

A subtype of idiopathic ventricular fibrillation and its relevance to catheter ablation and genetic variants



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Introduction

Idiopathic ventricular fibrillation (VF) develops in structurally normal hearts and comprises various clinical entities.¹ In particular, site-specific premature ventricular complexes (PVCs), such as PVCs originating from the right ventricular outflow tract² or left ventricular papillary muscles,^{3,4} have been reported to provoke idiopathic VF. PVCs originating from papillary muscles and the moderator band (MB) in the right ventricle (RV) are also among the causes of ventricular arrhythmias (VAs).^{5,6}

Case report

A 57-year-old male patient had his first syncopal episode during desk work, and he regained consciousness spontaneously after a few minutes. He was admitted to our hospital for a medical examination. He had no history of previous syncope, other illnesses, or familial cardiac sudden death. On admission, his electrocardiogram (ECG) showed that the PVCs emerged with a bigeminal cycle with a coupling interval of 360 ms (Figure 1A). The QRS morphology was relatively narrow, with a duration of 138 ms, and had a left bundle branch block (LBBB) pattern with a precordial transition later than lead V₄. The intrinsicoid deflections in the precordial leads were 55 ms. The frontal plane axis of the PVCs was left superior, with a positive QRS complex in leads I and aVL. The characteristics implied that the PVC originated from the MB in the RV. An intensive examination including coronary computed tomography, echocardiography, and cardiac magnetic resonance imaging could not detect any structural heart disease.

The ECG monitor revealed a nonsustained polymorphic ventricular tachycardia (VT) on the next morning, which was triggered by an LBBB-type PVC (Figure 1B). To rule

out any genetic arrhythmias such as Brugada syndrome, long QT syndrome (LQTS), or early repolarization syndrome, pharmacologic tests, such as those with pilsicainide (class Ic sodium channel blocker), epinephrine, isoproterenol, and disopyramide (class Ia sodium channel blocker), were performed. However, none of the pharmacologic responses was associated with any specific disease. We also noticed J waves in the inferolateral leads, but we concluded that they were bystanders because they lacked dynamicity before the onset of the VA or drug administration.

Because the PVC could trigger a polymorphic VT, which was responsible for his syncope, catheter ablation targeting the PVC was performed. The patient provided written informed consent before the procedure. An electrophysiological study was performed with the patient under deep sedation. A 3.5-mm saline-irrigated mapping ablation catheter (NaviStar Thermocool SF, Biosense Webster, Diamond Bar, CA) was inserted into the RV utilizing a steerable sheath. From the left femoral vein, an intracardiac echocardiography (ICE) catheter (Soundstar, Biosense Webster, CA) was advanced up into the right atrium. Radiofrequency (RF) energy was delivered with 30–35 W and a saline irrigation rate of 8 or 15 mL/min.

We mapped the earliest activation site of the PVC, which was located on the free wall of the RV, and the ICE results revealed the insertion of the MB on the free wall of the RV as well (Figures 2A and 2B). Pace mapping from the earliest activation site exhibited a morphology similar to that of the PVC (Figure 2C). At that site, an early potential was seen at the onset of the PVC. The local activation at the successful ablation site preceded the onset of the QRS of the PVC by 25 ms, and a sharp potential like a Purkinje potential was recorded by the ablation catheter (Figure 2D). During sinus rhythm, the potential was observed to precede the QRS wave (Figure 2E). The CARTO image and ICE demonstrated that the earliest activation site matched the location of the MB (Figures 3A and 3B).

After a radiofrequency energy delivery, the PVCs disappeared and the ECG exhibited a complete right bundle branch block (Figure 3C). Following that, the same PVC could no longer be induced by programmed stimulation under an isoproterenol infusion. The patient underwent an implantable cardioverter-defibrillator (ICD) implantation for secondary

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KEY TEACHING POINTS

- Premature ventricular complexes originating from the moderator band are responsible for ventricular arrhythmias, and catheter ablation is the among the possible therapies.
- Bipolar electrocardiograms may have Purkinje potentials at the successful ablation site, and intracardiac echocardiography may be useful.
- Ankyrin-B syndrome should be considered as a differential diagnosis of idiopathic ventricular fibrillation.

prevention. During 6 months of follow-up, he has experienced no further episodes of syncope or ICD therapies.

