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FULL-LENGTH ORIGINAL RESEARCH

Defining Dravet syndrome: An essential pre-requisite for precision medicine trials

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Abstract

Objective: The classical description of Dravet syndrome, the prototypic developmental and epileptic encephalopathy, is of a normal 6-month-old infant presenting with a prolonged, febrile, hemiclonic seizure and showing developmental slowing after age 1 year. *SCN1A* pathogenic variants are found in >80% of patients. Many patients have atypical features resulting in diagnostic delay and inappropriate therapy. We aimed to provide an evidence-based definition of *SCN1A*-Dravet syndrome in readiness for precision medicine trials.

Methods: Epilepsy patients were recruited to the University of Melbourne Epilepsy Genetics Research Program between 1995 and 2020 by neurologists from around the world. Patients with *SCN1A* pathogenic variants were reviewed and only those with Dravet syndrome were included. Clinical data, including seizure and developmental course, were analyzed in all patients with *SCN1A*-Dravet syndrome.

Results: Two hundred and five patients were studied at a median age of 8.5 years (range 10 months to 60 years); 25 were deceased. The median seizure-onset age was 5.7 months (range 1.5–20.6 months). Initial seizures were tonic-clonic (52%) and hemiclonic (35%), with only 55% being associated with fever. Only 34% of patients presented with status epilepticus (seizure lasting ≥30 minutes). Median time between first and second seizure was 30 days (range 4 hours to 8 months), and seven patients (5%) had at least 6 months between initial seizures. Median ages at onset of second and third seizure types were 9.1 months (range 3 months–25.4 years) and 15.5 months (range 4 months–8.2 years), respectively. Developmental slowing occurred prior to 12 months in 27%.

Significance: An evidence-based definition of *SCN1A*-Dravet syndrome is essential for early diagnosis. We refine the spectrum of Dravet syndrome, based on patterns of seizure onset, type, and progression. Understanding of the full spectrum of *SCN1A*-Dravet syndrome presentation is essential for early diagnosis and optimization of treatment, especially as precision medicine trials become available.

Wenhui Li and Amy L Schneider contributed equally to the manuscript

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1 | INTRODUCTION

With the promise of precision medicine now becoming a reality, prompt diagnosis for patients with the most severe group of epilepsies, the developmental and epileptic encephalopathies (DEEs), is vital.[1] Dravet syndrome (OMIM 607208), due to pathogenic *SCN1A* variants in >80% patients, is the prototypic DEE.[1–4] The tantalizing success of emerging gene therapy for *Scn1a* murine models highlights the urgent need for prompt diagnosis of patients with Dravet syndrome.[5] Earlier diagnosis informs the optimization of anti-seizure medicines and identifies patients in readiness for trials of precision therapies, which hold the promise of altering the trajectory of this devastating disorder.[5]

A diagnosis of Dravet syndrome is frequently delayed, even as late as 3 years of age, as clinicians are cautious about making such a serious diagnosis until all the clinical features emerge. This often means the wrong anti-seizure medicines are prescribed, which causes seizure exacerbation and adversely affects development.[6] With the advent of next-generation sequencing, earlier molecular diagnosis can be achieved, even in the first year of life. However, although molecular identification of pathogenic variants in *SCN1A* is possible, it is not sufficient for a diagnosis of Dravet syndrome. Genotype-phenotype correlation is essential given the broad spectrum of *SCN1A*-related epilepsy syndromes, ranging from the self-limited phenotypes within genetic epilepsy with febrile seizures plus (GEFS+)[7] to the profound impairment of early infantile *SCN1A*-DEE.[8] Patients with GEFS+ would not warrant inclusion in a high-risk precision medicine trial. Conversely, neither would patients with early infantile *SCN1A*-DEE, which is caused by a gain-of-function mutation,[9] whereas Dravet syndrome is associated with loss-of-function mutations. Incorrect use of a Dravet precision medicine could be life-threatening for these profoundly impaired patients.

Historically, epilepsy syndromes are described in an initial small cohort of patients and, as more patients are recognized, the phenotypic spectrum of that syndrome expands.[1, 4, 10] Despite many patients having typical clinical presentations, there are patients who have atypical features, often leading to a delay in diagnosis. These observations emphasize the need for evidence-based diagnostic criteria based on large cohorts of patients.

We aimed to define the full phenotypic spectrum of *SCN1A*-positive Dravet syndrome based on deep phenotyping

Key Points

- Dravet syndrome has broader phenotypic limits than often recognized, highlighting the need for evidence-based epilepsy syndrome definitions.
- The initial seizure in Dravet syndrome is febrile in only 55% of patients, and 3% of patients never have seizures with fever.
- More than 50% of patients with Dravet syndrome present with a tonic-clonic seizure, whereas only 35% present with a hemiclonic seizure.
- Only one-third of patients present with status epilepticus, and 7% of patients never have status epilepticus.
- Age at onset in Dravet syndrome can occur up to 19 months of age in patients with heterozygous *SCN1A* pathogenic variants.

of a large cohort of patients. These data will inform evidence-based diagnostic criteria to enable early recognition of Dravet syndrome and facilitate involvement in precision medicine trials.

2 | PATIENTS AND METHODS

2.1 | Patients

Patients with *SCN1A*-related epilepsies were recruited to the University of Melbourne Epilepsy Genetics Research Program between 1995 and 2020, referred by neurologists from Australia and internationally. Patients with *SCN1A*-epilepsies, including Dravet syndrome, GEFS+, myoclonic-atonic epilepsy, and early infantile *SCN1A*-DEE, were reviewed by the authors who are all experts in diagnosis of Dravet syndrome. Only patients with Dravet syndrome were included, whereas patients with other phenotypes were excluded from the study.[7, 8] We searched the literature using the term "Dravet syndrome" and the Medical Subject Headings (MeSH) thesaurus terms "phenotype" or "syndrome" before September 10, 2020 to identify published patients with Dravet syndrome associated with mosaic *SCN1A* pathogenic variants and patients with *SCN1A* mutations with onset after age 12 months.

