ILLUSTRATIVE CASE STUDY

A four-day-old neonate, born at 38 weeks of gestation from an uncomplicated pregnancy, was admitted to the hospital because of frequent paroxysmal events with stereotyped motor activity. He presented with sequential seizures, characterized by asymmetric tonic posturing progressing to unilateral clonic movements of the limbs, that were often accompanied by autonomic features (e.g., cyanosis). They lasted for 1–2 min, occurred multiple times a day, and alternated between sides. Clinical and neurological examination in between these events was completely normal. Laboratory tests screening for infection and metabolic disturbances were normal. Interictal EEG showed sporadic focal sharp waves in central brain regions, and ictal EEG showed attenuation of the EEG followed by rhythmic spike discharges with shifting lateralization. Post-ictal EEG suppression quickly evolved to well-organized interictal brain activity with a normal EEG background. Brain MRI was normal. When the parents were asked about a possible family history of epilepsy, the child's mother recalled that she and her sister experienced neonatal seizures and that her sister had also a single seizure at adolescent age.
Questions
• Based on the current information, what is the most likely etiology of the child’s seizures?
• Which treatment would you start, based on the current information?
• What would you tell the parents regarding prognosis and risk of recurrence?

2 | SELF-LIMITED (FAMILIAL) NEONATAL EPILEPSY

Self-limited (familial) neonatal epilepsy (SeLNE), formerly called benign familial neonatal epilepsy (OMIM 121200), is an autosomal dominant disorder first described by Rett and Teubel in 1964. It is characterized by unprovoked seizures starting between Day 2 and 7 of life, in an otherwise healthy infant. Seizures are typically sequential, characterized by tonic features at the onset that may progress in a sequential pattern to clonic features, automatisms, and non-motor autonomic features, including apnea leading to oxygen desaturation and cyanosis. Lateralization typically changes between or during seizures. Seizures occur multiple times a day at seizure onset. They tend to remit within the first 6 months of life, as reflected in the term “self-limited”. However, seizure recurrence later in life may occur. Clinical and neurological examinations, as well as brain MRI, are normal. Neurodevelopment is normal and prognosis is favorable. Patients typically have a positive family history for neonatal epilepsy which suggests the presence of a genetic epilepsy, but sporadic occurrence is possible.

Neonatal seizures occur in approximately 1–4 per 1000 term-born neonates and are associated with unfavorable developmental outcomes in >50% of cases. Therefore, it is crucial to correctly identify seizure etiology in a short period of time, to choose the correct therapeutic approach, and to make a reliable prognosis. Next to structural causes (e.g., hypoxic–ischemic encephalopathy and stroke), genetic causes are most frequently identified. SeLNE, as part of the genetic epilepsy group, accounts for 3% of all cases of neonatal seizures. Neonatal seizure in the context of a genetic developmental and epileptic encephalopathy (DEE) is the most important differential diagnosis (see KCNQ2-DEE below).

3 | SELF-LIMITED (FAMILIAL) INFANTILE EPILEPSY

Self-limited (familial) infantile epilepsy (SeLIE), formerly known as benign familial infantile epilepsy (OMIM 607745), is an autosomal dominant disorder characterized by unprovoked seizures starting between 3 and 20 months of age (median: 6 months). Seizures tend to be brief, occur in clusters and are most often focal-onset motor seizures with or without impaired awareness and focal to bilateral tonic–clonic seizures. As in the neonatal form, seizures are treatment-responsive and “self-limited” after a few months or, sporadically, years. Nevertheless, seizure recurrence may occur at a later age. Some children develop paroxysmal kinesigenic dyskinesia later in life. Interictal EEG recordings are normal or show sporadic focal epileptiform activity, and brain MRI is generally without abnormalities. In addition, neurodevelopment before and after the onset of seizures is completely normal. A positive family history of infantile seizures and/or paroxysmal dyskinesia is noted in most cases, but sporadic occurrence exists.

4 | SELF-LIMITED FAMILIAL NEONATAL-INFANTILE EPILEPSY

Self-limited familial neonatal-infantile epilepsy (SeLFNIE), formerly known as benign familial neonatal-infantile epilepsy, is a diagnosis that can only be made in the presence of a familial history, as it requires individuals with both neonatal or infantile onset of seizures within the same family. Seizures have an onset between 1 day and 23 months of age (median: 13 weeks). Seizures resemble those seen in SeLNE, with sequential seizures...
consisting of tonic and sometimes autonomic (apnea and cyanosis) features. Clonic seizures can also be seen. Interictal EEG and brain MRI are normal. Seizures remit by the age of 12–24 months, and psychomotor development before and after the onset of seizures is normal.