In our institute, we analyze the patient's genome by using the Next Generation Sequencer (MiSeq, Illumina, San Diego, CA) with a commercially available gene panel targeting 4813 genes associated with known clinical phenotypes (TruSight One, Illumina). Nucleotide variants, including a small insertion or deletions that would affect the amino acid sequences

or could affect the splice sites, were annotated. We defined a variant as a mutation of which the minor allele frequency was <0.02 in all public databases. We detected a heterozygous single T-to-A nucleotide substitution at the position 4603 of the *ANK2* gene (NM_020977.3), which encoded ankyrin-B, leading to a replacement of tryptophan by arginine at amino acid residue 1535 (W1535R; NP_066187.2). This rare variant was confirmed by the Sanger method (Figure 3D). Family screening was not performed, because consent could not be obtained from the patient's parents or child.

We retrospectively reviewed the incidence of *ANK2* mutations in patients with inherited primary arrhythmia syndrome (IPAS) who underwent genetic screening in our university hospital. All patients who harbored *ANK2* variants resulting in a nonsynonymous substitution of the amino acid are shown as a supplementary table. *ANK2* mutations were identified in various IPASs such as Brugada syndrome, idiopathic VF, LQTS, and short QT syndrome.

Discussion

The MB is a component of the septomarginal trabeculation, which crosses from the septum to the free wall of the RV. The MB plays a pivotal role in the conduction system

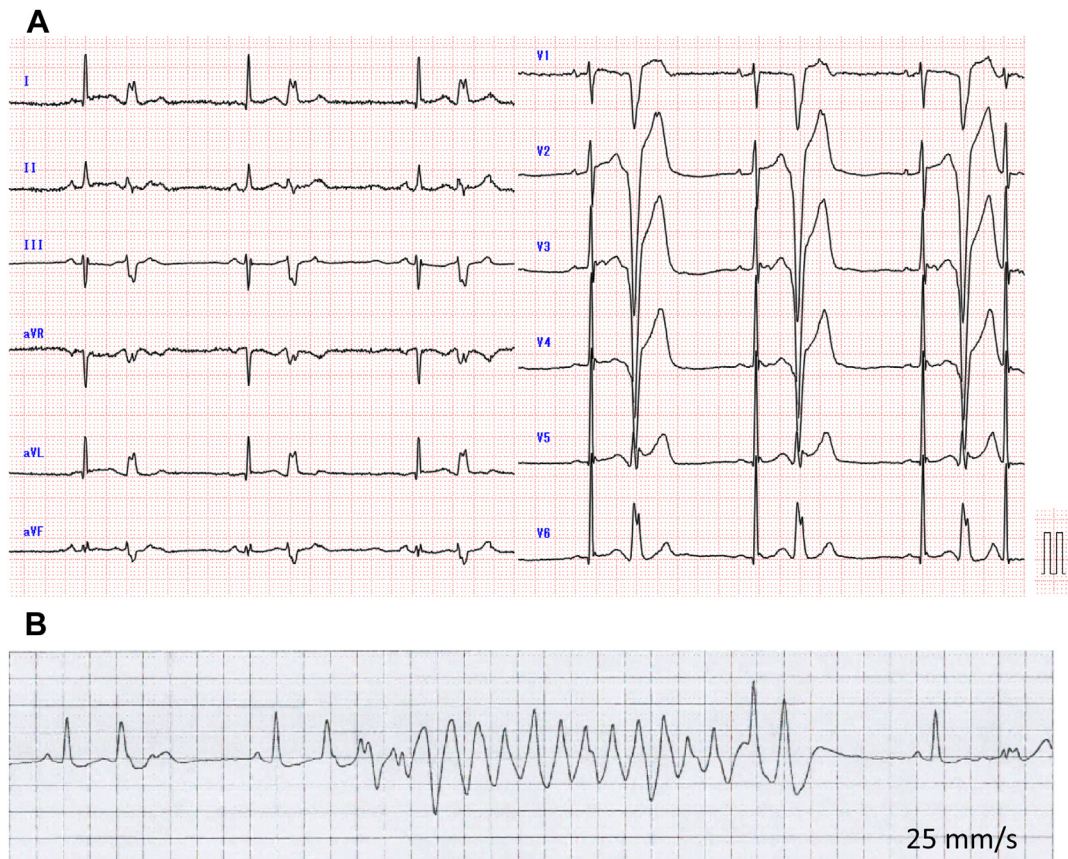


Figure 1 The 12-lead electrocardiogram (ECG) of the premature ventricular complexes and ECG monitor recording of the ventricular arrhythmia. **A:** 12-lead ECG. The premature ventricular contraction exhibited a left bundle branch block morphology. The heart rate was 65 beats per minute, and no Brugada-type ECG sign was evident. The PR and QTc intervals were within normal range. **B:** The ECG monitor recording after admission. A few seconds of premature ventricular complexes were observed preceding the ventricular arrhythmia.

