered steroids (IV methylprednisolone or adrenocorticotropic hormone). These patients had early infantile EE. Response to steroids was noted but short-lasting and no child had complete remission from seizures. One proband presented with refractory focal seizures with multiple episodes of status epilepticus. Ictal EEG was suggestive of right posterior quadrant onset and MR imaging was normal. Further pre-surgical workup was abandoned as a non-sense mutation (p.Trp190Ter) was identified on exome sequence.

DISCUSSION

Channelopathies constitute an important paradigm for genetic epilepsies. In this study, we identified mutations in
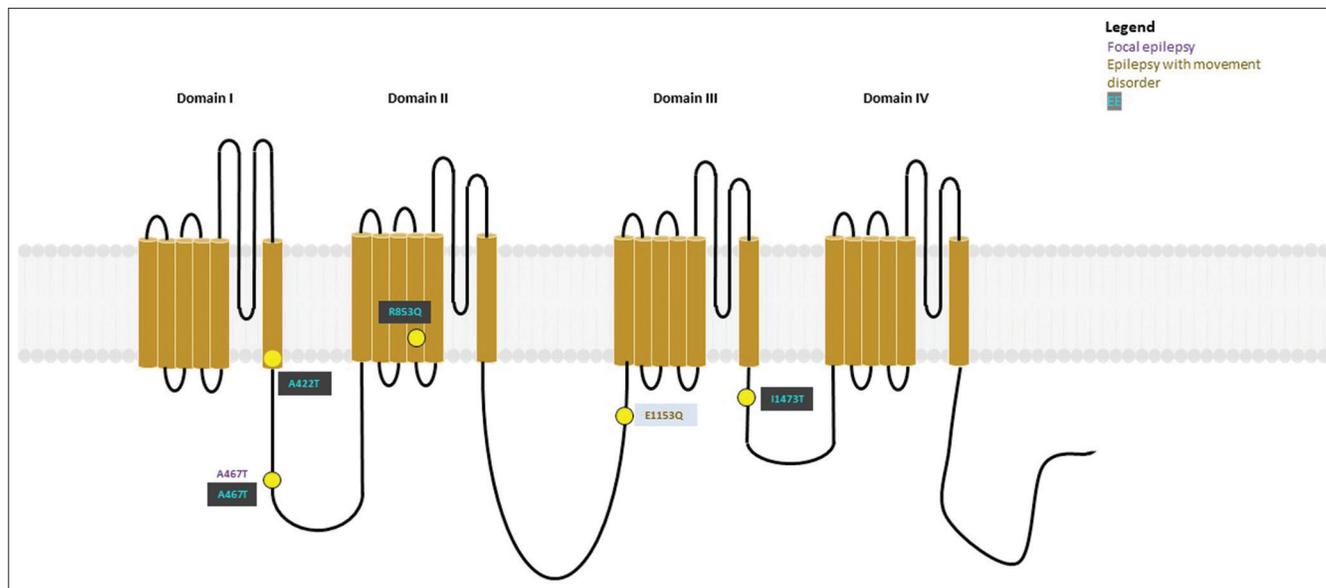
Figure 1: Variants (*n* = 13) identified in SCN1A have been depicted as yellow dots. Colored text in the boxes represents various phenotypes as described in the figure.
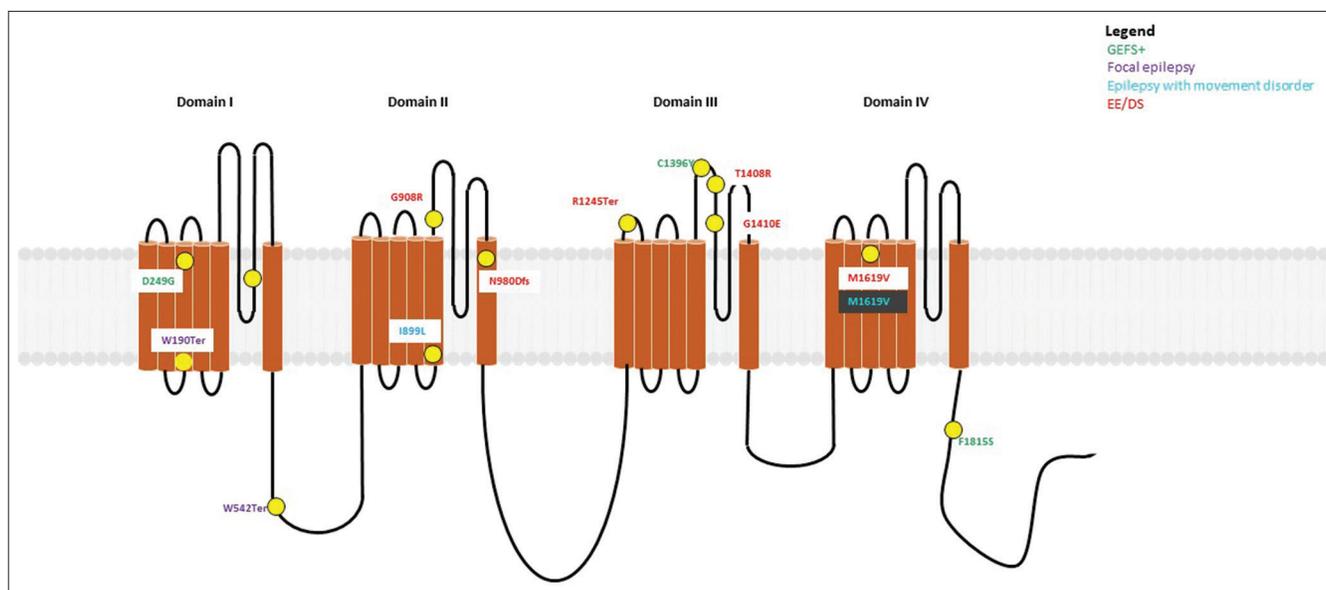

