Case Report

Ventricular Fibrillation in a Family with Short QT Syndrome Type 2 Carrying a Heterozygous *KCNQ1*-V141M Variant

Fumie Takechi, MD[1)], Koichi Kato, MD, PhD[2)], Takeru Makiyama, MD, PhD[3)], Seiko Ohno, MD, PhD[2, 4)], Masashi Kabasawa, MD, PhD[5, 6)], Hiroko Morishima, MD, PhD[1)], Yasutaka Kawasoe, MD, PhD[1)], Yoshitomo Okajima, MD, PhD[1)], Kozo Matsuo, MD, PhD[5)], Minoru Horie, MD, PhD[2)], and Shigeru Tateno, MD, PhD[1, 7)]

[1)] Department of Pediatrics, Chiba Cerebral and Cardiovascular Center, Ichihara, Japan
[2)] Department of Cardiovascular Medicine, Shiga University of Medical Science, Otsu, Japan
[3)] Department of Community Medicine Supporting System, Kyoto University Graduate School of Medicine, Kyoto, Japan
[4)] Department of Bioscience and Genetics, Cerebral and Cardiovascular Center, Suita, Japan
[5)] Department of Cardiovascular Surgery, Chiba Cerebral and Cardiovascular Center, Ichihara, Japan
[6)] Department of Cardiovascular Surgery, Chiba, Kaihin Municipal Hospital, Chiba, Japan
[7)] Department of Pediatrics, Chiba Kaihin Municipal Hospital, Chiba, Japan

Short QT syndrome (SQTS) is an inheritable cardiac electrical disease presenting both atrial and ventricular arrhythmias associated with abnormally short QT intervals on electrocardiograms (ECGs). SQTS is mainly associated with mutations of the genes encoding three different cardiac potassium channels. Among them, type 2 SQTS (SQT2) can be caused by gain-of-function of *KCNQ1*, resulting in accelerating ventricular repolarization. Several studies reported that patients with SQT2 bearing the *KCNQ1* c.421G＞A: p.V141M variant occasionally suffered from atrial fibrillation or bradycardia but rarely developed ventricular arrhythmias, and thus the variant has been considered as benign. However, when we observed an SQT2 family with the *KCNQ1* p.V141M variant, one of the family members had developed ventricular fibrillation. The proband was referred to our hospital due to severe bradycardia (atrial standstill) and short QT intervals at the age of two and received a pacemaker implantation (PMI) using epicardial ventricular leads. The proband's father also underwent a PMI at the age of 20 due to sick sinus syndrome. Genetic testing, performed to investigate familial bradycardia, identified a heterozygous *KCNQ1* p.V141M variant in the proband and the father. Since the PMI, the father had been stable until at the age of 42 when he had a syncope due to ventricular fibrillation (VF). The VF was successfully terminated by an automated external defibrillator, and an implantable cardioverter-defibrillator was implanted. This is the first reported case of a patient with SQT2 bearing the *KCNQ1* p.V141M variant showing lethal ventricular arrhythmia.

Keywords: fetal bradycardia, short QT, sick sinus syndrome, ventricular fibrillation, ICD

Introduction

The short QT syndrome (SQTS) is an inheritable cardiac electrical disease characterized by remarkably shortened QT intervals which creates electrical substrates for atrial and ventricular arrhythmias. Though it was first reported by Gussak et al. in 2000,[1)] its natural history and risk stratification remain unclear due to its rarity. Though six genes have been reported causative of SQTS, it mainly results from gain-of-function mutations in the potassium channel genes. They are classified into three subtypes, SQT1, SQT2 and SQT3, depending on

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Corresponding author: Fumie Takechi, MD, Department of Pediatrics, Chiba Cerebral and Cardiovascular Center, 575 Tsurumai, Ichihara-shi, Chiba 290–0512, Japan
E-mail: fumie_t_1121@yahoo.co.jp
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the associated genes, *KCNH2*, *KCNQ1*, and *KCNJ2*, respectively.[2–4)]

