

# Arrhythmogenic right-ventricular cardiomyopathy with plakophilin-2 genetic variant concomitant with early manifestation of ventricular tachyarrhythmia: a case series

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## Background

Arrhythmogenic right-ventricular cardiomyopathy (ARVC) is a hereditary cardiomyopathy characterized by fibro-fat replacement of the right-ventricular myocardium. There are many factors associated with poor prognosis in patients with ARVC. Among these factors, intensive physical exertion is considered an important risk factor for sudden cardiac death.

## Case summary

Herein, we report a case series of siblings with ARVC and an early manifestation of ventricular tachyarrhythmia. Plakophilin-2 (PKP2) genetic variant, which is one of the causative genetic variants of ARVC, was detected by genetic testing in all three siblings. They were young athletes with lethal/symptomatic ventricular tachycardias. The eldest sibling was implanted with a transvenous implantable cardioverter defibrillator (ICD) due to resuscitated cardiopulmonary arrest at 18 years of age; the next oldest patient was treated with successful catheter ablation at 17 years; the youngest patient was treated with catheter ablation and subcutaneous ICD implantation at 17 years.

## Discussion

A recent experimental model revealed that physical exertion in PKP2 knockout mice diminished cardiac muscle mass and increased cardiac myocyte apoptosis, despite enhanced arrhythmogenicity such as increased fractional shortening and calcium transient amplitude. The three siblings were heterozygous for the previously reported pathologic splice site variant c.2489 + 1G > A in Intron 12 of the PKP2. The variant might play an important role in facilitating the vulnerability to arrhythmia under intensive endurance training. Most ARVC patients with PKP2 variant, especially pathologic splice site variant c.2489 + 1G > A in Intron 12 of the PKP2, might have to be managed strictly regarding daily exercise.

## Keywords

Arrhythmogenic right-ventricular cardiomyopathy • Early manifestation • Ventricular tachyarrhythmia • Implantable cardioverter defibrillator • Catheter ablation • Case report

## ESC Curriculum

5.6 Ventricular arrhythmia • 5.10 Implantable cardioverter defibrillators • 5.1 Palpitations • 6.5 Cardiomyopathy • 6.7 Right heart dysfunction

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## Learning points

- ARVC patients with PKP2 genetic variant, especially pathologic splice site variant c.2489 + 1G > A in Intron 12 of the PKP2, might have to be managed strictly regarding daily exercise to prevent sudden cardiac death.
- In addition to the diagnostic importance of genetic testing to identify the causative genetic variant of ARVC, genetic testing may also be useful in risk stratification of sudden cardiac death in ARVC.