Figure 2: Variants (*n* = 5) identified in SCN2A have been depicted as yellow dots. Colored text in the boxes represents various phenotypes as described in the figure.

SCN1A, 1B, 2A, and 8A across a wide spectrum of epilepsy phenotypes affecting children right from early infancy to 3.5 years of age. Fever-triggered seizures which are quite common in sodium channelopathies were noted in 75% of patients, which parallels a finding that was also reported in another study. Five children presented with phenotypic features of DS and all had mutations in SCN1A. Loss of function mutations in SCN1A are seen in up to 80% of patients with DS. Deleterious missense (*n* = 3) and non-sense (*n* = 2) were detected in the affected subjects of this study.

Ceuleman *et al.* hypothesized that truncated proteins due to frameshift and non-sense variants would invariably result in a severe phenotype as it would adversely affect channel function.[3] It is hypothesized that the truncated protein exerts a dominant negative effect on the wild-type allele resulting in abnormal sodium channel function.[4,5] Missense mutations, on the other hand, may lead to haploid insufficiency resulting in disease. Brunklaus *et al.* commented that the type of SCN1A mutation may not have a critical bearing of the phenotype or severity of DS.[6] In this study, non-sense
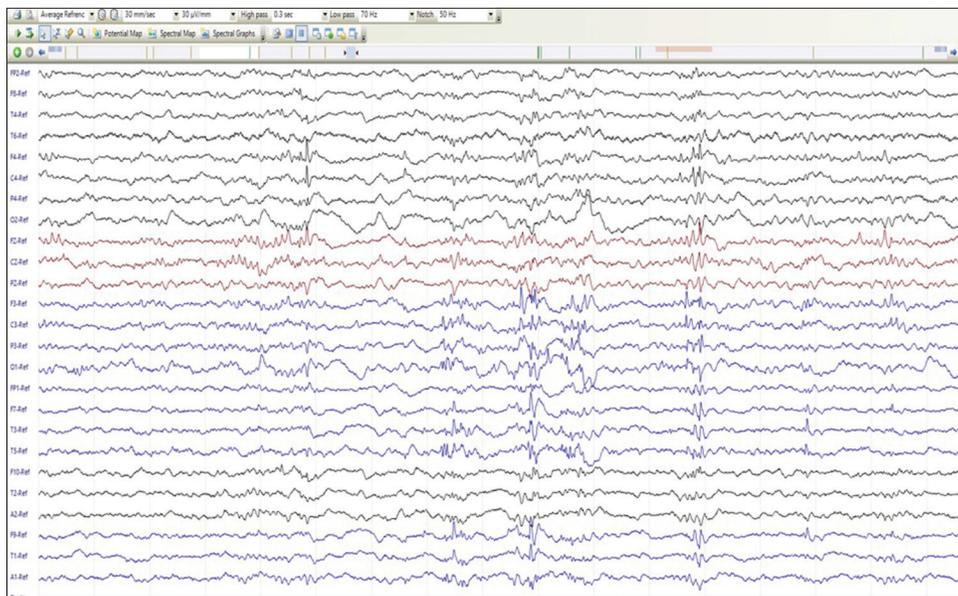
Figure 3: Sleep electroencephalography of P2 (Dravet syndrome) showing polyspike–spike wave discharges from the left hemispheric leads. Furthermore, note a solitary spike-wave discharge from the right frontocentral region (F4 and C4).

