



Learn more about Dravet Syndrome with a free educational programme

Enrol here

The complete educational programme is now available

Learn more around the rare, severe epilepsy known as Dravet syndrome through video, infographic and clinical article content, which has been guided by an expert steering group.

A certificate of continuing education is available for each module on successful completion of all the multiple-choice questions.

Developmental and epilepsy spectrum of *KCNB1* encephalopathy with long-term outcome

Claire Bar^{1,2}  | Mathieu Kuchenbuch^{1,2}  | Giulia Barcia^{2,3} | Amy Schneider⁴ |
 Mélanie Jennesson⁵ | Gwenaél Le Guyader^{6,7} | Gaetan Lesca^{8,9}  | Cyril Mignot^{10,11} |
 Martino Montomoli¹² | Elena Parrini¹² | Hervé Isnard¹³ | Anne Rolland¹⁴ |
 Boris Keren¹¹ | Alexandra Afenjar¹⁵ | Nathalie Dorison^{16,17} | Lynette G. Sadleir¹⁸  |
 Delphine Breuillard^{1,2} | Raphael Levy¹⁹ | Marlène Rio^{3,20} | Sophie Dupont^{10,21}  |
 Susanna Negrin²² | Alberto Danieli²² | Emmanuel Scalais²³ | Anne De Saint Martin²⁴ |
 Salima El Chehadeh²⁵ | Jamel Chelly²⁵ | Alice Poisson²⁶ | Anne-Sophie Lebre²⁷ |
 Anca Nica^{28,29} | Sylvie Odent^{30,31} | Tayeb Sekhara³² | Vesna Brankovic³³ |
 Alice Goldenberg³⁴ | Pascal Vrielynck³⁵ | Damien Lederer³⁶ | Hélène Maurey³⁷ |
 Gaetano Terrone³⁸ | Claude Besmond³⁹ | Laurence Hubert³⁹ | Patrick Berquin⁴⁰ |
 Thierry Billelte de Villemeur¹⁷ | Bertrand Isidor⁴¹ | Jeremy L. Freeman^{42,43} | Heather
 C. Mefford⁴⁴ | Candace T. Myers⁴⁴ | Katherine B. Howell^{42,43} | Andrés Rodríguez-
 Sacristán Cascajo^{45,46} | Pierre Meyer^{47,48} | David Genevieve⁴⁹ | Agnès Guët⁵⁰ |
 Diane Doummar¹⁷ | Julien Durigneux⁴² | Marieke F. van Dooren⁵¹ | Marie Claire Y. de
 Wit⁵² | Marion Gerard⁵³ | Isabelle Marey¹¹ | Arnold Munnich^{2,3} | Renzo Guerrini¹² |
 Ingrid E. Scheffer^{4,42,43,54}  | Edor Kabashi² | Rima Nabbout^{1,2}

¹Department of Pediatric Neurology, Reference Center for Rare Epilepsies, Assistance Publique-Hôpitaux de Paris (AP-HP), Necker-Enfants Malades Hospital, Paris, France

²Imagine Institute, Mixed Unit of Research 1163, University of Paris, Sorbonne University, Paris, France

³Department of Clinical Genetics, AP-HP, Necker-Enfants Malades Hospital, Paris, France

⁴Department of Medicine, Epilepsy Research Centre, Austin Health, University of Melbourne, Heidelberg, Victoria, Australia

⁵Department of Pediatrics, American Memorial Hospital, Reims, France

⁶Department of Genetics, Poitiers University Hospital Center, Poitiers Cedex, France

⁷EA3808-NEUVACOD Neurovascular and Cognitive Disorders Unit, University of Poitiers, Poitiers, France

⁸Department of Genetics, Lyon Civil Hospices, Lyon, France

⁹NeuroMyoGène Institute, National Center for Scientific Research, Mixed Unit of Research 5310, National Institute of Health and Medical Research U1217, University of Lyon, Claude Bernard Lyon 1 University, Villeurbanne, France

¹⁰National Institute of Health and Medical Research, U1127, National Center for Scientific Research Mixed Unit of Research 7225, Pierre and Marie Curie University Paris 6 Mixed Unit of Research S1127, Brain and Spine Institute, Sorbonne University, Paris, France

¹¹Department of Genetics, Rare Causes of Intellectual Disability Reference Center, AP-HP, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France

¹²Pediatric Neurology, Neurogenetics, and Neurobiology Unit and Laboratories, Neuroscience Department, A. Meyer Children's Hospital, University of Florence, Florence, Italy

