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CASE REPORT

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# SCN5A p.P1725L variant that showed ventricular fibrillation and recurrent pericarditis, and a family member with sick sinus syndrome

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## Abstract

**Background:** In Brugada syndrome (BrS), the arrhythmogenic substrate is suggested to be located in the epicardial surface of the right ventricle outflow tract. Postmortem examinations of BrS described epicardial and interstitial fibrosis, the causes of which remain unclear.

**Case presentation:** We present a family in whom the proband is a case of aborted sudden cardiac death from ventricular fibrillation (VF) without spontaneous Brugada-type electrocardiogram, and his mother underwent pacemaker implantation due to sick sinus syndrome. The proband showed recurrent acute pericarditis two consecutive years before the VF episode. These events occurred twice in mid-spring, the same season when the lethal arrhythmia occurred.

**Conclusions:** This case suggests a possibility in the pathogenesis of epicardial fibrosis of BrS that the RVOT lesions induced by *SCN5A* mutations have not only fibrotic characteristics but also in some patients, inflammatory characteristics which may be manifested as repeated mild pericarditis or occult pericarditis.

**Keywords:** Brugada syndrome, Sick sinus syndrome, SCN5A mutation, Acute pericarditis, Ventricular fibrillation

## Introduction

Mutations in the *SCN5A* gene, which encodes the sodium channel protein α subunit, $Na_V1.5$, result in various phenotypes, such as long QT syndrome type 3 (LQT3), Brugada syndrome (BrS), sick sinus syndrome (SSS), familial atrial fibrillation, conduction disease, dilated cardiomyopathy (DCM), and left ventricular non-compaction [1, 2]. The concept of *SCN5A*-related diseases is used to summarize these diseases. Of these phenotypes, LQT3 and BrS are major phenotypes; the former is derived from gain-of-function mutations and the latter from loss-of-function mutations. Different phenotypes depend on different genotypes; however, as shown in the E1784K variant, both phenotypes are sometimes present in the same genotype family, or in the same person, for which the term *SCN5A* overlap syndrome is used, [1, 3]. Thus, other factors such as sex, age, drugs, and other conditions that modify the phenotypes are speculated. Furthermore, approximately 70% of *SCN5A* variants reported so far are considered functionally uncertain significance according to the descriptions of ClinVar [4].

Here, we present a family in which the proband is the case of near sudden cardiac death from ventricular fibrillation (VF) without spontaneous Brugada-type electrocardiogram, together with pacemaker implantation due to sick sinus syndrome in his mother. Genetic testing showed that three family members had a heterozygous *SCN5A* p.P1725L variant [5]. Both VF and SSS appear to be due to loss-of-function mutations. However, this mutation has already been reported in a person who has LQT, which is supposed to be a gain-of-function

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mutation [6]. Furthermore, the proband showed recurrent acute pericarditis in two consecutive years before the VF episode. In BrS, the arrhythmogenic substrate is suggested to be located on the epicardial surface of the right ventricular outflow tract (RVOT). Postmortem examinations of BrS described epicardial and interstitial fibrosis, the causes of which remain unclear, but epicardial inflammation may be involved [7]. *SCN5A*-linked DCM cases have been reported in over 20 different *SCN5A* mutations, including p.C335R and p.D1275N [8, 9].

## Case report

A 40-year-old man was admitted to our hospital with a cardiopulmonary arrest in March. The patient returned home after finishing work, and half an hour after eating breakfast, he collapsed due to cardiopulmonary arrest. When the ambulance arrived, ECG revealed ventricular fibrillation. Defibrillation was attempted twice, and VF turned out to have a pulseless electrical activity just before arrival at our hospital. Immediately, extracorporeal membrane oxygenation (ECMO) was commenced; blood pressure soon recovered and sinus rhythm was restored. Coronary angiography was normal, and ECG showed non-specific ST-T changes. With hemodynamic stabilization, ECMO and ventilator were removed. ECG on the 30th day when he had a fever of 38 °C showed coved-type ST elevation in leads V1, suggesting that the underlying disease was BrS (Fig. 1a–c).

