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Case Report

Variable phenotype expression with a frameshift mutation of the cardiac sodium channel gene *SCN5A*

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ABSTRACT

Loss-of-function mutations in the cardiac sodium channel α-subunit gene *SCN5A* result in multiple inherited arrhythmic syndromes. This case report describes 2 unrelated probands carrying an identical *SCN5A* frameshift mutation, V1764fsX1786, who exhibited distinct clinical manifestations: progressive cardiac conduction defect (PCCD)/Brugada syndrome (patient #1) and idiopathic ventricular fibrillation (IVF) (patient #2). Using a whole-cell patch clamp technique, cells expressing V1764fsX1786 showed no observable Na^+ current. Therefore, a significant phenotypic overlap was found between IVF and PCCD/Brugada syndrome in the 2 probands with the V1764fsX1786, loss-of-function frameshift mutation of the cardiac sodium channel gene *SCN5A*.

1. Introduction

Loss-of-function mutations in the cardiac sodium (Na^+) channel gene have been implicated in Brugada syndrome, progressive cardiac conduction defect (PCCD), sick sinus syndrome, and idiopathic ventricular fibrillation (IVF) [1]. In the present study, we describe 2 unrelated index cases of PCCD/Brugada syndrome and IVF who share an identical 1-base deletion mutation of *SCN5A* resulting in a large truncation at the cytoplasmic C-terminal of the cardiac Na channel (V1764fsX1786). Despite carrying the non-functional allele, the 2 probands exhibit distinct clinical manifestations and electrophysiological properties. These results support the notion that the ultimate clinical manifestations of the cardiac sodium channelopathies are profoundly affected by many undetermined factors, including genetic variations of genes other than *SCN5A*.

2. Case report

2.1. Patient 1

A 47-year-old man had recurrent syncope, and his 12-lead electrocardiogram (ECG) demonstrated a complete right bundle branch block (QRS width 200 ms), left axis deviation, and the first degree of atrio-ventricular block (Fig. 1A). He subsequently underwent echocardiography, coronary angiography, and left ventriculography, none of which demonstrated any structural heart diseases. However, continuous ECG monitoring revealed an episode of sinus arrest for 4 s. A subsequent electrophysiological study (EPS) demonstrated a prolongation of the atrio-ventricular conduction time (A-H interval, 100 ms; H-V interval, 75 ms) and extension of sinus node recovery time (SNRT > 1500 ms), but neither sustained ventricular tachycardia (VT) nor ventricular fibrillation (VF) was induced by programmed electrical stimulation (up to 500/280/220/210 ms from the right ventricular apex). Based on these results, the patient was diagnosed with advanced atrio-ventricular block and sick sinus syndrome, and a pacemaker was implanted. Although he had no history of obvious VT or VF during the follow-up, he had palpitations during sleep at night, and coved-type Brugada-ECG findings

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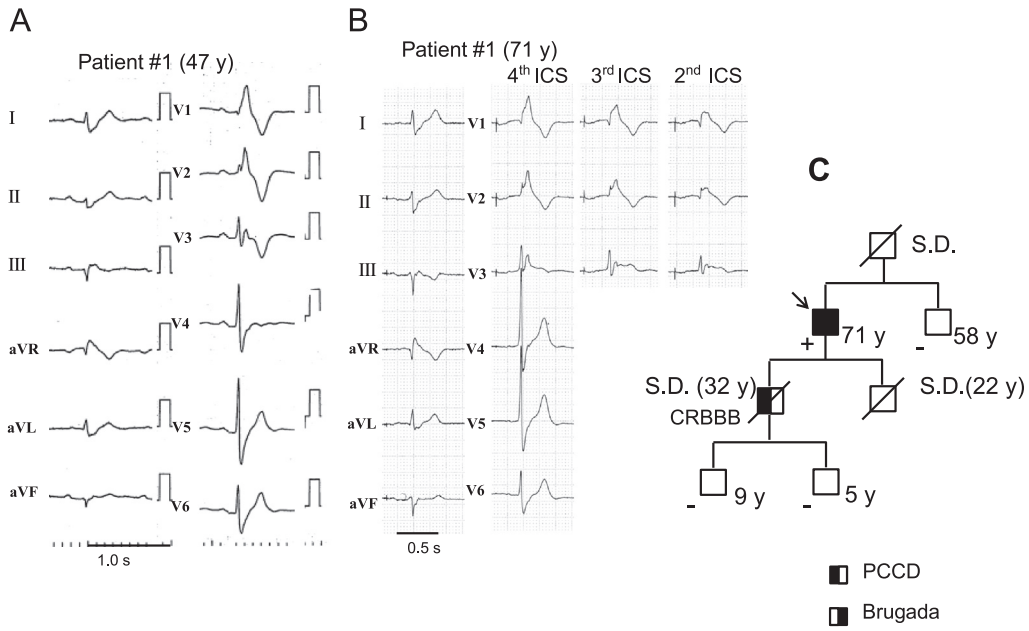

