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Incidence of Dravet Syndrome in a US Population

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abstract

OBJECTIVE: De novo mutations of the gene sodium channel 1α (*SCN1A*) are the major cause of Dravet syndrome, an infantile epileptic encephalopathy. US incidence of DS has been estimated at 1 in 40 000, but no US epidemiologic studies have been performed since the advent of genetic testing.

METHODS: In a retrospective, population-based cohort of all infants born at Kaiser Permanente Northern California during 2007–2010, we electronically identified patients who received ≥2 seizure diagnoses before age 12 months and who were also prescribed anticonvulsants at 24 months. A child neurologist reviewed records to identify infants who met 4 of 5 criteria for clinical Dravet syndrome: normal development before seizure onset; ≥2 seizures before age 12 months; myoclonic, hemiclonic, or generalized tonic-clonic seizures; ≥2 seizures lasting >10 minutes; and refractory seizures after age 2 years. *SCN1A* gene sequencing was performed as part of routine clinical care.

RESULTS: Eight infants met the study criteria for clinical Dravet syndrome, yielding an incidence of 1 per 15 700. Six of these infants (incidence of 1 per 20 900) had a de novo *SCN1A* missense mutation that is likely to be pathogenic. One infant had an inherited *SCN1A* variant that is unlikely to be pathogenic. All 8 experienced febrile seizures, and 6 had prolonged seizures lasting >10 minutes by age 1 year.

CONCLUSIONS: Dravet syndrome due to an *SCN1A* mutation is twice as common in the United States as previously thought. Genetic testing should be considered in children with ≥2 prolonged febrile seizures by 1 year of age.

WHAT'S KNOWN ON THIS SUBJECT: De novo mutations of the sodium channel gene *SCN1A* are the major cause of Dravet syndrome, an infantile-onset epileptic encephalopathy. The incidence of this genetic disorder in the United States is unclear.

WHAT THIS STUDY ADDS: Dravet syndrome due to *SCN1A* mutation is twice as common in the United States as previously thought. Genetic testing should be considered in children with ≥2 prolonged febrile seizures by 1 year of age.

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Dr Wu conceptualized and designed the study; performed data collection, data analysis, and interpretation of data; and drafted the initial manuscript; Drs Sullivan, McDaniel, and Kuzniewicz contributed substantially to the design of the study and to the collection and interpretation of the data and each critically reviewed and revised the manuscript; Dr Meisler contributed substantially to the analysis and interpretation of the data, drafted portions of the manuscript, and critically reviewed and revised the manuscript; Ms Walsh and Ms Li contributed substantially to the design of the study, data collection, and data analysis and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Dravet syndrome (Online Mendelian Inheritance in Man number 607208), previously known as severe myoclonic epilepsy of infancy, is a devastating disorder characterized by intractable epilepsy and poor neurodevelopmental outcome. Hallmarks of this disorder include onset before 12 months of age; normal development before seizure onset; frequent and prolonged febrile seizures; refractory hemiclonic, myoclonic, and generalized tonic-clonic seizures; and later neurodevelopmental impairments including cognitive deficits and ataxia.[1–3] A mutation in the voltage-gated sodium channel 1α gene (*SCN1A*) is present in up to 85% of children with Dravet syndrome.[4–7] Making an early diagnosis of Dravet syndrome is critical to providing optimal treatment, because the management of Dravet syndrome differs from that of febrile seizures and other epilepsy syndromes.[2,8–10] However, because the initial clinical presentation can mimic benign atypical or complicated febrile seizures,[11,12] and because many pediatricians may not be familiar with this genetic epileptic encephalopathy, early recognition and diagnosis of Dravet syndrome often remain a challenge.

The incidence of Dravet syndrome in the United States is unclear. In the US National Collaborative Perinatal Project of the 1960s and 1970s, only 1 in 40 000 infants was diagnosed with this disorder.[13] Similarly, the rate of Dravet syndrome in Sweden has been estimated at 1 in 33 000.[14] The incidence of *SCN1A* mutations causing Dravet syndrome in Europe ranges from 1 in 41 000[15] to 1 in 22 000.[16] There have been no epidemiologic studies of DS in the United States since the advent of genetic testing. Thus, we set out to determine the incidence of Dravet syndrome in a recent cohort of California births.