The Austin Health Human Research Ethics Committee approved the study. Written informed consent was obtained from the patients, or their parents or legal guardians if the patients were younger than 18 years of age or had intellectual disability. Written patient consent forms are archived at the senior author's institution. Individual-level data and clinical data have been deidentified for publication. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

2.2 | Study design

We analyzed patient data by detailed in-person clinical consultation where possible, and also interviewed parents using a validated seizure questionnaire[11] together with medical record review; prospective and retrospective data were analyzed. We determined the age, nature, duration, and temperature of the first seizure for each patient; the timing and duration of the first five consecutive seizures; and age at onset of additional seizure types that evolved over the patient's life, where possible. Seizure types were classified according to the 2017 International League Against Epilepsy (ILAE) classification.[1, 12] Intellectual outcome was determined by neuropsychological assessment or from reports of developmental milestones and school performance. The age at which developmental plateauing or regression occurred was ascertained according to parental and clinician report. The pathogenicity of SCN1A variants was classified according to the American College of Medical Genetics guidelines.[13] Frequency calculations were determined using all patients with the available information for each feature to account for missing data.

3 | RESULTS

Our research program included 261 patients with SCN1A pathogenic variants. Of these, 209 had Dravet syndrome, 44 had GEFS+,[7] one had epileptic spasms,[14] and 7 had early infantile SCN1A-DEE.[8]

We identified 205 of 209 patients with SCN1A-Dravet syndrome with clinical data available for analysis (115 female, 56%). The cohort had a median age at study of 8.5 years (range 10 months to 60 years); 25 patients (12%) were deceased (Table S1).

3.1 | Age at first seizure

Our cohort had a median age at seizure onset of 5.7 months (range 1.5 to 20.6 months, Figure 1A). Onset before 3 months of age occurred in 10 patients, including the youngest two patients at 6 to 7 weeks.

Five patients had seizure onset after 12 months: at 13, 13, 18, 19, and 20 months (Table S1). The patient with the latest onset at 20 months was mosaic for her SCN1A pathogenic variant (Patient 171; 22% p.Val1390Met allele frequency in lymphocyte DNA). In contrast, our three other patients with mosaicism had seizure onset at 6, 10, and 13 months.

Our literature search revealed an additional nine patients with onset between age 13 months and 18 months.[15–17] Conversely, in two articles reporting 10 patients with SCN1A mosaicism (13%–40% allele frequency) associated with Dravet syndrome, all had onset by age 12 months.[18, 19] Taken together, our findings extend the seizure-onset age in Dravet syndrome to 19 months in patients with heterozygous pathogenic SCN1A variants.

3.2 | Initial seizure type

In 195 of 205 patients (95%), information regarding the initial seizure type was available. Contrary to the classical description of onset with hemiclonic seizures, the most common presentation was a tonic-clonic seizure in 101 of 195 (52%, Table 1, Figure 1B). The second most frequent presentation was a hemiclonic seizure in 69 of 195 patients (35%), followed by rare patients with focal impaired awareness seizures (FIAS) (10/195, 5%), myoclonic seizures (7/195, 4%), tonic seizures (1/195, 0.5%), or absence seizures (1/195, 0.5%). Multiple seizure types occurred at onset in 6 of 195 patients (3%).

Fever is considered a hallmark of the initial seizure in Dravet syndrome; however, only 102 of 184 (55%) had a fever with their first seizure based on parent or clinician report. Formal documentation of the temperature by parents or medical staff was available for 52 of 205 patients (25%) and 36 of 52 (69%) had a temperature of ≥38 degrees Celsius. Vaccination-related seizure onset (within 2 days of vaccination) occurred in 55 of 119 patients (46%), of whom 29 (53%) were febrile and 19 (34%) were afebrile; 7 (13%) did not have data regarding temperature at onset. It is important to note that 5 of 179 individuals (3%) never had seizures triggered by fever.

Infants with Dravet syndrome classically present with status epilepticus. We found that the first seizure lasted 30 minutes or more in only 56 of 164 (34%) of our cohort (Figure 1C, Table 1). The median duration of the first seizure across the cohort was 15 minutes (ranging from a few seconds to 3 hours), with 45 of 164 patients (27%) having initial seizures lasting 5 minutes or less (28/164, 17% patients ≤3 minutes). Of the remaining cohort, 39 of 164 (24%) had seizures lasting 6–15 minutes, whereas 24 of 164 (15%) had seizures lasting
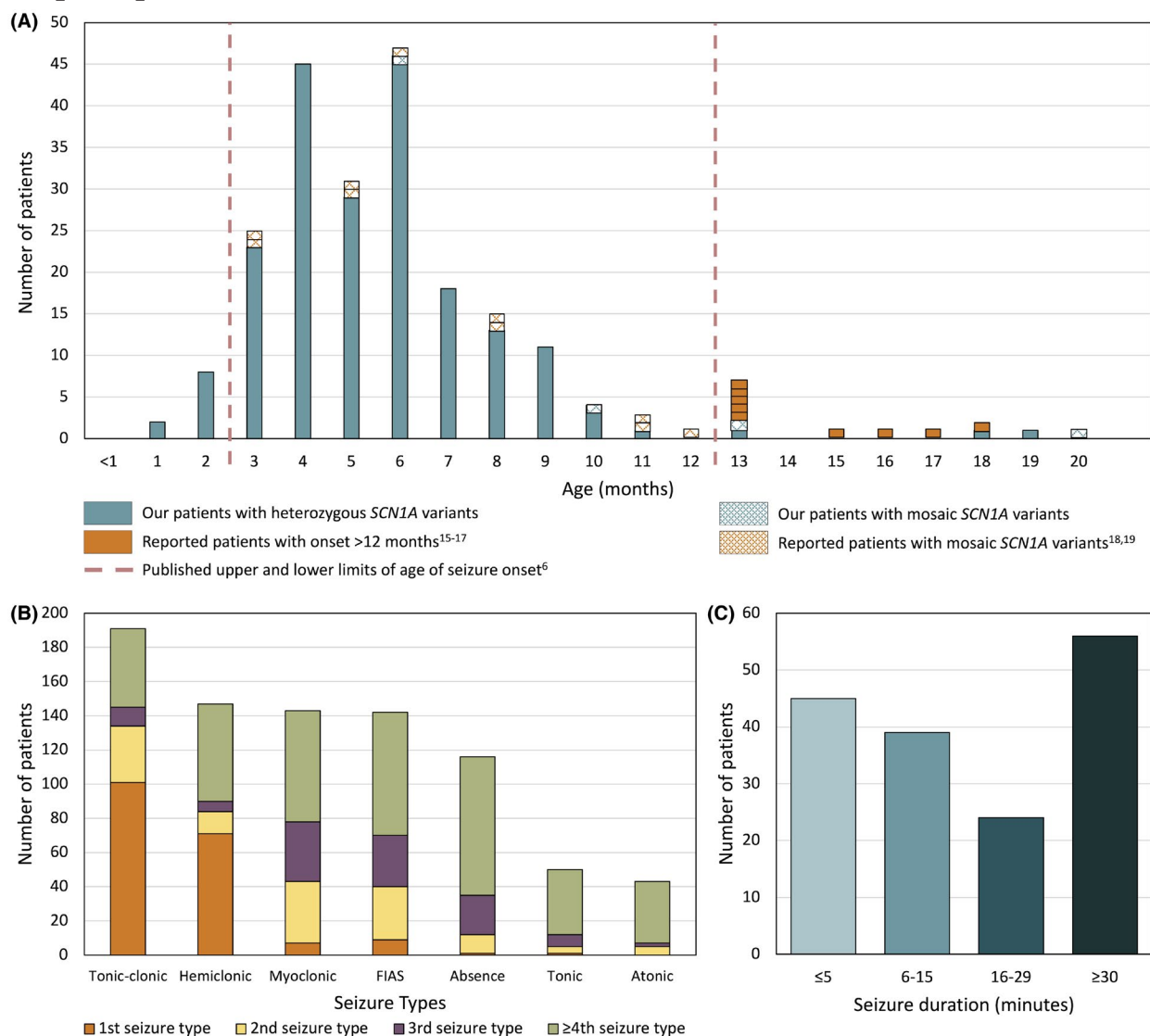
FIGURE 1 (A) Age at seizure onset in our cohort of 205 patients with *SCN1A*-Dravet syndrome together with published patients with onset after 12 months or with pathogenic mosaic *SCN1A* variants. (B) First, second, third, and fourth or more seizure type to develop in patients. (C) Duration of first seizure in 164 patients with *SCN1A*-Dravet syndrome