Fig. 1. A: 12-Lead ECG of patient #1 (proband) at 47 years of age with a complete right bundle branch block (QRS width 200 ms), left axis deviation, and the first degree of atrioventricular block. B: ECG recordings of 12-leads and V1-3 leads on higher inter-cordial spaces (ICS) of patient #1 at 71 years of age with atrial pacing and CRBBB and coved type ST-segment elevation (0.2 mV at V2 3rd ICS). **C**: Pedigree and phenotypes of the family members affected by Brugada syndrome and/or conduction disease. +, V1764fsX1786 carrier; −, non-carrier; S.D., sudden death; and y, years.

were observed (Fig. 1B). Moreover, his father (age uncertain) had suddenly died during sleep, as had both of his sons at 32 and 22 years old (Fig. 1C). Therefore, when he was 73 years old, a pacemaker was prophylactically upgraded to an implantable cardioverter defibrillator (ICD). In 2 years after implantation of the ICD, he had 1 episode of nonsustained VT (CL 380 ms, 4 s), but did not receive any appropriate ICD-shock therapy.

2.2. Patient 2

An 18-year-old high school student had syncope during marathon training in a physical education class and had cardiopulmonary resuscitation. VF was detected and defibrillated by automated external defibrillator (Fig. 2A), but his consciousness level did not fully recover (Japan Coma Scale III-300). He underwent tracheal intubation and cerebral hypothermia therapy immediately after hospitalization. Emergency coronary artery angiography was not performed because he had no coronary risk, lack of ST-T changes on ECG, and no asynergy or anomalous coronary artery origin on echocardiography. The patient recovered consciousness without any cerebral disorder after being rewarmed. He had no family history of sudden cardiac death. His 12-lead ECG at admission (Fig. 2B, right panel) showed no significant ST-T changes, Brugada-ECG findings, J-waves, or prolongation/abbreviation of the QT interval. No significant change in ECG was observed during exercise or during pharmacologic stress test (pilsicainide or isoproterenol). He had no abnormal physical or laboratory findings, and computed tomography and magnetic resonance imaging did not reveal any structural heart diseases such as arrhythmogenic right ventricular cardiomyopathy and dilated cardiomyopathy. Although the patient had episodes of spontaneous sinus bradycardia (heart rate 37/min) and atrio-ventricular block (Wenckebach type) (Fig. 2**C**), PCCD was excluded since he exhibited no obvious atrio-ventricular block or bundle branch block of ECGs, and his previous ECGs were normal (Fig. 2B, left panel). His signal-averaged ECG (SAECG) was positive, but T-wave alternans was negative. EPS showed that the atrio-ventricular conduction time was prolonged (AH interval, 91 ms; H-V interval, 93 ms) and programmed electrical stimuli at the right ventricular apex (up to 500/220/210 ms) induced VF. Based on these results, the patient was diagnosed with IVF and an ICD was implanted without any medications. The patient has not had any ICD-shock therapy during 2-year of follow up.

2.3. Genetic and functional analysis

Genetic testing was performed on these 2 unrelated probands and family members, demonstrating the same V1764fsX1786 frameshift mutation of the *SCN5A* gene (Fig. 3A). The same mutation was not found in the #1 patient's brother and 2 grandsons, or the #2 patient's mother. To functionally characterize the frameshift mutation, we performed whole-cell patch clamp recordings as previously described [2]. The mutant or wild-type Na^+ channel was heterologously expressed in tsA-201 cells, and cells expressing mutant Na^+ channel showed no observable sodium current (Fig. 3B) showing a compatible loss-of-function mutation.

3. Discussion

Mutations in the cardiac Na^+ channel α-subunit gene *SCN5A* cause several inherited arrhythmogenic syndromes such as long QT syndrome type 3 (LQT3), Brugada syndrome, PCCD, and sick sinus node syndrome. [3–7] Furthermore, loss-of- function mutations in *SCN5A* have been reported to be a disease gene for IVF [8]. Even with the same mutation (e.g. E1784K) of *SCN5A*, different phenotypes such as LQT3 and Brugada syndrome were observed [2]. PCCD and Brugada syndrome present significant overlap and can coexist in the same family and even in the same individual [9–11].

Here we identified, for the first time, 2 unrelated probands who carried the same *SCN5A* frameshift mutation, V1764fsX1786, but exhibited distinct clinical manifestations: PCCD/Brugada syndrome and IVF, suggesting overlap Na^+ channelopathies. V1764fsX1786 mutation causes an overlap phenotype between PCCD and Brugada syndrome [12,13]. As shown in Fig. 1, patient