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Genetic and clinical features of *SCN8A* developmental and epileptic encephalopathy

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ABSTRACT

Objective: We aim to delineate the genetic and clinical features of *SCN8A* developmental and epileptic encephalopathy.
Methods: Nine patients with *SCN8A* developmental and epileptic encephalopathy were included in this study. Genetic and clinical features and effectiveness of sodium channel blockers were assessed in patients who were confirmed with *SCN8A* mutations.
Results: The onset of seizures ranged from the neonatal period to 18 months of age. Seizure types were diverse and predominantly involved focal seizures or spasms. The most common initial epilepsy syndrome was West syndrome in four patients, followed by neonatal-onset focal seizures in three patients and unclassified focal epilepsy in two patients. Electroencephalograms (EEGs) showed slow and disorganized background and epileptiform abnormalities with occipital predominance. Six patients presented intractable seizures including one patient with recurrent nonconvulsive status epilepticus. Sodium channel blockers were effective in seven patients among eight patients given them. All patients showed developmental delay or regression. Severe hypotonia or ataxia was also presented in some patients. Microcephaly was also characteristic. *De novo* missense mutations in *SCN8A* were found in the inactivation gate, C-terminal, loop 2, and transmembrane segments (S1, 4, 5, and 6). There was no correlation between the location of the mutation in the protein and phenotype or response to sodium channel blockers.
Conclusion: *SCN8A* developmental and epileptic encephalopathy presents intractable seizures including spasms, focal seizures, neonatal status epilepticus, and nonconvulsive status epilepticus. Sodium channel blockers were effective irrelevant to the location of the mutation in the protein.

1. Introduction

Voltage-gated sodium channels play a key role in electrical signaling by their action potential initiation and propagation in the membranes of neurons and other electrically excitable cells (Catterall, 2000). *SCN8A* is one of nine genes that encodes a voltage-gated sodium channel α subunit. *SCN8A* encodes the sodium channel $Na_v1.6$, which is widely expressed in the brain, where it plays a role in regulation of neuronal excitability (Caldwell et al., 2000).

SCN8A mutations are associated with a wide spectrum of epilepsy phenotypes, ranging from benign familial infantile epilepsy (Anand et al., 2016; Bagnasco et al., 2018; Gardella et al., 2016) to severe developmental epileptic encephalopathy (Gardella et al., 2018; Larsen et al., 2015; Ohba et al., 2014). *SCN8A* mutations are also known to be associated with movement disorders or even early mortality (Gardella et al., 2016; Johannesen et al., 2018; Pons et al., 2018; Xiao et al., 2018).

Early infantile epileptic encephalopathy type 13 (EIEE13, OMIM #614,558) is a recently defined severe developmental epileptic encephalopathy syndrome caused by de novo gain-of-function mutations of *SCN8A*, which was first identified in 2012 (Veeramah et al., 2012). As *SCN8A* mutations can cause diverse epilepsy phenotypes, phenotypic classification is crucial for predicting prognosis and guiding therapeutic strategies.

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Table 1
SCN8A mutations and patient responses to sodium channel blockers.

Pt	Nucleotide change	Amino acid change	Mutation type	Protein location	SCB response*
1	c.4423 G > A	p.Gly1475Arg	Missense	Inactivation gate	Effective[2]
2	c.2549 G > A	p.Arg850Gln	Missense	DII S4	Effective[2]
3	c.782 G > T	p.Cys261 Phe	Missense	DI S5	Effective[2]
4	c.424A > G	p.Ile142Val	Missense	DI S1	Effective[2]
5	c.5614C > T	p.Arg1872Trp	Missense	C-terminal	Effective[2]
6	c.4475 T > C	p.Met1494Thr	Missense	Inactivation gate	No trial
7	c.5276A > C	p.Asn1759Thr	Missense	DIV S6	Ineffective[3]
8	c.2911C > G	p.Leu971Val	Missense	DII S6	Effective[1]
9	c.2934C > A	p.Ser978Arg	Missense	Loop2	Effective[1]

D, domain; SCB, sodium channel blocker; *[1], seizure free; [2], seizure reduction; [3], no effect; [4], worsening.

