

## Genetic Analysis of Children with Dravet Syndrome in a Resource-limited Setting

Sorawit Viravan, M.D.<sup>1</sup>, Chutima Meesamarnpong, B.Sc.<sup>2</sup>, Wanna Thongnoppakhun, Ph.D.<sup>2</sup>, Mongkol Chanvanichtrakool, M.D.<sup>1</sup>

<sup>1</sup>Division of Neurology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

<sup>2</sup>Division of Medical Genetics Research and Laboratory, Research Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

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### Abstract:

**Objective:** To identify the common causal gene mutations in Thai children with the Dravet (DS) phenotype, using single gene analysis.

**Material and Methods:** The study was carried out on 20 DS patients at Siriraj Hospital, Bangkok, Thailand. Sanger sequencing of the Voltage-Gated Sodium Channel Alpha Subunit 1 (*SCN1A*) gene was conducted in all patients. In *SCN1A*-negative patients, multiplex ligation-dependent probe amplification of the *SCN1A* gene was performed in all cases; however, direct sequencing of the Protocadherin-19 (*PCDH19*) gene was analyzed in girls only.

**Results:** Fourteen (70.0%) DS patients were found to carry pathogenic *SCN1A* mutations, with 6 novel mutations. In *SCN1A*-negative patients; 1 of the 4 girl patients (25.0%) had a novel *PCDH19* mutation, while none of the 6 patients had a large deletion or duplication in the *SCN1A* gene.

**Conclusion:** The *SCN1A* gene is the most common causative mutation in Thai children with DS phenotype. This study emphasizes the benefit of Sanger sequencing of the *SCN1A* gene in resource-limited countries to aid in making appropriate therapeutic decisions.

**Keywords:** Dravet syndrome, *SCN1A*, *PCDH19*, Thai children, Sanger sequencing

**Contact:** Mongkol Chanvanichtrakool, M.D.  
Division of Neurology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital,  
Mahidol University, Bangkok 10700, Thailand.  
E-mail: Mongkol.cha@mahidol.edu

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## Introduction

Severe myoclonic epilepsy in infancy (SMEI), or Dravet syndrome (DS), is a rare developmental and epileptic encephalopathy (DEE) occurring before 1 year of age. Patients usually present with recurrent febrile seizures, unilateral clonic seizures, and prolonged febrile status epilepticus. After the first year of life, they also present with nonfebrile seizures, and multiple types of other seizures, including myoclonic seizures, absences seizures, atonic seizures, and focal seizures.<sup>1-3</sup> Such seizures often resist treatment, and are aggravated by fever, hot weather<sup>4</sup>, vaccines<sup>5</sup>, and sodium channel blocker agents.<sup>6</sup>

In several studies<sup>3,7,8</sup>, Voltage-Gated Sodium Channel Alpha Subunit 1 (*SCN1A*) mutations, as analyzed by the Sanger method, have been mainly reported in 68.4–76.7% of DS cases. In two studies<sup>7,9</sup>, 12.5–13.3% of the negative cases were detected to have deletion and duplication, according to multiplex ligation-dependent probe amplification (MLPA) analysis. In addition, Protocadherin-19 (*PCDH19*) mutations were found in 24.4% of girls with *SCN1A*-negative DS.<sup>10</sup> *PCDH19* mutations are now considered to cause epilepsy in females with mental retardation (EFMR); although a few DS cases have been reported to be caused by other gene mutations; such as, to the *GABRG2*<sup>11</sup>, *SCN1B*<sup>12</sup>, and *SCN2A*<sup>13</sup> genes.

The *SCN1A* gene consists of 26 exons, and is located on chromosome 2q24. The type-I sodium channel is expressed in the brain and plays an important role in the firing action potential. In a rodent study, heterozygous *SCN1A* mutation was found to cause a reduced firing action potential in inhibitory interneurons, but not in excitatory pyramidal neurons; resulting in hyperexcitatory and seizures.<sup>14</sup>

In Thailand, a resource-limited setting, there is no previous study concerning the clinical characteristic of DS, or its causative gene among Thai Children. Hence, we aimed to identify the common causal mutations in Thai children with

the DS phenotype, at Siriraj Hospital, by using the Sanger sequencing method. With the appropriate chosen patients, we also wanted to demonstrate the benefit of single gene analysis in resource-limited settings.