Among these three genes, *KCNQ1* encodes the alpha-subunit of slowly-activating delayed rectifier potassium channel (I_{Ks}). To date, six *KCNQ1* variants have been reported in SQT2: p.V307L[2)], p.V141M,[5)] p.I274V,[6)] p.F279I,[7)] p.R259H,[8)] and p.A287T.[9)] Patients, except those bearing the p.V141M variant, often show lethal arrhythmias. In contrast, the phenotypes of SQT2 caused by the p.V141M variant differ from the others in that most patients occasionally suffer from atrial fibrillation (AF) or severe bradycardia but rarely develop ventricular arrhythmias.[5, 10–12)]

We herein report an unusual case of a family bearing the *KCNQ1* p.V141M variant. The proband showed early onset bradycardia, and the proband's father developed ventricular fibrillation (VF) in addition to long-term sick sinus syndrome (SSS). Our observation questions the classification of p.V141M as a benign variant and requires reconsideration of the therapeutic strategy in the treatment of patients bearing this variant.

Case 1: Proband

A two-year-old male was referred to our hospital to indicate the necessity of a pacemaker implantation (PMI). The following measurements were taken at this visit: height, 87.4 cm; weight, 12.4 kg; heart rate, 50 beats per minute (bpm); and blood pressure, 81/49 mmHg. He showed no objective findings of heart failure. There were no audible rales nor cardiac murmurs. His chest X-ray showed an increased cardiothoracic ratio (CTR) of 62% without pulmonary congestion (Fig. 1A). Upon reviewing his birth history, at the gestational age of 24 weeks, he presented bradycardia with a heart rate of 80 bpm, and by 35 weeks, his heart rate decreased to 55 bpm. He was diagnosed with SSS and patent ductus arteriosus (PDA) at birth. His father also underwent a PMI at the age of 20 due to bradycardia that had been occurring since infancy.

His 12-lead electrocardiogram (ECG) (Fig. 2A) showed atrial standstill with junctional rhythm at a rate of 50 bpm and short QT intervals (QTc: 308 ms by Bazett formula and 315 ms by Fridericia formula). His Holter monitoring showed that total heart beats were 69,445 beats per day with a minimum heart rate of 29 bpm and a max R-R interval of 3.04 second. His transthoracic echocardiography showed that the left ventricular ejection fraction was within normal range (68%) but the left ventricular end-diastolic volume increased to 193% of the normal values. His computed tomography with contrast materials revealed a small PDA with the narrowest portion with a diameter of <1 mm. The shunt flow of the PDA was clinically negligible, and we concluded that the persistent bradycardia caused cardiomegaly. An electrophysiological study along with a PMI was planned under general anesthesia.

During the operation, an intravenous injection of atropine sulfate induced a narrow QRS tachycardia. Its R-R intervals were irregular, with a range from 100 to 200 bpm, and no P waves nor atrial fibrillation waves

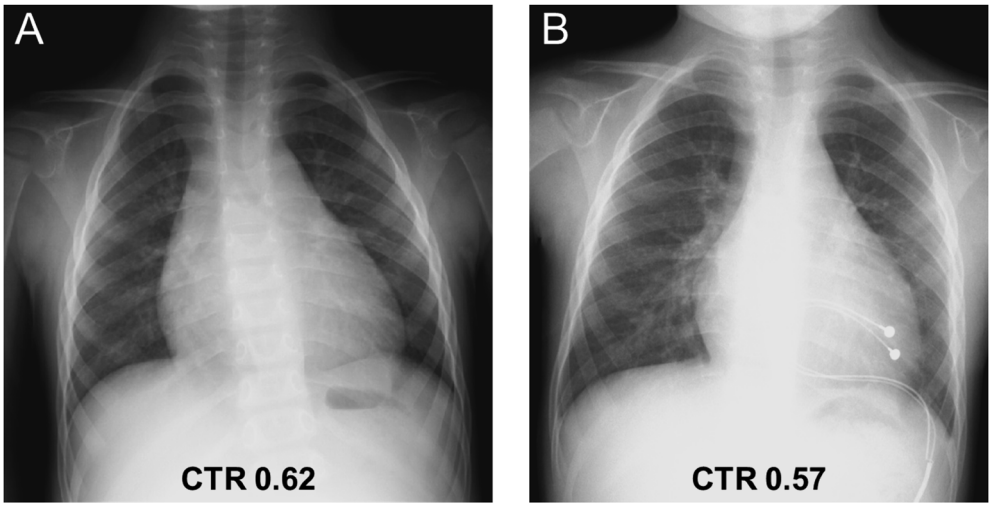

Fig. 1 Chest X-ray of the proband
A: Before pacemaker implantation. B: After pacemaker implantation. CTR, cardiothoracic ratio.