16–29 minutes. One hundred and sixty-seven of 188 patients (89%) had a single seizure in the first 24 hours.

3.3 | Time between first five seizures

The median time between the first and second seizure was 30 days (data available for 132/205, 64%), with the time interval ranging from 4 hours to 8 months (Figure 2A). For the second to third seizure, the median interval was also 30 days (101/205, 49%), with a similarly broad range of 2 days to 11 months. The interval between the third and fourth seizure then decreased to a median of 21 days (79/205, 39%; range <1 day to 5.6 months), and 24 days between the fourth and fifth seizure (70/205, 34%; range 15 hours to 3 months).

3.4 | Evolution of additional seizure types

Hemiclonic seizures are considered the hallmark seizure type of Dravet syndrome, yet only 147 of 201 (73%) of our cohort had hemiclonic seizures (Table 1, Figure 1B). For the 84 of 147 individuals (57%) in whom lateralization was known, 13 of 84 (16%) had hemiclonic seizures involving only one side, whereas the remaining patients had hemiclonic seizures involving either side independently. The most frequent seizure type was tonic-clonic, occurring in 191 of 200 patients (96%), followed by myoclonic seizures (143/200, 72%), FIAS (142/196, 72%), absence (116/200, 58%), tonic (50/190, 26%), and atonic seizures (43/194, 22%, Figure 1B).

Status epilepticus is frequent in Dravet syndrome. We found that, over time, 186 of 200 patients (93%) had status

TABLE 1 Clinical features of 205 patients with *SCN1A*-Dravet syndrome

		Percentage	Number of patients	Number of patients with data available
Female		56%	115	205
Characteristics of first seizure				
Tonic-clonic		52%	101	195
Hemiclonic		35%	69	195
Focal impaired awareness		5%	10	195
Myoclonic		4%	7	195
Tonic-clonic + myoclonic		2%	4	195
Hemiclonic + myoclonic		1%	2	195
Absence		0.5%	1	195
Tonic		0.5%	1	195
Febrile		55%	102	184
Status epilepticus (≥30 min)		34%	56	164
Duration 5 min or shorter		27%	45	164
>1 seizure in 24 h		11%	21	188
Additional seizure types and median age of onset (range)				
Tonic-clonic	6 m (1.6 m−15 y)	96%	191	200
Convulsive status epilepticus	7.5 m (3 m−11.2 y)	89%	178	199
Hemiclonic:	6.1 m (1.5 m−9.8 y)	73%	147	201
Alternating sides		84%	71	84
Always the same side		16%	13	84
Myoclonic	12 m (2.5 m−10 y)	72%	143	200
Focal impaired awareness	18 m (3 m−35.7 y)	72%	142	196
Absence	20 m (6 m−7.6 y)	58%	116	200
Tonic	3 y (3.7 m−25.4 y)	26%	50	190
Nonconvulsive status epilepticus	3.6 y (3 m−25.5 y)	24%	43	178
Atonic	2 y (5 m−7 y)	22%	43	194
Fever sensitive seizures		97%	174	179
Number of different seizure types				
One		1.5%	3	205
Two		11%	22	205
Three		19%	38	205
Four		31%	64	205
Five		27%	56	205
Six		9%	19	205
Seven		1.5%	3	205
Developmental characteristics				
Normal development before seizures		98%	194	198
Ambulant		99%	185	187
Verbal		97%	184	190
No intellectual disability		1%	1	143
Borderline IQ		6%	8	143
Mild intellectual disability		22%	32	143
Moderate intellectual disability		27%	38	143

TABLE 1 (Continued)

	Percentage	Number of patients	Number of patients with data available
Severe intellectual disability	45%	64	143
Autism spectrum disorder	38%	39	103
First epileptiform EEG abnormalities recorded			
Generalized spike-wave	44%	61	139
Focal/multifocal	42%	59	139
Generalized spike-wave + focal/multifocal	14%	19	139

Abbreviations: EEG, electroencephalography; h, hours; IQ, intelligence quotient; m, months; min, minutes; y, years.

epilepticus; 178 of 199 (89%) had convulsive status epilepticus; and 43 of 178 (24%) had non-convulsive status epilepticus.

