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

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## 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.<sup>1</sup> 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.<sup>2</sup> The term *epileptic encephalopathy* alone applies to individuals without preexisting developmental delay where the adverse developmental impact is due to seizures and epileptiform activity.<sup>2,3</sup> 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.<sup>2</sup>

Pathogenic variants in ion-channel genes represent a major cause of DEE.<sup>4,5</sup> 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*.<sup>4</sup> *KCNB1* codes for the  $\alpha$  subunit of the voltage-gated potassium channel subfamily 2 (K<sub>v</sub>2.1).<sup>6</sup> In 2014, de novo pathogenic variants in *KCNB1* were first recognized to cause infantile onset epileptic encephalopathy in three patients.<sup>7</sup> Two series, including six and 25 individuals in total, have been reported, in addition to case reports.<sup>8–15</sup> Individuals exhibited global developmental delay, behavioral disorders, and various epilepsies.<sup>8–15</sup> A few individuals had developmental delay without seizures.<sup>11,16</sup> Outcome data are

## Key Points

- *KCNBI* encephalopathy has a wide phenotypic spectrum, typically with poor long-term cognitive, psychiatric, and behavioral outcomes.
- *KCNBI* 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.<sup>11,16</sup>

Here, we analyze a series of 36 individuals with pathogenic *KCNBI* variants to delineate the phenotypic spectrum of *KCNBI* 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 *KCNBI* 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 *KCNBI* 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.<sup>2,17</sup> Individuals were classified as having *KCNBI* DEE when epilepsy (seizures and EEG) resulted in developmental slowing or regression. Individuals were classified as *KCNBI* 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

*KCNBI* 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.<sup>18</sup> *KCNBI* variants were described according to Human Genome Variation Society variant nomenclature guidelines (<http://varnomen.hgvs.org/>),<sup>19</sup> 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 *KCNBI* pathogenic variants by combining the terms “*KCNBI*” 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 *KCNBI* 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 *KCNBI* variants<sup>16</sup> and eight new patients (Table S1). The 36 patients had 30 different *KCNBI* 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  $\gamma$ -aminobutyric acid type A receptor. Both variants were predicted to be damaging and thus considered pathogenic and contributing to the individual's phenotype.<sup>16</sup> 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 *KCNBI* 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 *KCNBI* DEE, whereas 16 (16/36, 44%) had *KCNBI* DE, including six without epilepsy (Figure 2).

The 20 patients with *KCNBI* 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 *KCNBI* 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.

