Not all SCN1A epileptic encephalopathies are Dravet syndrome
Early profound Thr226Met phenotype

ABSTRACT

Objective: To define a distinct SCN1A developmental and epileptic encephalopathy with early onset, profound impairment, and movement disorder.

Methods: A case series of 9 children were identified with a profound developmental and epileptic encephalopathy and SCN1A mutation.

Results: We identified 9 children 3 to 12 years of age; 7 were male. Seizure onset was at 6 to 12 weeks with hemiclonic seizures, bilateral tonic-clonic seizures, or spasms. All children had profound developmental impairment and were nonverbal and nonambulatory, and 7 of 9 required a gastrostomy. A hyperkinetic movement disorder occurred in all and was characterized by dystonia and choreoathetosis with prominent oral dyskinesia and onset from 2 to 20 months of age. Eight had a recurrent missense SCN1A mutation, p.Thr226Met. The remaining child had the missense mutation p.Pro1345Ser. The mutation arose de novo in 8 of 9; for the remaining case, the mother was negative and the father was unavailable.

Conclusions: Here, we present a phenotype-genotype correlation for SCN1A. We describe a distinct SCN1A phenotype, early infantile SCN1A encephalopathy, which is readily distinguishable from the well-recognized entities of Dravet syndrome and genetic epilepsy with febrile seizures plus. This disorder has an earlier age at onset, profound developmental impairment, and a distinctive hyperkinetic movement disorder, setting it apart from Dravet syndrome. Remarkably, 8 of 9 children had the recurrent missense mutation p.Thr226Met. Neurology® 2017;89:1035-1042

GLOSSARY

GEFS+ = genetic epilepsy with febrile seizures plus.

The finding of de novo SCN1A mutations in Dravet syndrome was paradigm shifting in our understanding of the etiology of the developmental and epileptic encephalopathies. Less commonly, inherited SCN1A mutations occur in the self-limiting familial epilepsy syndrome of genetic epilepsy with febrile seizures plus (GEFS+). Missense and truncation mutations are found in approximately equal frequency in Dravet syndrome, while GEFS+ is largely associated with missense mutations. Despite >1,200 reported SCN1A mutations and most patients having novel mutations, there are no clear phenotype-genotype correlations.

We have identified a distinctive SCN1A developmental and epileptic encephalopathy that is far more severe than Dravet syndrome and is associated with a recurrent missense mutation. It is
Clinical features and investigations of children with early infantile SCN1A encephalopathy

