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When Should Clinicians Order Genetic Testing for Dravet Syndrome?

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Abstract

The role of neuronal voltage-gated sodium channel, α -1 subunit (*SCN1A*) gene mutations in Dravet syndrome is well-established. With a broader phenotype than initially described, some patients lack features of Dravet syndrome as defined by the International League Against Epilepsy. We evaluated the predictive value of International League Against Epilepsy criteria for a positive mutation in a cohort of consecutively tested children. Mutations of *SCN1A* were evident in 16 of 69 children. Exhibiting 4 International League Against Epilepsy criteria demonstrated 100% sensitivity. Seven criteria (resistance to multiple antiepileptic drugs, multiple seizure types, abnormal electroencephalogram features, exacerbation with hyperthermia, normal development before seizure onset, seizures beginning before age 1 year, and psychomotor retardation) were present in 85% of mutation-positive cases. The three criteria that best predicted a mutation in *SCN1A* included exacerbation with hyperthermia, normal development before seizure onset, and the appearance of ataxia, pyramidal signs, or interictal myoclonus. We have demonstrated a high-sensitivity testing strategy for detecting mutations of *SCN1A* in children with suspected Dravet syndrome.

Introduction

Dravet syndrome, or severe myoclonic epilepsy in infancy, was first described by Charlotte Dravet [1,2]. The clinical presentation in Dravet syndrome consists of seizure onset within the first year of age in previously healthy children, usually presenting as prolonged seizures, and often associated with fever. These patients develop afebrile seizures, including other seizure types such as myoclonic, absence, atypical absence, and focal clonic. Seizures are usually refractory to antiepileptic drugs. Development is initially normal before the onset of seizures, with eventual psychomotor retardation between ages 1-4 years [3,4]. Marked slowing or stagnation of psychomotor development, accompanied by psychotic or autistic traits and hyperactivity, can be observed between ages 1-4 years. In subsequent years, cognitive function improves slightly, but remains at a low level. If severe mental retardation occurs, it is typically evident before age 6 years and globally affects skills in all areas [5]. Ataxia, pyramidal signs, and interictal myoclonus may also be observed during this period [6]. An electroencephalogram initially produces normal results, with the subsequent

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development of generalized and multifocal spikes and polyspike waves. The development of electrophysiologic abnormalities usually correlates with clinical deterioration [6]. Neuroimaging typically produces normal results.

The association of heterozygous mutations of the gene encoding the neuronal voltage-gated sodium channel, α -1 subunit (*SCN1A*), with Dravet syndrome is recognized. The neuronal voltage-gated sodium channel, α -1 subunit, will be referred to as *SCN1A* henceforth. The *SCN1A* gene is located on chromosome 2q24, and encodes for the α -1 subunit of the neuronal voltage-gated sodium channel [7]. The α subunit consists of four homologous domains, each with six transmembrane segments and a re-entrant S5-S6 pore loop, responsible for ion selectivity, that together form the pore-forming region of the protein [8]. The *SCN1A* gene can contain truncation, missense, deletions, and splice site mutations, which arise mostly de novo, and are spread throughout the entire gene [7,9]. Truncation mutations are commonly associated with more severe epilepsy phenotypes, such as severe myoclonic epilepsy in infancy, whereas missense mutations give rise to a broader range of epilepsy syndromes, including borderline severe myoclonic epilepsy in infancy, generalized epilepsy with febrile seizures-plus, intractable childhood epilepsy with generalized tonic-clonic seizures, and more recently, alleged vaccine-associated encephalopathy [8-13].

Mutations of *SCN1A* are evident in 70% of patients with the classic Dravet phenotype [9,13-16]. Approximately 600 mutations in the *SCN1A* gene have been detected in patients with Dravet syndrome. Most are either de novo or sporadic (www.scn1a.info; accessed in July 2011). Since the advent of *SCN1A* genetic analysis, mutations were detected in patients with other epilepsy phenotypes, as already described. The phenotype of patients with *SCN1A* mutations is thus much broader than that of the classic Dravet syndrome initially described. Several patients with *SCN1A* mutations lack the classic features of Dravet syndrome, as defined in the 1989 revised classification of the International League Against Epilepsy, such as myoclonic seizures, generalized spike-wave activity on electroencephalogram, or abnormal development after the onset of seizures [6,17,18]. Patients with mutations of *SCN1A* appear to represent a clinical spectrum that may be related to a specific *SCN1A* mutation, with contributions from other genetic and environmental factors.

