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Short communication

Further evidence of the association between LQT syndrome and epilepsy in a family with *KCNQ1* pathogenic variant

Coloma Tiron [a,b,1], Oscar Campuzano [c,d,1], Alexandra Pérez-Serra [c], Irene Mademont [c], Monica Coll [c], Catarina Allegue [c], Anna Iglesias [c], Sara Partemi [e], Pasquale Striano [f], Antonio Oliva [e], Ramon Brugada [a,c,d,*]

[a] *Cardiology Service, Hospital Josep Trueta, Girona, Spain*
[b] *Cardiology Department, Hospital of Palamós, Palamós, Spain*
[c] *Cardiovascular Genetics Center, Institut d'Investigació Biomèdica de Girona-IDIBGI, Unversitat de Girona, Girona, Spain*
[d] *Medical Science Department, School of Medicine, University of Girona, Girona, Spain*
[e] *Institute of Public Health Section of Legal Medicine, School of Medicine, Catholic University, Rome, Italy*
[f] *Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, "G. Gaslini" Institute, Genova, Italy*

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ABSTRACT

Purpose: Ion channels are expressed both in the heart and in the brain, being advocated as responsible for sudden unexpected death in epilepsy but few pathogenic mutations have been identified. We aim to identify a novel gen associated with channelopathies and epilepsy in a family.
Methods: We assessed a family showing epilepsy concomitant with LQTS. Index case showed prolonged QT interval. His father suffers of LQT and epilepsy. We performed a direct sequencing analysis of *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2* and *SCN5A* genes.
Results: We identified a non-synonymous heterozygous *missense* pathogenic mutation (p.L273F) in exon 6 of the *KCNQ1* gene. All clinically affected relatives carried the same mutation.
Conclusion: We report, for a first time, a *KCNQ1* mutation in a family suffering of both phenotypes, suggesting that *KCNQ1* genetic variations may confer susceptibility for recurrent seizure activity increasing the risk or lead to sudden death.

1. Introduction

In recent years, it has been suggested that pathogenic signaling excitability could underlie both epilepsy and inherited cardiac arrhythmias, such as long QT syndrome (LQTS) [1]. The LQTS is a rare inherited ion channelopathy characterized by prolonged QT interval, predisposing patients to ventricular arrhythmias that can lead to syncope and sudden cardiac death (SCD) [2]. The three most prevalent genes associated with LQTS are *KCNQ1* (LQT type 1), *KCNH2* (LQT type 2), and *SCN5A* (LQT type 3) [3]. From the clinical point of view, LQTS may be misdiagnosed as epilepsy due to seizures triggered by cerebral hypoperfusion during a ventricular arrhythmia. However, some patients can be affected by LQTS and also epilepsy caused by channel dysfunction in myocardial and neuronal cells [4]. Hence, there has been increased interest in a possible association between epilepsy channelopathies and cardiac arrhythmias. Johnson et al. [1], identified a 'seizure phenotype' in about 30% of unrelated LQTS patients carrying pathogenic variants in the *KCNH2* gene. A post-mortem study in diagnosed epileptic samples identified nearly 13% of LQTS pathogenic variants in the *KCNH2* and *SCN5A* genes [5]. A loss-of-function (c.246T>C) pathogenic variation in the *KCNH2* gene was also reported in a pedigree featuring LQTS, idiopathic epilepsy, and increased risk of sudden death, supporting a strong link between epilepsy and LQTS [6].

Sudden unexpected death in epilepsy (SUDEP) is a catastrophic complication of epilepsy, causing up to 20% of patient deaths. However, the pathogenetic mechanisms of this fatal condition

Abbreviations: LQTS, long QT syndrome; SCD, sudden cardiac death; SUDEP, sudden unexpected death in epilepsy.

* Corresponding author at: Medical Science Department, School of Medicine, University of Girona, 17003 Girona, Spain. Tel.: +34 972183366; fax: +34 972183367.
E-mail address: ramon@brugada.org (R. Brugada).
[1] Both authors equally contributed.

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remain still unknown [7]. In a recent report of our group, we identified three cases suffering SUDEP who carried genetic variants in the *KCNQ1* gene, but consistent relation between both entities remains to be demonstrated [8]. To our knowledge, no report correlates LQTS type 1 and epilepsy in humans so far. We report a family featuring the LQTS and epilepsy due to a pathogenic variant in the *KCNQ1* gene.