### Table 1

<table>
<thead>
<tr>
<th>Self-limited familial epilepsy characteristics</th>
<th>Major associated disorder</th>
<th>Less common associations</th>
<th>Median age at seizure-onset</th>
<th>Median age at seizure-remission</th>
<th>Special features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant disorder</td>
<td>&gt;80% of SeLNE</td>
<td>SeLFNIE and SeLIE</td>
<td>&lt;1 week</td>
<td>6 weeks (&gt;90% by 6 months)</td>
<td>Increased risk of seizures later in life</td>
</tr>
<tr>
<td>SCN8A</td>
<td>&lt;5% of SeLIE</td>
<td>SeLFNIE</td>
<td>6 months</td>
<td>&lt;5 years</td>
<td>33% seizure recurrence later in life, 33% develop PKD or ataxia</td>
</tr>
</tbody>
</table>

Abbreviations: PKD, paroxysmal kinesigenic dyskinesia; SeLFNIE, self-limited familial neonatal-infantile epilepsy; SeLIE, self-limited (familial) infantile epilepsy; SeLNE, self-limited (familial) neonatal epilepsy.

### 5 | Genetic Architecture of the Self-Limited Familial Epilepsies with Onset in Neonatal Age and Infancy

#### 5.1 | Inheritance

Pathogenic variants leading to the self-limited (familial) epilepsies are generally inherited in an autosomal dominant mode. Consequence, there is often a positive family history of epilepsy that may lead to the suspicion of the disorder. Since parents do not always recall having had neonatal seizures themselves, the family history should often be sought from the grandparents. Incomplete penetrance of around 75%–80% has been described for pathogenic variants in all associated genes, so asymptomatic carriers are seen in some families. Occasionally, variants arise de novo, and patients present as isolated cases. When individuals with self-limited epilepsy carry a heterozygous de novo pathogenic variant, caution must be taken regarding the possibility of carrying the variant in a mosaic state. Specific variants in some of the self-limited (familial) epilepsy genes (i.e., KCNQ2, SCN2A, and SCN8A) will lead to a developmental and epileptic encephalopathy (DEE) when carried in a non-mosaic state, but will cause a milder phenotype in cases of mosaicism. The offspring will have a risk of between 0% and 50% of inheriting the variant in a non-mosaic state. They will thus be more seriously affected and will not only have early-onset seizures, but neurodevelopmental delay as well. The main characteristics of self-limited familial epilepsy syndrome associated with the most commonly implicated genes are presented in Table 1.

#### 5.2 | Implicated genes

##### 5.2.1 | KCNQ2

KCNQ2 (OMIM 602235) is by far the most common gene associated with SeLNE, and pathogenic variants in this
gene are identified in over 80% of cases.\(^{14,15,18}\) The gene is located on chromosome 20 and encodes a voltage-gate potassium channel subunit, Kv7.2, that underlies the so-called “M-current”, which controls neuronal excitability.\(^{19}\) KCNQ2 is expressed in both excitatory and inhibitory neurons from early fetal life, and expression decreases after birth.\(^{20}\) Pathogenic variants in KCNQ2 can lead to a spectrum of disorders ranging from SeLNE to DEE.\(^{21}\) Pathogenic variants associated with SeLNE include splice, nonsense, frameshift, deletion, and missense variants, that are distributed across the gene, and result in loss-of-function (LoF).\(^{19,22}\) A penetrance of approximately 80% has been estimated for KCNQ2-SeLNE.\(^{15}\) KCNQ2-DEE, on the other hand, is caused by missense or in-frame deletions that are located in functional hotspots and have dominant-negative effects.\(^{19,22}\) KCNQ2-DEE is also associated with frequent neonatal seizures with similar seizure semiology, but children with this disorder have a clear neurodevelopmental delay.\(^{21}\) Neonates with KCNQ2-DEE are often born with hypotonia, have feeding problems from the start, and do not have a positive family history of neonatal epilepsy.\(^{21,23}\) Finally, also variants with gain-of-function (GoF) effects are described, leading to a different phenotype with neurodevelopmental delay without neonatal seizures (but potential infantile or childhood-onset seizures).\(^{24-27}\) Known pathogenic KCNQ2 variants and related phenotype are summarized in the KCNQ2 patient registry (www.rikee.org).