The patient's mother had sick sinus syndrome and had undergone pacemaker implantation at the age of 66 years. Her ECG results are shown in Fig. 1d. The patient's sister did not show any ECG abnormalities so far. We examined the *SCN5A* gene of this male patient, his mother, and his sister, revealing that all three members had *SCN5A* mutation at c.5174 from C to T (Fig. 2b, c). This mutation

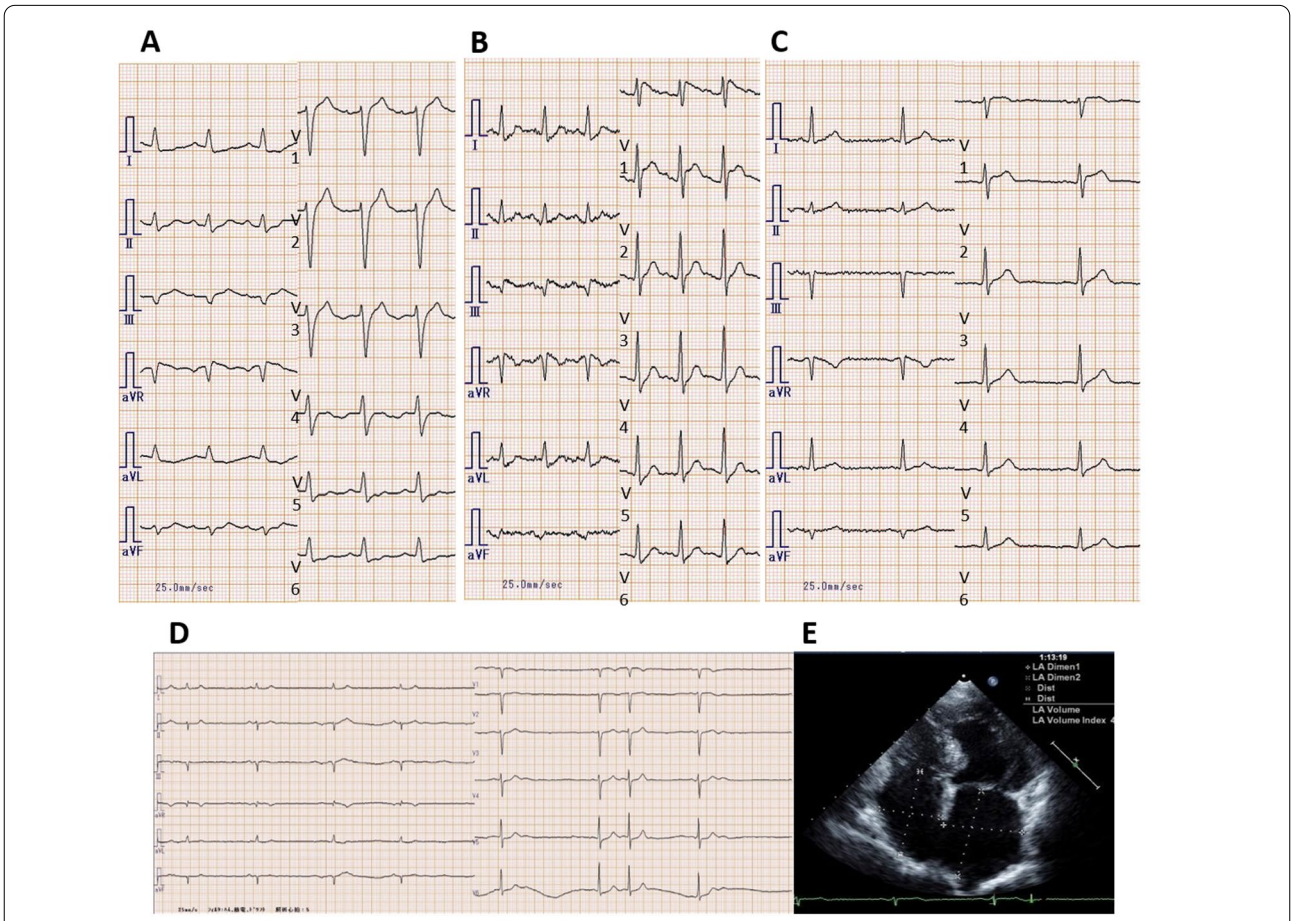


**Fig. 1** Electrocardiographic changes after ventricular fibrillation. **a** ECG two days after ventricular fibrillation. **b** ECG 30 days after ventricular fibrillation showing typical coved-type ST elevation in lead V1. **c** ECG five months after ventricular fibrillation. **d** ECG and echocardiography of the patient's mother just before pacemaker implantation, showing no Brugada-type ST elevation. **e** Echocardiography showed mild left ventricular hypertrophy