2. Methods and results

A 20-year-old soccer player (III-4 in Fig. 1) was referred to our unit after detection of prolonged QT interval in a 12-lead ECG performed in a routine medical control (corrected QT 487 ms) (Fig. 1). He had no family history of sudden death, but his father had been suffering from epilepsy for several years (II-3). We recommended him to stop playing competitive soccer, to avoid drugs that could prolong QT interval and to start treatment with a beta blocker (bisoprolol 5 mg/day). In the follow up visits, six months and a year later, he remained asymptomatic.

The patient's father (II-3 in Fig. 1), who was 47 years old, had 12-lead ECG showing a prolonged QT interval (Bazett corrected QT of 476 mseg). He was diagnosed of focal epilepsy at the age of 16. He had prodromal symptoms seconds before losing consciousness, and, just at the first signs, he preventively placed his wallet in his mouth to protect himself from biting. He noticed tingling around his mouth, his hands and progressively his arms, neck and head, with a subsequent tonic–clonic seizure. He was seizure-free on carbamazepine until, the age of 25 years, when his neurologist withdrawn the antiepileptic therapy. We recommended him to avoid drugs that could prolong the QT interval and start treatment with a beta blocker (bisoprolol 5 mg/day). In the follow up visits six months and a year later he has remained asymptomatic.

The remaining first-degree family members were asymptomatic and had normal QT interval on their ECG. Patient I-1 died from pulmonary infection at 82 years of age. Patient I-4 died from myocardial infarction at 84 years of age.

We performed a direct sequencing analysis of *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2* and *SCN5A* genes in the proband and identified a non-synonymous heterozygous *missense* pathogenic variant (c.817C>T) in exon 6 of the *KCNQ1* gene (Fig. 1). The variant had been previously reported in Human Gene Mutation Database – HGMD (http://www.hgmd.cf.ac.uk/ac/index.php), and associated with LQTS (rs120074180, CM960899) [9,10]. The variant is conserved in many species suggesting that this region has structural or functional importance (http://www.uniprot.org/). In addition, it is absent in exome variant server (http://evs.gs.washington.edu/EVS/) and 1000 genomes (http://www.1000genomes.org/) databases, suggesting to be an uncommon genetic variant in the population. Finally, *in silico* prediction in PROVEAN (Protein Variation Effect ANalyzer) (http://provean.jcvi.org/index.php), Mutation Taster (http://www.mutationtaster.org/), and PolyPhen2 (http://genetics.bwh.harvard.edu/pph2) databases predicted a pathogenic/deleterious effect. No other non-common (MAF > 1%) genetic variants were identified in index case. After that, a genetic test was performed in close relatives (Fig. 1). The same variant p.L273F_*KCNQ1* was identified in the father of the proband (II-3), but not in the other tested relatives.

3. Discussion

In recent years, there has been an increased interest on cardiac alterations in patients affected by epilepsy. Despite similar molecular pathophysiology, ion channelopathies, separation of phenotypes may be due to organ-specific gene expression [11,12]. So far, numerous pathogenic variants have been identified in patients suffering cardiac arrhythmia and epilepsy, mainly in the *SCN5A* and *KCNH2* genes [13,14]. A study performed in mouse lines bearing dominant pathogenic variants in the Kv1.1 Shaker-like potassium channel, associated with LQTS type 1 in humans, showed epilepsy and premature death [15], supporting that arrhythmogenic cardiac variants in this ion channel might also cause epileptic changes in brain [13]. Recently, a collaborative study from our group genetic variants in the *KCNQ1* gene in a large series of subjects featuring epilepsy or a family history of sudden death, although the absence of a family study did not allow a definite causal correlation [8]. Hence, a consistent association between *KCNQ1* and LQT/epilepsy remains to be demonstrated.