KCNQ2-related self-limited familial epilepsies are characterized by seizures starting in the first week of life in an otherwise healthy neonate. Rarely, seizure onset exceeds neonatal age, and starts during infancy (between 1 and 6 months of age), which is sometimes attributed to prematurity.\(^{15,28,29}\) Rare SeLFNIE and SeLIE families with pathogenic KCNQ2 variants have been described, accounting for approximately 3% of SeLIE cases.\(^{29}\) Seizures are sequential and have the typical motor semiology of asymmetric tonic posturing with changing laterality that can evolve into unilateral or bilateral clonic movements. They can be accompanied by ocular movements, head or eye deviation, automatisms (e.g., shrill cry, chewing), and autonomic symptoms, including apnea causing desaturation and cyanosis.\(^{30}\) Seizures are usually brief (1–2 min), but can take up to 10 min, and often occur multiple times a day at seizure onset.\(^{15,30}\) Status epilepticus is only seldom described.\(^{15}\) Post-ictal phase is short or absent, and neonates behave normal interictally.\(^{30}\) Seizures remit after a few weeks to months (median: 6 weeks of life, with >90% remitted at 6 months of age) with or without anti-seizure medication.\(^{15,30}\) However, about 10%–30% of individuals have seizure recurrence later in life (febrile or afebrile), starting mostly in childhood or early adolescence.\(^{15,30}\) Interictal EEG recordings are generally normal but can show (multi-) focal epileptiform activity.\(^{15,31}\) Ictal EEG often shows generalized suppression of amplitude at onset, followed by symmetric or asymmetric slow waves, evolving into high-voltage polyspike discharges which become intermittent with suppression periods in between.\(^{30}\) Amplitude-integrated EEG (aEEG) seizure pattern typically consists of a sudden rise of the lower and upper margins immediately followed by a marked depression of the amplitude due to postictal generalized EEG suppression.\(^{32}\) Brain MRI is typically normal. Long-term neurodevelopmental outcome is normal, but interfamilial variability and patients with learning disabilities, behavioral problems (e.g., autism) or mild developmental delay are described.\(^{18,30,31,33}\)

Both KCNQ2-SeLNE and KCNQ2-DEE present with frequent neonatal seizures with similar clinical and electrographic seizure semiology. Prognosis is, however, clearly different, and differential diagnosis is crucial for proper counseling of parents. Contrary to KCNQ2-SeLNE, interictal EEG for KCNQ2-DEE is abnormal and is marked by a burst-suppression pattern or multifocal epileptic abnormalities on a discontinuous background. Hypotonia, feeding difficulties, and poor visual attention are indicative of a KCNQ2-DEE phenotype, but the use of sedating anti-seizure medication such as phenobarbital can complicate clinical evaluation. A positive family history, if present, and information on the exact genotype, when it becomes available, can inform prognosis.

### 5.2.2 | KCNQ3

KCNQ3 (OMIM 602232) variants are identified in approximately 5% of SeLNE families.\(^{15}\) The gene is located on chromosome 8 and encodes a voltage-gated potassium channel subunit, Kv7.3, that forms heterotetrameric potassium channels together with KCNQ2 subunits. KCNQ3 is expressed in excitatory and inhibitory neurons and expression increases from late fetal life to infancy.\(^{20}\) Pathogenic variants in KCNQ3 are associated with a spectrum of SeLNE to DEE. SeLNE is caused by heterozygous missense KCNQ3 variants.\(^{31,34}\) A penetrance of approximately 80% has been estimated for KCNQ3-SeLNE.\(^{3}\) KCNQ3-DEE is associated with recessive inheritance, as homozygous frameshift and compound heterozygous missense KCNQ3 variants are described in children with neonatal-onset DEE.\(^{35,36}\) KCNQ3 missense variants leading to a GoF have been identified in individuals with developmental delay without neonatal seizures.\(^{37}\)

