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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 hypsarrhythmia. 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.

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## Glossary

ADNFLE = autosomal dominant nocturnal frontal lobe epilepsy; AED = antiepileptic drug; CZP = clonazepam; EIMFS = epilepsy of infancy with migrating focal seizure; EOEE = early-onset epileptic encephalopathy; LTG = lamotrigine.

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.<sup>1,2</sup> In 50% of patients with EIMFS, gain-of-function mutations are identified in the *KCNT1* gene (OMIM608167), encoding the sodium-activated potassium channel.<sup>3</sup> *KCNT1* mutations result in a severe form of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE),<sup>4</sup> in some patients with other developmental and epileptic encephalopathies,<sup>5–8</sup> in patients with focal and multifocal epilepsies,<sup>9,10</sup> and patients with no seizures but presenting with cardiac arrhythmia.<sup>11</sup>

Genotype-phenotype correlations are rather complicated due to the association of the same *KCNT1* mutation with different epilepsy phenotypes.<sup>9</sup> 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<sup>+</sup> channel gain-of-function effect of the mutation as shown by in vitro studies.<sup>12</sup> Although the clinical use of quinidine is controversial, administration of quinidine resulted in varying degrees of efficacy in some patients.<sup>8,13–21</sup>

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.<sup>1,2</sup>

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](https://www.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 (I2, 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 (#5, 6, 7, 9, 10, and 11), 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** Demographic, clinical, EEG, MRI, and genetic features of the cohort

Patient, sex	Age at last FU (y)	Origin	Familial history, consanguinity	KCNT1 mutation (NM_020822.2)	Functional study	Inheritance	Phenotype	Age at seizure onset	Seizure type	Brain MRI	EEG	Neurologic examination	Aggravation period	AEDs	Follow-up
1, F	1.1	French	No	c.862G>A p.Gly288Ser	Gain of function	De novo	EIMFS	2 mo	Focal motor (tonic)	Normal	Migrating pattern	Microcephaly and hypotonia	2 mo-FU (13 mo)	PB, PHT, CBZ, LEV, KD, TPM, VGB, VPA, and DZP	Deceased during SE (13 mo)
2, M	6	French	Father with ADNPLE	c.1193G>A p.Arg398Gln	Gain of function	Heterozygous father	EIMFS	10 d	Clonic seizures of L + gaze deviation	Normal (4 mo) atrophy and myelination delay (1.8 y)	Migrating pattern	Axial hypotonia, microcephaly, erratic eye movements, and NGF	2 mo–6.5 mo	Combination of STP and CZP relatively improved at age of 3 y	Deceased during SE (6.5 mo)
3, M	2	French	No	c.1283G>A p.Arg428Gln	Gain of function	De novo	EIMFS	3 wk	Focal motor (tonic)	Normal	Migrating pattern	Axial hypotonia and microcephaly	2 mo-FU (22 mo)	PB, PHE, LEV, VPA, CBZ, VGB, STP, and KD	Deceased during SE (22 mo)
4, F	9	French	No	c.1283G>A p.Arg428Gln	Gain of function	De novo	EIMFS	4 mo	Focal motor (clonic) and autonomic (cyanosis)	Normal	Migrating pattern	Microcephaly and hypotonia	4 mo–1.2 y	VPA, STP, LTG, LEV, ZNS, TPM, PHT, OXC, CZP, KD, and quinidine	Profound ID; no walk; no language
5, M	11	French	No	c.1283G>A p.Arg428Gln	Gain of function	De novo	EIMFS-SB-West	1 d	Focal motor and spasms	Thin CC	Migrating pattern, SB, and hypsarrhythmia	Hypotonia and pyramidal syndrome	NA	PB, VGB, CZP, and KD	Deceased
6, M	1.5	French	No	c.1283G>A p.Arg428Gln	Gain of function	De novo	EIMFS	1 d	Focal motor and autonomic; tonic	Normal (4 d and 1.5 mo)	Migrating pattern	Hypotonia and NGF	NA	PHE, LEV, CLB, CZP, VGB, and KD	Profound DD
7, F	2	French	No	c.1309C>T p.Leu437Phe	NP	De novo	EIMFS	2 d	Focal motor (hemiclonic) autonomic	Normal	Migrating pattern	Microcephaly and hypotonia	2 mo–1 y	PB, VGB, and VPA	Profound DD No walk; no language
8, M	1.5	French-Moroccan	No	c.1420C>T p.Arg474Cys	NP	De novo	EIMFS	1.5 mo	Focal and generalized tonic	Myelination delay and thin CC (6 mo)	Migrating pattern + SB	Microcephaly and hypotonia	2 mo-FU (1.5 y)	VGB, LEV, and CZP	Deceased (1.5 y)
9, F	5	French	No	c.1420C>T p.Arg474Cys	NP	De novo	EIMFS	1 h	Focal motor (tonic)	Myelination delay (1 mo)	Migrating pattern	Microcephaly, hypotonia, and pyramidal syndrome	1 mo-FU	LEV, VGB, CLB, PB, and quinidine	Profound DD No walk; no language; NGF
10, M	2	French	No	c.1421G>A p.Arg474His	Gain of function	De novo	EIMFS	2 d	Focal motor (tonic) and autonomic (cyanosis)	Myelination delay and thin CC (6 mo)	Migrating pattern–SB	Microcephaly, hypotonia, and pyramidal syndrome	NA	PB, LEV, CBZ, VGB, VPA, CZP, and KD Seizure aggravation with RFM	Profound DD; no walk; no language

