

# Left-dominant arrhythmogenic cardiomyopathy: an association with desmoglein-2 gene mutation—a case report

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## Background

Desmosomes are specialized intercellular adhesive junctions of cardiac and epithelial cells that provide intercellular mechanical coupling through glycoproteins, one of which is desmoglein (DSG). DSG-2 mutations are frequently associated with biventricular arrhythmogenic cardiomyopathy (ACM). We report a case of left-dominant ACM in a patient who initially was misclassified as dilated cardiomyopathy (DCM).

## Case summary

A 28-year-old-woman was found to have a moderately reduced left ventricular (LV) systolic function and frequent premature ventricular contractions (PVCs). Targeted genetic testing revealed a heterozygous likely pathogenic variant associated with ACM in exon 15 of the DSG-2 gene (c.3059\_3062del; p.Glu1020Alafs\*18). Subsequent cardiac magnetic resonance (CMR) imaging showed epicardial and mid-myocardial fatty infiltration involving multiple LV wall segments, multiple areas of mid-myocardial fibrosis/scar, regional dyskinesia involving both ventricles, and an overall reduced left ventricular ejection fraction. The patient's right ventricular (RV) cavity size and overall RV systolic function were normal. Based on the patient's frequent PVCs, family history, fibrofatty myocardial replacement in multiple LV segments, and dyskinetic motion of multiple ventricular wall segments (predominantly affecting the LV), the patient was diagnosed with left-dominant ACM.

## Discussion

Identifying a likely pathogenic mutation associated with ACM in a patient with ventricular arrhythmias and a family history of sudden cardiac death increased the possibility of ACM. Subsequent CMR imaging confirmed the diagnosis of left-dominant ACM by demonstrating regional biventricular dyskinesia and a characteristic pattern of fibrofatty myocardial replacement. Our case highlights the importance of targeted genetic testing and advanced cardiac imaging in distinguishing left-dominant ACM from DCM.

## Keywords

Arrhythmogenic cardiomyopathy • Left-dominant arrhythmogenic cardiomyopathy • Dilated cardiomyopathy • Cardiac magnetic resonance imaging • Desmoglein-2 gene • Case report

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## Learning points

The learning points include:

- Emphasizing the importance of a detailed family history, Holter monitoring, targeted genetic testing, and advanced cardiac imaging in distinguishing left-dominant arrhythmogenic cardiomyopathy (ACM) from dilated cardiomyopathy and other aetiologies of non-ischaemic cardiomyopathy.
- Describing the morphological findings of left-dominant ACM associated with a likely pathogenic desmoglein-2 mutation.
- Recognizing the limitations of the International Task Force criteria and further additions might be needed to properly diagnose left-dominant ACM.

## Introduction

It is well established that mutations in different components of the desmosomal complex are commonly associated with arrhythmogenic cardiomyopathy (ACM), including classic right ventricular arrhythmogenic cardiomyopathy (ARVC/D), biventricular ACM (left-dominant or right-dominant variants), and isolated left ventricular (LV) ACM with no significant right ventricular (RV) involvement.<sup>1–4</sup>

An inherited form of heart disease, ACM is characterized pathologically by abnormal fibrofatty myocardial replacement and clinically by prominent ventricular arrhythmias in addition to impairment of ventricular systolic function. ACM occurs at an estimated rate of 1:1000–5000 and is considered one of the leading causes of sudden cardiac death (SCD) in young people.<sup>5,6</sup> The diagnosis of ACM involves identification of genetic factors, electrocardiogram (ECG) abnormalities, arrhythmias, and functional ventricular dysfunction. We report a case of left-dominant ACM in a patient with a likely pathogenic mutation in the desmoglein 2 gene (DSG-2) who initially was misclassified as having a dilated cardiomyopathy (DCM).