causes the substitution of proline at the 1725 amino acid site with leucine, which has already been reported to result in a phenotype of LQT.

Interestingly, the patient had a history of two episodes of pericarditis, with both episodes occurring during the spring season, the same season as when he sustained cardiopulmonary arrest. The two episodes of pericarditis occurred 3 years and 2 years, respectively, before the VF episode. During both episodes, he experienced chest pain with ST elevation in the precordial leads and a fever of 37.6 °C (Fig. 3). On the second admission, the C-reactive protein level was elevated to 9.1 mg/dL (Table 1). Viral antibody levels did not elevate, and any other etiologies of these pericarditides could not be found. Magnetic resonance imaging showed no late gadolinium enhancement; however, there was mild pericardial effusion. The time course of the C-reactive protein level is shown in Fig. 3a.

After 8 months of treatment, the patient's disturbance of consciousness due to VF episode had not fully recovered, but gradual improvement of consciousness was observed.

## Discussion

This family belongs to *SCN5A*-related disease. The sodium channel α subunit, which is encoded by *SCN5A*, is composed of 2016 amino acids, which contain four domains (D1–D4). Each domain is further composed of six transmembrane segments. Between the 5th and 6th segments, there is a pore region composed of extracellularly extending amino acids named P-loop (Fig. 2a) [10]. Our patient's mutation site p.P1725L is located in the pore region of domain 4. Patients with pore region variants have a poorer prognosis than those with non-pore region variants [11].

The proband belongs to Brugada syndrome because the ECG which was taken one month after the lethal arrhythmic episode when he had a fever of 38 °C showed typical type 1 Brugada-like ST elevation in V1 of height 2 mm with a coved-type morphology. All ECGs taken during the four years since the first pericarditis did not show Brugada-type ECG except for only this ECG which was taken one month after the VF episode. Therefore, much consideration should be taken for judging the baseline diseases of any VF patients. There are several papers that report ECG findings that do not meet the criteria of BrS, even with lethal arrhythmia that appertains to *SCN5A*-related disease [4]. Akai et al. reported that the S1710L mutation in *SCN5A* showed the same phenotype, and interestingly, the position of these mutations was also located in the pore region of domain 4, as in our case [12].

The mother of the proband had sick sinus syndrome without ECG changes of BrS and without long QT. BrS predominantly occurs in men; the ratio of affected men to women is approximately 9:1. Aizawa et al. reported in a follow-up study of 25 familial BrS patients that ten out of 12 female patients developed sick sinus