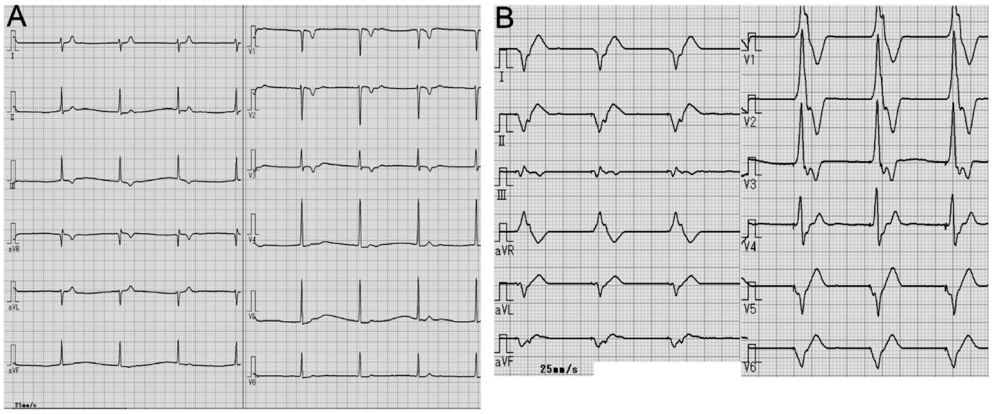

Fig. 2 Electrocardiogram (ECG) of the proband
A: An ECG recorded at our hospital showed junctional rhythm at a rate of 50 bpm and short QT-intervals (QTc: 308 ms by Bazett formula and 315 ms by Fridericia formula). B: An ECG after pacemaker implantation. All beats were ventricular pacing. ECG, electrocardiogram.

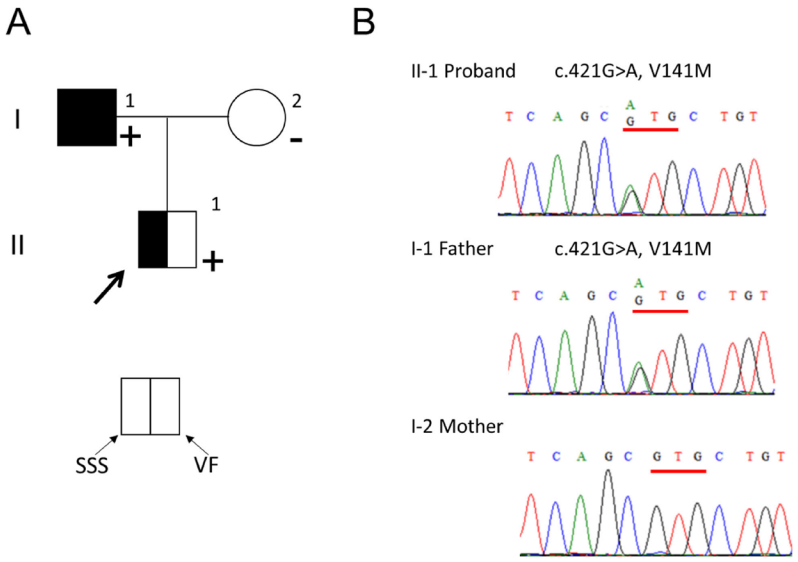

Fig. 3 Genetic analysis
A: A pedigree of the family with SQTS. The arrow depicts the proband; +, variant carrier; −, non carrier. B: Electropherograms of the Sanger sequence. A nucleotide substitution of G to A was observed in the proband and his father. SQTS, short QT syndrome.

were detected, indicating a diagnosis of junctional tachycardia (data not shown). Under the left thoracotomy for the PMI, we couldn't obtain any atrial electrograms and observed no atrial contractions (i.e., atrial standstill). Maximum output of electrical stimulation failed to pace the atrium, thus only ventricular leads were sutured at left ventricular apex. The pacing mode was VVI, and lower rate was programmed at 80 bpm. After the PMI, cardiomegaly improved; the CTR decreased to 57% (Fig. 1B). The amount of ventricular pacing was 99%, and none of his own beats were detected by a 12-lead ECG after the PMI (Fig. 2B). The proband is now 7 years old and presents no ventricular arrhythmias thus far.