## Timeline

September 2019	A 28-year-old woman presented to the office with complaints of palpitations and episodic dyspnoea. A 12-lead electrocardiogram showed premature ventricular contractions (PVCs). A subsequent Holter monitor revealed frequent PVCs and seven episodes of 3–10 beat runs of non-sustained monomorphic ventricular tachycardia with rates up to 152 b.p.m.
October 2019	Transthoracic echocardiogram showed a dilated cardiomyopathy with a reduced left ventricular ejection fraction of ~30%. Started on guideline-directed medical therapy for heart failure

*Continued*

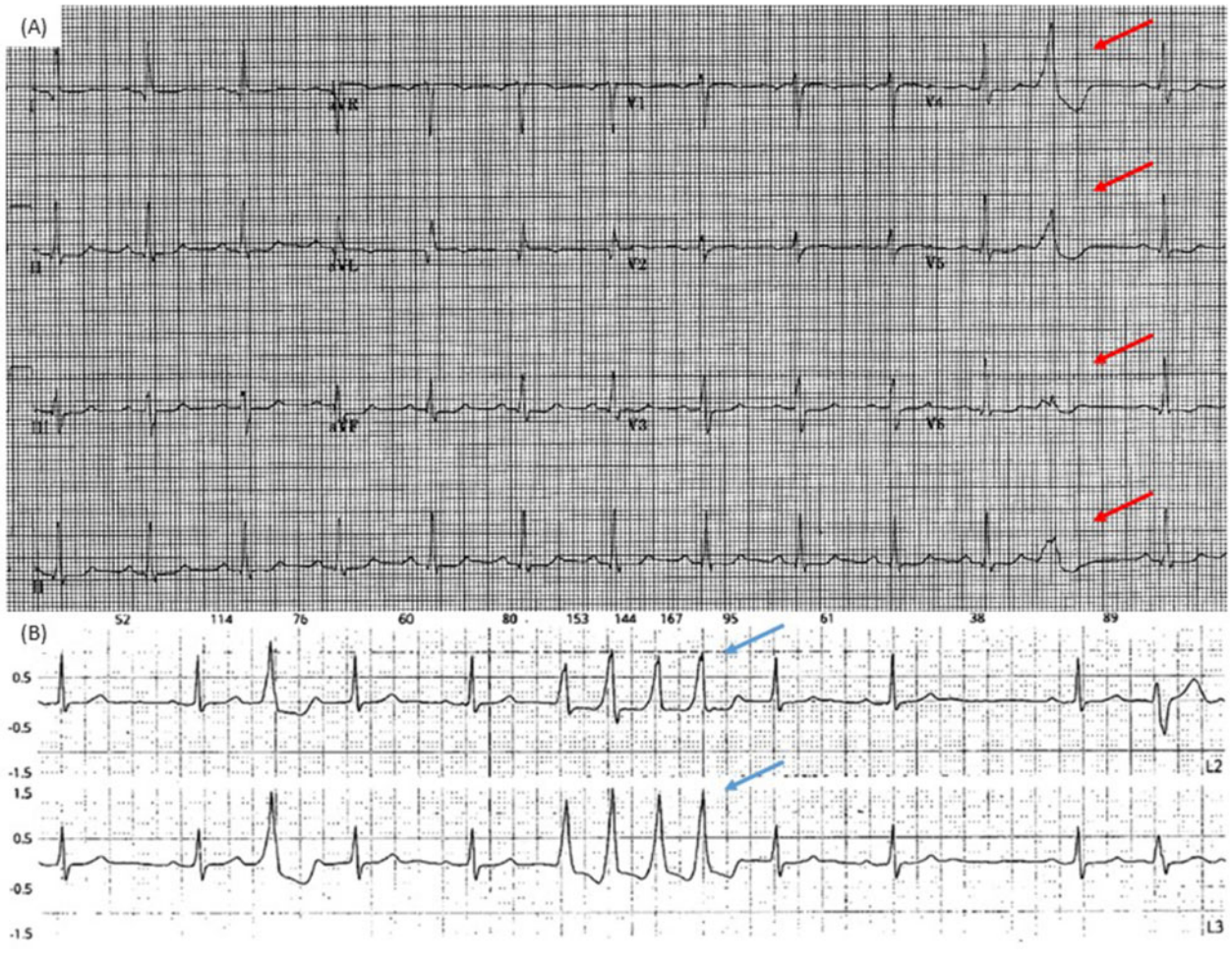
February 2020	Computed tomography angiography revealed normal coronary anatomy. This prompted genetic evaluation. Comprehensive genetic analysis revealed a desmoglein-2 gene mutation
March 2020	Cardiac magnetic resonance imaging findings revealed fibrofatty replacement in multiple left ventricular (LV) segments and regional biventricular dyskinesia predominantly affecting the LV. The patient was diagnosed with arrhythmogenic cardiomyopathy with a left-dominant phenotype
July 2020	Implantation of a cardiac defibrillator for primary prevention. Given her severely reduced LV ejection fraction and increased risk for sudden cardiac death

