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KCNQ1 and KCNH2 Mutations Associated with Long QT Syndrome in a Chinese Population

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Abstract

The long QT syndrome (LQTS) is a cardiac disorder characterized by prolongation of the QT interval on electrocardiograms (ECGs), syncope and sudden death caused by a specific ventricular tachyarrhythmia known as *torsade de pointes*. LQTS is caused by mutations in ion channel genes including the cardiac sodium channel gene SCN5A, and potassium channel subunit genes KCNQ1, KCNH2, KCNE1, and KCNE2. Little information is available about LQTS mutations in the Chinese population. In this study, we characterized 42 Chinese LQTS families for mutations in the two most common LQTS genes, KCNQ1 and KCNH2. We report here the identification of four novel KCNQ1 mutations and three novel KCNH2 mutations. The KCNQ1 mutations include L191P in the S2–S3 cytoplasmic loop, F275S and S277L in the S5 transmembrane domain, and G306V in the channel pore. The KCNH2 mutations include L413P in transmembrane domain S1, E444D in the extracellular loop between S1 and S2, and L559H in domain S5. The location and character of these mutations expand the spectrum of KCNQ1 and KCNH2 mutations causing LQTS. Excitement, exercises, and stress appear to be the triggers for developing cardiac events (syncope, sudden death) for LQTS patients with KCNQ1 mutations F275S, S277L, and G306V, and all three KCNH2 mutations L413P, E444D and L559H. In contrast, cardiac events for an LQTS patient with KCNQ1 mutation L191P occurred during sleep or awakening from sleep. KCNH2 mutations L413P and L559H are associated

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with the bifid T waves on ECGs. Inderal or propranolol (a beta blocker) appears to be effective in preventing arrhythmias and syncope for an LQTS patient with the *KCNQ1* L191P mutation.

Keywords

Long QT Syndrome; LQTS; cardiac arrhythmia; *KCNQ1*; *KVLQT1*; *KCNH2*; *HERG*; potassium channel; mutation; *torsade de pointes*; sudden death; ion channel; I_{Ks} , I_{Kr}

INTRODUCTION

The long QT syndrome (LQTS; MIM# 192500; 152427) is a cardiac disorder characterized by an abnormality in cardiac repolarization that leads to prolongation of the QT interval, T wave changes, and *torsade de pointes* (TdP) on the surface electrocardiograms (ECG) (Schwartz et al., 1975; Moss et al., 1991; Roden, 1998; Vincent et al., 1998; Zhang et al., 2000). LQTS causes syncope and sudden cardiac death, usually in the young. The incidence of sudden cardiac deaths in untreated patients approaches 50% over 10 years (Roden and Spooner, 1999). Arrhythmogenic syncope and sudden death often occur in association with acute physical, emotional or auditory arousal, or during sleep (Schwartz et al. 2001). The syncopal episodes were frequently misinterpreted as a seizure disorder. The prevalence rate of LQTS in the United States is estimated at 1 in 5,000 (Roden and Spooner, 1999), but the rate in China is not clear. Molecular genetic studies have established that LQTS is caused by mutations in several cardiac ion channel genes (reviewed by Wang et al., 2002). LQTS has been reported on chromosome 11q15.5 (LQT1), 7q35-36 (LQT2), 3p21 (LQT3), 4q25-27 (LQT4), 21q22 (LQT5), and 21q22 (LQT6). Five LQTS genes have been cloned or identified as the cardiac sodium channel gene *SCN5A* (LQT3) and potassium channel subunit genes *KCNQ1* (LQT1), *KCNH2* (LQT2), *KCNE1* (LQT5), and *KCNE2* (LQT6).

LQTS-causing mutations have been reported in patients and families from the Europe, North America, and Japan. Few genetic studies have been carried out with LQTS patients and families from China. In this report, we studied 42 LQTS families from China for mutations in *KCNQ1* and *KCNH2*, the two most common LQTS genes (Wang et al., 1996; Splawski et al., 2000). We identified four disease-causing mutations in *KCNQ1* and three in *KCNH2* in a Chinese population. The mutation findings were correlated to clinical phenotype.

METHODS

Identification and clinical evaluation of LQTS patients

LQTS patients were identified from medical clinics throughout China. Informed consent was obtained according to the standards established by the People's Hospital of Peking University and the United Hospital Committee on Clinical Investigations. Family members were evaluated by family history, physical examinations, and 12-lead electrocardiography. Historical data (the presence of syncope, number of syncopal episodes, age of onset of symptoms, and occurrence of sudden death) and the length of QTc were obtained. Phenotypic criteria used were as follows: (1) individuals without any symptoms and with QTc of ≤ 410 ms were classified as unaffected; (2) symptomatic individuals with QTc of ≥ 450 ms and asymptomatic individuals with QTc of ≥ 470 ms were classified as affected, and (3) symptomatic individuals with QTc of ≤ 440 ms and asymptomatic individuals with QTc between 410 and 460 ms were classified as uncertain (Schwartz et al., 1993).