Herein, we delineated the genetic and clinical features in patients with *SCN8A* developmental and epileptic encephalopathy who were diagnosed through targeted gene-panel sequencing.

2. Methods

2.1. Patients

Patients with *SCN8A* developmental and epileptic encephalopathy were identified from a cohort of 730 pediatric patients with early-onset developmental epileptic encephalopathy of unknown etiology at Severance Children's Hospital. The patients were tested using a targeted gene-panel sequencing between 2015–2018. One patient with *SCN8A* developmental and epileptic encephalopathy from Gachon University Gil Medical Center was also included.

2.2. Clinical data

Detailed clinical features were retrospectively reviewed. Clinical data included demographics, age of seizure onset, seizure type, classification of epilepsy syndrome, treatment of epilepsy, response to sodium channel blockers, head circumference, development, typical clinical features, EEG data, and brain MRI. Seizure types and epilepsy syndromes were classified according to the 2017 International League Against Epilepsy classification guidelines (Scheffer et al., 2017). Initial epilepsy syndromes were selected if they changed over time. Response to sodium channel blockers was considered effective if seizure frequencies were decreased more than 50% from baseline.

2.3. Mutation analysis

One hundred seventy-two genes, including *SCN8A*, associated with developmental epileptic encephalopathy were included in our targeted gene panel; the genes are listed in the Appendix. Genomic DNA was extracted from leukocytes using the QIAamp Blood DNA mini kit (Qiagen, Hilden, Germany). The pooled libraries were sequenced using a MiSeq sequencer (Illumina, San Diego, CA, USA) and the MiSeq Reagent Kit v2 (300 cycles). Sequencing data were aligned against appropriate reference sequences and analyzed using Sequencher 5.3 software (Gene Codes Corp., Ann Arbor, MI, USA). Parental studies were performed by Sanger sequencing on a 3730 DNA Analyzer with the Bigdye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, Foster City, CA, USA). Large deletions and duplications were confirmed using the MLPA kit (MRC Holland, Amsterdam, The Netherlands). The variants were interpreted based on the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) classification (Richards et al., 2015).

3. Results

We collected the data of nine patients. Five patients (patient 1–5) were previously published (Ko et al., 2018) in less detail and four patients were unpublished.

3.1. Mutation analysis

We identified nine patients with heterozygous, pathogenic, missense mutations. All were different variants and were predicted to be deleterious by prediction tools (PolyPhen-2, SIFT, MutationTaster). Four variants (patient 1,2,4,5) have been previously reported to be associated with *SCN8A* developmental and epileptic encephalopathy. Parental studies were done in seven patients (patients 1, 3, 4, 5, 6, 8, and 9); all of them showed *de novo* mutations. In patient 7, parental testing was performed only in her mother due to family matters, who showed no mutation in *SCN8A*. The mutations were found in inactivation gate, Loop2, C-terminal, and transmembrane segments (S1, 4, 5, and 6). Sodium channel blockers were tried in eight patients; seven patients showed effectiveness unrelated to the location of the mutation in the protein (Table 1, Fig. 1).

3.2. Clinical features of SCN8A developmental and epileptic encephalopathy

The patients ranged in age from 5 months to 9 years. The onset of seizures ranged from 1 day to 18 months of age. Seizure semiology was variable and included epileptic spasms, focal seizures, generalized tonic clonic seizures, myoclonic absence seizures, and nonconvulsive status epilepticus (NCSE). The most common initial epilepsy syndrome was West syndrome in four patients. One patient showed neonatal focal seizures evolving to West syndrome, two patients showed neonatal status epilepticus, and two patients showed unclassified focal epileptic encephalopathy (Table 2). Six patients presented intractable seizures, including one patient with recurrent nonconvulsive status epilepticus; three of these patients reached seizure-free status. Sodium channel blockers were tried in eight patients and were effective in seven patients and ineffective in one patient. Ketogenic diets were tried in five patients; and it was effective in only one patient. Epilepsy surgery was performed on one patient (patient 3), involving corpus callosotomy and right temporal disconnection. Patient 3 showed intractable seizures in spite of multiple antiepileptic drugs, ketogenic diet, and corpus callosotomy tried at 6 years. After corpus callosotomy, epileptic discharges were localized to right temporal area. Therefore, right temporal disconnection was performed at 8 years, which was also ineffective. After confirmation of *SCN8A* mutation, multiple sodium channel blockers were tried and lamotrigine, lacosamide, and zonisamide reduced seizure frequency more than 50%. Patient 6 was not given sodium channel blockers, because his seizures were effectively controlled with levetiracetam, before *SCN8A* mutation was confirmed.