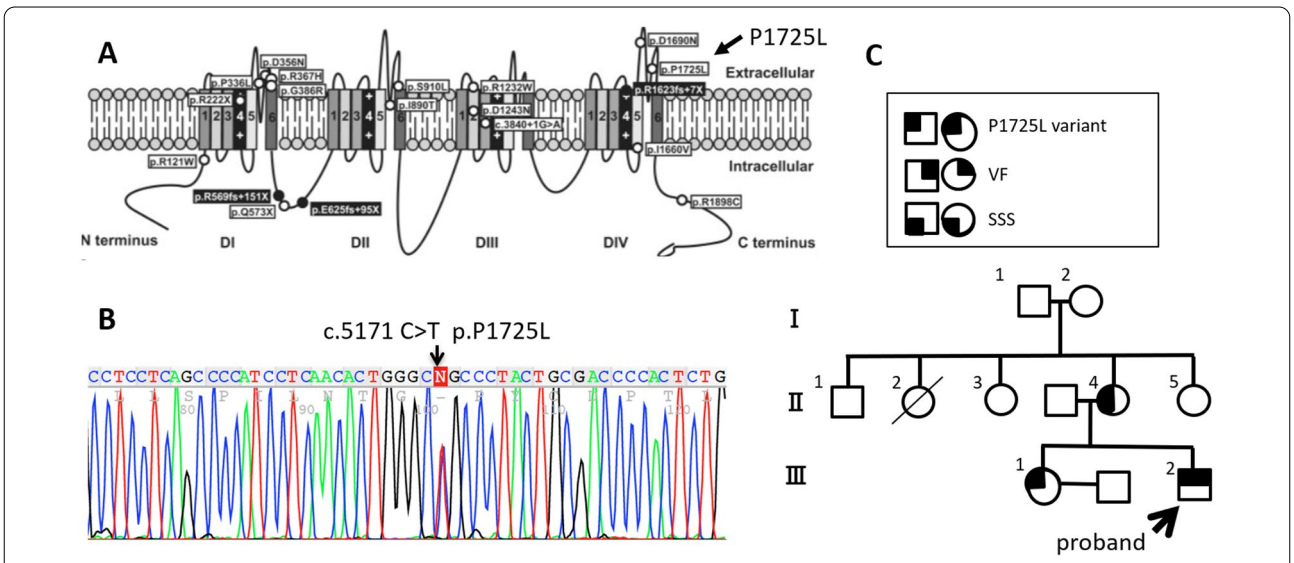


**Fig. 2** Pedigree of the affected family and genetic testing of *SCN5A* gene revealing c.5174C>T, p.P1725L variant. **a** Topographic schema of sodium channel type 5 α-subunit. The mutation site p.P1725L is located in the pore region of domain 4 (figure was cited from Selga et al. [10]). **b** Sanger's method shows three individuals had heterogeneous c.5174C>T (CCG > CTG), p.P1725L variant, which was previously reported in a patient with long QT syndrome. **c** The arrow indicates the proband, and the solid left upper quarter indicates members with P1725L variant, the solid right upper quarter indicates members with VF, and the solid left lower quarter indicates members with SSS. Oblique lines indicate dead persons.

