Extending the *KCNQ2* encephalopathy spectrum

Clinical and neuroimaging findings in 17 patients

Sarah Weckhuysen, MD
Vanja Ivanovic, MD
Rik Hendrickx, BSc
Rudy Van Coster, MD, PhD
Helle Hjalgrim, MD, PhD
Rikke S. Møller, MSc, PhD
Sabine Grønberg, MD
An-Sofie Schoonjans, MD
Berten Ceulemans, MD, PhD
Sinead B. Heavin, PhD
Christin Eltze, MD, Res
Rita Horvath, MD, PhD
Gianluca Casara, MD
Tiziana Pisano, MD
Lucio Giordano, MD
Kevin Rostasy, MD
Edda Haberlandt, MD
Beate Albrecht, MD
Andrea Bevo, MD
Ira Benkel, MD
Steffan Syrbe, MD
Beth Sheidley, MS, CGC
Renzo Guerrini, MD
Annapurna Poduri, MD, MPH
Johannes R. Lemke, MD
Simone Mandelstam, MB, ChB
Ingrid Scheffer, MBBS, PhD
Marco Angriman, MD
Pasquale Striano, MD, PhD
Carla Marini, MD, PhD
Arvid Suls, PhD
Peter De Jonghe, MD, PhD
On behalf of the *KCNQ2* Study Group

Correspondence to
Dr. De Jonghe:
peter.dejonghe@molgen.vib-ua.be

Supplemental data at
www.neurology.org

ABSTRACT

Objectives: To determine the frequency of *KCNQ2* mutations in patients with neonatal epileptic encephalopathy (NEE), and to expand the phenotypic spectrum of *KCNQ2* epileptic encephalopathy.

Methods: Eighty-four patients with unexplained NEE were screened for *KCNQ2* mutations using classic Sanger sequencing. Clinical data of 6 additional patients with *KCNQ2* mutations detected by gene panel were collected. Detailed phenotyping was performed with particular attention to seizure frequency, cognitive outcome, and video-EEG.

Results: In the cohort, we identified 9 different heterozygous de novo *KCNQ2* missense mutations in 11 of 84 patients (13%). Two of 6 missense mutations detected by gene panel were recurrent and present in patients of the cohort. Seizures at onset typically consisted of tonic posturing often associated with focal clonic jerking, and were accompanied by apnea with desaturation. One patient diagnosed by gene panel had seizure onset at the age of 5 months. Based on seizure frequency at onset and cognitive outcome, we delineated 3 clinical subgroups, expanding the spectrum of *KCNQ2* encephalopathy to patients with moderate intellectual disability and/or infrequent seizures at onset. Recurrent mutations lead to relatively homogenous phenotypes. One patient responded favorably to retigabine; 5 patients had a good response to carbamazepine. In 6 patients, seizures with bradycardia were recorded. One patient died of probable sudden unexpected death in epilepsy.

Conclusion: *KCNQ2* mutations cause approximately 13% of unexplained NEE. Patients present with a wide spectrum of severity and, although rare, infantile epilepsy onset is possible.

Neurology® 2013;81:1697-1703

GLOSSARY

ACTH = adrenocorticotrophic hormone; **BFNS** = benign familial neonatal seizure; **EE** = epileptic encephalopathy; **ID** = intellectual disability; **NEE** = neonatal epileptic encephalopathy; **SUDEP** = sudden unexpected death in epilepsy.

Mutations in *KCNQ2* and *KCNQ3*, encoding the voltage-gated potassium channel Kv7.2 and Kv7.3, are found in 60% to 70% of families with the autosomal dominant self-limiting syndrome of benign familial neonatal seizures (BFNS).^{1,2} In contrast, we recently identified 8 patients with novel de novo *KCNQ2* mutations who presented with a severe neonatal epileptic encephalopathy (NEE). They were identified through screening of *KCNQ2* in 80 patients with