KCNQ3-related SeLNE is characterized by seizures starting during the first week of life in an otherwise healthy infant.\(^{38}\) Occasionally, seizure onset starts during infancy.\(^{39,39,40}\) Seizures are clinically similar to the
sequential seizures in KCNQ2-related SeLNE. They are characterized by head and eye deviation and/or asymmetric clonic or tonic movements, and are often accompanied by autonomic changes (e.g., cyanosis and tachycardia).\textsuperscript{4,38} Seizures occur multiple times a day and last <2 min.\textsuperscript{34} Ictal EEG shows a generalized decrease in EEG amplitude that evolves into bilateral sharp-wave discharges or shows focal epileptiform discharges.\textsuperscript{4,34} Seizures are treatment-sensitive and remit during the neonatal-infantile period, although seizure recurrence is described.\textsuperscript{38} Brain MRI is unremarkable. Neurodevelopmental outcome is favorable, but mild to moderate intellectual disability (ID) sporadically co-occurs.\textsuperscript{31,38}

5.2.3 | SCN2A

SCN2A (OMIM 182390) is located on chromosome 2 and encodes the alpha subunit of voltage-gated sodium channels, Nav1.2, predominantly expressed in cortical excitatory neurons and the cerebellar cortex.\textsuperscript{8} Pathogenic variants in SCN2A are associated with a spectrum of disorders ranging from self-limited familial epilepsy to episodic ataxia, autism spectrum disorder (ASD), and DEE.\textsuperscript{8} SCN2A missense variants with GoF effects are related to either self-limited familial epilepsy or DEE, and these variants tend to cluster in functional hot spots (e.g., transmembrane segments and connecting loops).\textsuperscript{8} In contrast, SCN2A missense variants with LoF effects and truncating variants or deletions are related to ID without epilepsy and/or autism spectrum disorders.\textsuperscript{8}

Pathogenic SCN2A variants causing self-limited familial epilepsy result in seizures that either start during the neonatal period or during infancy, and SCN2A is the major gene associated with SeLFNIE. Age at onset can vary between family members from Day 1 to 23 months (median: 3 months), with approximately 50% having seizure onset within the first month of age.\textsuperscript{8,12,15} SCN2A variants can also be found in rare families with SeLNE, and SeLIE.\textsuperscript{29} Seizures are afebrile and are characterized by focal motor seizures with impaired awareness (e.g., head and eye deviation) with possible evolution to bilateral tonic-clonic seizures. Apnea and staring are often reported during seizures.\textsuperscript{12,41} Seizures are clustered, last <4 min (mostly <1 min), occur multiple times a day, and are treatment-responsive.\textsuperscript{12,41} Seizures are resolved by 2 years of age (median: 5 months), but some develop seizure recurrence or episodic ataxia later in life.\textsuperscript{8,12,13,29,42} Ictal EEG shows epileptiform activity with focal onset (typically occipital) that evolves with bilateral discharges. Intercital EEGs are either normal or show (multi-) focal spikes with normal background activity.\textsuperscript{12,13} Brain MRI, clinical neurological examination, and neurodevelopmental outcome are normal.\textsuperscript{12}

5.2.4 | PRRT2

PRRT2-related epilepsy (OMIM 614386) has an incidence of 1 per 9970 live births and pathogenic variants are detected in approximately 80% of patients with SeLIE.\textsuperscript{28,29,43,44} The gene is located on chromosome 16 and encodes the proline-rich transmembrane protein 2, which has an important role in exocytosis and neurotransmitter release.\textsuperscript{45} Pathogenic variants in PRRT2 are associated with a spectrum of disorders ranging from SeLIE to paroxysmal (non-)kinesigenic dyskinesia, hemiplegic migraine, and childhood absence epilepsy.\textsuperscript{44} Heterozygous pathogenic variants in PRRT2 associated with SeLIE result in LoF and include nonsense, frameshift, and missense variants. c.649dupC [p.Arg217Profs*8] and c.649delC [p.Arg217Glufs*12] are known to be hot spot variants.\textsuperscript{28} A penetrance of approximately 75% has been estimated for PRRT2-SeLIE.\textsuperscript{16} Homozygous or compound heterozygous variants in PRRT2, on the other hand, are associated with more severe phenotypes, such as DEE, learning abilities, behavioral problems, prolonged periods of ataxia, or combinations of persistent paroxysmal disorders (e.g., paroxysmal non-kinesigenic dyskinesia and episodes of ataxia).\textsuperscript{28,46,47}

