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Mutations in *KCNT1* cause a spectrum of focal epilepsies

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Interictal EEG features of patients from family 1, III.6 (to the left) and IV.5 (to the right), respectively, during drowsiness and during stage 2 non–rapid eye movement (NREM) sleep.

Table S1. List of other genes analyzed for patients described in this study.

Data S1. Methods.

Disclosure

None of the authors has any conflicts of interest to disclose. 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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Summary

Autosomal dominant mutations in the sodium-gated potassium channel subunit gene *KCNT1* have been associated with two distinct seizure syndromes, nocturnal frontal lobe epilepsy (NFLE) and malignant migrating focal seizures of infancy (MMFSI). To further explore the phenotypic spectrum associated with *KCNT1*, we examined individuals affected with focal epilepsy or an epileptic encephalopathy for mutations in the gene. We identified *KCNT1* mutations in 12 previously unreported patients with focal epilepsy, multifocal epilepsy, cardiac arrhythmia, and in a family with sudden unexpected death in epilepsy (SUDEP), in addition to patients with NFLE and MMFSI. In contrast to the 100% penetrance so far reported for *KCNT1* mutations, we observed incomplete penetrance. It is notable that we report that the one *KCNT1* mutation, p.Arg398Gln, can lead to either of the two distinct phenotypes, ADNFLE or MMFSI, even within the same family. This indicates that genotype–phenotype relationships for *KCNT1* mutations are not straightforward. We demonstrate that *KCNT1* mutations are highly pleiotropic and are associated with phenotypes other than ADNFLE and MMFSI. *KCNT1* mutations are now associated with Ohtahara syndrome, MMFSI, and nocturnal focal epilepsy. They may also be associated with multifocal epilepsy and cardiac disturbances.

Keywords

KCNT1; Autosomal dominant nocturnal frontal lobe epilepsy; Epileptic encephalopathy; Cardiac arrhythmia; Sudden unexpected death in epilepsy

KCNT1 encodes a sodium-gated potassium channel subunit that plays an important role in regulating excitability in neurons.[1] We recently reported heterozygous *KCNT1* mutations in a severe form of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)[2] in which a significant proportion of individuals have comorbidities of intellectual disability (ID), psychiatric features, and refractory seizures.[2] Heterozygous *KCNT1* mutations were also described in patients with malignant migrating focal seizures of infancy (MMFSI).[3] A heterozygous *KCNT1* mutation has also been described in a patient with leukoencephalopathy and severe epilepsy[4] and a homozygous mutation was reported in a patient with Ohtahara syndrome.[5]

The involvement of *KCNT1* in the phenotypically distinct disorders ADNFLE and MMFSI suggests that *KCNT1* mutations may be associated with a spectrum of phenotypes encompassing focal epilepsy, psychiatric disorders, and epileptic encephalopathies. To investigate this, we studied patients and families with focal epilepsies, including 22 with psychiatric comorbidities, as well as patients with epileptic encephalopathies, including MMFSI, for mutations in *KCNT1*. We also sought to further explore the mutational

spectrum, that is, the positions and classes of *KCNT1* mutations, in epileptic disorders as these may provide insights into the resulting pathogenic mechanisms.

Methods

The study was approved by the ethics committees of Western Sealand, the University of South Australia, and Austin Health, Melbourne, Australia. Genomic DNA from study participants was extracted from peripheral blood leukocytes. One hundred forty-three patients, including 92 with focal epilepsies (22 with psychiatric comorbidities), who were negative for *CHRNA2, CHRNA4*, and *CHRNB2* mutations, and 51 unrelated patients with epileptic encephalopathies including 19 with MMFSI, were tested for mutations in *KCNT1* using high-resolution melting-curve (HRM) analysis as described previously.[2] Additional Danish, Dutch, and Italian samples underwent targeted resequencing for selected epilepsy genes including *KCNT1* using gene panels as described in Data S1 and Table S1. Variants were validated and familial segregation was analyzed by Sanger sequencing. Whole exome sequencing (WES) was performed as described in Data S1.

Results

We identified a total of 12 new unrelated patients with missense mutations in *KCNT1*. The mutations are listed in Table 1 along with the clinical features found in each individual. The positions of these mutations within the KCNT1 protein are shown in Figure 1B.