Genetic Analysis

Genetic studies were approved by the Medical Ethical Committee of the Shiga University of Medical Science (IRB reference number G2011-128), and informed consents were obtained while preserving the anonymity of the patients. After obtaining informed consents, we performed a genetic analysis of the proband for investigation of familial bradycardia and short QT intervals

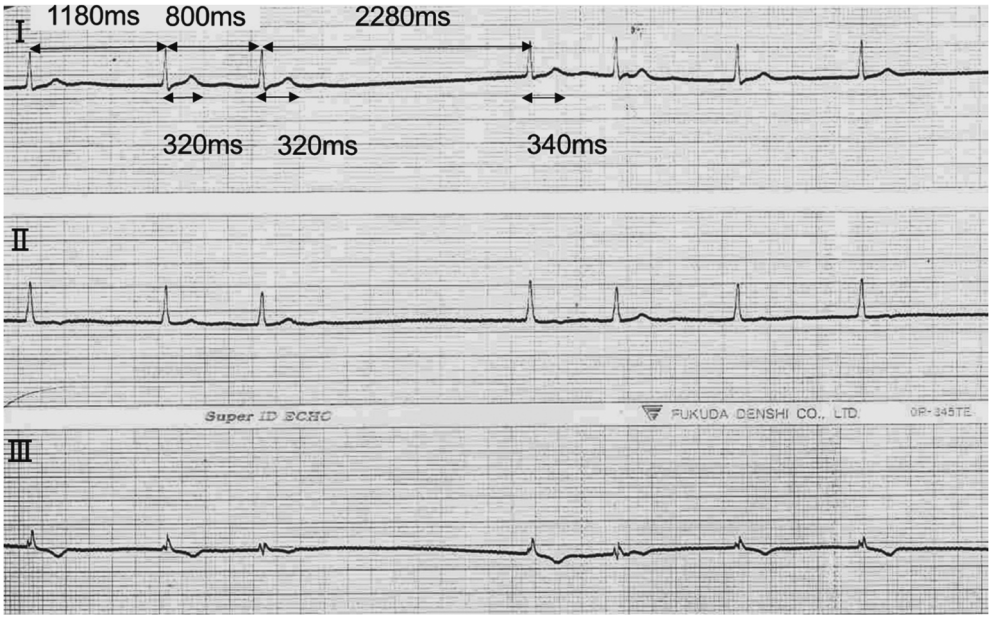

Fig. 4 Electrocardiogram of proband's father at 18 years old
The QT intervals (average values of three beats) were short (QTc: 293 ms by Bazzett formula and 302 ms by Fridericia formula).

using a gene panel test targeting 60 arrhythmia-related genes, HaloPlex Custom Kits (Agilent, Santa Clara, CA, USA). As a result, a *KCNQ1* heterozygous missense variant c.421G＞A:p.V141M (rs199472687), located in the transmembrane segment 1, was detected. The variant was confirmed by Sanger methods, and his father was also found to carry the same variant by Sanger sequencing (Fig. 3). It was not identified in the proband's asymptomatic mother (Fig. 3), and it was not identified in the general population (gnomAD v.2.1.1.).

Case 2: Proband's Father

The proband's father was shown to have bradycardia and diagnosed with multifocal atrial tachycardia in his infancy. At the age of eight, an electrophysiological study revealed atrial standstill, and at the age of 20, he underwent a transvenous PMI. The ventricular lead was located at right ventricular apex. His previous ECG obtained at the age of 18 showed SSS with irregular junctional rhythm and very short QT intervals (QTc: 293 ms by Bazett formula and 302 ms by Fridericia formula; Fig. 4). He underwent a genetic analysis triggered by his son's PMI (result as above).