Multiple seizure types are usual in Dravet syndrome; 202 of 205 patients (99%) developed multiple seizure types. Myoclonic, FIAS, and absence seizures occurred earlier in their disease course (Figure 1B). Of the cohort, 64 of 205 (31%) had four seizure types and 56 of 205 (27%) had five seizure types (range 1–7, Table 1). Tonic and atonic seizures typically occurred in patients with at least three other seizure types.

In Dravet syndrome, the onset of additional seizure types is classically described between 1 and 4 years of age.[4] In our cohort, the median age at onset of the second seizure type was 9.1 months (range 3 months to 25.4 years, data available for 130 of 202 patients [64%], Figure 2B) where 88 of 130 patients (68%) developed a second seizure type before 12 months. The median age at onset of the third seizure type was 15.5 months (range 4 months to 8.2 years, data available for 86 of 179 patients [48%]).

At the onset of tonic-clonic seizures, hemiclonic seizures, and FIAS, we reviewed the duration of each seizure type. FIAS lasted ≤5 minutes in 20 of 35 patients (57%). In contrast, convulsive seizures were longer, lasting between 6 and 29 minutes in 21 of 45 patients (47%) having tonic-clonic seizures and 17 of 33 individuals (52%) having hemiclonic seizures (Figure 2C).

3.5 | Developmental course

Development in Dravet syndrome is described as normal in the first year of life followed by developmental slowing or regression.[4] In our cohort, 194 of 198 (98%) had normal development prior to seizure onset (Table 1). The remaining 4 of 198 patients (2%) had a history of developmental delay prior to seizure onset; all had truncation mutations, consistent with loss-of-function, and severe intellectual disability with seizure onset from 2–6.5 months.

Although the median age at developmental slowing or plateauing was 20 months (range 3 months to 5 years; data available for 104/202 patients [52%]), we found that 28 of 104 (27%) showed slowing in the first year of life, which is earlier than usually accepted (Figure 3). At the mild end, there were 2 of 104 patients (2%), who did not show definite slowing until 5 years of age. Lack of independent walking occurred in 2 of 187 patients (1%) and 6 of 190 patients (3%) were nonverbal. Eight patients had borderline intellect and one patient had emerging learning difficulties at the time of his death at age 5 years.

3.6 | EEG findings

One hundred and thirty-nine of 205 patients (68%) had EEG results available. The median age at first EEG showing epileptiform abnormalities was 26 months (range 4 months to 18 years). The first epileptiform EEG findings were generalized spike-wave (GSW) in 61 of 139 patients (44%), focal or multifocal epileptiform abnormalities in 59 of 139 (42%), and GSW with focal or multifocal epileptiform abnormalities in 19 of 139 (14%, Table 1).

3.7 | MRI findings

MRI brain reports, available for 189 of 205 patients (92%), were normal in 130 of 189 patients (69%). In the 59 with abnormalities, only 5 had hippocampal sclerosis, with the remainder having nonspecific findings (Table S1).

3.8 | Mortality

Twenty-five of 205 patients (12%) died at a median of 6.5 years (range 11 months to 39 years, Figure 4). Causes of death included sudden unexpected death in epilepsy (SUDEP) or probable SUDEP in 13 of 25 (52%),[20] cerebral edema in 5 of 25 (20%),[21] accidental drowning in 4 of 25
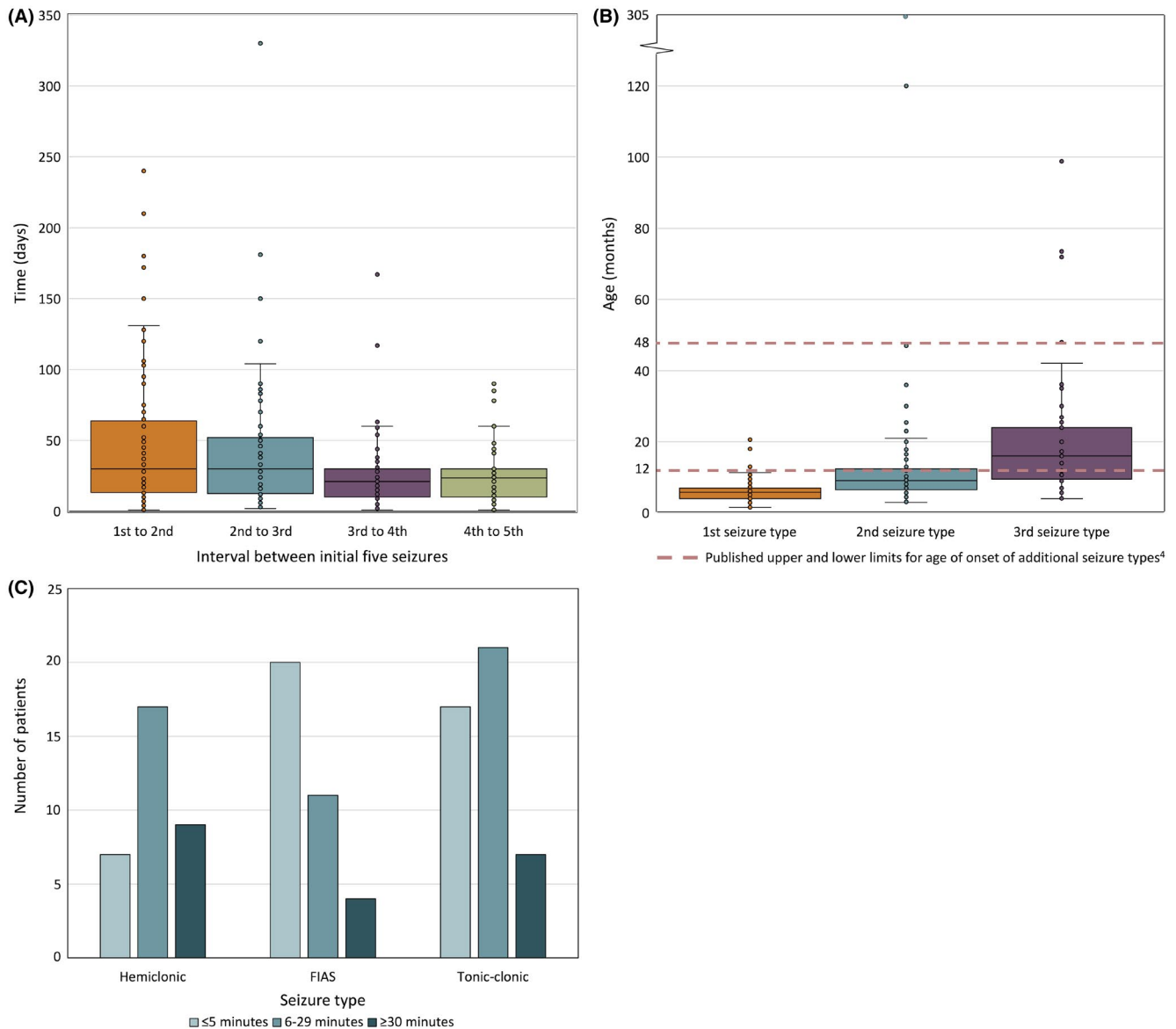
FIGURE 2 (A) Days between each of the first five seizures. Boxplots show individual data points (dots), median (solid line), interquartile range (boxes), and 1.5× the interquartile range (whiskers). (B) Age at onset of the first three seizure types. Boxplots show individual data points (dots), median (solid line), interquartile range (boxes), and 1.5× the interquartile range (whiskers). Dashed lines denote published upper and lower limits for age of onset of additional seizure types.[4] (C) Average duration of initial hemiclonic, focal impaired awareness seizures, and tonic-clonic seizures in 33, 35, and 45 patients with available data, respectively

