Original article

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The phenotype and treatment of *SCN2A*-related developmental and epileptic encephalopathy

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ABSTRACT – *Aims*. We aimed to delineate the phenotypic spectrum of *SCN2A*-related developmental and epileptic encephalopathy (DEE) and determine the effectiveness of various treatment modalities, including sodium channel blockers and the ketogenic diet.
Methods. Eleven patients with *SCN2A*-related DEE were included in the study. The characteristics of *SCN2A* mutations, electroclinical features, clinical course, and response to treatment modalities were analysed.
Results. The 11 patients were aged between 0.4 and 9.7 years. The onset of seizures ranged from neonate (six patients) to infant (four patients), to childhood (one patient). Epilepsy presented as Ohtahara syndrome, West syndrome, epilepsy of infancy with migrating focal seizures (EIMFS), and focal epilepsy in neonatal- to infantile-onset patients. The only childhood-onset patient in our study presented with focal epilepsy with autism. Neonatal-to infantile-onset patients had drug-resistant epilepsy (9/10), however, sodium channel blockers were effective in all treated patients (9/9). The ketogenic diet (6/8) and high-dose steroid treatment (4/5) were also effective. The seizures in the childhood-onset patient worsened during treatment with sodium channel blockers. All mutations in neonatal- to infantile-onset patients were missense mutations, whereas the mutation in the childhood-onset patient was a truncation mutation.
Conclusions. These results support earlier observations regarding the epilepsy syndromes and response to antiepileptic drugs in patients with *SCN2A*-related DEE.

Key words: *SCN2A*, developmental and epileptic encephalopathy, sodium channel blockers

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Voltage-gated sodium channels play a role in electrical signalling through action potential initiation and conduction in neurons and other excitable cells (Catterall, 2000). *SCN2A* encodes one of the α subunits of voltage-gated sodium channels, $Na_v1.2$ (Oliva *et al*., 2012).

Since the first identification of *SCN2A* mutation as a cause of epilepsy in benign familial neonatal/infantile seizures (BFNIS) (Heron *et al*., 2002), a wide spectrum of phenotypes including epilepsy and non-epileptic disorders, such as episodic ataxia, have been recognized (Schwarz *et al*., 2019).

In particular, *de novo SCN2A* mutations have been increasingly reported to cause severe disorders such as developmental and epileptic encephalopathies (DEE), intellectual disability and/or autism with/without epilepsy (Ogiwara *et al*., 2009; Liao *et al*., 2010a; Rauch *et al*., 2012; Sanders *et al*., 2012; Dhamija *et al*., 2013; Nakamura *et al*., 2013; Sundaram *et al*., 2013; Touma *et al*., 2013; Baasch *et al*., 2014; Howell *et al*., 2015; Wong *et al*., 2015; Liang *et al*., 2017; Wolff *et al*., 2017). Reported phenotypes of DEE with *SCN2A* mutations include Ohtahara syndrome (Nakamura *et al*., 2013; Touma *et al*., 2013), West syndrome (Ogiwara *et al*., 2009; Sundaram *et al*., 2013; Wong *et al*., 2015), epilepsy of infancy with migrating focal seizures (EIMFS) (Dhamija *et al*., 2013; Howell *et al*., 2015), and unclassified severe epilepsy (Liao *et al*., 2010a; Baasch *et al*., 2014; Liang *et al*., 2017).

Despite the heterogeneity of the phenotype, further delineation of the phenotype with regard to mutation characteristics is essential for predicting prognosis and choosing proper treatment, especially in DEE.

Herein, we describe the phenotypic spectrum of *SCN2A*-related DEE in a Korean population, and report the effectiveness of treatment modalities including the use of sodium channel blockers and a ketogenic diet.

Methods

Patients

Patients with *SCN2A*-related DEE were identified from a cohort of 730 paediatric patients with early-onset DEE of unknown aetiology from the Severance Children's Hospital who had undergone targeted gene panel sequencing from March 2015 to December 2018. All patients had seizure onset before the age of three years and accompanied developmental delay. This study was approved by the Institutional Review Board of the Severance Hospital (IRB No. 4-2016-0080). We identified 11 patients with *SCN2A* mutations.

Clinical data

Detailed clinical features were retrospectively reviewed. Clinical data included: demographics; age at seizure onset; seizure type; classification of epilepsy syndrome; treatment of epilepsy and response to the treatment including sodium channel blockers, high-dose steroid, and the ketogenic diet; seizure outcome; development; typical clinical features; EEG; and brain MRI. Seizure types and epilepsy syndromes were classified according to the new 2017 International League Against Epilepsy classification (Scheffer *et al*., 2017). Response to the treatment was considered effective if seizure frequencies were decreased more than 50% from baseline.

