

## **KCNH2 variants in a family with epilepsy and Long QT syndrome: a case report and literature review**

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**Abstract**

**Background** Genes associated with Long QT syndromes (LQTS), such as *KCNQ1*, *KCNH2*, and *SCN5A*, are common causes of epilepsy. The Arg 744\* variant of *KCNH2* has been previously reported in people with epilepsy or LQTS, but none of these patients were reported to simultaneously suffer from epilepsy and LQTS.

**Case study** Here, we report the case of a family with epilepsy and cardiac disorders. The proband, a 25-year-old woman, experienced her first seizure at the age of seven. Video electroencephalograms (vEEGs) showed epileptic discharges. Her 24-hour dynamic electrocardiograms (ECGs) showed QTc prolongation. The proband's mother, who is 50 years old, had her first generalized tonic-clonic seizure (GTCS) at the age of 18 years old. After she gave birth at the age of 25, the frequency of seizures increased, so antiepileptic therapy was initiated. When she was 28 years old, she complained of palpitations and syncope for the first time, and QTc prolongation was detected on her 24-hour dynamic ECGs. The proband's grandmother also had complaints of palpitations and syncope at the age of 73. Her 24-hour dynamic ECGs indicated supraventricular arrhythmia, with the lowest heart rate being 41 bpm, so she agreed to a pacemaker. A *KCNH2* Arg 744\*

pathogenic variant was found in both the proband and her mother.

**Conclusion** We report a *KCNH2* Arg 744\* pathogenic variant in a family with both epilepsy and LQTS. This study expands the clinical phenotype of the Arg 744\* *KCNH2* pathogenic variant. In the context of channelopathies, because of the genetic susceptibility of the brain and the heart, the risk of comorbidity should be considered. This also indicates the importance of precise antiepileptic drug (AED) management and regular ECG monitoring for patients with channelopathies.

**Keywords:** seizure, *KCNH2* gene, LQTS, mutation, SUDEP

### Introduction

Genes associated with Long QT syndrome (LQTS) are often found in patients with epilepsy. Most cases of LQTS are associated with five ion channel genes (potassium and sodium): *KCNQ1*, *KCNE1*, *KCNH2*, *KCNE2*, and *SCN5A* [1-6]. In a cohort study of sudden unexpected death in epilepsy (SUDEP), a high proportion of cases were associated with clinically relevant gene variants in cardiac arrhythmia, including *KCNQ1* (which leads to LQTS1), *KCNH2* (which leads to LQTS2), and *SCN5A* (which leads to LQTS3) [7]. LQTS is a cardiac disorder characterized by arrhythmias (specifically torsade de pointes and ventricular fibrillation), syncope, and sudden death [8, 9]. LQTS is now

recognized as an inherited arrhythmogenic disorder, and familial clustering has often been reported [8]. Variants in *KCNQ1*, *KCNH2*, and *SCN5A* account for more than 70% of all LQTS cases, and transcripts from all three major LQTS genes have been detected in the human brain [10-12]. Channelopathies can lead to epilepsy and arrhythmias. In a retrospective study, epilepsy phenotypes were recorded in patients with LQTS1, LQTS2, and LQTS3 [13].

The *KCNH2* gene, also known as the *human ether-a-go-go-related gene* (hERG) and encoding the ERG1 potassium channel, is expressed in the hippocampus and frontal cortex [11]. Variants in *KCNH2* have been reported to potentially affect both neuronal firing patterns and cardiac excitability, which can explain the epilepsy phenotype as well as LQTS [14].

Here, we report a family with epilepsy, LQTS, syncope, and cardiac arrhythmias carrying a *KCNH2* Arg 744\* (the "\*" is defined as a termination codon) pathogenic variant. The same pathogenic variant was previously reported in one case in a SUDEP cohort, but the QT interval corrected for heart rate (QTc) was normal[7]. The *KCNH2* Arg 744\* pathogenic variant has also been previously reported in people with LQTS, but with no associated epilepsy [15, 16].