A heterozygous missense mutation *KCNT1* c.2782C>T; p.Arg928Cys was identified in family 1 of Danish origin. The mutation cosegregates with the nocturnal frontal lobe epilepsy (NFLE) phenotype (Fig. 1A) and affected individuals showed a mean age of onset of nocturnal seizures of 9 years (range 1–15 years). Learning impairment, memory deficit, and psychiatric problems, including depression, suicide attempt, anxiety, and attention-deficit/hyperactivity disorder (ADHD) occurred in four of five affected family members, consistent with our earlier report of *KCNT1* causing ADNFLE with intellectual disability (ID) and psychiatric features.[2] Interictal EEG data available in two individuals (III.6 and IV. 5) showed epileptiform abnormalities in the frontotemporal regions (Fig. S1). Individual III. 1 (Fig. 1A) had frequent nocturnal seizures and died suddenly and unexpectedly during the night at 23 years of age. His death was classified as sudden unexplained death in epilepsy (SUDEP). Although the *KCNT1* mutation segregated in his family, we were unable to test this deceased individual for the *KCNT1* mutation. Video-polygraphic study of individual IV-5 with the *KCNT1* mutation and ADNFLE showed irregularity in the heart rhythm during wakefulness, increasing significantly during sleep especially during the rapid eye movement (REM) periods. These abnormalities included an ST elevation in the J point plus several supraventricular extra systoles, suggesting Brugada syndrome. Whole exome sequencing of individual IV-5 revealed no mutations in any gene listed in Online Mendelian Inheritance in Man (OMIM) as associated with cardiac arrhythmia.

In the analysis of 92 unrelated families with focal epilepsy, a heterozygous *KCNT1* mutation c.1193G>A; p.Arg398Gln co-segregating with affected status was identified in family 2 (Fig. 1A). The family comprised five affected individuals, one with ADNFLE, one with

likely ADNFLE, one with focal epilepsy, and two with MMFSI. Notably, in this family the same *KCNT1* mutation, p.Arg398Gln can lead to either ADNFLE or MMFSI.

Patient 10 with sporadic NFLE had the *KCNT1* mutation c.2782C>T; p.Arg928Cys. Prior to seizure onset the patient had normal intelligence, with subsequent regression (TIQ 78 at 8 years of age), and did not exhibit any psychiatric features. Patient 8, who had multifocal epilepsy with onset associated with limbic encephalitis due to anti-GAD65 antibodies, had the *KCNT1* mutation c.1018G>A; p.Val340- Met.

Eight unrelated patients with MMFSI (patients 3–7, 9, 11, and 12) were found to have *KCNT1* mutations. These were c.769C>G; p.His257Asp, c.785G>A; Arg262Gln, c. 862G>A; p.Gly288Ser (seen in three patients), c.1283G>A; p.Arg428Gln, c.2800G>A; p.Ala934Thr and c.2849G>A; p.Arg950Gln. None of the mutations were present in publicly available variant datasets (dbSNP, NHLBI, Exome Variant Server) and each was predicted to be possibly damaging by both the PolyPhen-2 and SIFT in silico prediction tools, consistent with being pathogenic. Mutations were shown to have occurred de novo in five of the eight patients, consistent with previous reports of de novo *KCNT1* mutations in MMFSI.[3,6,7] One patient (patient 11) inherited a mutation (p.Ala934Thr) from an unaffected parent who was shown to be mosaic for the *KCNT1* mutation by restriction fragment length assays (*Hha*I and *Bst*UI digests). Quantitation of bands from the *Bst*UI digest indicated that the mutation was present in approximately 60% of peripheral blood derived cells (data not shown).

Discussion

We have identified a total of 12 new unrelated cases (2 families and 10 sporadic) with mutations in *KCNT1*. All *KCNT1* mutations identified both previously[2-9] and here are missense mutations, with no nonsense or other truncating mutations reported. This suggests that perturbation of normal KCNT1 protein function, rather than loss of function, underlies the pathogenicity associated with *KCNT1* mutations. The mutations initially reported in ADNFLE and MMFSI were clustered around the RCK and NAD^+ binding domains of the protein.[2-4] More recently, mutations have been reported within the S5 transmembrane segment of the protein,[6,7,9] indicating that alteration of other regions of KCNT1 is also pathogenic. Here we report three novel mutations in patients with multifocal epilepsy and MMFSI in or near the S5 and S6 region of the KCNT1 channel subunit. These findings provide further evidence for the contribution of mutations in this region of KCNT1 to the pathogenesis of MMFSI.

