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CASE REPORT
Arrhythmias/electrophysiology

Novel ACTN2 missense variant is associated with idiopathic ventricular fibrillation: a case report

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Background Idiopathic ventricular fibrillation (VF) is a diagnosis of exclusion made in patients who experience VF without an attributable cause. Pathogenic variants of the *ACTN2* gene encoding the sarcomeric protein alpha-actinin-2 are known to cause hypertrophic and dilated cardiomyopathy. We show that *ACTN2* variants may also be associated with malignant arrhythmias in the absence of overt structural heart disease.

Case summary A 48-year-old female presented with cardiac arrest due to VF without any history of cardiovascular disease or family history of sudden cardiac death. Troponin I was elevated at 0.698 ng/mL, but coronary angiography showed no significant coronary artery disease. Substance abuse testing showed elevated benzodiazepine and sertraline levels, which she was taking for anxiety. Electrocardiogram showed normal QRS complexes without prolonged PR or QTc intervals. She underwent therapeutic hypothermia. Cardiac magnetic resonance imaging at 2 weeks showed normal biventricular function without structural abnormalities, fibrosis, or evidence of myocardial infarction. A targeted gene panel revealed a heterozygous missense variant of unknown significance (VUS) in exon 18 of the *ACTN2* gene (c.2162G > A/p.R721H).

Discussion The identified VUS is located in a highly conserved residue of a spectrin-like repeat domain of alpha-actinin-2. Spectrin-like domains of alpha-actinin-2 bind and regulate the ion channels $Na_v1.5$, $K_v1.4$, and $K_v1.5$, which contribute to the myocardial action potential. The VUS was predicted as pathogenic by MutationTaster, Polymorphism Phenotyping v2, and Sorting Intolerant From Tolerant *in silico* missense prediction tools. The c.2162G > A/p.R721H alpha-actinin-2 variant may result in dysregulation of cardiac ion channels, leading to arrhythmias.

Keywords Arrhythmia • Mutation Out-of-hospital cardiac arrest • Targeted gene panel • Missense prediction tool • Cardiac ion channel • Case report

ESC Curriculum 5.6 Ventricular arrhythmia • 5.8 Cardiac ion channel dysfunction

Learning points

- When clinical assessment for an aetiology of ventricular fibrillation such as structural heart disease or primary arrhythmia syndromes is inconclusive, genetic testing may be useful.
- Pathogenic variants of the *ACTN2* gene encoding the sarcomeric protein α-actinin-2 are well known to cause hypertrophic and dilated cardiomyopathy. We show that *ACTN2* variants might be associated with malignant arrhythmias such as idiopathic ventricular fibrillation in the absence of overt structural heart disease.
- *In silico* missense prediction tools may help determine whether variants of unknown significance may be pathogenic.

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Introduction

Idiopathic ventricular fibrillation (VF) is a diagnosis of exclusion made in patients resuscitated from cardiac arrest who experience VF without identified cardiac, respiratory, metabolic, and/or toxicological causes.[1] When clinical assessment for an aetiology such as structural heart disease or primary arrhythmia syndromes is inconclusive, genetic testing may be useful.[1] Here, we present a case of a patient cardiac history who was referred to genetic counselling and subsequently identified to have a novel variant of unknown significance (VUS) of the *ACTN2* gene, c.2162G > A/p.R721H.

