Focal epilepsy in SCN1A-mutation carrying patients: is there a role for epilepsy surgery?

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Pathogenic variants in SCN1A, the gene encoding the alpha 1 pore-forming subunit of the sodium channel, are the most common genetic cause for Dravet syndrome and the wider genetic epilepsy with febrile seizures plus (GEFS+) spectrum. GEFS+ includes clinical phenotypes ranging from classical febrile seizures in typically developing individuals to Dravet syndrome with drug-resistant epilepsy and intellectual disability.1 Even though febrile seizures are the characteristic initial seizure type of Dravet syndrome and GEFS+, focal seizures occur in both GEFS+ and Dravet syndrome.2

Most patients with an SCN1A variant have normal magnetic resonance imaging (MRI), although diffuse, cerebral or cerebellar, atrophy, increased white matter signal, and focal abnormalities are reported. Hippocampal sclerosis has been reported in Dravet syndrome, even though the incidence is unclear.4–6 Further, Barba et al.7 reported six patients with Dravet syndrome and SCN1A variants who had cortical malformations.

The co-occurrence of focal onset seizures and focal MRI findings in patients with SCN1A variants raises the question of whether these patients could benefit from resective epilepsy surgery, or whether the presence of a genetic abnormality implies an unfavourable outcome. Previous reports of postoperative outcome in patients with Dravet syndrome have been discouraging.8

We report a series of eight individuals with SCN1A variants who underwent resective epilepsy surgery.

**CASE SERIES**

**Method**

We conducted a retrospective note review in five epilepsy surgery centres on eight patients with drug-resistant epilepsy and SCN1A variants who underwent resective epilepsy surgery. In order to identify the epileptogenic zone and in line with current recommendations,9 all patients underwent a full presurgical evaluation; this included MRI, ictal video-electroencephalogram (EEG) monitoring, and neuropsychological assessment. Three patients also underwent positron emission tomography, one an ictal single-photon emission computerized tomography, and one a stereo-EEG recording. Histopathology was assessed on all surgical specimens. The Engel classification was used to assess postsurgical outcome.10 We classified seizures
Clinical genetic testing was performed. In order to evaluate the pathogenicity of missense variants in SCN1A, in silico prediction algorithms were used: SIFT (sorting tolerant from intolerant), PolyPhen-2 (polymorphism phenotyping v2), and MutationTaster. We determined if variants were present in control exomes (150 000 exomes in the Genome Aggregation Database [gnomAD, gnomad.broadinstitute.org]) and performed a literature search to determine if they were recurrent and reported in affected individuals. In one case (patient 8), in vitro functional testing was undertaken. Whole-cell patch-clamp recordings of tsA201 cells transfected with either wildtype or mutant alpha 1 subunits together with beta1- and beta2-subunits were performed as described previously.

**Patients**

Mean age at surgery was 13 years 11 months (SD 8y 1mo, range: 3–26y). Mean age at seizure onset was 8.25 months (SD 4mo, range: 2–14mo). Four patients were female and four male. Patient characteristics and investigation results are summarized in Table 1. According to their electroclinical phenotype, patients were divided into three groups.

Group 1 consisted of four patients who presented with infantile febrile seizures, who subsequently developed unilateral seizures with mesial temporal semiology and temporal onset on EEG. Two patients (patients 1, 3) also had preoperative generalized tonic-clonic seizures (GTCS) and interictal generalized spike wave discharges. No other seizure types were documented. All four patients had hippocampal sclerosis and underwent anterior temporal lobectomy.

Group 2 consisted of three patients with a clinical diagnosis of Dravet syndrome, characterized by multiple seizure types and multifocal, as well as generalized, EEG findings. MRI demonstrated focal cortical dysplasia in two and hippocampal sclerosis in one. In an attempt to ease their seizure burden, patients 5 and 6 underwent resection of the focal cortical dysplasia, and patient 7 an anterior temporal lobe resection.

Group 3 consisted of one patient (patient 8) with focal seizures involving the occipital lobe and negative MRI who underwent an occipital lobe resection. This patient had a personal and family history of uncomplicated febrile seizures, and a wider family history, through the maternal line, of occipital lobe epilepsy.