Although ID and psychiatric disorders have previously been reported in ADNFLE, these phenotypic features are infrequent in ADNFLE families with mutations in the other ADNFLE-associated genes *CHRNA4, CHRNB2*, and *CHRNA2*.[2] Our finding of ADNFLE, intellectual disability, and psychiatric features associated with mutation of *KCNT1* in family 1 provides further evidence that *KCNT1* mutations cause a distinct form of ADNFLE that is more severe and includes comorbidities.[2,10] Patients presenting with these features should be tested for *KCNT1*.

In addition to the neurologic phenotypes observed in the families in this study, one individual in family 1 had cardiac arrhythmia and another had SUDEP, which is thought to have cardiac involvement.[11,12] This suggests the involvement of *KCNT1* mutations in cardiac disorders. Indeed, a *KCNT1* mutation has recently been reported in a patient with epilepsy and Brugada syndrome.[13] The coexistence of epilepsy and Brugada syndrome has been reported previously in a family with a sodium channel mutation (*SCN5A*).[14] Further clinical examination of patients with *KCNT1* mutations to look for cardiac features and functional studies of the KCNT1 protein are required to explore the possible relationship between *KCNT1* mutations and cardiac arrhythmias.

ADNFLE families with *KCNT1* mutations have previously shown 100% penetrance of the mutation.[2] In contrast, in the current study one individual (family 1, III.3) with a *KCNT1* mutation did not have seizures. The nonpenetrance in this individual is unlikely to be due to somatic mosaicism, as she is inferred to have inherited a *KCNT1* mutation from her affected mother (II.2, deceased and unavailable for mutation analysis). Thus her unaffected status is most likely due to incomplete penetrance, which has not been previously described for *KCNT1* mutations.

In this study, we have identified recurrent mutations in *KCNT1*, with p.Gly288Ser found three times and p.Arg928Cys seen twice, suggesting that there are mutational “hot spots” in *KCNT1*. Consistent with this, some mutations identified in the 12 patients described here have been seen previously in other patients, with 5 of the 16 different *KCNT1* mutations described to date being observed multiple times (Fig. 1B). This is likely due to the occurrence of these mutations in CpG di-nucleotides, which are particularly susceptible to mutation.[15] Therefore, it is emerging that there are recurrent pathogenic mutations in *KCNT1*. This is important when making diagnoses for patients.

Somatic mosaicism of the *KCNT1* mutation p.Ala934Thr was observed in the unaffected parent of one patient (patient 11), with the mutation estimated to be present in 60% of peripheral blood cells. This indicates that significant levels of somatic mosaicism of *KCNT1* mutations can exist without causing an overt phenotype. Parental mosaicism of a *KCNT1* mutation poses the risk of recurrence of affected offspring; thus this finding has important implications for the genetic counseling of families with *KCNT1* mutations.

Although seizures are the predominant feature so far associated with *KCNT1* mutations, this study highlights the pleiotropic effects of mutations in this gene. The severity of the observed epilepsy phenotypes ranges from mild (a single seizure) to severe (epileptic encephalopathy). Moreover, we report here that the same *KCNT1* mutation, p.Arg398Gln can lead to either ADNFLE or MMFSI within the same family, indicating that genotype–phenotype correlations are not straightforward. The association of both phenotypes with the p.Arg398Gln mutation was unexpected, as previous data indicated that mutations associated with MMFSI cause a significantly larger increase in current amplitude than those associated with ADNFLE in mutant KCNT1 channels expressed in vitro in *Xenopus* oocytes, providing an explanation for how different mutations cause different phenotypes. [8] However, a more recent study[9] shows that the p.Gly288Ser mutation can also cause both phenotypes. Furthermore, that study[9] did not show the same pattern of differences in the current

increases as the original study,[8] casting doubt on the conclusion that differences in the increase in current amplitude caused by the different mutations explain the different phenotypes associated with *KCNT1* mutations. The association of the different phenotypes with the same mutation may instead be the result of either genetic modifiers or environmental factors.

