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Epilepsy with migrating focal seizures
KCNT1 mutation hotspots and phenotype variability

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Abstract

Objective
To report new sporadic cases and 1 family with epilepsy of infancy with migrating focal seizures (EIMFSs) due to KCNT1 gain-of-function and to assess therapies’ efficacy including quinidine.

Methods
We reviewed the clinical, EEG, and molecular data of 17 new patients with EIMFS and KCNT1 mutations, in collaboration with the network of the French reference center for rare epilepsies.

Results
The mean seizure onset age was 1 month (range: 1 hour to 4 months), and all children had focal motor seizures with autonomic signs and migrating ictal pattern on EEG. Three children also had infantile spasms and hypersrrhythmia. The identified KCNT1 variants clustered as “hot spots” on the C-terminal domain, and all mutations occurred de novo except the p.R398Q mutation inherited from the father with nocturnal frontal lobe epilepsy, present in 2 paternal uncles, one being asymptomatic and the other with single tonic-clonic seizure. In 1 patient with EIMFS, we identified the p.R1106Q mutation associated with Brugada syndrome and saw no abnormality in cardiac rhythm. Quinidine was well tolerated when administered to 2 and 4-year-old patients but did not reduce seizure frequency.

Conclusions
The majority of the KCNT1 mutations appear to cluster in hot spots essential for the channel activity. A same mutation can be linked to a spectrum of conditions ranging from EMFSI to asymptomatic carrier, even in the same family. None of the antiepileptic therapies displayed clinical efficacy, including quinidine in 2 patients.
Epilepsy of infancy with migrating focal seizures (EIMFS) is a rare and severe epileptic syndrome characterized by (1) seizure onset during the first months of life, (2) focal seizures migrating from one cortical region to another, (3) marked pharmacoresistance, and (4) severe cognitive long-term disability. In 50% of patients with EIMFS, gain-of-function mutations are identified in the KCNT1 gene (OMIM608167), encoding the sodium-activated potassium channel. KCNT1 mutations result in a severe form of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), in some patients with other developmental and epileptic encephalopathies, in patients with focal and multifocal epilepsies, and patients with no seizures but presenting with cardiac arrhythmia.

Genotype-phenotype correlations are rather complicated due to the association of the same KCNT1 mutation with different epilepsy phenotypes. Additional studies are necessary to evaluate the spectrum of phenotypes caused by KCNT1 mutations and for correlation of phenotype-genotype.

In addition, the identification of KCNT1 mutations could have therapeutic implications because quinidine rescues the K+ channel gain-of-function effect of the mutation as shown by in vitro studies. Although the clinical use of quinidine is controversial, administration of quinidine resulted in varying degrees of efficacy in some patients.

We report a new series of 17 patients with EIMFS and KCNT1 mutations, pointing out intrafamilial phenotype heterogeneity in a 3-generation family. We discuss genotype-phenotype correlations based on this new case series and the previously reported cases in the literature.

Methods

Seventeen patients with EIMFS and KCNT1 mutations were collected through a multicentric study in the hospitals of the network of reference centers for rare epilepsies in France and Spain. The EIMFS diagnosis was according to the following criteria: (1) onset under age 6 months, (2) presentation with focal seizures progressing to frequent or almost continuous polymorphous seizures with a migrating pattern; and (3) developmental arrest at seizure onset and progressive cognitive decline.

We collected the clinical and EEG data, including family history of seizure disorders, psychomotor development evaluation, seizure onset and type, EEGs recordings with video monitoring, neurologic examination, neuroimaging studies, and response to antiepileptic drugs (AEDs).

The KCNT1 mutation detection was by using Sanger sequencing or next-generation sequencing panels targeting 71 to 151 genes involved in childhood epilepsies (table e-1, links.lww.com/NXG/A187). In addition, we reviewed all KCNT1 reports referenced in PubMed up to 2018. We compared the genotype-phenotype of the KCNT1 mutations reported in the literature with special attention on “hotspots.”