¹³Pediatric Neurologist, Medical Office, Lyon, France

- ¹⁴Department of Pediatrics, Nantes University Hospital Center, Nantes, France
- ¹⁵Department of Genetics and Medical Embryology, Reference Center for Malformations and Congenital Diseases of the Cerebellum and Rare Causes of Intellectual Disabilities, Sorbonne University, AP-HP, Trousseau Hospital, Paris, France
- ¹⁶Pediatric Neurosurgery Department, Rothschild Foundation Hospital, Paris, France
- ¹⁷Department of Pediatric Neurology, AP-HP, Armand Trousseau Hospital, Sorbonne University, Paris, France
- ¹⁸Department of Pediatrics and Child Health, University of Otago, Wellington, New Zealand
- ¹⁹Department of Pediatric Radiology, Necker-Enfants Malades Hospital, Paris, France
- ²⁰Laboratory of Developmental Brain Disorders, National Institute of Health and Medical Research Mixed Unit of Research 1163, Imagine Institute, Sorbonne University, Paris, France
- ²¹Epileptology Unit and Rehabilitation Unit, AP-HP, Pitie-Salpêtrière-Charles Foix Hospital, Paris, France
- ²²Epilepsy and Clinical Neurophysiology Unit, Scientific Institute, IRCCS E. Medea, Treviso, Italy
- ²³Pediatric Neurology Unit, Luxembourg Hospital Center, Luxembourg City, Luxembourg
- ²⁴Department of Pediatric Neurology, Strasbourg University Hospital, Hautepierre Hospital, Strasbourg, France
- ²⁵Department of Medical Genetics, Strasbourg University Hospitals, Hautepierre Hospital, Strasbourg, France
- ²⁶GénoPsy, Reference Center for Diagnosis and Management of Genetic Psychiatric Disorders, le Vinatier Hospital Center and EDR-Psy Team (National Center for Scientific Research and Lyon 1 Claude Bernard University), Villeurbanne, France
- ²⁷Reims University Hospital Center, Maison Blanche Hospital, Biology Department, Reims, France
- ²⁸Neurology Department, Center for Clinical Research (CIC 1414), Rennes University Hospital, Rennes, France
- ²⁹Laboratory of Signal Processing, National Institute of Health and Medical Research Mixed Unit of Research 1099, Rennes, France
- ³⁰Reference Center for Rare Developmental Abnormalities CLAD-Ouest, Rennes University Hospital Center, Rennes, France
- ³¹National Center for Scientific Research Mixed Unit of Research 6290, Institute of Genetics and Development of Rennes (IGDR), University of Rennes, Rennes, France
- ³²Department of Pediatric Neurology, C.H.I.R.E.C, Brussels, Belgium
- ³³Clinic for Child Neurology and Psychiatry, Belgrade, Serbia
- ³⁴Reference Center for Developmental Anomalies and Malformation Syndromes, Rouen University Hospital Center, Rouen, France
- ³⁵Reference Center for Refractory Epilepsy, Catholic University of Louvain, William Lennox Neurological Hospital, Ottignies, Belgium
- ³⁶Human Genetic Center, IPG, Gosselies, Belgium
- ³⁷Department of Pediatric Neurology, AP-HP, Bicêtre University Hospital, Kremlin Bicêtre, France
- ³⁸Department of Translational Medical Sciences, Section of Pediatrics, Child Neurology Unit, Federico II University, Naples, Italy
- ³⁹Translational Genetics, National Institute of Health and Medical Research Mixed Unit of Research 1163, Imagine Institute, University of Paris, Paris, France
- ⁴⁰Department of Pediatric Neurology, Amiens-Picardie University Hospital Center, University of Picardy Jules Verne, Amiens, France
- ⁴¹Department of Clinical Genetics, Nantes University Hospital Center, Nantes, France
- ⁴²Departments of Neurology and Paediatrics, Royal Children's Hospital, University of Melbourne, Melbourne, Victoria, Australia
- ⁴³Murdoch Children's Research Institute, Melbourne, Victoria, Australia
- ⁴⁴Department of Pediatrics, Division of Genetic Medicine, University of Washington, Seattle, Washington, United States
- ⁴⁵Pediatric Neurology Unit, Department of Pediatric, Virgen Macarena Hospital, Seville, Spain
- ⁴⁶Department of Pediatrics, School of Medicine, University of Seville, Seville, Spain
- ⁴⁷Department of Pediatric Neurology, Montpellier University Hospital Center, Montpellier, France
- ⁴⁸PhyMedExp, National Institute of Health and Medical Research, U1046, National Center for Scientific Research Mixed Unit of Research 9214, University of Montpellier, Montpellier, France
- ⁴⁹Department of Medical Genetics, Rare Disease, and Personalized Medicine, IRMB, University of Montpellier, National Institute of Health and Medical Research, Montpellier University Hospital Center, Montpellier, France
- ⁵⁰Department of Pediatrics, Louis-Mourier Hospital, Colombes, France
- ⁵¹Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, the Netherlands
- ⁵²Department of Pediatric Neurology and ENCORE Expertise Center, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, the Netherlands
- ⁵³Clinical Genetics, Côte de Nacre University Hospital Center, Caen, France
- ⁵⁴Florey Institute of Neurosciences and Mental Health, Heidelberg, Victoria, Australia

Correspondence

Rima Nabbut, Department of Pediatric Neurology, Reference Center for Rare Epilepsies, Necker Enfants Malades Hospital, 149 rue de Sèvres, 75015 Paris, France.
Email: rimanabbut@yahoo.com

Funding information

FP7 Ideas: European Research Council; National Health and Medical Research Council; Health Research Council of New Zealand; Curekids New Zealand; Agence Nationale de la Recherche, Grant/Award Number: ANR-10IAHU-01; Medical Research Future Fund of Australia; Fondation Bettencourt Schueller; Ligue Française Contre l'Épilepsie; European Commission Seventh Framework Program, Grant/Award Number: 602531

Abstract

Objective: We aimed to delineate the phenotypic spectrum and long-term outcome of individuals with *KCNB1* encephalopathy.

Methods: We collected genetic, clinical, electroencephalographic, and imaging data of individuals with *KCNB1* pathogenic variants recruited through an international collaboration, with the support of the family association “KCNB1 France.” Patients were classified as having developmental and epileptic encephalopathy (DEE) or developmental encephalopathy (DE). In addition, we reviewed published cases and provided the long-term outcome in patients older than 12 years from our series and from literature.

Results: Our series included 36 patients (21 males, median age = 10 years, range = 1.6 months–34 years). Twenty patients (56%) had DEE with infantile onset seizures (seizure onset = 10 months, range = 10 days–3.5 years), whereas 16 (33%) had DE with late onset epilepsy in 10 (seizure onset = 5 years, range = 18 months–25 years) and without epilepsy in six. Cognitive impairment was more severe in individuals with DEE compared to those with DE. Analysis of 73 individuals with *KCNB1* pathogenic variants (36 from our series and 37 published individuals in nine reports) showed developmental delay in all with severe to profound intellectual disability in 67% ($n = 41/61$) and autistic features in 56% ($n = 32/57$). Long-term outcome in 22 individuals older than 12 years (14 in our series and eight published individuals) showed poor cognitive, psychiatric, and behavioral outcome. Epilepsy course was variable. Missense variants were associated with more frequent and more severe epilepsy compared to truncating variants.

Significance: Our study describes the phenotypic spectrum of *KCNB1* encephalopathy, which varies from severe DEE to DE with or without epilepsy. Although cognitive impairment is worse in patients with DEE, long-term outcome is poor for most and missense variants are associated with more severe epilepsy outcome. Further understanding of disease mechanisms should facilitate the development of targeted therapies, much needed to improve the neurodevelopmental prognosis.

KEYWORDS

autism spectrum disorders, developmental and epileptic encephalopathy, developmental encephalopathy, drug-resistant epilepsy, potassium channels, sudden unexpected death in epilepsy

1 | INTRODUCTION

Over the past decade, the large application of next generation sequencing has significantly increased the discovery of genes involved in both neurodevelopmental disorders and epilepsy.¹ The International League Against Epilepsy introduced the term *developmental and epileptic encephalopathy* (DEE) to define severe neurodevelopmental disorders in which developmental consequences arise directly from the underlying etiology, which is often genetic, as well as from frequent epileptic activity.² The term *epileptic encephalopathy* alone applies to individuals without preexisting developmental delay where the adverse developmental impact is due to seizures and epileptiform activity.^{2,3} The term *developmental encephalopathy* (DE) should be used for individuals presenting with developmental impairment without

frequent epileptic activity causing regression or further slowing of development.²

Pathogenic variants in ion-channel genes represent a major cause of DEE.^{4,5} Despite the genetic heterogeneity, some strong phenotypes are emerging in relation to pathogenic variants in some specific genes, as for *KCNT1*, *KCNQ2*, *SCN1A*, and *SCN2A*.⁴ *KCNB1* codes for the α subunit of the voltage-gated potassium channel subfamily 2 ($K_v2.1$).⁶ In 2014, de novo pathogenic variants in *KCNB1* were first recognized to cause infantile onset epileptic encephalopathy in three patients.⁷ Two series, including six and 25 individuals in total, have been reported, in addition to case reports.^{8–15} Individuals exhibited global developmental delay, behavioral disorders, and various epilepsies.^{8–15} A few individuals had developmental delay without seizures.^{11,16} Outcome data are

Key Points

- *KCNB1* encephalopathy has a wide phenotypic spectrum, typically with poor long-term cognitive, psychiatric, and behavioral outcomes.
- *KCNB1* pathogenic variants are associated with developmental and epileptic encephalopathies or developmental encephalopathies with or without epilepsy.
- Patients with developmental and epileptic encephalopathy show a worse cognitive outcome, emphasizing the impact of early epilepsy.
- Epilepsy is less frequent and less severe in individuals with truncating variants compared to those with missense variants.

limited, as few adults have been described. It has been suggested that truncating variants in the C-terminal domain correlate with less severe epilepsy outcome.^{11,16}

Here, we analyze a series of 36 individuals with pathogenic *KCNB1* variants to delineate the phenotypic spectrum of *KCNB1* encephalopathy. We explore genotype-phenotype correlations and long-term outcome to guide patient management and inform genetic and prognostic counseling.