Continued

**Table** Demographic, clinical, EEG, MRI, and genetic features of the cohort (*continued*)

Patient, sex	Age at last FU (y)	Origin	Familial history, consanguinity	KCNT1 mutation (NM_020822.2)	Functional study	Inheritance	Phenotype	Age at seizure onset	Seizure type	Brain MRI	EEG	Neurologic examination	Aggravation period	AEDs	Follow-up
11, M	0.9	French	No	c.1421G>A p.Arg474His	Gain of function	De novo	EIMFS	1 d	Focal motor and autonomic; tonic	Normal (3 mo)	Migrating pattern—SB—Hypsarrhythmia	Hypotonia	3 mo-FU	TPM, VGB, and HC	Profound DD
12, M	2	Moroccan	Consanguineous	c.1546A>G p.Met516Val	Gain of function	De novo	EIMFS	13 d	Focal clonic	Normal	Migrating pattern	Hypotonia	7 mo-FU (2 y)	CZP, PHE, VGB, LEV, CLB, and TPM	Profound DD; no walk; no language
13, F	10	French	No	c.2688G>A p.Met896Ile	Gain of function	De novo	EIMFS	2 mo	Focal motor (clonic)	Normal	Migrating pattern	Microcephaly and hypotonia	NA	VPA, OXC, STP, KD, and TPM	Profound ID; no walk; no language
14, M	10	Spanish	No	c.2800G>A p.Ala934Thr	Gain of function	De novo	EIMFS-West	2 wk	Generalized tonic + flushing	Normal	Migrating pattern—hypsarrhythmia (hemi-spasms)	Axial hypotonia and microcephaly	NA	NK	Profound ID; no walk; no language
15, F	20	French	No	c.2800G>A p.Ala934Thr	Gain of function	De novo	EIMFS	2.5 mo	Loss of contact and tonic	Normal	Migrating pattern	Axial hypotonia and microcephaly	3.5 mo–2 y	VGB, PHE, DZP, VPA, HC, CBZ, STP, and LTG	Profound ID; no walk; no language
16, F	0.8	French	No	c.2894C>T p.Ala965Val	NP	De novo	EIMFS	1.5 mo	Focal motor and autonomic; tonic	Normal (1.5 mo)	Migrating pattern	Hypotonia	NA	TPM, CZP, PB, CBZ, STP, KD, and VPA Seizure aggravation with PHE and VGB	Profound DD
17, F	12	French-Korean	No	c.3317G>C p.Arg1106Pro	NP	De novo	EIMFS-West	2 mo	Tonic and autonomic (cyanosis, flushing) seizures and spasms (7 mo)	Normal (1 mo) and global atrophy (1.5 y)	Migrating pattern—hypsarrhythmia	Hypotonia, pyramidal syndrome, and scoliosis	1 mo–7.5 y	PB, VGB, CLB, VPA, HC, TPM, LTG, and LEV	Profound ID; no walk; no language