## Material and Methods

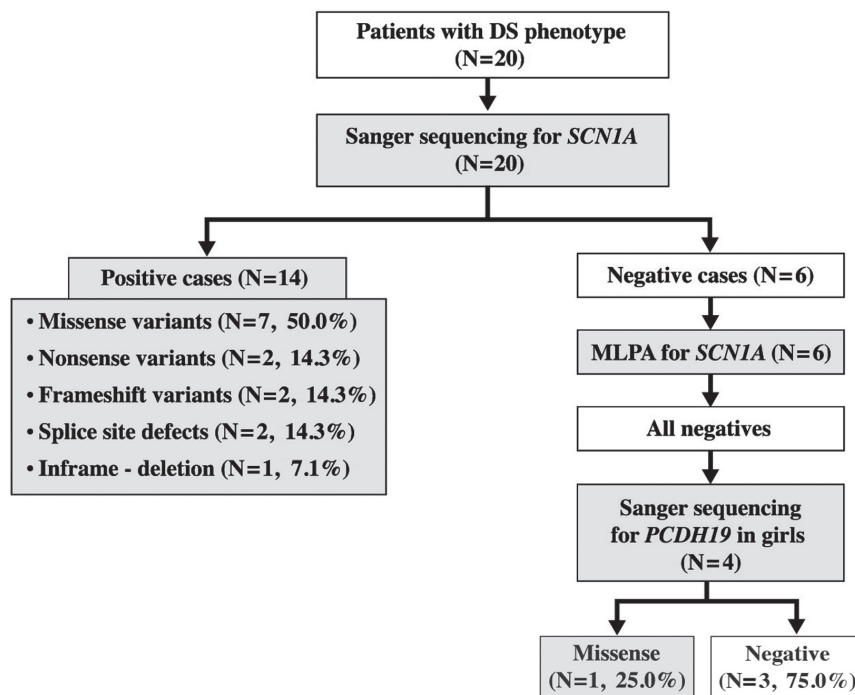
This study represents a cross-sectional study. We reviewed the medical records of patients, aged 4 months–15 years old, with epilepsy and febrile seizure, who were followed-up at the Department of Pediatrics, Siriraj Hospital; between January 1, 2007 and March 31, 2017. Our study included all patients with the DS phenotype, identified by reviewing their previous medical records. We defined DS phenotype as infantile-onset recurrent complex febrile seizure; such as, a unilateral clonic seizure, prolonged seizure or repetitive seizures; plus at least one of the following features: multiple types of seizures (>2 seizure types), developmental delay after onset of seizure, and drug resistance. The exclusion criteria were patients with known causes of epilepsy; such as, previous cerebral insult (asphyxia, intracerebral hemorrhage, central nervous system infection), inborn error of the metabolism, brain malformation, or neurocutaneous syndrome. We reviewed the patients' demographic data, characteristics of the seizures, neuroimaging results, and electroencephalography (EEG) results from the patients' medical records. Genetic analysis was then performed in all patients. The protocol for this study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Written informed consents were obtained from the guardians.

The genetic analysis was performed in patients with DS phenotype; as shown in Figure 1. DNA was extracted from the peripheral blood lymphocytes by a salting-out procedure, then amplified by polymerase chain reaction (PCR), focusing on 28 fragments covering 26 exons of the *SCN1A* gene (NM\_001165963.4), using the published

primers.<sup>8</sup> The *SCN1A* PCR products were then directly sequenced in both directions via Sanger sequencing. Once available, the patients' parental origins were also determined, by direct sequencing of the corresponding exons, to investigate the specified variants found in patients. In female children without *SCN1A* mutations, direct Sanger sequencing of the *PCDH19* gene (NM\_001184880.2) in both DNA strands of 11 PCR fragments covering 6 exons was also performed. Detailed information regarding the newly designed PCR primers for the *PCDH19* gene are provided in the Supplemental Table S1. Furthermore, in cases that were negative for *SCN1A* point mutations, MLPA analysis of the *SCN1A* gene was performed to identify any large deletions or duplications. The commercially available MLPA kit (SALSA<sup>®</sup> MLPA<sup>®</sup> Probemix P137-C1 *SCN1A*;

MRC-Holland, Amsterdam, the Netherlands) was utilized, according to the manufacturer's instructions.