Table 1: Phenotype-Genotype characteristics

Patient	Age at onset	Sex	Development	Fever Triggered Seizures	Clinical Phenotype	Gene	Location (exon)	DNA	Aminoacid
P1	3	F	DR	+	DS	SCN1A	19	c.3733C>T	p.Arg1245Ter
P2	6	M	DD	+	DS	SCN1A	21	c.4222T>C	p.Trp1408Arg
P3	12	F	R	+	DS	SCN1A	26	c.4855A>G	p.Met1619Val
P4	9	M	N	+	GEFS+	SCN1A	28	c.5444T>C	p.Phe1815Ser
P5	3	F	N	+	GEFS+	SCN1A	21	c.4187G>A	p.Cys1396Tyr
P6	4	M	DD	+	DS	SCN1A	15	c.2930_2936 Dup	p.Asn980 AspfsTer19
P7	6	M	DD	+	DS	SCN1A	21	c.4229G>A	p.Gly1410Glu
P8	48	F	N	-	GEFS+	SCN1A	9	c.746A>G	p.Asp249Gly
P9	3	M	DR	-	EIEE	SCN2A	10	c.1264G>A	p.Ala422Thr
P10	8	M	DR	-	WS	SCN2A	15	c.2558G>A	p.Arg853Gln
P11	5	F	DR	-	WS	SCN1A	26	c.4855A>G	p.Met1619Val
P12	0.3	M	DD	-	EIEE	SCN2A	24	c.4418T>C	p.Ile1473Thr
P13	1.5	F	DR	-	Epilepsy with chorea and dystonia	SCN1A	18	c.2695A>C	p.Ile899Leu
P14	4	M	DR	+	Epilepsy with ADHD	SCN1A	10	c.1624C>T	p.Arg542Ter
P15	40	M	N	-	Focal epilepsy	SCN1B	3	c.595C>T	p.Pro199Ser
P16	21	M	DD	-	EE	SCN2A	11	c.1399G>A	p.Ala467Thr
P17	18	F	DD	+	Epilepsy with ataxia	SCN2A	18	c.3457G>C	p.Glu1153Gln
P18	30	M	R	-	Refractory epilepsy	SCN2A	11	C.1399G>A	p.Ala467Thr
P19	6	F	DR	-	EIEE	SCN8A	27	c.5615G>A	p.Arg1872Gln
P20	1	M	DD	-	Refractory Epilepsy	SCN1A	8	c.1166A>C	p.Gln389Pro
P21	6	F	DD	-	EIEE	SCN1A	15	c.2722G>C	p.Gly908Arg
P22	3	F	N	+	Refractory epilepsy	SCN1A(-)	4	c.569G>A	p.Trp190Ter
P23	3	F	DR	-	Epilepsy with IDD	SCN8A(+)	25	c.4423G>A	p.Gly1475Arg

DD-developmental delay, DR-delay with regression, R- regression only, N normal, DS Dravet syndrome, EIEE early infantile epileptic encephalopathy, IDD intellectual and developmental disabilities

mutations were also observed in other phenotypes. P22 (c.569G>A[p.Trp190Ter]) suffered from drug-resistant focal epilepsy. She was evaluated as a possible candidate for epilepsy surgery. Plans for invasive EEG were deferred after the genetic diagnosis was made. A series published by Skjei *et al.* characterized the outcomes in children with SCN1A mutations who underwent epilepsy surgery.[7] Half of those probands were noted to have normal findings on MRI and the rest had mesial temporal sclerosis. Surgical resection did not improve the frequency of seizures. Intuitively, one may be concluded that diffuse cellular physiological changes induced by SCN1A mutants would obviate focal brain resection. Comparable results were noted by Venezyroglou *et al.*[8] Apart from epilepsy, SCN1A has also been implicated in certain movement disorders. Proband (P13) carrying c.2695A>C (p.Ile899Leu) suffered from epilepsy, chorea and dystonia, developmental delay, and regression. Sadleir *et al.* have described a similar phenotype due to a mutation in exon 5 (c.677C>T, p.Thr226Met).[9] Hyperkinetic movement disorders are not rare in SCN1A mutations. Due to the co-existence with complex seizure semiologies, these may be difficult to distinguish from epilepsy in a few cases.

Developmental encephalopathy with profound intellectual impairment can also be seen in SCN1A-related disorders. P11 presented with infantile spasms and went on to have multiple seizure semiologies, similar to the results described by Gowda. P14 (c.1624C>T[p.Arg542Ter]) presented with autism and refractory epilepsy and regression of milestones.[10] Till *et al.* had reported a proband with DS with the same variant.[11] Grantham scores of variants that cause GEFS+ tend to be lower than those causing developmental and epileptic encephalopathy (DEE) and DS. More severe phenotypes thus occur due to amino acid substitutions that harm proper ion channel function.