PRRT2-related SeLIE is characterized by clusters of focal to bilateral tonic-clonic seizures. During seizures, patients often show eye or head deviation, hypertonia, clonic movement of limbs, and/or cyanosis.\textsuperscript{46} Seizure onset ranges from 2 to 8 months of age (median: 6 months), and seizures tend to disappear before 3 years of age with or without anti-seizure medication.\textsuperscript{29} Sporadically, earlier seizure onset has been reported.\textsuperscript{45} Seizure recurrence later in life is described in isolated cases.\textsuperscript{29,48} Ictal EEG shows (multi-) focal epileptic activity that may generalize, while interictal EEG is normal.\textsuperscript{46} Neurodevelopmental outcome is generally good, but learning difficulties are described.\textsuperscript{48}

During childhood or adolescence, some patients with SeLIE develop paroxysmal kinesigenic dyskinesia (PKD), known as “infantile convulsions with paroxysmal choreathetosis syndrome” (“ICCA”) (OMIM: 602066). Patients with PKD experience short episodes of dystonia, paroxysmal chorea, and/or athetosis, triggered by sudden voluntary movements.\textsuperscript{44} In ICCA families, individuals with self-limited infantile seizures, PKD, or both are described, thus no clear genotype–phenotype correlations exist for any of the three phenotypes.\textsuperscript{44} Interestingly, patients with SeLIE who later develop PKD tend to have later seizure remission (median: 17 months) and sometimes have more treatment-resistant seizures than patients who do not develop PKD (median: 6 months).\textsuperscript{46}
SCN8A (OMIM: 600702) is located on chromosome 12 and encodes the alpha subunit of the voltage-gated sodium channel subunit, Nav1.6. Pathogenic variants in the gene are associated with a spectrum of disorders ranging from SeLIE to ASD, movement disorders without epilepsy, ID or DEE. Pathogenic variants exerting GoF effects (mostly missense variants) cause SeLIE or DEE, while variants with LoF effects (mostly truncating variants, deletions, and missense variants) are associated with generalized epilepsy (median onset age of 24 months), ASD, movement disorders (e.g., myoclonus, or ataxia), and ID without epilepsy. Some variants are associated with SeLIE as well as DEE (e.g., p.Asn1877Ser, p.Arg1872Gln, p.Gly1475Arg, and p.Arg1617Trp). SCN8A-SeLIE is characterized by focal motor-onset epilepsy with impaired awareness that may evolve into bilateral tonic–clonic seizures, but also focal tonic seizures are described. Seizure onset ranges from 2 weeks to 1 year of age (median: 6 months), and seizures are treatment-responsive. Sporadically, seizures start in the neonatal period. Seizure remission occurs within the first year, but seizure recurrence later in life has been described in one-third of patients. Intercital EEG is normal or may show rare epileptiform activity. Brain MRI is unremarkable. Neurodevelopmental outcome is typically normal, but interfamilial variability is described, with some family members having some degree of ID. Remarkably, one-third develop PKD (ICCA) or ataxia later in life.

6 | GENETIC TESTING

Self-limited familial epilepsy should be considered in normal developing children with neonatal- or infantile-onset focal motor seizures, who have a family history of neonatal- or infantile-onset epilepsy. Clinical examination, laboratory tests, and brain MRI should be normal. If self-limited familial epilepsy is suspected, genetic screening should be performed, as the genetic diagnosis can help to make the correct therapeutic choices, perform proper genetic counseling, and give a reliable prognosis. In this selected patient population, a genetic diagnosis can be made in approximately 80%–90% of cases. Given the genetic heterogeneity, most laboratories perform targeted panel analysis or whole-exome sequencing as a first step. Sanger sequencing of the most likely involved gene can be an option in areas that lack access to next-generation sequencing (NGS) techniques. If first-tier testing is negative in the case of clinical suspicion of either KCNQ2 or PRRT2-related epilepsy, one should specifically ask the laboratory whether a deletion of this gene can be excluded, as this might be missed by some NGS techniques. Genetic testing of affected family members can aid in variant interpretation.

7 | PRACTICAL MANAGEMENT CONSIDERATIONS

When self-limited familial epilepsy is suspected, sodium channel blocking antiseizure medications (e.g., carbamazepine, oxcarbazepine, phenytoin) are considered as first-line treatment. These medications are believed to be most effective in patients carrying KCNQ2 and KCNQ3 LoF, SCN2A and SCN8A GoF, and PRRT2 variants. Seizures are generally treatment-responsive. Caution must be taken when infants with SCN8A variants start to display generalized-onset seizures (e.g., absence, generalized tonic–clonic, and myoclonic seizures), because these can be caused by SCN8A LoF variants. In this group of patients, no effect or even worsening of seizures with sodium channel-blocking antiseizure medications can occur.