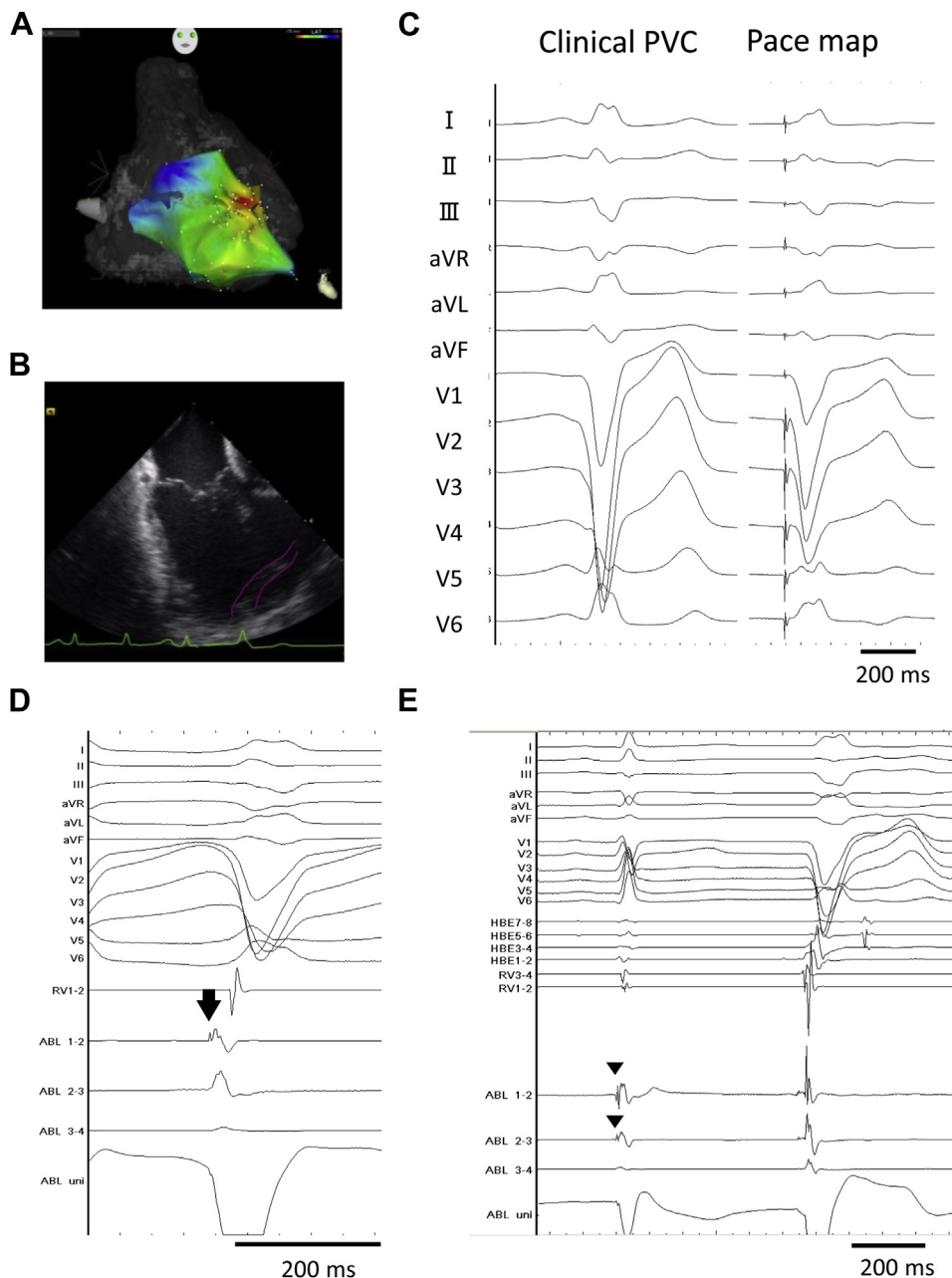


Figure 2 The optimal ablation site was guided by intracardiac echocardiography and electroanatomic mapping. **A:** The CARTO activation mapping image. The electroanatomic image shows the earliest activation site at the free wall of the right ventricle. **B:** The intracardiac echocardiography imaging of the moderator band in the right ventricle. The purple lines indicate the moderator band. **C:** The pace mapping from the earliest activation site. **D:** The intracardiac electrocardiograms at the ablation site. The black arrow shows the sharp potential that preceded the ventricular activation during the premature ventricular complex (PVC). **E:** A Purkinje potential during sinus rhythm was recorded at the successful ablation site (arrowheads).