Mutation analysis

One hundred and seventy-two genes, including *SCN2A*, associated with DEE were included in our targeted gene panel; the genes are listed in *supplementary table 1*. 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 analysed 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). 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).

Results

SCN2A mutations

All except one truncation mutation were missense mutations. All seven patients whose parents were tested in the parental study showed *de novo* variants. Parental studies were not conducted in cases where the variant was proven to be pathogenic through conventional bioinformatics analysis or where the same variant was reported in the literature as a causative mutation in DEE. Five mutations had been previously reported and six were not. Patient 8 showed two missense mutations; a pathogenic *de novo* mutation and a non-pathogenic paternally inherited mutation (*table 1*). There was no consanguinity and none of the patients had a family history of epilepsy.

The mutations were found in the inactivation gate, Loop1, C-terminal, and transmembrane segments (S1, 4, 5, 6). Ten patients were treated with sodium channel blockers. This treatment was effective in the nine patients with missense mutations but resulted in seizure aggravation in the only patient with a truncation mutation (*table 1*, *figure 1*).

Clinical features of *SCN2A*-related DEE

The patients' ages ranged from 0.4 to 9.7 years, and the age at onset of seizures ranged from one day to 30 months of age. The patients were separated into three groups, with six in the neonate group, four in the infant group, and one in the childhood group. Seizure semiology was variable and included

Table 1. *SCN2A* mutations and response to sodium channel blockers.

Pt	Nucleotide change	Amino acid change	Mutation type	Protein location	Inheritance	SCB response
1	c.5327T>C	p.Leu1776Pro	Missense	C-terminal	*De novo*	Effective
2	c.5308A>C	p.Met1770Val	Missense	DIV S6	*De novo*	Effective
3	c.5317G>A	p.Ala1773Thr	Missense	DIV S6	*De novo*	Effective
4	c.1747C>T	pArg583Ter	Truncation	Loop1	NA	Aggravation
5	c.4886G>T	pArg1629Leu	Missense	DIV S4	NA	Effective
6	c.4622T>A	pIle1541Asn	Missense	DIV S1	*De novo*	NA
7	c.788C>T	pAla263Val	Missense	DI S5	NA	Effective
8	c.819C>A	p.Asn273Lys	Missense	Extracellular; near DI S5	*De novo*	Effective
	c.5753G>A	p.Arg1918His	Missense	C-terminal	Paternal	
9	c.4499C>T	p.Ala1500Val	Missense	Inactivation gate	*De novo*	Effective
10	c.658A>G	p.Arg220Gly	Missense	DI S4	NA	Effective
11	c.4877G>T	p.Arg1626Leu	Missense	DIV S4	NA	Effective