All patients showed a developmental delay or regression. Six patients showed a developmental delay after seizure onset, whereas three patients showed a developmental delay before seizure onset. Severe hypotonia or ataxia were frequently observed. Microcephaly was also

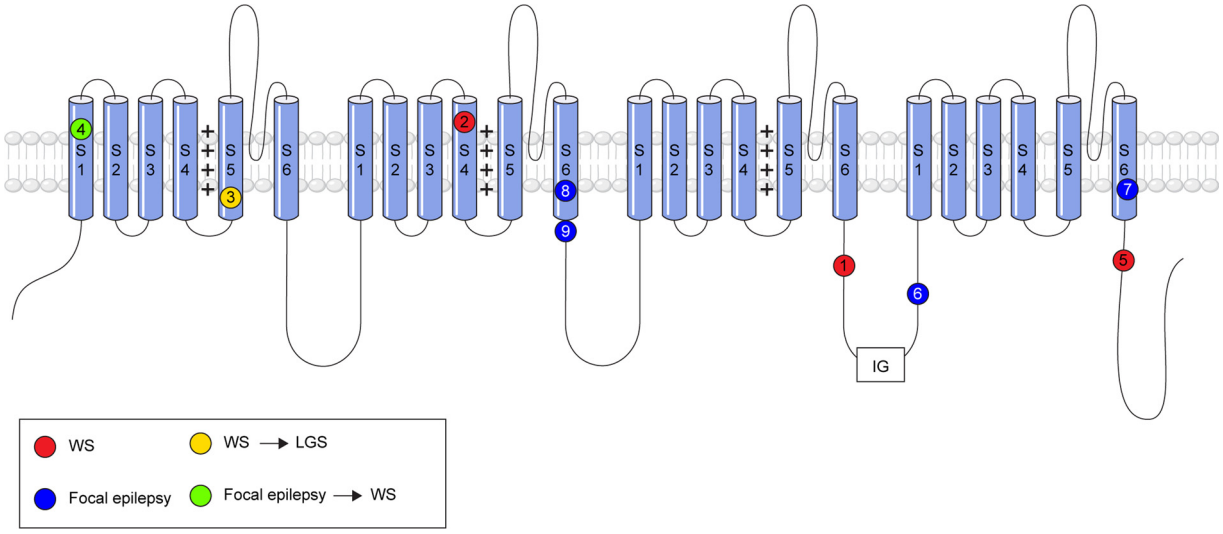

Fig. 1. Gene structure and position of pathogenic variants.
Voltage-gated sodium channel alpha subunits are composed of four homologous domains (DI-DIV), which each contain four voltage sensing transmembrane segments (S1-S4), two pore forming transmembrane segments (S5-S6) and pore forming loop between the S5 and S6.
The numbers in the circle correspond to the patient identification in the tables.
(IG, inactivation gate; LGS, Lennox-Gastaut syndrome; WS, West syndrome)

characteristic. Four patients (patients 2, 3, 4, and 5) were given prior genetic tests before targeted gene-panel sequencing such as chromosomal analysis, FISH, or methylation PCR for Prader-Willi/Angelman syndrome, mitochondrial gene-panel testing, or direct sequencing for *SMN1* or *SCN1A*, because of severe hypotonia and developmental delay accompanying epilepsy. EEGs showed slow and disorganized background and epileptiform abnormalities with occipital predominance. Brain MRI showed normal or mild cerebral atrophy (Table 2).