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.<sup>14</sup> 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.M896I (#13), p.A934T (#14 and 15), p.A965V (#16), 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,<sup>3,4,8,9,13,17,22–27,30,31,36</sup> p.R428Q and p.R474H in EIMFS and early-onset epileptic encephalopathies,<sup>3–7</sup> p.R474C and p.M516V in EIMFS,<sup>7,21,25,28,29</sup> p.M896I in ADNFLE,<sup>4</sup> and p.R1106P in Brugada syndrome.<sup>11</sup> These *KCNT1* mutations occur on the C-terminal cytoplasmic domain, except for p.G288S affecting

the protein pore (#1). Many mutations are recurrent, namely p.G288S (#1), p.R398Q (#2), p.R428Q (#3, 4, 5, and 6), and p.A934T (#14 and 15) and arose *de novo* except the p.R398Q inherited from the proband’s father affected by ADNFLE (#2). The familial study showed the presence of the p.R398Q mutation in a heterozygous state in both paternal uncles, one being asymptomatic and the other presenting with a single tonic-clonic seizure at 25 years (figure 1). The paternal grandfather, likely affected by ADNFLE, could not be tested.

### Genotype-phenotype correlation of our series with literature review

We carefully reviewed 35 articles on patients with *KCNT1* mutations and established the phenotype in 120 patients from 116 families. Seventy-five presented with EIMFS,<sup>3,7,9,13,14,16,17,20–22,24–32,34–37</sup> 33 with ADNFLE,<sup>4,9,35</sup> 4 with other focal seizures,<sup>10,16,24</sup> 4 with West syndrome,<sup>7,8,26,33</sup> 4 with early-onset epileptic encephalopathy (EOEE),<sup>6,7,15,36</sup> and 1 with Brugada syndrome without epilepsy phenotype.<sup>11</sup> 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.<sup>3,4,7,9,17,26</sup>

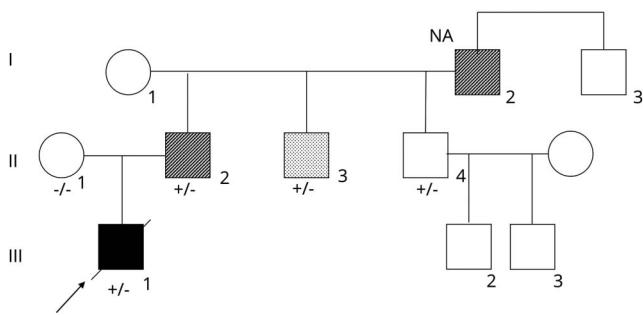
### Discussion

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 *KCNT1* 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).<sup>3,4,7,8,13,16,17,22–31,37</sup> Hotspots are rarely reported in other genes encoding K<sup>+</sup> channels that are involved in developmental and epileptic encephalopathies. Notably, only 1 recurrent mutation identified in the *KCNK1* voltage-gated potassium channel is responsible for autosomal dominant progressive myoclonic epilepsy phenotype.<sup>38</sup> In contrast to *KCNK1*, 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.<sup>7</sup> Our findings emphasize the overlap of the EEG and seizure phenotypes of EOEE with EIMFS.

*KCNT1* encodes the sodium-activated potassium channel K<sub>Ca4.1</sub> (also called SLACK and Slo2.2) and is responsible for the slow hyperpolarization following repetitive firing.

**Figure 1** Pedigree of patient 2



The sign  $\pm$  points to family members carrying the heterozygous c.1193G>A *KCNT1* pathogenic variant;  $-/-$  indicates the patients with wild-type variants. Individual I2 presented nocturnal paroxysmal events, behavioral and psychiatric disorders; II2, 30 years, had ADNFLE and was seizure-free with AEDs; II3, 36 years, had a single episode of TC seizure at age 25 years, average intellect, and fair social and professional integration. II4, 34 years, healthy, average intellect, and fair social and professional integration; III1 (proband) had EIMFS (patient 2, table). ADNFLE = autosomal dominant nocturnal frontal lobe epilepsy; AED = antiepileptic drug; EIMFS = epilepsy of infancy with migrating focal seizures; NA = blood sample not available.

