Atrial fibrillation associated with Wolff-Parkinson-White syndrome in a patient with concomitant Brugada syndrome

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Introduction

Atrial fibrillation (AF) is most prevalent in cardiac arrhythmic disease. It may be the first presenting manifestation in certain cases, such as Brugada syndrome (BrS) and Wolff-Parkinson-White (WPW) syndrome. BrS is an inherited cardiac arrhythmic disorder characterized electrocardiographically by coved-type ST-segment elevation in the right precordial leads (V_1–V_3).[1] Patients with BrS are susceptible to ventricular tachycardia (VT) and consequently to sudden cardiac death (SCD). It is reported to be more common in Asia than in Western countries, with the estimated prevalence ranging from 1:1000 to 1:10000.[1] There are 20 genes associated with BrS, and *SCN5A* is the major causative one.[2] Implantable cardioverter-defibrillator (ICD) is the most effective therapy to prevent SCD, and quinidine, isoproterenol, and catheter ablation are also recommended to reduce the incidence rate of arrhythmic events.[1] WPW syndrome is the most common cause of preexcitation, and usually it is presented with supraventricular tachycardia and AF. Even if the WPW syndrome case is asymptomatic, it may also lead to SCD.[3] Because both disease forms could have similar symptoms, coexistence of BrS and WPW syndrome raises question about exact pathogenesis, possible interaction, related risk stratification, and therapy. In this report, by analyzing a male case with BrS and WPW syndrome with *paroxysmal* AF (PAF), we aim to explore this phenomenon in a deeper level and summarize the current research status.

KEYWORDS Brugada syndrome; Wolff-Parkinson-White syndrome; Atrial fibrillation; Genetics; Sudden cardiac death
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Case report

In 2004, a 37-year-old man (II-5) admitted to the hospital because of an 8-year palpitation (once a year) and recurrent palpitation in the last 4 months (3 times). The palpitation was not associated with exercise and emotion, and the longest one lasted over 14 hours. A representative electrocardiogram (ECG) at rest revealed WPW syndrome with a short PR interval and positive delta waves in leads I, II, aVL, and V_1–V_6 and negative delta waves in leads III and aVF (Figure 1A). One episode of wide QRS tachycardia with irregular RR intervals was initiated at rest. Certain beats, which were conducted over the normal pathway, were compatible with type 1 Brugada ECG in leads V_1 and V_2 (Figure 1B). The proband did not experience any episode of syncope or SCD, but since he had a positive family history of SCD and typical Brugada pattern ECG, he was diagnosed with BrS.

Physical examination showed an irregular heart rhythm. The results of the laboratory tests, chest radiography and echocardiography, and biochemistry tests were within the normal range. The transesophageal electrophysiology study (EPS) revealed orderly (1) normal function of the sinoatrial node and atrioventricular node; (2) antegrade right accessory pathways (APs) and atrioventricular reentry tachycardia (AVRT); and (3) inducible AF, which was spontaneously terminated after a short duration.

Radiofrequency catheter ablation (RFCA) was performed under a drug-free and unsedated state. Three right posterior APs, located at 7:30, 8:00, and 8:30 positions, respectively, were ablated. After the procedure, both antegrade and retrograde conductions disappeared, and cardiac tachycardia could not be induced in the right ventricular apex and atria. However, stimulation was not performed in the right

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KEY TEACHING POINTS

- We first report a rare case with a family history of sudden cardiac death, who suffered from Brugada syndrome, Wolff-Parkinson-White syndrome with multiple accessory pathways, and atrial fibrillation, and who has undergone a comprehensive medical evaluation and systematic treatment with long-term follow-up.
- Although limited literature is available and standard treatment protocol is not provided, the management of Brugada syndrome and Wolff-Parkinson-White syndrome in the patient with atrial fibrillation should generally include implantable cardioverter-defibrillator and radiofrequency catheter ablation.
- Our genetic screening in the family first discloses that *SCN5A* could be, at least partially, the culprit gene in this kind of scenario, and further underlying mechanism study and clinical intervention are warranted.

ventricular outflow tract to induce VT/ventricular fibrillation (VT/VF). Two days after the procedure, the ECG showed disappearance of delta waves and appearance of coved-type ST-segment elevation followed by negative T waves in leads V_1 and V_2 (Figure 2A). One month later, the follow-up ECG confirmed that WPW syndrome and AF were diminished, but a typical type 2 Brugada pattern in the fourth intercostal space and a type 1 Brugada pattern in the second intercostal space were observed (Figure 2B). A similar Brugada pattern is discovered in the ECG after 9 and 12 years (Figures 2C and 2D).

