Multigenerational Inheritance of Long QT Syndrome Type 2 in a Japanese Family

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Abstract

Congenital long QT syndrome (LQTS) is an important cause of sudden cardiac death in young people without any other structural disease. Mutations in the genes encoding the cardiac ion channels or associated proteins have been shown to result in ion channel dysfunction and thereby causing LQTS. We investigated a Japanese family with LQTS for four generations, with the female family members showing severe symptoms. We performed genetic tests for LQTS-related genes and identified a heterozygous KCNH2 mutation (p. K638del). In the family, the KCNH2 mutation had a very high multigenerational inheritance, and female genotype positives showed more severe phenotypes.

Key words: long QT syndrome, multigenerational inheritance, KCNH2, sex hormones


Introduction

Sudden cardiac death (SCD) occurs in approximately 50,000 people per year in Japan. Congenital long QT syndrome (LQTS) is one of the major causes of SCD in young people without any structural disease. Genetic mutations are identified in from 50-70% of LQTS probands, and >90% of these are genotyped as one of the LQTS type 1-3 mutations (LQT1-3). The cardiac event risk and treatment in LQT1-3 are dependent on the genotype; therefore, genetic testing is indispensable for the management of patients with LQTS, particularly those with a family history of the disease. We herein described a Japanese family with LQTS type 2 (LQT2) showing multigenerational inheritance.

Case Report

Proband (indicated by an arrow in the family tree of Fig. 1: II-3)

The proband was a 56-year-old man who suffered from a loss of consciousness while driving. At first, he was diagnosed with transient cerebral ischemic attack as the cause of syncope because he was temporarily paralyzed on the left side after the event. At the age of 59 years, he was first pointed out to have a QT prolongation and was referred to our hospital for evaluation of LQTS. His 12-lead electrocardiography (ECG) (Fig. 2A) displayed a marked QT prolongation (QTc: 597 ms), biphasic T waves in V4 and V5 and a heart rate of 51 bpm. He had no previous syncope except for that experienced during the traffic accident. There were no abnormal physical findings and no structural cardiac abnormalities on the ultrasound cardiography (UCG). His Schwartz scores were 4.5; QT prolongation, bradycardia, and syncope were observed, and he was therefore diagnosed...
with LQTS. Genetic tests identified a deletion of three bases (c.1913-1915del) of KCNH2 that resulted in a single amino acid deletion (p.K638del; Fig. 3). He had a strong family history of LQTS as shown in the pedigree (Fig. 1).

**Proband’s mother** (Fig. 1: I-2)

The proband’s mother suddenly died at night when she was only 30 years of age, and when the proband was a four-month-old infant. There were no ECG recordings available.

**Proband’s daughter** (Fig. 1: III-4)

One of the proband’s two daughters had experienced repeated loss-of-consciousness since her teenage years, and her ECG revealed a QT prolongation at the age of 17 years. At the age of 26 years, 5 months after her first delivery of a neonate girl (Fig. 1: IV-1), she suffered from repetitive syncope with seizures in the early morning. Because of the neonate’s crying at night, she was not sleeping well. At that time, she was diagnosed with epilepsy, and a family doctor initiated the administration of antiepileptic medication.

At 31 years of age, repetitive syncope with seizures recurred, and she consulted a neurologist and underwent electroencephalography (EEG) recordings. During the EEG examination, syncope with seizures recurred, and bradyarrhythmia-related Torsades de Pointes (TdPs) were recorded. Her rest 12-lead ECG (Fig. 2B) showed a marked QT prolongation (QTc: 504 ms) with biphasic T waves, and her serum potassium level was found to be low (3.3 mEq/L). This serum potassium level was corrected, and lidocaine and mexiletine hydrochloride were thus administered; however, her TdP occurred again (Fig. 2C) and temporary ventricular pacing was initiated, followed by pacemaker implantation (AAI at 80).

The atrial pacing rate was set relatively high because bradycardia <60 bpm produced frequent TdPs. Finally, her TdPs were suppressed by the procedure. At 33, she was genotyped as carrying the same heterozygous KCNH2-K638 del mutation as her father (Fig. 3).

