Genetic analysis of Brugada syndrome and congenital long-QT syndrome type 3 in the Chinese

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ABSTRACT

Background: Brugada syndrome and congenital long-QT syndrome (LQTS) type 3 (LQT3) are 2 inherited conditions of abnormal cardiac excitability characterized clinically by an increased risk of ventricular tachyarrhythmias. SCN5A gene that encodes the cardiac sodium channel α subunit is responsible for the 2 diseases, and more work is needed to improve correlations between SCN5A genotypes and associated clinical syndromes. **Methods and Results:** Four patients diagnosed as having Brugada syndrome, 9 patients suspected to have Brugada syndrome, and 3 LQTS patients suspected to be LQT3 without mutations in KCNQ1 and HERG participated in the study. DNA samples from these patients were analyzed using direct sequencing. One patient with Brugada syndrome had 2 novel mutations, V95I and A1649V. The former was identified in the N-terminus of SCN5A and the latter was in the DIVS4/S5 linker of SCN5A. One patient suspected to have Brugada syndrome had a mutation, delF1617, in the DIIIS3/S4 linker of SCN5A. A novel mutation in the C-terminus of SCN5A, delD1790, was found in a patient with LQT3. No other mutations of SCN5A were found in the remaining patients. These 4 mutations were not detected in 50 unrelated control subjects. **Conclusions:** Two novel and a reported SCN5A mutations were found in Chinese patients with Brugada syndrome, and a novel SCN5A mutation was found in a Chinese patient with LQT3.

Key words: Brugada syndrome, cardiac sodium channel, long-QT syndrome, SCN5A gene mutation
DOI: 10.4103/0975-3583.64437

INTRODUCTION

Brugada syndrome and congenital long-QT syndrome type 3 (LQT3) are 2 allelic diseases associated with mutations in SCN5A gene that encodes the cardiac sodium channel α subunit. Brugada syndrome was first described as a clinical entity by Brugada and Brugada in 1992.[1] It is characterized by a typical electrocardiogram (ECG) pattern of ST-segment elevation in leads V_1 through V_3, a complete or incomplete right bundle-branch block (RBBB), and a high incidence of sudden cardiac death in patients with structurally normal hearts. The syndrome is believed to be responsible for at least 4% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts.[2] It is inherited in an autosomal dominant mode and SCN5A gene is an important gene to be linked to the disease. It has been agreed that patients with the syndrome who have experienced syncopal episodes or been resuscitated from cardiac arrest should receive an implantable cardioverter defibrillator (ICD).[3] However, controversies exist in the treatment of asymptomatic patients who might become symptomatic and develop sudden cardiac death resulting from the first attack of ventricular fibrillation (VF).

Long-QT syndrome (LQTS) is a cardiovascular disorder characterized by prolongation of the QT interval on the surface ECG and episodes of syncope and/or life-threatening cardiac arrhythmias, specifically of polymorphic ventricular tachycardia (VT) (torsade de pointes [TdP]). The molecular basis of LQTS is the prolongation of action potential duration resulting from defects in several ion channel genes. Mutations in KCNQ1 (LQT1) and HERG (LQT2) cause

defects in the delayed rectifier potassium currents,[4,5] whereas mutations in SCN5A (LQT3) cause a persistent cardiac sodium current.[6] LQT1 and LQT2 account for ≈90% of all genotyped patients. LQT3 is about 10–15% of all LQTS.[7] LQT3 has different features from LQT1 and LQT2. One of the most important clinical features is the basic therapy for LQTS, β-blocker, is less effective for LQT3, but mexiletine and flecainide might be beneficial.[8]

Determination of Brugada syndrome or LQT3-associated mutations can improve presymptomatic diagnosis, enable better follow-up of asymptomatic patients and facilitate choosing effective therapies earlier. In this study, we performed a genetic analysis in the translated region of SCN5A in the following Chinese patients: 4 patients diagnosed as Brugada syndrome, 9 patients suspected to have Brugada syndrome, and 3 LQTS patients suspected to be LQT3 without mutations in KCNQ1 and HERG. We identified 2 novel and a reported SCN5A mutations in patients with Brugada syndrome and a novel SCN5A mutation in a patient with LQT3.