Patient 7 showed recurrent nonconvulsive status epilepticus. Her baseline EEG showed slow and disorganized background rhythms with occasional sharp wave discharges from both occipital areas (Fig. 2A). Her baseline seizures were focal seizures every few months. Abrupt seizure aggravation was noticed with the onset of myoclonic absence seizures and progression to absence status epilepticus and decreased alertness. The EEGs showed frontal dominant, 2-Hz generalized spikes and wave discharges (Fig. 2B). NCSE was controlled with continuous midazolam, ketamine, and high-dose phenobarbital. However, 4 months later, NCSE recurred with decreased mentality, which correlated with high-voltage, generalized slow spikes and waves (Fig. 2C). This was also hardly controlled with continuous midazolam. Sodium channel blockers were not effective during NCSE. Seizures in patient 7 showed gradual onset and abrupt aggravation and led to status epilepticus. However, patients 8 and 9 showed stormy seizure onsets during neonatal periods with status epilepticus, and became stable and achieved a seizure-free state.

4. Discussion

In our cohort, *SCN8A* mutations were found in eight patients among the 730 patients of early-onset developmental epileptic encephalopathy with previously unknown etiologies, which was in agreement with the known percentage of approximately 1% of developmental epileptic encephalopathies (Larsen et al., 2015; Meisler et al., 2016).

We described detailed phenotypes and genotypes of the patients with *SCN8A* developmental and epileptic encephalopathy, including five previously published cases (Ko et al., 2018).

Onset of seizures ranged from 1 day to 18 months of age. Patients were classified into three categories according to seizure onset. Three patients were neonatal onset; one patient evolved to West syndrome, and two patients showed neonatal focal seizures with status epilepticus. Four patients showed seizure onset between 3–5 months, with West syndrome. The other two patients showed seizure onset at 12months and 18months, respectively, with unclassified focal epileptic encephalopathy. The two patients (patients 6, 7) who showed later seizure onset with focal seizures had slowly emerging onset of infrequent seizures. Therefore the diagnosis of developmental and epileptic encephalopathy was delayed to 6 months and 4 years respectively after seizure onset. The other patients (patients 1–5, 8, and 9) had the abrupt severe onset of seizures including infantile spasms, neonatal status epilepticus or severe neonatal focal seizures. Therefore these patients were diagnosed with developmental and epileptic encephalopathy within one month after seizure onset. Recent another study also identified that there are two modes of onset of epilepsy in *SCN8A* developmental and epileptic encephalopathy; one with very progressive and the other with sudden frequent onset (Denis et al., 2019). Compared to the Dravet syndrome of *SCN1A* mutations, the age of seizure onset and seizure types are varied. Previously identified *SCN8A* epileptic encephalopathy showed a wide spectrum of epilepsy phenotypes with rare presentation of West syndrome (Gardella et al., 2018; Larsen et al., 2015; Ohba et al., 2014). However, West syndrome was found in five cases among the nine cases in our study. Seizures were variable, including focal, generalized tonic clonic, myoclonic absence seizures, and spasms. Most of the patients presented intractable seizures. Convulsive status epilepticus was noted in two neonatal patients with initial seizure attack, and recurrent NCSE was noticed in one patient. In a recent study, NCSE was reported to be common in *SCN8A* developmental epileptic encephalopathy (Gardella et al., 2018; Larsen et al., 2015). Our patient was similar to the typical features of NCSE of the previously reported patients. Neonatal status epilepticus had not been previously described, but it also would be characteristic of *SCN8A* developmental epileptic encephalopathy.

The EEG features were diffuse background slowing with focal epileptiform discharges predominantly in the posterior quadrant. These characteristic EEG features were in accordance with recently described typical EEG patterns of *SCN8A* developmental epileptic encephalopathy (Gardella et al., 2018).

Sodium channel blockers were effective in seven out of eight patients who received them, whereas ketogenic diets were effective only in one patient out of five patients. Treatment responses were contrary to the Dravet syndrome, in which ketogenic diets were effective, whereas

Table 2
Clinical findings.