| Case (sex/age) | Mutation | Sz onset age (offset) | Other Sz onset age | Sz triggers | MD onset | MD description | Age DD noted | Development outcome | Medication trials | Examination |
|---------------|----------|-----------------------|-------------------|-------------|----------|----------------|--------------|-------------------|------------------|-------------|
| 1 (M/8 y)     | c.677C>T, p.Thr226| 12 wk; HC-SE         | 18 mo-TC, T, 2 y-Ab, 3 y-M, ES; 5 y-F, NCS | M: sound and waking | 11 mo     | Hyperkinesis; dystonia; choreoathetosis including orofacial | 4 mo          | NV, communicates with facial gestures, smiles and sounds; NA, G-tube | VGB, CZP, VPA, steroids, PB, LTG, LEV, CLB, TPM | Hypertelorism, high forehead, small mouth; axial hypotonia; variable limb tone; kyphoscoliosis |
| 2 (M/6 y)     | c.677C>T, p.Thr226 | 9 wk; HC-SE          | 3 mo-TC, M, F; 2 y-ES, NCS | Excitement and water; ES: feeding and drinking | 3 mo      | Dystonia; choreoathetosis; myoclonic movements, especially orofacial, exacerbated by visual stimuli; tremulous on waking | 9 wk          | NV but vocalizes, NA-stands with support | PB, CBZ, VPA, CLB, KD | Axial hypotonia; variable limb tone |
| 3 (M/9 y)     | c.677C>T, p.Thr226 | 9 wk; HC-SE          | 18 mo-TC, 4 y-T, At; 7 y-ES | T: fever and feeding | 9 wk      | Continuous myoclonic movements, especially orofacial; exacerbated by excitement and bathing; severely tremulous on waking | 9 wk          | NV, NA-sits with support | PB, PHT, TPM, VPA, CBZ, AZD, steroids, LEV, STP, CBD, KD | Hypotonia |
| 4 (M/8 y)     | c.677C>T, p.Thr226 | 8 wk; TC-SE          | 9 wk-SE, 21 mo-M, 3 y-Ab, NCS; 5 y-MA | Fever, illness, and hot environment | 20 mo     | Dystonia; choreoathetosis; continuous unilateral horizontal nystagmus; myoclonic movements; profound ataxia | <6 mo         | NV, NA-sits with support | PB, VPA, CBZ, TPM, LEV, STP | Hypotonia |
| 5 (M/9 y)     | c.677C>T, p.Thr226 | 8 wk; TC-SE          | 6 wk-SE, 12 mo-TC, M, TC, F | Bowel movements | 9 mo      | Hyperkinesis; especially orofacial; continuous multifocal myoclonic movements; dystonia; nystagmus; vertical and horizontal | 9 mo          | NV-smiles, NA, G-tube | PB, VPA, CBZ, HB, TPM, STP | Microcephaly; axial hypotonia; variable limb tone with brisk reflexes; scoliosis |
| 6 (M/10 y)    | c.677C>T, p.Thr226 | 11 wk; TC (8 y)      | 10 wk-TC, ES; 6 mo-M; 1 y-Ab; 2 y-SE, F; 5 y-T | Fever, excitement, and overstimulation | 4 mo      | Continuous hyperkinesis and chorea; exacerbated by overstimulation | 10 wk         | NV, NA, G-tube | PB, PRD, ACTH, TPM, LEV, KD, CLB, CBZ, CZP, THP, AZD, LEV | Spasmus nutans; tone increased at 3 mo but hypotonic later |
| 7 (F/1 y)     | c.677C>T, p.Thr226 | 8 wk; LC | 6 wk; ES | Fever | 11 mo     | Continuous hyperkinesis; multifocal myoclonic movements; exacerbated by tiredness, drowsiness, and waking | 8 wk         | NV, NA, G-tube | CBZ, PB, VGB, VPA, PHT, CLB, LTG, steroids, LEV, KD, cannabis oils | Axial hypotonia; hypertonia of limbs |
| 8 (F/3 y)     | c.677C>T, p.Thr226 | 10 wk; HC, possible ES-6 wk | 10 wk-TC, ES; 6 mo-M; 1 y-Ab; 2 y-SE, F; 5 y-T | Fever | 11 mo     | Hypokinesia; choreoathetosis; myoclonic movements, especially orofacial | 10 wk         | Only 2 single words, NA, G-tube | CBZ, PB, VGB, VPA, PHT, CLB, LTG, steroids, LEV, KD, cannabis oils | Axial hypotonia; variable limb tone |
| 9 (M/12 y)*   | c.677C>T, p.Thr226 | 6 wk; ES             | 8 wk; HC | T: excitement, noise, light, and hot environment | 11 mo     | Continuous hyperkinesis; multifocal myoclonic movements; exacerbated by tiredness, drowsiness, and waking | 8 wk         | Only 2 single words, NA, G-tube | CBZ, PB, VGB, VPA, PHT, CLB, LTG, steroids, LEV, KD, cannabis oils | Axial hypotonia; variable limb tone |

Table: Clinical features and investigations of children with early infantile SCN1A encephalopathy