Timeline

Day 1	Found to be in ventricular fibrillation and received five defibrillations, intravenous amiodarone, and epinephrine before return of spontaneous circulation. Patient sedated and intubated. Cardiac catheterization showed no significant coronary artery disease. Computed tomography angiography was negative for pulmonary embolism (PE). Therapeutic hypothermia was initiated in the intensive care unit.
Day 2	Initial transthoracic echocardiography (TTE) showed decreased left ventricular ejection fraction (LVEF) 30–35% and severe diffuse hypokinesis. Thrombus found on hypothermia catheter, and heparin infusion started. Rewarming initiated.
Day 8	Patient extubated to high-flow nasal cannula.
Day 9	Repeat TTE showed increased LVEF of 60–65% and normalized right ventricular function, chamber size, wall motion, and thickness.
Day 13	Cardiac magnetic resonance imaging (MRI) showed normal biventricular function without structural abnormalities, fibrosis, or evidence of myocardial infarction. Cardiac MRI also showed evidence of PE.
Day 16	Computed tomography angiography showed pulmonary emboli. Patient started on apixaban.
Day 19	Implanted with Boston Scientific EMBLEM™ MRI subcutaneous implantable cardioverter defibrillator.
Day 20	Patient discharged.
3 months later	Patient consulted with genetic counselor and consented to Ambry Genetics' CardioNext® targeted gene panel.
4 months later	Targeted gene panel showed heterozygous variant of unknown significance of the *ACTN2* gene, c.2162G > A/p.R721H.
2 years later	No ICD discharges controlled on antiarrhythmic therapy.

Case presentation

A 48-year-old female without any history of cardiovascular disease or family history of sudden cardiac death experienced an out-of-hospital cardiac arrest. She was returning home after briefly stepping outside when she suddenly felt nauseous and collapsed. Her family performed cardiopulmonary resuscitation for 10 min until emergency medical services (EMS) arrived. She was found to be in VF and received five defibrillations, intravenous amiodarone, and epinephrine before achieving return of spontaneous circulation. An initial differential diagnosis is displayed in *Table 1*. The patient was sedated and intubated by EMS and emergently admitted to the catheterization lab. Troponin I levels were elevated at 0.698 ng/mL, suggesting myocardial injury with ST changes noted on electrocardiogram (ECG) (*Figure 1*), but coronary angiography showed no significant coronary artery disease. Initial computed tomography angiography (CTA) was negative for pulmonary embolism. Substance abuse testing was only significant for elevated benzodiazepine and sertraline levels, which the patient was taking to control anxiety and depression, respectively.

A 12-lead ECG showed sinus tachycardia of 115 beats per minute with normal QRS complexes (80 ms) and absence of prolonged PR or QTc intervals (180 and 443 ms by Bazzett's formula, respectively) (*Figure 1*). Leads V1, V2, and aVR demonstrated ST segment elevation, while leads II, III, and aVF demonstrated reciprocal ST segment depression. The patient subsequently underwent therapeutic hypothermia with a ZOLL Medical Thermoguard XP® catheter (Chelmsford, MA, USA). Initial transthoracic echocardiography (TTE) showed decreased left ventricular ejection fraction (LVEF) 30–35%, severe diffuse hypokinesis, normal left ventricle wall thickness, early diastolic dysfunction, and moderately decreased right ventricle function. On lower right extremity ultrasound, an incidental thrombus on the hypothermia catheter was found, and low-intensity heparin was subsequently started.

The patient recovered well and was extubated on day 8. Repeat TTE showed significant recovery with increased LVEF of 60–65% and normalized right ventricular function, chamber size, wall motion, and thickness. Cardiac magnetic resonance imaging (MRI) with gadolinium enhancement confirmed normal left and right ventricle function without structural abnormalities, fibrosis, or evidence of myocardial infarction. Cardiac MRI also revealed suspected pulmonary emboli likely due to the hypothermia catheter. CTA confirmed non-occlusive pulmonary emboli in the right lower lobar pulmonary artery and right upper segmental and subsegmental pulmonary arteries. She was therefore started on apixaban.

She subsequently underwent a successful subcutaneous implantable cardioverter defibrillator (ICD) implant with a Boston Scientific EMBLEM™ MRI subcutaneous ICD (Marlborough, Massachusetts, USA) on day 19 and was discharged the day after the procedure. ECG post-ICD implant showed borderline tachycardic sinus rhythm

Table 1 Initial differential diagnosis of the patient's presentation

Anterior ST-elevation myocardial infarction
Acute pulmonary embolism
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Long-QT syndrome
Brugada syndrome
Catacholaminergic polymorphic ventricular tachycardia

