Dravet Syndrome: A Genetic Epileptic Disorder

Mari Akiyama*, Katsuhiro Kobayashi, and Yoko Ohtsuka

Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, and Okayama University Hospital, Okayama 700-8558, Japan

Dravet syndrome (DS), or severe myoclonic epilepsy in infancy, is one of the most severe types of genetic epilepsy. It is characterized by the initial occurrence of febrile or afebrile seizures that often evolve into status epilepticus in infants with normal development, and by the subsequent appearance of myoclonic and/or atypical absence seizures as well as complex partial seizures. The key feature that characterizes DS is fever sensitivity, although photosensitivity and pattern-sensitivity are also often seen. The prognosis is unfavorable in most cases. Seizures become drug-resistant and persist, with many patients suffering from motor and cognitive impairment. Mutations of SCN1A, which encodes the voltage-gated sodium channel Nav1.1, are the most frequent genetic cause of this syndrome. SCN1A mutations and/or microchromosomal rearrangements involving SCN1A are detected in about 85% of patients. Mutations of PCDH19 have also been reported in female patients with clinical findings compatible with DS. PCDH19 mutations might account for 5% of overall DS cases. Thirty years after its first description, DS is considered as a model of channelopathy. This survey reviews recent developments in the research literature on DS, focusing on the clinical course, as well as its genetic causes.

Key words: Dravet syndrome, long-term outcome, SCN1A, PCDH19

Dravet syndrome (DS) is a rare form of childhood-onset epilepsy with a genetic etiology. DS was originally named "severe myoclonic epilepsy in infancy" [1, 2], and is characterized by a variety of treatment-resistant seizures and a poor cognitive prognosis. DS is considered to be a form of epileptic encephalopathy, in which the epileptic activity itself may contribute to severe cognitive and behavioral impairments [3].

DS is a representative type of channelopathy which is, in most cases, caused by mutation of genes encoding ion channels [4]. In this survey of the recent literature, the most significant findings are summarized to promote greater understanding of the clinical course and pathogenesis of DS.

Clinical and Electroencephalographic Aspects of DS

Onset of epilepsy. The onset of seizures in DS occurs during the first year of life, with a mean age of 5–8 months. DS patients usually have no pathological history or developmental delay before the onset of seizures [5].

The first seizure is typically a clonic, generalized or unilateral, convulsive seizure. Seizures are often triggered by fever. Afebrile seizures, focal seizures, and complex partial seizures can also occur. These seizures, with or without fever, tend to last for more than 20 min, and evolve into status epilepticus.
At onset, the electroencephalogram (EEG) is usually normal for infants at this age, with only rare, if any, epileptic discharges [2].

**Evolution of epilepsy.** Patients with typical DS have multiple seizure types during the course of the disease [2].

Convulsive seizures, including generalized tonic-clonic seizures (GTCS), generalized clonic seizures (GCS), and alternating unilateral clonic seizures, are the main seizure types occurring throughout life in most patients. These convulsive seizures may be prolonged or repeated, developing into status epilepticus that lasts longer than 30 min and requires intravenous antiepileptic drug administration. The frequency of convulsive status epilepticus in the first year of life is very high, and then decreases gradually [6, 7].

Myoclonic seizures appear at the ages of 1–5 years, with an average of around 2 years. The symptoms can be either massive or segmental, and are often observed in clusters - particularly before convulsive seizures. Myoclonus observed in DS patients can be divided into 2 groups, epileptic myoclonic seizures and non-epileptic myoclonia. The former is concomitant with paroxysmal discharges (mainly with general-ized spike and wave complexes) on the EEG, whereas the latter does not have an EEG correlate. Both types can occur during the clinical disease course, and it is often difficult to distinguish the former from the latter without precise analyses using video-EEG-EMG simultaneous monitoring [5].