## Case study

The proband (Fig. 1A, IV-1), a 25-year-old woman, experienced her first seizure at the age of seven. She had two main seizure types: generalized tonic-clonic seizures (GTCS) during sleep, usually lasting less than two minutes, and auras during her menstrual period or when getting a cold, such as palpitations and a sense of impending onset, approximately one to two times a month. The patient uses antiepileptic drugs (AEDs), which are a combination of levetiracetam (LEV), valproate (VPA), and clonazepam (CZP), and has been GTCS seizure-free for three years. An MRI of the brain revealed no significant lesions. Interictal video electroencephalograms (vEEGs) showed left-temporal spikes (Fig. 2A), and ictal vEEGs started with low-wave sharp waves and spikes that mingled with electromyographic artifacts (Fig. 2B). Her 24-hour dynamic electrocardiograms (ECGs) showed QTc prolongation (Figs. 2C and 2D). QT intervals were measured on ECGs, and QTc intervals were calculated using the Bazett formula, where  $QTc = QT/\sqrt{RR}$  (RR = 60 divided by heart rate).

The proband's mother (Fig. 1A, III-2), aged 50 years, had her first GTCS seizure at the age of 18. Antiepileptic therapy was not initiated because the seizures were infrequent. However, after she gave birth at the age of 25, the frequency of seizures increased, and antiepileptic therapy with phenytoin (PHT) and oxcarbazepine (OXC) was initiated at her local hospital. When she was 28

years old, she complained of palpitations and syncope for the first time, and QTc prolongation was detected on her 24-hour dynamic ECGs two years later (Fig. 2D). She became seizure-free after switching AEDs to valproate (VPA) and carbamazepine (CZP), but palpitations and dizziness occasionally occurred, especially with high-intensity exercise.

The proband's grandmother (Fig. 1A, II-2) complained of palpitations and syncope when she was 73. Her 24-hour dynamic ECGs indicated supraventricular arrhythmia with the lowest heart rate of 41 bpm, and she agreed to a pacemaker.

Considering the young patient's family history, blood samples were collected from the patient and her parents after obtaining informed consent. Trio whole exome sequencing was performed using the chip capture probe of the IDT XGen Exome Research Panel V2.0 and the strategy of the Illumina NovaSeq 6000 PE150 with high-throughput sequencing technology. Three steps were included in the sequencing: mutation screening with high-throughput sequencing, genetic data analysis with bioinformatics and clinical information, and validation of suspected pathogenic mutations by Sanger sequencing. High-throughput whole mitochondrial genome sequencing was also performed to identify potential genetic causes; however, no pathogenic variants were found. A heterozygous variant of *KCNH2* [c.2230 (exon9) C>T, p. Arg744Ter,

416, NM\_000238, rs189014161] was found. The same variant was detected in the patient's mother. According to the guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, we classified the *KCNH2* variant as pathogenic [17].

## Discussion

We reviewed the literature on people with epilepsy carrying *KCNH2* variants (Table 1) and found a high proportion of sudden, unexpected deaths. Nearly all patients had prolonged QTc, and epileptic discharges on EEG were found in most patients. Although the *KCNH2* Arg 744\* variant has been previously reported in patients with epilepsy or LQTS, none of these cases had a dual phenotype of epilepsy and LQTS (Table 2). As shown in Table 2, two studies reported sudden death among affected people, indicating that the gene variant has a high associated risk [7, 13, 15, 16, 18-29].

Here, we report a family with a *KCNH2* Arg 744\* pathogenic variant presenting with both epilepsy and LQTS. The same variant was previously reported in patients with epilepsy or LQTS, but none of these cases had a dual phenotype of epilepsy and LQTS [7, 15, 16]. To the best of our knowledge, this is the first case of a patient with a *KCNH2* Arg 744\* pathogenic variant presenting with both epilepsy and LQTS. The *KCNH2* gene, encoding the ERG1 potassium channel, was originally isolated from a hippocampal cDNA library [30]. ERG1