METHODS

This is a retrospective, population-based cohort study of all infants born at 15 Kaiser Permanente Northern California (KPNC) hospitals between January 1, 2007, and June 30, 2010. KPNC is an integrated community medical care delivery system that serves 3.7 million members, comprising nearly half of the insured population of Northern California. The study was approved by the institutional review boards at KPNC and the University of California, San Francisco.

Patients with Dravet syndrome typically present with seizures by 1 year of age and continue to have refractory epilepsy after age 2. We performed an electronic search for patients who had ≥2 inpatient or outpatient encounters generating a diagnosis of seizure, ie, epilepsy (International Classification of Diseases, 9th revision [ICD-9], 345), convulsion (ICD-9 780.39), or febrile convulsion (ICD-9 780.31), before 12 months of age and who were also prescribed an anticonvulsant medication at 24 months of age. We excluded those whose first seizure diagnosis occurred at an encounter during the neonatal period (ie, <1 month).

A child neurologist reviewed all neurology, genetics, pediatrics, and therapy medical notes, as well as neurophysiology and neuroimaging reports, to determine whether the child met clinical criteria for Dravet syndrome. A diagnosis of clinical Dravet syndrome was given to patients who met at least 4 of 5 inclusion criteria, as follows: (1) normal or near-normal cognitive and motor development before seizure onset; (2) ≥2 febrile or afebrile seizures before 1 year of age; (3) seizure semiology consisting of myoclonic, hemiclonic, or generalized tonic-clonic seizures; (4) ≥2 seizures lasting longer than 10 minutes; and (5) failure to respond to first-line antiepileptic drug therapy with continued seizures after 2 years of age. All individuals in the birth cohort were >3 years of age at the onset of the study.

From medical records, we abstracted data regarding patient demographic characteristics; type, duration, and frequency of seizures; and brain MRI and EEG findings. We excluded patients with a brain malformation, traumatic or hypoxic-ischemic brain injury, brain tumor, neurocutaneous syndrome, other known genetic/metabolic disorders, and other epilepsy syndromes such as infantile spasms and malignant migrating seizures. All identified cases were discussed by the pediatric epileptologists (J.S., S.S.M.) and child neurologist (Y.W.W.) to achieve a consensus opinion regarding the clinical diagnosis of Dravet syndrome.

Patients who met the criteria for clinical Dravet syndrome had their *SCN1A* gene sequenced as part of routine medical care. All identified *SCN1A* gene abnormalities were evaluated by consideration of evolutionary conservation, affected protein domain, previous patient mutations, and results from the pathogenicity prediction programs Polyphen2 and SIFT.[17,18] Two patients without a previous diagnosis of Dravet syndrome were identified in the course of this study to fit clinical criteria and were found subsequently to have de novo *SCN1A* mutations.

To ensure complete case ascertainment, we solicited additional patients with Dravet syndrome from the 12 treating child neurologists at KPNC and performed an electronic search of all KPNC medical records for the words "Dravet" and "*SCN1A*." These procedures identified no additional cases of Dravet syndrome in the study cohort. We compared clinical characteristics in patients with and without Dravet syndrome using χ^2 and Fisher's exact test.

RESULTS

Of 125 547 births in the study population, 730 infants (0.6%) received ≥2 seizure diagnoses by 12 months of age. Infants who were not prescribed an anticonvulsant medication after age 2 (n = 492) and those whose first seizure diagnosis occurred during the neonatal period

(n = 149) were excluded. The remaining 89 patients underwent further medical record review.

Eight infants met the study criteria for clinical Dravet syndrome, yielding a population incidence of 1 per 15 700 births (95% confidence interval: 1 per 8000 to 1 per 31 000 births). The remaining 81 patients whose records were reviewed were excluded from the diagnosis of Dravet syndrome for the following reasons: they did not fulfill at least 4 inclusion criteria (n = 27), their seizures began before 30 days of age (n = 14), their brain MRI revealed a brain malformation (n = 14), no anticonvulsant medication was prescribed after age 2 (n = 12), or they were diagnosed with a different genetic/metabolic disorder (n = 11) or hypoxic-ischemic brain injury (n = 3).