**Molecular genetics**

All patients had heterozygous variants in SCN1A (Table 2); none were present in gnomAD. Patient 5 and 7 had recurrent nonsense variants. The remaining six patients had missense variants, with four recurrent and two novel. Variant c.985G>T (p.Gly329Cys) (patient 6) is predicted to be disease-causing by SIFT, MutationTaster, and Polyphen 2. Variant c.1804G>A (p.Glu602Lys) (patient 8) is predicted to be damaging by MutationTaster, tolerated by SIFT, and benign by Polyphen 2; the variant was present in the mother and sister, who both had febrile seizures, but not in the wider family with occipital lobe epilepsy. In vitro functional testing demonstrated that the variant caused a clear loss of function by significantly reducing the current density (Fig. S1, online supporting information). Patient 3 has previously been published as case 3 in Livingston et al.; patient 7 has been described as patient 9 in Cooper et al.

**Surgical outcome**

Patients in groups 1 and 3 benefited from surgery; outcomes were Engel class IA (patient 8), IB (patient 2), ID (patient 1 and 4), and IIA (patient 3). All patients in these groups experienced no further focal seizures after surgery but some had occasional or isolated GTCS (Engel class ID and IIA). Histopathology confirmed hippocampal sclerosis in all four group 1 patients postoperatively. Patients with Dravet syndrome in group 2 did not improve with surgery: outcomes were Engel class III (patient 7) and IV (patients 5 and 6). Patient 7 preoperatively experienced seizures semiologically and electrographically consistent with right temporal origin as well as GTCS. She underwent surgery at 3 years of age. The focal seizures initially ceased after her right temporal lobectomy, but GTCS continued and additional myoclonic seizures developed. She died of sudden unexpected death in epilepsy 4 years after surgery.

**DISCUSSION**

There is increasing interest in whether a pathogenic variant in SCN1A precludes successful epilepsy surgery. Interpretation of the significance of a genetic variant in individuals undergoing presurgical evaluation, their relevance to the patient’s phenotype, and implications for surgical outcome require careful consideration. We describe a series of eight patients with SCN1A variants who underwent epilepsy surgery. Those who had focal onset seizures with concordant preoperative investigations benefited from focal resection, whereas those with a clinical phenotype of Dravet syndrome had poor postoperative outcome, despite resection of a structural lesion.

Little has been published about the outcome of epilepsy surgery in patients with SCN1A variants. Barba et al. described two patients with Dravet syndrome and SCN1A pathogenic variants who underwent epilepsy surgery for associated structural lesions, both with poor outcomes. Skjei et al. reported six patients with SCN1A variants who had epilepsy surgery, again with poor outcomes. Five patients had classical Dravet syndrome and one had GEFS with a history of severe head trauma.
| Patient | Sex | First seizure | Seizure types | Epilepsy classification | Ictal/interictal EEG | MRI | Further investigations | Age at surgery (y) | Surgery type | Histology | FU (y) | Engel class | Cognition |
|---------|-----|---------------|---------------|------------------------|---------------------|-----|------------------------|------------------|--------------|-----------|--------|------------|----------|
| 1       | F   | Febrile hemiclonic right | 15min | Focal, left temporal semiology, GTCS | Combined generalized and FTME with HS and SCN1A variant | Left temporal seizure onset, interictal, general bilateral SW | Left HS | PET: left temporal hypometabolism SPECT: not done | 13 | Left temporal lobectomy | HS | 12 | ID | IQ 66, improvement after surgery |
| 2       | F   | Hemiclonic right >30min | Focal, left temporal semiology | FTME with HS and SCN1A variant | Left temporal seizure onset | Left HS | PET: left temporal hypometabolism SPECT: not done | 25 | Left temporal lobectomy | HS | 8 | IB | IQ 63, stable after surgery |
| 3       | M   | Febrile 25min | Focal, left temporal semiology, GTCS | Combined generalized and FTME with HS and SCN1A variant | Left temporal seizure onset, interictal general bilateral SW | Left HS | Not done | 13 | Left temporal lobectomy | HS | 1 | IIA | IQ-50, stable after surgery |
| 4       | F   | Febrile GTCS-60min | Focal, right temporal semiology | FTME with HS and SCN1A variant | Right temporal seizure onset | Right HS | Not done | 9 | Right temporal lobectomy | HS | 6 | ID | IQ 59, stable after surgery |
| 5       | M   | Afebrile GTCS-20min | GTCS, atonic seizures, AA, MS | Dravet syndrome | Multifocal, documented left and right seizure onset | Right temporoparietal FCD | Not done | 15 | Right temporal lobectomy | FCD | 10 | IVA | IQ-30, stable after surgery |
| 6       | M   | Febrile hemiclonic left | GTCS, atonic seizures, AA, MS | Dravet syndrome | Multifocal, documented left and right seizure onset | Left temporoparietal FCD | PET: left temporoparietal hypometabolism Ictal SPECT: left hemispheric hyperperfusion excl. temporal lobe | 7 | Extended left temporoparietal mesial lesionectomy + AHE | FCD | 12 | IVB | IQ-50, deteriorating after surgery |
| 7*      | F   | Febrile hemiclonic 40min | Focal, right temporal semiology, MS | Dravet syndrome | Right temporal seizure onset, generalized bilateral SW Developmental delay | Right HS | Not done | 3 | Right temporal lobectomy | HS | 4 | III/ | SUDEP |
| 8       | M   | Febrile seizure | Focal, right occipital semiology, frequently evolving to bilateral GTCS | Focal occipital epilepsy with SCN1A variant | Right occipital seizure onset | Negative | Stereo-EEG: right occipital seizure onset | 26 | Partial right occipital lobectomy | Negative | 2 | IA | Normal cognition |