2 | MATERIALS AND METHODS

2.1 | Individuals

Individuals with *KCNB1* pathogenic variants were collected through a large international collaboration between the network of the French Reference Center for Rare Epilepsies and centers in Belgium, Italy, Spain, Luxembourg, New Zealand, and Australia, with the support of the family association KCNB1 France. For each individual, we collected information on medical and developmental history, epilepsy, clinical examination, electroencephalography (EEG), and brain imaging findings. The severity of intellectual disability (ID) was classified by the referring physician according to developmental scales used at their institution or based on clinical evaluation. We classified seizures and epilepsy types and, where possible, epilepsy syndromes according to the International League Against Epilepsy proposal.^{2,17} Individuals were classified as having *KCNB1* DEE when epilepsy (seizures and EEG) resulted in developmental slowing or regression. Individuals were classified as *KCNB1* DE when they had less active epilepsy, often with late onset seizures and without clear regression or slowing of development. The DE group also included individuals without seizures. Because

of the limited number of patients and their broad age range, the cutoff age of 12 years was chosen to look at long-term outcome and to include a sufficient number of patients. Informed written consent was obtained for all participants for research participation, including the use of photographs, according to the human research ethics committee of each participating institution.

2.2 | Variant analysis

KCNB1 variants were identified by targeted next generation sequencing gene panels or whole exome sequencing. Sanger sequencing confirmed single nucleotide variants, and segregation analysis was performed in each family. We classified variants according to the guidelines of the American College of Medical Genetics.¹⁸ *KCNB1* variants were described according to Human Genome Variation Society variant nomenclature guidelines (<http://varnomen.hgvs.org/>),¹⁹ using the reference sequence RefSeq NM_004975.2. Variants have been submitted to the ClinVar database (<https://www.ncbi.nlm.nih.gov/clinvar/>).

2.3 | Literature review

PubMed was searched for reports of individuals with *KCNB1* pathogenic variants by combining the terms “*KCNB1*” and “variants” or “mutations”. Articles were reviewed and compared with variants listed in professional databases (Human Gene Mutation Database, Biobase, and Qiagen). The accuracy of variant description was checked using Alamut 2.10 (Interactive Biosoftware).

2.4 | Statistics

Descriptive data are represented as median (interquartile range). Statistical tests were performed using a two-sided Fisher exact test with statistical significance determined by $P < .05$.

3 | RESULTS

3.1 | Series

3.1.1 | Demographic data

Our cohort included 36 unrelated individuals (21 males) with *KCNB1* pathogenic variants (Table S1). Age at study ranged from 1.6 months to 34 years (median = 10 years, interquartile range = 6-15 years). Pregnancy and delivery were unremarkable for 32 of 36 (89%) individuals. Patient 19's mother reported decreased fetal movements

and Patient 23's mother suspected in utero seizures. Emergency Caesarean section for fetal deceleration was performed at term for Patients 17 and 28, without neonatal distress.

3.1.2 | Variants

Our series comprises 28 patients with previously reported *KCNB1* variants¹⁶ and eight new patients (Table S1). The 36 patients had 30 different *KCNB1* pathogenic variants, including 25 (83%) missense, four (13%) nonsense, and one (3%) frameshift. Three variants were recurrent: p.Arg312His in five patients, and p.Arg306Cys and p.Gly395Arg in two patients each. Patient 1 with p.Glu43Gly affecting the cytoplasmic N-terminal region also carried a de novo variant in *GABRA5* (p.Thr301Met), which encodes the alpha 5 subunit of the γ -aminobutyric acid type A receptor. Both variants were predicted to be damaging and thus considered pathogenic and contributing to the individual's phenotype.¹⁶ Variants occurred de novo in 31 of 36 individuals. In four individuals (Patients 2, 10, 25, 30), segregation could not be completed because parental samples were not available. Patient 36 inherited p.Arg583* from her heterozygous mother who had mild ID without epilepsy. The variant arose de novo in the mother.

3.1.3 | Neurodevelopment

All individuals had developmental delay, recognized in the first year of life in 32 of 36 (89%) patients (Table S1). ID ranged from mild in five of 36 (14%), to moderate (10/36, 28%), severe (19/36, 53%), and profound (2/36, 6%). Of 33 of 36 patients older than 3 years, 17 of 33 (52%) had no words, nine of 33 (27%) used some words, and seven of 33 (21%) spoke short sentences. Orofacial apraxia was reported in two of 36 (6%). Behavioral and psychiatric disorders were reported in 28 of 34 (82%), including stereotypies and other autistic features in 18 of 34 (53%), uncontrolled aggression in 11 of 34 (32%), and impulsiveness or attention-deficit/hyperactivity disorder in 13 of 34 (38%). Antipsychotic treatments were used in eight of 36 (22%) and psychostimulants in three of 36 (8%) patients. In 12 of 36 (33%) patients aged 2-29 years, families reported sleep disorders, particularly frequent waking during nighttime sleep. Polysomnography was performed on two of them, revealing parasomnia and frontal motor seizures in Patient 6 and central apnea in Patient 23. Twenty-nine of 35 (83%) patients older than 2 years acquired independent walking at a median age of 24 months (interquartile range = 18-36 months, range = 16-54 months).

3.1.4 | Examination

Hypotonia was observed in 19 of 36 (53%) patients in infancy and varied in severity. Hyperlaxity and ataxia were each reported in eight of 36 (22%) patients. Pyramidal signs, dystonia, and choreoathetosis were each observed in six of 36 (17%) different patients. Normal head circumference was present in all but three patients, who had acquired microcephaly reaching -2 to -3 SD. Two patients had a gastrostomy with some oral intake. Morphological analysis of 14 patients revealed minor dysmorphic features including sunken eyes in 13 and large median incisors in six (Figure 1). Of note, Patient 8 had more pronounced dysmorphic features. He had chromosomal microarray without evidence for copy number variants and, except for the *KCNB1* pathogenic variant, no other pathogenic variants have been found on whole exome sequencing. He is the oldest patient (34 years), and morphological evolution over time has not yet been documented in this population.

3.1.5 | Epilepsy

Thirty patients (30/36, 83%) had epilepsy (Table S1). Median age at seizure onset was 17 months (interquartile range = 8-35 months, range = 10 days-25 years), with preexisting developmental delay in all patients. Twenty patients (20/36, 56%) had *KCNB1* DEE, whereas 16 (16/36, 44%) had *KCNB1* DE, including six without epilepsy (Figure 2).