The 8 patients with clinical Dravet syndrome were all born at term gestation. Their race/ethnicity was African-American (3), white (2), Asian (1), Hispanic (1) and other (1). Seizures occurred in 7 (88%) of the children by 8 months of age (Table 1), and all experienced febrile seizures in the first year of life. None reported seizures that were induced by hot water. All 8 patients had a normal EEG at presentation. Brain MRI performed at age 4 to 13 months was normal in 7 and abnormal in 1 (mildly thin corpus callosum) patient. However, 3 patients who had a repeat MRI at 26 to 36 months of age developed the following abnormalities: global atrophy, delayed myelination, and a single T2 hyperintense white matter lesion in the anteromedial temporal lobe.

Mean maternal age was not statistically different in mothers of children with Dravet syndrome compared with all mothers in the study population (31.3 vs 29.7 years; P = .65). Fathers of children with Dravet syndrome spanned the ages of 24 to 45 years, and 3 fathers were >40 years old. However, paternal ages of the entire study population were not available for this study.

Among 89 infants who had ≥2 inpatient or outpatient encounters for seizures by 12 months, and who were also prescribed anticonvulsants at 24 months, record review revealed several clinical characteristics that were associated with increased risk of Dravet syndrome. Having a prolonged seizure (>10 minutes) was more common in patients with Dravet syndrome than in those without this diagnosis (50% vs. 6%; P = .004). Only 2 patients with Dravet syndrome did not have a prolonged seizure by 12 months of age, and the other 6 affected patients had an average of 2.8 (range: 1–8) prolonged seizures by age 12 months. All affected patients had febrile seizures, and the number of febrile seizures before 12 months was significantly higher in those with Dravet syndrome than in those without this condition (mean: 2.8 vs 0.7; $P < .001$). Patient gender and family history of seizures were not associated with risk of Dravet syndrome.

Six of the 8 patients with Dravet syndrome carried de novo mutations of *SCN1A* on the basis of parental testing. All 6 de novo mutations were predicted to be pathogenic (Table 2 and below), yielding an incidence of *SCN1A*-associated cases of Dravet syndrome of 1 per 20 900 (95% confidence interval: 1 per 9600 to 1 per 45 700). One patient (patient 3) inherited a single nucleotide substitution from an unaffected parent that did not alter the encoded amino acid (p.Glu602Glu) and was not considered to be pathogenic; this patient had no additional pathogenic mutations identified on comprehensive epilepsy gene panel testing.[19] The patient with no *SCN1A* gene abnormalities (patient 8) was found to have no pathogenic mutations on epilepsy gene panel testing but did have 2 variants of unknown significance, one in the *MECP2* gene and one in the *POLG* gene, both of which were inherited from a parent.

The 6 de novo mutations include 4 missense mutations, 1 in-frame insertion of 9 amino acids, and 1 deletion of a single amino acid (Table 2). None of these mutations have been observed previously, but 3 occur at amino acid residues that were previously mutated in patients with Dravet syndrome.[20] Five of the de novo variants are predicted to be pathogenic because they alter amino acid residues that are highly conserved in invertebrate and vertebrate sodium channels and are located in protein domains that are essential for channel function. The sixth is a 9-amino acid insertion into an evolutionarily conserved region of cytoplasmic loop 2 that is located only 20 residues downstream of transmembrane segment D2S6. None of these de novo mutations are present in the Exome Aggregation Consortium database of 60 000 exomes from individuals lacking severe pediatric disorders (http://exac.broadinstitute.org/).

DISCUSSION

We found that clinical Dravet syndrome occurs in 1 in 15 700 births and is more than twice as common as previously reported in the United States.[13] Most but not all patients with clinical Dravet syndrome have an underlying mutation in the *SCN1A* gene to account for their symptoms. In our study, 6 of 8 patients who met the clinical criteria for Dravet syndrome were found to have a pathogenic *SCN1A* mutation. Our estimated incidence of *SCN1A*-associated Dravet syndrome is therefore 1 in 20 900 births, which is also higher than previous estimates from Europe, which ranged from 1 in 22 000 to 1 in 41 000.[15,16]