D: domain; NA: not applicable; SCB: sodium channel blocker

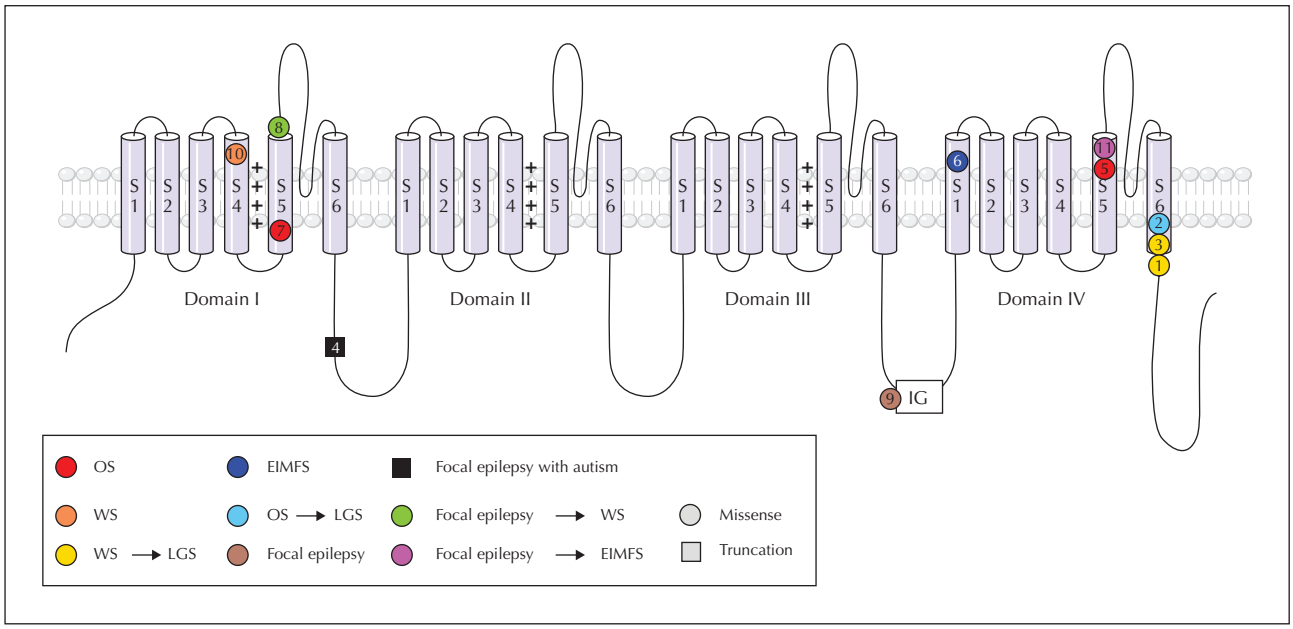

Figure 1. Structure of *SCN2A* and position of pathogenic variants. Voltage-gated sodium channel alpha subunits are composed of four homologous domains (DI-DIV), which each contain four voltage-sensing transmembrane segments (S1-S4), two pore-forming transmembrane segments (S5-S6) and a pore-forming loop between S5 and S6. Numbers in circles correspond to the patients listed in the tables.

epileptic spasms, focal seizures, tonic seizures, tonic-clonic seizures, and atypical absence seizures. Epilepsy syndrome presented as Ohtahara syndrome in three of the six neonatal-onset patients. Epilepsy syndrome in the other three presented as unclassified and evolved into West syndrome, EIMFS, and focal epilepsy, respectively. Three infantile-onset patients presented with West syndrome and one presented with EIMFS. The only childhood-onset patient presented with focal epilepsy with autism (*table 2*). All the patients with neonatal- and infantile-onset epilepsy had missense mutations in diverse locations within the protein, whereas the childhood-onset patient with focal epilepsy with autism had a truncation mutation in Loop1 (*table 1, figure 1*).

All patients showed developmental delay or regression. Severe hypotonia was observed in six patients, and spasticity was observed in one patient. Cocktail treatment with coenzyme Q10, vitamin B complex, and L-carnitine was administered to four out of six hypotonic patients because of suspected mitochondrial disease. EEG showed slow and disorganized background and multifocal epileptiform abnormalities. Brain MRI results were normal in six patients but revealed atrophy in five patients (*table 2*).

Treatment effects

The childhood-onset patient (Patient 4) was first treated with carbamazepine and lamotrigine, but these drugs aggravated his seizures. In contrast, this patient became seizure-free with topiramate treatment. The neonatal- to infantile-onset patients presented with drug-resistant epilepsy (9/10). Only Patient 6, who had EIMFS, became seizure-free with three antiepileptic drugs. Therefore, no further treatment modality was tried. Nine patients who were intractable to antiepileptic drugs underwent multimodal treatment, including sodium channel blockers, high-dose steroid, the ketogenic diet, and vagus nerve stimulation. Sodium channel blockers were effective in all patients (9/9), and high-dose steroid (4/5) and ketogenic diet (6/8) were effective in most patients. Finally, four patients (Patients 2, 3, 5, 8) became seizure-free. Death due to respiratory failure during the treatment of pneumonia occurred in one patient (Patient 11). Prior to death, this patient benefited from treatment with carbamazepine and valproic acid, which improved his seizures and resulted in a seizure-free state that was sustained for several months before his death (*table 2*).

Discussion

Among 730 patients with early-onset DEE of unknown aetiology, 11 patients had *SCN2A* mutations. The frequency of *SCN2A* mutations in our study (1.5% [11/730]) is similar to that of a previous study, which reported a frequency of 1.2% among patients with infantile epileptic encephalopathy (Sanders *et al*., 2018).

Our study delineated the phenotype and treatment response of 11 patients with *SCN2A*-related DEE. Patients with neonatal- or infantile-onset DEE, caused by *SCN2A* missense mutation, presented with intractable epilepsy. We found, however, that sodium channel blockers, the ketogenic diet, and high-dose steroid were effective treatments for seizures in these patients. The patient with childhood-onset focal epilepsy with autism, caused by truncation mutation, presented with seizures that were not intractable. In this patient, sodium channel blockers aggravated the seizures.