The identified variants were evaluated for their pathogenicity, and were classified based on a variety of supporting evidence; such as the literature, public databases, population allele frequencies, and in silico prediction tools. For missense variants, an integrated tool, VarCards, was applied for their pathogenicity evaluation based on 23 different algorithms.<sup>15</sup> To assess the effects of the identifiable variants on the mRNA splicing process, varSEAK online (URL: <https://varseak.bio/>) was used. In addition, a versatile variant search engine, VarSome, was also applied.<sup>16</sup> The variant interpretation was performed in accordance with the standards and guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.<sup>17</sup>



DS=Dravet syndrome, MLPA=multiplex ligation-dependent probe amplification, PCDH19=Protocadherin-19, SCN1A=Voltage-Gated Sodium Channel Alpha Subunit

**Figure 1** Summarized flowchart of the genetic analysis of the patients with the Dravet syndrome phenotype

We used descriptive statistics to analyze the demographic data and genetic testing results, and reported these by number, percentage, and mean and standard deviation for normal distributions, and median and range for non-normal distributions.

## Results

We identified 369 patients with epilepsy and febrile seizures, treated at Siriraj Hospital; between 2007 and 2017: 349 patients were then excluded as they did not meet the criteria. The 20 remaining DS-phenotype patients were enrolled into this study. These patients had been previously diagnosed as drug resistant epilepsy (DRE) (65.0%), DS (15.0%), epilepsy (15.0%), and Lennox-Gastaut syndrome (5.0%).

The enrolled patients' demographic data are demonstrated in Table 1. Among the 20 enrolled patients, 14 (70.0%) were males. Their median age was 5 years old (ranging from 1–14 years old). Only two patients had a history of first-degree relatives with febrile seizures. The most common clinical features were complex febrile seizure, recurrent febrile seizures, and seizures provoked by low-grade fever, which were seen in all patients.

### Seizure characteristics

The mean age of seizure onset was 5.6±1.9 months old. The majority of seizure types were generalized tonic-clonic/generalized tonic seizure or focal seizures. Eleven patients (55.0%) had status epilepticus. Of the 14 patients who received Na-channel blocker antiseizure medication (ASM), 13 (92.8%) had an increased seizure frequency. The seizures were not controlled by at least two ASM in 17 patients (85%). Other characteristics of the seizures and the aggravating factors are shown in Table 1.

**Table 1** Clinical phenotype and seizure characteristics of 20 patients with Dravet syndrome

Clinical phenotype	n (%)
Age (years) (median, range)	5, 1–14
Gender (male)	14 (70.0%)
Family history of febrile seizure	2 (10.0%)
Developmental regression after seizure onset	19 (95.0%)
Crouch gait	9 (45.0%)
<b>Seizure characteristics (n=20)</b>	
Onset of seizure (months) (mean±SD)	5.6±1.9
Number of seizures in first year (episodes) (median, range)	8, 1–35
Complex febrile seizure	20 (100.0%)
Duration >15 minutes	8 (40.0%)
Focal seizure (hemiclonic seizure)	12 (60.0%)
Recurrent seizures in 24 hours	18 (90.0%)
Seizure type	
GC/GT/GTC seizure	18 (90.0%)
Focal seizure	15 (75.0%)
Myoclonic seizure	9 (45.0%)
Atypical absence seizure	6 (30.0%)
Atonic seizure	2 (10.0%)
Status epilepticus	11 (55.0%)
Age onset of status epilepticus (months) (median, range)	13, 6–101
Number of status epilepticus (episodes) (median, range)	1, 1–10
Aggravating factor	
Vaccine	13 (65.0%)
Na-channel blocker (n=14)	13 (92.8%)
Hot weather	6 (30.0%)
Exercise	5 (25.0%)

GC=generalized clonic, GT=generalized tonic, GTC=generalized tonic-clonic

### Investigations

The first EEG was abnormal in 10 patients (50.0%). Nine patients had epileptiform discharge: 7 frontal, 1 central, and 1 in the parietal region. In addition, intermittent slow activities were observed in 2 patients. None of the patients

had photoparoxysmal response (PPR). Magnetic resonance imaging (MRI) of the brain was performed in 15 patients. Seven (46.6%) of these revealed abnormalities, including a non-specific increased signal intensity on T2W (33.3%), cerebellar atrophy (6.7%), and delayed myelination (6.7%).

### Genetic analysis

Summaries of the results of the genetic analysis in this study are shown in Table 2. Pathogenic and likely pathogenic *SCN1A* variants were detected by the Sanger method in 14 out of 20 (70.0%) patients; 6 of these were novel, as described in Table 2. All the identified *SCN1A* variants were in a heterozygous state, comprising 7 missense, 2 frameshift, 2 nonsense mutations, 2 splicing defects, and 1 inframe deletion.