The 20 patients with *KCNB1* DEE had a median age at seizure onset of 10 months (interquartile range = 8-17 months, range = 10 days-3.5 years). Eleven individuals showed developmental slowing or plateauing after seizure onset, whereas nine had developmental regression. The first seizure was generalized in 16 individuals (16/20, 80%), including epileptic spasms ($n = 6$), tonic or tonic-clonic seizures ($n = 3$), atypical absences ($n = 3$), myoclonic ($n = 2$), and atonic seizures ($n = 1$). With increasing age, most individuals developed several seizure types; 15 of 20 (75%) had >2 seizure types and 12 of 20 (60%) >3 seizure types. Only five patients (5/20, 25%) could be classified into a specific epilepsy syndrome such as infantile spasms ($n = 3$) and Lennox-Gastaut syndrome ($n = 2$). The remaining 15 patients (15/20, 75%) had "unclassified DEE," with frequent multifocal epileptiform activity on EEG (Figure 3). Four individuals (4/20, 20%) had activation of EEG abnormalities during sleep. At follow-up, median age for individuals with *KCNB1* DEE was 9 years (interquartile range = 4-16, range = 19 months-34 years). Fourteen patients (14/20, 70%) had drug-resistant epilepsy, with daily seizures in eight of 14, weekly in four of 14, and monthly in two of 14. Two patients with infantile spasms were in remission by 8 and 14 months, respectively. Patients received a median of



FIGURE 1 Photographs of patients with *KCNB1* encephalopathy. Note sunken eyes (A, C) and large median incisors (A-C, E, G, H)

seven antiseizure medications (ASMs; interquartile range = 3-10). Response to vigabatrin occurred in five of seven patients with epileptic spasms. All five individuals receiving the ketogenic diet were responders.

In the 16 patients with *KCNB1* DE, 10 had epilepsy. The first seizure occurred at a median age of 5 years (interquartile range = 2-5 years, range = 18 months-25 years). Epilepsy was generalized in three of 10, focal in three of 10, and combined generalized and focal in one of 10. Three individuals only had a few motor seizures of unknown onset and did not require ASM. Seizures remitted in three patients at age 16 months, 6 years, and 12 years, respectively. Six patients aged 4.5-20 years had not had seizures.

ID and language disorder were more severe in patients with *KCNB1* DEE compared to those with *KCNB1* DE and epilepsy. Sixteen of 20 patients with *KCNB1* DEE had severe to profound ID compared to four of 10 patients with *KCNB1* DE and epilepsy ($P = .04$). Of patients older than 3 years, 13 of 17 with *KCNB1* DEE were nonverbal compared with three of 10 with *KCNB1* DE and epilepsy ($P = .04$). However, we found no difference in independent walking and behavioral or psychiatric characteristics between these two groups.

3.1.6 | Magnetic resonance imaging data

Twenty-five individuals (25/33, 76%) had a normal brain magnetic resonance imaging (MRI) performed at a median age of 3 years (interquartile range = 2-6; Table S1). Patient 6 with *KCNB1* DE and focal epilepsy had two areas of focal cortical dysplasia (Figure 4). Brain MRI of Patient 20, who did not develop epilepsy, showed small bilateral periventricular heterotopia. Cortical and subcortical nonspecific findings and moderate atrophy were reported in three patients. In Patient 31 with *KCNB1* DEE, atrophy was probably progressive. He showed moderate atrophy on MRI at 7 years after a previous normal MRI at 2.5 years. In the other three patients, MRI showed delayed myelination at 3.5 years (Patient 16), nonspecific bilateral central tegmental tract hyperintensity on serial MRI (Patient 24), and a mild brachycephaly (Patient 26).

3.2 | Analysis of all cases

In addition to our series of 36 individuals, 37 published individuals with *KCNB1* encephalopathy were identified in nine reports.^{7,8,10,11,13-15,20,21} Taken together, this series of 73

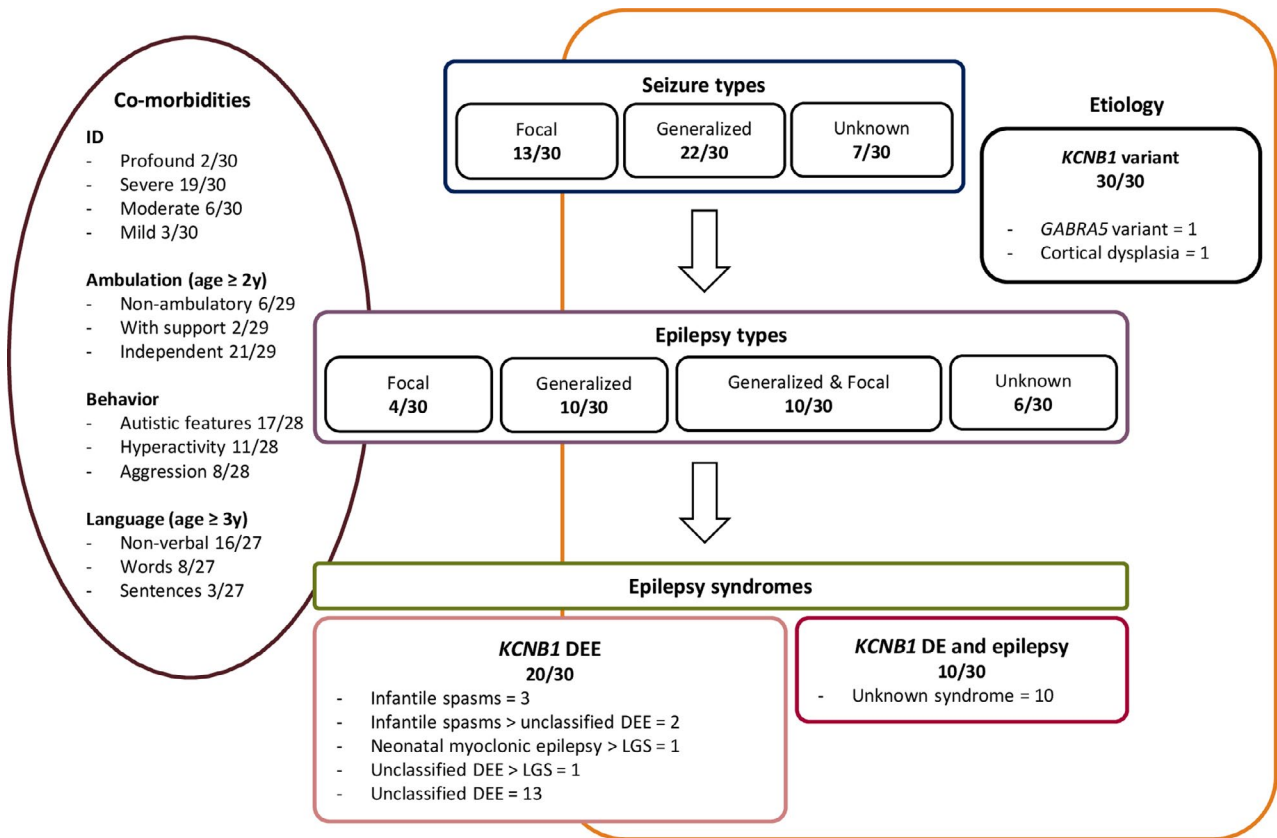


FIGURE 2 Epilepsy phenotype of the 30 individuals with *KCNB1* encephalopathy and epilepsy, according to the International League Against Epilepsy classification. Individuals with epilepsy were classified as having *KCNB1* developmental and epileptic encephalopathy (DEE) or *KCNB1* developmental encephalopathy (DE) and epilepsy. Number of individuals with each seizure type and epilepsy type are indicated as well as the epilepsy syndromes for each group. Comorbidities represent the neurodevelopmental phenotype of individuals with epilepsy. Data on ambulation and oral language are indicated for individuals older than 2 and 3 years, respectively. ID, intellectual disability; LGS, Lennox-Gastaut syndrome