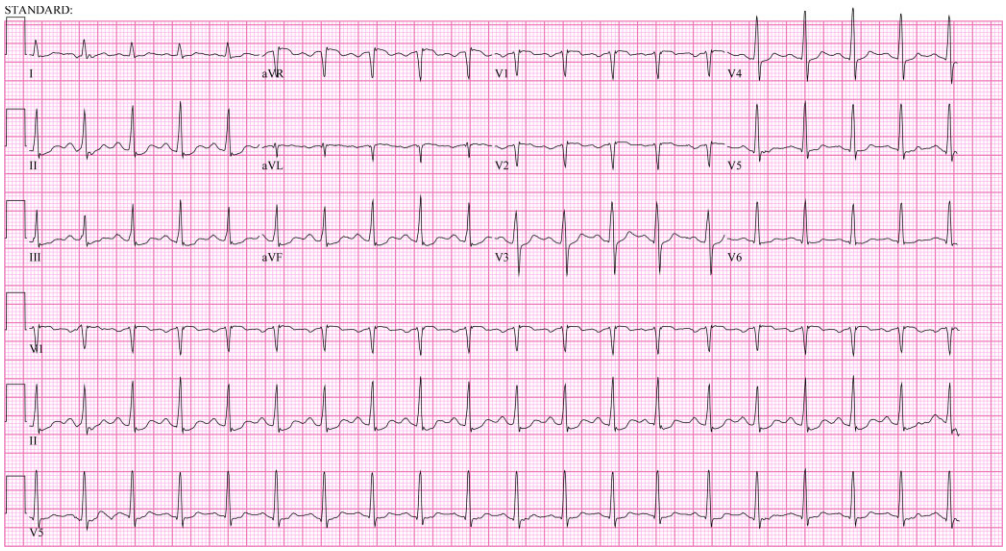

Figure 1 Twelve-lead electrocardiogram after admission.

at 97 beats per minute with normal PR and QTc intervals (140 and 413 ms by Bazzett's formula, respectively) and persistent T-wave inversions (*Figure 2*).

The patient was admitted into cardiac rehabilitation and recovered uneventfully with significant gains in exercise tolerance. As the aetiology of the VF was unknown, genetic testing was discussed with the patient, which she consented to having it performed. Her family history revealed that the patient's father was diagnosed with paroxysmal atrial tachycardia at age 37, and her paternal grandmother had a history of paroxysmal atrial tachycardia and heart block with a 'cardiac event' of unspecified aetiology in her 50s. Genomic DNA from a sputum sample was analyzed via Ambry Genetics' CardioNext® targeted gene panel (Aliso Viejo, CA, USA). Testing revealed a VUS identified as a heterozygous c.2162G > A/p.R721H variant within exon 18 of the *ACTN2* gene. The variant was predicted *in silico* as 'disease causing' by MutationTaster2, 'probably damaging' by Polymorphism Phenotyping v2 (PolyPhen-2), and 'deleterious' by Sorting Intolerant From Tolerant missense prediction tools.[2–4] On anti-arrhythmic therapy, no further episodes occurred with no discharges from her ICD.

Discussion

Idiopathic VF is a diagnosis of exclusion made in patients resuscitated from cardiac arrest who experience VF without identified cardiac, respiratory, metabolic, and toxicological causes. This case report details the first known c.2162G > A/p.R721H missense variant of the *ACTN2* gene associated with idiopathic VF.

The *ACTN2* gene encodes the alpha-actinin-2 protein, which has been shown to interact with cardiac sodium and potassium ion channels via the protein's spectrin-like repeats. Alpha-actinin-2 is a dimeric protein which functions to link cardiac F-actin filaments from neighbouring sarcomeres to the Z-disc and anchor protein components of the Z-disc.[5–7] Alpha-actinin-2 was shown to modulate and increase the expression of cardiac $Na_v1.5$ sodium channels (encoded by *SCN5A*) at the cell membrane via binding to its spectrin-like repeat domains.[8] Alpha-actinin-2 was also shown to interact with and regulate ion currents through cardiac $K_v1.4$ and $K_v1.5$ potassium channels (encoded by *KCNA4* and *KCNA5*, respectively) via the spectrin-like repeats.[9,10] In ventricular cardiac action potentials, $Na_v1.5$ is responsible for the rapid depolarization current I_{Na} during phase 0; $K_v1.4$ controls the slow transient outward current $I_{to,\,s}$ during phase 1; and $K_v1.5$ also contributes to phase 1 by the ultrarapid delayed rectifier current I_{Kur}.[11] Thus, alterations of the spectrin-like repeats could interfere with regulation and function of cardiac ion channels and disrupt ventricular action potentials.