After the PMI, he had been asymptomatic and ventricular arrhythmias were not documented. The pacing mode was VVI, and lower-rate was programmed at 50 bpm. The amount of his ventricular pacing was about 20%, and based on his rate histogram, his heart rate didn't exceed 130 bpm often. However, at the age of 42, he had a syncopal attack and collapsed on exercise. He was resuscitated by an automated external defibrillator (AED), and the ECG trace stored in the AED showed VF (Fig. 5A). Intracardiac ECG stored in his pacemaker also showed ventricular tachy-event before the shock (Fig 5B). When he was transferred to our hospital, he was conscious and stable (pulse rate: irregular at 66 bpm; and blood pressure:136/78 mmHg). His height and weight were 161 cm and 105 kg, respectively (BMI 40.5). No rales nor cardiac murmurs were audible. His 12-lead ECG showed atrial standstill with irregular and slow junctional beats with occasional ventricular pacing. The QT intervals were 325 ms by Bazett formula and 319 ms by Fridericia formula measured at junctional beats (Fig. 5C). His computed tomography with contrast materials did not detect any significant coronary arterial stenosis, and his blood examination was void of abnormal electrolytes and myocardial damages. Since his VF was not associated with correctable conditions such as cardiac ischemia and electrolyte disturbances, he received an implantable cardioverter-defibrillator (ICD). In the past two years since the implantation, no ICD shocks were discharged.

