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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

A novel life-threatening mutation in long QT2 syndrome

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Abstract

Background and aim: The aim of the report was to present a novel mutation in *KCNH2* in a family with life-threatening long QT syndrome.

Methods: A genetic study using the method of next generation sequencing was performed in a 47-year-old woman after several episodes of syncope and torsade de pointes after sudden stress, with familial history of sudden death in first-degree female relatives. The study was performed also in her three asymptomatic children. Prolongation of QTc and typical ECG pattern of long QT2 were seen in the index case and in her youngest son.

Results: Novel mutations (p.F617V) in exon 7 of *KCNH2* were found in the index case and in her youngest son.

Conclusions: A novel heterozygous missense mutation in exon 7 of *KCNH2* gene, causing a protein change p.F617V, was found in a family with life-threatening arrhythmias in women and clinical outcome typical for long QT2 syndrome.

Key words: long QT syndrome, mutation, sudden cardiac death, *HERG/KCNH2* F617V

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INTRODUCTION

Inherited long QT type 2 syndrome (LQT2) is caused by mutations in the *KCNH2* gene encoding the alpha-subunit of the rapidly activating delayed rectifier K^+ channel current of cardiac myocytes. Mutations in the *KCNH2* gene are the second most common cause of congenital long QT syndrome (LQTS) and are responsible for about 25–45% of all genotyped LQTS patients [1–3]. Recently it has been reported that the risk of sudden cardiac death in LQT2 is as high as in LQTS type 3 [4]. Thus, genetic studies are essential for the diagnosis, prognosis, and treatment [1]. We report a family with LQTS presenting life-threatening arrhythmias, in which a novel autosomal mutation in the *KCHN2* gene was identified.

METHODS

Patients

A 47-year-old woman (index case, II-1) with a history of several episodes of syncope during psychological stress was diagnosed with LQTS at the age of seventeen. After a syncope sinus bradycardia, QTc 0.540 s and several episodes of torsade de pointes (TdP) were observed. To enable beta-blocker therapy a pacemaker AAI was inserted and propranolol 120 mg per day given. Since that time neither arrhythmia nor syncope have been observed. Electrocardiogram (ECG) (available only with AAI pacing) shows prolonged QT (QTc 0.498 s) (Fig. 1A) with normalisation during exercise test.

ECG was performed in her three asymptomatic children (20, 17, and 12 years old). In the youngest, QTc of 0.560 s and significant ST-T changes were observed (Fig. 1B). The mother and the sister of the index case patient died suddenly at the age of 42 and 20 years, respectively. The sister died in her sleep. Her father died because of other causes in late age (Fig. 2).

Genetic study

The patient was subjected to genetic study including LQT1, LQT2, and LQT3 genes. In order to identify the mutation, genomic DNA was extracted from 10 mL of peripheral blood and was used for library preparation. Polymerase chain reaction (PCR) of extracted DNA for all exons with exon-intron boundaries regions was performed with specific primers. The sizes of PCR-amplified fragments were about 400 bp. After the