## Introduction

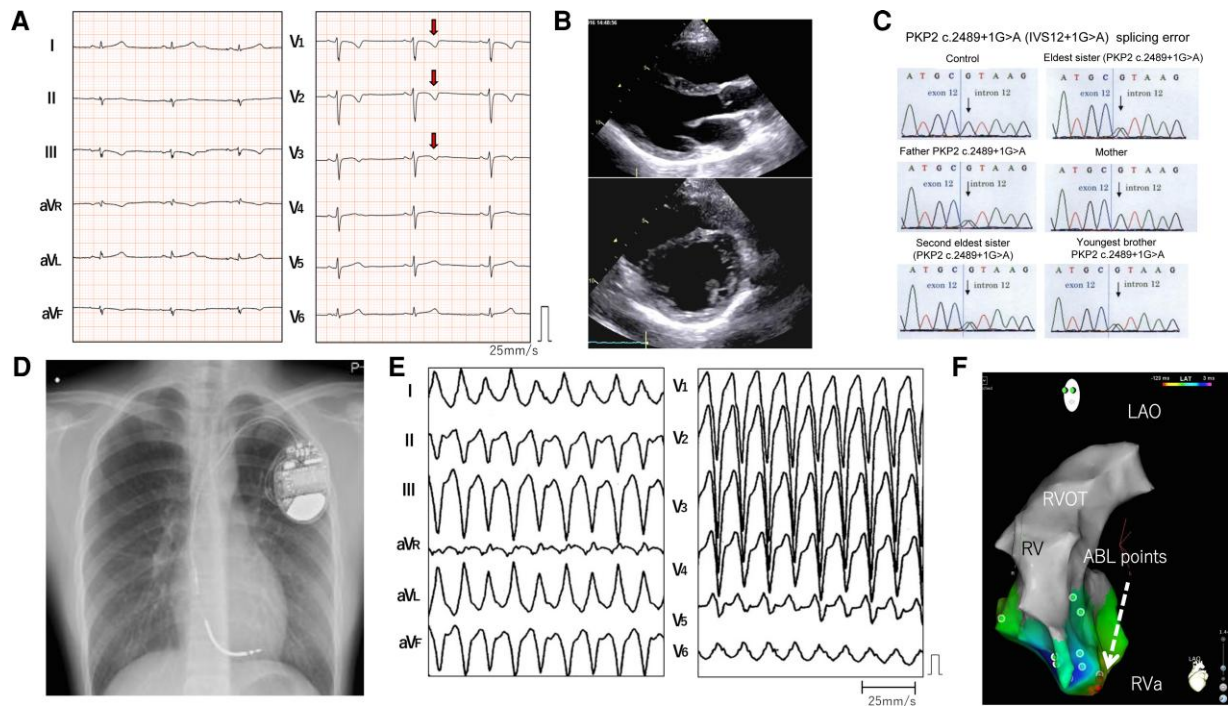
Arrhythmogenic right-ventricular cardiomyopathy (ARVC) is an inherited myocardial disease characterized by fibro-adipose replacement of the right-ventricular myocardium.<sup>1</sup> Initial clinical presentation is variable, ranging from asymptomatic cases to chronic heart failure and sudden cardiac death due to malignant arrhythmias.<sup>2–4</sup> The prevalence of ARVC is estimated at 1:2500–1:5000 cases per person.<sup>5</sup> There are many factors associated with poor prognosis in patients with ARVC, with intensive physical exertion considered an important risk factor for sudden cardiac death.<sup>6</sup> Recently, new imaging modalities and genetic testing have been useful for improving diagnoses, risk stratification, and prevention in high-risk groups.<sup>7,8</sup> Plakophilin-2 (PKP2) genetic variants has been shown to enhance progression of pathogenesis in ARVC in terms of systolic cardiac function and lethal arrhythmia.<sup>9</sup> A recent study using genetically PKP2 knockout mice showed that loss of the PKP2 function reduced ventricular systolic function and enhanced vulnerability to ventricular arrhythmia. The current study presents a case series of three siblings (sports athletes) with PKP2 genetic variants, where intensive training potentially promoted the pathogenesis of ARVC through early manifestation of ventricular tachyarrhythmia. Catheter ablation or implantable cardioverter defibrillators (ICDs) were required to control ventricular tachyarrhythmia in these adolescents.

## Timeline

## Patient 1: eldest sister

An 18-year-old girl with 16 years of experience in athletic swimming was admitted to our hospital after experiencing sudden cardiopulmonary arrest. She had been consistently selected as a representative prefectural swimmer at the Japanese National Sports Festival and participated in high-frequency, long-duration, and high-intensity endurance training (>6000 MET minutes per week). As a high-school student, she became aware of severe palpitations while swimming. She experienced sudden cardiopulmonary arrest during training. Her friends noticed this collapse and called for emergency medical services, and bystander cardiopulmonary resuscitation was performed. An automated external defibrillator identified ventricular fibrillation (VF), which was successfully defibrillated, and sinus rhythm was restored. The patient was intubated and transferred to the intensive care unit of the nearest emergency medical hospital. After confirming the absence of significant findings on coronary angiography, the patient was administered hypothermia therapy. Fortunately, her consciousness was restored, and she was transported to our hospital to investigate her underlying disease. Her electrocardiogram (ECG) showed sinus rhythm with occasional premature ventricular complexes (PVCs) and negative T waves in the V<sub>1</sub>–V<sub>3</sub> leads but without epsilon waves (Figure 1A). Echocardiography revealed only mild-to-moderate right-ventricle dilatation without any other abnormal findings (Figure 1B). The left-ventricular ejection fraction (LVEF) was preserved to a normal level of 63%.