- **Mutation**: c.677C>T, p.Thr226Met de novo
- **Sz onset age (offset)**: 12 wk; HC-SE
- **Other Sz onset age**: 18 mo-TC, T, 2 y-Ab, 3 y-ES, 5 y-M, NCS
- **Sz triggers**: M: sound and waking
- **MD onset**: 11 mo
- **MD description**: Hyperkinesis; dystonia; choreoathetosis including orofacial; myoclonic movements, especially orofacial; exacerbated by visual stimuli; tremulous on waking
- **Age DD noted**: 4 mo
- **Development outcome**: NV, communicates with facial gestures, smiles and sounds; NA, G-tube
- **Medication trials**: VGB, CZP, VPA, steroids, PB, LTG, LEV, CLB, TPM
- **Examination**: Hypertelorism, high forehead, small mouth; axial hypotonia; variable limb tone; kyphoscoliosis
The Austin Health Human Research Ethics Commi-

RESULTS We identified 9 (7 boys) unrelated chil-
dren 3 to 12 years of age (table). They presented with
seizures at a mean age of 9 weeks (range 6–12 weeks)
with predominantly hemiclonic seizures (n = 6) but
also with bilateral tonic-clonic seizures (followed 1
week later by hemiclonic seizures in 1 patient) or
epileptic spasms. All children developed tonic-clonic
seizures by 18 months. Eight had episodes of con-
volutive status epilepticus with onset between 8 weeks
and 2 years (table). Myoclonic seizures (7 of 9),
tonic seizures (5 of 9), and spasms (5 of 9) were also seen.
Epilepsy was refractory to multiple antiepileptic
medications in all cases, although 1 child became
seizure free at 8 years. Five children had seizures
associated with fever or illness, and 2 children had
seizures exacerbated by high environmental tem-
perature. There were no reports of vaccination triggering
seizures. Other seizure triggers included auditory
stimuli (2), excitement (3), feeding (2), and bowel
movements (1).

METHODS Case 1 presented with an early infantile profound
developmental and epileptic encephalopathy. Because he had
hemiclonic seizures, the senior author (I.E.S.) requested SCN1A
testing that revealed a de novo missense variant (Thr226Met).
Because this phenotype was distinctive, we interrogated the Ep-
ilepsy Genetics Database at the University of Melbourne, which
contained 981 individuals with solved and unsolved developmen-
tal and epileptic encephalopathies tested for SCN1A mutations.
We searched for children with de novo SCN1A variants who
presented at <4 months of age and had a movement disorder.
All identified patients were included. This identified 3 additional
cases: cases 2 and 6 with the Thr226Met variant and case 9 with
the Pro1345Ser variant. Because 3 of the 4 cases had the
Thr226Met variant, we searched our database and the literature
for other cases with this variant and attempted to contact the
authors for more phenotypic information. This resulted in an
additional 2 cases (cases 3 and 4). The final 3 cases (cases 5, 7,
and 8) were recruited when collaborators asked the first (L.G.S.)
and senior (I.E.S.) authors about the role of the de novo SCN1A
Thr226Met variant that they had identified in their patients who
presented with an atypical phenotype for Dravet syndrome.

Epilepsy and medical history, neurologic examination,
and MRI and EEG data were obtained for each patient.
SCN1A mutations were identified by clinical or research test-
ing; segregation testing in parents was possible for 8
individuals.

Standard protocol approvals, registrations, and patient
consents. The Austin Health Human Research Ethics Com-
mitee and the New Zealand Health and Disability Ethics Commit-
tees approved the study. Informed consent was obtained for each
patient from the parents or legal guardian. In addition, specific
written consent for authorization of video use was obtained for
the 3 cases in the video.

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Initial development was considered normal by all parents, who gave reports of normal early developmental milestones. Delay was evident, however, by 6 to 16 weeks. At last review (range 3–12 years), 8 children were nonverbal, and 1 child spoke 2 single words. All were nonambulatory, and 7 required enteral feeding. The children had periods of regression or developmental plateauing resulting in profound intellectual disability. One child died at 10 years of sudden unexplained death in epilepsy.