Pt(sex)	Age	Seizure onset	Seizure type	Epilepsy diagnosis	Epilepsy treatment; (+) effective, (-) not effective	Seizure frequency/outcome	Head circumference	Development /motor before seizure onset	Development after seizure onset	EEG	Brain MRI
1(F)	3 yr, 9 mo	5 mo	Sp, FS → GTC	WS	(-)VGB; (+)CBZ, CLB,PHT,VPA	Every 3 months/ progressively worse, now stable	2 P (5mo) → 2 P (2 yr 8mo)	Normal	Delayed	Hyps → Slow BG	Normal (5mo)
2(F)	2 yr, 11 mo	3 mo	Sp, FS → Sp	WS	(-)PB, CTx; (+)VPA,ZNS, KD	Daily 5–10 spasms → every 3 day spasms/worse	1 P (10mo) → 1 P (1 yr 11mo)	Delayed/ Hypotonic	Delayed /Regression	Hyps, Slow BG, both O PFA → Slow BG, GPFA	Atrophy (10mo)
3(F)	9 yr	5 mo	Sp, FS, GTC → GTC	WS to LGS	(-)VPA, PB,CLB,KD, CC, Rt.T disconnection; (+)LTG,ZNS,LCM	Weekly → monthly/ progressive worse until age 8, now somewhat stable	5P (6 yr) → 15 P (9 yr)	Normal/ Hypotonic	Delayed	Hyps → Slow BG, multifocal sharp	Normal (5mo) → Normal (7 yr 10mo)
4(M)	4 yr	14 d	FS, Sp → GTC	WS from neonatal-onset focal seizure	(-) LEV,KD, CTx; (+)OXC, PHT, ZNS, PB, VPA	Weekly/progressive worse, bed ridden, PEG state	42 P (5mo) → 10 P (2 yr 4mo)	Normal	Delayed /Regression	Slow BG, both O sharp → Slow BG, Lt. O sharp	Atrophy (8mo)
5(M)	5 yr, 1 mo	3 mo	Sp → GT	WS	(-)KD; (+)OXC,VPA, PB, LEV	Every other day → monthly/ progressive worse, now stable	< 1 P (2 yr 10mo) → < 1 P (5 yr)	Normal/ Hypertonic	Delayed /Regression	Hyps → Slow BG, Lt. O sharp	Atrophy (3 yr)
6(M)	4 yr, 8 mo	18 mo	FS → GT	Unclassified focal EE	(+)LEV	Monthly → seizure free (18months)	7P(3 yr 3mo) → 2 P (4 yr 10mo)	Delayed	Delayed	Slow BG, Rt. F sharp	Normal (1 yr 7mo)
7(F)	6 yr, 4 mo	12 mo	FS → GT, MA, NCSE	Unclassified focal EE	(-)VPA, OXC; (+) ZNS, LEV, PB	Every 3mo → weekly/ progressive worse	25 P (3 yr 4mo) → 8 P (6 yr)	Delayed/ Ataxia	Delayed /Regression	Slow BG, both PO delta, sharp	Normal (3 yr4mo) →Atrophy (6 yr)
8(F)	5 m	1 d	FS, status → GTC	Neonatal onset focal seizure	(-)KD;(+)OXC, ZNS, PTH, LTG	Status → sz free (4months)	< 1 P (2mo) → < 1 P (5mo)	Normal	Delayed	Slow BG, Lt. O sharp → Slow BG	Normal (1mo) → Normal (2mo)
9(F)	1 yr, 2 mo	14 d	FS, GTC → GTC	Neonatal onset focal seizure	(-)LEV; (+) LCM	Status → sz free (12months)	7P (1 yr) → 9 P (1 yr 2mo)	Normal	Delayed	Slow BG, Lt. PO sharp	Normal (1mo) → Normal (2mo)