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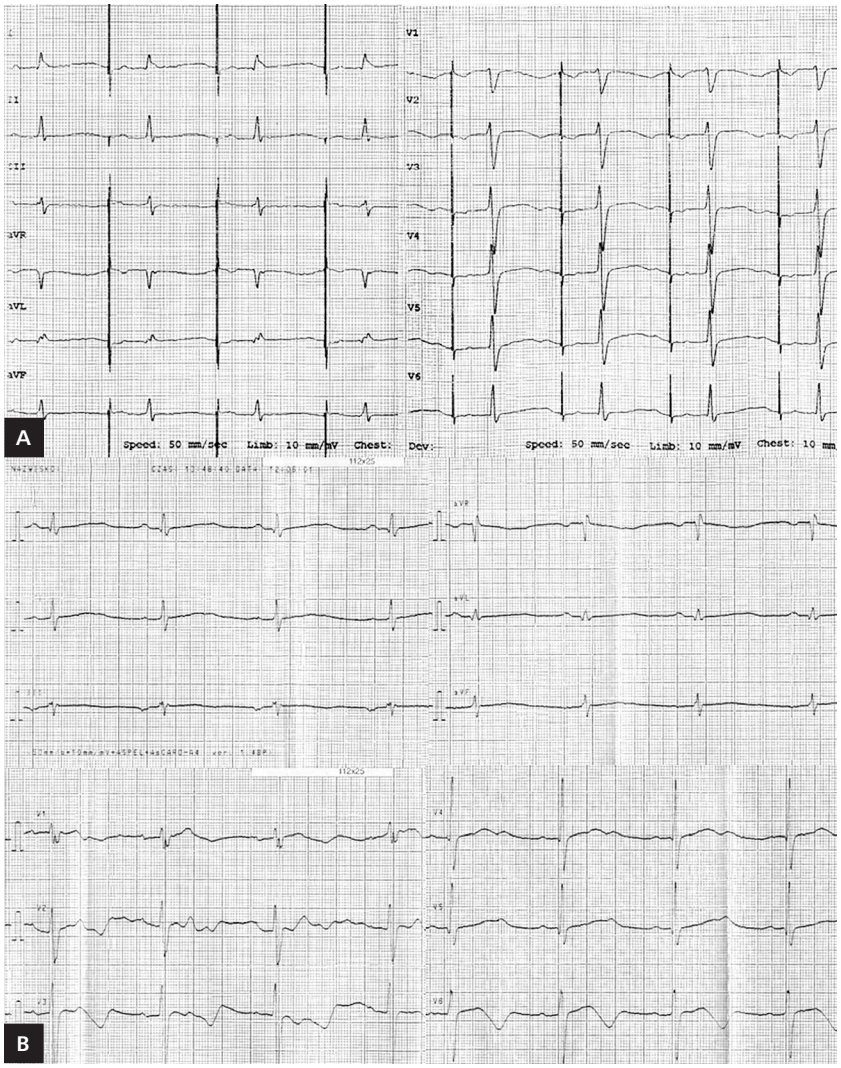

Figure 1. **A**. Electrocardiogram of patient II-1 (index case). AAI pacing at 90/min. Low-amplitude broad T wave with double--peak T-wave; corrected QT interval (QTc) of 0.498 s; **B**. Electrocardiogram of patient III-3. Broad double-peak T and biphasic (V_6) waves; corrected QT interval (QTc) of 0.560 s

adapters ligation and short sequence index introduction, multiplex sequencing was performed using a Junior-Roche platform. Each change was validated using the Sanger sequencing method (3130 xL Genetic Analyser, Applied Biosystem). The obtained sequences were compared to the consensus sequences for the LQT1 and LQT2 genes (GenBank Accession number, respectively: NG_008935 and NG_008916). The putative mutation was further investigated in 100 unaffected, unrelated controls and in the family members (three children) to determine its familial transmission.

Informed consent for the genetic study was obtained from each patient or his/her legal representatives.

RESULTS

Genetic screening for *KCNQ, KCNH2*, and *SCN5A* identified a new heterozygous missense mutation in exon 7 of the *KCNH2* gene (TTC>GTC), causing a protein change p.F617V in the index case and in her youngest son. The mutation has not been reported in the dbSNP, HGMD, or other genomic databases. The mutation was not seen in 100 unaffected, unrelated control individuals.

DISCUSSION

A specific correlation between genotypes and phenotypes in patients with LQT1, LQT2, and LQT3 is well known [5]. Given the cardiac events present (bradycardia, stress-induced arrhythmia, significant ST-T changes), we expected LQT2; consequently, the detection of *KCNH2* mutation was not a surprise.

The familial genetic study revealed the mutation in the *KCNH2* gene only in the index case and in her youngest son, who presented with prolonged QTc and significant ST-T changes.