*Deceased. Group 1 = patients 1-4. Group 2 = patients 5-7. Group 3 = patient 8. Neurological examination was normal for all patients, except for patient 5, who was hypotonic and ataxic, and patient 6, who was hypotonic. EEG, electroencephalography; MRI, magnetic resonance imaging; FU, follow-up; GTCS, generalized tonic-clonic seizure; FTME, focal temporal mesial epilepsy; HS, hippocampal sclerosis; SW, spike waves; PET, positron emission tomography; SPECT, single-photon emission computerized tomography; AA, atypical absences; MS, myoclonic seizures; FCD, focal cortical dysplasia; AHE, amygdalohippocampectomy; SUDEP, sudden unexplained death in epilepsy.
In contrast, epilepsy surgery was beneficial in five out of eight patients in our series (Engel class I and II outcomes). These included all four patients in group 1 who had early prolonged febrile seizures with later development of temporal lobe seizures. They all had anatomic-electroclinical findings consistent with mesial temporal epilepsy with hippocampal sclerosis, rather than Dravet syndrome. Patients 1 and 3 also had experienced GTCS with interictal generalized spike wave and these two patients had ongoing rare GTCS postoperatively (Engel class I and II). After 4 years of postoperative seizure freedom, patient 4 experienced two GTCS. After adjusting her antiepileptic medication she has been seizure free for a further 2 years. One could speculate, as Tiefes et al. suggest, that the initial prolonged seizures, due to the SCN1A pathogenic variant, resulted in hippocampal sclerosis which, in turn, led to temporal lobe epilepsy. The GTCS in patients 1, 3, and 4, as well as the cognitive impairment of the four patients in group 1, could be the result of the SCN1A pathogenic variant.2

An excellent surgical outcome was observed in patient 8 (Engel class IA) who did not have a lesion on MRI, or on postoperative histopathology. He had occipital seizures with concordant surface and stereo-EEG findings. The SCN1A variant he carried was proven to cause a marked loss of function in an in vitro model system, but was not the cause of his familial occipital lobe epilepsy on clinical genetic grounds, and did not influence his postsurgical outcome. It can be argued that it may have caused the nuclear familial febrile seizures, but was not the cause of his familial occipital lobe epilepsy. Despite this, we decided to include him in this series to stress the point that the presence of an SCN1A variant, even if confirmed pathogenic and especially if not, should not automatically exclude a patient from presurgical assessment for epilepsy surgery. Critical assessment of the pathogenicity of the variant is essential.