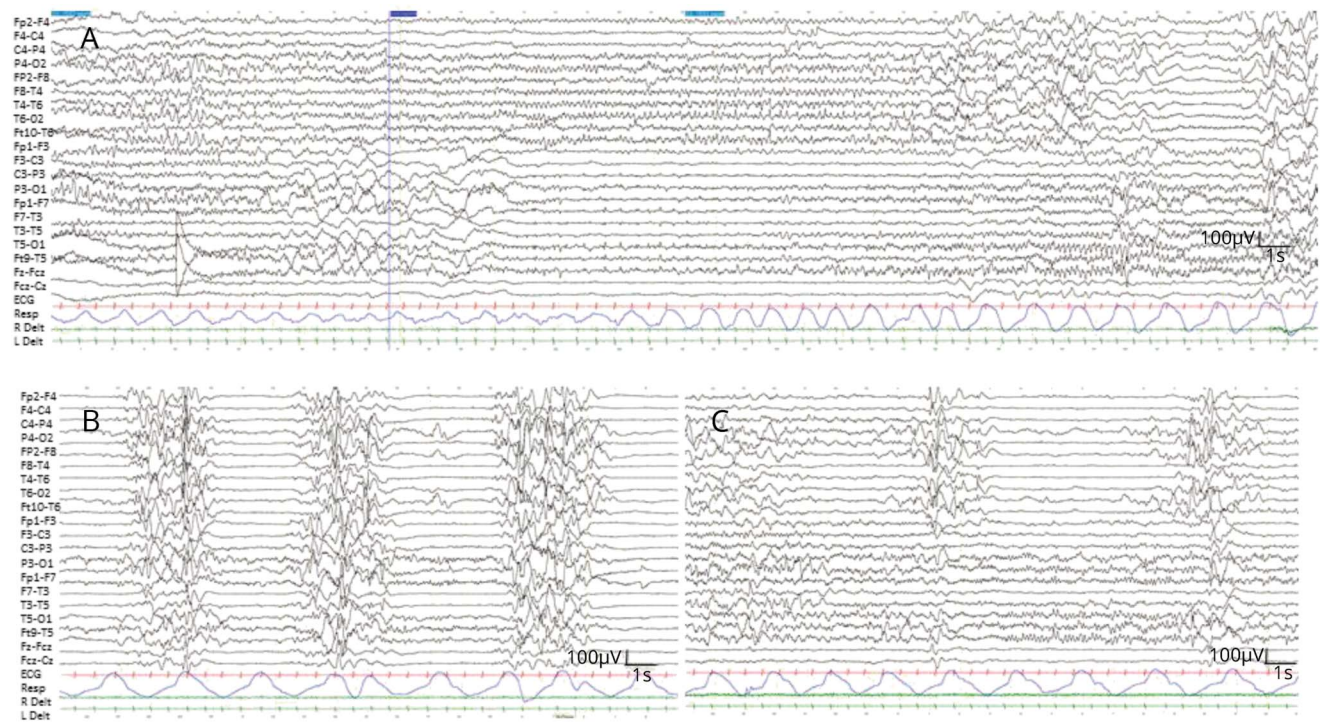
*KCNT1* is widely expressed in the nervous system and in the dorsal root ganglia, kidney, and heart.<sup>3</sup> Gain-of-function *KCNT1* variants emerged as a leading cause of EIMFS, affecting about 50% of patients.<sup>3</sup> Overall, including the present study, about 150 patients harboring *KCNT1* 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).<sup>3-37</sup> *KCNT1* mutations are present in ADNFLE,<sup>4,9,35</sup> focal or multifocal epilepsies,<sup>9,10,16,24</sup> and other developmental and epileptic encephalopathies.<sup>5-8,15,33,37</sup> *KCNT1* variants are causal of a clinical phenotypic spectrum because identical mutations can be associated with different epileptic phenotypes (figure 3). The p.R398Q and p.R950Q mutations were associated with intrafamilial variable expressivity in 2 families where a child affected by EIMFS who inherited the mutation from the father with ADNFLE-like phenotype.<sup>9,17</sup>

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.