From the Neurogenetics Group (S.W., R.H., A.S., P.D.J.), Department of Molecular Genetics, VIB, Antwerp; Laboratory of Neurogenetics (S.W., R.H., A.S., P.D.J.), Institute Born-Bunge, University of Antwerp, Belgium; Epilepsy Centre Kempenhaeghe (S.W.), Oosterhout, the Netherlands; Department of Paediatrics (V.I.), University Hospital Centre Zagreb, Croatia; Division of Pediatric Neurology and Metabolism (R.V.C.), Department of Pediatrics, University Hospital Ghent, Belgium; Danish Epilepsy Centre (H.H., R.S.M.), Dianalund; Institute for Regional Health Research (H.H.), University of Southern Denmark, Odense; Department of Child Neurology (S.G.), Juliane Marie Center, Rigshospital, Copenhagen, Denmark; Pediatric Neurology (A.-S.S., B.C.), Department of Neurology (A.-S.S., B.C., P.D.J.), Antwerp University Hospital, Antwerp University, Antwerp, Belgium; Epilepsy Research Centre (S.B.H., S.M., I.S.), Department of Medicine, University of Melbourne, Austin Health, Australia; Great Ormond Street Hospital (C.E.), London; Institute of Genetic Medicine (R.H.), Newcastle University, UK; Child Neurology and Neurorehabilitation Unit (G.C., M.A.), Department of Pediatrics, Central Hospital of Bolzano; Neurology Unit and laboratories (T.P., R.G., C.M.), A. Meyer Children's Hospital, Florence; Child Neuropsychiatry Unit (L.G.), Spedali Civili, Brescia, Italy; Pädiatrie I (K.R., E.H.), Division of Pediatric Neurology, University Hospital Innsbruck, Austria; University Hospital Essen (B.A.), University Duisburg-Essen; Department of Paediatric Neurology and Developmental Medicine (A.B.), University Children's Hospital Tübingen, Eberhard Karls University of Tübingen; Center for Child Neurology (I.B.), Sana Krankenhaus Gerresheim, Düsseldorf; Department of Neuropediatrics (S.S.), Hospital for Children and Adolescents, University of Leipzig, Germany; Department of Neurology (B.S., A.P.), Boston Children's Hospital, Harvard School of Medicine; Department of Biology (B.S.), Brandeis University, Waltham, MA; University Children's Hospital (J.R.L.), Division of Human Genetics, Inselspital Bern, Switzerland; Departments of Radiology (S.M.) and Pediatrics (S.M., I.S.), University of Melbourne, Royal Children's Hospital, Melbourne; Florey Institute (I.S.), Melbourne, Australia; and Pediatric Neurology and Muscular Diseases Unit (P.S.), Department of Neurosciences, University of Genoa, G. Gaslini Institute, Genova, Italy.

Coinvestigators from the *KCNQ2* Study Group are listed on the *Neurology®* Web site at www.neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

epileptic encephalopathy (EE) and onset in the first 3 months of life. All individuals carrying a mutation had epilepsy onset in the first week of life. We concluded that *KCNQ2* screening should be considered in patients with refractory neonatal seizures of unknown origin.³

In the study presented here, we aimed to determine the frequency of *KCNQ2* mutations in a selected cohort of patients with an NEE defined by onset in the first month of life. We furthermore collected detailed clinical information of 6 patients with *KCNQ2* encephalopathy diagnosed using an epilepsy gene panel. We describe the clinical and radiologic features of 17 patients, make a first attempt to establish genotype-phenotype correlations, and discuss treatment options.

METHODS Patients. We screened a cohort of 84 patients with unexplained NEE. Patients were referred for this study by collaborating child neurologists. All patients had onset of seizures within the first month of life associated with delayed development. Additional neurologic deficits such as hypotonia or spasticity were present in some individuals. Because patients were referred from multiple clinical centers, no uniform etiologic screening protocol was used. However, in all patients, routine diagnostic investigations such as metabolic screening (at least amino acids in blood and urine, organic acids in urine, and blood lactate) and chromosomal analysis were negative. MRI of the brain excluded causal structural abnormalities. An experienced pediatric neuroradiologist reexamined the brain MRI of affected individuals when available. Additionally, we collected clinical data of 6 patients with EE in whom a de novo *KCNQ2* mutation was found in a diagnostic setting.

Standard protocol approvals and patient consents. Parents or the legal guardian of each patient signed an informed consent form for participation. The study was approved by the Commission for Medical Ethics of the University of Antwerp and by the Human Research Ethics Committee of Austin Health.