**Proband’s granddaughter** (Fig. 1: IV-1)

The proband’s granddaughter, the daughter of III-4, underwent an ECG examination at 8 years of age, when her mother was genotyped and was pointed out to have a marked QT prolongation (Fig. 2D; QTc: 500 ms). At that time, she was asymptomatic and received no medication. However, at 12 years of age, she began to have repetitive syncope at rest which was later shown by ECG to be a result of TdP in the early morning (Fig. 2E). Her TdPs started with sinus bradycardia (<60 bpm). Her resting 12-lead ECG
Figure 3. Sequencing electropherogram of the control (upper) and II-3 (lower). Three bases (AGG) deletion caused a deletion of Lysine 638.

showed QT prolongation (QTc: 506 ms) and biphasic T waves similar to those observed in III-4. Furthermore, she had severe sinus bradycardia at night that triggered TdPs; therefore, she underwent pacemaker implantation (AAI at 80). Since then she has experienced no syncope without medication. At 15 years of age, she was identified to have the same heterozygous KCNH2-K638del mutation as her grandfather and mother (Fig. 3).

Discussion

We investigated a four-generation Japanese family with LQT2. The family members carried a heterozygous KCNH2-K638del mutation that was located in the pore region of the Kv11.1 channel. Mutations in the pore region of Kv11.1 have been well known to result in severe phenotypes (1-3).

In this family, female carriers showed more severe phenotypes than male carriers; I-2 and III-4 developed cardiac arrest or syncope after parturition, and IV-1 suffered syncope because of TdP immediately after the onset of puberty (4). In contrast, a male index patient, II-3, was asymptomatic except for syncope onset which resulted in a traffic accident at 56 years of age. Although the average frequency of cardiac events has been reported to be 46% (5) in LQT2, all genotype-positive females in this family experienced fatal events, which is consistent with previous reports suggesting that LQT2 females suffer more severely than males (6).

There are two previous reports of LQT2 families over four-generations (7, 8). Consistent with our observations, both their KCNH2-G572R and R863X mutations showed a high penetrance, particularly in female carriers.

The causes of increased cardiac risk among LQT2 women after puberty have been explained with respect to the serum levels of sex hormones (9). Nakagawa et al. reported that QTc intervals changed during the menstrual cycle in healthy women aged 18-32 years based on Holter ECG recordings; the QTc intervals were longer during the follicular than luteal phase (10).

Estrogen has been reported to cause QT prolongation. Among postmenopausal women who received estrogen-alone therapy (ET) or estrogen plus progesterone therapy (EPT), the women who received ET showed significantly longer QTc intervals than those who received EPT. These studies suggested the counterbalancing effects of exogenous oral estrogen and progesterone on the QTc intervals (11, 12).

The functional effects of female hormones on ion channels were extensively analyzed using patch clamp methods and computational modeling. In those analyses, estrogen suppressed the rapid component of the delayed-rectifier K channel current (IKr) and up-regulated the L-type Ca channel currents (Ica,L). In contrast, progesterone decreased Ica,L and increased the slow component of delayed-rectifier K channel currents (IKs) (13, 14). The mean age of puberty onset in Japanese girls is reportedly 10.0 ± 1.4 years (4). In females after puberty, these torsadogenic effects of estrogen may result in QT prolongation, which was the case for the granddaughter in our study (Fig. 1: IV-1).

In addition, Nagaoka et al. indicated a basal heart rate < 60 bpm to be a notable risk factor for the prediction of life-threatening arrhythmias in LQT2 patients (15). In III-4 and IV-1, TdP was triggered by bradycardia and suppressed by pacing at 80 bpm. Although the association between bradycardia and gender remains unclear, we should pay attention to bradycardia, particularly in severe LQT2 patients.

In conclusion, we investigated multigenerational inheritance in a Japanese family with LQT2 with high penetrance.
Female LQT2 patients showed more severe phenotypes. Therefore, we recommend that clinicians should therefore treat female family members more cautiously, particularly after puberty, to prevent the occurrence of cardiac events.

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