Figure 3A displayed the family pedigree of the index case. His elder brother (II-1) suffered from SCD during sleeping at the age of 39 years before the first admission of the proband. His asymptomatic younger brother (II-7) also had a spontaneous type 1 Brugada ECG pattern then (Figure 3B). However, both of them refused to receive an ICD. Nine years later, unfortunately, proband's youngest brother (II-7) also experienced SCD at night. Then, in 2013, the proband agreed to receive an ICD to prevent a lethal cardiac event. By screening all susceptible genes associated with BrS and WPW syndrome in this family, the *SCN5A*-R1193Q variant was found in the proband and his nephew (III-3, Figures 3A and 3C). After 12-year follow-up, the patient did not report any recurrence of palpitation, but still presents a type 1 Brugada ECG pattern. He has not received any antiarrhythmic drugs and has not experienced ICD discharge by far (Figure 3D). The lifestyle changes, as well as avoidance of inducible drug and fever, are recommended to the patient.

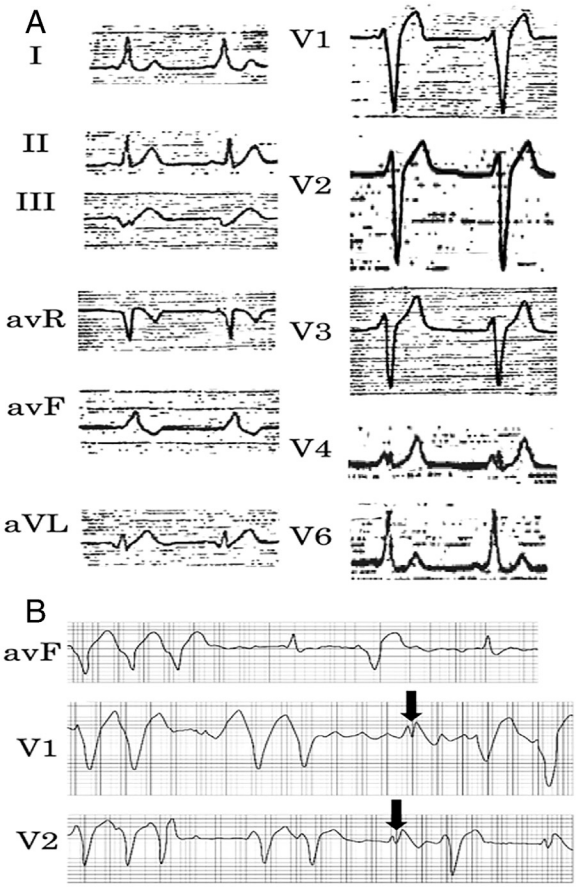

Figure 1 Proband's ECGs before ablation. **A:** Baseline ECG shows positive delta waves in leads I, II, aVL, and V_1–V_6 and negative delta waves in leads in leads III and aVF. **B:** One episode of atrial fibrillation in the presence of an accessory pathway recorded before ablation. Black arrows indicate concomitant type 1 Brugada ECG. ECG = electrocardiogram.

Discussion

Although the cases of BrS or WPW syndrome together with PAF have been reported in several medical literatures,[4,5] BrS with WPW syndrome has also been noticed around the world;[6–11] and a patient with the combination of all these and a comprehensive medical history with long-term follow-up is rare. AF is the most usual atrial arrhythmia in BrS, with an incidence between 6% and 53%,[12] because the substrate responsible for the development of ventricular arrhythmias may also contribute to atrial arrhythmogenesis. The presence of AF is considered as a marker of more advanced stage in BrS alone, since it has been related to a more vicious prognosis with a higher incidence of symptom and ventricular arrhythmias.[13,14] Kusano et al[13] demonstrated that syncopal episode, documented VF, and spontaneous type 1 ECG were observed in a larger percentage of patients with BrS with spontaneous AF than in those without AF. However, family history, *SCN5A* mutation, and VF induction during the EPS were not related to spontaneous AF episodes.[13] It is also well known that AVRT is the most