Mutation analysis. In the research cohort of 84 patients, mutation analysis of *KCNQ2* was performed on genomic DNA extracted from peripheral blood using standard methods as described previously.³ For numbering mutations in *KCNQ2*, which has several splice variants, we used the longest mRNA transcript (isoform a; NM_172107.2) encoding a protein containing 872 amino acids. Sequenom analysis was performed to check for identified mutations in patients and parents. To confirm paternity, we genotyped 15 short tandem repeat markers located on 10 different chromosomes.

Six patients were referred for diagnostic genetic testing using 1 of 2 different next-generation sequencing epilepsy panels enriched for 50 and 38 genes, respectively, known to be associated with EEs and overlapping phenotypes, as well as respective exon-intron boundaries (as described by Lemke et al.⁴ in 2012 and at <http://www.genedx.com/test-catalog/available-tests/infantile-epilepsy-panel/>). Putatively pathogenic variants were validated in patients and parents using direct Sanger sequencing.

RESULTS Mutation analysis. We identified 9 novel heterozygous missense mutations in *KCNQ2* in 11 of 84 patients (13%) of the screening cohort (table e-1 on

the *Neurology*[®] Web site at www.neurology.org). Six heterozygous missense mutations were detected with the gene panel (table e-2). There were 3 recurrent mutations with 2 mutations present in 2 patients (D, E and J, O) and the other in 3 (G, H, N). Two different mutations in the same codon were also found (F, M). Sixteen mutations arose de novo (parental data not available for patient P). None of the mutations were previously reported in BFNS nor were they identified in the Exome Variant Server of the NHLBI GO Exome Sequencing Project or in the 1000 Genomes Project. All substituted amino acids were highly conserved evolutionary in mammals. PolyPhen-2 and SIFT predicted a very high probability of a damaging effect for all mutations, further supporting their pathogenic nature.

Interestingly, 2 different mutations in the same codon as found in patient C but with a different substitution (p.Ala265Pro and p.Ala265Val) have previously been reported in 2 patients with *KCNQ2* encephalopathy.^{3,5}

Clinical features of patients with *KCNQ2* mutations. The clinical features of the 17 patients in whom a mutation was detected are summarized in tables e-1 and e-2. Sixteen patients had seizure onset during the first 3 days of life. The mother of patient H reported rhythmic fetal movements during the last month of pregnancy reminiscent of seizures. One patient (Q) diagnosed using the gene panel had epilepsy onset at the age of 5 months. Fourteen patients presented with daily highly frequent seizures (range: 10 per day—status epilepticus requiring intubation) that were difficult to control for several weeks. Seizures had a prominent tonic component with or without associated clonic jerking of face or limbs and were often associated with apnea and desaturation. Three patients (J, K, O) had infrequent tonic seizures at onset. Patient B presented with daily bursts of myoclonic seizures intermixed with tonic contraction of axial and proximal limb muscles. After the neonatal period, tonic, clonic, tonic-clonic, myoclonic, spasm-like seizures, and focal seizures were seen. Eleven patients eventually became seizure-free between the age of 1 month and early adolescence. Three patients (D, M, N) also had nonepileptic dystonic episodes. Cognitive outcome varied widely with mild to moderate intellectual disability (ID) in 5 patients to severe or profound ID in 10. For 2 patients (N, O) aged, respectively, 4 and 8 months with developmental delay, cognitive outcome could not yet be defined. Only 3 patients were able to walk independently at the time of inclusion in the study. Thirteen patients had severe axial hypotonia, in some associated with limb spasticity.

EEG at onset showed a burst suppression pattern in 12 of 17 patients, which in 2 patients (H, I) was only seen during sleep (figure 1, A and D). In 2 of 17 patients, the initial EEG showed multifocal epileptic