## Case presentation

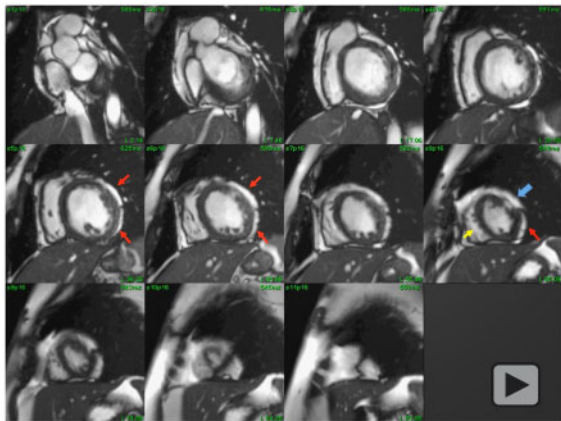
A 28-year-old Caucasian woman presented with palpitations and episodic dyspnoea. She had a significant family history of her mother developing DCM in her 30s complicated with sudden cardiac arrest (SCA). The patient had a past medical history of mild persistent asthma and obesity. She had two uneventful pregnancies when she was 23 and 26 years of age. She did not have any history of tobacco, alcohol, or substance use. She denied participating in sports or that she performed strenuous physical activities on a regular basis. The patient's physical examination revealed a blood pressure of 128/70 mmHg and heart rate of 90 beats per minute (b.p.m.). Her cardiac examination was unremarkable for any murmurs, gallops, rubs, jugular venous distention, or rales. An electrocardiogram (ECG) showed a premature ventricular contraction (PVC) in the pre-cordial leads. In addition, Holter monitoring revealed frequent PVCs (>5000 PVCs/24 hours) and sixteen episodes of nonsustained monomorphic ventricular tachycardia (VT) with rates up to 152 bpm (Figure 1).<sup>1</sup>

A transthoracic echocardiogram showed a DCM with a reduced left ventricular ejection fraction (LVEF) of ~30%. After the patient's coronary anatomy was found to be normal on coronary computed tomography angiography, she underwent a comprehensive analysis of 67 genes primarily associated with inherited forms of arrhythmia and cardiomyopathy (PKP2, DSG2, TTN, DES, DSP, LMNA, KCNA5, etc.; Invitae Corporation; San Francisco, CA, USA). She was found to have a heterozygous likely pathogenic variant in exon 15 of the DSG-2 gene (c.3059\_3062del; p.Glu1020Alafs\*18). The sequence caused a premature translational stop signal in the DSG-2 gene and was expected to disrupt the last 99 amino acids of the DSG-2 protein as seen in the functional protein analysis. A similar likely pathogenic DSG-2 variant was previously reported in individuals affected with ACM (rs74685437B, ExAC 0.007% ClinVar Variation ID: 199827).<sup>5</sup>

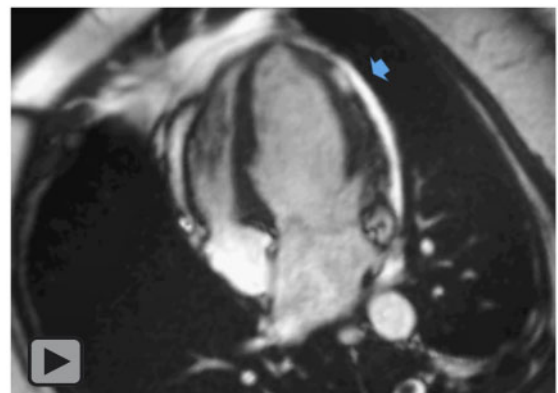
To further assess the aetiology of her cardiomyopathy, the patient underwent cardiac magnetic resonance (CMR) imaging which revealed regional biventricular systolic dysfunction, including dyskinesia of the mid-inferolateral, mid-anterolateral, distal septal, distal