DNA isolation and mutational analysis

Genomic DNA was isolated from peripheral blood lymphocytes using the DNA Isolation Kits for Mammalian Blood according to the manufacturer's instruction (Roche Biochemical, Inc.). The exons and exon-intron boundaries of *KCNQ1* and *KCNH2* were PCR-amplified and sequenced for identifying LQTS-causing mutations. PCR primers were designed as described (Wang et al., 1996; Splawski et al., 1998). Mutations were confirmed by cloning the PCR products into pBlueScript SK (+) using the T-vector cloning kit (Promega) and by sequencing several independent clones, or by RFLP (restriction fragment length polymorphism) analysis.

RESULTS

KCNQ1 mutations in the Chinese population

We characterized 42 families with LQTS from a Chinese population. We screened LQTS-causing mutations in *KCNQ1* and *KCNH2* with all probands with LQTS. As shown in Figure 1 and Table 1, four disease-causing mutations in *KCNQ1* were identified in four independent LQTS families.

The proband of kindred F2 contained a T to C change at nucleotide position 572 (572T>C) (Figure 1A). This mutation leads to substitution of a leucine residue by a proline residue at codon 191 (L191P) in the intracellular domain between transmembrane domains S2 and S3 of the *KCNQ1* channel. Mutation L191P was present in affected family members only, and was not present in unaffected family members or in 100 normal unrelated individuals (data not shown), suggesting that it is a pathogenic mutation. The proband in kindred F2 (individual III:1, Figure 1A) developed an episode of syncope while awakening in an early morning at the age of 29 years, and recovered from syncope shortly. A few hours later, she developed the second episode of syncope that lasted for 18s. Her QTc was 580 ms. After admitting to the hospital, she developed *torsade de pointes* and another round of syncope (19 seconds) that required cardioversion. X-ray, echocardiography, and blood chemistry were normal. The patient was prescribed with a beta blocker (Inderal, propranolol, 70 mg/day), and the medication appears to be effective because the patient has not developed syncope since 1999. The proband's father's ECGs showed QTc of 600 ms, inverted T waves at leads V1 to V5, and the U wave (Table 1), and he developed three episodes of syncope. Individual I:1 has QTc of 480–500 ms, and developed one episode of syncope. The paternal uncle (II:5, Figure 1A, F2) died suddenly at the age of 2 years (Table 1). Two other individuals in the family were also diagnosed with LQTS with QTc of 480 ms and 520 ms, respectively, but did not develop syncope (III:2 and III:3, Figure 1A, Table 1).

Mutational analysis in kindred F1 identified a T to C change at nucleotide position 824 (824T>C), which leads to substitution of a phenylalanine residue by a serine residue at codon 275 (F275S) (Figure 1A; Table 1). The F275S mutation is located in transmembrane domain S5. Mutation F275S co-segregated with affected family members only, and was not present in unaffected family members or 100 normal unrelated individuals (data not shown). The proband in kindred F1 (individual III:4, Figure 1A, F1) developed syncope in a crowded after-skiing gathering. ECGs showed QTc of 530 ms and detected *torsade de pointes* and ventricular fibrillation that required cardioversion. One day later, the patient died from ventricular tachycardia and ventricular fibrillation. Individual I:2 in the family also died from arrhythmia that was triggered by excitement.

The third *KCNQ1* mutation occurs in exon 6 and changes nucleotide 830C into T (830C>T), which results in substitution of the serine residue at codon 277 by leucine (S277L). This mutation was observed in LQTS patients in family F8 (Figure 1A), but not in normal individuals in the family and 100 normal controls (data not shown). Mutation S277L is a non-conservative

change and it is located in transmembrane domain S5. These results suggest that S277L is a pathogenic mutation. The proband in F8 (individual II:1, Figure 1A) died suddenly one year after enrolled in this study. The proband's mother also died suddenly. Exercises and excitement are the trigger for sudden deaths in the family (Table 1).

The fourth *KCNQ1* mutation also occurs in exon 6 and results in substitution of the glycine residue at codon 306 by valine (G306V) (Figure 1A, F4). Mutation G306V was present in another affected family member in kindred F4, but not in normal individuals in the family and 100 normal controls (data not shown). It is located in the pore region of the *KCNQ1* channel. The proband in F4 (individual II:6) developed syncope during exercises and excitements (Table 1).