The two missense novel variants in this study include c.4222T>C (p.Trp1408Arg) variant and c.4229G>A (p.G1410E), respectively. They were found to be *in silico* damaging by SIFT, polyphen 2, and mutation taster. Both these mutations were in domain 3 of the channel in close relation to the inactivation gate between domain III and IV and could explain its damaging effect.

MRI was abnormal in only 3 patients (23%). Changes including atrophy and white matter changes were observed. Similarly, Guerrini *et al.* also described normal imaging in most patients only a few showed abnormalities such as hippocampal sclerosis, focal brain atrophy, and cortical dysplasia.[12] These abnormalities were however not detected in our cohort.

SCN2A mutations also present with a wide clinical spectrum including GEFS plus, DS, acute encephalopathy with refractory, repetitive partial seizures, autism, and severe IDD.[13-17] In this study, six patients carried SCN2A mutations;

all of which were missense. Two probands P10 presented with EE and harbored reported pathogenic variant.[16] P16 and 18 carried that same missense novel variant C.1399G>A (p.Ala467Thr). Both probands had presented with a similar phenotype characterized by refractory epilepsy with developmental delay. This variant is located on the connecting link between the alpha subunits (domains 1 and 2), functional implication of this variant causes protein instability and has been described with phenotype having an intellectual disability without epilepsy in the study by Howell *et al.*[18] and as DEE in the study by Reynolds *et al.*[19] these were different as compared to phenotype in this study. P17 (c.3457G>C [p.Glu1153Gln]) presented with epilepsy associated with ataxia. A similar phenotype has been described in subjects carrying variants: c.5644C>G(p. R1882G), c.4565G>C (p.G1522A), c.788C>T(p.A263V), and c.788C>T(p.A263V) as shown in Schwarz *et al.*[20] These patients usually have disease onset between 15 months and 3.7 years. It was hypothesized that cerebellar ataxia in part could be due to the upregulation of Na1.2 in cerebellar granule cells.

Imaging of these patients revealed only non-specific findings such as mild atrophy or subtle white matter hyperintensities in periventricular areas in most patients. Other abnormalities such as cerebral or cerebellar atrophy, thin corpus callosum,[15] dentate-olivary dysplasia,[21] posterior perisylvian, and bilateral parietal polymicrogyria[22] have been described in SCN2A-related disorders. The role of the sodium channels in the migration and maturation of oligodendroglial progenitor cells may explain the occurrence of such abnormalities.[23]

Mutations in SCN8Aand SCN9A may result in epilepsy and other neurodevelopmental disorders including autism. More than 150 additional *de novo* missense mutations have now been reported to date.[24,25]

In this study known (P19) and one novel (P23), missense variants have been recorded.[26]

P19: (c.5615G>A[p.Arg1872Gln]) presented with EE. Larsen *et al.* described the same variant with a DS-like phenotype, moderate IDD, seizures of multiple semiologies, autistic features, and motor stereotypies.[27] P23 (c.4423G>A[p. Gly1475Arg]) presented with epilepsy and IDD. The proband also had clusters of seizures followed by regression of milestones. It has been noted that SCN8A mutants almost always cause moderate-to-severe IDD and/or autistic traits. The reported variant at position 1872 is an emerging hotspot. Most SCN8A are gain of function mutations and sodium channel blockers may be a useful therapeutic option to control seizures in these individuals.

Although SCN1B was the first gene associated with GEFS+ to date, only a few variants are reported in the literature.[28] In this study, P15 carried c.595C>T(p.Pro199Ser) missense

variant presented with epilepsy (focal seizures), with normal development. Interestingly, this patient also had central tegmental tract hyperintensities which were restricting. A GEFS+-like phenotype and myoclonic epilepsy have been associated with SCN1B mutations. Fenfluramine has been found to be of benefit in cases with difficult-to-control seizures.[29]

CONCLUSION

This study highlights a few key aspects of the genotype – phenotype spectrum of sodium channelopathies. Early recognition of epilepsy phenotypes may aid in choosing/avoiding certain anti-seizure medications. A few of these patients may also present with refractory focal epilepsy. Appropriately used genetic testing methods may avoid pre-surgical workup/epilepsy surgery in these patients as post-operative outcomes in such epilepsies are usually poor. An early genetic diagnosis may aid in equipping both the treating clinician and the family with more information for better management of epilepsy and associated conditions.

Ethical approval

The authors declare that they have taken the ethical approval from IRB/IEC.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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