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# A novel KCNH2 frameshift mutation (c.46delG) associated with high risk of sudden death in a family with congenital long QT syndrome type 2

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## Abstract

**Background:** The congenital long QT syndrome type 2 is caused by mutations in KCNH2 gene that encodes the alpha subunit of potassium channel Kv11.1. The carriers of the pathogenic variant of KCNH2 gene manifest a phenotype characterized by prolongation of QT interval and increased risk of sudden cardiac death due to life-threatening ventricular tachyarrhythmias.

**Results:** A family composed of 17 members with a family history of sudden death and recurrent syncopes was studied. The DNA of proband with clinical manifestations of long QT syndrome was analyzed using a massive DNA sequencer that included the following genes: KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, ANK2, KCNJ2, CACNA1, CAV3, SCN1B, SCN4B, AKAP9, SNTA1, CALM1, KCNJ5, RYR2 and TRDN. DNA sequencing of proband identified a novel pathogenic variant of KCNH2 gene produced by a heterozygous frameshift mutation c.46delG, pAsp16Thrfs\*44 resulting in the synthesis of a truncated alpha subunit of the Kv11.1 ion channel. Eight family members manifested the phenotype of long QT syndrome. The study of family segregation using Sanger sequencing revealed the identical variant in several members of the family with a positive phenotype.

**Conclusions:** The clinical and genetic findings of this family demonstrate that the novel frameshift mutation causing haploinsufficiency can result in a congenital long QT syndrome with a severe phenotypic manifestation and an elevated risk of sudden cardiac death.

**Keywords:** Long QT syndrome, KCNH2, Frameshift mutation, Sudden death

## Background

The congenital long QT syndrome (LQTS) is characterized by prolongation of QT interval on the electrocardiogram (ECG) and increased risk of sudden cardiac death due to life-threatening ventricular tachyarrhythmias like torsades de pointes and ventricular fibrillation [1–3].

Since 1995, mutations have been identified in 20 different genes responsible for congenital LQTS. Most of them are clinically known as Romano–Ward syndrome inherited with autosomal dominant pattern. In contrast, those included in Jervell and Lange-Nielsen syndrome show autosomal recessive inheritance pattern and are associated with sensorineural hearing loss [4–7].

The LQTS type 2 represents 30–45% of all cases of LQTS [8]. It is caused by mutations in the KCNH2 gene that encodes the alpha subunit of voltage dependent

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potassium channel known as Kv11.1 (or hERG) responsible for rectifier current *IKr* (OMIM # 613688).

We report a novel pathogenic variant of *KCNH2* in a family whose members manifest LQTS type 2 with high penetrance and severe phenotype characterized by long QT interval, recurrent syncope and multiple family antecedents of sudden death.

## Methods

### Study participants

A family composed of 17 members with a family history of sudden death and recurrent syncope was studied.

### DNA isolation and sequencing

After signing the informed consent, peripheral blood samples were obtained from the proband and first and second degree relatives. Initially, the proband's DNA sample was sent to Molecular Biology and Pathology Laboratory of High Medical Group (Buenos Aires, Argentina). Sequencing was carried out on a Next-Seq500 instrument (Illumina, San Diego, CA, USA) as 151-bp paired-end runs. Exome analysis of the proband yielded a mean coverage of 149.89X. The most common genes associated with LQTS were selected from ClinVar, OMIM (Online Mendelian Inheritance in Man) databases and the international public literature [9]. The exonic and adjacent intronic regions of the following 17 genes were sequenced: *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *ANK2*, *KCNJ2*, *CACNA1*, *CAV3*, *SCN1B*, *SCN4B*, *AKAP9*, *SNTA1*, *CALM1*, *KCNJ5*, *RYR2* and *TRDN*.

Read alignment and variant calling were performed with Burrows-Wheeler Aligner and FreeBayes. The variants have been annotated according to reference sequences cited in the Human Gene Mutation Database. For the filtering of variants, the quality of the genotype, the allelic frequency and the coverage of the position were considered. For variant validation and family segregation analysis, Sanger sequencing was performed. Genomic DNA (gDNA) was extracted using the EasyPure Blood Genomic DNA Kit (Trans, China, Cat. No. EE121), and then quantified using a Qubit fluorometer (Invitrogen, California, USA). Amplifications corresponding to exon 1 were carried out on a Verity® thermal cycler (Applied Biosystems, Massachusetts, USA). The PCR products were purified using AccuPrep®PCR Purification Kit (Bioneer, cat. No. K3034). Finally, the Sanger-sequencing was performed on an ABI PRISM 3730XL Analyzer 96 capillary type (Applied Biosystems, Massachusetts, USA) and subsequently analyzed with Variant Reporter

Software Version 1.1 at the next-generation sequencing facility of MacroGen (Seoul, Republic of Korea).