In addition to the four novel disease-causing mutations, we also identified two other changes in *KCNQ1*: a C to T change in intron 11 of *KCNQ1* (IVS11+18C>T) in one of 42 patients and an A to G change at nucleotide position of 873 (873A>G or S291S) in another patient. The first change occurs in an intron and the second change is an unclassified variant that did not result in any amino acid substitution.

KCNH2 mutations in the Chinese population

In *KCNH2*, we identified three novel mutations: L413P in transmembrane domain S1, E444D in the extracellular loop between domains S1 and S2, and L559H in domain S5 (Figure 1B and Table 2). All three *KCNH2* mutations were observed only in the LQTS patients in corresponding families (Figure 1B), but not in the normal family members and 100 normal controls. These data provide genetic evidence that L413P, E444D, and L559H are mutations. Mutations L413P and L559H in families F21 and F20 are non-conservative changes in critical domains (S1 and S5, respectively) of the *KCNH2* channel. The proband in F21 developed syncope and *torsade de pointes* due to exercises and excitement (Table 2). The proband in F20 also developed syncope due to exercises and excitement (Table 2). The ECG patterns for the patients with *KCNH2* mutations L413P and L559H mutation are characterized by the typical bifid T wave on leads V2–V4 (Figure 2). E444D is a conservative amino acid substitution, and similar conservative mutations have been identified in *KCNQ1* (E261D, V310I) and in *KCNH2* (V630L) (<http://www.serum.dk/en/forskning/lqtsdb>). Both patients with *KCNH2* mutation E444D in kindred F3 developed syncope triggered by exercises and excitement (Table 2).

Finally, in one of 42 LQTS patients we detected a C to T polymorphism at the nucleotide position of 1467 (1467C>T) in *KCNH2* that does not result in any amino acid substitution (I489I) and appears to be a polymorphism (<http://pc4.fsm.it:81/cardmoc/>).

DISCUSSION

We have identified four *KCNQ1* mutations (L191P, F275S, S277L, G306V) and three *KCNH2* mutations (L413P, E444D, L559H) in seven of 42 Chinese families with LQTS. These data indicate that LQTS in the Chinese population is caused by similar genes to ones identified in the Caucasian and Japanese populations. All seven mutations appear to be novel, therefore, they expand the spectrum of *KCNQ1* and *KCNH2* mutations causing LQTS. Due to the sheer size of the Chinese population (1.4 billion people), the finding of LQTS mutations suggests that mutation studies and genetic testing for LQTS will benefit many individuals. Presymptomatic diagnosis will be particularly important for individuals from families with a history of sudden death.

The triggers of developing cardiac events (syncope, sudden death) for LQTS patients are under active investigation. Clinical characterization of the four LQTS families with *KCNQ1*

mutations suggests that the triggers of developing cardiac events for LQTS patients with *KCNQ1* mutations include both excitement/exercise/stress (mutations F275S, S277L, G306V), and sleep or awakening from sleep (mutation L191P). The triggering factors for cardiac events for the probands carrying *KCNH2* mutations L413P, E444D, and L559H are exercises and excitements. It has been reported that LQTS patients with mutations in the cardiac sodium channel gene *SCN5A* experience cardiac events during sleep or awakening from sleep (Schwartz et al., 2001). It is interesting to note that the LQTS patient with *KCNQ1* mutation L191P developed syncope while awakening in an early morning.

LQT1 and LQT2 are the two most common types of LQTS, as mutations in *KCNQ1* and *KCNH2* account for 42% and 45% of the identified LQTS mutations in North America, Europe, and Japan, respectively (Splawski et al., 2000). We, however, were able to detect *KCNQ1* or *KCNH2* mutations in only 10% (4/42) and 7% (3/42) of LQTS families in the Chinese population, respectively. The true prevalence rate of *KCNQ1* and *KCNH2* mutations in the Chinese population may be slightly higher due to our small sample size. Future studies with a large sample size of LQTS families will reveal the true prevalence rate of *KCNQ1* and *KCNH2* mutations in the Chinese population.