All patients had a prominent movement disorder that developed within the first 2 years of life (9 weeks–20 months). Initially, they presented with subtle, low-amplitude myoclonic jerks. Over time, a hyperkinetic movement disorder comprising chorea, dystonia, and low-amplitude myoclonic movements was noted, particularly evident in the orofacial area (video at Neurology.org). Although not always present, the movement disorder was persistent and exacerbated on awakening and excitement. The abnormal movements were not seen during sleep. EEG recordings showed no epileptiform activity with these movements.

Eight of our 9 cases were trialed on antiepileptic drugs that could induce or exacerbate movement disorders or myoclonic seizures such as vigabatrin or sodium channel blockers (e.g., phenytoin, carbamazepine, oxcarbazepine, lamotrigine). In several cases, these drugs were begun well after the movement disorder had been recognized. Subsequent discontinuation of the medication had no effect on the movement disorder. There was also no clear exacerbation of their seizures with these medications; however, their seizures were so frequent that it may have been difficult to assess.

Neuroimaging was normal or showed nonspecific abnormalities. Four children had developmentally abnormal hippocampi; 2 had dysmorphic corpus callosum; and 2 had progressive white matter loss (table and figure). EEGs were initially normal in 3 children, but by 2 years of age, all had developed multifocal discharges and diffuse background slowing. Four children had generalized spike and slow wave or polyspike and slow wave.

All patients had SCN1A mutations; 8 were confirmed de novo. The mother of case 3 was negative, and the father was unavailable. Cases 1, 2, and 9 were identified on molecular inversion probe–targeted resequencing; cases 3, 4, and 8 were identified on clinical panels; case 5 was identified on whole-exome sequencing; and cases 6 and 7 were identified by SCN1A sequencing. No additional likely pathogenic variants were found in other genes in the cases that had targeted resequencing, clinical panels, or whole-exome sequencing. Eight children had the same missense mutation, p.Thr226Met, resulting from c.677C>T in exon 5. In silico tools suggested that it was deleterious (Grantham D = 81, Polyphen2 = 1, SIFT = 0, GERP = 5.77, CADD = 20.5). The ninth child had a de novo missense mutation,
Case History Case 1. Case 1 is an 8-year-old boy who presented at 12 weeks of age with afebrile hemiconic status epilepticus lasting 30 minutes. Frequent pharmacoresistant hemiconic seizures lasting 1 minute to 6 hours occurred daily. The lateralization of the clonic activity varied and occasionally migrated from 1 upper limb, to hemiconic, to both lower limbs, to hemiconic on the other side. Bilateral tonic-clonic and tonic seizures began at 18 months, absence seizures at 2 years, and myoclonic seizures or epileptic spasms at 3 years. By 5 years, he developed focal impaired awareness seizures that could progress to nonconvulsive status epilepticus lasting hours, frequent nocturnal tonic seizures, and weekly series of epileptic spasms. Seizures were triggered by waking but not by illness or fever. He has had multiple hospital admissions for status epilepticus and poor seizure control, the longest a 3-month admission at 18 months. Trials of phenobarbital, phenytoin, nitrazepam, clonazepam, levetiracetam, and topiramate were ineffective. The ketogenic diet was initiated at 4 years and resulted in improved control with cessation of myoclonic seizures. By 8 years, he was on ketogenic diet monotherapy and continued to have weekly tonic-clonic, focal impaired awareness, and tonic seizures in sleep and required admission every few months.

From birth, he had significant early feeding difficulties. Developmental milestones were otherwise normal with good head control, smiling, and fixating and following by 6 weeks. From 4 months, his development plateaued and fluctuated over the next few years with regression between 3 and 4 years. He lost eye contact, smiling, vocalization, head control, and the ability to roll over. He required a gastrostomy for feeding. When he was initiated on the ketogenic diet at 4.5 years, he had a marked improvement in alertness and developmental gains. At 8 years, he smiled, laughed, and vocalized vowel sounds but was nonverbal. He did not feed orally. He was able to roll over but could not sit.