because it contains Purkinje fibers. The right bundle of the Purkinje fibers goes through the septomarginal trabeculation in the interventricular septum and transits to the Purkinje fibers at the junction where the MB inserts into the anterior papillary muscle to the RV free wall. This location is considered to be the breakthrough point of the conduction system to the RV. A previous study showed that PVCs originating from the MB were responsible for VAs and that catheter ablation was among the therapies for preventing cardiac arrest and ICD shocks.⁶ The characteristics of the PVCs originating from the MB were a narrow duration with a

mean of 152.7 ± 15.2 ms, LBBB pattern with a precordial transition later than V₄, intrinsicoid deflection in the precordial leads of <100 ms, and a left superior axis.⁶ Those characteristics corresponded to those of the PVCs in this case. For mapping the PVC, the earliest ventricular activation and a perfect pace map suggested a closer proximity to the PVC origin. However, the pace map from the ablation site was not excellent in this case. Local activation mapping appeared to be more useful than pace mapping, because of the difficulty in maintaining a stable contact of the catheter tip with the MB. In addition, it was considered that the site of

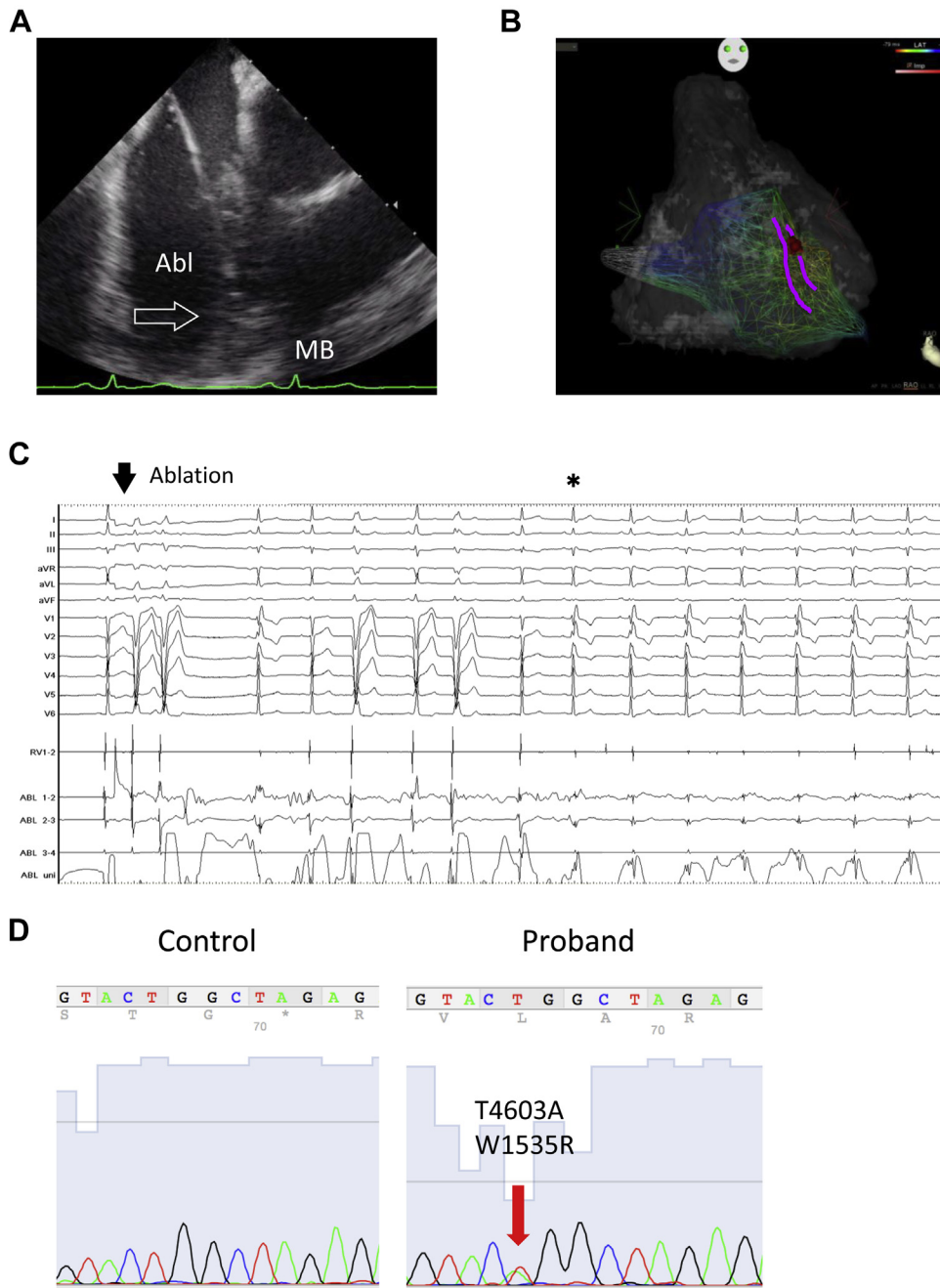


Figure 3 Ablation at the earliest activation site on the moderator band (MB). **A:** ICE imaging of the tip of the ablation catheter (Abl) on the moderator band. The arrow shows the catheter in good contact with the moderator band. **B:** The merge of the CARTO view. The red points indicate the sites where radiofrequency energy was delivered. The purple lines show the moderator band. **C:** The arrow shows the start of the ablation point. The asterisk demonstrates the suppression of the PVCs, and complete right bundle branch block was induced by the ablation. **D:** Results of DNA sequencing in a patient demonstrating a heterozygous single T-to-A nucleotide substitution at position 4603 of the *ANK2* gene leading to a W1535R missense mutation.

the PVC origin may be deeper relative to the endocardial surface. That study reported that as the outcome of the procedures, 6 of 10 patients required a second procedure. The long-term prognosis of patients with PVCs originating from the MB is not obvious because cases with PVCs causing VAs are relatively few. Catheter ablation therapy is effective for preventing VAs, and ICD implantations are required for secondary prevention. The mechanism of the ar-