individuals included 50 distinct *KCNB1* pathogenic variants. Variants typically arose de novo except for the maternally inherited variant p.Arg583* in Patient 36. Variants were scattered throughout the KCNB1 protein, with 27 of 50 (54%) located in the pore-forming region (S5-S6 transmembrane domains). Thirty-nine variants (78%) were missense, and 11 were truncating (22%). Eleven variants were recurrent in two to eight individuals (Figure 5). Median age was 9 years (interquartile range = 5-15, data available for n = 70/73). We summarized the epilepsy and developmental spectrum of all 73 individuals (55% males; Table 1).

3.2.1 | Phenotype-genotype correlation

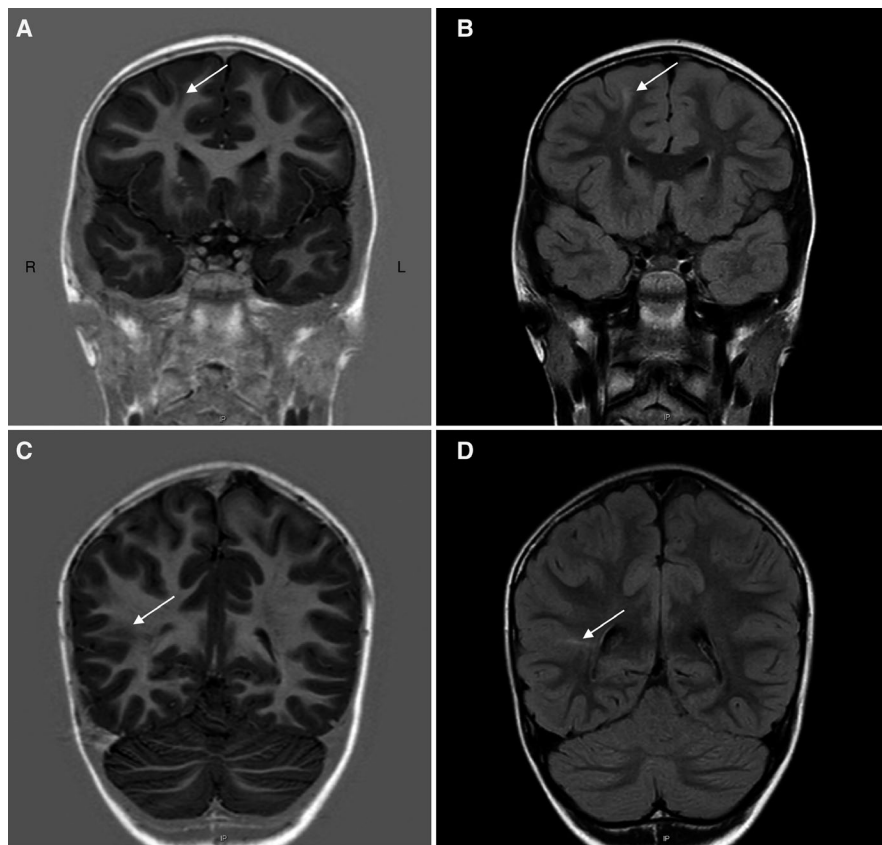
Epilepsy was more frequent in individuals with missense variants (55/59) compared to those with truncating variants (8/13, $P = .008$). Epilepsy was also more frequently drug-resistant in individuals with missense (25/34) compared to those with truncating variants (0/4, $P = .01$). Epilepsy was less frequent in individuals with variants in the C-terminal

domain (5/7 vs 4/61, $P = .0002$). This was expected, because all variants of the C-terminal domain were truncating. We observed no further correlations between the neurodevelopmental phenotype and the variant type or its position in the protein (Figure 5). Individuals with recurrent variants had a similar range of neurodevelopmental disorders. Their phenotypic spectrum ranged from DE with or without mild epilepsy to drug-resistant DEE (Figure 5).

3.2.2 | Long-term outcome

We reviewed the long-term outcome of *KCNB1* encephalopathy in 22 patients older than 12 years: 14 from our series and eight published cases.^{11,13} Median age was 17 years (interquartile range = 15-22 years, range = 12-34 years). Nineteen patients (19/22) had epilepsy. Epilepsy beginning in infancy or early childhood remitted in five individuals who became seizure-free at a median age of 11 years (interquartile range = 9-16 years), and ASMs were progressively withdrawn. Three of them had *KCNB1* DE, one had *KCNB1*

FIGURE 4 Brain magnetic resonance image (MRI) revealing two areas of focal cortical dysplasia in Patient 6 with *KCNB1* encephalopathy and focal epilepsy. Brain MRI of Patient 6 performed at epilepsy onset at 4 years shows a right frontal cortical dysplasia with transmantle sign (arrow) and blurring on T1 inversion recovery coronal sequence (A) and fluid-attenuated inversion recovery (FLAIR) sequence (B), and a right temporoparietal focal cortical dysplasia with transmantle sign (arrow) and blurring on T1 inversion recovery coronal sequence (C) and Flair sequence (D). L, left; R, right



In addition, we identified 10 individuals with *KCNB1* DE and epilepsy who presented later and had pharmacoresponsive epilepsy, without evidence of epileptic encephalopathy. These individuals showed better cognitive outcome compared to those with *KCNB1* DEE, emphasizing the impact of early onset seizures and severe epilepsy on neurodevelopment. Importantly, we studied six individuals aged 4.5–20 years who had not yet had seizures, along with three who had been previously reported, confirming that *KCNB1* also causes early onset DE without epilepsy.

The long-term outcome observed in 22 individuals older than 12 years from our current series and from literature showed that the natural history of epilepsy was highly variable, ranging from individuals with drug-resistant epilepsy to others in remission, allowing ASM withdrawal. Unfortunately, cognition remained poor, with moderate to severe ID in most individuals. Patients also had severe expressive language disorder and frequent behavioral and psychiatric issues impacting on everyday life of the individuals, and their caregivers and families.