Multiple prolonged febrile seizures in an otherwise well child, usually starting by 8 months of age, are the early clinical hallmarks of Dravet syndrome. Other typical features of this devastating disorder include refractory and multiple seizure types

TABLE 1 Clinical Characteristics of 8 Patients With Clinical Dravet Syndrome Identified Within a US Birth Cohort, 2007–2010

	SCN1A Abnormal	Age at Onset, mo	Seizure Types	Febrile Seizures by 12 Months, *n*	Prolonged Seizures by 12 Months, *n*	Brain MRI Findings (Age at Last MRI, mo)	Follow-up, y	Developmental Abnormalities
1	Yes	3	GTC, hemiclonic, focal	3	2	Global atrophy (26)	3.2	Language delay, motor delay
2	Yes	4	GTC, myoclonic, focal	6	1	Myelination delay (36)	5.8	Language delay, autism
3	Yes	4	Myoclonic, focal	2	2	Normal (9)	5.9	Language delay, cognitive dysfunction
4	Yes	6	GTC, hemiclonic, focal	4	3	Normal (9)	6.0	Cognitive dysfunction
5	Yes	6	Myoclonic, hemiclonic, focal	1	2	Normal (23)	3.9	Behavior problems, special education
6	Yes	6	GTC, focal	2	1	Thin corpus callosum (6)	5.4	Language delay, motor delay
7	Yes	8	GTC, focal	2	0[a]	Normal (13)	3.5	Language delay, behavior problems
8	No	10	GTC, tonic	2	0[a]	White matter lesion (32)	5.0	Language delay, motor delay

GTC, generalized tonic-clonic seizures.

[a] Both patients developed refractory and prolonged seizures after 1 year of age.

after 12 months of age, including partial, myoclonic, atonic, and absence seizures, and developmental delays and motor impairment such as ataxia and spasticity. Prolonged seizures in the first year of life were present in the majority of (75%) but not all infants with Dravet syndrome. Similarly, in a Japanese cohort, only 60% of children with Dravet syndrome had an episode of status epilepticus in the first year of life.[10] The classic hot water–induced seizures that have been described in Japanese patients[10] was not noted in our population, although patients were not specifically asked about this potential trigger, so the presence of hot water–induced seizures could not be excluded.

Making an early diagnosis of Dravet syndrome is important in allowing providers to choose appropriate treatments.[2,8–10] Several antiepileptic drugs (eg, lamotrigine and carbamazepine) should be avoided because they may exacerbate seizures in Dravet syndrome,[9,15,21] whereas medications such as stiripentol, topiramate, and valproate appear to have superior efficacy.[9,22–24] Making a correct early diagnosis of Dravet syndrome can increase the use of appropriate anticonvulsant medications and reduce the frequency of misdiagnosis and unnecessary testing.[8] Improved seizure control may also result in better neurodevelopmental outcomes because uncontrolled status epilepticus may lead to neurologic deterioration,[25,26] although confirmation from additional studies is needed.

The *SCN1A* gene is 1 of 9 genes that encode mammalian voltage-gated sodium channel α subunits.[4] A mutation in the *SCN1A* gene, perhaps the most common known genetic cause of epilepsy,[20] can be found in 70% to 85% of patients with Dravet syndrome,[4–7,10] as well as in 3% to 6% of patients with generalized epilepsy with febrile seizures plus, or GEFS+.[27,28] Most Dravet syndrome mutations result in loss-of-function and haploinsufficiency of *SCN1A*. Knockout mouse models of Dravet syndrome have suggested that decreased *SCN1A* function causes seizures by impairing inhibitory interneuron activity.[29,30] In contrast, a study using induced pluripotent stem cells from 2 patients with Dravet syndrome suggested that the *SCN1A* mutations led to increased excitability of both pyramidal neurons and interneurons, independent of inhibitory inputs.[31]

A recent review that compiled all 1257 known pathogenic *SCN1A* mutations found that 82% of known mutations have been reported in only 1 family.[20] Thus, the majority of identified *SCN1A* mutations are newly described, as was the case in all of our patients. For those patients with *SCN1A*-negative Dravet syndrome,

TABLE 2 *SCN1A* Abnormalities Identified in 7 Patients With Clinical Dravet Syndrome