channels are members of the ERG channel family and are voltage-gated channels. During depolarization, ERG channels quickly turn into an inactivated state, thereby suppressing the current at depolarized potentials. Upon repolarization, ERG channels quickly recover from the inactivated state but, owing to the slow deactivation time course, remain in a conductive state and diminish electrical activity during prolonged stimuli. Unique current profile of the ERG channels contributes to regulation of neuronal action potential firing frequency, spike frequency adaptation, and resting membrane potential [31]. ERG potassium channels expressed in various tissues, many of which are linked to disease [32]. ERG potassium channels are also widely expressed in the brain, where they contribute to regulating the frequency and discharge stability of neurons [33]. Blockade of ERG potassium channels in the hippocampus increases potassium concentrations extraneuronally [34], and such changes are epileptogenic [35]. The variant reported here because they may affect both neuronal firing patterns and cardiac excitability, which could explain both the epilepsy phenotype and LQTS [14]. LQTS2 patients with epilepsy have a higher prevalence and risk of arrhythmias than those without epilepsy, which partly depends on the shared genetic susceptibility between epilepsy and arrhythmia, in which channelopathies play a major role [18, 36]. Kohli, U., C. Ravishankar, and D. Nordli reported a case of *KCNT1* mutation associated with epilepsy, systemic-to-pulmonary artery "collateralopathy," and intermittent QTc prolongation [37]. Although *KCNT1* mutations are known to be



more common in epilepsy, the risk of heart disorders should be considered due to the genetic susceptibility of the heart. As mentioned above, because ERG potassium channels are expressed in numerous tissues, the pathogenicity of ERG potassium channels in different tissues and organs should be considered, as is the case for other channelopathies.

Young adults with epilepsy have a 24-fold increased risk of sudden death [38]. SUDEP is the most common cause of premature epilepsy-related mortality [39]. Moreover, inherited heart disease may also be a significant risk factor for SUDEP [40]. One study considered LQT+, type of LQTS, LQTS2 variant domain, QTc duration, and female sex as important factors for predicting epilepsy susceptibility [18], and so attention to these markers has the potential to reduce morbidity and SUDEP in young individuals with epilepsy. It should be emphasized that complete seizure freedom is the best way to reduce the risk of SUDEP, which in most cases can be achieved with the optimal use of AEDs.

Some AEDs, such as PHT, phenobarbital (PB), and lamotrigine (LTG), should be avoided in patients with LQTS. Although these drugs are not classified as medications associated with an increased risk of torsade de pointes on the CredibleMeds list [41], studies suggest an increased risk of arrhythmia and SUDEP with these drugs. For example, a previous study demonstrated that PHT and PB can inhibit potassium ion currents, which might be clinically

relevant to the risk of arrhythmia and SUDEP [42]. Further, a clinical cohort study showed that sodium channel blocker AEDs (e.g., PHT) were associated with an increased risk of cardiac events in participants with QTc prolongation, specifically LQTS2 [43]. LTG has been shown to block potassium ion currents [44], but a study of the effects of LTG on the QTc interval in healthy subjects found no significant increase in the QTc interval [45]. However, a case-control study of female patients with epilepsy showed that the incidence of SUDEP was significantly higher among those who were being treated with LTG than among those who were not [46]. Therefore, comorbidities should be considered when prescribing AEDs. It is worth noting that the proband's mother complained of palpitations and syncope for the first time after taking PHT, but it was difficult to prove whether it was due to AEDs or the natural progression of the disease.

## Conclusion

Here, we report a *KCNH2* Arg 744\* pathogenic variant in a family with both epilepsy and LQTS, thus expanding the clinical phenotype associated with this variant. The co-occurrence of epilepsy and LQTS underscores the importance of considering the risk of comorbidity due to the genetic susceptibility of both the brain and the heart in channelopathies. Our findings also highlight the importance of precise AED management and regular ECG monitoring in patients with channelopathies.

## **Declarations**

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## **Availability of Data and Materials**

Anonymized data will be shared by reasonable requests from any qualified investigator to the corresponding author.

### **Authors' Contributions**

YZ and NY were responsible for the follow-up of the patient. YZ, NY and WX prepared the first draft with all other authors' feedback. YZ and NY were involved in collecting and managing data. JWS revised the manuscript and provided critical intellectual input. All authors read and approved the final manuscript.

### **Ethics Approval and Consent to Participate**

The Ethics Board of West China Hospital, Sichuan University (approval 2019[48]) approved the study.