Among the 4 girls without *SCN1A* mutation, one (25.0%) was found to carry a novel heterozygous, likely pathogenic, variant in the *PCDH19* gene. This missense variant was not found in her parents: indicating a *de novo* change. In the 6 patients without *SCN1A* mutations detected by Sanger sequencing, no large deletions or duplications in the *SCN1A* gene were found from MLPA analysis.

Table 2 presents the scoring of the variant classification following the 2015 American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines, shown as abbreviations; such as, pathogenic-very strong (PVS), pathogenic-strong (PS), pathogenic-moderate (PM), and pathogenic-supporting (PP). Variant interpretations were then performed by integration of all the met criteria. For example, *SCN1A*:c.429\_430delGT (p.Phe144Tyrfs\*5) was interpreted as pathogenic, because of PVS1 (null variant, frameshift deletion), PM2 (absent from controls), PM6 (assumed *de novo*), and PP4 (phenotype specific for DS). Alternatively, *PCDH19*:c.1124A>T (p.Asp 375Val) was interpreted as likely pathogenic, due to PS2 (approved *de novo*), PM2 (absent from the controls), PP3 (pathogenic

computational predictions), and PP4 (phenotype specific for DS).

### Discussion

The causative gene and mutation types of DS in our ethnic group are similar to those in other studies; which reported that 68.4–76.7% of patients had positive *SCN1A* mutations.<sup>3,7</sup> Missense mutations were the most common, followed by nonsense mutations, frameshift mutations, splicing defects, and inframe mutations, respectively. Large deletions or duplications in *SCN1A*, analyzed by the MLPA method, were not found in our *SCN1A* mutation-negative patients. This may be due to our lower number of DS patients, which contrasts with previous studies that reported an incidence of 12.5–13.3%.<sup>7,9</sup> The *PCDH19* mutation was also detected in 1 female patient with negative *SCN1A* mutation (25.0%), which is the same as in a previous study.<sup>10</sup>

Before the availability of *SCN1A* gene test for DS, most of our patients were misdiagnosed with DRE; which misled to ASM treatment, such as Na-channel blockers, causing seizure worsening. After the diagnosis was confirmed with the *SCN1A* gene test, it could help physician avoid aggravated ASM and choose an appropriate ASM; such as, sodium valproate, clobazam, stiripentol leading to improvement of seizure control. This highlights the importance of performing genetic tests on DS patients, and also encourages physicians to perform genetic tests. In the future, the treatment of epilepsy should be changed so as to be based on genetic results. Nowadays, advanced genetic tests; such as, whole exome sequencing (WES) and epilepsy multigene panel tests, are available worldwide, and have demonstrated a diagnostic benefit for DEE. They are also more useful now in identifying various causative genes; especially in atypical presentations of DS.<sup>18</sup>

However, in Thailand these advanced genetic tests are expensive as well as less available. They also require experienced scientists, and have a longer turnaround

**Table 2** Variants identified in this study in the *SCN1A* gene (NM\_001165963.4, No. 1–14) and *PCDH19* gene (NM\_001184880.2, No. 15)