Figure 1 Representative early EEG of patients with *KCNQ2* encephalopathy

Each panel contains 20 seconds of EEG, sensitivity 70 μ V/mm. (A, B) Interictal EEG of patient D on days 4 and 12, respectively. Burst suppression pattern evolving into a discontinuous and asynchronous background with multifocal epileptic activity. (C) Ictal EEG of patient D on day 4. Slow wave followed by flattening of background (desynchronization) with superimposed low-voltage fast activity. Clinically tonic seizure with bilateral contraction of deltoids as seen in EMG recordings. (D) Interictal EEG of patient G on day 9. Burst suppression pattern. (E) Ictal EEG of patient G on day 9 (seizure duration approximately 60 seconds). Onset of rhythmic epileptic activity in the left hemisphere, with migration to the right hemisphere. Ictal activity in the right hemisphere only during the last 20 seconds of the seizure. Clinically, the seizure starts with opening of the eyes, a minimal tonic contraction, and a subtle vibratory component. During the subsequent 20 seconds, there is clonic eye movement. In the last 30 seconds, tonic asymmetrical posture with clonic eye movement and desaturation occur.

activity on an immature background, and in the 3 patients with infrequent seizures at onset, only focal epileptic activity was seen. During follow-up, multifocal epileptic activity was seen, often on an immature or slow background. When available, ictal EEG showed a tonic seizure pattern consisting of a high-voltage slow wave followed by flattening of the background with superimposed low-voltage fast activity, or seizures with a focal rhythmic ictal pattern and onset zone changing between seizures (figure 1, C and E).

In patients A, D, H, M, N, and O, seizures accompanied by pronounced bradycardia were documented. Figure e-1 shows a seizure with a particularly prolonged bradycardia in patient D. After an initial tachycardia, bradycardia occurred and lasted for more than 3 minutes. It was accompanied by intermittent ventricular escape rhythms and the disappearance of EEG activity for 8 minutes.

Patient B continued to have frequent tonic spasm-like seizures at the age of 2.5 years, mostly on

awakening. She was severely impaired and frequently required oxygen supplementation due to respiratory problems. Shortly after she was diagnosed with *KCNQ2* encephalopathy, she was found dead in bed. Death due to sudden exacerbation of respiratory distress seemed unlikely and a possible sudden unexpected death in epilepsy (SUDEP) was hypothesized.

Brain MRI performed shortly after onset of epilepsy was available for review for 11 patients; for patients K and Q, only MRI performed after the first year of life was available. Findings are summarized in table 1.

DISCUSSION Since 1998, inherited *KCNQ2* mutations and deletions have been known to underlie approximately 60% to 70% of familial cases of BFNS.^{1,2,6} A minority of the BFNS families has a mutation in *KCNQ3*.^{7,8} Although seizures at onset can occur several times a day, they remit in the first months of life and developmental outcome is good. Recently, we described 7 novel missense *KCNQ2* mutations in 8 patients with NEE, thereby showing that certain *KCNQ2* mutations lead to a more devastating epilepsy disorder.³ Subsequently, 3 novel de novo missense *KCNQ2* mutations were detected by whole exome sequencing in 3 of 12 patients with Ohtahara syndrome, confirming its significance in this group of patients.⁵

In the study presented here, we found *KCNQ2* mutations in 11 of 84 patients (13%) with unexplained NEE. Clinical data of 6 additional patients detected with an epilepsy gene panel in a diagnostic setting are also described. Our data confirm that most patients with *KCNQ2* encephalopathy present with neonatal seizures with a prominent tonic component and autonomic signs. Seizures are often accompanied by clonic jerking or more complex motor behavior. One patient (F) presented with bursts of myoclonic seizures, but these were often followed by tonic contraction of proximal muscles. The combination of frequent tonic seizures and burst suppression pattern on EEG in 11 of 17 patients might suggest a diagnosis of Ohtahara syndrome at onset. The evolution of the disease differs from the normal course of Ohtahara syndrome, however, as 11 of the patients with *KCNQ2* encephalopathy described here became seizure-free, and evolution to West syndrome was rare. Although spasm-like seizures were common later in life, only 2 patients (J, N) had hypsarrhythmia on EEG. Patient J had epileptic spasms at that time but never had Ohtahara syndrome because she never had a burst suppression EEG pattern; patient N on the contrary never had epileptic spasms.

All 28 patients with *KCNQ2* encephalopathy described to date had seizure onset in the first week of life except for patient Q, diagnosed using an epilepsy

gene panel. This patient presented with epileptic spasms at the age of 5 months. Infantile onset of seizures has also been documented for a few patients with “benign” *KCNQ2* mutations.⁹ Because seizure onset in the first month of life was an inclusion criterion for the current study cohort, patients with *KCNQ2* encephalopathy with later onset might be underreported. In our previous study, patients with onset of EE up to 3 months were included however, and all mutation carriers had seizure onset in the first week. Later onset thus seems to be rare, although further studies are needed to elucidate the exact frequency of *KCNQ2* mutations in patients with infantile EE.

