Clinical and histopathological outcomes in patients with \textit{SCN1A} mutations undergoing surgery for epilepsy

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OBJECT Mutations in the sodium channel alpha 1 subunit gene (\textit{SCN1A}) have been associated with a wide range of epilepsy phenotypes including Dravet syndrome. There currently exist few histopathological and surgical outcome reports in patients with this disease. In this case series, the authors describe the clinical features, surgical pathology, and outcomes in 6 patients with \textit{SCN1A} mutations and refractory epilepsy who underwent focal cortical resection prior to uncovering the genetic basis of their epilepsy.

METHODS Medical records of \textit{SCN1A} mutation–positive children with treatment-resistant epilepsy who had undergone resective epilepsy surgery were reviewed retrospectively. Surgical pathology specimens were reviewed.

RESULTS All 6 patients identified carried diagnoses of intractable epilepsy with mixed seizure types. Age at surgery ranged from 18 months to 20 years. Seizures were refractory to surgery in every case. Surgical histopathology showed evidence of subtle cortical dysplasia in 4 of 6 patients, with more neurons in the molecular layer of the cortex and white matter.

CONCLUSIONS Cortical resection is unlikely to be beneficial in these children due to the genetic defect and the unexpected neuropathological finding of mild diffuse malformations of cortical development. Together, these findings suggest a diffuse pathophysiological mechanism of the patients’ epilepsy which will not respond to focal resective surgery.

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KEY WORDS epilepsy surgery; histopathology; Dravet syndrome; \textit{SCN1A} mutations; cortical malformations

Mutations in the sodium channel alpha 1 subunit gene (\textit{SCN1A}), encoding the alpha subunit of the neuronal voltage gated sodium channel, Nav1.1, have been linked to several epilepsy phenotypes. These include severe phenotypes such as Dravet syndrome or severe myoclonic epilepsy of infancy (SMEI), severe infantile multifocal epilepsy, and intractable childhood epilepsy with generalized tonic-clonic seizures. Generally, Dravet syndrome is characterized by onset of febrile or afebrile clonic and tonic-clonic, generalized, and hemiclonic seizures in the 1st year of life.\textsuperscript{5} As the child grows, multiple seizure types along with developmental delays and behavioral disorders appear. Mutations in \textit{SCN1A} have also been identified in more benign phenotypes, including generalized epilepsy with febrile seizures plus (GEFS+) and isolated febrile seizures.\textsuperscript{5,10,12,21,25} These syndromes likely represent a spectrum of the same disorder, as the same \textit{SCN1A} mutations and deletions can cause SMEI in some children and GEFS+, intractable childhood epilepsy with generalized tonic-clonic seizures, idiopathic epilepsy, or febrile seizures alone in others.\textsuperscript{10,17} The lack of a precise genotype-phenotype relationship suggests that other genetic and/or environmental influences are involved.

Findings on structural neuroimaging studies (CT and MRI) in patients with Dravet syndrome are usually normal or show slight diffuse atrophy, although focal imaging findings have been documented.\textsuperscript{11,19,20} Unilateral or bilateral hippocampal sclerosis is an increasingly recognized finding in patients with Dravet syndrome and/or \textit{SCN1A} mutations and may develop after an initially normal MRI.\textsuperscript{5,10,22}
However, other authors have hypothesized that SCN1A mutations may actually protect from hippocampal sclerosis.\(^2\) Few pathological cases of Dravet syndrome have been published to date.\(^3,5,13,15,18\) Most were case reports of autopsy specimens, and many had not undergone SCN1A testing. In this study, we review the clinical features and surgical pathology in 6 patients with treatment-resistant epilepsy who underwent surgery for intractable focal seizures and were later found to have presumed pathogenic mutations in SCN1A. We also review their outcomes and seek to draw conclusions regarding surgical evaluation and management.