BG, back ground; CBZ, carbamazepine; CC, corpus callosotomy; CLB, clobazam; CTx, mitochondrial cocktail treatment; EE, epileptic encephalopathy; EOEE, early onset epileptic encephalopathy; F, frontal; FS, focal seizures; GT, generalize tonic seizures; GTC, generalize tonic clonic seizures; Hyps, hypsarrhthmia; KD, ketogenic diet; LCM, lacosamide; LEV, levetiracetam; LGS, Lennox-Gastaut syndrome; MA, myoclonic absence seizures; NCSE, non convulsive status epilepticus; O, occipital; OXC, oxcarbazepine; P, Percentile; PB, phenobarbital; PEG, percutaneous endoscopic gastrostomy; PFA, paroxysmal fast activities; PHT, phenytoin; PO, parietooccipital; Sp, spasm; VGB, vigabatrin; VPA, valproic acid; WS, west syndrome; ZNS, zonisamide; arrow, changes over time; underline, seizure at onset.

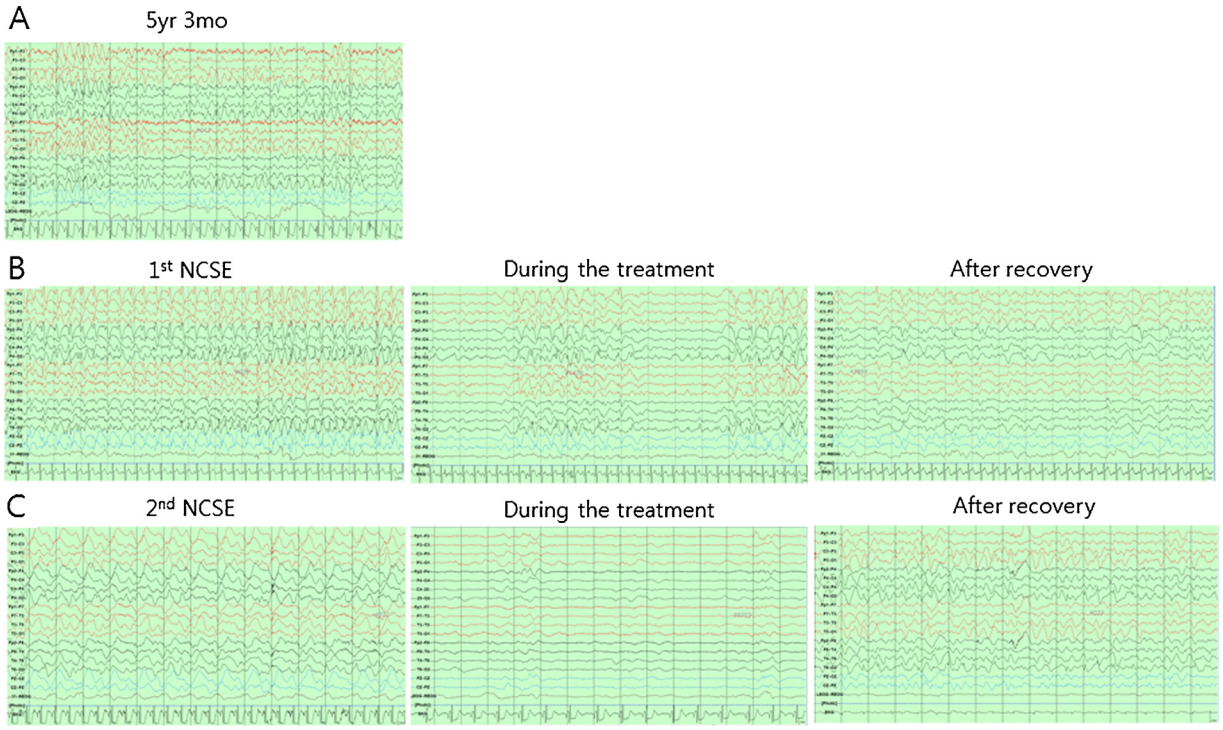

Fig. 2. EEG of patient 7.
Interictal EEG at 5 years and 3months old showing slow and disorganized background rhythms with occasional sharp wave discharges from both occipital areas. (B) EEG showing frontal dominant, 2-Hz generalized spikes and wave discharges at first attack of NCSE. (C) EEG of high-voltage, generalized slow spikes and waves at second attack of NCSE. (NCSE, nonconvulsive status epilepticus)

sodium channel blockers aggravated seizures.