As seen in BFNS, seizures in *KCNQ2* encephalopathy are often accompanied by apnea with desaturation and cyanosis. In 6 patients, at least one seizure with prolonged bradycardia was recorded. Ictal bradycardia normally is a rare phenomenon, reported to occur in only 8% of children with epilepsy and 3% of seizures.¹⁰ *KCNQ2* subunits are not expressed in the heart so it is unlikely that mutations affect heart function directly.¹¹ Whether bradycardia is an epileptic phenomenon or occurs in response to hypoxia, a reflex often seen in infants, remains to be elucidated with time-locked EEG-ECG-saturation monitoring. In at least 2 patients (M, N), bradycardia occurred only after apnea, so reflex bradycardia seems a plausible mechanism. Whatever the pathophysiologic mechanism is, the simultaneous occurrence of desaturation and bradycardia in an infant with frequent seizures is a hazardous combination and may lead to an increased risk of SUDEP. Indeed, one patient with frequent seizures (B) was found dead in bed shortly after a diagnosis of *KCNQ2* encephalopathy was made. Seizure control should therefore be optimized at all times, even though it may be difficult to achieve.

Response to antiepileptic drugs was variable, but 5 patients (D, G, H, I, J) showed at least a temporary good response to carbamazepine. Two of these patients (G, H) also responded well to IV phenytoin during the initial acute phase after failure of several antiepileptic drugs. A trial with a sodium channel blocker should therefore be considered early in the disease. One patient with *KCNQ2* encephalopathy described in the literature became seizure-free on adrenocorticotrophic hormone (ACTH) therapy.^{12,13} This could not be confirmed in the 3 individuals (C, M, N) in our study treated with ACTH or steroids because they responded only partially or not at all. Larger studies on the use of ACTH in this disease entity are needed before conclusions on efficacy can be drawn. Finally, one patient was treated with retigabine, an activator of neuronally expressed KCNQ channels.¹⁴ Both seizure severity and frequency reduced markedly when high doses were used. He is the only patient with *KCNQ2* encephalopathy

Table 1 Imaging findings in patients with a *KCNQ2* mutation

	Patient A	Patient B	Patient D	Patient E	Patient F	Patient G	Patient H	Patient I	Patient K	Patient M	Patient N	Patient P	Patient Q
Basal ganglia/thalami	Patchy ↑ T2 signal in thalami (3 d)	Normal (1 wk)	Normal (4 d); small thalami (11 and 21 mo)	↑ T1 GP and putamina (6 d)/ GP and tegmentum (14 d); subtle patchy ↑ T2 thalami (14 d)	Normal (8 d)	↑ T1 and T2 GP (12 d)	Normal (3 wk); ↑ T1 lateral thalami (10 mo); ↑ T1 and T2 GP (10 and 16 mo)	↑ T1 lateral thalami (6 d); mild ↑ T2 GP (11 mo); normal (21 mo)	Normal (4 y, 11 mo)	Small thalami (3 wk); small thalami, ↑ T2 GP (4 mo)	Normal (3 wk)	Normal (4 and 24 d)	Small thalami (18 mo)
Frontal lobe	Atrophy	Atrophy	Severe atrophy (11 and 21 mo)	Atrophy (CT scan 7 mo)	Atrophy (2 and 15 mo)	Normal	Normal	Normal	Normal	Severe atrophy (4 mo)	Normal	Normal	Large frontotemporal extra-axial CSF spaces; morphologically normal frontal lobes
Corpus callosum	Thin (genu)	Normal	Thin (11 and 21 mo)	Thin	Thin (2 and 15 mo)	Normal	Normal	Normal (6 d); thin (11 and 21 mo)	Normal	Thin (3 wk and 4 mo)	Normal	Normal	Thin
White matter	Normal	Generalized ↑ T2; abnormal myelination of the PLIC	Generalized volume loss (11 and 21 mo); restricted diffusion in a deep rim of PWM; delayed myelination	Generalized volume loss (7 mo)	Delayed myelination	Normal	Normal	↑ T2 posterior PWM; normal myelination	Normal	PLICs not myelinated; few petechial hemorrhages in PWM on T1 (3 wk); general volume loss; myelination progressed but still delayed (4 mo)	Normal	Normal	Decreased white matter volume, mainly frontotemporal
Ventricles	Normal	Prominent with cavum vergae	Dilated ex vacuo (11 mo)	Dilated ex vacuo (7 mo)	Normal	Normal	Normal (3 wk); prominent (10 and 16 mo)	Normal	Mild prominence of atria	Dilated ex vacuo; cavum vergae (3 wk and 4 mo)	Normal	Mild dilation of left lateral ventricle	Big ventricles