There are some patients with clinical characteristics similar to those of “typical” DS but lacking epileptic myoclonic seizures and atypical absence seizures, although appearance of these seizure types is a unique feature of DS. These patients have been defined as having “borderline” DS by some researchers [8, 9]. Myoclonic seizures and atypical absence seizures tend to disappear during the course in typical DS patients, and it becomes difficult to distinguish typical DS from borderline DS from adolescence onward. Several long-term studies [2, 7] have shown that patients with typical DS and those with borderline DS experience fundamentally similar late clinical courses, including seizure frequencies and mental prognoses. In addition, both types have high rates of SCN1A mutations [10, 11, 12], which led to the perception that the spectrum of typical and borderline DS cases constitutes a single syndromic entity.

Atypical absence seizures can appear either at 1–3 years, together with myoclonic seizures, or later on, at 5–12 years of age. The symptoms can be divided into atypical absence seizures characterized by unresponsiveness, or may include an additional myoclonic component. This seizure type corresponds to several seconds of bursts of generalized, irregular spike and wave complexes in EEG [5].

Obtundation status is a type of nonconvulsive status epilepticus that consists of an impairment of consciousness of variable intensity with fragmentary and segmental, erratic myoclonia involving the limbs and face. Sometimes it is associated with drooling and a slight increase of muscle tone. Convulsive seizures can either occur at the onset, during, or at the end of obtundation status. These periods can be prolonged for several hours, or even days. EEGs usually show diffusely slow background, intermingled with focal and diffuse epileptic discharges [13].

Simple partial seizures or complex partial seizures also occur in many patients. They can appear as early as 4 months up until the age of 4 years.

DS seizure onset is characterized by very severe sensitivity to fevers. In addition to high fevers, seizures can also be induced by subtle elevation of body temperature caused by the very beginning stage of infection, hot bath immersion, exercise, and hot weather [14].

Photosensitivity can be manifested as a pathological response to intermittent photic stimulation, bright light, or intense contrast between bright light and darkness. All kinds of contrasting patterns, such as geometrical designs or dotted lines, can provoke seizures [15, 16].

The EEG background often becomes progressively slower and more poorly organized. The peculiar theta activity in fronto-central areas that is already observed at onset in some patients, appears in most cases, and persists throughout follow-up. Epileptic discharges are represented by spikes, spike and wave complexes, and poly spike-waves [13, 16].

**Long-term outcomes.** DS was originally believed to be always associated with unfavorable outcomes. All patients were reported to have persistent seizures and to be cognitively impaired, often severely. Several authors have published longitudinal studies following a series of patients through to adolescence, but only a few series included patients older than 20 years [7,
17–20].

All seizure types are extremely resistant to any kind of treatment during the first several years. Later on, partial seizures, myoclonic seizures and atypical absences tend to disappear but convulsive seizures persist. However, in 2 very long-term studies, seven patients were reported to have become seizure-free for at least 1 year and up to 5 years [7, 18]. In our series, 5 out of 31 patients (16.1%) were seizure-free in adulthood. The seizure-free patients had experienced significantly fewer episodes of convulsive status epilepticus. Prevention of the occurrence of convulsive status epilepticus might improve seizure prognosis in DS [7, 21].

In the remaining patients, the frequency of convulsive seizures gradually decreased, despite recurrent periods of worsening during adolescence and early adulthood in some patients. At the end of the follow-up, the frequency of seizures was reported to range from 1–12 per year [18].

The convulsive seizures in adult DS have not been fully clarified. Some researchers describe them as tonic-clonic seizures without providing detailed information, whereas others report focal features [2, 6, 22]. In our study, 35 (87.5%) of the 40 apparently generalized convulsive seizures were demonstrated to actually be partial seizures, mostly having a frontal origin, with or without secondary generalization in the ictal EEG records [7].