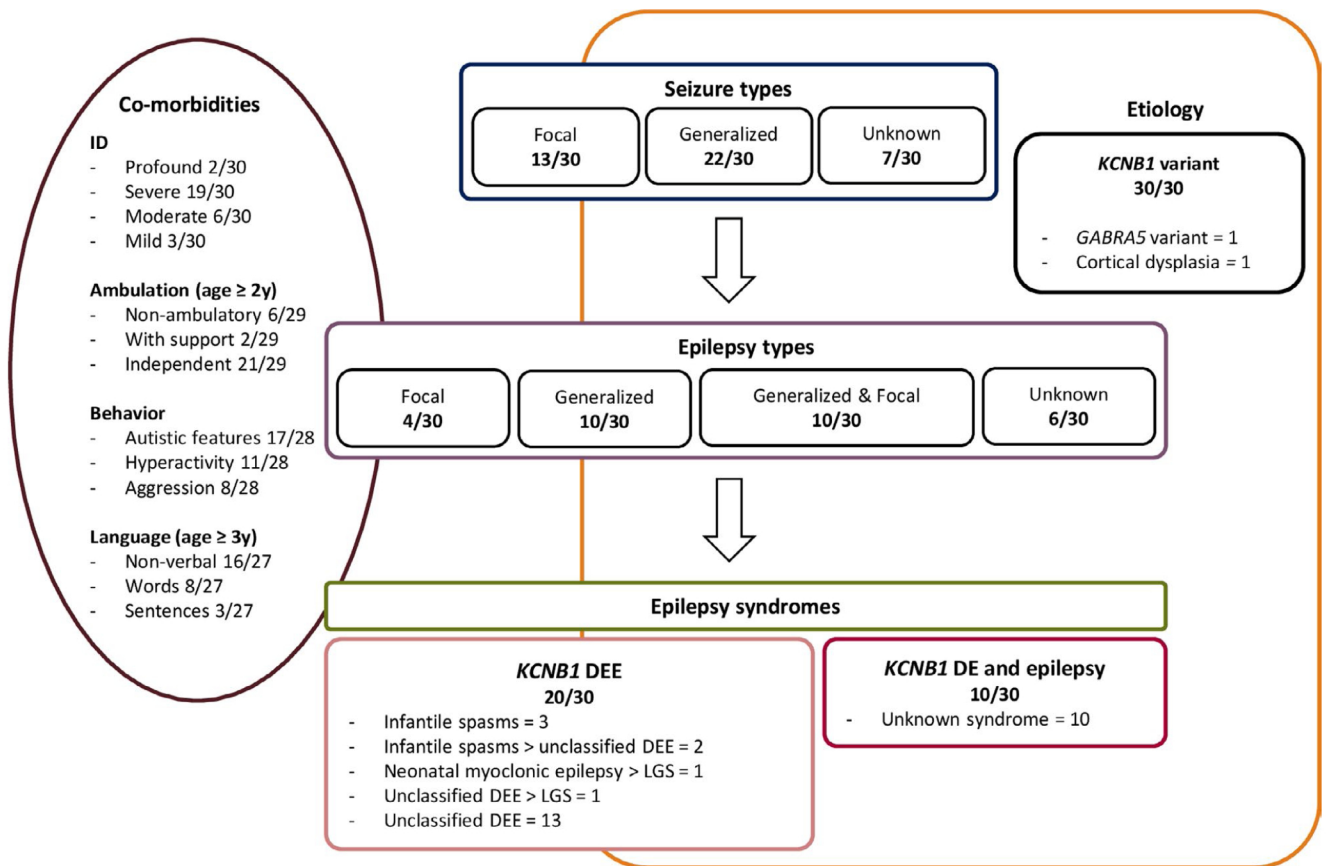
ID and language disorder were more severe in patients with *KCNB1* DEE compared to those with *KCNB1* DE and epilepsy. Sixteen of 20 patients with *KCNB1* DEE had severe to profound ID compared to four of 10 patients with *KCNB1* DE and epilepsy ( $P = .04$ ). Of patients older than 3 years, 13 of 17 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.<sup>7,8,10,11,13-15,20,21</sup> 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