While recorded *ACTN2* variants to date have also been associated with either dilated or hypertrophic cardiomyopathy, we propose that the c.2162G > A/p.R721H *ACTN2* gene variant was responsible for this patient's idiopathic VF.[6,12] The p.R721H residue is located within the fourth spectrin-like repeat (SR4) of the alpha-actinin-2 protein and is highly conserved.[7] While the variant may not alter the structural function of the protein at cardiac Z-discs, as evidenced by the lack of structural heart changes on TTE and cardiac MRI, the variant could alter binding sites in the spectrin-like repeat and contribute to dysregulation of the cardiac ion channels $Na_v1.5$, $K_v1.4$, and $K_v1.5$. This could have resulted in aberrant ventricular cardiac action potentials and induced the idiopathic VF observed in this case (*Figure 3*). *In vitro* testing of the altered alpha-actinin-2 protein is needed to determine pathogenicity of this VUS.

Genetic testing is a subject of debate in patients with idiopathic VF. Plausible pathophysiology guided by a positive result may help with treatment and closure for the patient, especially in patients with a high clinical suspicion for a specific genetic aetiology or in a proband with a family history.[1] On the other hand, genetic testing also comes with limitations. Yields for targeted exome sequencing based on clinical

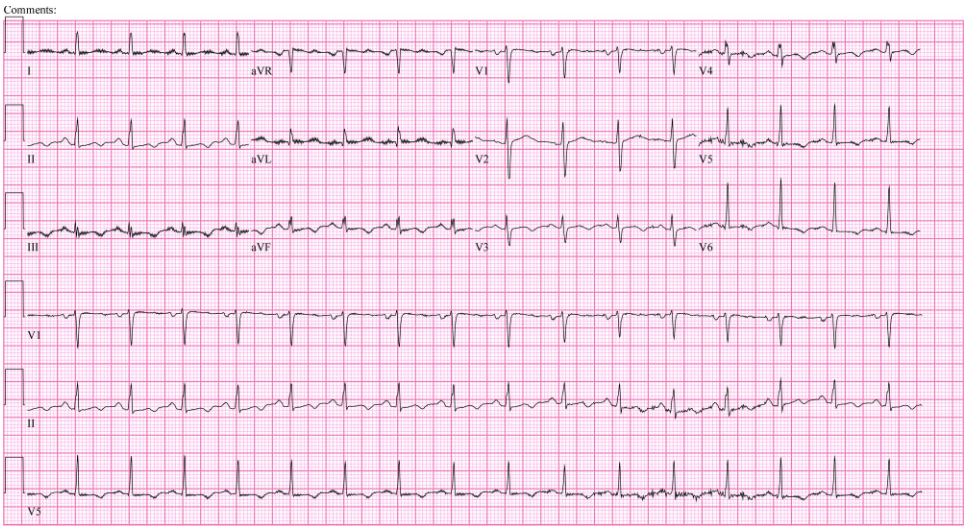

Figure 2 Twelve-lead electrocardiogram post-implantable cardioverter defibrillator implantation just before discharge.