Convulsive status epilepticus was no longer observed in most adult patients, although it still occurred in adulthood in only a few patients. Obtundation status remained in most severely affected patients [19]. Fever and infections were triggering factors for only one-third to half of the cases in adulthood. Photosensitivity and pattern sensitivity disappeared in most patients [7, 18].

Intercal epileptic EEG abnormalities can disappear completely or become sporadic. They are characterized by focal and multifocal spikes, spike-waves and sharp waves, and are only rarely associated with generalized spike-waves. Photosensitivity becomes progressively less apparent. Nevertheless it persists in some cases and was observed in 12% of patients older than 18 years in one series [13].

It is generally believed that almost all patients with DS show severe mental deficits [12, 16], although recently published long-term studies showed that some patients had only moderate to minimum mental disability in adulthood. Among these patients, only a small number could live independent lives. In our series, a lack of occipital alpha rhythms on follow-up EEGs was significantly correlated with severe mental handicaps in adulthood, and it is thought that a slow EEG background must represent brain dysfunction. To improve the mental prognosis of DS, suppression of seizures might have a positive effect, especially when seizure control is achieved at a young age, although this may not be enough to exert a significant effect [7].

Review of the Genetic Aspects of DS (Table I)

**Sodium channel α1 subunit gene (SCNIA) and Dravet syndrome.** Mutations of SCNIA are the most frequent genetic cause of DS. At present, more than 700 mutations have been associated with DS and are randomly distributed along the gene [23–25]. SCNIA (on chromosome 2q24.3) encodes the voltage-gated sodium channel NaV1.1. Voltage-gated sodium channels (VGSCs) play an essential role in neuronal excitation.

Mutations of SCNIA were first discovered in the syndrome of generalized epilepsy with febrile seizures plus (GEFS+) [26], which has been renamed “genetic epilepsy with febrile seizures plus” [27]. A family history of epilepsy or febrile seizures is sometimes found in patients with DS and most affected relatives have GEFS+ phenotypes [28]. In view of the predisposition to seizures with fever that typically occurs in Dravet syndrome, Claes et al. performed a mutation analysis on SCNIA in 7 children and found that all had *de novo* mutations [4].

**Functional effects of voltage-gated sodium channel α1 mutations.** Most mutations responsible for DS are either missense or truncation mutations, both of which would give rise to nonfunctional channels.

Epilepsy is a disorder characterized by brain hyperexcitability and it initially seemed puzzling that mutations in a VGSC lead to loss of function and reduced Na⁺ current. However, data from *Sen1a* knock-out mice [29] and knock-in mice with a nonsense mutation in the *Sen1a* gene [30] have shown that the α1 subunit is fundamental for the excitability of at least some types of γ-aminobutyric acid (GABA)-ergic
interneurons in the neocortex and hippocampus. Therefore, reduced firing of inhibitory neurons and compromised network inhibition could be the major pathophysiologic mechanism causing SCNIA-related genetic epilepsies.

**Detection of SCNIA mutations.** The overall frequency of SCNIA alterations in DS, which includes sequence-based mutations, single or multiple exon deletions, and chromosomal rearrangements, is around 85%. By classical Sanger sequencing, mutations are found in about 80% of cases and comprise truncating (40%) and missense (40%) mutations, with the remaining alterations being splice site changes [31].

Patients with a clinical diagnosis of DS who test negative for SCNIA mutations after sequencing may still have exonic deletions or chromosomal rearrangements involving SCNIA [23, 24, 32-34]. The size of these genomic alterations varies from the megabase range, involving a large number of contiguous genes, down to one exon within SCNIA. Duplications and amplifications involving SCNIA can be identified with multiplex ligation-dependent probe amplification (MPLA) and further characterized by comparative genome hybridization (CGH) to determine the size of the abnormality and identify any additional genes involved. Intragenic and whole-gene deletions including SCNIA and/or contiguous genes account for 2–3% of Dravet syndrome cases and for about 12.5% of those who are mutation-negative on classical Sanger sequencing [35].