**Figure 1** (A) 12-lead ECG showing a premature ventricular contraction (red arrows). (B) Holter monitor rhythm strip demonstrating non-sustained ventricular tachycardia (blue arrows) and two premature ventricular contractions.



**Video 1** Short axis balanced steady-state free precession (bSSFP) cine demonstrating dyskinesia of the mid inferolateral, mid anterolateral and distal lateral walls (red arrows) and distal septal walls (yellow arrow). Mid and epicardial myocardial fatty infiltration of the distal lateral wall is also seen (blue arrow).



**Video 2** Four chamber balanced steady-state free precession (bSSFP) cine demonstrating myocardial fatty infiltration and dyskinesia of the distal lateral wall (blue arrow).

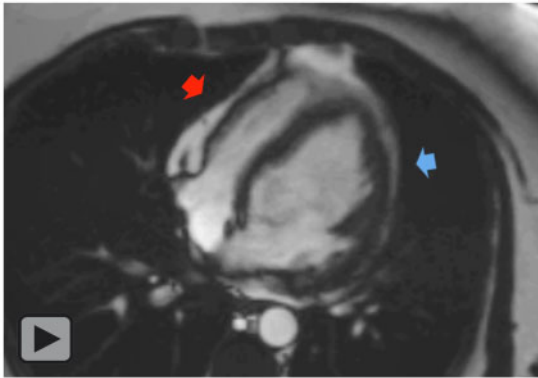
lateral walls, and basal RV free wall (*Videos 1–3*). The patient's LVEF was moderately reduced at 35% and RV cavity size and overall right ventricular ejection fraction (RVEF) were normal. She had mid-myocardial and epicardial fatty infiltration involving multiple LV wall segments that were most pronounced in the dyskinetic segments. She also had mid-myocardial late gadolinium enhancement (LGE), consistent with fibrosis, of the distal septal wall and epicardial LGE of the basal to mid-inferolateral wall (*Figures 2 and 3*). Further tissue characterization utilizing T1 weighted mapping (SHMOLLI) demonstrated reduced global myocardial T1 relaxation time with focal areas of

greatly reduced myocardial T1 relaxation time in the anteroseptal and anterolateral walls, most consistent with focal areas of myocardial fatty infiltration (*Figure 4*).