He developed a hyperkinetic movement disorder by his first birthday consisting of choreiform movements including the orofacial area, dystonic posturing of the upper and lower limbs, and myoclonus without EEG correlate (video). Video monitoring at 16 months confirmed that all the abnormal movements did not have an epileptiform correlate. He has normal tone in his limbs with reduced truncal tone. He has hypertelorism, a high forehead, a small mouth, a normal head circumference, and a mild kyphoscoliosis. EEGs from 4 months showed multifocal epileptiform activity with background slowing. At 4 months, MRI brain revealed bilateral small hippocampi with a dysmorphic corpus callosum. By 3 years, he had developed left hippocampal sclerosis and progressive white matter atrophy (figure, A).

Case 2. Case 2 is a 6-year-old boy who presented at 9 weeks with 5 independent afebrile right and left hemiconic seizures lasting from 1 to 20 minutes over a 2-hour period that were treated with buccal and intravenous midazolam and intravenous phenytoin. Occasional hemiconic seizures continued despite the introduction of phenobarbital and topiramate. He developed myoclonic, focal impaired awareness and bilateral tonic-clonic seizures by 13 weeks. The seizures were not associated with fever but were more likely to occur on waking. At 13 weeks, he developed a periodic movement disorder initially lasting 10 to 30 minutes consisting of choreoathetosis, dystonia, and small-amplitude myoclonic jerks, which his parents called “dancing.” This was triggered by waking and excitement, particularly bathing. His movement disorder progressed over the next 18 months so that by 2 years it occurred almost continuously, although it settled in sleep. He did, however, have massive myoclonic jerks without EEG correlate on awakening. His epilepsy was refractory to sodium valproate, lamotrigine, and levetiracetam. From 2 years, he had infrequent episodes of focal nonconvulsive status epilepticus, characterized by loss of awareness, eye deviation, and facial twitching, lasting up to 2 hours. The EEG showed high-voltage rhythmic focal delta in the centro-parietal region. At 2.5 years, he developed flexor epileptic spasms when eating or drinking. The spasms occurred every 10 to 20 seconds for 3 minutes shortly after food or liquid was put in his mouth and interfered with his ability to chew and swallow. The spasms were controlled for 2 months but then relapsed and are ongoing. By 4 years, the massive myoclonic jerks were awakening him overnight, which triggered his movement disorder and prevented him from sleeping, posing a major problem for the family’s quality of life.

His development was normal at 9 weeks; he smiled and fixed and followed by 6 weeks. Within a week of seizure onset, he regressed with loss of visual fixation and head control. By 5 months, he was rolling over, and by 8 months, he was sitting and finger-feeding. After 9 months, his development plateaued with a period of regression at 2 years. At 6 years, he vocalizes but is nonverbal, nor can he sit or walk independently.

On examination, he was not dysmorphic and had almost continuous choreiform movements involving the limbs and orofacial region (video). His limb tone was variable with axial hypotonia. Early EEGs between 10 weeks and 4 months were normal, but
multifocal epileptiform abnormalities had developed by 2 years. MRI at 1 year showed bilateral small hippocampi with left hippocampal malrotation (figure, C).

**DISCUSSION** 

SCN1A is the most relevant epilepsy gene. Despite considerable effort, no phenotype-genotype correlation has been shown for the hundreds of SCN1A mutations identified, with the majority associated with Dravet syndrome and a small proportion with GEFS+. Here, we show a phenotype-genotype correlation for SCN1A describing a distinct SCN1A phenotype, early infantile SCN1A encephalopathy, that is far more severe than Dravet syndrome. We bring together novel cases and reanalyze the phenotype of reported cases with the recurrent mutation to identify a distinctive entity of early-onset developmental and epileptic encephalopathy with profound impairment and a prominent movement disorder.