Abbreviations: GP = globus pallidi; PLIC = posterior limb of internal capsule; PWM = periventricular white matter.

reported to date in which this designer drug has been trialed. This is probably related to the minimal experience child neurologists have with the drug because it is currently US Food and Drug Administration approved in adults only. Clinical studies on the use of retigabine in infants and children as well as in vitro studies in *KCNQ2* mutant animal models will lead to increased confidence in using retigabine in infants with *KCNQ2* encephalopathy.

Confirming our previous findings,³ variable T1 and T2 hyperintensities were seen in the basal ganglia and/or thalami in 6 of 11 patients of which brain MRI performed during the first year of life was available for review. Half of the patients (7/13) also had frontotemporal atrophy, a thin corpus callosum, and/or global loss of white matter volume that worsened on sequential imaging in the first 2 years of life.

The current report broadens the *KCNQ2* encephalopathy spectrum, as 3 clinical subgroups can be distinguished. The first and largest group (patients A–F, L, M, and Q of the current report and 7 of our 8 original patients) has a stormy onset with frequent therapy-resistant seizures. Some patients become seizure-free after several months to years (10/16 patients; median age of seizure freedom 24 months, range 2 months to adolescence), but all develop a severe to profound ID with axial hypotonia, sometimes accompanied by limb spasticity. Frontotemporal atrophy and/or white matter loss is seen on brain MRI of all patients in this group and in none of the other patients. A second group (patients G, H, I, P, and patient 3 of our first report) presents in a similar way. Nevertheless, seizures are controlled in all patients (median age of seizure freedom 4 months, range 1 to 20 months) and they have only mild to moderate ID. In the last group (patients J, K, and O), seizure frequency is lower at onset and although EEG shows epileptic activity, a typical burst suppression pattern or frequent multifocal epileptic activity is not seen. Despite this apparent less dramatic start similar to BFNS, ID does ensue and outcome ranges from moderate to severe ID.

Our patient groups are too small to define prognostic factors. Seizure severity has a role as seizures are more easily controlled in group 2, and developmental regression occurred at the time of seizure exacerbation in patients J, K, and O. This does not seem to be the sole prognostic factor, however, because patient 8 of the first report also became seizure-free at the age of 2 months and nevertheless profound ID ensued. Remarkably, the 4 patient pairs with the 2 recurrent mutations reported so far (patients 7–8 in the first report, patients D–E, G–H, and J–O in the current report) have a comparable disease evolution. Interestingly, there is also marked similarity in disease severity in the patient pairs F–M and 5–D carrying a mutation in the same codon. This suggests that, perhaps not

surprisingly, disease outcome depends to a major extent on the underlying mutation. This is further supported by the fact that all *KCNQ2* encephalopathy mutations are novel mutations not reported in BFNS.

The reason *KCNQ2* mutations lead to phenotypes ranging from BFNS to *KCNQ2* encephalopathy with profound ID remains enigmatic. From the occurrence of *KCNQ2* deletions in BFNS, it is known that a total loss of function of one allele leads to the benign phenotype only.¹ Haploinsufficiency alone therefore cannot explain the more severe *KCNQ2* encephalopathy. Although genetic and environmental background factors might influence the phenotype, it is remarkable that all *KCNQ2* encephalopathy mutations published so far are (often recurrent) missense mutations, and never loss-of-function mutations. Most likely, these specific missense mutations exert a dominant negative effect. A conditional mouse model expressing a dominant negative *KCNQ2* mutation indeed not only had seizures but also behavioral changes and memory deficits.¹⁵