Patient 1 : Eldest sister		Patient 2 : Second Eldest sister		Patient 3 : Youngest brother	
1997	*Year of Birth	1999	*Year of Birth	2003	Year of Birth
1999-2012	*High-frequency/long-duration/intermediate-intensity endurance training (2880 MET minutes weekly) *Symptom-free	2001-2014	*High-frequency/long-duration/intermediate-intensity endurance training (2880 MET minutes weekly) *Symptom-free	2009-2016	*High-frequency/long-duration/intermediate-intensity endurance training (2880 MET minutes weekly) *Symptom-free
2013-2015	*High-frequency/long-duration/high-intensity endurance training (6000 MET minutes weekly) *Recurrent exercise-induced palpitations	2015-2017	*High-frequency/long-duration/high-intensity endurance training (6500 MET minutes weekly) *Recurrent exercise-induced chest pain and palpitations	2017-2018	High-frequency/long-duration/high-intensity endurance training (7000 MET minutes weekly) *Recurrent exercise-induced palpitations and presyncope
2015	*Resuscitated cardiac arrest *Catheter ablation to ventricular tachycardia *Implantation of implantable cardioverter defibrillator (ICD) *Exercise restriction	2017	*Catheter ablation to ventricular tachycardia *Wearable cardioverter defibrillator for 3 months after catheter ablation *Exercise restriction	2018	*Catheter ablation to ventricular tachycardia (1 <sup>st</sup> session) *No exercise restriction due to his physically demanding jobs
				2020	*Recurrent ventricular tachycardia with presyncope *Implantation of subcutaneous ICD
				2021	*Epicardial catheter ablation to recurrent ventricular tachycardia (2 <sup>nd</sup> session)