**Methods**

The medical records of 6 children with SCN1A mutations who underwent epilepsy surgery for medically refractory epilepsy were reviewed retrospectively. Patients were identified at the Children’s Hospital of Philadelphia by surveying the epilepsy group to identify patients who had undergone epilepsy surgery and were later found to have SCN1A mutations. An additional patient was identified at the Cincinnati Children’s Hospital. Data extracted included age at seizure onset, initial seizure types, clinical course, and neuroimaging and electroencephalography (EEG) reports. Surgical outcomes were classified using the International League Against Epilepsy (ILAE) surgical outcome scale as of their last follow-up visit.\(^24\) SCN1A mutation testing was done at commercially available laboratories (Athena and Transgenomics). A mutation was considered pathogenic if it was previously described as such, was a truncation mutation, or was a novel mutation with predicted pathogenicity (based on PolyPhen software, location, function, and conservation of amino acid change) and found either de novo or with appropriate family history.

Surgical pathology specimens were reviewed, separately, by 2 board-certified neuropathologists independent of, and blinded to, the original pathological reports. All tissue had been prepared by the clinical pathology laboratory for the original pathological examinations. Sections reviewed were all sectioned at 4 μM and stained with H & E. Immunohistochemical analysis had been performed for glial fibrillary acid protein (GFAP), NeuN (a neuronal marker), and neurofilament light chain (NFI) antibodies. The pathology was classified using the Palmini criteria from Blümcke et al.\(^4\)

**Results**

**Clinical Findings**

**Seizure History**

Six patients who underwent resective surgery and were later found to have SCN1A mutations were identified. A summary of all the clinical and genetic data are presented in Tables 1–3. In all cases seizure onset occurred within the 1st year of life. Three patients presented with partial seizures at onset. All eventually developed partial motor seizures (hemiconvulsions with or without secondary generalization) and/or complex partial seizures. All patients experienced generalized seizure types as well, including myoclonic seizures, atomic/head drops, and absence seizures. Exacerbation of seizures by fever or overheating was seen in 4 of the 6 patients, and 5 of the 6 patients had a history of status epilepticus. The clinical phenotype of the majority of patients was consistent with Dravet syndrome (Table 1). However, the patient in Case 5 had a phenotype most consistent with GEFS+. This was the one patient operated on with a known change in SCN1A. He had been found to carry a sequence variant of unknown significance, but his mother had a history of epilepsy and died as a consequence of epilepsy. His history was complicated by previous closed head injury resulting in hemorrhagic contusions in the left anterior frontal lobe and scattered subdural and subarachnoid hemorrhages. After the trauma he began having multiple daily seizures that localized to the region of injury, and he underwent a focal resection of the area of encephalomalacia. He had a brief seizure-free period following surgery, but the seizures later recurred.

**Developmental History**

All patients exhibited varying degrees of developmental cognitive impairments ranging from borderline IQ with learning disabilities to moderate mental retardation with autistic features (Table 1). Three of the patients had normal development prior to seizure onset and one was delayed prior to seizure onset. The timing of cognitive impairment of the others is unknown. Two patients also developed ataxia.

**Electrophysiology and Imaging**

EEG and imaging features are summarized in Table 2. The initial EEG findings were normal in all children whose early data were available. Soon after, the EEG background became slow and poorly organized with irregularly generalized or multifocal sharps in all patients. Three of the 6 patients had normal MRI results originally, with 2 of these 3 having abnormal findings on follow-up studies. The patient in Case 5 had an area of encephalomalacia from previous head trauma and developed mesial temporal sclerosis (MTS). Of the 3 patients with abnormal findings on initial MRI, 2 had subtle, nonspecific findings and the third had MTS. Imaging results are described in Table 2.

**Surgical History**

Age at surgery ranged from 18 months to 20 years. Five of the 6 patients underwent either complete or partial frontal lobectomies (Table 3). One of these patients also underwent an anterior 2/3 corpus callosotomy, while another patient underwent a temporal lobectomy along with an inferior frontal resection. The sixth patient (Case 4) underwent a focal resection of a parasagittal posterior frontoparietal lesion. These operations were based on clinical and diagnostic findings indicating focal seizure onset and presumed focal pathology prior to the discovery of the SCN1A variant.