When seizures start in neonates or young infants, finding a pathogenic variant in the genes KCNQ2, SCN2A or SCN8A may raise doubts about the benign course of the disease, as heterozygous variants in these genes have been associated both with self-limited familial epilepsy and DEE. Some clues may lead to the diagnosis of DEE rather than self-limited familial epilepsy, i.e. absence of a familial history of self-limited familial epilepsy, hypotonia and feeding difficulties from birth, treatment-resistant seizures, and/or a burst-suppression pattern or marked slow background on EEG. Once a genetic diagnosis is made, it is recommended to check the literature and public variant databases to determine whether the variant has already been described, and is indeed associated with self-limited familial epilepsy (e.g. for KCNQ2/3: www.rikee.org, for SCN8A: www.scn8a.net). If the variant has already been described before, a more reliable prognosis can be offered. It should, however, be stressed that phenotypic variability between persons carrying the same pathogenic variant exists, even within a single family. As such, some patients carrying a presumed self-limited familial epilepsy variant might have seizure recurrence later in life, develop PKD or episodic ataxia (SCN2A, SCN8A, and PRRT2), have behavioral problems and/or have some mild degree of ID. This suggests the existence of genetic and/or environmental modifiers and complicates genetic counseling for individual patients. Close clinical follow-up with a specific focus on developmental milestones and seizure symptoms is therefore recommended for all patients.
8 | CASE RESOLUTION

Based on the characteristic electroclinical phenotype and the positive family history, a diagnosis of SeLNE was made. Therefore, low-dose carbamazepine (10mg/kg/day) was started with rapid resolution of seizures. Targeted panel analysis was performed, and identified a maternally inherited KCNQ2 c.1342C>T (p.Arg448*) variant. This variant has been previously reported in several SeLNE families.15,29,58,59

Reassurance about the self-limiting character of the disorder with subsequent normal neurodevelopment was offered, taking into account a small increased risk of development of seizures later in life (10%–15%). In addition, the recurrence risk of 50% and the possibility of genetic testing for the maternal aunt were discussed. There is little information to guide practitioners in the duration of antiepileptic medications for SeLNE. Anecdotal reports have suggested that seizures can recur if medications are weaned in the first year of life, and drug withdrawal between the age of 12 and 18 months has been proposed.60,61 At 13 months of age, treatment with carbamazepine was discontinued. The child experienced one simple febrile seizure at 4 years of age, for which no treatment was started. At the last follow-up visit, the child was 6 years of age and showed normal neurodevelopment.

This manuscript in the Genetic Literacy series maps to Learning Objective 1.2 of the ILAE Curriculum for Epileptology.62

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REFERENCES


SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

APPENDIX 1
Full list of ILAE Genetics Commission Members:

Piero Perucca (Bladin-Berkovic Comprehensive Epilepsy Program, Austin Health, Australia, and Department of Medicine (Austin Health), Melbourne Medical School, The University of Melbourne, Australia). J. Helen Cross (UCL-Institute of Child Health, Great Ormond Street Hospital for Children, London & Young Epilepsy, Lingfield, UK). Holger Lerche (Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany). Alina I. Esterhuizen (UCT/MRC Genomic and Precision Medicine Research Unit, Division of Human Genetics, Department of Pathology, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa). Iscia Lopes-Cendes (Department of Translational Medicine, University of Campinas, Campinas, Brazil). Meng-Han Tsai (Department of Neurology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan). Samuel F. Berkovic (Epilepsy Research Centre, University of Melbourne, Heidelberg, Victoria, Australia). Daniel H. Lowenstein (Department of Neurology, University of California, San Francisco, USA). Nigel C. K. Tan (Department of Neurology, National Neuroscience Institute, Singapore, Singapore). Ingo Helbig (Division of Neurology, The Children’s Hospital of Philadelphia, Philadelphia, USA). Heather C. Mefford (Center for Pediatric Neurological Disease Research, St. Jude Children’s Research Hospital, Memphis, USA). Andreas Brunklaus (Institute of Health and Wellbeing, University of Glasgow, UK). Gaetan Lesca (Department of Genetics, Hospices Civils de Lyon, Bron, France).