This study was designed to provide guidance for clinicians regarding the appropriate indications for mutational analysis of the *SCN1A* gene. To this end, we compared clinical, imaging, and electrophysiologic features of a consecutively tested series of children who were tested for mutations of the *SCN1A* gene. We then evaluated individual and grouped predictive values of International League Against Epilepsy criteria for Dravet syndrome, to characterize the utilities of different testing strategies.

Methods

Study population

A retrospective chart review was performed of patients evaluated at Cincinnati Children's Hospital Medical Center who had undergone *SCN1A* mutational analysis from 2004 (when commercial testing for mutations of the *SCN1A* gene became available) to February 2010. The Cincinnati Children's Hospital Medical Center provides the majority of primary child neurology care in the greater metropolitan area of Cincinnati, as well as care for many families traveling longer distances or seeking second opinions. A survey was sent to all child neurologists at our institution, asking them to list all of their patients who had undergone testing for mutations of *SCN1A*. Most tests were performed at Athena Diagnostics, Inc. (Worcester, MA), and one was performed at Transgenomic, Inc. (Omaha, NE). In addition,

we requested a list of patients tested at Athena Diagnostics, Inc. This study was approved by the Institutional Review Board of the Cincinnati Children's Hospital Medical Center.

Data abstraction

Clinical and demographic data were abstracted from paper and electronic medical records, including office notes from child neurologists at the Cincinnati Children's Hospital Medical Center. The extracted information included the nine criteria for Dravet syndrome obtained from the 1989 Commission on Classification and Terminology of the International League Against Epilepsy, i.e., a family history of epilepsy or febrile convulsions; normal development before the onset of seizures; seizures beginning before age 1 year; pleomorphic epilepsy (myoclonic, focal clonic, absence, and generalized seizures); an electroencephalogram indicating generalized spike-waves and polyspike-waves; early photosensitivity or focal abnormalities; psychomotor retardation after age 2 years; the appearance of subsequent ataxia, pyramidal signs, or interictal myoclonus after the onset of psychomotor retardation; resistance to multiple antiepileptic drugs; and the exacerbation of seizures by hyperthermia [18]. Other important data obtained from all patients included neuroimaging, if any, and reports of status epilepticus, febrile status epilepticus, and febrile or afebrile status epilepticus before age 12 months. Information from the *SCN1A* test results, which included date of collection, location of mutations, and relationship to a known mutation, was available for each patient. A mutation was considered pathogenic if it was previously described as a pathogenic mutation, and if it was a truncation mutation, a de novo mutation, a mutation in a transmembrane region, or a mutation in a highly conserved region of the gene [8].

Statistical analysis

For each patient, the presence or absence of individual criteria from the International League Against Epilepsy was coded. The sensitivity, specificity, and prevalence for a specific number of criteria were tested. We then performed Fisher's exact test to compare proportions of children meeting each criterion of the International League Against Epilepsy in the mutation-positive versus mutation-negative group. We then used the Bonferroni correction for multiple comparisons.

Results

Sixty-nine patients (27 male and 42 female) at the Cincinnati Children's Hospital Medical Center had undergone genetic testing for mutations of *SCN1A*. Nineteen patients in our study tested positive for mutations of *SCN1A*, but only 16 were included in our final analysis. Table 1 presents a description of the 16 mutation-positive patients. Two patients manifested mutations of *SCN1A* that were silent (considered to be benign polymorphisms). Therefore, they were placed in the mutation-negative group. In the other patient, the father manifested the same two mutations of *SCN1A* as his child, but was asymptomatic. One of these two mutations did not produce an amino acid change, and the other occurred in a non-evolutionarily conserved region. These mutations were considered benign polymorphisms, and the patient was placed in the mutation-negative group. The pathogenic mutations included seven missense, seven truncation, one frame shift, and one splice site. The locations of five missense mutations were in the transmembrane or poreforming regions of the *SCN1A* gene. Seven patients manifested previously described pathogenic mutations [3,9,11,13,14,17-19].

Mutational analyses were available in eight other sets of parents of mutation-positive patients, in addition to the parental data described previously. Of these, seven sets were normal, indicating de novo mutations in the children. In the remaining two sets of parents,

the mothers manifested the same mutations as their children. In one case, the mutation of *SCN1A* was inherited from a mother with a history of febrile seizures, consistent with the spectrum of generalized epilepsy with febrile seizures-plus. In the other case, the mother manifested a history of epilepsy that began in childhood. Two brothers in the study manifested identical pathogenic mutations. However, the parents of these brothers were not tested. No significant difference was evident between mutation-positive and mutation-negative groups with respect to a family history of febrile seizures or epilepsy (44% vs 32%, respectively).