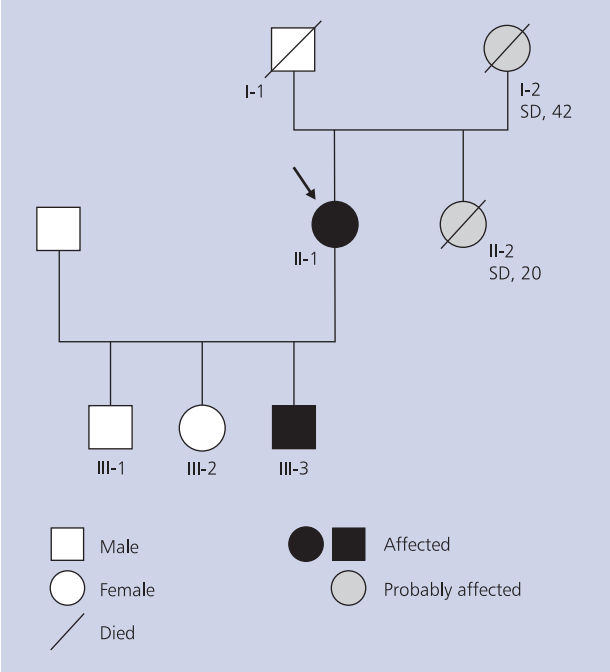

Figure 2. Pedigree of the family. Index patient marked by an arrow. Individuals with black circles carry the mutation and the clinical phenotype with symptoms and/or electrocardiogram changes. Index case's mother (I-2) and sister (II-2) (grey circles) died suddenly; no genetic data were available

The revealed mutation is located in the transmembrane pore region (S5-loop-S6). It is known that the QTc interval is longer and cardiac events are more common in patients with mutations in this location than in those with mutations in the transmembrane non-pore (S1-S4), N-terminus, or C-terminus location [6]. The phenotype-genotype correlation and the "pore" region localisation of the novel mutation strongly suggest its causative role in this family. The absence of the mutation in 100 healthy individuals decreases the likelihood that it is a rare polymorphism.

A history of sudden death in the first-degree relatives, TdP, and syncope in the index case patient suggested that the mutation is potentially life threatening in young women. This implies that the new mutation, discovered by us, represents a pathogenic LQTS mutation. We do not know the clinical significance of this mutation in men. In the youngest son carrying the mutation, propranolol was given as a prophylactic treatment, and sport involvement was discouraged. Both mother and son were informed that they should avoid drugs that prolong QT interval. During the 30-year follow-up of the index case and the 12-year follow-up (since his birth) of her son no cardiac events have occurred, so no other treatment has been proposed.

CONCLUSIONS

A novel heterozygous missense mutation in exon 7 of the *KCNH2* gene, causing a protein change p.F617V, was found in a family with life-threatening arrhythmias in women and clinical outcome typical of LQT2.

Conflict of interest: *none declared*

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Nowa groźna mutacja w zespole wydłużonego QT typu 2

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Streszczenie

Wstęp i cel: Celem pracy było przedstawienie nowej mutacji w *KCNH2* w rodzinie z zespołem wydłużonego odstępu QT (LQT) o groźnym przebiegu.

Metody: Badanie genetyczne za pomocą sekwencjonowania nowej generacji wykonano u 47-letniej kobiety po wielokrotnych, związanych ze stresem, utratach przytomności w mechanizmie częstoskurczu komorowego *torsades de pointes*, z wywiadem rodzinnym nagłych zgonów wśród krewnych pierwszego stopnia płci żeńskiej. Badanie przeprowadzono także u jej trojga bezobjawowych dzieci. Wydłużenie odstępu QTc i typowe elektrokardiograficzne cechy LQT2 stwierdzono u probandki i jej najmłodszego syna.

Wyniki: Nową heterozygotyczną mutację typu zmiany sensu (p.F617V) w eksonie 7 genu *KCNH2* stwierdzono u probandki i jej najmłodszego syna.

Wnioski: Nowa heterozygotyczna mutacja typu zmiany sensu (p.F617V) w *KCNH2* została wykryta w rodzinie z typowym obrazem klinicznym dla LQT2 i groźnym przebiegiem u kobiet.

Słowa kluczowe: zespół wydłużonego QT, mutacja, nagły zgon sercowy, *HERG/KCNH2* F617V

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