Our study showed that truncating *KCNB1* variants were associated with less frequent and less severe epilepsy compared with missense variants. Of the nine individuals with truncating variants and available data, five did not develop seizures, and four had infantile spasms with remission on either vigabatrin or adrenocorticotrophic hormone allowing cessation of ASM. This finding suggests that ASM can be withdrawn in

individuals with *KCNB1* truncating variants whose seizures have remitted. This will limit potential side effects related to ongoing ASM use. All truncating variants were in the last exon and thus expected to produce a truncated protein rather than nonsense-mediated mRNA decay.²² However, few functional studies have been performed to date, with limited data on truncating variants. One recent study showed altered current density for two truncating variants when expressed as homotetramers but normalized current density when coexpressed with wild-type subunits.²³ The epilepsy phenotype might be related to the extent of mutation-induced functional K_v2.1 channel impairment, influenced by other genetic or environmental factors. No other phenotype-genotype correlations were found.

Epilepsy phenotypes associated with variants in other potassium channel genes show similar phenotypic heterogeneity, such as *KCNA2*, *KCNQ2*, *KCNQ3*, *KCNH1*, *KCNJ10*, and *KCNT1*.^{24–29} The underlying pathophysiological explanations for such pleiotropy remain largely unknown. For *KCNA2*, different functional effects of some variants have been associated with distinct epilepsy phenotypes.³⁰ However, a recent functional study of 17 *KCNB1* variants did not support such a correlation,²³ consistent with the observation that recurrent missense variants cause a spectrum of phenotypes.

In addition to epilepsy and neurodevelopmental phenotypes, pathogenic variants in ion-channel genes have been associated

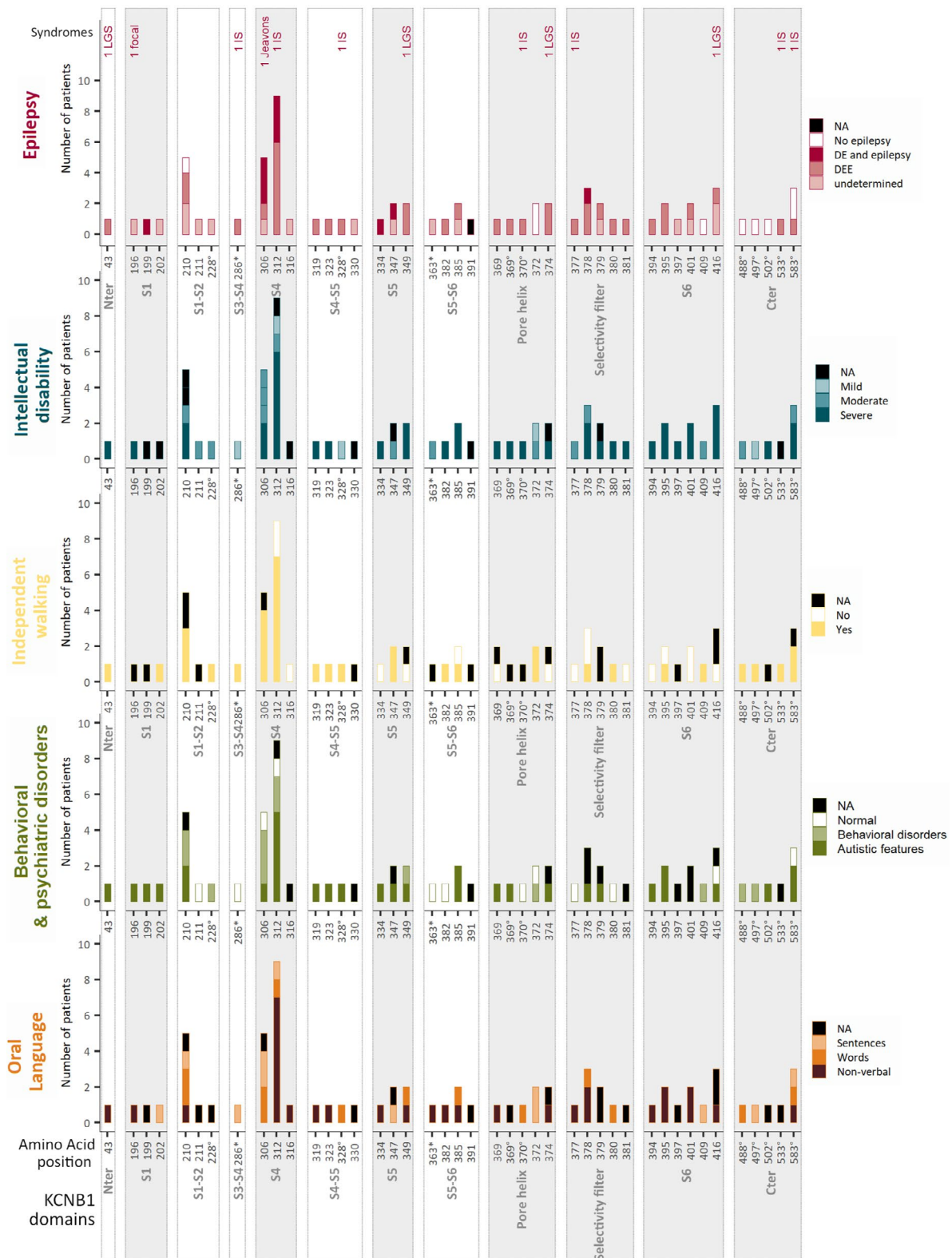


FIGURE 5 Distribution of phenotypes according to the type and position of *KCNB1* variant. The phenotypic spectrum (y-axis) associated with each reported *KCNB1* variant is represented according to its amino acid position and domain of the protein (x-axis). Stars and circles beside amino acid position indicate frameshift and nonsense variants, respectively. Functional transmembrane domains of the protein are represented in gray (S1, S4, S5, pore helix, selectivity filter, S6) while extramembrane domains are represented in white columns (N-terminal domain [Nter], S1-S2, S3-S4, S5-S6). Cter, C-terminal domain; DE, developmental encephalopathy; DEE, developmental and epileptic encephalopathy; IS, infantile spasms; LGS, Lennox-Gastaut syndrome; NA, not available; S, segment

TABLE 1 Phenotypic spectrum of the 73 individuals from this series and published reports

Characteristic	Patients/ patients with available data, n (%) ^a
Median age at study, y (IQR)	9 (5-15)
Clinical examination	
Global or truncal hypotonia	32/62 (52)
Pyramidal signs [hypertonia with spasticity]	15/62 (24)
Ataxia	14/62 (23)
Dystonia, choreoathetosis	10/62 (16)
Hyperlaxity	9/62 (15)
Apraxia, dyspraxia	5/62 (8)
Motor milestones [individuals ≥ 2 y old]	
Independent walking	36/50 (72)
Median age at walking, mo (IQR)	24 (18-36)
Walk with support	4/50 (8)
Nonambulatory	10/50 (20)
Language development [individuals ≥ 3 y old]	
Nonverbal	25/49 (51)
Single words	13/49 (27)
Speaks short sentences	11/49 (22)
Intellectual disability	
Mild	5/61 (8)
Moderate	15/61 (25)
Severe	39/61 (64)
Profound	2/61 (3)
Behavioral and psychiatric impairment	
Autistic features	32/57 (56)
Aggression	22/57 (39)
Impulsiveness/hyperactivity	20/57 (35)
Epilepsy	
Patients with epilepsy	63/72 (88)
Median age at seizure onset, mo (IQR)	13 (9-24)
Seizure types	
Generalized onset seizures	50/61 (82)
Generalized tonic-clonic seizures	29/61 (48)
Generalized epileptic spasms	21/61 (34)
Generalized tonic seizures	18/61 (30)
Atypical absences	15/61 (25)
Generalized myoclonic seizures	15/61 (23)
Generalized atonic seizures	10/61 (16)
Generalized clonic seizures	4/61 (7)
Absence with eyelid myoclonic	1/61 (2)
Focal onset seizures	30/61 (49)
Focal motor seizures	18/61 (30)

