# Case report: Potassium sodium-activated channel subfamily T member 1 gene mutation related epilepsy.

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**OBJECTIVES:** KCNT1, a gene that encodes a sodium-activated potassium channel (subfamily T member 1) that is highly expressed in the nervous system and regulating excitability by hyperpolarization following repetitive firing (1,2). Variants in KCNT1 have been associated with a spectrum of epilepsies and neurodevelopmental disorders. These range from familial autosomal dominant or sporadic sleep-related hypermotor epilepsy to epilepsy of infancy with migrating focal seizures (EIMFS) and associated with intellectual disability include developmental and epileptic encephalopathies (Table 1) (3). Quinidine has been used as an off-label anticonvulsant with success in some individuals (4) .

We want to emphasize the clinical phenotype diversity of KCNT-1-associated epilepsy with a case, which started with focal seizures and progressed with a benign course.

**METHOD**: An 14-year-old male patient admitted to our hospital with focal motor seizures (starting with blank staring, licking, sucking, swallowing and secondary generalized tonic-clonic seizure) lasting 5-10 minutes. Seizures were developed at the age of 8. He was borned in nonconsangious family at term with a normal spontaneous vaginal delivery weighting 3400 gram. Macrocephaly was present in neurologic examination (Figure 1). Biochemical/Metabolic screening tests and cranial magnetic resonance imaging were normal. Echocardiography and electrocardiography were normal.. Electroencephalogram (EEG) showed asynchronous sharp wave activity in the left centro-parietal and right parieto-temporal regions. Seizure control was achieved with 30 mg/kg/day levetiracetam and the patient has been seizure-free since 2016. The patient suffered from moderate mental retardation, learning disability, obsessions, attention deficit and hyperactivity disorder. Molecular karyotyping and Fragile X CGG codon repeat tests were normal.

**RESULTS**: Heterozygous mutation in the KCNT1 gene (NM:c.1961C>T, p.(Thr654Met) detected in epilepsy gene panel. This sequence change replaces threonine with methionine at codon 654 of the KCNT1 protein, p.(Thr654Met). The variant has not been seen or seen very little in social databases (ESP, 1000G, GnomAD).

| ***KCNT1*-related epilepsy of infancy with migrating focal seizures (EIMFS)** | ***KCNT1*-related autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)** | ***KCNT1*-related epilepsy has been less frequently identified in individuals** |
|---|---|---|
| • Normal prenatal course and birth without history, clinical features, or imaging suggestive of traumatic, anoxic, vascular, or infectious injury<br>• Sporadic, asynchronous focal seizures arising independently from either hemisphere with patterns of intracortical "migration" occurring by age six months, with subsequent escalation of seizure frequency<br>• Developmental plateau or regression following the onset of seizures<br>• Intractability to anticonvulsant medication | • Frequent brief, nocturnal seizures<br>• Mild-to-moderate intellectual disability<br>• Psychiatric disease (e.g., depression, anxiety, suicidality, attention-deficit/hyperactivity disorder)<br>• Family history of ADNFLE or EIMFS | • West syndrome<br>• Ohtahara syndrome (early-infantile epileptic encephalopathy)<br>• Early myoclonic encephalopathy<br>• Leukodystrophy/leukoencephalopathy<br>• Focal epilepsy<br>• Multifocal epilepsy |

**Table 1:** *KCNT1*-related epilepsy phenotypes

**Figure 1,** Photos of the reported case

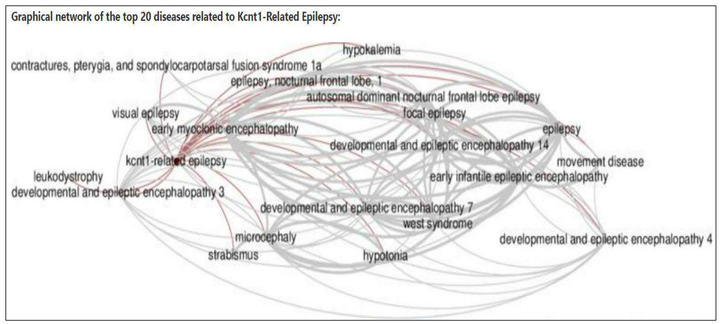


**Figure 2:** Graphical network of the top 20 diaseases to KCNT-1 related epilepsy

**CONCLUSION:** KCNT1-related epilepsy encompasses a range of epilepsy syndromes and the clinical phenotype diversity of KCNT-1-associated epilepsy is remarkable (Figure 2) (5).