Early infantile SCN1A encephalopathy can be readily distinguished from Dravet syndrome by several features. It has a younger age at onset, beginning at <3 months compared with the typical seizure onset age range of 4 to 15 months in Dravet syndrome. It is associated with profound developmental impairment rather than the severe to mild intellectual disability usually seen in Dravet syndrome. Infantile movement disorders are not part of the Dravet phenotype, whereas our patients have a distinctive movement disorder with choreoathetosis, dystonia, and perioral hyperkinesia. Other features differentiating early infantile SCN1A encephalopathy from Dravet syndrome are epileptic spasms, which are not seen in Dravet syndrome. Tonic seizures are described in adults with Dravet syndrome but are not part of the childhood phenotype.

We describe that the Thr226Met mutation is associated with a distinctive profound SCN1A encephalopathy. Three of the 8 patients with Thr226Met (cases 3, 4, and 6) have been previously reported as having Dravet syndrome. Case 6 was identified in 2007 in our large study delineating the phenotypic spectrum of Dravet syndrome. Cases 3 and 4 were drawn from a 2014 study of sleep problems associated with SCN1A-confirmed Dravet syndrome, but the phenotype was not described in the report. The phenotype, early infantile SCN1A encephalopathy, was not yet recognized, and Dravet-like features such as hemiclonic seizures led to the diagnosis of Dravet syndrome. We have reanalyzed the phenotype of these patients, and all share a homogeneous profound phenotype.

In addition, there are 2 further individuals reported with the Thr226Met mutation. One is a child described as having progressive myoclonus epilepsy; however, the limited available clinical information suggests that the phenotype of this child could be consistent with early infantile SCN1A encephalopathy. Overlap between the movement disorder and a progressive myoclonus epilepsy could be challenging to distinguish, especially given that the patient was middle-aged at the time of review. The remaining child presented with febrile status epilepticus at 6 months. However, she then developed extensor epileptic spasms at 10 months, which would be extraordinary for Dravet syndrome. This patient was not reported to have a movement disorder, but at 9 months, she had continuous myoclonic activity diagnosed as nonconvulsive status epilepticus. This could be a differential diagnosis of the movement disorder in our patients, but overall, she had better developmental progress. She also had an SCN9A variant (p.W1538R) that may have modified her phenotype. Perhaps this caused loss of function of SCN9A, which in some way modified the functional alteration due to the SCN1A Thr226Met mutation.

The Thr226Met mutation is not the only SCN1A mutation described at this specific codon. There are 2 reports of missense SCN1A mutations at codon c.677 that result in a different amino acid change to Thr226Arg or Thr226Lys. Not enough clinical information is provided in the reports to allow assessment of whether these children have a similarly profound phenotype.

A Japanese group has previously described a single case of infantile epileptic encephalopathy with a hyperkinetic movement disorder and hand stereotypes associated with a different novel SCN1A mutation. This Japanese child’s presentation sounds like early infantile SCN1A encephalopathy in terms of seizure onset age of 8 weeks; seizure types included epileptic spasms, hemiclonic seizures, myoclonic seizures, generalized tonic-clonic seizures, and status epilepticus, with profound impairment. The child also had an early-onset severe hyperkinetic movement disorder and a different SCN1A missense mutation (c.1264 G>T, p.Val422Leu) from that found in our cohort.

Despite there being >1,200 different reported SCN1A mutations, only 18% of mutations are recurrent. Mutations associated with GEFS+ are more likely to have a lower Grantham score than those that cause Dravet phenotypes. Missense mutations in the pore region lead to complete loss of function, similar to haploinsufficiency, but are seen in both Dravet syndrome (54%) and GEFS+ (31%). It is therefore not usually possible to predict an individual’s phenotype on the basis of their specific SCN1A mutation. Here, however, we have identified a severely striking SCN1A phenotype, early infantile SCN1A encephalopathy, that has a recurrent mutation at
c.677 in almost all cases. Somewhat counterintuitively, this more severe phenotype is associated with missense, rather than truncation, mutations.