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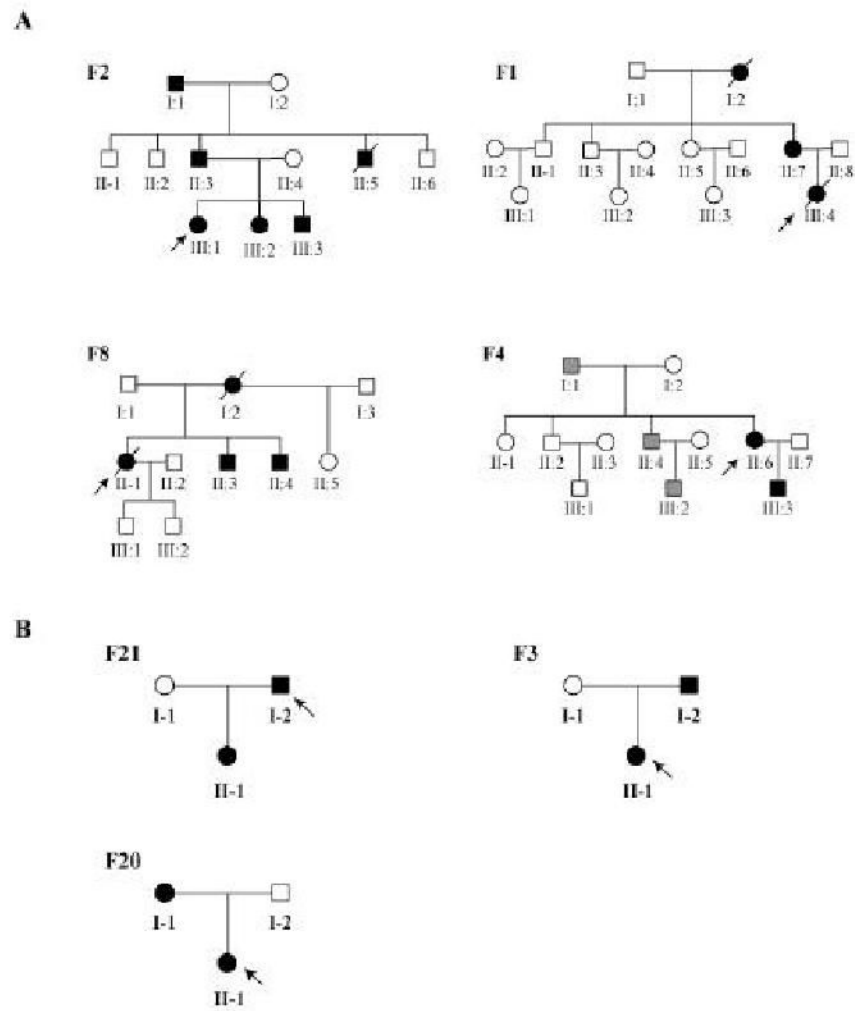
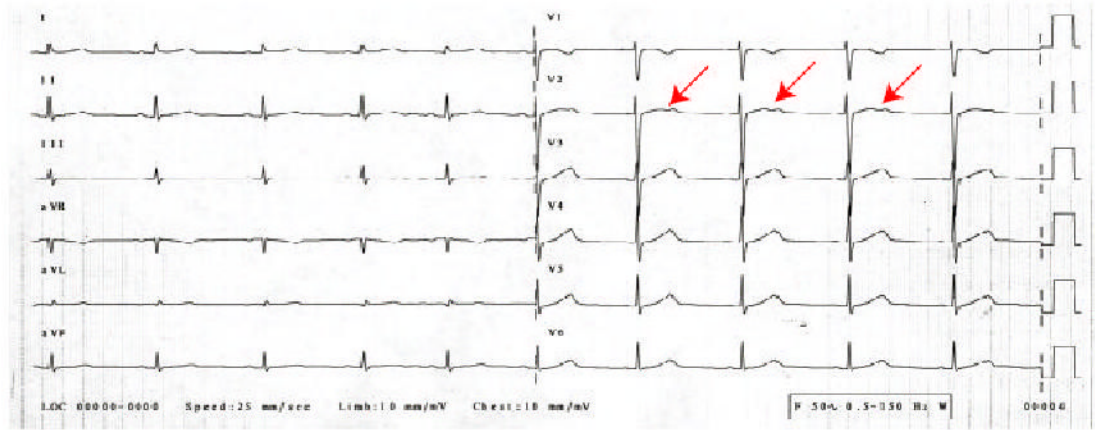
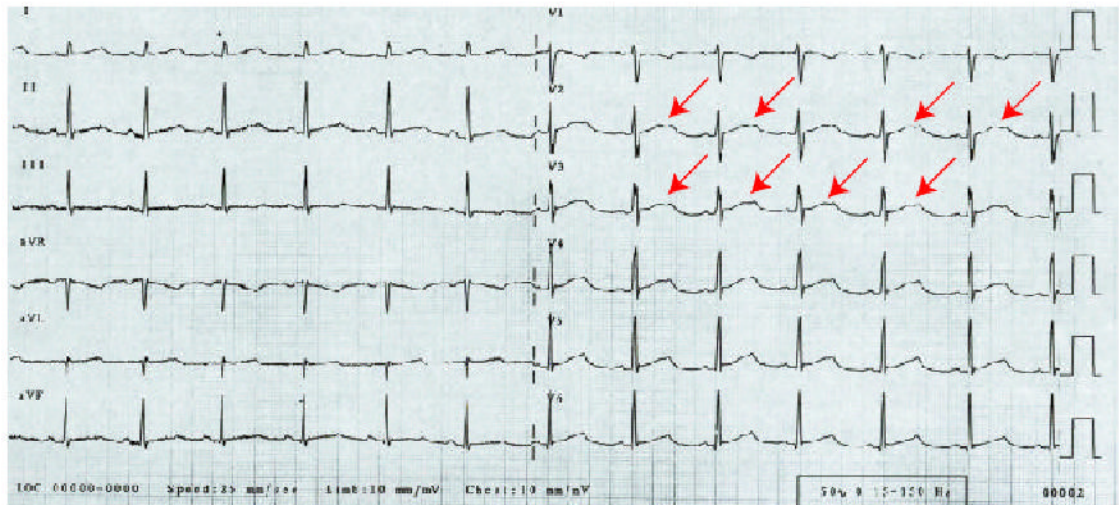