(16%), status epilepticus in 2 of 25 (8%) and one patient died of asphyxia due to aspiration of gastric contents, which may have occurred during a seizure.

4 | DISCUSSION

The recent revolution in next generation sequencing has led to a remarkable increase in genetic diagnoses in individuals with DEEs. The prototypic DEE, Dravet syndrome, is associated with *SCN1A* pathogenic variants in 92% of our cohort of 228 patients with Dravet syndrome, whereas 8 patients had pathogenic variants in other genes (*GABRA1* in 3 patients

and one each of *GABRG2*, *SCN1B*, *STXBP1*, *HCN1*, and *KCNA2*) and 11 did not have a pathogenic variant identified. Understanding how Dravet syndrome presents is essential for early, accurate diagnosis of patients, which, together with an understanding of the natural history, is critical for evaluating the impact of novel therapies on disease course. Never has this been more pertinent than with the imminent promise of precision medicine trials, following recent success in murine models of Dravet syndrome.[5] As molecular studies are increasingly performed at seizure onset in infancy, interpreting their significance depends on the patient's phenotype. For an *SCN1A* pathogenic variant, the distinction between a benign self-limited outcome such as GEFS+,[7] and a more
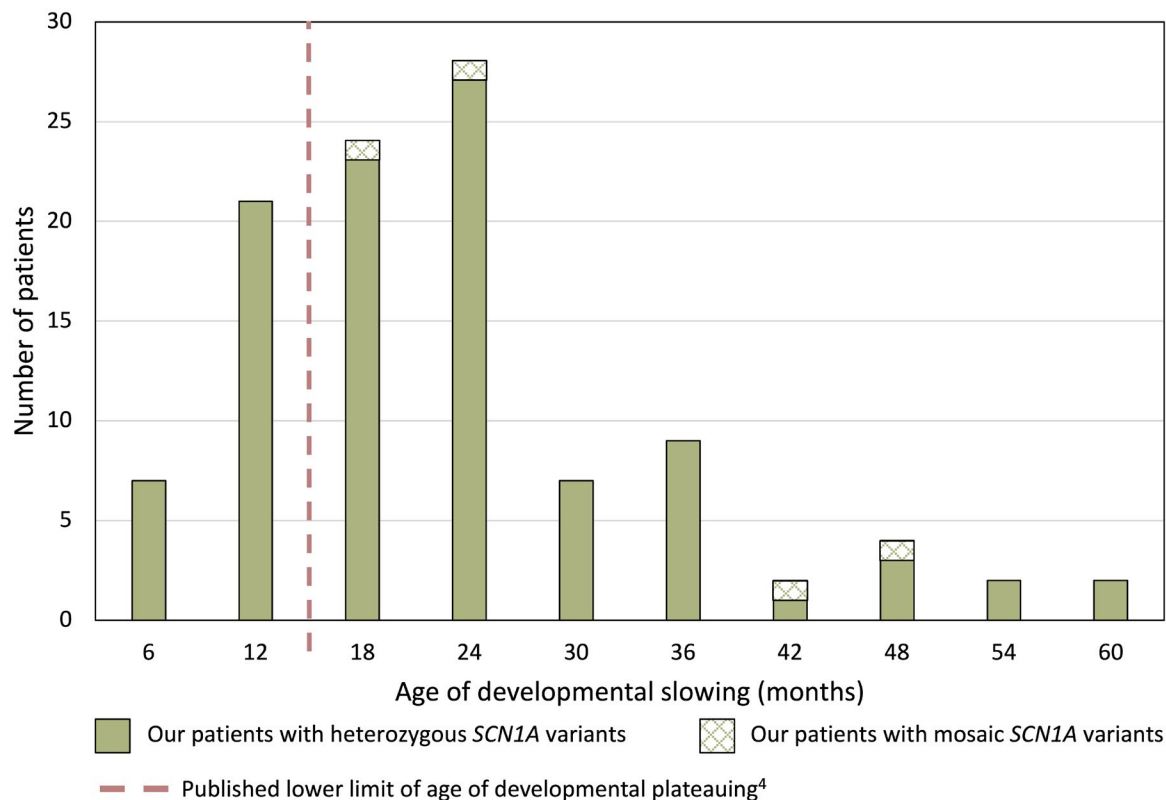
FIGURE 3 Age at onset of developmental plateauing in 106 patients with *SCN1A*-Dravet syndrome

severe outcome due to a loss-of-function mutation in Dravet syndrome or a gain-of-function mutation in early infantile *SCN1A*-DEE is crucial.[8, 9]

Epilepsy syndromes are defined initially by recognition of seizure types that co-occur, developmental course, EEG, and imaging features.[1] With increasing recognition of an epilepsy syndrome, the phenotypic spectrum is often expanded with relatively small series of cases. As more patients are identified, the limits of the diagnostic criteria may be drawn into question. Here, we carefully dissect phenotypic features in patients with *SCN1A*-positive Dravet syndrome. By drawing on a large, well-phenotyped cohort, we distil the key elements underpinning a diagnosis of Dravet syndrome and provide a diagnostic algorithm (Figure 5). This will allow clinicians to make an earlier diagnosis in patients who are not presenting with the heretofore considered classical phenotype.