Standard protocol approvals, registrations, and patient consents

All parents or legal guardians gave written informed consent for genetic diagnostic procedures following the guidelines of the ethics committee of our institution. Approval for the research protocols was from the local institutional review board and ethics committee.

Data availability

Anonymized data not published within this article will be made available by request from qualified investigators.

Results

Clinical and EEG features

In this study, the cohort of patients with KCNT1 mutations consisted of 8 females and 9 males. Patient demographic data are shown in the table. Patients did not have any family history of seizures or neurologic diseases except for patient 2. The father of patient 2 (II2, figure 1) with a diagnosis of ADNFLE, had seizure onset during adolescence. He was seizure-free on antiepileptic treatment since age 17 years and had a healthy social and professional integration. One of the patient 2 paternal uncles (II3, figure 1) presented with a single unprovoked generalized tonic-clonic seizure at age 25 years. He had a healthy social and professional life and did not receive any treatment. Patient 2 paternal grandfather (12, figure 1) likely had severe ADNFLE since he experienced nocturnal paroxysmal events and psychiatric and behavioral problems during adulthood (figure 1).

The birth of all 17 patients was uneventful after full-term pregnancies except for a premature spontaneous delivery at 34 weeks of gestation without perinatal distress in patient 15, and patient 16 showed intrauterine growth delay and polyhydramnios. Seizures occurred at a mean age of 1 month (range: 1 hour to 4 months), within the first week of life for 6 patients, and all children presented with focal motor seizures accompanied by autonomic signs. Patients 5, 14, and 17 had clusters of infantile spasms recorded on video-EEG, in addition to focal seizures (table). Their interictal EEG showed hypsarrhythmia (figure 2). All patients...
<table>
<thead>
<tr>
<th>Patient, sex</th>
<th>Age at last FU (y)</th>
<th>Origin</th>
<th>Familial history, consanguinity</th>
<th>KCNT1 mutation (NM_020822.2)</th>
<th>Functional study</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Age at seizure onset</th>
<th>Seizure type</th>
<th>Brain MRI</th>
<th>EEG</th>
<th>Neurologic examination</th>
<th>Aggravation period</th>
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<tbody>
<tr>
<td>1, F</td>
<td>1.1</td>
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<td>c.862G&gt;A p.Gly288Ser</td>
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<td>De novo</td>
<td>EIMFS</td>
<td>2 mo</td>
<td>Focal motor (tonic)</td>
<td>Normal</td>
<td>Migrating pattern</td>
<td>Microcephaly and hypotonia</td>
<td>2 mo-FU (13 mo)</td>
<td>PB, PHT, CBZ, LEV, KD, TPM, VGB, VPA, and DZP</td>
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<tr>
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<td>Gain of function</td>
<td>Heterozygous</td>
<td>EIMFS</td>
<td>10 d</td>
<td>Clonic seizures of L + gaze deviation</td>
<td>Normal (4 mo)</td>
<td>Migrating pattern</td>
<td>Axial hypotonia, microcephaly, erratic eye movements, and NGF</td>
<td>2 mo-6.5 mo</td>
<td>Combination of STP and CZP relatively improved at age of 3 y</td>
<td>Deceased during SE (6.5 mo)</td>
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<td>Gain of function</td>
<td>De novo</td>
<td>EIMFS</td>
<td>3 wk</td>
<td>Focal motor (tonic)</td>
<td>Normal</td>
<td>Migrating pattern</td>
<td>Axial hypotonia and microcephaly</td>
<td>2 mo-FU (22 mo)</td>
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<td>De novo</td>
<td>EIMFS</td>
<td>4 mo</td>
<td>Focal motor (clonic) and autonomic (cyanosis)</td>
<td>Normal</td>
<td>Migrating pattern</td>
<td>Microcephaly and hypotonia</td>
<td>4 mo-1.2 y</td>
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<td>Gain of function</td>
<td>De novo</td>
<td>EIMFS-SB-West</td>
<td>1 d</td>
<td>Focal motor and spasms</td>
<td>Thin CC</td>
<td>Migrating pattern</td>
<td>Hypotonia and pyramidal syndrome</td>
<td>NA</td>
<td>PB, VGB, CZP, and KD</td>
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<tr>
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<td>No</td>