SUBJECTS AND METHODS

Subjects

Four unrelated sporadic patients diagnosed as having Brugada syndrome, 9 unrelated sporadic patients suspected to have Brugada syndrome, and 3 unrelated patients suspected to be LQT3 without mutations in KCNQ1 and HERG confirmed by a previous research.[9] The patients and control subjects who participated in this study were all Chinese, all of whom provided informed consent, and were recruited from the Department of Cardiology, Peking University People's Hospital, China. Clinical diagnosis of Brugada syndrome was based on a consensus report in 2005,[3] namely, a typical ECG pattern characterized by a coved ST-segment elevation ≥ 2 mm in more than 1 right precordial lead (V_1 to V_3) at baseline in association with 1 or more clinical findings that include syncope, documented VF/polymorphic VT, or a family history of sudden cardiac death at age less than 45 years, and no other explanation for the ECG abnormality. The patients suspected to have Brugada syndrome were those having syncope, normal echocardiograms, and a coved ST-segment elevation < 1 mm (1 patient) or a saddleback ST-segment elevation (7 patient) or a normal ECG (1 patient). LQT3 was suspected on the basis of QTc (the QT interval corrected for heart rate) ≥ 460 ms and late onset of abnormal T wave, the presence of syncope or TdP, and excluding acquired LQTs.[10] Clinical and laboratory investigations included a review of medical history, a complete physical examination, 12-lead ECG, 24-h ambulatory electrocardiographic monitoring (Holter), transthoracic echocardiography, and blood biochemical test.

The control samples consisted of 50 unrelated healthy Chinese. None had Brugada-type or QT interval prolongation ECG findings, or a history of VT/VF or syncope. The protocol was approved by the Health Sciences Research Ethics Board of the Peking University.

Mutation analysis

Genomic DNA was prepared from the peripheral blood lymphocytes by standard methods. All 28 exons of the SCN5A gene were amplified by polymerase chain reaction (PCR) using primers designed by Wang *et al.*[11] The PCR products were amplified and sequenced on both strands by the dideoxynucleotide chain termination method with fluorescent dideoxynucleotides, using an ABI 377 automated sequencer. The obtained sequence data were compared with previously reported SCN5A cDNA sequence (GenBank Accession number GI: 37622906). The probands were analyzed for mutations first. If a proband was found to have a mutation, the patient's family members and control subjects would be investigated for the mutation in the exon where mutation occurs.

RESULTS

Patients diagnosed with Brugada syndrome

Four patients diagnosed with Brugada syndrome were all men presenting syncope. Each patient had a coved-type ST-segment elevation ≥ 2 mm in leads V1 to V_2 on the 12-lead ECG. RBBB was noted in 3 patients (patient 1, 2, and 4). A family history of sudden cardiac death at <45 years of age was noted in 1 patient (patient 2). All patients were recommended ICD, but none could afford the therapy. During follow-up, patient 2 was lost; patients 1, 3, and 4 were followed-up for 60, 7, and 24 months, respectively. No syncope occurred in 3 patients except that patient 4 had presyncope occasionally. Patient 1, 38 years old, had first syncope at the age of 33 years at rest in the night. He had a typical ECG of Brugada syndrome [Figure 1] and no abnormal physical condition and other significant laboratory abnormalities.

The 4 patients with clinical evidence of Brugada syndrome were sequenced for mutations in SCN5A. Two novel mutations were identified in patient 1. One heterozygous missense mutation was a G→A transition at nucleotide position 283 in exon 3 of SCN5A [Figure 2, upper panel] that led to the replacement of Valine by Isoleucine at codon 95 (V95I) in the N-terminus of the human cardiac sodium