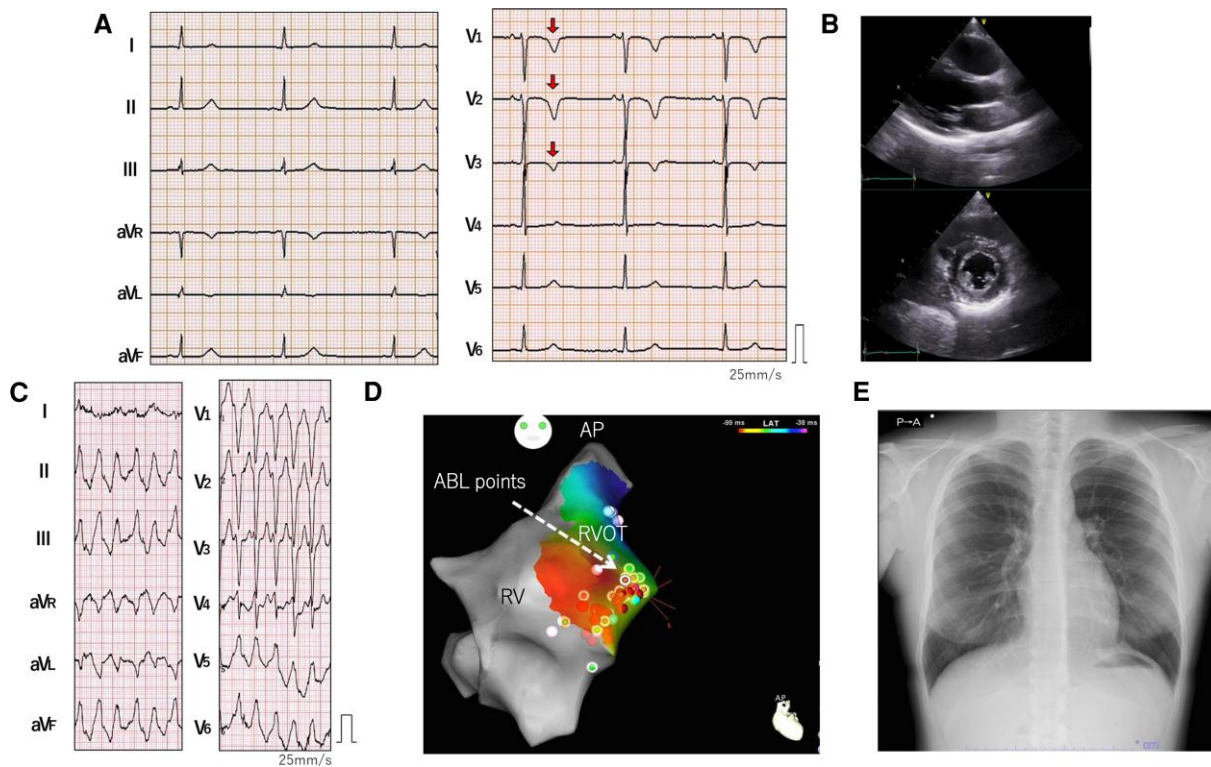
**Figure 1** Clinical findings of eldest sister. (A) Twelve-lead electrocardiogram on admission (arrows indicate negative T waves in the  $V_1$ – $V_3$  leads). (B) Mild right-ventricular dilatation in echocardiographic, long- and short-axis view. (C) Pathogenic splice site variant c.2489 + 1G > A in Intron 12 of the plakophilin-2 detected by genetic testing in eldest sister, second eldest sister, youngest brother, and father. (D) Chest X-ray after transvenous implantable cardioverter defibrillator implantation. (E) Induced ventricular tachycardia during electrophysiological study. (F) Successful ablation points in the right-ventricular apex. ABL, ablation; LAO, left anterior oblique; RVa, right-ventricular apex; RV, right ventricle; RVOT, right-ventricular out flow tract.

Cardiac evaluations, including coronary angiography with acetylcholine provocation test, cardiac computed tomography and magnetic resonance imaging, biopsy of the right-ventricular cardiac muscle from the ventricular septum, and myocardial scintigraphy, showed no significant findings. Genetic testing was performed in the patient, her younger sister, younger brother, father, and mother. Genomic deoxyribonucleic acid (DNA) was isolated from their peripheral blood lymphocytes and a benchtop next generation sequencer was used for screening genes related to ARVC. The results identified a PKP2 genetic variant [PKP2 c.2489 + 1G > A (IVS12 + 1G > A) splicing error] in the patient, her younger sister, youngest brother, and father, leading to the diagnosis of ARVC (Figure 1C). As per current recommendations, an implantable cardioverter defibrillator (ICD) was used for secondary prevention. After ICD placement (Figure 1D), an electrophysiological study (EPS) and radiofrequency catheter ablation (RFCA) were performed to reduce the probability of appropriate ICD therapy, as Holter ECG documented frequent PVCs (>20% of total heartbeats) and non-sustained ventricular tachycardias. Sustained VT was reproducibly induced in the EPS with stable haemodynamics (Figure 1E), enabling the unmasking of the critical isthmus of the VT circuit (Figure 1F). RFCA successfully eliminated this VT and achieved non-inducibility of any other sustained VT. During a 6-year follow up with continuous exercise restriction and no medication, VT/VF episodes were not detected by the ICD, and no progression of symptoms or echocardiographic findings were observed. The patient's definitive diagnosis of ARVC was satisfied by the presence of three major criteria from different categories according to the task force criteria (inverted T waves in right precordial leads; non-sustained or sustained ventricular

tachycardia of left bundle-branch morphology with superior axis; and PKP2 genetic variant).