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<td>Gain of function</td>
<td>De novo</td>
<td>EIMFS</td>
<td>1 d</td>
<td>Focal motor and autonomic tonic</td>
<td>Normal (4 d and 1.5 mo)</td>
<td>Migrating pattern</td>
<td>Hypotonia and NGF</td>
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<td>PHE, LEV, CLB, CZP, VGB, and KD</td>
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<td>De novo</td>
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<td>Focal motor (hemispheric) autonomic</td>
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<td>Migrating pattern</td>
<td>Microcephaly and hypotonia</td>
<td>2 mo-1 y</td>
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<td>1.5 mo</td>
<td>Focal and generalized tonic</td>
<td>Myelination delay and thin CC (6 mo)</td>
<td>Migrating pattern + SB</td>
<td>Microcephaly and hypotonia</td>
<td>2 mo-FU (1.5 y)</td>
<td>VGB, LEV, and CZP</td>
<td>Deceased (1.5 y)</td>
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<tr>
<td>9, F</td>
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<td>De novo</td>
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<td>1 h</td>
<td>Focal motor (tonic)</td>
<td>Myelination delay (1 mo)</td>
<td>Migrating pattern</td>
<td>Microcephaly, hypotonia, and pyramidal syndrome</td>
<td>1 mo-FU</td>
<td>LEV, VGB, CLB, PB, and quinidine</td>
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<td>De novo</td>
<td>EIMFS</td>
<td>2 d</td>
<td>Focal motor (tonic) and autonomic (cyanosis)</td>
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<td>Migrating pattern-SB</td>
<td>Microcephaly, hypotonia, and pyramidal syndrome</td>
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<tr>
<th>Patient, sex</th>
<th>Age at last FU (y)</th>
<th>Origin</th>
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<th>KCNT1 mutation (NM_020822.2)</th>
<th>Functional study</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Age at seizure onset</th>
<th>Seizure type</th>
<th>Brain MRI</th>
<th>EEG</th>
<th>Neurologic examination</th>
<th>Aggravation period</th>
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<td>1 d</td>
<td>Focal motor and autonomic; tonic</td>
<td>Normal (3 mo)</td>
<td>Migrating pattern—SB—Hypsarrhythmia</td>
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<td>3 mo-FU</td>
<td>TPM, VGB, and HC</td>
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<td>De novo</td>
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<td>13 d</td>
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<td>Normal</td>
<td>Migrating pattern</td>
<td>Hypotonia</td>
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<td>CZP, PHE, VGB, LEV, CLB, and TPM</td>
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<td>De novo</td>
<td>EIMFS</td>
<td>2 mo</td>
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<td>Normal</td>
<td>Migrating pattern</td>
<td>Microcephaly and hypotonia</td>
<td>NA</td>
<td>VPA, OXC, STP, KD, and TPM</td>
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<td>De novo</td>
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<td>2 wk</td>
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<td>Normal</td>
<td>Migrating pattern—hypsarrhythmia (hemi-spasms)</td>
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<td>De novo</td>
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<td>2.5 mo</td>
<td>Loss of contact and tonic</td>
<td>Normal</td>
<td>Migrating pattern</td>
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<td>De novo</td>
<td>EIMFS</td>
<td>1.5 mo</td>
<td>Focal motor and autonomic; tonic</td>
<td>Normal (1.5 mo)</td>
<td>Migrating pattern</td>
<td>Hypotonia</td>
<td>NA</td>
<td>TPM, C2P, PB, CBZ, STP, KD, and VPA; Seizure aggravation with PHE and VGB</td>
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<td>17, F</td>
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<td>De novo</td>
<td>EIMFS- West</td>
<td>2 mo</td>
<td>Tonic and autonomic (cyanosis, flushing) seizures and spasms (7 mo)</td>
<td>Normal (1 mo) and global atrophy (1.5 y)</td>
<td>Migrating pattern—hypsarrhythmia</td>
<td>Hypotonia, pyramidal syndrome, and scoliosis</td>
<td>1 mo–7.5 y</td>
<td>PB, VGB, CLB, VPA, HC, TPM, LTG, and LEV</td>
<td>Profound ID; no walk; no language</td>
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</tbody>
</table>