KCNT1 is not getting any less mysterious. No clear genotype-phenotype correlations have been reported, though the number of patients described is still small. Although most of the patients with KCNT1 variants have drug-resistant epilepsy, our case has been seizure-free for 6 years with an antiepileptic drug. Quinidine has been used as an off-label anticonvulsant with success in some individuals (5).

We emphasized the difference of our case from the cases in the literature in terms of seizure type, clinical course and current mutation. Our patient exemplifies how KCNT1-related epilepsies encompass a broad spectrum of clinical phenotypes and provides additional evidence for a better understanding of KCNT1 pathogenesis.

## REFERENCES :

1.)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 Nov;44(11):1255-9.

2.) Bhattacharjee A, Gan L, Kaczmarek LK, et al. Localization of the Slack potassium channel in the rat central nervous system. J Comp Neurol 2011: Dec;454(3):241–54.

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4).Fitzgerald MP, Fiannacca M, Smith DM, et al. Treatment responsiveness in KCNT1-related epilepsy. Neurotherapeutics. 2019;16(3):848–857

5.)MalaCards Human Diasease Database ; MalaCards integrated aliases for Kcnt1-Related Epilepsy:

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## OBJECTIVES

KCNT1, a gene that encodes a sodium-activated potassium channel that is highly expressed in the nervous system and regulating excitability in neurons. KCNs are highly expressed in the brain and regulates hyperpolarization following repetitive firing (1,2). KCNT1 gene encodes a sodium-gated potassium channel subunit that plays an important role in variants in KCNT1-related epilepsy . Variants in KCNT1, encoding a sodium-gated potassium channel (subfamily T member 1), have been associated with a spectrum of epilepsies and neurodevelopmental disorders. These range from familial autosomal dominant or sporadic sleep-related hypermotor epilepsy to epilepsy of infancy with migrating focal seizures (EIMFS) and include developmental and epileptic encephalopathies (3). We want to emphasize the clinical phenotype diversity of KCNT-1-associated epilepsy with a case , *which started with focal seizures and progressed with a benign course.*

## METHODS:

*An 14-year-old male patient admitted to our hospital with focal motor seizure at the age of 8. The patient presented with seizures (starting with blank staring, licking, sucking, swallowing and secondary generalised tonic-clonic seizure) lasting 5-10 minutes. He was borned at term with a normal spontaneous vaginal delivery weighting 3400 gram. There was no consanguinity between his parents. Except for the head circumference being macrocephalic (Figure 1,2), no pathological features were observed in the physical examination. Neurologic examinations was normal. Routine laboratory investigations, metabolic screening and cranial magnetic resonance imaging tests were evaluated as normal. Echocardiography was considered normal and no rhythm disturbance was observed in electrocardiography.*

Electroencephalogram (EEG) *showed asynchronous sharp wave activity in the left centro-parietal and right parieto-temporal regions.* Seizure control was achieved with 30 mg/kg/day levetiracetam and the patient has been seizure-free since 2016. The patient suffered from moderate mental retardation, learning disability, obsessions, attention deficit and hyperactivity disorder. For this reason, he was followed by a child psychiatrist and received special education support.