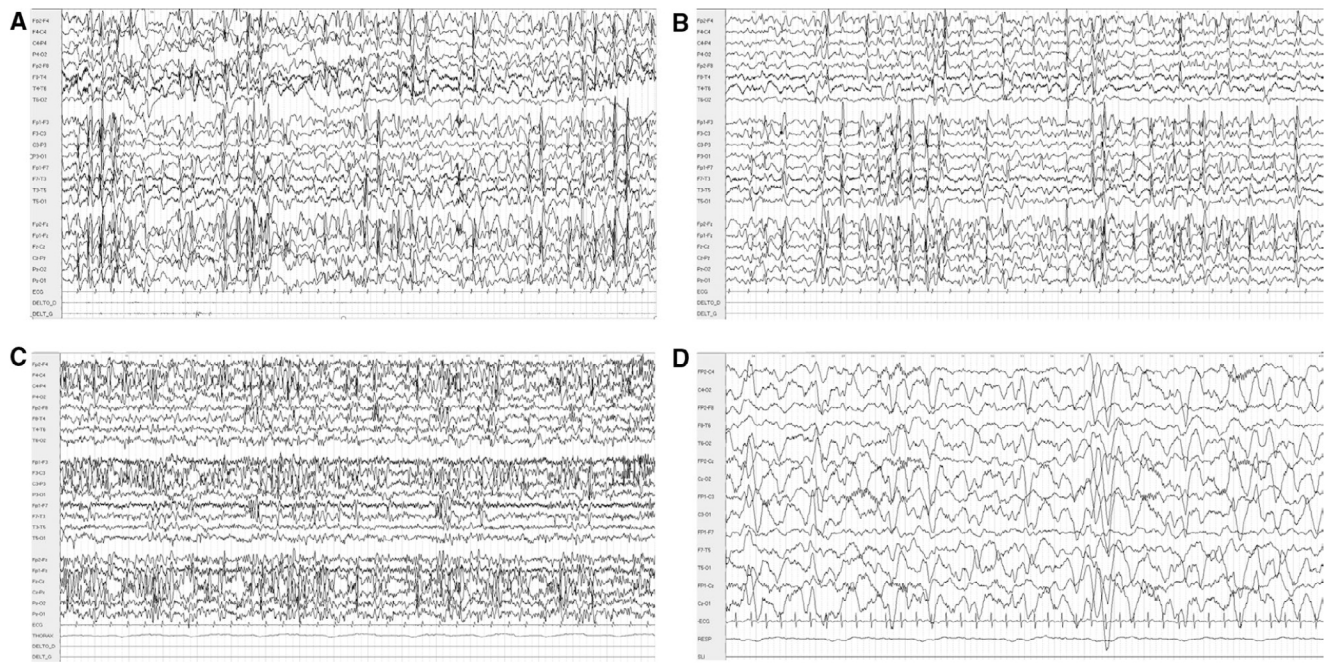
Epilepsy was more frequent in individuals with missense variants (55/59) compared to those with truncating variants (8/13,  $P = .008$ ). Epilepsy was also more frequently drug-resistant in individuals with missense (25/34) compared to those with truncating variants (0/4,  $P = .01$ ). Epilepsy was less 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.<sup>11,13</sup> 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 3** Interictal electroencephalographic (EEG) recordings of patients with *KCNB1* encephalopathy (longitudinal bipolar montage, right derivations above left derivations). A, B, Interictal EEG recording of Patient 28 with *KCNB1* developmental and epileptic encephalopathy (DEE) showing slowing of background activity with frequent diffuse spike-and-waves, predominant in anterior regions, during wakefulness (A) and sleep (B) at 9 years. C, Interictal sleep EEG recording of Patient 14 with *KCNB1* DEE showing abundant and multifocal paroxysmal activity at 4 years. D, Interictal sleep EEG recording of Patient 16 with *KCNB1* developmental encephalopathy showing normal background activity with sleep spindles and K-complexes at 12 months

DEE, and the last one from the literature cannot be classified. Duration of remission ranged from 2 to 24 years. Seizure frequency decreased over time in three individuals. Five individuals still had daily to weekly seizures; three evolved to Lennox-Gastaut syndrome of whom one previously had neonatal myoclonic DEE, and the remaining two had unclassified DEE. One individual had a few sporadic seizures at age 25 years and was not treated. Epilepsy outcome was not documented in five individuals.

Developmental outcome was not constantly reported from previous literature reports. Seventeen patients (17/21, 81%) had severe developmental delay, with no information for one patient. Three individuals, two aged 12 and one aged 20 years, did not have epilepsy, and their ID varied from mild to severe. In the 18 patients with reported language skills, 11 of 18 (61%) were nonverbal, four of 18 (22%) spoke words, and three of 18 (17%) used short sentences. Information on behavioral and/or psychiatric disorders was available in 19 individuals, with reported disorders in 16 of 19 (84%). Seven of them required antipsychotic drugs. Finally, walking information was reported in 17 individuals, with 13 of 17 (76%) walking independently, one walked with support, and three needed a wheelchair.

Mortality did not appear to be increased, as there was no history of sudden unexpected death in epilepsy (SUDEP) and only one individual with Lennox-Gastaut syndrome