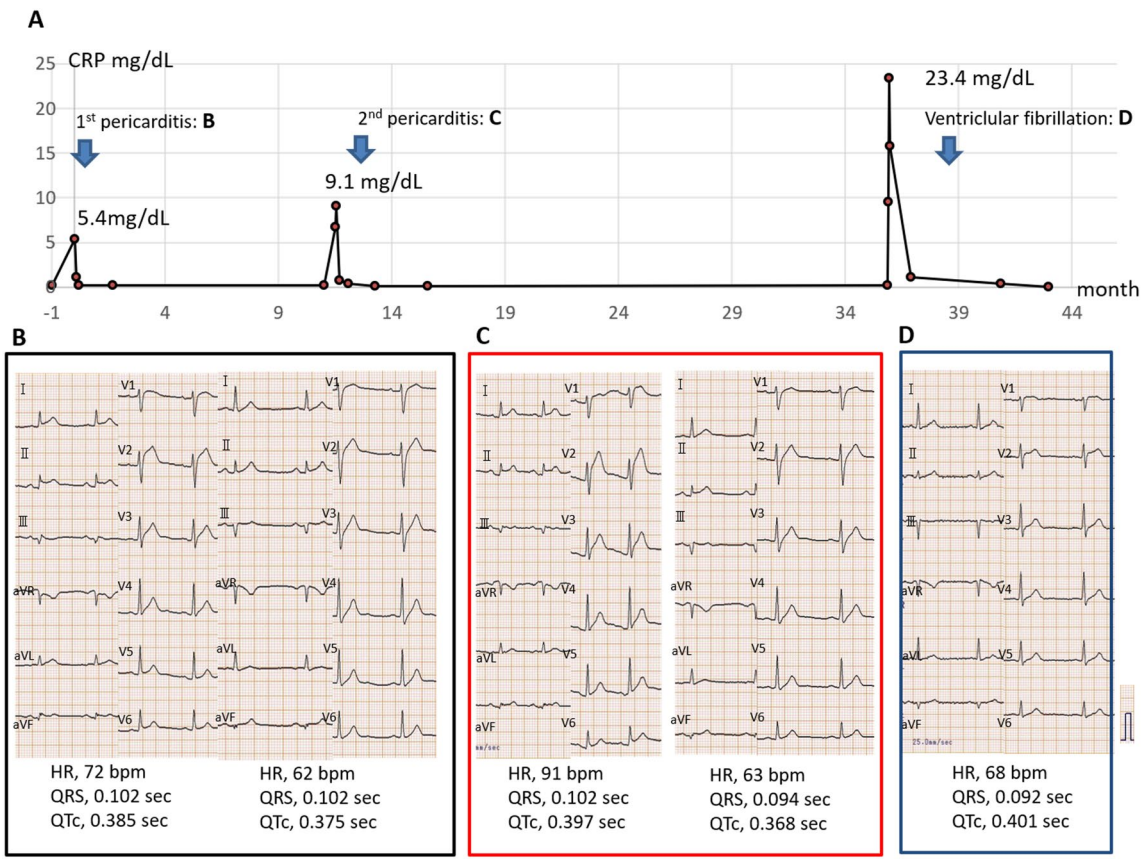


**Fig. 3** Time course of C-reactive protein level in preceding two episodes of pericarditis with corresponding ECG changes. **a** Time course of C-reactive protein level in preceding two episodes of pericarditis and ventricular fibrillation episode. **b** ECG of first pericarditis, in which left side shows the ECG on admission day, and the right side shows that on 6th day. **c** ECG of second pericarditis, in which left side shows the ECG on admission day, and the right side shows that on 6th day. **d** ECG of five months after ventricular fibrillation

syndrome, the so-called *SCN5A* overlap syndrome, and none of the 13 male patients developed sick sinus syndrome [13]. Thus, SSS is a sex-dependent phenotype in *SCN5A* mutations, as observed in the family presented here.

Genetic testing showed that the three family members had a heterozygous *SCN5A* p.P1725L variant. Both VF and SSS appear to be due to loss-of-function mutations. However, this mutation has already been reported in a person who has LQT, which is supposed to be due to a gain-of-function mutation [6]. These overlap syndromes of combined loss-of-function and gain-of-function mutations are known to exist in some variants. Makita et al. found overlapping cases and showed a high prevalence of the E1784K mutation in *SCN5A*. Of the 41 E1784K carriers, 93% had LQT3, 22% had BrS, and 39% had sick sinus syndrome. A negative shift in the inactivation and enhanced tonic block are common biophysical properties observed among *SCN5A* mutations with the LQT3/BrS overlapping phenotype [3].

According to the descriptions of ClinVar, this *SCN5A* p.P1725L variant is classified as being of uncertain significance [4]. However, approximately 70% of *SCN5A* variants that have been reported to date are considered functionally uncertain according to ClinVar, which is based on the ACMG/AMP guidelines in 2015. The main reason for this uncertainty is the lack of electrophysiological studies for each variant. In 2021, Ishikawa et al. disclosed the electrophysiological properties of 55 *SCN5A* variants by the patch-clamp method, which had been considered to be of uncertain significance, in which, however, this p.P1725L variant was not included [14].

The most curious issue in our patient was that he had a history of two episodes of acute pericarditis 2 and 3 years, respectively, before this lethal arrhythmic event. In our case, acute pericarditis occurred twice in mid-spring, the same season when lethal arrhythmia occurred. To our knowledge, a similar case of pericarditis cannot be found in the literature. Several studies conducted on BrS have shown that the substrate of the VF is located on