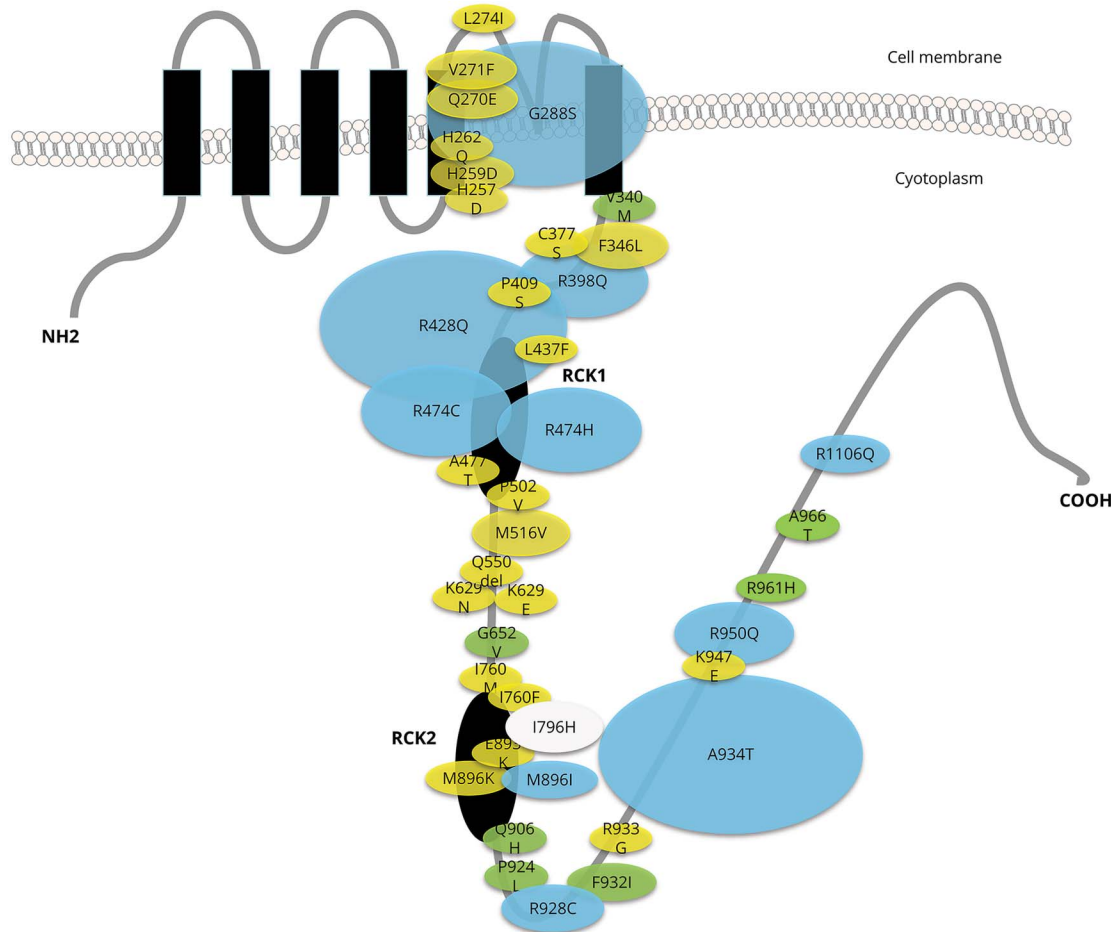
The variable expressivity of *KCNT1* mutations could extend beyond the CNS. One patient (#17) in our series carries the

**Figure 2** EEG recording of patient 9 at age 6 months



(A) Display of the migrating pattern. (B) Intermittent suppression burst pattern. (C) EEG recording of right hemispheric discontinuous background concomitant to left posterior rhythmic alpha discharge.