This observation has interesting therapeutic implications. Until now, the focus of treatment of patients with epilepsy in general has always been on treating the symptoms, i.e., seizures. Nevertheless, now that increasing numbers of genetic causes of EE are being discovered, we should start targeting the underlying cause rather than the symptom. In the last few years, gene therapies for neurologic diseases are being intensively studied in neuromuscular disorders and Huntington disease.^{16–19} Therapies using antisense oligonucleotides are being specifically developed for diseases with known dominant negative mutations. In the field of epilepsy, we are still lagging behind in targeted gene therapy development, and it is time to make the mental shift when we think about developing novel epilepsy therapies. Indeed, specifically inhibiting transcription or translation of the mutated *KCNQ2* allele would lead to a loss-of-function situation, mimicking a *KCNQ2* deletion, which in turn is known to lead to the milder BFNS phenotype. Such a strategy therefore has the potential to turn a severe EE into a benign neonatal epilepsy syndrome.

In summary, the vast majority of patients with *KCNQ2* encephalopathy present in the first week of life with highly frequent therapy-resistant seizures often with a prominent tonic component and autonomous signs. EEG at onset shows a burst suppression pattern or multifocal epileptic activity, and outcome ranges from mild to profound ID. Much fundamental and clinical research remains to be done to fully understand the entity of *KCNQ2*-related epilepsy. We advocate reporting of more patients to improve understanding through genotype-phenotype correlation, and broader screening of patients with infantile epilepsy to identify additional patients with later onset. Given a mutation frequency of 13% in the group of patients with

unexplained NEE, we highly recommend screening of *KCNQ2* at presentation in infants with frequent neonatal seizures of unknown origin. The physiologic observation of seizure-related bradycardia deserves further study and may offer an avenue to reduce the likelihood of SUDEP. While gaining more experience with the use of retigabine in children with *KCNQ2* mutations is an enticing treatment strategy, an early trial of a sodium channel blocker may also prove useful.

AUTHOR CONTRIBUTIONS

S.W.: design of the study, interpretation of the data, drafting the manuscript. V.I.: interpretation of the data, drafting the manuscript. R.H.: analysis of the data. R.V.C., H.H., R.S.M., S.G., A.-S.S., B.C., S.B.H., C.E., R.H.: interpretation of the data, revising the manuscript for intellectual content. G.C., T.P., L.G., K.R.: revising the manuscript for intellectual content. E.H., B.A., A.B., I.B., S.S., B.S., R.G., A.P., J.R.L., S.M., I.S., M.A., P.S., C.M.: interpretation of the data, revising the manuscript for intellectual content. A.S.: design of the study, interpretation of the data, drafting the manuscript. P.D.J.: design of the study, interpretation of the data, revising the manuscript for intellectual content.

ACKNOWLEDGMENT

The authors thank the patients and their family members for their cooperation and participation in this study, and the VIB Genetic Service Facility (<http://www.vibgeneticservicefacility.be>) for the genetic analyses. A.S. is a postdoctoral fellow of the Fund for Scientific Research Flanders (FWO).

STUDY FUNDING

Supported by the Fund for Scientific Research Flanders (FWO) (P.D.J.), Methusalem excellence grant of the Flemish Government (P.D.J.), University of Antwerp, the Eurocores program EuroEPINOMICS of the European Science Foundation (P.D.J.), and National Health and Medical Research Council of Australia (I.S.).

DISCLOSURE

S. Weckhuysen, V. Ivanovic, R. Hendrickx, R. Van Coster, H. Hjalgrim, R. Möller, and S. Grønborg report no disclosures. A. Schoonjans is a postdoctoral fellow of the Fund for Scientific Research Flanders (FWO). B. Ceulemans, S. Heavin, C. Eltze, R. Horvath, G. Casara, T. Pisano, L. Giordano, K. Rostasy, E. Haberlandt, B. Albrecht, A. Bevoit, I. Benkel, S. Syrbe, B. Sheidley, and R. Guerrini report no disclosures. A. Poduri is supported by the National Institute of Neurological Disorders and Stroke (K23NS069784). J. Lemke and S. Mandelstam report no disclosures. I. Scheffer has served on scientific advisory boards for UCB; may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has received speaker honoraria from Athena Diagnostics, UCB, and Janssen-Cilag EMEA; has received payment for development of educational presentations from UCB and Athena Diagnostics; has received funding for travel from Athena Diagnostics, Biocodex, UCB, GlaxoSmithKline, and Janssen-Cilag EMEA; and receives/has received research support from the National Health and Medical Research Council of Australia, Health Research Council of New Zealand, Australian Research Council, The University of Melbourne, American Epilepsy Society, the Jack Brockhoff Foundation, the Shepherd Foundation, and the Perpetual Charitable Trustees. M. Angriman, P. Striano, C. Marini, A. Suls, and P. De Jonghe report no disclosures. Go to Neurology.org for full disclosures.