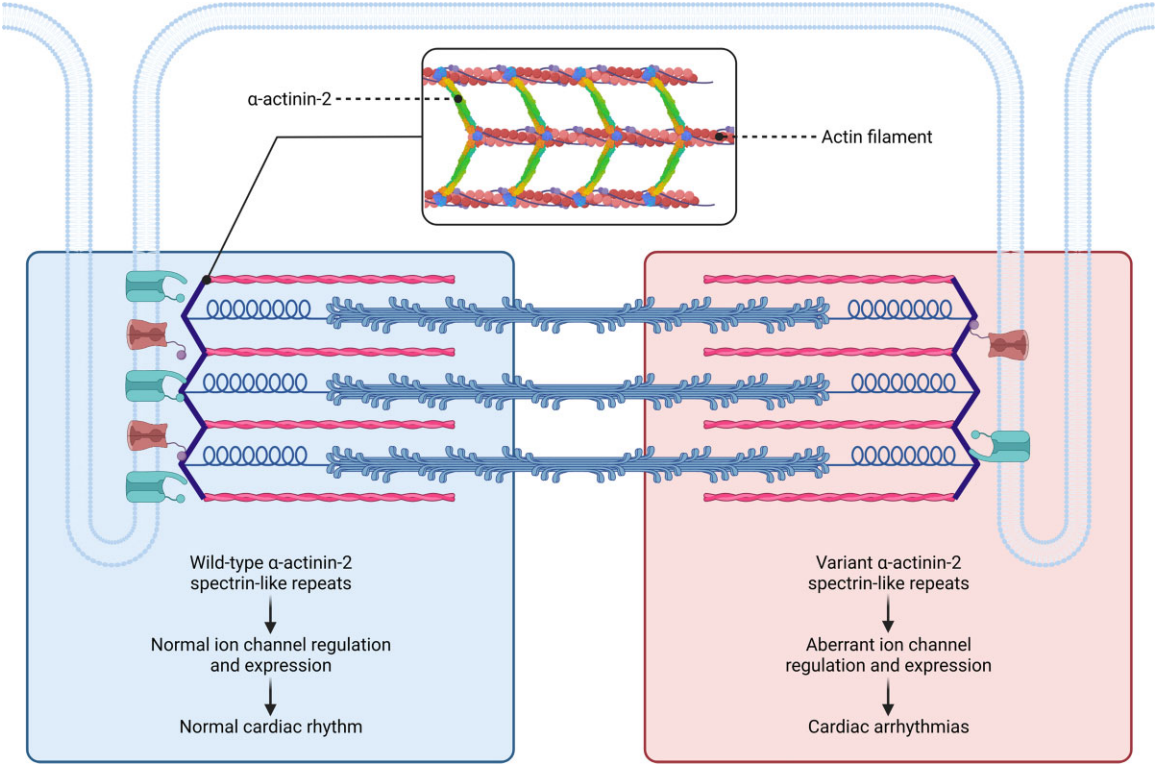

Figure 3 Pathogenic missense variants in the spectrin-like repeats of alpha-actinin-2 may lead to dysregulation of cardiac ion channels, leading to arrhythmias without the overt presence of cardiomyopathies. Figure created with BioRender.com.

suspicion range in several studies between 21–47%, and a negative genetic test does not preclude the possibility of a genetic aetiology for VF.[1,13] Additionally, genetic testing which reveals a VUS may result in unnecessary harm from excess treatment or anxiety to the patient.[1,13]

Conclusion

Pathogenic variants of *ACTN2* have not been associated with arrhythmias in the absence of overt structural heart disease. c.2162G > A/p.R721H is a newly identified missense variation of the *ACTN2*

gene that is associated with idiopathic VF. Variants of *ACTN2* gene located in the protein's spectrin-like repeats, which interact with and regulate the cardiac ion channels $Na_v1.5$, $K_v1.4$, and $K_v1.5$, may contribute to arrhythmias.

Lead author biography

Cody R. Hou is a second year medical student at the University of Minnesota, Twin Cities. He is spending a gap year conducting research as a Sarnoff Cardiovascular Research Fellow. He is currently interested in the field of cardiology, specifically electrophysiology. In his free time he enjoys landscape photography and road cycling.

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

The patient provided informed consent to publish this case report, with approval from the Institutional Review Board (IRB) of the University of Minnesota, IRB #STUDY00005846.

Conflict of interest: The authors have no conflicts of interest to declare.

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