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



*KCNT1* encodes the sodium-activated potassium channel  $K_{Ca4.1}$  (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.

p.R1106Q mutation, previously reported in a patient with Brugada syndrome.<sup>11</sup> 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.<sup>14</sup> 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.<sup>12</sup> Targeted therapy with quinidine in few patients based on *in vitro* results showed variable *in vivo* efficacy.<sup>8,13–16,18–21,30</sup> 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.<sup>20</sup> 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.<sup>20</sup> Response to quinidine treatment did not correlate with a specific mutation due to contradictory results observed in patients carrying the same p.R428Q mutation.<sup>13,15</sup>

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



years,<sup>16,20</sup> the recent results did not confirm this hypothesis,<sup>19,21</sup> 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 pathophysiologic 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,<sup>3</sup> 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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## References

- Coppola G, Plouin P, Chiron C, Robain O, Dulac O. Migrating partial seizures in infancy: a malignant disorder with developmental arrest. *Epilepsia* 1995;36:1017–1024.
- Coppola G, Veggioni P, Del Giudice EM, et al. Mutational scanning of potassium, sodium and chloride ion channels in malignant migrating partial seizures in infancy. *Brain Dev* 2006;28:76–79.
- Barcia G, Fleming MR, Deligniere A, et al. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. *Nat Genet* 2012;44:1255–1259.
- Heron SE, Smith KR, Bahlo M, et al. Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy. *Nat Genet* 2012;44:1188–1190.
- Allen AS, Berkovic SF, Cossette P, et al. Epi4K consortium; epilepsy phenome/genome project) de novo mutations in epileptic encephalopathies. *Nature* 2013;501:217–221.
- Martin HC, Kim GE, Pagnamenta AT, et al. Clinical whole-genome sequencing in severe early-onset epilepsy reveals new genes and improves molecular diagnosis. *Hum Mol Genet* 2014;23:3200–3211.
- Ohba C, Kato M, Takahashi N, et al. De novo KCNT1 mutations in early-onset epileptic encephalopathy. *Epilepsia* 2015;56:e121–128.
- Fukuoka M, Kuki I, Kawawaki H, et al. Quinidine therapy for West syndrome with KCNT1 mutation: a case report. *Brain Dev* 2017;39:80–83.
- Moller RS, Heron SE, Larsen LH, et al. Mutations in KCNT1 cause a spectrum of focal epilepsies. *Epilepsia* 2015;56:e114–120.
- Hansen N, Widman G, Hattingen E, Elger CE, Kunz WS. Mesial temporal lobe epilepsy associated with KCNT1 mutation. *Seizure* 2017;45:181–183.
- Juang JM, Lu TP, Lai LC, et al. Disease-targeted sequencing of ion channel genes identifies de novo mutations in patients with Non-Familial Brugada Syndrome. *Sci Rep* 2015;4:6733.
- Milligan CJ, Li M, Gazina EV, et al. KCNT1 gain of function in 2 epilepsy phenotypes is reversed by quinidine. *Ann Neurol* 2014;75:581–590.
- Bearden D, Strong A, Ehnnot J, DiGiovine M, Dlugos D, Goldberg EM. Targeted treatment of migrating partial seizures of infancy with quinidine. *Ann Neurol* 2014;76:457–461.
- Mikati MA, Jiang YH, Carboni M, et al. Quinidine in the treatment of KCNT-positive epilepsies. *Ann Neurol* 2015;78:995–999.
- Chong PF, Nakamura R, Saitsu H, Matsumoto N, Kira R. Ineffective quinidine therapy in early onset epileptic encephalopathy with KCNT1 mutation. *Ann Neurol* 2016;79:502–503.
- Abdelnour E, Gallentine W, McDonald M, et al. Does age affect response to quinidine in patients with KCNT1 mutations? Report of three new cases and review of the literature. *Seizure* 2018;55:1–3.
- McTague A, Nair U, Malhotra S, et al. Clinical and molecular characterization of KCNT1-related severe early-onset epilepsy. *Neurology* 2018;90:e55–e66.