Patients were monitored for 18 months to almost 6 years following resection. Five of the 6 patients showed some clinical improvement immediately following surgery but soon returned to an intractable state. Five patients had ILAE Class 5 surgical outcomes with persistent frequent intractable seizures without significant benefit following
TABLE 1. Clinical characteristics of 6 \textit{SCN1A} mutation–positive children

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Seizure Onset (in mos)</th>
<th>Family History of Seizures</th>
<th>Initial Seizure Type</th>
<th>Precipitating/Associated Factors</th>
<th>Other Seizure Types</th>
<th>Status Epilepticus</th>
<th>Psychomotor Status</th>
<th>Clinical Diagnosis</th>
<th>SCN1A Mutation</th>
<th>Mutation Interpretation</th>
<th>Ataxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>Yes</td>
<td>Focal motor w/unresponsiveness</td>
<td>Seizures common w/fevers, over-heating, illness</td>
<td>Myoclonic, atonic, focal sensory or motor seizures w/ &amp; and w/o secondary generalization</td>
<td>Yes</td>
<td>Normal prior to seizure onset, later mild to moderate MR</td>
<td>Dravet syndrome</td>
<td>c.2927del; p.M976fs</td>
<td>Predicted SMEI phenotype</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>No</td>
<td>Focal myoclonus, focal motor</td>
<td>Onset shortly after DPT immunization</td>
<td>GTCs</td>
<td>Yes</td>
<td>Moderate MR w/autistic features</td>
<td>Dravet syndrome</td>
<td>Deletion at exons 17–20</td>
<td>Previously reported SMEI phenotype</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>No</td>
<td>GTCs</td>
<td>Unknown</td>
<td>Myoclonic, atonic, tonic, absence, complex partial</td>
<td>Yes</td>
<td>MR, autism, ADHD</td>
<td>Dravet syndrome</td>
<td>c.5434T&gt;G; p.W1812G</td>
<td>Previously reported SMEI phenotype</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Yes</td>
<td>Focal motor</td>
<td>Seizures common w/fevers, overheating</td>
<td>GTCs, myoclonus, head drops, apnea, focal motor seizures</td>
<td>Yes</td>
<td>Normal prior to seizure onset, later moderate MR, ADHD, OCD</td>
<td>Dravet syndrome</td>
<td>c.4587del; p.K1529fsX</td>
<td>Predicted SMEI phenotype</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>Yes</td>
<td>GTCs w/fever</td>
<td>Seizures initially only w/fever</td>
<td>≥1 complex partial seizure</td>
<td>No</td>
<td>Normal milestones, borderline IQ, ADHD</td>
<td>GEFS+</td>
<td>c.5018T&gt;G; p.J1673T</td>
<td>Presumed pathogenic</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>No</td>
<td>Refractory febrile status epilepticus</td>
<td>Fevers</td>
<td>GTCs, atonic &amp; myoclonic seizures, complex partial seizures w/2 distinct semioologies</td>
<td>Yes (both febrile &amp; afebrile)</td>
<td>Normal prior to seizure onset, later mild MR</td>
<td>Dravet syndrome</td>
<td>c.1661A&gt;G; p.E554R</td>
<td>Predicted SMEI phenotype</td>
<td>No</td>
</tr>
</tbody>
</table>

ADHD = attention deficit hyperactivity disorder; DPT = diphtheria, pertussis, and tetanus; GTC = generalized tonic-clonic seizure; MR = mental retardation; OCD = obsessive-compulsive disorder.
surgery. The patient in Case 6 showed no improvement immediately following surgery but did show a greater than 50% improvement in seizure frequency approximately 2 years after the surgery, following the addition of stiripentol to her medication regimen.

**Genetic Findings**

Five of the 6 patients underwent epilepsy surgery before their SCN1A mutations were identified. The SCN1A mutations included 3 deletions (Cases 1, 2, and 4) and 3 missense mutations (Table 1). One deletion (in Case 2) was a previously reported mutation with known association with the severe SMEI phenotype. The other 2 deletions, both leading to frame shifts, were both predicted to result in the severe SMEI phenotype. Of the 3 missense mutations, 1 had been previously associated with the severe SMEI phenotype, while the other 2 (in Cases 5 and 6) were unknown variants. Parental testing demonstrated the latter patient’s (i.e., Case 6) mutation to be de novo. The patient in Case 5 underwent epilepsy surgery after SCN1A testing revealed a previously unidentified mutation that was of unclear significance at that time. His parents were not available for testing. His mutation, consisting of a T to G transition in nucleotide 5018 codon 1673, resulting in an amino acid change from isoleucine to threonine, however, is now predicted to be pathogenic in PolyPhen2 (Probably Damaging, Score 1.00) and is in a transmembrane region that is highly conserved in all species from fish to humans.