	Age of Onset, mo	Mutation Likely Pathogenic	De Novo	*SCN1A* Abnormality		Protein Domain	Mutation Predication Programs	
				Nucleotide	Amino Acid		Polyphen-2	SIFT[18]
1	3	Yes	Yes	c.5516T>C	p.Leu1839Pro	C terminal	Probably damaging	Deleterious
2	4	Yes	Yes	c.3034delins28	p.Leu1012delins9	Loop 2	NA	NA
3	4	No	No	c.1806G>A	p.Glu602Glu	Loop 1	NA	NA
4	6	Yes	Yes	c.1156A>T	p.Glu385Asp	DIS5-S6	Probably damaging	Deleterious
5	6	Yes	Yes	c.5164A>G	p.Thr1722Ala	D4S5-S6	Probably damaging	Deleterious
6	6	Yes	Yes[a]	c.974_976del	p.Tyr325del	DIS5-S6	Probably damaging	Deleterious
7	8	Yes	Yes[a]	c.4655G>A	p.Cys1552Tyr	D4S1	Probably damaging	Deleterious

NA, not applicable because not an amino acid substitution.

[a] Maternal testing revealed no *SCN1A* mutation. The father was not available for testing.

a mutation can sometimes be found in other epilepsy genes including *SCN1B*, *GABRA1*, *STXBP1*, and *SCN8A*.[32–34]

In a patient with a newly identified *SCN1A* variant, it is not always easy to determine whether this genetic abnormality is the cause of the epilepsy syndrome. If the variant is inherited from an unaffected parent and/or is not predicted to affect the protein, it is unlikely to be related to the illness, and this was the case in one of our patients. Thus, it is important to test both parents to determine if they also carry the gene variant. Approximately 50% of Dravet syndrome mutations result in protein truncation.[20,35] The other 50% are missense mutations causing amino acid substitutions. Among the missense mutations that have been tested in functional assays, 22 of 27 or 80% also resulted in loss of channel activity.[20] Thus, haploinsufficiency of *SCN1A* is the outcome of most protein truncation and missense mutations. Although functional testing of each new *SCN1A* mutation could further enhance our understanding,[36] such testing is beyond the scope of this study.

Developmental delay, plateau, or regression is usually present in children with Dravet syndrome after the onset of seizures.[37,38] However, we did not require the presence of developmental delay in our case definition, because we wanted to avoid missing patients whose development might appear to be relatively unaffected during the early years of life. Seven of 8 patients with clinical Dravet syndrome did exhibit typical developmental delays after seizure onset. One patient (patient 5) had no reports of developmental delay at age 6 years, but he exhibited behavior abnormalities, required special education classes, had the typical seizure semiology of Dravet syndrome, and a pathogenic *SCN1A* mutation. This patient most likely represents a child with Dravet syndrome with relatively spared development at an early age. Unfortunately, in this retrospective study, no cognitive or developmental testing was available to determine the specific degree of impairment in our patients.

Our study is subject to additional limitations. Our incidence rate may underestimate the rate of Dravet syndrome because we did not include individuals who left KPNC before age 2 years or who had a first seizure earlier than 1 month or later than 12 months of age. Of note, 92% of newborns are followed past 12 months at KPNC. As with any retrospective study, our study may have relied on missing or inaccurate data regarding seizure occurrences. Thus, our data provide a minimum estimate of the incidence of Dravet syndrome, and the actual incidence could be higher. In addition, our study does not include patients with *SCN1A* mutations who have less severe epilepsy syndromes such as GEFS+ and thus underestimates the population prevalence of *SCN1A* mutations.

CONCLUSIONS

Dravet syndrome is usually caused by an *SCN1A* genetic abnormality and is more than twice as common in the United States as previously described. Increased awareness of this severe epileptic encephalopathy may lead to earlier diagnosis and improved seizure control in affected children. Genetic testing for *SCN1A* mutation should be considered in all children who have had ≥2 prolonged febrile seizures by 1 year of age.

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ABBREVIATIONS

ICD-9: International Classification of Diseases, 9th revision
KPNC: Kaiser Permanente Northern California
SCN1A: sodium channel 1α

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