(Continues)

TABLE 1 (Continued)

Characteristic	Patients/ patients with available data, n (%) ^a
Focal nonmotor seizures	13/61 (21)
Seizures with unknown onset	7/61 (11)
Epilepsy syndromes	
Unclassified DEE	23/45 (51)
Infantile spasms	7/45 (16)
Lennox-Gastaut syndrome	4/45 (9)
Jeavons syndrome	1/45 (2)
Unknown	10/45 (22)

Abbreviations: DEE, developmental and epileptic encephalopathy; IQR, interquartile range.

^aUnless otherwise indicated.

with other central nervous system (CNS) and extra-CNS manifestations. Extra-CNS manifestations are thought to be related to the expression of these genes in different organs outside the CNS.^{31,32} *KCNB1* encodes the α subunit of K_v2.1, which is widely expressed across the CNS but also in the heart, lung, liver, colon, kidney, and adrenal gland.³³ Cardiac disorders and SUDEP have not yet been reported in individuals with *KCNB1* encephalopathy. Hypotonia was reported in half of the patients and likely has a central basis considering the strong expression of K_v2.1 in the cortex and its major role in regulating excitability in pyramidal neocortical neurons.^{34,35} Although ataxia was reported in 20% of individuals, no evidence of cerebellar abnormality was seen on MRI nor signs of motor neuropathy on clinical examination.

Patient 6 had focal epilepsy, beginning at 4 years, with focal cortical dysplasia (Figure 4). She had the recurrent missense variant p.Arg306Cys, identified in three individuals (including Patient 5), and none had focal cortical dysplasia.^{8,11} Malformations of cortical development have been described in epilepsies due to ion-channel gene variants, including *SCN1A* and *KCNT1*.^{36,37} However, the underlying pathogenesis of cortical malformation due to these genes remains unclear, especially as neuropathological data are scarce given the ongoing debate regarding the efficacy of epilepsy surgery in this population.³⁸

The retrospective nature of our study, without quantitative evaluation of neurodevelopment and ASD, is a limitation. Recruitment of most individuals occurred via tertiary epilepsy centers, which may have led to an underestimation of the prevalence of individuals with *KCNB1* DE without epilepsy. However, the frequency of *KCNB1* DE without epilepsy was higher in our series (6/36) than in published cases (3/37).¹¹

We establish *KCNB1* as an important cause of DEE, early DE, and DE and epilepsy. All are associated with a poor long-term cognitive, psychiatric, and behavioral prognosis. Although frequent, epilepsy exhibits a wide phenotypic

spectrum, ranging from drug-resistant early onset DEE to DE and pharmacoresponsive epilepsy. These findings highlight the urgent need to develop experimental models to gain insight to the underlying pathophysiological mechanisms of *KCNB1* encephalopathy and to develop targeted compounds that can ameliorate the neurodevelopmental outcome.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ACKNOWLEDGMENTS


The authors thank the association KCNB1 France as well as all patients and their families from around the world for their participation in this study. This study was funded by grants from the National Research Agency under the "Investissements d'avenir" program (ANR-10IAHU-01), the Bettencourt Schueller Foundation (C.Ba. and R.N.), the French League Against Epilepsy (C.Ba.), the ERC Consolidator Grant (E. K.), Curekids New Zealand and the Health Research Council of New Zealand (L.G.S. and I.E.S.), the National Health and Medical Research Council of Australia and Medical Research Future Fund of Australia (I.E.S.), and the European Commission Seventh Framework Program under the project DESIRE (grant agreement 602531, R.G.).


CONFLICT OF INTEREST

I.E.S. serves/has served on the editorial boards of the *Annals of Neurology*, *Neurology*, and *Epileptic Disorders*; may accrue future revenue on pending patent WO61/010176 (filed in 2008), "Therapeutic Compound"; has a patent for SCN1A testing held by Bionomics and licensed to various diagnostic companies; has a patent "Molecular Diagnostic/Theranostic Target for Benign Familial Infantile Epilepsy (BFIE) [PRRT2]" 2011904493, 2012900190, and PCT/AU2012/001321 (TECH ID: 2012-009), with royalties paid; has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia, Rogcon, and Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin, and Eisai; has consulted for UCB, Zynerva Pharmaceuticals, and Ovid Therapeutics; and receives/has received research support from the National Health and Medical Research Council of Australia, Health Research Council of New Zealand, CURE, Australian Epilepsy Research Fund, March of Dimes, and National Institutes of Health/National Institute of Neurological Disorders and Stroke. None of the other authors has any conflict of interest to disclose.