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### Key points

- This article reported a family with a *KCNH2* Arg 744\* pathogenic variant manifested epilepsy and LQTS.
- The *KCNH2* gene encodes ERG1 potassium channel, which is expressed in

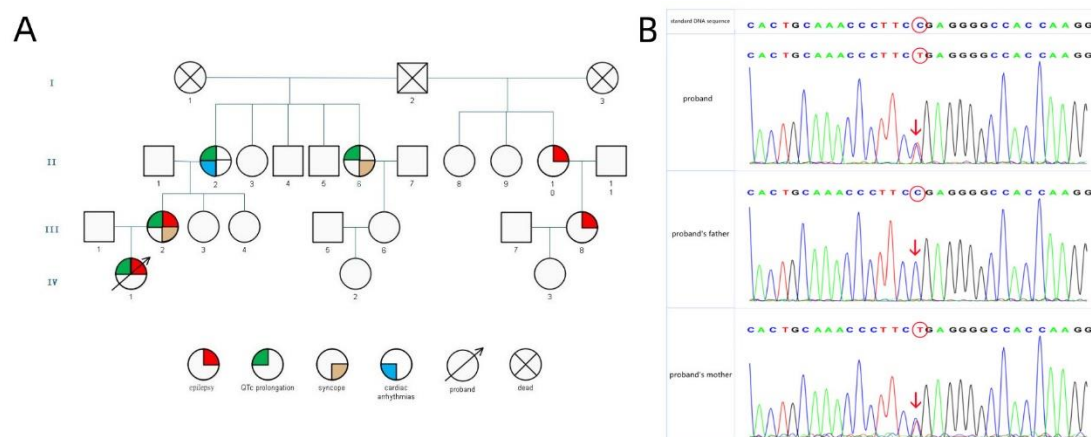
the brain and heart and can cause epilepsy and arrhythmias.

- People with epilepsy and LQTS should avoid some AEDs, such as PHT, phenobarbital (PB) and lamotrigine (LTG).
- Precise AEDs management and regular ECG monitoring are important for patients with epilepsy and LQTS.

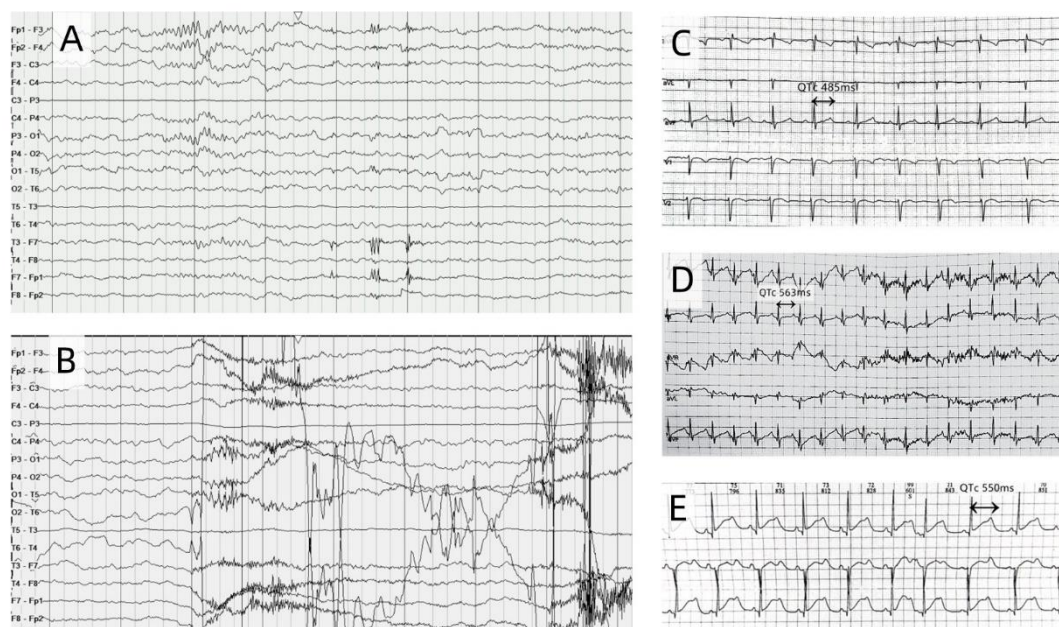
### **TEST YOURSELF**

1. For people with epilepsy, if their ECGs indicate arrhythmias, such as bradycardia, AV conduction blocks and QT prolongation, what kind of AEDs should be avoided?
2. What channelopathies genes are associated with epilepsy and arrhythmias?