The ages of patients in our study at the time of chart review ranged from 2 months to 19 years. We included all patients tested for mutations of *SCN1A*, regardless of the reason for testing. The minimal number of International League Against Epilepsy criteria needed to achieve 100% sensitivity for a patient with a mutation in the *SCN1A* gene was four. Table 2 contains a complete list of frequencies for each characteristic.

Fourteen mutation-positive patients (88%) manifested their initial onset of seizures before age 1 year. The other two patients manifested their first onset of seizures at ages 13 and 16 months, respectively. The average age of seizure onset was 7.4 months, with a range of 2-16 months. In contrast, the average age of seizure onset in mutation-negative patients was 19.5 months. In the mutation-positive patients, 11 of 16 patients (69%) experienced status epilepticus before age 12 months, vs only five of 53 mutation-negative patients (9%). Twelve mutation-positive patients (75%) experienced febrile status epilepticus either before or after age 12 months, vs four of 53 mutation-negative patients (8%).

After the initial onset of seizures, all 16 mutation-positive patients developed multiple seizure types, including generalized tonic-clonic, absence, atypical absence, focal clonic, atonic, and myoclonic. Ten of these patients (63%) developed myoclonic seizures. Ataxia was specifically mentioned upon the examination of five patients, and tremor was evident in seven patients. One patient manifested a persistent, positive, bilateral Babinski sign. Fifteen mutation-positive patients (94%) exhibited normal development before their onset of seizures. Subsequent psychomotor abnormalities were evident in 14 patients in this group, and included hyperactivity, obsessive compulsive behaviors, global cognitive impairment, learning disabilities, and language regression. One of these patients was aged 2 years at the time of her chart review, and psychomotor retardation had not been evident at that point. In the mutation-negative group, 42% demonstrated normal development before their onset of seizures. Of those patients, 14 later developed psychomotor abnormalities, which included speech delay/regression, autism, global developmental delay, and cognitive slowing and regression with seizures.

All 16 patients who tested positive for mutations of *SCN1A* had undergone at least one electroencephalogram. Fourteen of these children produced electroencephalograms with abnormal results: seven manifested both generalized and focal discharges, five manifested only generalized spike-wave discharges, and two manifested only focal spike and polyspike-wave discharges. Only one patient exhibited photosensitivity and both generalized spike-wave and polyspike-wave discharges.

At the time of our study, mutation-positive patients were more likely to produce normal magnetic resonance imaging scans (i.e., 69% versus 53% in mutation-negative patients). Abnormal findings in the mutation-positive group included delayed myelination, diffuse cerebral/cerebellar volume loss, gliosis, and an arachnoid cyst. The most frequent magnetic resonance imaging abnormalities in the mutation-negative group included abnormal myelination and cerebellar atrophy/hypoplasia or parenchymal volume loss.

Discussion

Mutations of *SCN1A* were evident in 16 of 69 children. No individual criterion of the International League Against Epilepsy was 100% accurate in predicting the presence of a mutation in *SCN1A*, which supports the idea that a syndrome is involved that requires the presence of multiple factors to establish a diagnosis. The three criteria that best distinguished mutation-positive from mutation-negative children comprised exacerbation with hyperthermia, normal development before the onset of seizures, and the appearance of ataxia, pyramidal signs, or interictal myoclonus. These criteria remained significant after correction for multiple comparisons (Table 2 and Fig 1). Using either exacerbation with hyperthermia or normal development before the onset of seizures as the sole factor in the decision to perform mutation testing in children with features broadly consistent with Dravet syndrome (i.e., a sample similar to the one in this study) would yield a sensitivity of 94% and a specificity of about 60%. This strategy would reduce the number of children tested by approximately 50%, but would result in missing approximately 5% of diagnoses. Using the criterion regarding the appearance of ataxia, pyramidal signs, or interictal myoclonus yields a sensitivity of 63% and specificity of 72%, and would not in itself provide effective guidance in testing.