No.	Case	Age of onset (months)	Exon	SCN1A variant (Except No.15, PCDH19 variant)	In silico predictions	Allele frequency	Family history	Parental variant testing	ACMG variant scoring	Variant interpretation
1	P4	3	3	c.423_428delCTGTG <sup>†</sup> (p.Asn141_Val143delinsLys)	ND	Absent	Yes	ND	PM1, PM2, PM4, PP3, PP4	Likely pathogenic
2	P9	4	3	c.429_430delGT (p.Phe144Tyrfs*5)	ND	Absent	No	ND	PVS1, PM2, PM6, PP4	Pathogenic
3	P2	3	IVS6	c.965-2A>G <sup>†</sup> (IVS6-2A>G)	ND	Loss	No	Absent	PVS1, PS2, PM2, PP3, PP4	Pathogenic
4	P7	4	7	c.1007G>A (p.Cys336Tyr)	Damaging	Absent	No	ND	PS1, PM1, PM2, PM5, PM6, PP3, PP4	Pathogenic
5	P19	6	9	c.1178G>A (p.Arg393His)	Damaging	Absent	No	ND	PS1, PS3, PM1, PM2, PM5, PM6, PP3, PP4	Pathogenic
6	P16	9	13	c.2244G>A <sup>†</sup> (p.Trp748*)	ND	Absent	No	Absent	PVS1, PS2, PM2, PP4	Pathogenic
7	P11	7	15	c.2606T>C (p.Leu869Ser)	Damaging	Absent	No	Absent	PS2, PM1, PM2, PP3, PP4, PP5	Pathogenic
8	P10	4	16	c.3105delA <sup>†</sup> (p.Gln1035Hisfs*11)	ND	Absent	No	ND	PVS1, PM2, PM6, PP4	Pathogenic
9	P17	10	IVS22	c.4339-1G>A (IVS22-1G>A)	ND	Loss	No	ND	PVS1, PM2, PM6, PP3, PP4, PP5	Pathogenic
10	P6	6	26	c.4997C>T (p.Ser1666Phe)	Damaging	Absent	No	ND	PM1, PM2, PM6, PP3, PP4, PP5	Pathogenic
11	P18	6	26	c.5116A>G <sup>†</sup> (p.Asn1706Asp)	Damaging	Absent	No	ND	PM1, PM2, PM6, PP3, PP4	Likely pathogenic
12	P1	6	26	c.5223T>G <sup>†</sup> (p.Cys1741Trp)	Damaging	Absent	No	Absent	PS2, PM1, PM2, PM5, PP3, PP4	Pathogenic
13	P3	6	26	c.5734C>T (p.Arg1912*)	ND	Absent	No	ND	PVS1, PM2, PM6, PP4, PP5	Pathogenic
14	P5	9	26	c.5743G>A (p.Glu1915Lys)	Damaging	Absent	No	ND	PM2, PM6, PP3, PP4, PP5	Likely pathogenic
15	P14	5	1	PCDH19c.1124A>T <sup>†</sup> (p.Asp375Val)	Damaging	Absent	No	Absent	PS2, PM2, PP3, PP4	Likely pathogenic

ND=Not done, †=novel variants, ACMG=The American College of Medical Genetics and Genomics, PM=pathogenic moderate, PP=pathogenic supporting, PS=pathogenic strong, PVS=pathogenic very strong, IVS=intervening sequences

time (up to 6 months). On the other hand, DS has more distinctive clinical phenotypes, and our data has shown that the majority of DS is caused by *SCN1A* gene mutation in the Thai population. Moreover, the *SCN1A* single gene test is more economical, and has a shorter turnaround time (up to 3 months), with the same detection rate as in other methods. Therefore, in resource-limited countries, single analysis of the *SCN1A* gene is a reasonable choice as the first genetic test in patients with the DS phenotype. After this, WES or epilepsy multigene panel testing may be the next step of investigation, if the results returned negative.

The clinical characteristics of seizures in our ethnic group were similar to that of previous studies.<sup>2,3,19,20</sup> The most common symptoms of DS are cluster, prolonged, fever-related, intractable seizures, and developmental delay after the onset of seizure.

In the aspect of our investigations, half of the patients had a normal EEG at the first study. The abnormalities found on the EEGs; including, focal spike, a multifocal spike predominating over the frontal region, and a slow background, are similar to those found in the study by Lee.<sup>21</sup> However, our patients had no PPR on their EEG compared with 30.7–34.7% in other studies.<sup>19,22</sup> The incidence of cerebral and cerebellar atrophy detected in our study is lower than in previous studies.<sup>22,23</sup> The abnormalities in brain MRI mainly depend on the age of the patient, and in our study, the mean age for MRI examinations was lower than in Striano's study<sup>23</sup>; therefore, obvious brain atrophy may not have been found in our patients.

Single gene analysis has limitations, as our study only identified the main causative genes of DS; such as, *SCN1A* and *PCDH19* genes. Therefore, we could not identify other causative genes of DS; such as, *GABRG2*<sup>1</sup>, *SCN1B*<sup>2</sup>, and *SCN2A*<sup>13</sup> genes. Therefore, WES or an epilepsy multi-panel would be the next step of testing.

## Conclusion

The single gene analysis of *SCN1A* could identify the majority of causative genes for the DS phenotype in Thai children. Therefore, in resource-limited countries, it would be reasonable to be used as the first genetic test in patients with the typical DS phenotype. This also emphasizes the benefit of Sanger sequencing of the *SCN1A* gene, which can help lead to appropriate therapeutic decisions. Additionally, as EFMR can mimic the DS phenotypes, *PCDH19* mutation testing should be considered in female patients with a mimic of the DS phenotype.

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## Conflict of interest

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

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