There is increasing recognition of the overlap of developmental epileptic encephalopathies and movement disorders. Severe hyperkinetic (dystonia, choreoathetosis, myoclonus) movements have been described in a range of genetic encephalopathies caused by SCN2A, SCN8A, FOXG1, STXBP1, GNAO1, ARX, and DNM1, among others.12,15–17 Distinguishing a movement disorder from seizures may affect therapeutic approaches in terms of when to introduce antiepileptic therapy or other treatment modalities.

There is a large group of early-onset developmental and epileptic encephalopathies defined by their onset age of <3 months, often not fitting within a recognized epilepsy syndrome. These disorders have been recently associated with a large, heterogeneous range of genetic etiologies.18 They share common features such as multiple seizure types, profound to severe developmental delay, and movement disorders. It is unlikely that the seizures or the treatment per se cause the profound developmental impairment or movement disorders, given that a similar spectrum of seizure types with onset in later infancy or childhood does not have the same developmental sequelae. For example, infants with the self-limited “benign” early infantile seizure disorders may have frequent seizures with an abnormal EEG but without the long-term sequelae. Thus, we hypothesize that specific SCN1A mutations cause the overall phenotype. However, it is conceivable that this complex phenotype could be due to frequent seizures at a younger age.

SCN2A and SCN8A encephalopathies both are associated with gain-of-function mutations and respond well to sodium channel blockers.15,16 Here, we show that SCN1A also contributes to the severe early infantile–onset developmental encephalopathies, but we do not yet understand why this recurrent mutation causes this profound phenotype. It is interesting to speculate that it is possibly associated with a gain of function akin to SCN2A and SCN8A, but functional studies are required to prove the mechanism of this devastating disorder.

ACKNOWLEDGMENT
The authors thank the families for participating in their research.

STUDY FUNDING
Supported by the Health Research Council of New Zealand, Cure Kids New Zealand, the Ted and Mollie Carr Endowment Trust, the NIH (National Institute of Neurologic Disorders and Stroke), and the National Health and Medical Research Council of Australia. The DDD Study presents independent research commissioned by the Health Innovation Challenge Fund (grant HICF-1009-003); see Nature. 2015; 519:223-238 or www.ddduk.org/access.html for full acknowledgement.

DISCLOSURE
I. Sadleir serves on the epilepsy advisory board for Nutricia. A/Prof. Sadleir and E. Mountier are funded by Health Research Council of New Zealand grant 15/070, Cure Kids, and the Ted and Mollie Carr Endowment Trust. E. Mountier and D. Gill report no disclosures relevant to the manuscript. S. Davis has received Food and Drug Administration funding (1R01FD004147-01A1; ClinicalTrials.gov identifier NCT01720667). C. Joshi, C. DeVile, M. Kurian, S. Mandelstam, E. Wirrell, K. Nickels, and H. Murak report no disclosures relevant to the manuscript. G. Carvill is a member of the scientific advisory board of Amybry Genetics. C. Myers reports no disclosures relevant to the manuscript. H. Mefford is funded by NIH grant NINDS R01NS069605. I. Scheffer serves on the editorial boards of Neurology® and Epileptic Disorders and has served on the editorial board of Annals of Neurology. Epilepsy Currents; has received revenue from Medvet Science and Bioinformatics for patents; serves on the epilepsy advisory board for Nutricia; may accrue future revenue on a pending patent on therapeutic compound; has received speaker honoraria from Athena Diagnostics, UCB, GSK, Eisai, and Triagenetics; has received funding for travel from Athena Diagnostics, UCB, and GSK; and receives/have received research support from the National Health and Medical Research Council, Australian Research Council, NH, Health Research Council of New Zealand, March of Dimes, Weizmann Institute, Citizens United for Research in Epilepsy, US Department of Defense, and Perpetual Charitable Trustees. Go to Neurology.org for full disclosures.