**Histopathological Findings**

There were no gross morphological abnormalities in the pathology specimens of any patient. On histological examination, the density of cell bodies seen with H & E staining appeared normal overall, and a clear 6-layered cortex was identified. Immunohistochemistry with Neurofilament antibody showed normal-appearing neurons with no dysmorphic, large, or balloon neurons. Staining directed against NeuN revealed a well-organized cortex with 6 layers and normal definition of the gray-white boundaries. However, the NeuN staining also revealed significantly increased numbers of cells in the molecular layer of the cortex and the white matter throughout the stained tissue in 4 of the 6 patients (Cases 1, 2, 3, and 5) (Fig. 1). The temporal lobe specimen in Case 2 showed gliosis consistent with MTS. The specimen from Case 5 also demonstrated a prominent region of gliosis extending from the pial surface into the white matter, consistent with his known history of traumatic brain injury. The pathological specimens from Cases 4 and 6 were quite limited, consisting of tiny, irregular bits of cortex and a minimal amount of white matter. Neither specimen demonstrated clear evidence of dysplasia or gliosis.

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**TABLE 2. EEG and imaging characteristics**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Initial EEG</th>
<th>Interictal EEG Abnormalities</th>
<th>Extracranial Ictal EEG</th>
<th>Structural Imaging</th>
<th>Functional Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Slow, disorganized bkgd, irregularly generalized &amp; independent bitemporal epileptiform discharges</td>
<td>All seizures (including 6 w/ head version) w/ irregularly generalized onset</td>
<td>Tiny focus of nonspecific hyperintensity in lt parietal periventricular white matter</td>
<td>MEG showed predominant focus over lt frontal lobe, greatest over lt superior frontal gyrus, although sharp activity noted on rt SPECT</td>
</tr>
<tr>
<td>2</td>
<td>Unknown</td>
<td>Slow, disorganized bkgd, frequent bifrontal &amp; irregularly generalized discharges</td>
<td>One seizure w/ lt frontal onset, 5 nonlocalizing</td>
<td>Initial MRI normal, repeat MRI at age 19 yrs lt MTS</td>
<td>SPECT showed possible lt temporal focus</td>
</tr>
<tr>
<td>3</td>
<td>Unknown</td>
<td>Slow, disorganized bkgd, irregularly generalized &amp; multifocal discharges</td>
<td>LTM: rt frontal onset</td>
<td>Lt MTS (present age 3 yrs)</td>
<td>MEG showed rt posterior frontal/rt midtemporal sharp waves</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>Slow, disorganized bkgd, irregularly generalized &amp; independent bifrontal discharges</td>
<td>3 nonlocalized seizures, 1 seizure w/ lt parietal-parasagittal onset</td>
<td>Small area of abnormal signal in lt posterior frontal parasagittal subcortical WM</td>
<td>Ictal SPECT showed radiotracer activity increased in rt frontal lobe, decreased in lt frontal lobe</td>
</tr>
<tr>
<td>5</td>
<td>Normal</td>
<td>Slow, disorganized bkgd</td>
<td>1 seizure w/ lt frontal onset, 1 nonlocalizing</td>
<td>Normal prior to closed head injury, then lt frontal hemorrhage/encephalomalacia</td>
<td>Not done</td>
</tr>
<tr>
<td>6</td>
<td>Normal</td>
<td>Slow, disorganized bkgd, multifocal sharp waves, generalized epileptiform patterns, continuous slowing over rt frontal &amp; temporal regions during sleep</td>
<td>9 seizures w/ rt temporal onset, 1 each arising from rt &amp; lt parietal region, &amp; 1 poorly localized</td>
<td>Multiple normal MRIs</td>
<td>PET showed decreased uptake in lt posterior temporal lobe, MEG &amp; SISCOM studies both suggested predominant focus in rt parietal region</td>
</tr>
</tbody>
</table>

Bkgd = EEG background; LTM = long-term inpatient video-EEG monitoring; MEG = magnetoencephalography; SISCOM = subtracted ictal SPECT co-registered on MRI; SPECT = single photon emission CT; WM = white matter.
We present 6 patients who underwent epilepsy surgery for intractable focal seizures and were later noted to have clinical histories consistent with the spectrum of SCN1A-related disorders. Although a genetic diagnosis was not made, and in some cases was not available, prior to undergoing surgery, all patients were eventually found to have pathogenic mutations in SCN1A. In this cohort, mild malformations of cortical development (MCDs) were discovered in 4 of 6 patients' surgical specimens, with excessive numbers of cells in the white matter and molecular layer of the cortex in all 4.