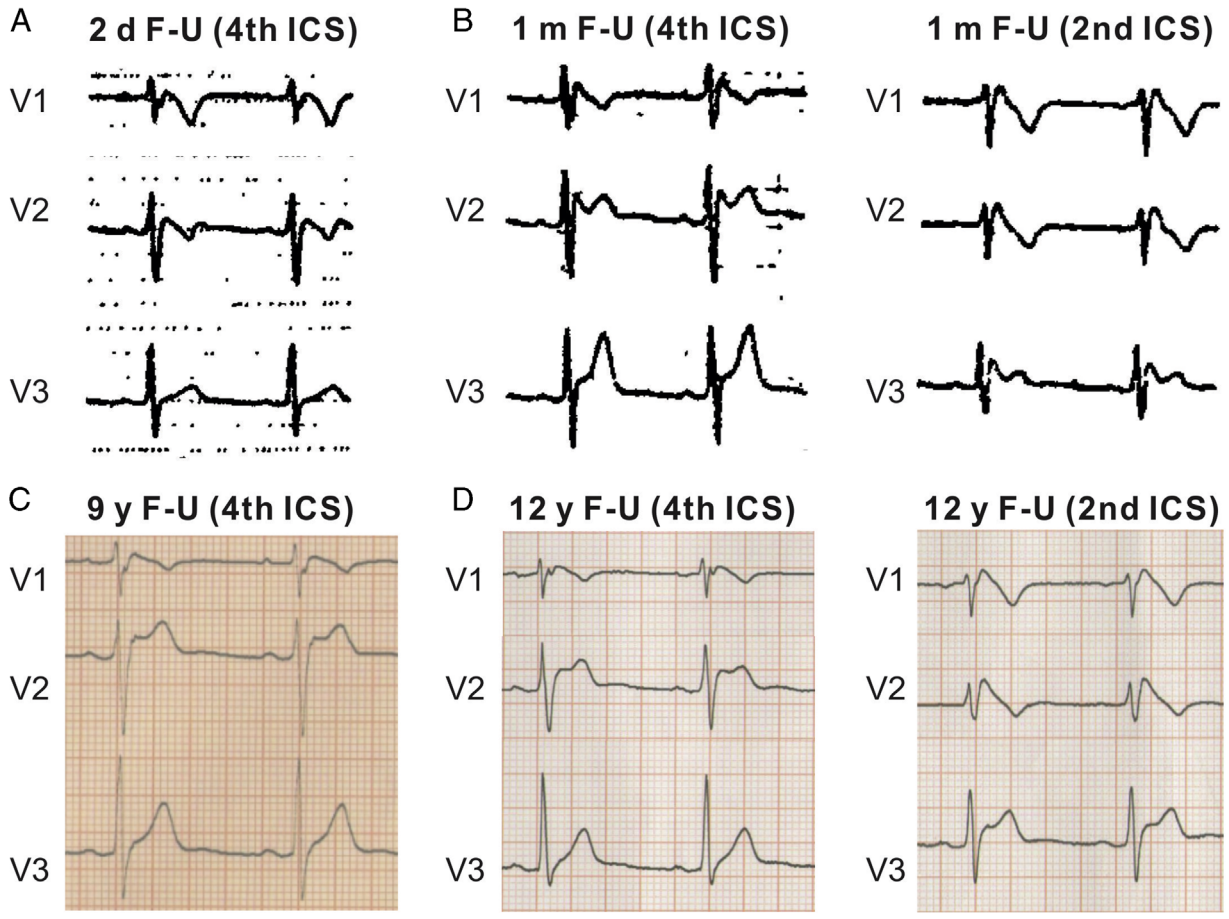

Figure 2 Follow-up ECGs of the proband after ablation. After radiofrequency catheter ablation, the regular ECG displays disappearance of delta waves and onset of coved-type ST-segment elevation followed by negative T waves in leads V_1 and V_2 in 2 days (**A**). One month (**B**) later, it shows a type 2 Brugada pattern in the fourth ICS and a typical type 1 Brugada pattern in the second ICS. A similar ECG pattern is discovered after 9 and 12 years (**C & D**). ECG = electrocardiogram; F-U = follow-up; ICS = intercostal space.

common arrhythmia in patients with WPW syndrome, and PAF develops in up to one-third of them.[15] Incident AF risk was higher in patients with WPW syndrome than in the control population (hazard ratio 1.55). However, the mechanism is not yet clearly understood. Several mechanisms including spontaneous degeneration of AVRT into AF, effects of APs on atrial architecture, and intrinsic atrial muscle vulnerability are responsible for the genesis of PAF in patients with WPW syndrome.[15] If an AP has a short anterograde refractory period, then rapid repetitive conduction to the ventricles during AF can result in a rapid ventricular response with subsequent degeneration to VF. As previously reported, the majority of PAF would be terminated after successful AP ablation procedures, which shows an important role of the AP itself in the initiation of PAF. We performed the EPS to confirm the presence of 3 APs and inducible orthodromic tachycardia, and the ablation procedure was performed. After the RFCA procedure, the patient presents no symptom and AF during 12-year follow-up, which indicates that AF in this case is associated with WPW syndrome, but not directly with BrS.