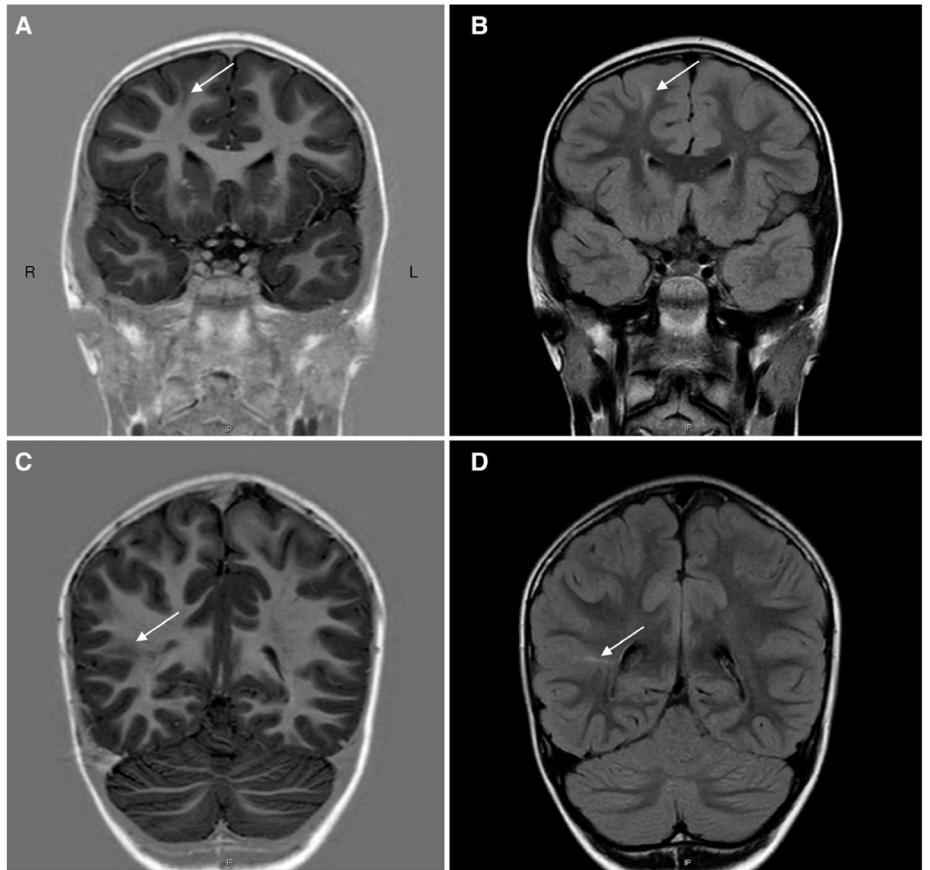
following a neonatal myoclonic DEE died at 17 years due to severe pneumonia.

## 4 | DISCUSSION

We report a large series of individuals with *KCNB1* encephalopathy, delineating the phenotypic spectrum and long-term outcome. This large series is the result of a successful collaboration between academia and a family support group (the family association *KCNB1* France) taking from the shadows dozens of families and patients, in addition to a large international collaboration through seven tertiary epilepsy centers. Early developmental delay is universal, with two-thirds of individuals having severe to profound ID. More than 80% develop epilepsy. Autism spectrum disorder (ASD) and other psychiatric and behavioral disorders occur in more than half of individuals.

The most common phenotype, occurring in 56% cases, was *KCNB1* DEE with infantile onset drug-resistant seizures associated with periods of developmental regression or plateauing. A range of seizure types may occur, including epileptic spasms, and generalized and focal seizures. *KCNB1* should now be included in epilepsy gene panels and interrogated for a pathogenic variant when performing genetic testing in patients with DEE.