Because this study is retrospective, we do not know exactly why each clinician ordered *SCN1A* mutational analysis. However, a careful review of clinical data suggests that the main reasons for ordering the test included intractability (i.e., resistance to multiple antiepileptic drugs), multiple seizure types, specific electroencephalogram features, and psychomotor retardation, which were present in 80% of all 69 patients tested. Each of the neurologists who treated patients with intractable epilepsy sent at least one test. Figure 1 indicates that intractability was present in 100% of mutation-positive patients. This intractability may explain why patients as young as 2 months of age were tested. Our findings, therefore, are relevant for clinicians who emphasize a high-sensitivity approach to genotype testing, but who wish to narrow their test population according to the most predictive clinical features.

A molecular diagnosis provides a foundation for expert-consensus medical treatment and discussions about prognosis, and therefore demonstrates high clinical value. In our study sample, the presence of at least four of nine criteria from the International League Against Epilepsy was 100% sensitive (negative predictive value, 100%) for a positive *SCN1A* mutation, with a positive predictive value of 26%. Using this result as a decision point for mutational testing does not greatly reduce the number of children tested. However, it offers a reasonable high-sensitivity strategy for testing.

At the time of our chart review, four of our 16 mutation-positive patients met all nine criteria for Dravet syndrome. The question of whether the remaining 12 mutation-positive patients manifest a variant of Dravet syndrome (e.g., severe myoclonic epilepsy in infancy or borderline Dravet syndrome) is not as easily answered. The syndrome of severe myoclonic epilepsy in infancy was defined as “children who lack several of the key features” of severe myoclonic epilepsy in infancy by Harkin et al. [3], who further subdivided these children according to the missed feature of severe myoclonic epilepsy in infancy. They included the category of severe myoclonic epilepsy in infancy-O, which they defined as “patients who had more than one feature that was not in keeping with” severe myoclonic epilepsy in infancy [3]. In a study by Fukuma et al. [16], patients with borderline myoclonic epilepsy in infancy were defined as lacking myoclonic seizures. However, patients with atypical absence seizures were placed in a group with severe myoclonic epilepsy in infancy, regardless of the presence or absence of myoclonic seizures [16].

Mutations in *SCN1A* of clinical significance were evident in 23% of our tested patients. This frequency is lower than that previously reported by Nabbout et al., who reported a frequency of 35% in a group of 93 patients who fulfilled all nine criteria for Dravet syndrome [9]. This finding suggests that a relatively broad testing strategy was used in our clinic, based on an expectation of variable phenotypes within the *SCN1A* genotype.

Several other clinical features in our sample bear emphasis. The incidence of status epilepticus in Dravet syndrome was reported at 67-77%, which is consistent with our findings of status epilepticus in 14 of 16 patients (88%) either before or after age 1 year [19]. A family history of febrile seizures or epilepsy was reported in 44% of mutation-positive patients vs 32% of mutation-negative patients, which is consistent with the incidence of 25-64% reported by Dravet et al. [6].

In our study, the mutation-positive patients who met at least eight of the International League Against Epilepsy criteria for Dravet syndrome were more likely to manifest a truncation mutation (six of nine patients). Location also affects severity insofar as mutations in severe myoclonic epilepsy in infancy occurred more frequently in the pore-forming region of the gene [8]. The mutations in our 16 mutation-positive patients most frequently located in the pore-forming region of the gene.

The limitations of this study include those inherent to retro-spective studies, primarily involving biases related to clinicians' decisions about testing. In addition, the majority of patients underwent *SCN1A* DNA sequence analysis only. These patients were examined before the commercial availability of multiplex ligation-dependent probe amplification testing. As a result, some duplications or deletions of the *SCN1A* gene may have been missed in our mutation-negative patients.

As we were performing our chart reviews, we had to make a few assumptions based on the limited amount of clinical data available at the time of the study. For the electroencephalographic criteria, if a patient demonstrated any one of the three electroencephalogram features defined by the International League Against Epilepsy, we considered that a positive finding. For pleomorphic epilepsy, if a patient manifested more than one type of seizure listed in the International League Against Epilepsy criteria, we considered that a positive finding. If ataxia, pyramidal signs, or interictal myoclonus were not documented in the chart, we assumed that to be a negative finding. We included febrile seizures in determining the presence of exacerbation by hyperthermia. If a chart did not mention exacerbation with hyperthermia, we assumed that the patient did not meet that criterion.