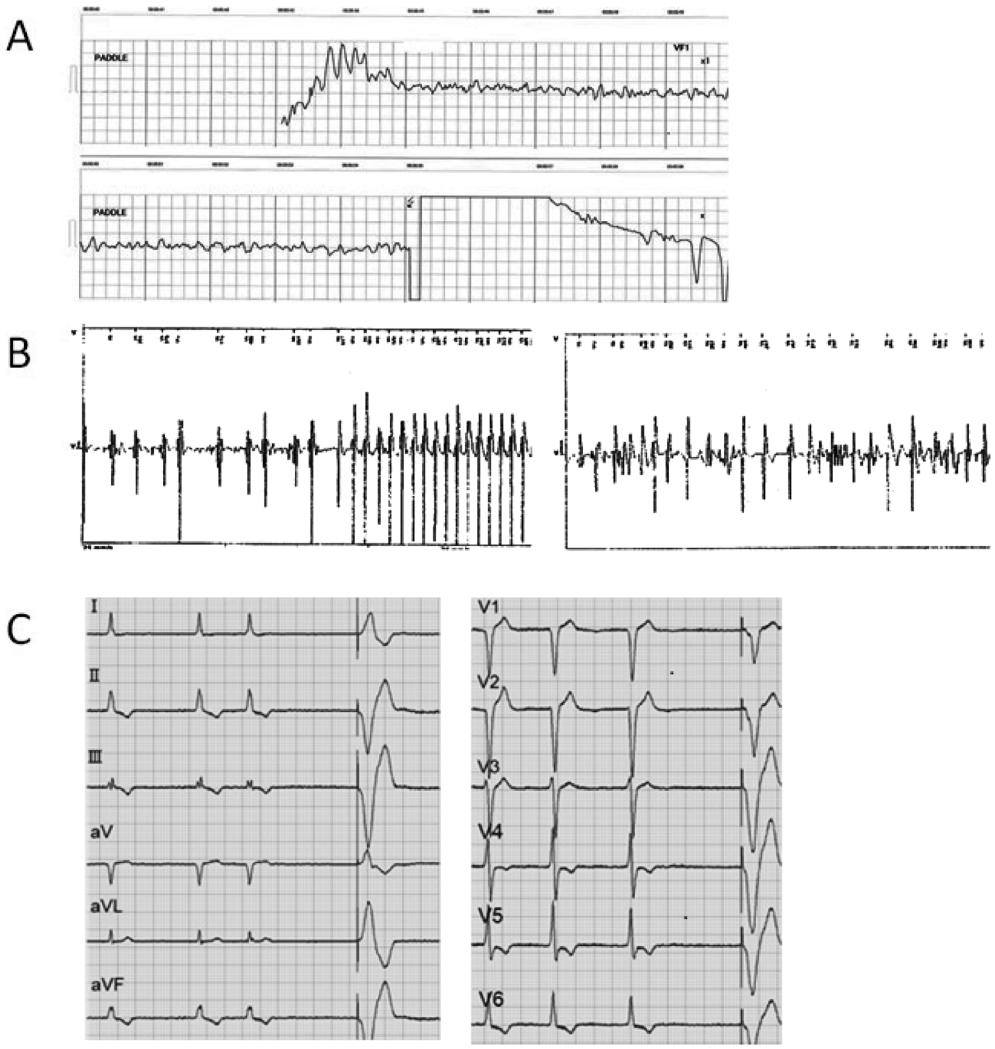

Fig. 5 Electrocardiogram (ECG) of proband's father
A: Ventricular fibrillation (VF) detected by automated external defibrillator; the VF was successfully terminated by a DC shock. B: Intracardiac ECG stored in his pacemaker also showed ventricular tachy-event before the shock. C: A 12-lead ECG recorded on admission showed atrial standstill with junctional beats at a rate of 66 bpm and occasional ventricular pacing. The QT intervals were short (QTc: 325 ms by Bazett formula and 319 ms by Fridericia formula). ECG, electrocardiogram; VF, ventricular fibrillation.

Discussion

In the current study, we report a family with SQT2 bearing the heterozygous *KCNQ1* p.V141M variant. Main clinical features of the family were atrial standstill with irregular junctional rhythm manifesting a very early onset bradycardia (i.e. SSS) and documented VF in the proband's father. Among six *KCNQ1* variants associated with SQT2, only the p.V141M variant was reportedly not associated with lethal ventricular arrhythmias.[5, 10–12] The *KCNQ1* p.V307L variant was reported by Bellocq et al.[2] In that report, the proband was a 70-year-old man who survived a VF. Rhodes et al.[6] identified the *KCNQ1* p. I274V variant in a patient who suffered from sudden infant death syndrome, and its functional assay showed a gain-of-function effect, shortening ventricular action potential durations.

Lee et al.[13] demonstrated that the p.V141M variant had also shortened ventricular action potentials and enhanced transmural action potential duration heterogeneity in the presence of β-adrenergic stimulation, which may lead to short refractory periods and formation of functional reentrant circuits. However, to date, no lethal ventricular arrhythmias have ever been

reported in SQT2 patients with the *KCNQ1* p.V141M variant as stated by Bjerregaard,[10] but these patients are susceptible to AF and early onset bradycardia such as SSS.

It couldn't be stated unconditionally that *KCNQ1* p.V141M variant was absolute cause of VF, because the mechanism of VF in the proband's father was unclear. Nevertheless, we thought this episode, that is, the proband's father in the current study developed a VF raised an important alarm for the treatment of patients with this *KCNQ1* variant. As there is some possibility that this variant causes a VF, we should carefully monitor and follow-up with the proband, even though his bradycardia had been treated by a cardiac pacemaker. Considering the VF in his father, an ICD may need to be implanted for the proband. However, currently, ICD implantation as a primary prevention in patients with SQTS bearing the *KCNQ1* p.V141M variant is controversial because there is little evidence of risk stratification due to a small number of cases and lack of prospective randomized studies.

To assess prognostic risks in SQTS patients who were younger than 21-years-old, Villafane et al.[14] reported that those who showed >5 points of Modified Gollob scores tended to suffer from ventricular arrhythmias though it is still controversial.[8] Giustetto et al.[15] implanted ICDs in the cases who had family history of sudden cardiac death or who showed inducible VF by EPS as a primary prevention. Though appropriate shocks were delivered, frequent inappropriate shocks or ICD-related complications were also observed. As for the medical treatment for this family, quinidine and sotalol that block rapidly-activating delayed rectifier potassium channels (I_{Kr}) should be considered.

Conclusion

To the best of our knowledge, this is the first reported case of a family with SQT2 bearing the *KCNQ1* p.V141M variant with a family member who had aborted sudden cardiac death due to ventricular fibrillation. The arrhythmia phenotypes in our case were atypical compared to previously reported cases.

Abbreviations

AED, automated external defibrillator; AF, atrial fibrillation; CTR, cardiothoracic ratio; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; PDA, patent ductus arteriosus; PMI, pacemaker implantation; SQTS, short QT syndrome; SSS, sick sinus syndrome; VF, ventricular fibrillation

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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