Received January 17, 2017. Accepted in final form June 16, 2017.

REFERENCES
1. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001;68:1327–1332.
2. Harkin LA, McMahon JM, Iona X, et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 2007;130:843–852.
3. Wallace RH, Schieffer IE, Barnett S, et al. Neuronal sodium-channel alpha1-subunit mutations in generalized epilepsy with febrile seizures plus. Am J Hum Genet 2001; 68:859–865.
4. Meng H, Xu HQ, Yu L, et al. The SCN1A mutation database: updating information and analysis of the relationships among genotype, functional alteration, and phenotype. Hum Mutat 2015;36:573–580.
5. Dhamija R, Erickson MK, St Louis EK, Wirrell E, Kotagal S. Sleep abnormalities in children with Dravet syndrome. Pediatr Neurol 2014;50:474–478.
6. Carvill GL, Heavin SB, Yendle SC, et al. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in CHD2 and SYNGAP1. Nat Genet 2013;45: 825–830.
7. Dravet C. The core Dravet syndrome phenotype. Epilepsia 2011;52(suppl 2):3–9.
8. Manna M, Berkhovic SF, Dibbens LM, et al. A recurrent de novo mutation in KCN1 causes progressive myoclonus epilepsy. Nat Genet 2015;47:39–46.
9. Mulley JC, Hodgson B, McMahon JM, et al. Role of the sodium channel SCN9A in genetic epilepsy with febrile

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seizures plus and Dravet syndrome. Epilepsia 2013;54:e122–e126.

10. Wang JW, Shi XY, Kurahashi H, et al. Prevalence of SCN1A mutations in children with suspected Dravet syndrome and intractable childhood epilepsy. Epilepsy Res 2012;102:195–200.

11. Catarino CB, Liu JY, Liagkouras I, et al. Dravet syndrome as epileptic encephalopathy: evidence from long-term course and neuropathology. Brain 2011;134:2982–3010.

12. Kobayashi Y, Tohyama J, Kato M, et al. High prevalence of genetic alterations in early-onset epileptic encephalopathies associated with infantile movement disorders. Brain Dev 2016;38:285–292.

13. Ohashi T, Akasaka N, Kobayashi Y, et al. Infantile epileptic encephalopathy with a hyperkinetic movement disorder and hand stereotypies associated with a novel SCN1A mutation. Epileptic Disord 2014;16:208–212.

14. Brunklaus A, Zuberi SM. Dravet syndrome: from epileptic encephalopathy to channelopathy. Epilepsia 2014;55:979–984.

15. Howell KB, McMahon JM, Carvill GL, et al. SCN2A encephalopathy: a major cause of epilepsy of infancy with migrating focal seizures. Neurology 2015;85:958–966.

16. Larsen J, Carvill GL, Gardella E, et al. The phenotypic spectrum of SCN8A encephalopathy. Neurology 2015;84:480–489.

17. EuroEPINOMICS-RES Consortium, Epilepsy Phenome/Genome Project, Epi4K Consortium, et al. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. Am J Hum Genet 2014;95:360–370.

18. McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. Lancet Neurol 2016;15:304–316.

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**Longitudinal diffusion changes following postoperative delirium in older people without dementia (see p. 1020)**

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the September 5, 2017, issue of Neurology. In the first segment, Dr. Pearce Korb talks with Dr. Michele Cavallari and Dr. David Alsop about their paper on longitudinal diffusion changes following postoperative delirium in older people without dementia. In the second part of the podcast, Dr. Jeff Burns focuses his interview with Dr. Barbara Bendlin on poor sleep and biomarkers of amyloid pathology in cognitively normal adults.

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