rhythmogenicity of the MB is not clear, but it is obvious that Purkinje cells affect the occurrence.

PVCs originating from the MB in the RV are also among the causes, and catheter ablation combined with an ICD and pharmacologic therapy are useful for suppressing VAs. *ANK2* mutations have also been reported as the cause of LQTS type 4,⁷ catecholaminergic polymorphic VT, and IPAS, including idiopathic VF. *ANK2* encodes ankyrin-B,

which links the integral membrane proteins to the spectrin-based cytoskeleton. Ankyrin-B is required for the coordinated assembly of the sodium-calcium exchanger, sodium-potassium adenosine triphosphatase, and inositol trisphosphate receptors in the cardiomyocytes.^{8,9} A recent study reported the prevalence of *ANK2* mutations was 2.2% of 535 Japanese IPAS probands.¹⁰ In particular, a previous study showed that W1535R was found in 6 of 12 probands (50%).¹⁰ Loss-of-function variants in the *ANK2* gene cause a various range of cardiac arrhythmias, including LQTS and VAs. We considered that *ANK2* mutations may be associated with the disease pathogenesis of some IPAS patients. However, on the other hand, *ANK2* mutations were also identified in patients who were considered to have other mutations underlying the disease phenotype. For example, *ANK2-I777V*, a rare variant, was found in a patient with LQTS (patient 2) and that patient was diagnosed with LQTS type 1 and a positive mutation of *KCNQ1-L250H*. Ankyrin-B is a form of a membrane protein complex with some ion transporters in cardiomyocytes, however, its function for the cardiac action potential is likely to be heterogeneous. Therefore, our findings indicate that *ANK2* mutations may play a role in IPAS as an “accessory mutation” as well as a causative mutation. Unification of the interpretation of *ANK2* mutations found in IPAS is essential for an accurate genetic diagnosis.

Conclusion

VAs caused by PVCs originating from the MB can be successfully ablated. A preferential potential might exist at the breakthrough point of the Purkinje fibers, where the MB connects to the free wall of the RV. Ankyrin-B syndrome should be considered as a differential diagnosis of IPAS, especially in those with malignant VAs.

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Appendix Supplementary data

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.hrcr.2017.03.004>.

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