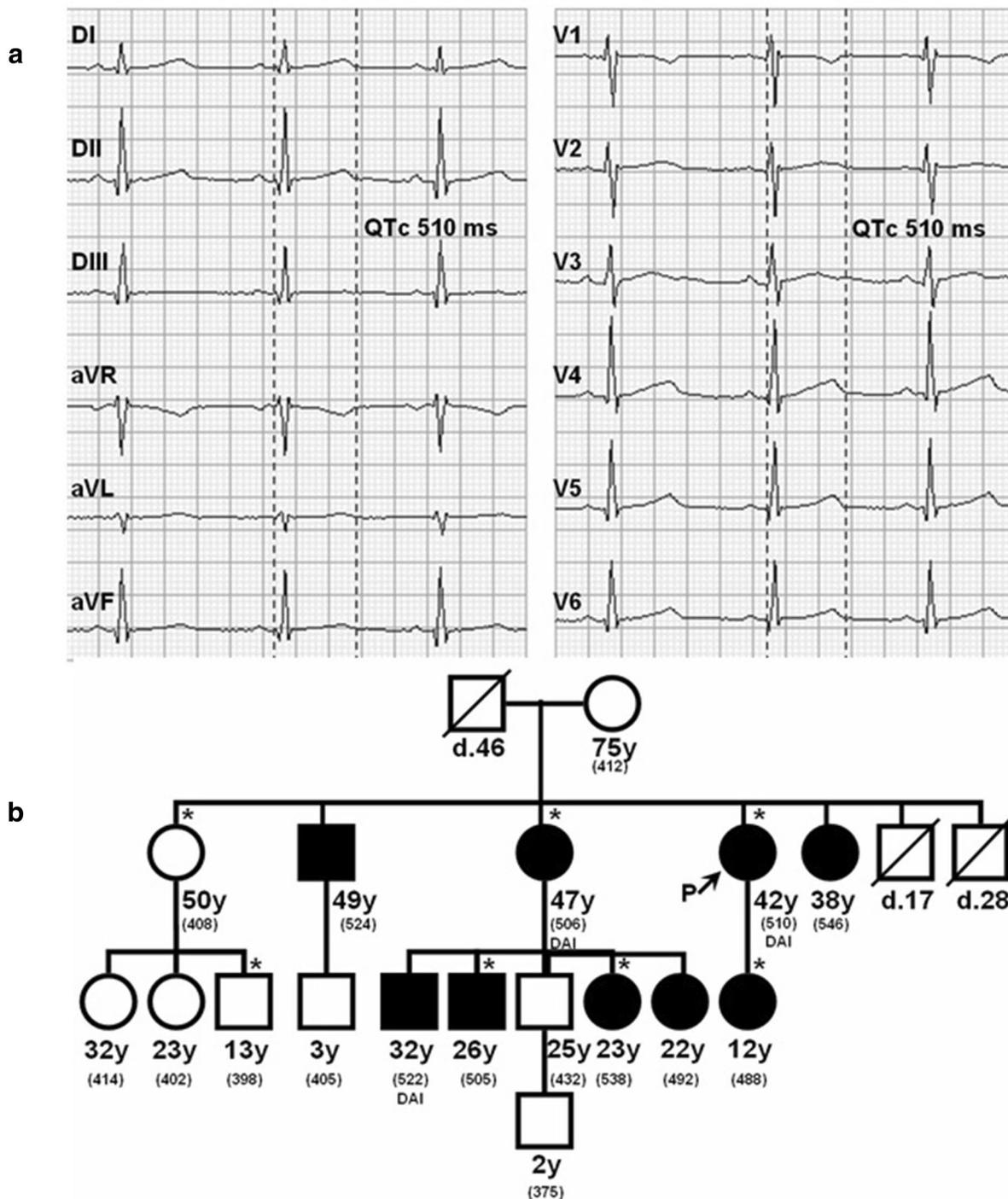
## Results

The proband was a 42-year-old Caucasian woman with family history of sudden death. Her father (46 years old) and 1 brother (28 years old) died while sleeping at night. Another brother (17 years old) died suddenly after doing physical activity. Since puberty, she had repeated episodes of syncope. The ECG showed a QTc interval (Bazett's formula:  $QTc = QT / RR^{1/2}$ ) of 510 ms (Fig. 1a). The 24-h Holter monitoring did not show significant cardiac arrhythmias. The tilt test was normal. Transthoracic echocardiogram and cardiac nuclear magnetic resonance showed no structural abnormalities. In the absence of a history of drug use that could prolong the QT interval, a diagnosis of LQTS was made according to diagnostic criteria of international guidelines (score of Schwartz: 4.5 points.  $QT > 480$  ms = 3 points; syncope without stress = 1 point; and unexplained sudden cardiac death at age < 30 years in immediate family = 0.5 points) [3, 10–12].

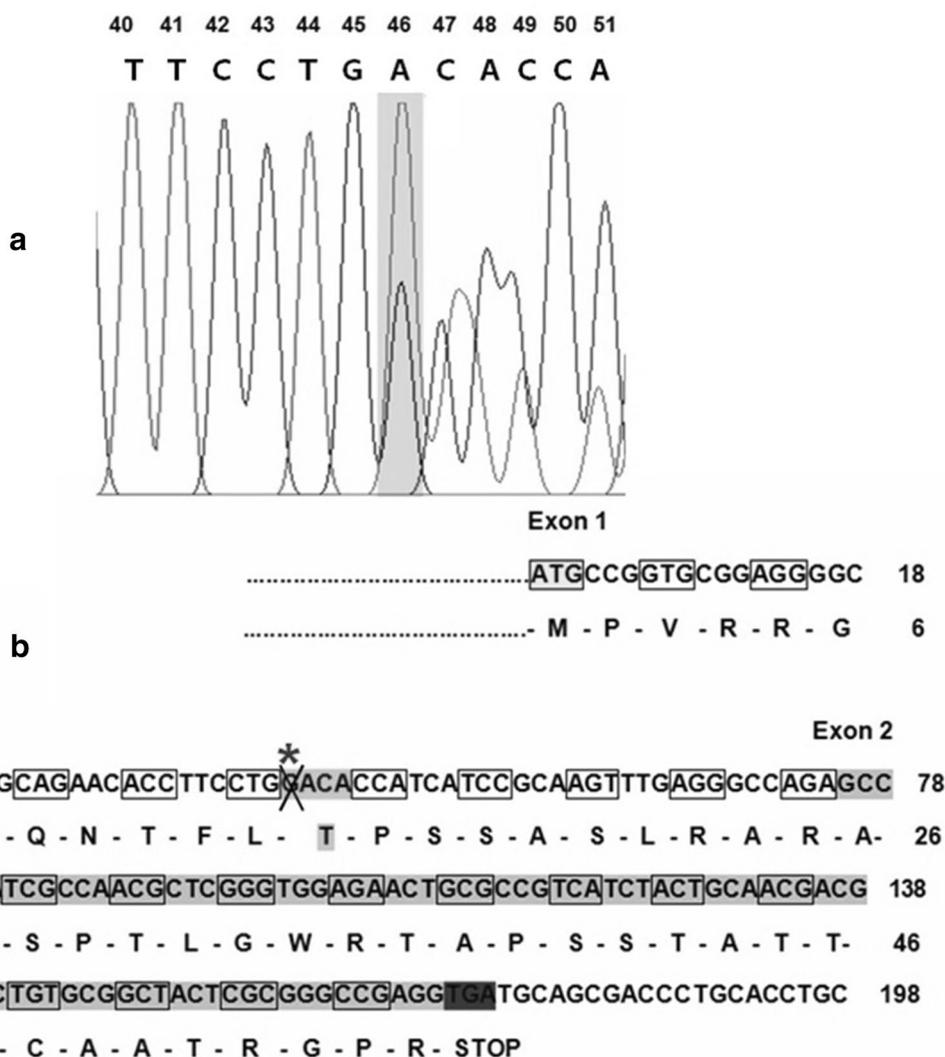
She received beta-blocker treatment with nadolol 40 to 80 mg/day or propranolol 120 to 240 mg/day orally. Despite beta-blocker therapy that did not result in a substantial reduction in the QTc interval, she had several recurrent episodes of syncope and non-sustained ventricular tachycardia. Because the patient had high-risk features of LQTS ( $QTc > 500$  ms, women with type 2 genotype long QT syndrome and recurrent syncope), an implantable cardiac defibrillator (ICD) was indicated [3, 13]. No electrical shocks were observed for ventricular arrhythmias after ICD.