The implications of our neuropathological findings are limited by poor clinical outcomes in these patients. Nevertheless, there are scant published data available on pathological findings in Dravet syndrome and/or patients with SCN1A mutations. Three pediatric case reports of autopsy tissue in patients with clinical diagnoses of Dravet syndrome and/or demonstrated SCN1A mutations were shown to have abnormal cortical histopathology that was similar to or more extensive than that seen in our series.13,15,18 Two of the 3 revealed excessive neurons in the white matter;13,18 similar to that described herein in addition to irregularities in the laminar structure of the cerebellum and cortex in one patient18 and polymicrogyria and hippocampal gliosis/calcification in the other.13 A third patient with an SCN1A duplication resulting in a frame shift revealed multifocal micronodular dysplasia of the left temporal cortex and bilateral hippocampal gliosis.15 Most recently, Barba et al. reported on 6 patients with SCN1A mutations with co-occurring MCDs.9 Two of these patients underwent epilepsy surgery, and they both had unfavorable seizure outcomes. In contrast to these reports, a study examining postmortem specimens of 8 adult and pediatric cases with clinical Dravet syndrome and/or documented SCN1A mutations failed to find any consistent pathological abnormalities.5 There are important differences between our cases and those described in previous studies. In our series all specimens were obtained in the process of epilepsy surgery. Therefore, we specifically examined areas identified as epileptogenic during presurgical evaluation. This may suggest that the mild cortical changes we observed are a reflection of the epileptogenicity of regions examined and techniques used. In contrast, Catarino et al. examined only one surgical specimen, so the epileptogenicity of the areas sampled in the postmortem studies is unknown.5 Be-

<table>
<thead>
<tr>
<th>Case No.</th>
<th>No. of Failed Medication Trials</th>
<th>Longest Seizure-Free Period</th>
<th>Age at Surgery</th>
<th>Intracranial Ictal EEG</th>
<th>Area Resected</th>
<th>Initial Response to Surgery</th>
<th>Long-Term Surgical Outcome (ILAE Class)</th>
<th>Duration of Follow-Up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;10 + VNS &amp; ketogenic diet</td>
<td>3 mos on topiramate</td>
<td>8 yrs</td>
<td>2 typical seizures w/ onset in lt frontal convexity &amp; midline</td>
<td>Lt frontal lobectomy</td>
<td>Decreased seizure frequency after surgery, increased alertness</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>1 yr on phenytoin</td>
<td>20 yrs</td>
<td>Not done</td>
<td>Lt temporal lobectomy &amp; lt inferior frontal gyrus resection</td>
<td>6 wks seizure free</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>10 + VNS</td>
<td>None significant</td>
<td>11 yrs</td>
<td>22 seizures w/ broad right frontal onset</td>
<td>Rt frontal lobectomy &amp; anterior 2/3 callosotomy</td>
<td>Intermittent periods of seizure freedom up to 2 wks</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>4 before surgery; 5 after + VNS</td>
<td>None significant</td>
<td>18 mos</td>
<td>Not done</td>
<td>Lt parietal/posterior frontal/mesial parietal lesion</td>
<td>Decreased seizure frequency &amp; intensity after surgery</td>
<td>5</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>2–3 yrs off all AEDs</td>
<td>17 yrs</td>
<td>Not done</td>
<td>Lesionectomy of area of lt frontal encephalomalacia</td>
<td>1 mo seizure free</td>
<td>5†</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>11 + VNS &amp; ketogenic diet</td>
<td>3 wks on clobazam, topiramate, &amp; stiripentol (2 yrs after surgery)</td>
<td>9 yrs</td>
<td>5 seizures w/ right superior frontal &amp; infratemporal onset</td>
<td>Rt frontoparietal resection</td>
<td>No improvement</td>
<td>4‡</td>
<td>43</td>
</tr>
</tbody>
</table>