Our findings crystallize the defining features of Dravet syndrome and dispel some of the rigid boundaries previously used. First, some authors state that age at onset must be in the first year of life.[22] In our cohort, five patients had seizure onset beyond the first year of life (13–20 months), confirming previous reports of nine patients (1/6, 2/26, 6/333) with onset from 13 to 18 months (Figure 1A).[15–17] Thus we extend the age at seizure onset in heterozygous *SCN1A*-Dravet syndrome to 19 months. Of interest,

mosaicism can be associated with later onset at 20 months (22% allele frequency) or under 1 year (13%–40% allele frequency).[18, 19] Another of our patients with 30% mosaicism had onset at 10 months but a more severe seizure phenotype, with 600 convulsive seizures per year and moderate intellectual disability. Considering early seizure onset, our 10 patients with onset before age 3 months did not have the profound impairment or movement disorder that are characteristic of early infantile *SCN1A*-DEE.[8]

Second, and somewhat surprisingly, only 55% of our patients had a fever at seizure onset, contrasting with previous studies (57%–74%[22–24]) and showing that the expectation of fever-related seizures at onset is not met in almost half the patients with Dravet syndrome. In infants with afebrile seizure onset, other factors may trigger the first seizure, such as vaccination-related onset, which we reported previously in one-third of patients with Dravet syndrome.[25] In our cohort, 46% of patients had vaccination-related seizure onset, 35% of whom were afebrile. Although ongoing seizures are often triggered by fever in Dravet syndrome,[4, 25] 3% of our cohort never had a seizure with fever.

Third, the most common type of seizure at onset was a tonic-clonic seizure (52%), with hemiclonic seizures the second most frequent seizure type (35%). This contrasts with the classical description of an infant with Dravet syndrome
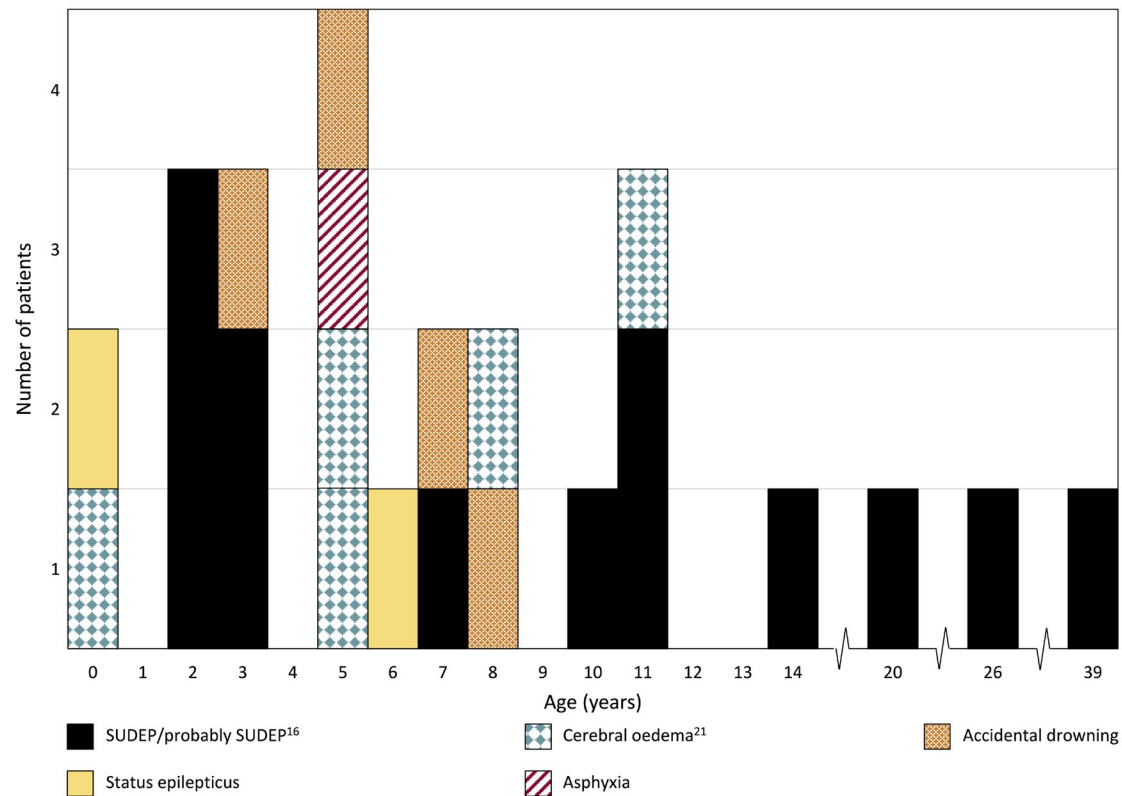
FIGURE 4 Age and cause of death in 25 patients from our cohort with *SCN1A*-Dravet syndrome

presenting with a hemiclonic seizure. Sixteen percent of those who had hemiclonic seizures always had seizures on the same side. Furthermore, only 73% of our patients had hemiclonic seizures over the course of their disease, highlighting that hemiclonic seizures are not an essential feature of Dravet syndrome.[23, 24, 26]

Fourth, when Dravet syndrome begins with nonconvulsive seizures, convulsive seizures are mooted to follow within days or weeks.[4] Of the 18 patients who had nonconvulsive seizures at onset, 7 had onset of convulsive seizures within 1 month. However, 10 of 18 patients did not have onset of convulsive seizures until 3–9 months after their initial nonconvulsive seizures (age at onset of convulsive seizures unknown for one patient).