ORCID

Claire Bar  <https://orcid.org/0000-0003-1489-0211>

Mathieu Kuchenbuch  <https://orcid.org/0000-0002-5944-2204>

Gaetan Lesca  <https://orcid.org/0000-0001-7691-9492>

Lynette G. Sadleir  <https://orcid.org/0000-0002-5355-7115>

Sophie Dupont  <https://orcid.org/0000-0003-2080-8253>

Ingrid E. Scheffer  <https://orcid.org/0000-0002-2311-2174>

REFERENCES

1. Bamshad MJ, Nickerson DA, Chong JX. Mendelian gene discovery: fast and furious with no end in sight. *Am J Hum Genet. Cell Press.* 2019;105:448–55.
2. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* 2017;58(4):512–21.
3. Nabbout R, Dulac O. Epileptic encephalopathies: a brief overview. *J Clin Neurophysiol.* 2003;20(6):393–7.
4. Wang J, Lin ZJ, Liu L, Xu HQ, Shi YW, Yi YH, et al. Epilepsy-associated genes. 2017;44:11–20.
5. 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(3):304–16.
6. Hwang PM, Fotuhi M, Brecht DS, Cunningham AM, Snyder SH. Contrasting immunohistochemical localizations in rat brain of two novel K⁺ channels of the Shab subfamily. *J Neurosci.* 1993;13(4):1569–76.
7. Torkamani A, Bersell K, Jorge BS, Bjork RL, Friedman JR, Bloss CS, et al. De novo KCNB1 mutations in epileptic encephalopathy. *Ann Neurol.* 2014;76(4):529–40.
8. Saitsu H, Akita T, Tohyama J, Goldberg-Stern H, Kobayashi Y, Cohen R, et al. De novo KCNB1 mutations in infantile epilepsy inhibit repetitive neuronal firing. *Sci Rep.* 2015;5:15199.
9. Thiffault I, Specie DJ, Austin DC, Cobb MM, Eum KS, Safina NP, et al. A novel epileptic encephalopathy mutation in KCNB1 disrupts Kv2.1 ion selectivity, expression, and localization. *J Gen Physiol.* 2015;146(5):399–410.
10. Calhoun JD, Vanoye CG, Kok F, George AL, Kearney JA. Characterization of a KCNB1 variant associated with autism, intellectual disability, and epilepsy. *Neurol Genet.* 2017;3(6):e198.
11. De Kovel CGF, Syrbe S, Brilstra EH, Verbeek N, Kerr B, Dubbs H, et al. Neurodevelopmental disorders caused by de novo variants in KCNB1 genotypes and phenotypes. *JAMA Neurol.* 2017;74(10):1228–36.
12. Latypova X, Matsumoto N, Vincelas-Muller C, Bézieau S, Isidor B, Miyake N. Novel KCNB1 mutation associated with non-syndromic intellectual disability. *J Hum Genet.* 2017;62(5):569–73.
13. Marini C, Romoli M, Parrini E, Costa C, Mei D, Mari F, et al. Clinical features and outcome of 6 new patients carrying de novo KCNB1 gene mutations. *Neurol Genet.* 2017;3(6):e206.
14. Miao P, Feng J, Guo Y, Wang J, Xu X, Wang Y, et al. Genotype and phenotype analysis using an epilepsy-associated gene panel in Chinese pediatric epilepsy patients. *Clin Genet.* 2018;94(6):512–20.
15. Samanta D. Epileptic spasm and de novo KCNB1 mutation: if it is not one potassium channel, it is another! *Acta Neurol Belg.* 2020;120(2):417–20.

16. Bar C, Barcia G, Jennesson M, Le Guyader G, Schneider A, Mignot C, et al. Expanding the genetic and phenotypic relevance of KCNB1 variants in developmental and epileptic encephalopathies: 27 new patients and overview of the literature. *Hum Mutat.* 2020;41(1):69–80.
17. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* 2017;58(4):522–30.
18. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17(5):405–24.
19. den Dunnen JT, Dalgleish R, Maglott DR, Hart RK, Greenblatt MS, McGowan-Jordan J, et al. HGVS recommendations for the description of sequence variants: 2016 update. *Hum Mutat.* 2016;37(6):564–9.
20. Soden SE, Saunders CJ, Willig LK, Farrow EG, Smith LD, Petrikin JE, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med.* 2014;6(265):265ra168.
21. Schönewolf-Greulich B, Bisgaard AM, Møller RS, Dunø M, Brøndum-Nielsen K, Kaur S, et al. Clinician's guide to genes associated with Rett-like phenotypes—investigation of a Danish cohort and review of the literature. *Clin Genet.* 2019;95:221–30.
22. Khajavi M, Inoue K, Lupski JR. Nonsense-mediated mRNA decay modulates clinical outcome of genetic disease. *Eur J Hum Genet.* 2006;14(10):1074.
23. Kang SK, Vanoye CG, Misra SN, Echevarria DM, Calhoun JD, O'Connor JB, et al. Spectrum of KV2.1 dysfunction in KCNB1-associated neurodevelopmental disorders. *Ann Neurol.* 2019;86(6):899–912.
24. Charlier C, Singh NA, Ryan SG, Lewis TB, Reus BE, Leach RJ, et al. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nat Genet.* 1998;18(1):53–5.
25. Singh NA, Charlier C, Stauffer D, DuPont BR, Leach RJ, Melis R, et al. A novel potassium channel gene, KCNQ2, is mutated in an inherited epilepsy of newborns. *Nat Genet.* 1998;18:25–9.
26. Sicca F, Imbrici P, D'Adamo MC, Moro F, Bonatti F, Brovedani P, et al. Autism with seizures and intellectual disability: possible causative role of gain-of-function of the inwardly-rectifying K⁺ channel Kir4.1. *Neurobiol Dis.* 2011;43(1):239–47.
27. Barcia G, Fleming MR, Deligniere A, Gazula V-R, Brown MR, Langouet M, et al. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. *Nat Genet.* 2012;44(11):1255–9.
28. Simons C, Rash LD, Crawford J, Ma L, Cristofori-Armstrong B, Miller D, et al. Mutations in the voltage-gated potassium channel gene KCNH1 cause Temple-Baraitser syndrome and epilepsy. *Nat Genet.* 2015;47(1):73–7.
29. Syrbe S, Hedrich UBS, Riesch E, Djémié T, Müller S, Møller RS, et al. De novo loss- or gain-of-function mutations in KCNA2 cause epileptic encephalopathy. *Nat Genet.* 2015;47(4):393–9.
30. Masnada S, Hedrich UBS, Gardella E, Schubert J, Kaiwar C, Klee EW, et al. Clinical spectrum and genotype–phenotype associations of KCNA2-related encephalopathies. *Brain.* 2017;140(9):2337–54.
31. Gitiaux C, Chemaly N, Quijano-Roy S, Barnerias C, Desguerre I, Hully M, et al. Motor neuropathy contributes to crouching in patients with Dravet syndrome. *Neurology.* 2016;87(3):277–81.
32. Goldman AM, Behr ER, Semsarian C, Bagnall RD, Sisodiya S, Cooper PN. Sudden unexpected death in epilepsy genetics: molecular diagnostics and prevention. *Epilepsia.* 2016;57(Suppl 1):17–25.
33. Schnitzler MM, Rinné S, Skrobek L, Renigunta V, Schlichthörl G, Derst C, et al. Mutation of histidine 105 in the T1 domain of the potassium channel Kv2.1 disrupts heteromerization with Kv6.3 and Kv6.4. *J Biol Chem.* 2009;284(7):4695–704.
34. Bekkers JM. Distribution and activation of voltage-gated potassium channels in cell-attached and outside-out patches from large layer 5 cortical pyramidal neurons of the rat. *J Physiol.* 2000;525(3):611–20.
35. Guan D, Tkatch T, Surmeier DJ, Armstrong WE, Foehring RC. Kv2 subunits underlie slowly inactivating potassium current in rat neocortical pyramidal neurons. *J Physiol.* 2007;581(3):941–60.
36. Barba C, Parrini E, Coras R, Galuppi A, Craiu D, Kluger G, et al. Co-occurring malformations of cortical development and SCN1A gene mutations. *Epilepsia.* 2014;55(7):1009–19.
37. Rubboli G, Plazzi G, Picard F, Nobili L, Hirsch E, Chelly J, et al. Mild malformations of cortical development in sleep-related hypermotor epilepsy due to KCNT1 mutations. *Ann Clin Transl Neurol.* 2019;6(2):386–91.
38. Stevelink R, Sanders MWCB, Tuinman MP, Brilstra EH, Koeleman BPC, Jansen FE, et al. Epilepsy surgery for patients with genetic refractory epilepsy: a systematic review. *Epileptic Disord.* 2018;20(2):99–115.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Bar C, Kuchenbuch M, Barcia G, et al. Developmental and epilepsy spectrum of *KCNB1* encephalopathy with long-term outcome. *Epilepsia.* 2020;61:2461–2473. <https://doi.org/10.1111/epi.16679>