In summary, our study confirms the role of *KCNT1* in severe ADNFLE with intellectual and psychiatric comorbidities and in MMFSI. We show that *KCNT1* also plays a role in focal and possibly in multifocal epilepsy and raise the possibility of an additional role in cardiac disorders and SUDEP. As with a number of genes containing mutations of major effect in neurologic disorders, deciphering genotype– phenotype correlations for *KCNT1* mutations is emerging as challenging. However, the identification of a *KCNT1* mutation in individuals presenting with a seizure phenotype will provide patients with a molecular diagnosis for their previously unsolved disorder. As more is learned about the effects of *KCNT1* mutations, we anticipate there will be improvements in the therapeutic treatment of patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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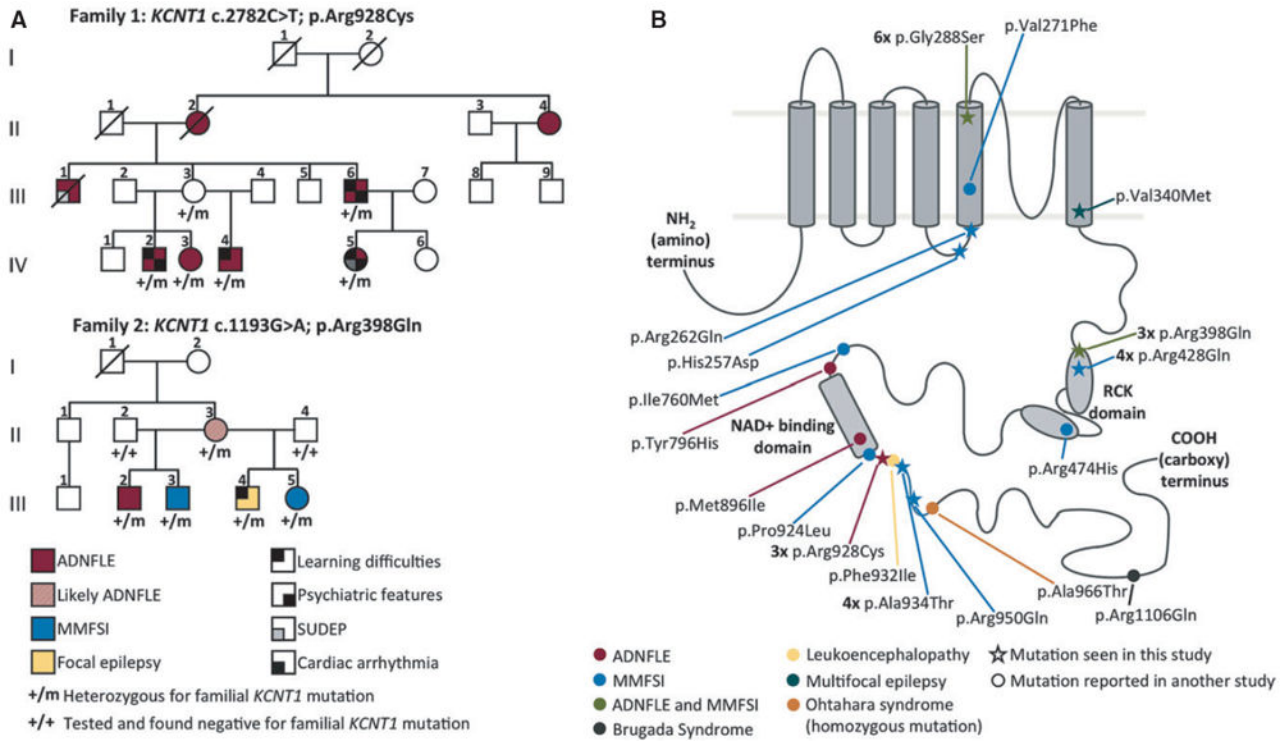

Figure 1.

(A) Pedigrees of families 1 and 2 with *KCNT1* mutations. Diagonal lines indicate deceased individuals. **(B)** Diagram of the KCNT1 protein showing the protein structure and the locations of the mutations identified in this and previous studies.[2-9,13] The KCNT1 protein consists of a small amino-terminal domain, a transmembrane domain containing six transmembrane segments with the pore-loop between segments 5 and 6 and a large intracellular carboxy-terminal domain containing tandem RCK domains and an NAD^+ binding domain. Mutations seen in this study are indicated by stars and those seen in other studies are indicated by dots. ADNFLE mutations are marked in red, MMFSI mutations in blue, the leukoencephalopathy mutation in yellow, the mutation seen in the multifocal epilepsy patient in blue-green, and mutations seen in both ADNFLE and MMFSI patients in green. The homozygous mutation seen in Ohtahara syndrome is marked in orange and the mutation seen in Brugada syndrome is marked in dark gray. Mutations observed in multiple families/patients are indicated by the numbers in bold type.