*In the genetic examinations of the patient; molecular karyotyping was normal. Fragile X CGG codon repeats were normal.*

*Figure 1:Photograph of the reported case*

*Figure 2:Photograph of the reported case*

## RESULTS

*Clinical exome sequencing identified a heterozygous mutation in the KCNT1 gene (NM:c.1961C>T, p.(Thr654Met). This sequence change replaces threonine with methionine at codon 654 of the KCNT1 protein, p.(Thr654Met). The variant has not been seen or seen very little in social databases (ESP, 1000G, GnomAD).*

*KCNT1*-related epilepsy encompasses a range of epilepsy syndromes (Table 1) and the clinical phenotype diversity of KCNT-1-associated epilepsy is remarkable (Figure 3) (4,5).

KCNT1-related epilepsy is often refractory to conventional anticonvulsants. Stiripenthol, benzodiazepines, levetiracetam, carbamazepine, phenobarbital, clobozam, valproic acid, alone or in combination. Recently, cannabidiol (CBD) and the ketogenic diet can be used for treatment. Quinidine has been used as an off-label anticonvulsant with success in some individuals [5] .

| *KCNT1*-related epilepsy of infancy with migrating focal seizures (EIMFS) | *KCNT1*-related autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) | *KCNT1*-related epilepsy has been less frequently identified in individuals with the following phenotypes: |
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| • Normal prenatal course and birth without history, clinical features, or imaging suggestive of traumatic, anoxic, vascular, or infectious injury<br>• Sporadic, asynchronous focal seizures arising independently from either hemisphere with patterns of intracortical "migration" occurring by age six months, with subsequent escalation of seizure frequency<br>• Developmental plateau or regression following the onset of seizures<br>• Intractability to anticonvulsant medication | • Frequent brief, nocturnal seizures<br>• Mild-to-moderate intellectual disability<br>• Psychiatric disease (e.g., depression, anxiety, suicidality, attention-deficit/hyperactivity disorder)<br>• Family history of ADNFLE or EIMFS | • West syndrome<br>• Ohtahara syndrome (early-infantile epileptic encephalopathy)<br>• Early myoclonic encephalopathy<br>• Leukodystrophy/leukoencephalopathy<br>• Focal epilepsy<br>• Multifocal epilepsy |

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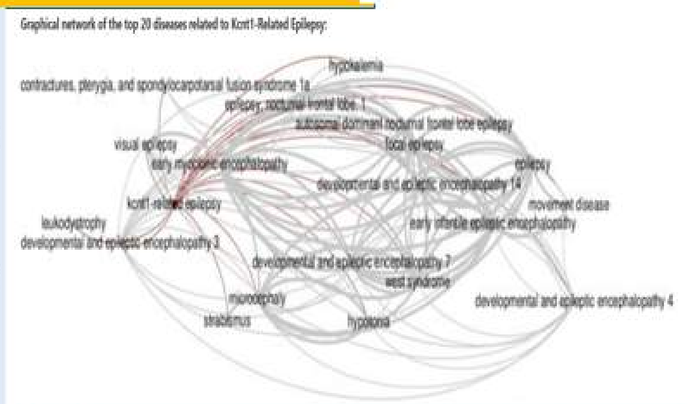


**Figure 3:** Graphical network of the top 20 diseases to KCNT-1 Related Epilepsy

## CONCLUSION

KCNT1 is not getting any less mysterious. No clear genotype-phenotype correlations have been reported, though the number of patients described is still small. Although most of the patients with KCNT1 variants have drug-resistant epilepsy, our case has been seizure-free for 6 years with an antiepileptic drug.

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References

1) Barcia G, Fleming MR, Deligniere A, Gazula VR, Brown MR, Langouet M, Chen H, Kronengold J, Abhyankar A, Cilio R, Nitschke P, Kaminska A, Boddaert N, Casanova JL, Desguerre I, Munnich A, Dufour O, Kaczmarek LK, Colleaux L, Nabbout R. 2012. ***De novo* gain-of-function *KCNT1* channel mutations cause malignant migrating partial seizures of infancy** Nat Genet. 44(11):1255-9

2) Bhattacharjee A, Gan L, Kaczmarek LK. Localization of the Slack potassium channel in the rat central nervous system. J Comp Neurol Dec;454(3):241-54.

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