### **Literature review**

**Figure 1.**

**Fig. 1.** A) Pedigree of the studied family: The arrow indicates the proband. Circles and squares represent females and males, respectively. Red, green, brown and blue represent subjects with epilepsy, QTc prolongation, syncope and cardiac arrhythmias, respectively. Cross represents dead subject. B) DNA sequence analysis: A C to T transition in *KCNH2* R744\* potassium channel gene was found in the proband and her mother.

**Figure 2.**

**Fig. 2.** A) Interictal vEEGs (10uV/mm, 30mm/sec) of the proband showed left-temporal spikes. B) Ictal vEEGs (10uV/mm, 30mm/sec) of the proband started with low-wave sharp waves and spikes, mingled with electromyographic artifacts. C) 24-hour dynamic ECGs of the proband (25

mm/s,10mm/mV), heart rate 73 bpm, corrected QT (QTc) interval of 485 ms. D) 24-hour dynamic ECGs of the proband (25 mm/s,10mm/mV) with the fastest heart rate of 147 bpm, corrected QT (QTc) interval of 563 ms. E) 24-hour dynamic ECGs of the proband's mother (25 mm/s,10mm/mV), heart rate 67 bpm, corrected QT (QTc) interval of 550 ms.

## Literature review

**Table 1** Clinical features of patients with epilepsy carrying *KCNH2* gene variant

References	Epilepsy with <i>KCNH2</i> variant case No./total case No.	Family history of epilepsy	Age at seizure onset (range or minimum age)	Sudden death of affected patients	Age of death of affected patients (range or minimum age)	Epileptiform EEGs	ECGs	Computer tomography (CT)/Magnetic resonance imaging (MRI)
Partemi, S., et al. [29]	4 affected family members	+	13	+	18	+	QT prolongation	Normal
Bagnall, R.D., et al. [7]	3/61	NA	10.3±8.2(0–34)	+	28.1±12.0 (1–53)	One was +, two were NA	LQTS(NA)	One was HS, two were NA
Auerbach, D.S., et al. [18]	75/1901	NA	NA	NA	NA	NA	LQTS(NA)	NA
Johnson, J.N. [13]	36/343	+	27±18	NA	NA	NA	LQTS(5NA)	NA
Zarroli, K. and H. Querfurth [19]	1/1	+	26	–	–	–	QT prolongation	slight prominence in the right temporal ventricular horn
Zamorano-León, J.J., et al. [20]	1/1	–	15	–	–	+	QT prolongation	NA
Tu, E., et al. [21]	5/68	NA	NA	+	39	NA	NA	NA
Omichi, C., Y. Momose, and S. Kitahara [22]	7 affected family members	+	20	+	Between 20 to 40	+	QT prolongation	Normal

Anderson, J.H., et al. [23]	7/610		NA	11±8	NA	NA	+	QT prolongation	2 of 7 were abnormal
Issa, N.P., W.G. Fisher, and J.T. Narayanan [24]	1/1		NA	10	-	-	+	QT prolongation	Non-specific change
Kang, H., et al. [25]	1/1		-	13	-	-	-	QT prolongation	Normal
Olberg, H.K., et al. [26]	1/1		NA	10+	-	-	+	QT prolongation	NA
Jorge, C., et al. [27]	1/1		+	2	+	NA	-	QT prolongation	Normal
Ichikawa, M., et al. [28]	4 affected members	family	+	26	+	30	NA	QT prolongation	NA

EEGs, electroencephalograms; ECGs, electrocardiograms; NA, not available; LQTS, long QT syndrome; HS, hippocampal sclerosis

**Table 2** Clinical features of patients carrying *KCNH2* Arg 744\* variant

References	Arg 744* variant case No./total case No.	Seizure	LQTS	Family history	Sudden death of affected patients	age of death of affected patients
Ko, Y.L., et al. [15]	8 affected family members	-	+	+	+	22
Kapplinger, J.D., et al. [16]	4/2500	NA	+	NA	NA	NA
Bagnall, R.D., et al. [7]	1/61	+	-	NA	+	28.1±12.0 (1-53)
Current study	6 affected family members	+	+	+	-	-

NA, not available; LQTS, long QT syndrome