The first question raised from our case is which kind of arrhythmia is attributable to the patient's symptom. The diagnosis of PAF and WPW syndrome was determined from clinical manifestation and ECG, and the exact location of APs was confirmed by the EPS. The diagnosis of BrS was determined from the family history, clinical manifestation, and ECG. The patient had no other symptom except palpitation, and no VT was recorded. Only AF was definitely recorded during the onset of symptom in his available medical records. Although AVRT was not recorded during the onset of palpitation, we could not completely rule out its possibility because of the typical clinical manifestation and existence of obvious APs. Despite the patient having a type 1 Brugada ECG pattern, the symptom could barely be attributed to BrS because of the absence of a typical episode of syncope or SCD as well as the lack of evidence of malignant ventricular arrhythmia. In conclusion, it is most probable that the palpitation mainly resulted from PAF, which was anterogradely conducted via APs.

The second question is whether there exists a common pathological or genetic substrate. To date, 20 genes have been associated with BrS. The genetic background includes mutations in genes encoding sodium, calcium, and potassium channels as well as proteins affecting ion channels.[2] Mutations in *SCN5A* are the most frequent genotype of BrS

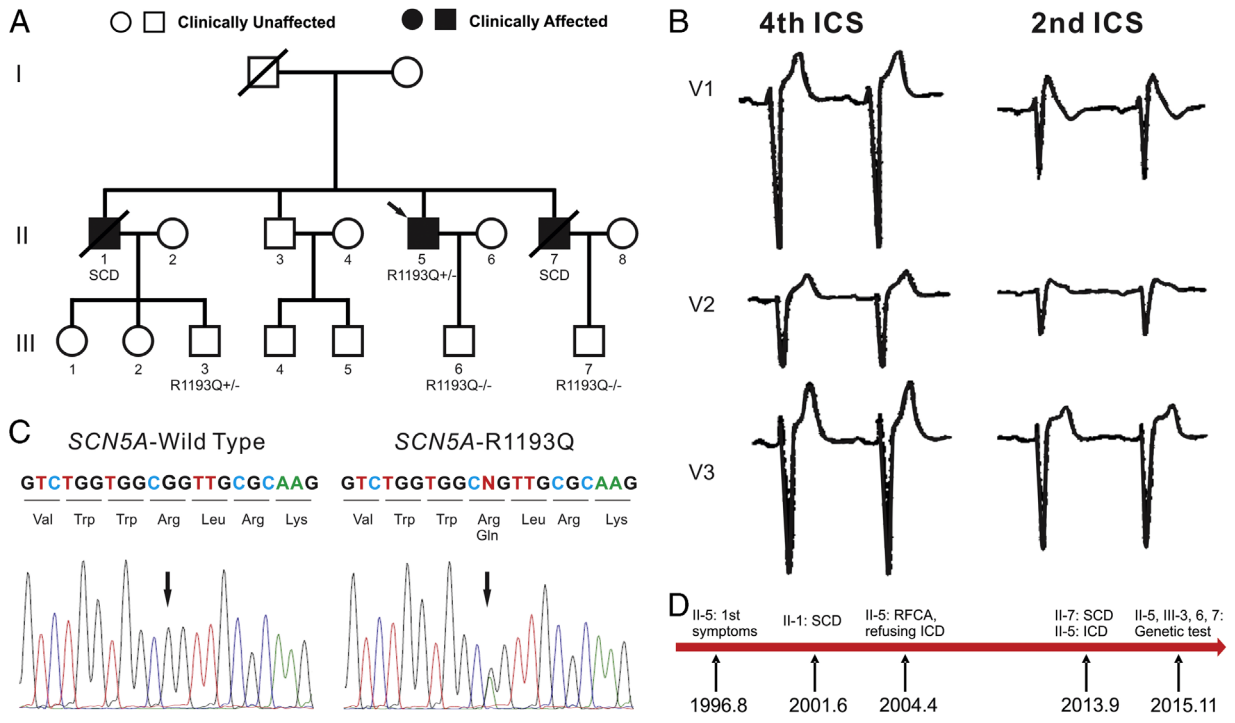

Figure 3 Summary of the genetic information and medical history of the family. **A:** Family pedigree of the index case. **B:** Baseline ECG of proband's youngest brother (II-7) in 4th ICS (left) and 2nd ICS (right) in 2004 who suffered from sudden cardiac death in 2013. **C:** DNA chromatogram of *SCN5A*-WT and *SCN5A*-R1193Q. The latter is discovered in the index case and his family member. **D:** Landmark events during follow-up for the family. ICS = intercostal space.