Abbreviations: ADNFLE = autosomal dominant nocturnal frontal lobe epilepsy; AED = antiepileptic drug; CBZ = carbamazepine; CLB = clobazam; CZP = clonazepam; DD = developmental delay; DZP = diazepam; EIMFS = epilepsy of infancy with migrating focal seizures; FU = follow-up; HC = hydrocortisone; ID = intellectual disability; KD = ketogenic diet; L = left; LEV = levetiracetam; LTG = lamotrigine; NA = not applicable; NGF = nasogastric feeding; NK = not known; NP = not performed; OXC = oxcarbazepine; PB = phenobarbital; PHT = phenytoin; RFM = rufinamide; SB = suppression burst; SE = status epilepticus; STP = stiripentol; TPM = topiramate; VPA = valproic acid; VGB = vigabatrin; ZNS = zonisamide.
had multiple daily seizures at the onset and continued to have frequent seizures, resistant to 3 or more AED trials in the first month to the first year of life (table).

EEG recorded at onset typically showed a migrating ictal pattern (figure 2A), whereas interictal EEG showed a slow background activity with lack of physiologic rhythms and rare multifocal spikes or spike and waves. In patients 5, 8, 10, and 11, migrating seizures preceded with a pattern of “suppression burst” on EEG (figure 2B). All children had long-lasting EEGs with ECG showing no cardiac rhythm abnormalities with normal Holter ECG (24-hour recording) in 5 patients.

Two patients (#4 and 9) were on the quinidine trial according to a previously reported protocol.14 For patient 4, quinidine was administered with lamotrigine (LTG), valproate, clonazepam (CZP), and a ketogenic diet at age 4 years, and for patient 9, quinidine was administered with LTG and CZP at 2 years. A dose of 10 mg/kg/d was achieved gradually over 1 week. The quinidine serum level at 1 month was 0.7 and 0.6 μg/mL for patients 4 and 9, respectively. The dose was increased over 1 week to 35 mg/kg/d in 3 divided doses. The serum level increased gradually up to 3 and 2.7 μg/mL in patients 4 and 9, respectively. After 1 month, we did not see any effect on seizure frequency. ECGs were normal, and the dose was increased a third time up to 50 mg/kg/d. After 2 weeks of this dose, the serum level of quinidine did not exceed 3 and 4.5 μg/mL for patients 4 and 9, respectively. This treatment failed to decrease the number of countable seizures (60 and 85 seizures per day for patients 4 and 9 over 3 months). Quinidine was provided at 35 mg/kg/d for the last 2 months. Neither seizure frequency nor EEG pattern showed any significant change, and quinidine was therapy discontinued. During the quinidine trial, patients did not present any noticeable side effects, and parents did not report any changes in appetite, eye contact, or sleep behavior.