## Patient 2: second eldest sister

The second eldest sister was 1 year younger than her sister. At 17 years, she felt palpitations while undergoing endurance training, after her sister's arrhythmic event. She was also a promising swimmer, who represented the prefecture, and had 15 years of athletic swimming experience. She trained to the same intensity as her older sister. An exercise stress test with more than seven METs of exercise easily induced sustained VTs with a heart rate of 190 b.p.m. Similar to her older sister, her resting ECG showed sinus rhythm with negative T waves in the  $V_1$ – $V_3$  leads (Figure 2A). Abnormal echocardiographic findings included mild dilatation of the right ventricle (Figure 2B). LVEF was preserved. Cardiac magnetic resonance imaging showed no significant findings, such as late gadolinium enhancement. EPS and RFCA were performed after consent was obtained. Reproducibly induced VT (VT1) was eliminated (Figure 2C and D), but another VT (VT2) remained inducible and unsustainable. She did not consent to ICD implantation (Figure 2E), thus she was monitored using a wearable cardioverter defibrillator (WCD) for 3 months to confirm RFCA efficacy and VT2 clinical irrelevance. Her exercise was severely restricted during this period. No VTs were documented by the WCD, and she was gradually far less likely to feel palpitations due to the restriction of exercise. A 5-year follow up with continued exercise restriction found no progression of symptoms or echocardiographic abnormalities.



**Figure 2** Clinical findings of second eldest sister. (A) Twelve-lead electrocardiogram on admission (arrows indicate negative T waves in the V<sub>1</sub>–V<sub>3</sub> leads). (B) Mild right-ventricular dilatation in echocardiographic, long- and short-axis view. (C) Induced ventricular tachycardia (VT1) during electrophysiological study. (D) Successful ablation points to ventricular tachycardia (VT1) in the right-ventricular outflow tract. (E) Chest X-ray at the time of hospital discharge (without implantable cardioverter defibrillator). ABL, ablation; AP, anteroposterior; RV, right ventricle; RVOT, right-ventricular out flow tract.