AEDs = antiepileptic drugs; VNS = vagal nerve stimulator.
* Of note, surgery was performed before genetic testing.
† Complicated by poor adherence to prescribed regimen.
‡ Seizure frequency remained unchanged until 2 years after surgery when stiripentol was added to medication regimen.
cause we were only able to review tissue deemed epileptogenic in the preoperative evaluation, the epileptogenicity of these histopathological findings cannot be proved. However, the diffuse nature of our findings, along with poor surgical success, point to the diffuse nature of this syndrome as would be expected in a genetic diagnosis. Immunohistochemical studies were only available in 4 of the 8 cases in the series by Catarino et al., and only 2 of these had documented SCN1A mutations. Moreover, there may be a discrepancy in conservativeness of the diagnosis of dysplasia. Indeed, the grading of mild MCD is still under debate and interrater reliability is somewhat variable. However, expert pathologists reviewed all data in both our series and the Catarino paper. In summary, our data along with the previous reports strongly argue that at least a subset of SCN1A/Dravet syndrome patients have some level of cortical disorganization.

It is unclear whether the pathological abnormalities described here and previously are reflective of disruption of neuronal migration or are secondary to the early-onset seizures seen in this disorder. Early infantile seizures could theoretically affect the final stages of neuronal migration that extend after birth. If abnormal migration is a direct result of postnatal seizures, similar histopathological abnormalities would be expected to be found in all epilepsy syndromes associated with SCN1A mutations with seizure onset in infancy, but not those with later seizure onset. However, the 2 patients in our series with later seizure onset (11–12 months vs 3–5 months) both demonstrated mild MCD. Furthermore, the one patient in our study whose surgical specimen did not show clear evidence of mild MCD suffered early seizure onset at 4 months (Case 4).

The importance of these findings for surgical decision making cannot be underestimated. All 6 patients described in this study, despite having focal seizure semiologies and focal findings on surgical evaluations, continued to have intractable seizures following resection of their predominant ictal onset zone. Both the genetic defect and the diffuse abnormalities in cortical cytoarchitecture as described herein could be contributing factors to the intractable nature of their epilepsy. Indeed, the functional change in the cellular physiology induced by alterations in SCN1A occurs diffusely and focal brain resection would not rectify the problem. A combination of these 2 mechanisms may be involved in a subset of patients like the group presented. Unfortunately, our data do not allow us to hypothesize further about the cause of the mild MCD seen in this patient cohort as well as in previous series.

Neurosurgeons and epileptologists should consider genetic testing in patients whose clinical presentation is consistent with Dravet syndrome before proceeding with surgery. Our experience indicates that these patients are unlikely to benefit from focal resection. This appears to be true even when the preoperative evaluation points to focal pathology and seizure onset. Up to this point, scant examples of Dravet syndrome histopathology in patients undergoing epilepsy surgery have been available. It is our hope that improved understanding of this syndrome will lead to better screening, diagnosis, and treatment, whether surgical or otherwise.

FIG. 1. NeuN staining revealed increased numbers of cells in the molecular layer of the cortex and white matter in the majority of samples. Figure is available in color online only.
Conclusions

We have described patients with medically refractory epilepsy with mixed seizure types in whom resective surgery failed and who were later found to be positive for SCN1A mutations. The majority of pathological specimens demonstrated increased numbers of neurons in the molecular layer of the cortex and in the white matter. In all cases the patients continued to experience seizures despite surgery. Patients with histories consistent with SCN1A-related syndromes would benefit from genetic testing as part of the surgical evaluation, as cortical resection did not result in sustained improved outcome in this population.

References


Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Marsh, Skjei, Church, Harding, Holland-Bouley, Clancy, Porter, Heuer. Acquisition of data: Skjei, Harding, Santi, Holland-Bouley, Clancy, Porter, Heuer. Analysis and interpretation of data: all authors. Approved the final version of the manuscript: all authors. Accepted for publication: Marsh. Study supervision: Marsh, Heuer.

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