Subsequent family study revealed that 8 of the proband's relatives, including her 12-year-old daughter, 3 siblings (2 women and 1 male), 2 nephews and 2 nieces manifested LQTS phenotype. Two of them (1 sister and 1 nephew) presented recurrent episodes of refractory syncope and non-sustained ventricular tachycardia requiring an implantable cardiac defibrillator (Fig. 1b).

The proband's DNA analysis identified the presence of a heterozygous variant occurred by deletion of guanine nucleotide from position 46 of exon 1 of *KCNH2* gene (c.46delG) that replaces aspartic acid with threonine at position 16 of the protein product. The reading frame shift generates the appearance of a premature stop codon in exon 2 after encoding 44 amino acids from mutation site (p.Asp16Thrfs\*44) and produces a truncated protein with a loss of 90% of amino acids (Fig. 2). Subsequent Sanger-sequencing to study familial segregation revealed the identical variant in 4 other



**Fig. 1** **a** The ECG of proband. The QTc interval was prolonged: 510 ms. **b** Family pedigree. Seventeen individuals with their respective ages and QTc interval values (between parentheses). Squares depict male subjects; circle, female subject; open symbols, unaffected members; and solid symbol, affected member. Arrow (P) denotes proband. Her father and 2 brothers died suddenly at a young age (cross). Three family members had recurrent syncope refractory to beta-blockers and/or non-sustained ventricular tachycardia requiring an implantable cardiac defibrillator (ICD). The genetic study was carried out on 7 family members (asterisk). The novel pathogenic variant was detected in five of them that manifested the LQTS phenotype



**Fig. 2** **a** Electropherogram of the sequence surrounding the heterozygous mutation in *KCNH2* from the proband’s genomic DNA. **b** Scheme of cDNA region involved in c.46delG variant. Nucleotides are separated into triplets (codon) with their corresponding amino acid. The deletion of guanine located at position 46 (asterisk) in exon 1 (codons marked in white) of *KCNH2* gene produces a reading frame shift in the mutant allele that generates a premature stop codon in exon 2 (codons marked in gray) resulting in a truncated protein

family members with positive phenotype (daughter, 1 sister, 1 nephew and 1 niece).

**Discussion**

The congenital LQTS is characterized by prolongation of the ventricular myocardial action potential due to the increase in sodium and calcium input currents (I<sub>Na</sub> and I<sub>Ca<sub>v</sub></sub>) or the decrease in potassium outflow currents (IKs, IKr and IK1). Molecular genetic studies identified mutations in 20 different genes that encode the subunits of cardiac ion channels and/or modulator proteins that

directly or indirectly intervene in the formation of these currents [7, 14].

The *KCNH2* (potassium voltage-gated channel subfamily H member 2) gene also known as hERG (human Ether-à-go-go-Related Gene) which is located on chromosome 7 (locus 7q35–36) is composed of 15 exons that encode the alpha subunit of the voltage-dependent potassium channel called Kv11.1 of 1159 amino acids. Four alpha subunits of Kv11.1 assemble a tetrameric ionic channel that generates the rapidly activating delayed rectifier potassium current (IKr) during phase 3 of the repolarization of myocardial cells. The loss of ion channel

function results in increase in the duration of myocardial action potentials manifested as prolonged QT intervals in the ECG of patients with LQTS type 2 [15, 16].

Approximately 40% of KCNH2 gene mutations related to LQTS type 2 are: (a) nonsense mutations (point mutation in a sequence of DNA that results in a premature stop codon) or (b) frameshift mutation caused by the insertion or deletion of nucleotides in a DNA sequence and results a completely different reading frame from the original [15]. These mutations alter protein synthesis and generate defective alpha subunits of Kv11.1 channel. The remaining 60% of the mutations of KCNH2 gene are missense mutations, where a single nucleotide change alters an amino acid codon causing loss of channel function by disrupting the intracellular traffic of Kv11.1 to the cell membrane, altering channel gating or negatively affecting ion permeability [15, 17].