- Mullen SA, Carney PW, Roten A, et al. Precision therapy for epilepsy due to KCNT1 mutations: a randomized trial of oral quinidine. *Neurology* 2018;90:e67–e72.
- Madaan P, Jauhari P, Gupta A, Chakrabarty B, Gulati S. A quinidine non responsive novel KCNT1 mutation in an Indian infant with epilepsy of infancy with migrating focal seizures. *Brain Dev* 2018;40:229–232.
- Dilena R, DiFrancesco JC, Soldovieri MV, et al. Early treatment with quinidine in 2 patients with epilepsy of infancy with migrating focal seizures (EIMFS) due to gain-of-function KCNT1 mutations: functional studies, clinical responses, and critical issues for personalized therapy. *Neurotherapeutics* 2018;15:1112.
- Numis AL, Nair U, Datta AN, et al. Lack of response to quinidine in KCNT1-related neonatal epilepsy. *Epilepsia* 2018;59:1889.
- Ishii A, Shioda M, Okumura A, et al. A recurrent KCNT1 mutation in two sporadic cases with malignant migrating partial seizures in infancy. *Gene* 2013;531:467–471.
- Kim GE, Kronengold J, Barcia G, et al. Human slack potassium channel mutations increase positive cooperativity between individual channels. *Cell Rep* 2014;9:1661–1672.
- Trump N, McTague A, Brittain H, et al. Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis. *J Med Genet* 2016;53:310–317.
- Rizzo F, Ambrosino P, Guacci A, et al. Characterization of two de novo KCNT1 mutations in children with malignant migrating partial seizures in infancy. *Mol Cell Neurosci* 2016;72:54–63.
- Allen NM, Conroy J, Shahwan A, et al. Unexplained early onset epileptic encephalopathy: exome screening and phenotype expansion. *Epilepsia* 2016;57:e12–e17.
- Zhang Q, Li J, Zhao Y, Bao X, Wei L, Wang J. Gene mutation analysis of 175 Chinese patients with early-onset epileptic encephalopathy. *Clin Genet* 2017;91:717–724.
- Shimada S, Hirano Y, Ito S, et al. A novel KCNT1 mutation in a Japanese patient with epilepsy of infancy with migrating focal seizures. *Hum Genome Var* 2014;1:14027.
- Kawasaki Y, Kuki I, Ehara E, et al. Three cases of KCNT1 mutations: malignant migrating partial seizures in infancy with massive systemic to pulmonary collateral arteries. *J Pediatr* 2017;191:270–274.
- McTague A, Appleton R, Avula S, et al. Migrating partial seizures of infancy: expansion of the electroclinical, radiological and pathological disease spectrum. *Brain* 2013;136(pt 5):1578–1591.
- Mori T, Imai K, Oboshi T, et al. Usefulness of ketogenic diet in a girl with migrating partial seizures in infancy. *Brain Dev* 2016;38:601–604.
- Parrini E, Marini C, Mei D, et al. Diagnostic targeted resequencing in 349 patients with drug-resistant pediatric epilepsies identifies causative mutations in 30 different genes. *Hum Mutat* 2017;38:216–225.
- Zhou P, He N, Zhang JW, et al. Novel mutations and phenotypes of epilepsy-associated genes in epileptic encephalopathies. *Genes Brain Behav* 2018;17:e12456.
- Rim JH, Kim SH, Hwang IS, et al. Efficient strategy for the molecular diagnosis of intractable early-onset epilepsy using targeted gene sequencing. *BMC Med Genomics* 2018;11:6.
- Zhu X, Padmanabhan R, Copeland B, et al. A case-control collapsing analysis identifies epilepsy genes implicated in trio sequencing studies focused on de novo mutations. *PLoS Genet* 2017;13:e1007104.
- Miao P, Feng J, Guo Y, et al. Genotype and phenotype analysis using an epilepsy-associated gene panel in Chinese pediatric epilepsy patients. *Clin Genet* 2018;94:512–520.
- Ko A, Youn SE, Kim SH, et al. Targeted gene panel and genotype-phenotype correlation in children with developmental and epileptic encephalopathy. *Epilepsy Res* 2018;141:48–55.
- Muona M, Berkovic SF, Dibbens LM, et al. A recurrent de novo mutation in KCNC1 causes progressive myoclonus epilepsy. *Nat Genet* 2015;47:39–46.

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