Previous studies demonstrated that *SCN8A* mutations, which cause epileptic encephalopathy, showed a gain-of-function based on electrophysiological studies (Blanchard et al., 2015; Bunton-Stasyshyn et al., 2019; Estacion et al., 2014; Liu et al., 2019; Veeramah et al., 2012; Wagnon et al., 2016). For this reason, sodium channel blockers may decrease sodium channel activity in excitatory neurons, then decrease seizure activity (Bunton-Stasyshyn et al., 2019). Recent studies found that *SCN8A* mutations that cause epilepsy present gain-of-function and *SCN8A* mutations that cause cognitive disability without epilepsy present loss-of-function (Liu et al., 2019). Furthermore, benign epilepsy presents intermediate gain-of-function and severe epilepsy presents severe gain-of-function biophysical changes (Liu et al., 2019).

Mutation types were all missense mutations, and the location of mutations were found in the inactivation gate, loop2, C-terminal, and transmembrane segments (S1, 4, 5, and 6). Most of the mutations in EIEE13 were known to be located in the highly conserved portions of the protein: transmembrane segments, inactivation gate, and proximal 2/3 of the C-terminal (Wagnon and Meisler, 2015). In contrast, the nonpathogenic variants of *SCN8A* were mainly located in the non-conserved portions: loop1, loop2, N-terminal, and distal 1.3 of the C-terminal regions (Wagnon and Meisler, 2015). In our results, most of the patients showed mutations in the conserved regions of the protein. One patient (patient 7), who only showed ineffective responses to sodium channel blockers, had a missense mutation in DIV S6. The missense mutations in this location (DIV S6) had been reported to present gain-of-function in a previous study in an EIEE13 patient (Veeramah et al., 2012). To understand why patient 7 with p.Asn1759Thr was not responsive to sodium channel blockers, further functional studies in this individual patient should be done.

We could not find any correlation between location or characteristics of mutations and typical sub-phenotypes of EIEE13 or responses to sodium channel blockers. A case of an EIEE13 patient with p.Gly1475Arg, without using sodium channel blockers reported refractory seizures and sudden unexpected death and epilepsy in early childhood (Xiao et al., 2018). For our patient (patient 1), sodium channel blockers were effective in seizure control. Further studies are required to determine if sodium channel blockers could be effective in stabilization of the sodium channel $Na_v1.6$ in cardiac muscles to prevent sudden unexpected death in epilepsy. The arginine at position 1872 represents a mutational hotspot; p.Arg1872Trp, p.Arg1872Leu, and p.Arg1872Gln were recurrently reported (Larsen et al., 2015; Lindy et al., 2018; Wagnon et al., 2016), and showed variable clinical presentations, but West syndrome was only found in one of our patient. Electrophysiological studies revealed increased current density and delayed inactivation (Liu et al., 2019). Another study using a p.Arg1872Gln cell line identified repurposed drug effects, which inhibited sodium channel currents, including amitriptyline, carvedilol, nilvadipine, and carbamazepine (Atkin et al., 2018).

In conclusion, *SCN8A* developmental and epileptic encephalopathy had a wide spectrum of phenotypes, with seizure onset from neonate to 18 months of age, with diverse seizure types, and dominant focal seizures or spasms. EEGs showed slow and disorganized background and epileptiform abnormalities with occipital predominance. Seizures were intractable and sodium channel blockers were effective in most of the patients, in contrast to ketogenic diets, which were not usually effective. *De novo* missense mutations in *SCN8A* are usually found in the highly conserved regions of the protein. There was no correlation between location of the protein mutation and phenotype or response to sodium channel blockers. Microcephaly and hypotonia were also characteristic. Although small number of patients were included, our study delineated the typical phenotype of *SCN8A* developmental and epileptic encephalopathy and showed the effectiveness of sodium channel blockers in seven patients. Our study also highlights the importance of genetic tests in developmental epileptic encephalopathy, which could guide therapeutic choices, predict clinical courses or comorbidities, and may guide to individualized counseling.

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Declaration of Competing Interest

The authors have no conflict of interest relevant to this article to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.106222.

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