Fifth, contrary to the teaching that infants with Dravet syndrome present with status epilepticus, we found that 66% of our cohort had seizures lasting less than 30 minutes at onset, mirroring the 75% and 66% of patients in Italian and French studies.[22, 27] The median duration was 15 minutes overall, and 27% of patients presented with seizures lasting 5 minutes or less. Some authors suggest that Dravet syndrome is unlikely in patients with onset of status epilepticus after 18 months[28]; however, 18 of our patients had their first episode of status epilepticus after age 18 months.
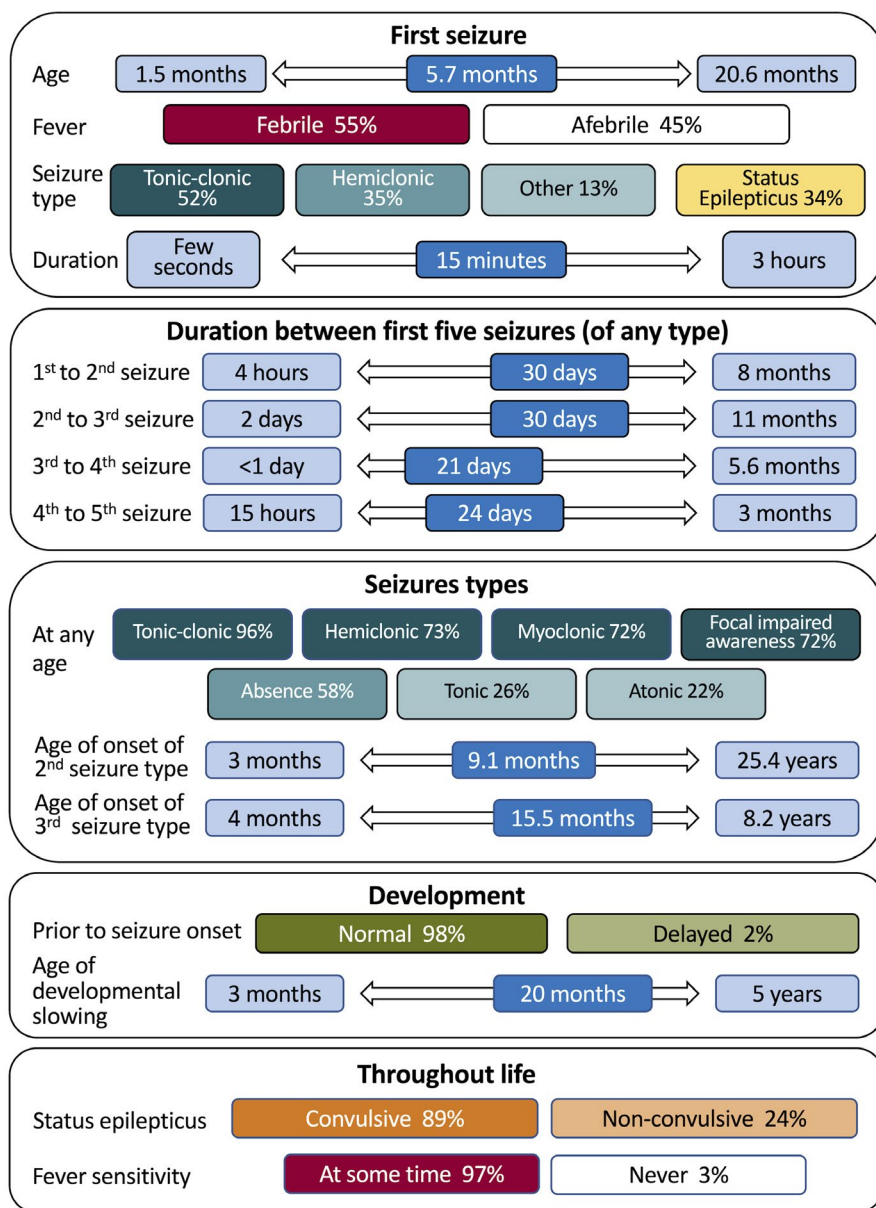
Sixth, the time between the first three seizures may be many months, thereby hampering consideration of a Dravet

syndrome diagnosis, for which seizures are usually expected to occur more frequently.[4] The median time between the first and second seizure, and the second and third seizure was brief (30 days); however, the range was broad from 4 hours to 11 months. A diagnosis of Dravet syndrome in a patient whose first three seizures occurred at 6 and 14 and 22 months would often not be contemplated. The interval between the subsequent seizures tightened up considerably, with all patients having their fourth and fifth seizures within 6 months.

Seventh, additional seizure types in Dravet syndrome are usually stipulated as beginning between 1 and 4 years of age.[4] Surprisingly, we found an earlier median age at onset of a second seizure type at 9.1 months and the third seizure type at 15.5 months. This highlights the need for clinicians to ask carefully about specific seizure types that may have escaped recognition by the family. Equally though, the second seizure type may not emerge until as late as the third decade.

Although the usual diagnostic criteria for Dravet syndrome state that development is normal in the first year of life,[4] we found that 27% of our cohort showed developmental slowing by 12 months. Three patients were never normal, and a fourth patient had developmental delay from 3 months with seizure onset at 5 months. Conversely, slowing did not emerge until 5 years of age in two patients. Developmental criteria should therefore be less rigid than is currently accepted.

Diagnostic algorithm for Dravet syndrome

FIGURE 5   Diagnostic algorithm for *SCN1A*-Dravet syndrome

First seizure

Age	1.5 months	5.7 months	20.6 months
Fever	Febrile 55%	Afebrile 45%	
Seizure type	Tonic-clonic 52%	Hemiclonic 35% · Other 13%	Status Epilepticus 34%
Duration	Few seconds	15 minutes	3 hours

Duration between first five seizures (of any type)

1st to 2nd seizure	4 hours	30 days	8 months
2nd to 3rd seizure	2 days	30 days	11 months
3rd to 4th seizure	<1 day	21 days	5.6 months
4th to 5th seizure	15 hours	24 days	3 months

Seizures types

At any age: Tonic-clonic 96% · Hemiclonic 73% · Myoclonic 72% · Focal impaired awareness 72% · Absence 58% · Tonic 26% · Atonic 22%

Age of onset of 2nd seizure type	3 months	9.1 months	25.4 years
Age of onset of 3rd seizure type	4 months	15.5 months	8.2 years

Development

Prior to seizure onset	Normal 98%	Delayed 2%	
Age of developmental slowing	3 months	20 months	5 years

Throughout life

Status epilepticus	Convulsive 89%	Non-convulsive 24%
Fever sensitivity	At some time 97%	Never 3%

In terms of which seizure types occur at which age, we found some interesting differences from previous series. Myoclonic seizures before age 12 months are reportedly rare,[4,29] yet they were seen in 44 patients (22%). Onset of myoclonic seizures before 2 years is said to be a key clinical feature of Dravet syndrome,[30] but this was observed in only 18 patients, or 9% of our cohort. The median age at onset of focal impaired awareness seizures was earlier in our cohort (18 months) compared to others (33–35 months),[4,29,30] and although absence seizures are usually seen in children older than 2 years of age,[30] 35 patients (18%) had onset before 2 years. We found that 26% of patients had tonic seizures with a median onset of 3 years (range 3.7 months to 25.4 years); previous reports suggest that tonic seizures occur in older patients with Dravet syndrome.[27,31,32] We acknowledge that

diagnosis of tonic seizures is challenging without ictal EEG studies, particularly as tonic seizures often occur in sleep and may be very subtle. In addition, 22% of patients had atonic seizures with median onset at 2 years and the latest onset at 7 years.