Table 1

Clinical and molecular features of patients with *KCNT1* mutations identified during this study

Family	*KCNT1* mutation	Inheritance	Individual	Phenotype	Age of seizure onset	Seizure type	Other features	Origin
1	c.2782C>T; p.Arg928Cys	Familial	III.3	Unaffected	–	–	–	Danish
			III.6	ADNFLE	1 year	Nocturnal frontal seizures, GTCS	Learning impairment, psychiatric features	
			IV.2	ADNFLE	12 years	Nocturnal frontal seizures	Learning impairment, psychiatric features	
			IV.3	ADNFLE	15 years	Nocturnal frontal seizure (only one)	–	
			IV.4	ADNFLE	7 years	Nocturnal frontal seizures	Learning impairment	
			IV.5	ADNFLE	6 years	Nocturnal frontal seizures evolving to GTCS, FDS	Learning impairment, psychiatric features, cardiac arrhythmia	
2	c.1193G>A; p.Arg398Gln	Familial	II.3	Likely ADNFLE	Unknown	Unconfirmed nocturnal events	–	Australian
			III.2	ADNFLE	8–14 months	Nocturnal frontal seizures evolving to GTCS		
					18 years	NFLE		
			III.3	MMFSI	3 months	Asymmetric tonic, FDS, status epilepticus	Profound intellectual disability, spastic quadriparesis, progressive microcephaly scoliosis, sleep apnea, gastroesophageal reflux	
			III.4	Focal epilepsy	6 months	Nocturnal focal epilepsy (mild)	Learning impairment	
			III.5	MMFSI	5 months	Asymmetric tonic, FDS	Profound intellectual disability, microcephaly, scoliosis, precocious puberty	
3	c.769C>G; p.His257Asp	De novo		MMFSI	2 weeks	Asymmetric tonic, TCS, status epilepticus, FDS	Intellectual disability, spastic quadriparesis, precocious puberty, cortical visual impairment	Australian
4	c.785G>A; p.Arg262Gln	De novo		MMFSI	8 weeks	Hemiclonic, GTCS, hemitonic, myoclonic	Developmental delay, hypotonia, hyperreflexia, progressive microcephaly, visual impairment	Australian, European origin
5	c.862G>A; p.Gly288Ser	De novo		MMFSI	2 months	Hemiclonic, NCSE TCS	Developmental delay, hypotonia	Dutch
6	c.862G>A; p.Gly288Ser	Unknown		MMFSI	3 months	Hemiclonic, spasms, FDS, asymmetric tonic, status epilepticus	Profound intellectual disability, acquired microcephaly, choreiform movements	American
7	c.862G>A; p.Gly288Ser	Unknown		MMFSI	5 weeks	Focal clonic, eye deviation, oculoclonic, TCS, focal	Global developmental delay	Australian Italian/Egyptian Origin
8	c.1018G>A; p.Val340Met	Unknown		Multifocal epilepsy	3 years	Atypical absences, atonic seizures, focal atonic seizures, TCS	Limbic encephalitis at seizure onset (encephalopathy, psychiatric features, Anti-GAD65 antibodies). Psychiatric features resolved, behavioral problems, learning impairment and epilepsy persisted	Dutch
9	c.1283G>A; p.Arg428Gln	De novo		MMFSI	3 weeks	Spasms, tonic, FDS	Profound early developmental arrest, visual impairment, acquired microcephaly, craniosynostosis	Canadian
10	c.2782C>T; p.Arg928Cys	Unknown		NFLE	5 years	Tonic seizures, TCS	Learning impairment	Dutch
11	c.2800G>A; p.Ala934Thr	Maternal mosaicism		MMFSI	8 weeks	FDS, asymmetric tonic, aura, myoclonic, NCSE	Profound developmental delay, generalized spasticity, hyperreflexia, precocious puberty	Australian

Family	*KCNT1* mutation	Inheritance	Individual	Phenotype	Age of seizure onset	Seizure type	Other features	Origin
12	c.2849G>A; p. Arg950Gln	De novo		MMFSI	5 months	Focal, tonic–clonic,	Developmental delay, hypotonia, hyperreflexia, progressive microcephaly, autistic tracts	Italian

FDS, focal dyscognitive seizure; TCS, tonic–clonic seizures; NCSE, nonconvulsive status epilepticus; MMFSI, malignant migrating focal seizures of infancy; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; NFLE, nocturnal frontal lobe epilepsy.