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/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.

Keywords: Progressive cardiac conduction defect SCN5A Ventricular fibrillation Sudden cardiac death Electrophysiology

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: progressive cardiac 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...
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-like 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. 2C), 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...
#1 had severe conduction abnormalities, coved-type Brugada ECG, syncope attack, and significant family history of sudden cardiac death. It was not possible to find out whether his sons had the frameshift mutation, as they died suddenly during sleep at night in their 20s or 30s, which might have resulted from VF. Conversely, patient #2 had an episode of VF without any other inherited or structural abnormalities, and was thus diagnosed with IVF. However, the age-dependent increased QRS duration of his ECG, a prolonged H-V interval, and positive late potential of the SAECG were associated with conduction abnormalities. The timing of events were completely different for patient #1 and his family (during sleep) and patient #2 (during exercise), but they are consistent with the phenotype of each (Brugada syndrome or IVF).

PCCD (Lev or Lenègre disease) manifests as progressive prolongation of cardiac conduction (P wave, PR, and QRS intervals), and right or left bundle branch block, without ST segment elevation or QT prolongation. These ECG changes are often

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Fig. 2. A: Monitoring ECGs of patient #2 with ventricular fibrillation detected by AED. Electrical cardioversions were performed three times by AED before hospitalization. B: 12-Lead ECGs of patient #2 at 13 years of age and 18 years of age. QRS width age-dependently increased over 6 years. C: Sinus bradycardia and atrioventricular block (Wenckebach type) were recognized by Holter electrocardiogram. D: Pedigree and phenotypes of the family members affected by idiopathic ventricular fibrillation. +, V1764fsX1786 carrier; −, non-carrier; and y, years.

Fig. 3. A: A single nucleotide deletion (G) at position 5290 of the SCN5A locus results in a frameshift mutation: V1764fsX1786. B: Representative whole-cell Na⁺ current recordings from tsA-201 cells expressing wild type (WT) or mutant (V1764fsX1786) Na⁺ channels. Currents were recorded from a holding potential of −120 mV and stepped from −90 mV to +50 mV for 15 ms in 10 mV increments.
accompanied by an age-related degenerative process, in which fibrosis may affect the conduction system. In young people, the impaired Na\(^+\) channels do not cause severe conduction defect, but with age, an increase in fibrosis in association with the genetic defect may impair the propagation of impulses through the conduction system and reveal the PCCD phenotype [6]. Therefore, haploinsufficiency of SCN5A and aging have been implicated in PCCD [14] and a heterozygous mouse model (SCN5A\(^{+/-}\)) has demonstrated age-related conduction slowing and fibrosis qualitatively similar to that seen in the PCCD patients [15]. This is relevant to the Brugada syndrome since conduction slowing is progressively accentuated in the Brugada probands with SCN5A mutation compared with those without SCN5A mutation [16]. Conversely, the same mutations in SCN5A (e.g. G1406R) led to either PCCD or Brugada syndrome in a large French family [9]. As shown in Fig. 4, more than half of the SCN5A mutations in PCCD overlap with Brugada syndrome, SSS, and LQT3 [17,1]. PCCD often predominates in the elderly. Makita et al. recently reported that the age of onset of PCCD probands showed a wide-range distribution with 2 peaks in the 20s and 60s [18]; therefore, manifestation of PCCD due to SCN5A mutations might be an age-dependent fibrotic change.

The functional analysis of this V1764fsX1786 mutation is shown in Fig. 3B; no current was observed, indicating severe loss-of-function. Although we did not investigate the mechanisms of this complete reduction in Na\(^+\) current in this mutation, Herfst et al. [19] reported a similar frameshift mutation of SCN5A (5280delG, A1711fsX1786) in a large cardiac conduction defect family, demonstrating that the A1711fsX1786 mutation results in the translation into non-function channel proteins that fail to reach the plasma membrane. Furthermore, Meregalli et al. showed that Na\(^+\) current reduction by frameshift or nonsense mutations is predicted to be a complete reduction of peak Na\(^+\) current associated with the severity of conduction slowing such as longer PR interval and more symptoms [20]. However, disease severity among mutation carriers is highly variable, and the sodium channel subunit β4 (SCN4B) may be one of the potential genetic modifiers of conduction and cardiac sodium channel disease [21]. Therefore, phenotype manifestation in the loss-of-function sodium channel mutations could interact with many factors such as age, sex, and other modifying genes and proteins. A further genetic study of patients or family members is important for diagnosis and risk stratification for conduction slowing leading to sudden cardiac death.

4. Conclusion

A significant phenotypic overlap was found between IVF and PCCD/Brugada syndrome in 2 probands with the V1764fsX1786, loss-of-function frameshift mutation of the cardiac Na\(^+\) channel gene SCN5A.

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Disclosures

None.

Conflict of interest

None.

References