Figure 1. (A) Chinese families with *KCNQ1* mutations. Kindred F2, mutation L191P; F1, F275S; F8, S277L; F4, G306V. (B) Chinese families with *KCNH2* mutations. Kindred F21, mutation L413P; F3, E444D; F20, L559H. Males are denoted by squares and females are indicated by circles. Affected individuals are shown as filled symbols, normal individuals as empty symbols, and individuals with uncertain diagnosis of LQTS based on ECGs are stippled. The probands are indicated by arrows, and the deceased individuals are shown with “/”.

A



B

**Figure 2.**

Typical bifid T waves associated with *KCNH2* mutations in Chinese families with LQTS. (A) ECG for a patient with *KCNH2* mutation L413P in kindred F21. (B) ECG for a patient with *KCNH2* mutation L559H in kindred F20. The bifid T waves are indicated by arrows.

Table 1*KCNQ1* Mutations in Chinese LQTS Families

Kindred	Nucleotide Change*	Codon* Change	Protein Domain	Clinical Characteristics of Mutation Carriers	Trigger for Arrhythmias
F2	572T>C	L191P	Intracellular loop between S2 and S3	I:1, QTc 480–500 ms; syncope, 1 episode II:3, QTc 600 ms; syncope, 3 episodes; inverted T-wave (V1–V5), appearance of U-wave II:5, sudden death at age of 2 years III:1, proband: QTc 580 ms; TdP, syncope, 2 episodes (early morning sleeping) III:2, QTc 480 ms III:3, QTc 520 ms	Sleeping or Awakening from sleep
F1	824T>C	F275S	S5	I:2, QTc 470 ms; TdP; sudden death triggered by excitement II:7, QTc 580 ms; history of palpitation III:4, proband: QTc 530 ms; syncope; sudden death at age of 19 years triggered by skiing, stress, and excitement	Excitement Exercise Stress
F8	830C>T	S277L	S5	I:2, sudden death. II:1, proband, QTc 680 ms; sudden death II:3, QTc 470 ms; no symptom. II:4, QTc 470 ms; no symptom.	Exercise Excitement
F4	917G>T	G306V	Pore	I:1, QTc 540 ms; no symptom. II:4, QTc 600 ms; no symptom. II:6, proband, QTc 560 ms; syncope III:3, QTc 500 ms; no symptom	Exercise Excitement

* Positions of nucleotides and codons for *KCNQ1* are based on NM-000218 and AF000571, respectively. TdP, *torsade de pointes*.

Table 2*KCNH2* Mutations in Chinese LQTS Families

Kindred	Nucleotide Change*	Codon* Change	Protein Domain	Clinical Characteristics of Mutation Carriers	Trigger for Arrhythmias
F21	1421T>C	L413P	S1	I:2, QTc 440 ms; syncope, TdP II:1, QTc 480 ms; no symptom	Exercise, excitement
F3	1332G>T	E444D	Extracellular loop between S1 and S2	I:2, QTc 520 ms; syncope symptom	Exercise, excitement
F20	1676T>A	L559H	S5	II:1, QTc 570 ms; syncope I:1, QTc 480 ms; no symptom	Exercise, excitement

* Positions of codons and nucleotides for *KCNH2* are based on NM_000238. TdP, *torsade de pointes*.