In heterozygous mutations of KCNH2 encoding truncated alpha subunits of Kv11.1 or disrupting intracellular traffic, the defective proteins are degraded by proteasomes. If alpha subunits encoded from the wild-type allele are still homomerized to form functional channels, the affected individuals manifest a less severe phenotype (haploinsufficiency). In contrast, individuals with point mutations that alter channel permeability or gating can assemble Kv11.1 heteromeric dysfunctional channels with alpha subunits encoded by both alleles (wild-type and mutant) and manifest a more severe phenotype (negative dominance) [18, 19].

In the sudden death risk stratification of patients with long QT syndrome, all patients with a mutation at the KCNQ1 gene (LQT1 locus) who have a QTc of 500 ms or more, male patients with a mutation at the KCNH2 gene (LQT2 locus) who have a QTc of 500 ms or more, all female patients with a mutation at the LQT2 locus irrespective of the QTc, and all patients with a mutation at the SCN5A gene (LQT3 locus) are considered high risk [20]. Most members of proband's family, irrespective of the sex, had QT interval of 500 ms or more (Fig. 1b) and recurrent episodes of syncope.

At present, the beneficial effect of beta blockers in the treatment of patients with LQTS is clear. There is consensus that nadolol, unfortunately not available in all countries (including Argentina since 2016), is probably one of the most effective drugs. The efficacy of other more commonly prescribed beta-blockers such as propranolol, metoprolol, and atenolol is in dispute, especially in symptomatic patients [21, 22].

For patients with symptomatic LQTS in whom the beta-blocker is ineffective or poorly tolerated, left cardiac sympathetic denervation (LCSD) and/or an ICD are recommended [3, 13]. LCSD may be more effective in patients with long QT syndrome type 1. Although

a marked reduction in the incidence of aborted cardiac arrest and syncope is usually seen after LCSD, 20% to 50% of patients with high-risk LQTS have experienced at least 1 recurrent arrhythmic event after LCSD [23, 24]. Therefore, LCSD is an important therapeutic option for the management of patients with a first episode of syncope that occurs despite beta-blocker therapy, but it should not be considered as a curative or alternative to ICD in patients with high risk of sudden cardiac death [25].

The genetic variant identified in this family is due to a heterozygous mutation resulting in a premature stop codon. According to the literature, these mutations would lead to haploinsufficiency causing a mild phenotype because there would be up to 50% loss of function, while the remaining wild-type Kv11.1 channels function normally [15, 18, 19].

However, the clinical and genetic findings of this family demonstrate that the mutations that cause haploinsufficiency can result in LQTS with a severe phenotypic manifestation and risk of arrhythmic events.

## Conclusions

The novel pathogenic variant of the KCNH2 gene identified in this family produces a heterozygous frameshift mutation that results in a premature stop codon and causes LQTS with a severe phenotypic manifestation and an elevated risk of sudden cardiac death.

## Abbreviations

LQTS: Long QT syndrome; ECG: Electrocardiogram; KCNH2: Potassium voltage-gated channel subfamily H member 2; Kv11.1: Voltage-dependent potassium channel 11.1; DNA: Deoxyribonucleic acid; OMIM: Online Mendelian Inheritance in Man; PCR: Polymerase chain reaction; LQT1: Long QT syndrome type 1; LQT2: Long QT syndrome type 2; LQT3: Long QT syndrome type 3; IKr: Rapidly activating delayed rectifier potassium current; ICD: Implantable cardiac defibrillator; LCSD: Left cardiac sympathetic denervation.

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## Authors' contributions

YHS has drafted the manuscript; MN performed the processing of the DNA sample; vWMA and CN acquired and analyzed the patient data; GHA contributed to interpretation of data and diagnosis; PA and PMB contributed to design of the work; ARS and CJ have substantively revised the work. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The ClinVar accession

numbers for the DNA variant data are reported in this manuscript (dbSNP: rs1584885912) is VCV000638156.1 [26].

#### Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Hospital Dr. José María Ramos Mejía, according to the Declaration of Helsinki. All individuals signed the informed consent before participating in the study.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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