Mutation analysis
All patients carried heterozygous missense mutations: p.G288S (#1), p.R398Q (#2), p.R428Q (#3, 4, 5, and 6), p.L437P (#7), p.R474C (#8 and 9), p.R474H (#10 and 11), p.M516V (#12), p.G288S (#1), p.R398Q (#2), p.R428Q (#3, 4, 5, and 6), p.L437P (#7), and p.R1106P (#17) (table, figure 3). We did not perform functional studies for the novel p.A965V variant (#16), as it modifies a strongly conserved amino acid and is predicted likely pathogenic by in silico software (PolyPhen-2, SIFT, and CADD). In addition, this mutation was not present in the Genome Aggregation Database (gnomAD, gnomad.broad-institute.org) and in-house databases. All the other mutations have been reported previously, namely p.G288S, p.R398Q, and p.A934T both in EIMFS and ADNFLE,3,7,9,13,14,15,17,20–22,24–32,34–35 33 with ADNFLE,4,9,35 4 with other focal seizures,10,16,24 4 with West syndrome,7,8,26,33 4 with early-onset epileptic encephalopathy (EOEE),6,7,15,36 and 1 with Brugada syndrome without epilepsy phenotype.11 A specific mutation can be reported in different phenotypes and therefore is not possible to establish a genotype-phenotype correlation based on single mutation or hot spots (figure 3). For example, the p.G288S, the p.R398Q, and the p.A934T mutations are present in both EIMFS and ADNFLE.3,4,7,9,17,26

Discussion
In a cohort of 17 new patients, we report the association of EIMFS with 1 novel mutation in the KCNT gene. The majority of the KCNT mutations cluster in the C-terminal KCNT1 region, except for p.G288S on the channel pore, and several variants in the transmembrane domain-5 (figure 3). Of interest as confirmed in this series, several KCNT1 mutations recur and occur in specific hot spots, namely p.G288S, p.R398Q, p.R428Q, p.R474C, p.R474H, and p.A934T (figure 3).3,4,7,8,13,16,17,22–31,37 Hotspots are rarely reported in other genes encoding K+ channels that are involved in developmental and epileptic encephalopathies. Notably, only 1 recurrent mutation identified in the KCNCl1 voltage-gated potassium channel is responsible for autosomal dominant progressive myoclonic epilepsy phenotype.38 In contrast to KCNC1, the same KCNT1 mutation may be involved in several phenotypes (figure 3).

The “suppression burst” pattern was recorded on EEG in 4 patients before the “migrating” pattern, and 3 children had infantile spasms during the disease with hypsarrhythmia. Hypsarrhythmia pattern, usually present in early-onset epileptic encephalopathy with suppression bursts, is rarely seen in EIMFS.5 Our findings emphasize the overlap of the EEG and seizure phenotypes of EOEE with EIMFS.

KCNT1 encodes the sodium-activated potassium channel KCa4.1 (also called SLACK and Slo2.2) and is responsible for the slow hyperpolarization following repetitive firing.
KCNT1 is widely expressed in the nervous system and in the dorsal root ganglia, kidney, and heart. Gain-of-function KCNT1 variants emerged as a leading cause of EIMFS, affecting about 50% of patients. Overall, including the present study, about 150 patients harboring KCNT1 mutations have been reported so far. The most consistent KCNT1-related clinical phenotype in 120 cases described with satisfactory clinical detail is EIMFS (55% of patients). KCNT1 mutations are present in ADNFLE, focal or multifocal epilepsies, and other developmental and epileptic encephalopathies. KCNT1 variants are causal of a clinical phenotypic spectrum because identical mutations can be associated with different epileptic phenotypes.

Here, we report the occurrence of the p.R398Q mutation in a large family resulting in various epilepsy phenotypes ranging from the most severe form (EIMFS) to asymptomatic carrier, with another family member presenting features of ADNFLE phenotype. These observations of intrafamilial variable expressivity should prompt genetic counseling in families with KCNT1 variants. Indeed, individuals harboring a KCNT1 mutation with fairly mild phenotype can transmit EIMFS, and this should be considered in prenatal diagnosis. In addition, the pathogenicity of KCNT1 variants inherited from unaffected parents cannot be ruled out and should undertake further functional studies.