and account for about 80% of genotype-positive patients. AF has also been associated with mutations in both sodium and potassium channels.[13] Recently, the causative relation between *SCN5A* and AF is confirmed not only by direct gene sequencing in small families but also by the large-scale genome-wide association (GWAS) study presented at Heart Rhythm 2016 (37th Annual Scientific Sessions). In the vast majority of cases, WPW syndrome has no clear familial involvement. In this manner, WPW syndrome is inherited as a simple or isolated trait of preexcitation. Syndromic presentations of WPW syndrome account for a minority of inherited forms of preexcitation and include congenital Ebstein anomaly (chromosome 11q); familial hypertrophic cardiomyopathy (sarcomeric mutations); Hypertrophic cardiomyopathy (HCM), WPW syndrome, and conduction system disease (PRKAG2 syndrome); metabolic myopathies and storage disorders (Pompe disease, Danon disease, and tuberous sclerosis); and mitochondrial syndromes (Leber hereditary optic neuropathy and RNA mutations). Unfortunately, no linkage between *SCN5A* and WPW syndrome has ever been reported by far. With the information available, WPW syndrome is presented only in one case in this family, but we still performed meticulous genetic testing including AF, BrS, and familiar WPW susceptible genes. As per a previous report, the global frequency of R1193Q (OMIM 600163.0023) is 0.0124. Although it was considered a mutation in Caucasian (0.00) and Black (0.00) population, R1193Q is a polymorphism in Asian population because of its prevalence in those populations, such as Chinese (0.05–0.08), Vietnamese (0.08), and Japanese (0.02). A functional study has already proved it to be a pathogenic variant for BrS and long QT syndrome;[16,17] however, whether it is related to AF or WPW syndrome in the index case is still unclear. To our knowledge, it is the first one to unmask the genetic background in this kind of scenario. Given the lack of formal evidence of association from the clinical observation or genetic study, we could reasonably deduce that WPW syndrome and BrS are more likely 2 separate disorders in our case.

The most important question is how this patient should be risk stratified and treated. In our experience, the optional management strategy should be decided according to the symptom and clinical judgment: if the patient has WPW syndrome, eliminate APs with RFCA; if the patient has symptomatic BrS, implant an ICD for primary prevention, and quinidine and ablation of the right ventricular outflow tract could also be the secondary choices; and if AF is continued, drug or interventional therapy should be considered accordingly. Based on the current evidence, even though he has a family history of SCD and spontaneous type 1 Brugada ECG pattern, this patient has a relatively low risk of arrhythmic events. Lifestyle changes and avoidance of predisposing factors are the primary therapeutic strategy to reduce the susceptibility of arrhythmic events. RFCA is a preferred option in our case to eliminate the symptoms and terminate WPW syndrome. By far, RFCA has a reported success rate of 95% with a recurrence rate of $<5\%$.[18] PAF in this case was related to WPW syndrome, since it is eliminated after successful ablation of APs. Because of a strong family history of SCD, a dual-chamber ICD was eventually implanted in the index case.

By reviewing literature, including the present patient, we found that only 8 similar cases have ever been reported.[6,16] Seven patients are men (87.5%) with age between 23 and 58 years (mean age 37.0 ± 12.9 years). Most patients present the first symptom with palpitation (75.0%) and few with aborted SCD (25.0%). But none of them complains of syncope. Interestingly, our case is the first one with a clear family history of SCD. There is no particularly concentrated location of APs, but we are the first one to report multiple APs in the index case. VF is induced during the EPS in 85.7% of the cases who underwent ventricular stimulation. RFCA is performed in half of the cases; ICD is implanted in 7 of them; and no medication is administered in all.

In the present report, we described a case of AF associated with WPW syndrome in a patient with concomitant BrS. The diagnosis of BrS was supported by spontaneous type 1 Brugada ECG recorded at rest and during PAF as well as by a positive family history of SCD. The case received RFCA for WPW syndrome in 2004 and ICD for the primary prevention of SCD in 2013. No ECG of WPW syndrome, paroxysmal supraventricular tachycardia (PSVT), and AF, or symptom of syncope and aborted SCD has been documented since ablation, and ICD is not discharged during the follow-up period. Meanwhile, we have data (unpublished) indicating that the *SCN5A*-R1193Q rare variant could play a relatively important role in Asian BrS cases, and so deeper and broader basic and clinical researches about this rare variant are definitely needed in the future.

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