Patients in group 2 with classical Dravet syndrome showed an unfavourable surgical outcome. Seizures failed to improve, or even worsened, after resection of a lesion (Engel class III/IV). For patients 5 and 6, their clinical semiology and EEG findings were not concordant with the MRI lesion. Arguably, based on clinical information, at the time of her surgery, patient 7 resembled patients 1 and 3 with GTCS and temporal onset focal seizures although the clinician suspected Dravet syndrome. She underwent surgery at 3 years, a time early in her natural history, and later went on to establish a full Dravet phenotype with ongoing GTCS and further seizure types (myoclonic seizures). Acknowledging the Dravet diagnosis was made in retrospect, it has to be recognized the surgery at an early age did not allow time for the full electroclinical phenotype to emerge, and might be a risk in patients with a likely pathogenic SCN1A variant. In analysis of this patient group, it has to be recognized the full phenotype of Dravet syndrome may not emerge until 4 years,1 and consequently when suspected should be considered in presurgical evaluation at this time.

We conclude that patients with the electroclinical phenotype of Dravet syndrome are not epilepsy surgery candidates, even in the presence of a single structural lesion, supporting the observations of Barba et al.7 and Skjøi et al.8 In the absence of electroclinical Dravet syndrome, when the presurgical evaluation reveals a single stereotyped

### Table 2: SCN1A variants in our cohort

| Patient | GRCh37/hg19 position | Allele change | Genomic reference sequence | Protein position | AA change | Variant effect | SIFT | Mutation taster | Polyphen 2 | Previously published |
|---------|----------------------|---------------|---------------------------|------------------|-----------|----------------|------|----------------|------------|----------------------|
| 1       | 2:166850722          | G/A           | c.4786C>T                 | 1596             | R/C       | Missense       | Disease causing | Probably damaging (1.000) | n/a        | Harkin et al.20       |
| 2+4     | 2:166848887          | C/T           | c.4888G>A                 | 1630             | V/M       | Missense       | Disease causing | Probably damaging (0.99) | n/a        | Marni et al.21        |
| 3       | 2:16690404           | A/G           | c.652T>C                  | 218              | F/L       | Missense       | Disease causing | Probably damaging (0.997) | n/a        | Livingston et al.22    |
| 5       | 2:166894639          | G/A           | c.2593C>T                 | 885              | R/*       | Missense       | Disease causing | Probably damaging (1.000) | n/a        | Xu et al.17           |
| 6       | 2:166905439          | C/A           | c.985G>T                  | 329              | G/C       | Missense       | Disease causing | Probably damaging (1.000) | n/a        | n/a                  |
| 7       | 2:166900385          | G/A           | c.1837C>T                 | 613              | R/*       | Missense       | Disease causing | Probably damaging (1.000) | n/a        | Kearney et al.18       |
| 8       | 2:166900418          | C/T           | c.1804G>A                 | 602              | E/K       | Missense       | Tolerated (0.18) | Disease causing | Benign (0.038) | Cooper et al.19       |

The table shows genomic location of the variants, protein position, and anticipated AA change, as well as the predicted effect of this change on protein function by in silico tools SIFT, polyphen 2, and mutation taster. In variants that have been previously published, the first paper describing the variant is cited. AA, aminoacid, SIFT, sorting tolerant from intolerant; Polyphen 2, polymorphism phenotyping V2.
focal seizure semiology with concordant EEG and imaging findings, patients may profit from epilepsy surgery even in the presence of a SCN1A pathogenic variant. However, the presence of preoperative generalized spike waves may be associated with ongoing GTCS, suggesting that a more guarded surgical prognosis with regard to seizure freedom should be offered. Clinicians should be cautious about postoperative antiseizure medicine withdrawal, maintaining pharmacological treatments likely to be effective for generalized seizures.

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SUPPORTING INFORMATION
The following additional material may be found online:

**Figure S1:** Transient Na+ currents recorded from transfected tsA201 cells.

REFERENCES

1. Scheffer IE, Zhang YH, Jansen FE, Dihlens L. Dravet syndrome or genetic (generalized) epilepsy with febrile seizures plus? Brain Dev 2009; 31: 394-400.