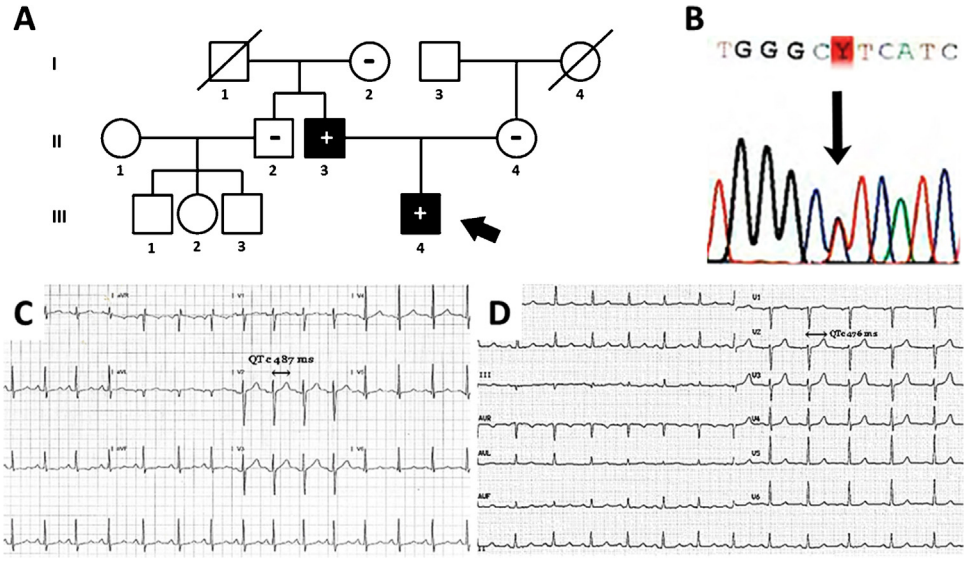

Fig. 1. (A) Pedigree of the family. Index case is III-4 (slanted arrow). Slashes round/squares indicate deceased members. White round/squares indicate normal corrected QT interval in the 12-lead ECG after clinical evaluation. Black squares indicate clinically affected by long QT syndrome and/or epilepsy. Plus sign (+) indicates carrier of genetic variation. Minus sign (−) indicates non-carrier of the genetic variation. (B) Electropherogram. DNA forward sequence of the *KCNQ1* gene showing the pathogenic genetic variation p.L273F in exon 6. Note the substitution c.817C>T (p.Leu273Phe). (C) Electrocardiogram of index case patient III-4 (25 mm/s, 10 mm/mV). Heart rate 89 bpm, corrected QT (QTc) interval of 487 ms. (D) Electrocardiogram of patient II-3 (25 mm/s, 10 mm/mV, 50 Hz). Heart rate 80 bpm, corrected QT (QTc) interval of 476 ms.

Here we report a family showing the association of epilepsy concomitant with LQTS. In our patients, prolonged QT interval supported the phenotype. On the other hand the genetic pathogenicity of p.L273F_*KCNQ1* has been confirmed as previously reported in LQTS cases [9,10]. In addition, the evolutionary conservation of the residue and its absence in healthy controls as well as *in silico* deleterious prediction supports its pathogenic/deleterious role. Despite cardiac arrhythmias and epilepsy can be misdiagnosed due to similar clinical manifestations, the father of our proband showed clear clinic features of epilepsy with focal onset and secondarily generalized seizure. Notably, in the series from Partemi et al. [8], all the 3 patients carrying a change in *KCNQ1* suffered from epilepsy of focal type, according to the present case. In this family, the variable clinical expression, with no reported seizures in the proband may be explained by an age-dependent expression of *KCNQ1* potential pathogenic variants and/or by the influence of additional genetic modifiers [16].

In summary, although our family does not necessarily provide the definite evidence for a link between LQTS and epilepsy, it further supports the view that *KCNQ1* genetic variations may confer susceptibility for recurrent seizure activity increasing the risk or lead to sudden death, according to the cardiocerebral channelopathy theory [11,17]. While further studies in large cohorts will be needed to be performed to clarify the correlation between cardiac and brain channelopathies, the identification of genetic variants which may cause SCD and epilepsy brings into question the need of simultaneous EEG and ECG recording with video-monitoring to elucidate a possible link between cardiac arrhythmia and epilepsy [18].

Conflict of interest

The authors declare no conflicts of interest. We have read the journal position on issues involved in ethical publication and affirm that our report is consistent with these guidelines.

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