Dravet syndrome is an epileptic encephalopathy that can present with prolonged febrile seizures in previously healthy children before age 1 year. This clinical picture shares similarities with several other disorders in their early stages. Patients with *SCN1A* mutations may be diagnosed with complex febrile seizures upon initial evaluation. The full phenotype often does not become apparent until after age 2 years, delaying genetic testing for clinicians who do not consider Dravet syndrome in their differential diagnosis because of a lack of familiarity with the disorder.

Conclusions

Testing decisions regarding *SCN1A* can be optimized according to criteria for Dravet syndrome by the International League Against Epilepsy. The two most helpful criteria comprise seizure exacerbation with hyperthermia and normal development before the onset of seizures. Testing children who meet 4 criteria should constitute a high-sensitivity strategy. However, additional studies are needed to identify children who may not present

with all of the classic features of Dravet syndrome. More accurately defining a test population for mutations of *SCN1A* by using appropriate clinical characteristics may prompt earlier recognition of the diagnosis and the initiation of treatment, potentially limiting additional testing and providing appropriate anticipatory guidance to families.

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Figure 1.

Frequency of ILAE criteria in mutation-positive vs mutation-negative patients. Mutation-positive frequencies are indicated in dark gray, and mutation-negative frequencies are indicated in light gray. AEDs, antiepileptic drugs; Dev't, development; EEG, electroencephalogram; FH, family history; ILAE, International League Against Epilepsy; nl, normal; sz, seizure; yr, year.

Table 1

Clinical characteristics of 16 SCN1A mutation-positive patients

Patient Identification Number	Sex	Age at chart Review	Normal Development Before Seizure Onset	Seizures Beginning Before Age 1 Year	Multiple Seizure Types	Family History of Epilepsy or Febrile Seizures	EEG findings	Psychomotor Retardation After Age 2 Years	Appearance of Ataxia, Pyramidal Signs, or Interictal Myoclonus	Resistance to Multiple Anticonvulsants	Exacerbations of Seizures With Hyperthermia
1	M	12 yr	+	–	+	–	+	+	+	+	+
2	M	15 yr	+	+	+	+	+	+	+	+	+
3	M	9 yr	+	+	+	–	+	+	+	+	+
4	F	5 yr	+	+	+	+	+	+	+	+	+
5	F	7 yr	–	+	+	–	+	+	–	+	+
6	F	4 yr	+	+	+	–	+	+	–	+	–
7	F	7 yr	+	+	+	–	+	+	+	+	+
8	F	14 yr	+	–	+	–	+	+	+	+	+
9	M	9 yr	+	+	+	+	+	+	+	+	+
10	F	4 yr	+	+	+	+	+	+	+	+	+
11	F	2 yr, 4.8 mo	+	+	+	–	–	–	–	+	+
12	M	8 yr	+	+	+	+	–	+	–	+	+
13	F	10 yr	+	+	+	–	+	+	–	+	+
14	F	10 yr	+	+	+	–	+	+	+	+	+
15	M	6 yr	+	+	+	+	+	+	–	+	+
16	F	2 yr	+	+	+	+	+	–	+	+	+

Abbreviations:

EEG = Electroencephalogram

F = Female

M = Male

mo = Months

SCN1A = Neuronal voltage-gated sodium channel, α -1 subunit

yr = Years

Table 2

Frequency of ILAE criteria in children tested for mutations in SCN1A

ILAE Criteria	Total	Mutation-Positive	Mutation-Negative	P Value
Resistance to multiple antiepileptic drugs	56(81%)	16(100%)	40 (75%)	0.029
Multiple seizure types	55 (80%)	16(100%)	39 (74%)	0.029
Normal development before onset of seizures	37 (54%)	15(94%)	22 (42%)	0.0002 *
Psychomotor retardation after onset of seizures	58(84%)	14 (88%)	44 (83%)	0.436
Abnormal results of EEG	60 (87%)	14 (88%)	46 (87%)	0.674
Exacerbation with hyperthermia	33 (48%)	15(94%)	18(34%)	0.00002 *
Onset of seizure before age 1 year	42(61%)	14 (88%)	28 (53%)	0.006
Ataxia, pyramidal signs, or interictal myoclonus	25 (36%)	10(63%)	15(28%)	0.003 *
Family history of febrile seizures or epilepsy	24 (35%)	7 (44%)	17 (32%)	0.23

Abbreviations:

ILAE = International League Against Epilepsy

SCN1A = Neuronal voltage-gated sodium channel, α -1 subunit* Significant ($P < 0.005$) after Bonferroni correction for multiple comparisons.