2. Zhang YH, Burgess R, Malone JP, et al. Genetic epilepsy with febrile seizures plus: refining the spectrum. Neurology 2017; 89: 1210-9.

3. Guerini R, Sztiano P, Catarino C, Siosiuya SM. Neuroimaging and neuropathology of Dravet syndrome. Epilepsia 2011; 52(Suppl 2): 10-4.

4. Siegler Z, Bari S, Neuwirth M, et al. Hippocampal sclerosis in severe myoclonic epilepsy in infancy: a retrospective MRI study. Epilepsia 2009; 46: 704-8.

5. Van Poppen K, Patay Z, Roberts D, et al. Mesial temporal sclerosis in a cohort of children with SCN1A gene mutation. J Child Neurol 2012; 27: 891-7.

6. Catarino CB, Liu JYW, Liagkouras I, et al. Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology. Brain J Neurol 2011; 134: 2982-1010.

7. Barbo C, Parrini E, Coras R, et al. Co-occurring malformations of cortical development and SCN1A gene mutations. Epilepsia 2014; 55: 1009-19.

8. Skjéti KL, Church EW, Harding BN, et al. Clinical and histopathological outcomes in patients with SCN1A mutations undergoing surgery for epilepsy. J Neurosurg Pediatr 2015; 16: 668-74.

9. Jayakar P, Gaillard WD, Tripathi M, Libenson MH, Mathern GW, Cross JH.Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia 2014; 55: 507-18.

10. Engel J Jr, Van Ness P, Rasmussen P, et al. Outcome with respect to epileptic seizures. In: Engel J, editor. Surgical Treatment of the Epilepsies. New York, NY: Raven Press, 1993: 609-21.

11. Fiore RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017; 58: 522-30.

12. Kumar P, Henikoff S, Ng PC. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. Nat Proto 2009; 4: 1073-81.

13. Aizhibei IA, Schmidt S, Peshkin L, et al. A method and server for predicting damaging missense mutations. Nat Methods 2010; 7: 248-9.

14. Schwarz JM, Cooper DN, Schuelke M, Seddow D. MutationTaster2: mutation prediction for the deep-sequencing age. Nat Methods 2014; 11: 361-2.

15. Laumann S, Boutry-Krysa N, Rivier C, et al. An SCN2A mutation in a family with infantile seizures from Madagascar reveals an increased subthreshold Na+ current. Epilepsia 2013; 54: e17-21.

16. Hedrich UBS, Laustard C, Kirschbaum D, et al. Impaired action potential initiation in GABAergic interneurons causes hyperexcitable networks in an epileptic mouse model carrying a human Na(V)1.1 mutation. J Soc Neurosci 2014; 34: 14874-89.

17. Xu X, Yang X, Wu Q, et al. Amplicon resequencing identified parental mosaicism for approximately 10% of ‘de novo’ SCN1A mutations in children with Dravet syndrome. Hum Mutat 2015; 36: 861-72.

18. Kearney J, Wiste AK, Stephani U, et al. Recurrent de novo mutations of SCN1A in severe myoclonic epilepsy of infancy. Pediatr Neurol 2006; 34: 116-20.

19. Cooper MS, McIntosh A, Crompton DE, et al. Mortality in Dravet syndrome. Epilepsy Res 2016; 128: 43-7.

20. Harkin LA, McMahon JM, Iona X, et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 2007; 130: 841-52.

21. Marinò C, Mei D, Temudo T, et al. Idiopathic epilepsies with seizures precipitated by fever and SCN1A abnormalities. Epilepsia 2007; 48: 1678-85.

22. Livingston JH, Cross JH, McElkan A, Birch R, Zuberi SM. A novel inherited mutation in the voltage sensor region of SCN1A is associated with Panayiotopoulos syndrome in siblings and generalized epilepsy with febrile seizures plus. J Child Neurol 2009; 24: 503-8.

23. Tiefes AM, Hartlieb T, Tacke M, et al. Mesial temporal sclerosis in SCN1A-related epilepsy: two long-term EEG case studies. Clin EEG Neurosci 2019; 50: 267-72.

24. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015; 17: 405-24.