Recent research based on the biophysical effects of mutations suggests that there are two distinct groups in *SCN2A*-related epilepsy (Wolff *et al*., 2017). The first group is characterized by early infantile-onset epilepsy, missense mutations with gain-of-function effects, and good response to sodium channel blockers. The second group is characterized by later-onset epilepsy, loss-of-function mutations (mainly truncations and splice site mutations), and relatively poor response to sodium channel blockers. Our cohort included patients whose seizure onset occurred before the age of three years with missense mutations, apart from one patient with the latest onset of epilepsy who had a truncation mutation, consistent with this previous study (Wolff *et al*., 2017).

Neonatal- to infantile-onset DEE, caused by *SCN2A de novo* missense mutation, presented as various epilepsy syndromes including Ohtahara syndrome, West syndrome, and EIMFS. Previously, Ohtahara syndrome and West syndrome were frequently reported as a presentation of *SCN2A*-related epilepsy (Ogiwara *et al*., 2009; Nakamura *et al*., 2013; Sundaram *et al*., 2013; Touma *et al*., 2013; Wong *et al*., 2015). Recently, EIMFS has also been reported, and *SCN2A* is known to be the second most common cause of EIMFS after *KCNT1* (Dhamija *et al*., 2013; Howell *et al*., 2015). We also encountered patients with neonatal- to infantile-onset DEE who presented as Ohtahara syndrome, West syndrome and EIMFS. EIMFS is one of the major epilepsy syndromes associated with *SCN2A*-related DEE.

Neonatal- to infantile-onset *SCN2A*-related DEE shares some similarities with *SCN8A*-related DEE. *SCN8A*-related DEE, caused by *de novo* missense mutation of *SCN8A*, is characterized by severe developmental delay, infantile-onset intractable epilepsies with multiple seizure types including spasms, and motor manifestations such as hypotonia. Sodium channel blockers are also effective in *SCN8A*-related DEE

Table 2. Clinical findings.

Pt(sex)	Age	Seizure onset	Seizure type	Epilepsy diagnosis	Effective AEDs	SD	KD	Other treatment	Seizure outcome	Development	Other features	EEG	Brain MRI
1(F)	9yr, 8mo	5mo	Sp, T, AA	WS→LGS	OXC, VGB	NA	Effective	VNS cocktail	Daily	Delayed	Hypotonia	Slow BG, both Fr sharp (16mo)	Atrophy (14mo)
2(M)	4yr, 1mo	1d	F, T, TC	OS→LGS	PHT	Effective	Effective		Sz-free	Delayed	Spasticity	Slow BG, multifocal sharp (1mo)	Atrophy (1mo)
3(F)	8yr, 9mo	5mo	Sp, T, TC, AA	WS→LGS	LCM	Effective	Effective	VNS	Sz-free	Delayed	Hypotonia	Slow BG, multifocal sharp, GSSW (8yr)	Normal (8yr)
4(M)	4yr, 5mo	30mo	F	Focal epilepsy with autism	TPM	NA	NA		Sz-free	Delayed		Slow BG (30mo)	Normal (30mo)
5(M)	1yr, 6mo	4d	F, T	OS	OXC	Effective	Effective (AE)		Sz-free	Delayed	Hypotonia	Slow BG, multifocal sharp (2mo)	Normal (1mo)
6(F)	2yr, 2mo	12mo	F, T	EIMFS	VGB, VPA, LEV	NA	NA		Sz-free	Delayed		Slow BG, multifocal sharp (12mo) →normal (2yr)	Normal (12mo)
7(M)	5yr, 6mo	14d	F, T	OS	LTG	NA	Effective (AE)	Cocktail	Weekly	Delayed	Hypotonia	Slow BG, multifocal sharp (1mo)	Normal (1mo)
8(M)	2yr, 1mo	2d	F, T, Sp	Neonatal onset focal seizure→ WS	OXC	Effective	NA		Sz-free	Delayed		Slow BG, multifocal sharp (14mo)	Normal (15mo)

Table 2. (*Continued*).