Received April 5, 2013. Accepted in final form August 9, 2013.

REFERENCES

- Heron SE, Cox K, Grinton BE, et al. Deletions or duplications in *KCNQ2* can cause benign familial neonatal seizures. *J Med Genet* 2007;44:791–796.
- Singh NA, Charlier C, Stauffer D, et al. A novel potassium channel gene, *KCNQ2*, is mutated in an inherited epilepsy of newborns. *Nat Genet* 1998;18:25–29.
- Weckhuysen S, Mandelstam S, Suls A, et al. *KCNQ2* encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. *Ann Neurol* 2012;71:15–25.
- Lemke JR, Riesch E, Scheurenbrand T, et al. Targeted next generation sequencing as a diagnostic tool in epileptic disorders. *Epilepsia* 2012;53:1387–1398.
- Saito H, Kato M, Koide A, et al. Whole exome sequencing identifies *KCNQ2* mutations in Ohtahara syndrome. *Ann Neurol* 2012;72:298–300.
- Biervert C, Schroeder BC, Kubisch C, et al. A potassium channel mutation in neonatal human epilepsy. *Science* 1998;279:403–406.
- Charlier C, Singh NA, Ryan SG, et al. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nat Genet* 1998;18:53–55.
- Singh NA, Westenskow P, Charlier C, et al. *KCNQ2* and *KCNQ3* potassium channel genes in benign familial neonatal convulsions: expansion of the functional and mutation spectrum. *Brain* 2003;126:2726–2737.
- Zara F, Specchio N, Striano P, et al. Genetic testing in benign familial epilepsies of the first year of life: clinical and diagnostic significance. *Epilepsia* 2013;54:425–436.
- Moseley BD, Nickels K, Britton J, Wirrell E. How common is ictal hypoxemia and bradycardia in children with partial complex and generalized convulsive seizures? *Epilepsia* 2010;51:1219–1224.
- Jentsch TJ. Neuronal *KCNQ* potassium channels: physiology and role in disease. *Nat Rev Neurosci* 2000;1:21–30.
- Dedek K, Fusco L, Teloy N, Steinlein OK. Neonatal convulsions and epileptic encephalopathy in an Italian family with a missense mutation in the fifth transmembrane region of *KCNQ2*. *Epilepsia Res* 2003;54:21–27.
- Serino D, Specchio N, Pontrelli G, Vigeveno F, Fusco L. Video/EEG findings in a *KCNQ2* epileptic encephalopathy: a case report and revision of literature data. *Epileptic Disord* 2013;15:158–165.
- Barrese V, Miceli F, Soldovieri MV, et al. Neuronal potassium channel openers in the management of epilepsy: role and potential of retigabine. *Clin Pharmacol* 2010;2:225–236.
- Peters HC, Hu H, Pongs O, Storm JF, Isbrandt D. Conditional transgenic suppression of M channels in mouse brain reveals functions in neuronal excitability, resonance and behavior. *Nat Neurosci* 2005;8:51–60.
- Muntoni F, Wood MJA. Targeting RNA to treat neuromuscular disease. *Nat Rev Drug Discov* 2011;10:621–637.
- Magaña JJ, Cisneros B. Perspectives on gene therapy in myotonic dystrophy type 1. *J Neurosci Res* 2011;89:275–285.
- Ramaswamy S, Kordower JH. Gene therapy for Huntington's disease. *Neurobiol Dis* 2012;48:243–254.
- Kole R, Krainer AR, Altman S. RNA therapeutics: beyond RNA interference and antisense oligonucleotides. *Nat Rev Drug Discov* 2012;11:125–140.