In 1998 and 2003, German and Japanese authors reported a form of Dravet syndrome in which only convulsive seizures (tonic-clonic and hemiclonic seizures) occurred using the syndromic names of Severe Idiopathic Generalized Epilepsy of Infancy with Generalized Tonic-Clonic Seizures and Intractable Childhood Epilepsy with Generalized Tonic-Clonic Seizures, respectively.[33,34] These patients follow a neurodevelopmental course similar to that of patients with classical Dravet syndrome, including status epilepticus, fever sensitivity, and drug-resistant seizures. Only 8 of 205 (4%) of

our patients had convulsive seizure types alone, akin to this specific Dravet phenotype.

Dravet syndrome carries a well-established mortality of 17% by 20 years of age.[20] Our overall figure was 12% (25 patients) but this likely reflects the young median age of our cohort of 8.5 years. Definite or probable SUDEP occurred in 52% of our deaths, including three adults up to 39 years of age.

Our study has a number of limitations. The diagnosis of Dravet syndrome was based on an understanding of the gestalt of this complex disease by three independent experts. Some of the data were retrospective, which is the case for many patients assessed in studies of DEEs. Although we strived to obtain objective data from the time of presentation (eg, hospital emergency department notes, temperature recordings, seizure durations), we sometimes relied on parental history, which is subject to recall bias. Of interest, 69% of patients with formal documentation of temperature had a fever at seizure onset, whereas only 55% of patients were reported as febrile at seizure onset when data from parental report was included. Limited EEG data were available for review, as 68% patients had early EEG reports available, which reflects the evolution of the seizure disorder that often seems mild at onset.

These data offer an opportunity to understand the key features underpinning a diagnosis of Dravet syndrome due to a *SCN1A* pathogenic variant. The most frequent features were:

1. *SCN1A* pathogenic variant in all (inclusion criteria)
2. Hemiclonic or tonic-clonic seizures (all patients)
3. Seizure onset <12 months (98%)
4. Normal development prior to seizure onset (98% patients with adequate data)
5. Developmental impairment prior to 5 years (98% patients with adequate data)
6. Fever-sensitive seizures (97% patients with adequate data)
7. Tonic-clonic seizures (96% patients with adequate data)
8. Intellectual disability (93% patients with adequate data)
9. Status epilepticus (93% patients with adequate data)

No single clinical feature was common to all patients, except the eventual occurrence of convulsive seizures (ie, hemiclonic or tonic-clonic seizures), making stringent rules regarding the diagnosis of Dravet syndrome challenging to define. We determined that two of the following three features will capture all patients in our cohort with *SCN1A*-Dravet syndrome: hemiclonic and/or tonic-clonic seizures, fever-sensitive seizures, and status epilepticus. It is noteworthy that only 115 of 205 patients (56%) presented with at least two of these three features at onset; yet by 12 months of age, 73% (149/205) and by 2 years of age, 79% (162/205) had developed two of these three features.

A diagnosis of Dravet syndrome is based on a complex gestalt of features, initially recognized by Charlotte Dravet in 1978.[35] Pediatric epileptologists identify patients with Dravet syndrome with a constellation of features, including those who may have features outside the classical criteria commonly taught.[4, 30] In psychiatry, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Revision (DSM-5) emphasizes that diagnosis should allow for integration of diagnostic criteria with clinical judgement, where clinical experience results in a more nuanced understanding of a specific disease.[36] The DSM-IV explicitly states that criteria need to serve as guidelines informed by clinical expertise rather than being applied in a "cookbook fashion."[37] Indeed, a World Health Organization (WHO) survey of psychiatrists found maximal utility where diagnostic manuals allowed flexible guidance based on clinical judgment rather than fixed diagnostic criteria.[38] Here we interrogated a large cohort of patients with Dravet syndrome diagnosed by three clinical experts who understand the gestalt of this complex presentation. We provide data to delineate the broader limits of Dravet syndrome so that evidence-based criteria can be developed and assist less-expert clinicians in making an earlier Dravet syndrome diagnosis.

Our study highlights that epilepsy syndrome definitions need to be based on deep phenotyping of substantial numbers of patients with each specific genetic DEE. As the prototypic DEE, our work and that of others defining cohorts of patients with Dravet syndrome highlight the critical features that underpin a clinical diagnosis. It is notable that patients without all of the classical features of a syndrome need to be used to refine syndromic definitions to paint a true phenotypic picture of the disease. Never has this been more crucial and more relevant to each genetic DEE, as we face the need for early accurate diagnosis in preparation for precision medicine trials.

CONFLICT OF INTEREST

I.E. Scheffer has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia, Rogcon, Chiesi, Encoded Therapeutics, Xenon Pharmaceuticals, and Knopp Biosciences; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, and Eisai; has received funding for

travel from UCB, Biocodex, GlaxoSmithKline, Biomarin, and Eisai; has served as an investigator for Zogenix, Zynerba, Ultragenyx, GW Pharma, UCB, Eisai, Anavex Life Sciences, Ovid Therapeutics, Epigenyx, Encoded Therapeutics and Marinus; and has consulted for Zynerba Pharmaceuticals, Atheneum Partners, Ovid Therapeutics, Care Beyond Diagnosis, Epilepsy Consortium, and UCB. She may accrue future revenue on a pending patent WO2009/086591 (filed: 2008); has a patent for *SCN1A* testing held by Bionomics Inc and licensed to various diagnostic companies (WO/2006/133508), and has a patent for a molecular diagnostic/therapeutic target for benign familial infantile epilepsy (BFIE) [PRRT2] WO/2013/059884. W. Li and A.L. Schneider declare no potential conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.