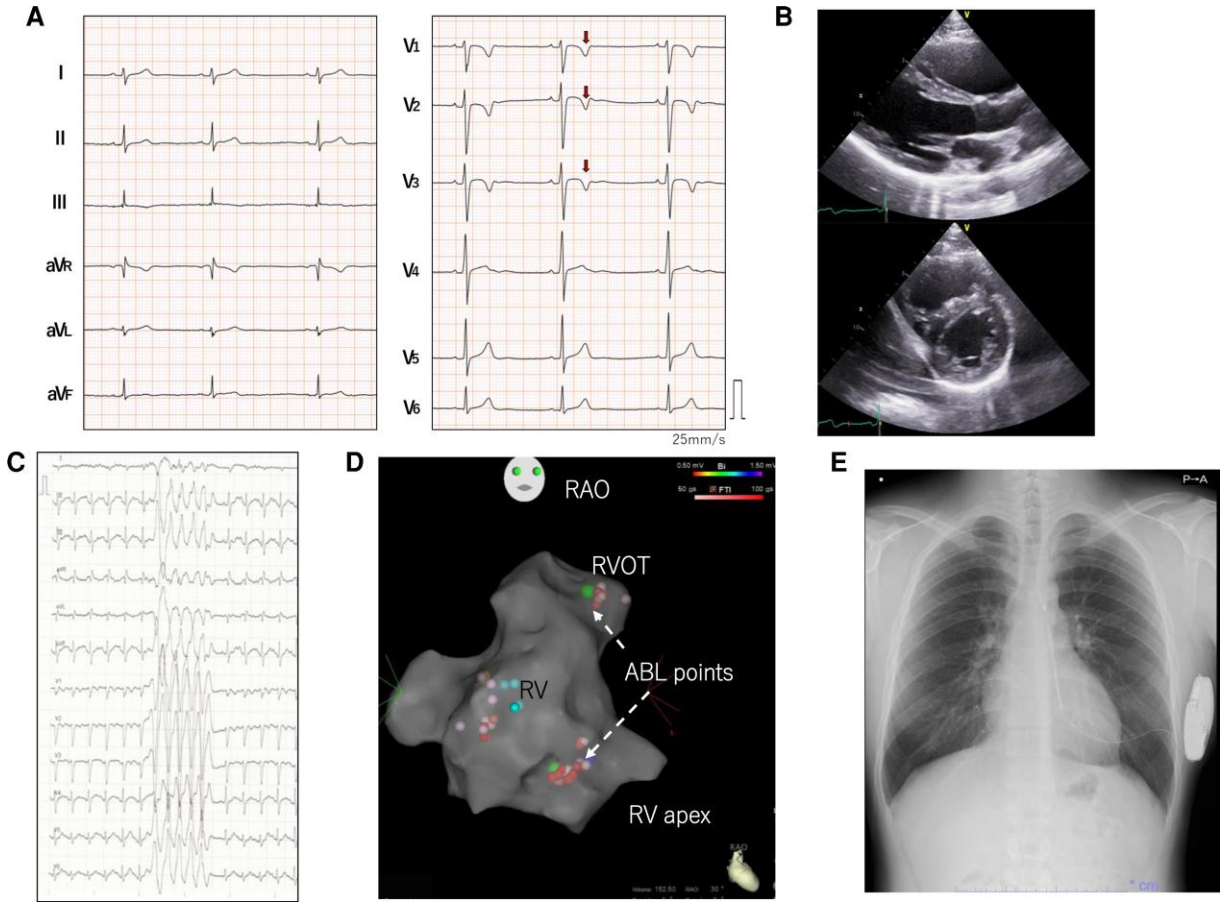
### Patient 3: youngest brother

The youngest brother was 5 years younger than the oldest sister. He was also a promising swimming athlete. He started swimming at 6 years of age and suffered from presyncope with preceding palpitations during endurance exercise at 15 years of age. For this patient, negative T waves were also observed in the V<sub>1</sub>–V<sub>3</sub> leads of the 12-lead ECG (Figure 3A). Mild-to-moderate RV dilatation was also confirmed on echocardiography (Figure 3B), while LVEF was within normal limits. There were no significant findings by cardiac magnetic resonance imaging. As expected, non-sustained VT was induced by an exercise stress test (Figure 3C). Three-dimensional activation mapping revealed that the earliest activation site of clinical VT (VT1) was located in the RV outflow tract, and triggering PVC frequently occurred on the posterior side of the RV. As RFCA to PVC origin and earliest activation site in the RV outflow tract (Figure 3D) successfully suppressed inducibility of VT1, with the same morphology as previously non-sustained VT, we decided to follow up without ICD implantation for this patient. However, the patient experienced VT recurrence with syncope 6 months after RFCA, possibly due to poor adherence to exercise restrictions (he continued swimming training). After obtaining consent from the patient and his family, a subcutaneous ICD (S-ICD) was successfully implanted (Figure 3E). A second session of RFCA was performed using both endocardial and epicardial approaches, diminishing the inducibility of VT1 and another inducible VT (VT2). However, non-sustained VT episodes were occasionally detected by the S-ICD, and right-ventricular

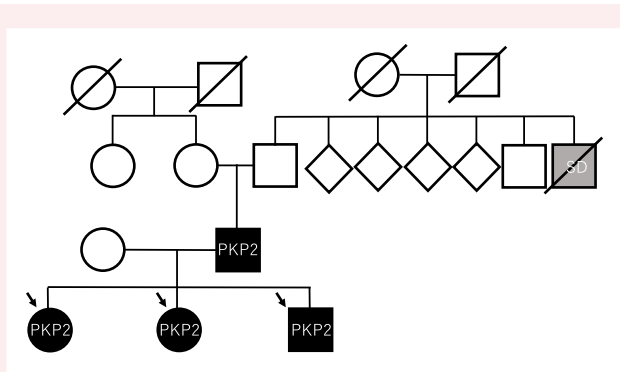
enlargement on echocardiography mildly progressed due to his physically demanding occupation.