The variable expressivity of KCNT1 mutations could extend beyond the CNS. One patient (#17) in our series carries the
**p.R1106Q** mutation, previously reported in a patient with Brugada syndrome.\(^{11}\) The patient in this study showed no cardiac rhythm abnormalities over 24 hours of Holter ECG recording. Available data are not strong enough for clinical recommendation on ECG surveillance, but a dedicated cardiac rhythm study should be useful before initiating quinidine treatment.

In this series, 2 patients carrying the p.R428Q and the p.R474C mutation had treatment with the antiarrhythmic drug quinidine according to a previously published protocol.\(^{14}\) Quinidine had no side effects and showed good tolerance in both patients. In particular, we did not observe an increase in the QTc interval on treatment with quinidine until a dose of 40 mg/kg. However, quinidine did not reduce seizure frequency, despite plasma levels within the therapeutic range.

Treatment with quinidine, a KCNT1 blocker, owing to its ability to reverse the in vitro channel hyperactivity has been considered a rational approach for seizure control in EIMFS.\(^{12}\) Targeted therapy with quinidine in few patients based on in vitro results showed variable in vivo efficacy.\(^{8,13–16,18–21,30}\) Seizure reduction was absent in about 40% of patients harboring the KCNT1 mutation with EIMFS or other early-onset developmental and epileptic encephalopathies (6/16, including the present series). The neurodevelopmental prognosis was altered marginally during quinidine treatment.\(^{20}\) Several factors, such as the mutation, the age at epilepsy onset, the age at quinidine treatment, and pharmacokinetic and pharmacodynamic factors such as blood-brain barrier penetration, account for the observed heterogeneity.\(^{20}\) Response to quinidine treatment did not correlate with a specific mutation due to contradictory results observed in patients carrying the same p.R428Q mutation.\(^{13,15}\)

Although the initial results showed that early treatment is essential for quinidine antiepileptic efficacy, with patients being responsive only when starting treatment younger than 4

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**Figure 3** Schematic localization of *KCNT1* mutations reported in this series and in previous studies

*KCNT1* encodes the sodium-activated potassium channel \(K_{Na4.1}\) (also called \(SLACK\) and \(Slo2.2\)), composed by a short cytoplasmic N-terminal region, 6 transmembrane domains with a pore-forming region, and a large C-terminal region with 2 regulators of potassium conductance domains (RCK1 and RCK2). Mutations associated with EIMFS shaded in yellow, and ADNFLE mutations shaded in light blue. Mutations involved in several phenotypes, including EIMFS and ADNFLE, are indicated in blue. Mutations involved in phenotypes other than EIMFS and ADNFLE shaded in green. The size of each circle is proportional to the number of reported patients (present series and previous report). ADNFLE = autosomal dominant nocturnal frontal lobe epilepsy; EIMFS = epilepsy of infancy with migrating focal seizure.
years, the recent results did not confirm this hypothesis, and this report shows quinidine inefficacy despite early treatment initiation in 1 patient.

We hypothesize that quinidine does not improve the developmental issues because it did not affect the KCNT1 nonconducting functions. A constitutive hyperactivation of K channels is the underlying pathophyslogic mechanism of epileptogenesis and is attenuated by quinidine in vitro. Nevertheless, KCNT1 mutations impair not only the gating of the channel but also its ability to interact with developmental signaling proteins coupled to its C-terminus, such as fragile X mental retardation-1 protein, thus identifying the KCNT1 nonconducting functions as a potential target of novel therapeutic strategies. These results emphasize the difficulties of bench-to-bed translational studies and the need for a prospective randomized multicentric trial in patients with KCNT1-related epilepsies.

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**Appendix (continued)**

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## References


Epilepsy with migrating focal seizures: KCNT1 mutation hotspots and phenotype variability
Giulia Barcia, Nicole Chemaly, Mathieu Kuchenbuch, et al.
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