Pt(sex)	Age	Seizure onset	Seizure type	Epilepsy diagnosis	Effective AEDs	SD	KD	Other treatment	Seizure outcome	Development	Other features	EEG	Brain MRI
9(F)	5mo	1d	F, T	Neonatal onset focal seizure→focal epilepsy	LTG, OXC, PHT	NA	Ineffective		Daily	Delayed		Slow BG, Lt. H sharp(2mo)	Atrophy (5mo)
10(M)	1yr, 1mo	4mo	Sp, F	WS	LCM	Ineffective	Effective	Cocktail	Daily	Delayed	Hypotonia	Hyps (4mo) →Slow BG, Rt. PQ sharp (10mo)	Atrophy (10mo)
11(M)	1yr, 5mo	3d	F, T	Neonatal onset focal seizure →EIMFS	CBZ, VPA	NA	Ineffective	Cocktail	Death	Delayed	Hypotonia	Slow BG, multifocal sharp	Atrophy (6mo)

AA: atypical absence; AE: adverse events; AED: antiepileptic drug; BG: background; CBZ: carbamazepine; EIMFS: epilepsy of infancy with migrating focal seizures; F: focal; Fr: frontal; GSSW: generalized slow-spike wave; Hyps: hypsarrhythmia; KD: ketogenic diet; LCM: lacosamide; LEV: levetiracetam; LGS: Lennox-Gastaut syndrome; LTG: lamotrigine; NA: not applicable; OS: Ohtahara syndrome; OXC: oxcarbazepine; PHT: phenytoin; PQ: posterior quadrant; SD: steroid; Sp: spasm; T: tonic; TC: tonic-clonic; TPM: topiramate; VGB: vigabatrin; VNS: vagus nerve stimulation; VPA: valproic acid; WS: West syndrome.

(Larsen *et al*., 2015; Gardella *et al*., 2018). However, *SCN8A*-related DEE shows later seizure onset than *SCN2A*-related DEE; *SCN8A*-related DEE has a median seizure onset age of five months and presentation of neonatal seizures is rare (Larsen *et al*., 2015; Gardella *et al*., 2018). This might reflect changes in voltage-gated sodium channels with maturation; namely, $Na_v1.2$ is expressed early in development, but expression is diminished and replaced by $Na_v1.6$ as a dominant channel during maturation (Liao *et al*., 2010b).

To date, no clear genotype-phenotype correlations have been explained in the literature (Howell *et al*., 2015; Wolff *et al*., 2017). In our study, a truncation mutation was found in Loop1 and missense mutations were found mainly in transmembrane segments, although each missense mutation was found in the inactivation gate or C-terminal. Patients with mutation in the inactivation gate (Patient 9) and C-terminal (Patient 1) could not achieve a seizure-free status. Because of the small number of patients, we could not find a clear correlation between mutation site and epilepsy type, severity, or treatment response.

Treatment response to sodium channel blockers can be explained by functional changes in voltage-gated sodium channels. Previous analysis of genetic and electrophysiological data has established *SCN2A* pathophysiology in this heterogeneous disease group. *De novo* gain-of-function mutation in excitatory neurons leads to DEE, whereas *de novo* loss-of-function mutation in excitatory neurons leads to autism spectrum disorder and/or intellectual disability with/without childhood-onset seizures (Sanders *et al*., 2018). Patient 4 might have diminished channel activities, therefore sodium channel blockers might be ineffective. In neonatal- to infantile-onset patients, the ketogenic diet (6/8) and high-dose steroid (4/5) were also effective. The ketogenic diet may be effective in Dravet syndrome (Yan *et al*., 2018). In our previous research, we assessed the efficacy of the ketogenic diet according to the causative genes in DEE and found that the ketogenic diet is especially effective in patients with *SCN1A*, *KCNQ2*, *STXBP1,* and *SCN2A* mutations (Ko *et al*., 2018). There have also been other reports of successful treatment of *SCN2A*-related DEE with the ketogenic diet (Turkdogan *et al*., 2019; Su *et al*., 2018). High-dose steroid, which was tried in patients with Ohtahara syndrome or West syndrome, was also effective (4/5). In conclusion, neonatal- to infantile-onset *SCN2A*-related DEE presents with intractable epilepsy, but sodium channel blockers, the ketogenic diet, and high-dose steroid are effective treatment modalities. These findings suggest that in cases of neonatal- to infantile-onset *SCN2A*-related DEE, sodium channel blockers should be considered as a first-line

treatment and the ketogenic diet and high-dose steroid can be applied at early stages if seizures are intractable.

SCN2A-related DEE presents with distinct features within two categories; namely, one with early-onset missense mutations and the other with later-onset truncation mutations. Although further studies including functional studies and large-scale clinical studies are required, the results of this observational study indicate that sodium channel blockers, the ketogenic diet, and high-dose steroid are effective treatments in neonatal- to infantile-onset *SCN2A*-related DEE. □

Supplementary data.

Supplementary table is available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What epilepsy syndromes are observed in *SCN2A*-related DEE?

(2) Do sodium channel blockers typically aggravate seizures in patients with *SCN2A*-related DEE with neonatal- to infantile-onset?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".