**Table 1** Laboratory findings at second pericarditis

| | | | | | |
|---|---|---|---|---|---|
| *Blood* | | | CRP | 9.1 | mg/dL |
| WBC | 12,900 | /μL | BNP | 13.1 | pg/mL |
| Neutrophil | 69.4 | % | *Serolory* | | |
| Lymphocyte | 21.1 | % | Antinuclear antibody | < 20 | |
| Monocyte | 8.8 | % | Rheumatoid factor | 0 | IU/ml |
| Eosinophil | 0.5 | % | Complement 3 | 119 | mg/mL |
| RBC | 524 | $\times 10^4$/μL | Complement 4 | 29 | mg/mL |
| Hemoglobin | 15.7 | g/dL | CH50 | 46 | U/ml |
| Hematcrit | 46.5 | $\times 10^4$/μL | *Microbe antibody*[†] | | |
| Platelet count | 11.8 | g/dL | Chlamydia Pneumoniae IgG | 0.21 | pg/mL |
| *Blood chemistry* | | | Chlamydia Pneumoniae IgA | 0.47 | pg/mL |
| Total protein | 6.8 | g/dL | Influenza virus type A | 16 | x |
| AST | 22 | IU/L | Coxsackievirus type B1-4 | < 4 | x |
| ALT | 55 | IU/L | Echovirus type 6, 9 | 16 | x |
| CK | 110 | IU/L | Poliovirus type 1–3 | 4 | x |
| CKMB | 11 | IU/L | RS virus | 4 | x |
| Troponin T | Negative | | Adenovirus type 7, 8 | < 4 | x |

*ALT* alanine aminotransferase, *AST* aspartate transaminase, *BNP* B-type natriuremic peptide, *CK* creatine kinase, *CKMB* creatine kinase MB, *CRP* C-reactive protein, *RBC* red blood cell count, *WBC* white blood cell count

[†] Almost all microbe antibodies levels did not change after 2 weeks

the epicardial site of the RVOT, and the ablation of this site can eliminate malignant arrhythmia [7, 15]. Nademanee et al. described six autopsy examinations and six biopsy specimens of RVOT before ablation, which showed increased amount of collagen in the subendocardial space, and fibrosis in the epicardial cardiomyocytes [7]. None of these changes were detectable using recently developed imaging technologies. Hence, several reports suggest that BrS is a structural heart disease or cardiomyopathy where the arrhythmogenic substrate is in the RVOT [1, 9]. Possible explanations for the relationship between VF and recurrent pericarditis, in this case, are as follows: (1) recurrent pericarditis occurred coincidentally, and (2) RVOT lesions induced by *SCN5A* mutations have not only fibrotic characteristics but also inflammatory characteristics, which manifested in our patient as repeated mild pericarditis or occult pericarditis, although there is no conclusive evidence for this. This case, therefore, suggests the possibility that RVOT lesions observed in BrS would have been formed from mutation-related fibrosis, and in some cases, from pericarditis-related inflammation.

## Conclusion

A family with *SCN5A* mutations (p.P1725L) with interesting phenotypes is presented. Several distinctive features are pointed out in this family: (1) the proband, a 40-year-old male with VF did not show spontaneous Brugada-type electrocardiogram; (2) his mother showed sick sinus syndrome which is a predominant female phenotype in patients with family histories of BrS; (3) this mutation has been reported in patients with long QT syndrome, which is caused by gain-of-function mutation, but phenotypes this family show are due to loss-of-function mutations; and (4) the proband experienced recurrent pericarditis twice before lethal arrhythmia. In BrS, the arrhythmogenic substrate is suggested to be located in the epicardial surface of the RVOT. Postmortem examinations of BrS revealed epicardial and interstitial fibrosis, the causes of which remain unclear. This case shed a suggestion on the pathogenesis of epicardial fibrosis in BrS that the RVOT lesions have not only fibrotic characteristics but also in some patients, inflammatory characteristics, which may be manifested as repeated mild pericarditis or occult pericarditis.

#### Abbreviations

LQT3: Long QT syndrome type 3; BrS: Brugada syndrome; SSS: Sick sinus syndrome; DCM: Dilated cardiomyopathy; VF: Ventricular fibrillation; RVOT: Right ventricular outflow tract; ECMO: Extracorporeal membrane oxygenation.

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#### Author contributions

HY conceived and designed the case study and drafted the manuscript. CI, HY, MH, and TK managed the patient. NY performed genetic testing and check the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**
Not applicable.

## Declarations

**Ethical approval and consent to participate**
Written informed consent before genetic testing was given.

**Consent for publication**
All data generated are anonymized and written informed consent for publication was given.

**Competing interests**
The authors declare no conflict of interest for this article.

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## Publisher's Note