**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.

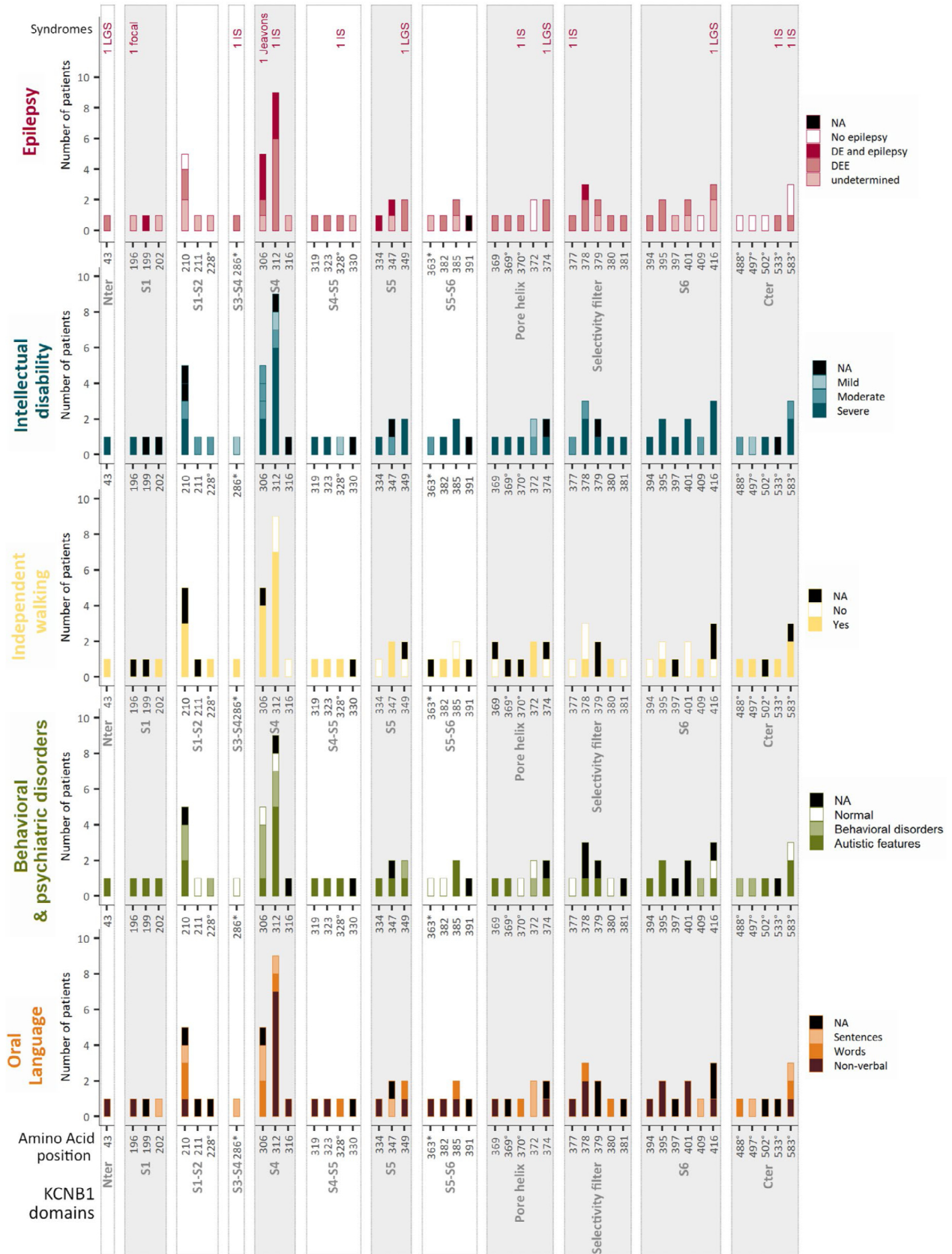
The long-term outcome observed in 22 individuals older than 12 years from our current series and from literature showed that the natural history of epilepsy was highly variable, ranging from individuals with drug-resistant epilepsy to others in remission, allowing ASM withdrawal. Unfortunately, cognition 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 adrenocorticotropic 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.<sup>22</sup> 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 co-expressed with wild-type subunits.<sup>23</sup> 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*.<sup>24-29</sup> 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.<sup>30</sup> However, a recent functional study of 17 *KCNB1* variants did not support such a correlation,<sup>23</sup> 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 (%) <sup>a</sup>
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 (%) <sup>a</sup>
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.

<sup>a</sup>Unless 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.<sup>31,32</sup> *KCNBI* encodes the  $\alpha$  subunit of  $K_v2.1$ , which is widely expressed across the CNS but also in the heart, lung, liver, colon, kidney, and adrenal gland.<sup>33</sup> Cardiac disorders and SUDEP have not yet been reported in individuals with *KCNBI* 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.<sup>34,35</sup> 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.<sup>8,11</sup> Malformations of cortical development have been described in epilepsies due to ion-channel gene variants, including *SCN1A* and *KCNT1*.<sup>36,37</sup> 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.<sup>38</sup>

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 *KCNBI* DE without epilepsy. However, the frequency of *KCNBI* DE without epilepsy was higher in our series (6/36) than in published cases (3/37).<sup>11</sup>

We establish *KCNBI* 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.

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## 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.

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