**Mode of inheritance.** Most mutations are de novo, comprising both truncating and missense changes. However, familial mutations also occur in 5–10% of cases and are usually missense in nature [4, 10, 36, 37]. In these cases, other family members with the SCNIA mutation have no symptoms or mild phenotypes consistent with the GEFS+ spectrum [10, 36].

An important genetic counseling issue is that several families with more than one child with DS have been recorded. Somatic or germine mosaic mutations might explain the presence of an unaffected or mildly-affected transmitting parent [38-41]. A recent study indicates that mosaicism is found in at least 7% of families with DS. The proportion of the mutated
allele in the blood of the 12 patients described varied from 0.04% to 85% and may be a significant factor underlying intrafamilial phenotypic variability [39, 42, 43].

**Genotype-phenotype correlations.** Some general genotype–phenotype correlations have been suggested: truncating, nonsense, frame shift mutations, and partial or whole-gene deletions are correlated with a classical DS phenotype and appear to have a significant correlation with an earlier age of seizure onset [24].

The severity of the phenotypes may also be correlated with the location of SCNIA missense mutations: for example, those in the pore-forming region of the sodium channel may cause DS, whereas missense changes associated with the GEFS+ spectrum may be more frequently located outside the pore-forming region [44]. However, this genotype-phenotype correlation is not consistent. Moreover, the same SCNIA mutations and deletions cause DS in some patients and GEFS+ in others [26, 45, 46], suggesting that modifier genes, the genetic background, and/or environmental factors may also play a role in some patients, and thus DS may sometimes follow a complex model of inheritance. SCN9A or CACNB4 mutations, along with SCNIA mutations, have been reported as candidates for modifier genes in DS patients [47, 48].

**Dravet Syndrome without SCNIA Alterations**

**PCDH19.** Mutations of PCDH19 (on chromosome Xq22), the gene encoding protocadherin 19, have been found in a disorder called “epilepsy limited to females with mental retardation” (EFMR) [49, 50]. EFMR is a disorder with an unusual X-linked inheritance pattern, where the disorder is expressed in heterozygous females, and hemizygous males are unaffected carriers.

Depienne et al. [51] reported PCDH19 familial and de novo point mutations in 13 female patients with clinical findings compatible with DS. A male patient with a similar phenotype carried a mosaic PCDH19 mutation. The authors estimated that 16% of their SCNIA-negative DS patients had PCDH19 mutations and that this gene might account for 5% of DS cases overall. The biologic role of PCDH19 is unknown; this gene is expressed in the developing brains of humans and mice, and is postulated to be involved in establishing neuronal connections and signal transduction at the synaptic membrane [52].

**Possible causative genes of DS.** The etiology of DS in about 10% to 20% of patients remains unknown, and additional genes are likely to be implicated. Among these patients, only a few cases with mutation of other genes (GABRG2, SCNIB, and SCN2A genes) have been reported [53–55].

**SCN1A Mutations Associated with Other Forms of Epilepsy**

The second most common phenotypes among SCNIA-related epilepsies are febrile seizures and related syndromes [56]. The remaining associated epileptic conditions comprise a heterogeneous group of cryptogenic focal and cryptogenic generalized epilepsy, as well as infrequent occurrences of myoclonic astatic epilepsy [57, 58], severe idiopathic generalized epilepsy of infancy [58], West syndrome [37], Lennox-Gastaut syndrome [57], and Rasmussen encephalitis [59].

**Conclusion**

It has been more than 30 years since the first description of DS, and the syndrome is now considered a model for channelopathy and is the subject of wide interest in the scientific and medical community. DS is one of the most severe types of genetic epilepsy, and we need further studies to understand its pathogenesis and the mechanisms by which it causes cognitive impairments. Finally, further study is needed to improve the care and treatment of afflicted patients.

**References**


57. Harkin LA, McMahon JM, Iona X, Dibbens L, Pelekanos JT,