### Discussion

To the best of our knowledge, this is the first case series of three siblings with ARVC with a PKP2 genetic variant, showing early manifestation of the ARVC phenotype. Three siblings consistently demonstrated normal findings by cardiac MRI and mildly dilated right ventricle at the time of diagnosis. Cardiac MRI was not repeated in the siblings. The family pedigree is shown in Figure 4. The reason for early manifestation of ARVC phenotype is most likely the highly intensive exercise performed by these three siblings from early childhood. The father, who did not intensely exercise in childhood, did not develop the arrhythmia phenotype. In addition, the two sisters' symptoms were gradually remitted by exercise restriction, but those of the younger brother, who performed physical labour, could not be controlled. An important case report of ARVC found that exercise exacerbates the clinical course.<sup>10</sup> The time-course of this case in childhood is consistent with that of the two sisters presented here; that is, cessation of regular workouts stopped progression of the ARVC phenotype. A recent experimental model revealed that endurance training in PKP2 knockout mice decreased cardiac muscle mass and increased cardiac myocyte apoptosis, despite enhanced arrhythmogenicity such as increased fractional shortening and calcium transient amplitude.<sup>9</sup> Based on these findings, most



**Figure 3** Clinical findings of youngest brother. (A) Twelve-lead electrocardiogram on admission (arrows indicate negative T waves in the V<sub>1</sub>–V<sub>3</sub> leads). (B) Mild right-ventricular dilatation in echocardiographic long- and short-axis view. (C) Induced ventricular tachycardia during electrophysiological study. (D) Successful ablation points to clinical ventricular tachycardia in the right-ventricular outflow tract and triggering premature ventricular complex in the right-ventricular apex. (E) Chest X-ray after subcutaneous implantable cardioverter defibrillator implantation. ABL, ablation; LAO, right anterior oblique; RVa, right-ventricular apex; RV, right ventricle; RVOT, right-ventricular out flow tract.



**Figure 4** Family pedigree. Circles = females, squares = males, arrows = three siblings, oblique stroke through symbol = dead, SD, sudden death.

ARVC patients with a PKP2 genetic variant might need to severely restrict daily exercise. The three siblings were heterozygous for the previously reported pathogenic splice site variation c.2489 + 1G > A in

Intron 12 of the PKP2.<sup>11–14</sup> This variant is predicted to cause abnormal RNA splicing, resulting in abnormal PKP2 genetic variants. Although the precise pathogenicity of this variant in PKP2 has not been fully elucidated, due to the lack of mechanistic studies, the variant could potentially play an important role in facilitating vulnerability to arrhythmia under physical exertion.

Considering the benefits of exercise on cardiovascular global health, mild-to-moderate exercise training in patients with ARVC is recommended based on individual conditions.<sup>15,16</sup> Given the risk of exercise in promoting arrhythmogenicity, mild exercise would be recommended in these three siblings.

Subcutaneous ICD is considered more appropriate for young active patients compared with transvenous ICD due to lead-associated complications. The eldest sister would have been implanted with S-ICD similar to her youngest brother, if S-ICD had been commercially available at that time.

Cardiovascular preparticipation screening including an ECG is very important for early detection of inherited myocardial disease such as ARVC, particularly in young people who may be exposed to high-intensity exercise. Cautionary screening could reduce development of disease and prevent related sudden cardiac death, if exercise restriction for those at risk could be implemented.

## Lead author biography



Dr Kawano received her MD from Oita University, Japan in 2013. She is working as a cardiologist in Oita University Hospital. Her research focuses on risk stratification of idiopathic ventricular fibrillation and hereditary arrhythmias, including Brugada syndrome, early repolarization syndrome, arrhythmogenic right-ventricular cardiomyopathy, long QT syndrome, and catecholaminergic polymorphic ventricular tachycardia.

## Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The authors confirm that written consent for submission and publication of this case series including images and associated text has been obtained from the patients in line with COPE guidance and ICMJE recommendation.

**Conflict of interest:** None declared.

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