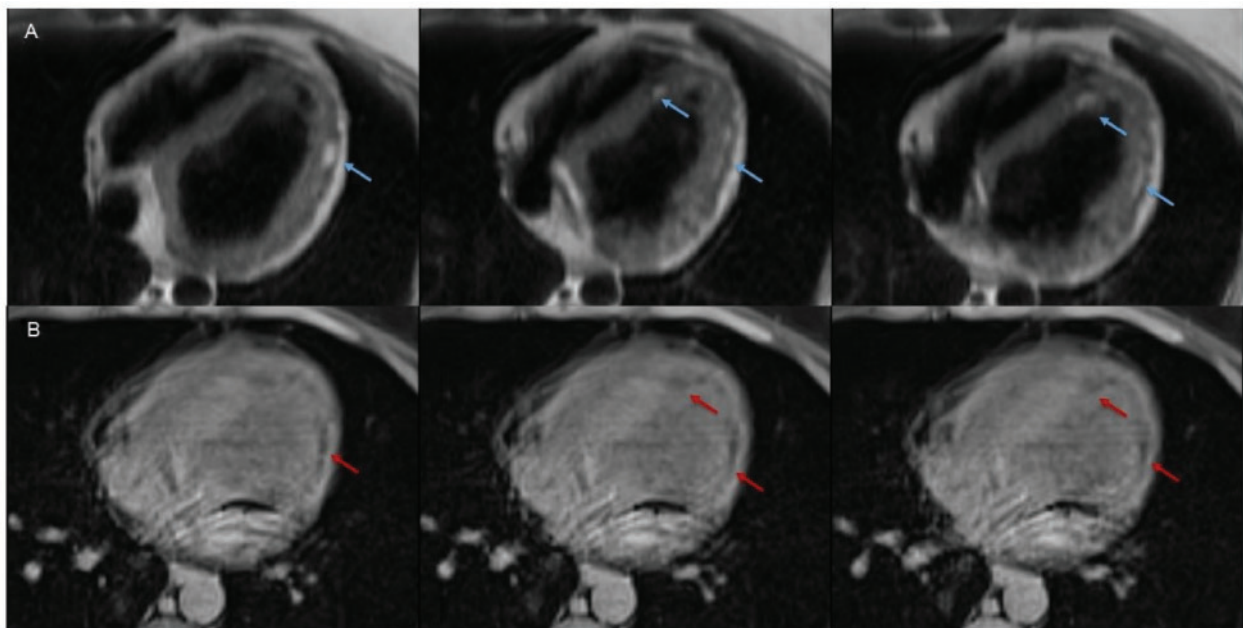
Based on the clinical presentation of ventricular arrhythmias, family history of SCA, known likely pathogenic mutation in the DSG-2 gene, abnormal fibrofatty replacement in multiple LV segments, and regional biventricular dyskinesia predominantly affecting the LV, the patient was diagnosed with left-dominant ACM and was managed according to published recommendations with guideline-directed medical therapy (carvedilol 12.5 mg twice daily and sacubitril–valsartan 49–51 mg twice daily) and cascade clinical screening of her first-degree family members.<sup>6,7</sup> She subsequently underwent implantation of a cardiac defibrillator for primary prevention given her significantly reduced LVEF despite guideline-directed medical therapy, ongoing heart failure symptoms, and an expected meaningful survival of more than 1 year.<sup>7,8</sup> At 6 months follow-up, the patient continued to do well on medical therapy with no major arrhythmic events.

## Discussion

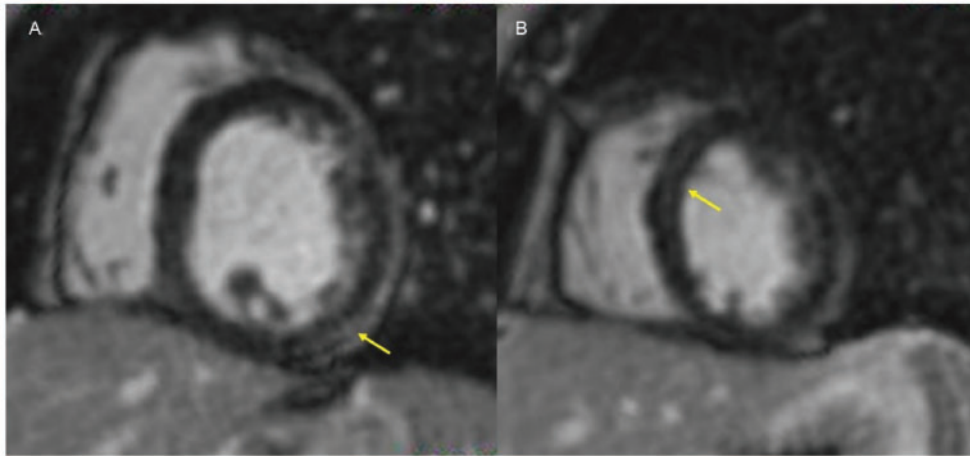
One of the main clinical hallmarks of ACM is ventricular dysfunction (not explained by hypertensive, ischaemic, or valvular disease) accompanied by symptomatic or documented arrhythmias.<sup>7</sup> Unlike classic ARVC affecting the right ventricle, left-dominant or isolated left ACM presenting with significant LV systolic dysfunction can overlap with a DCM phenotype presenting primarily with arrhythmias. For example, a recent large autopsy series of patients who suffered SCD found that some individuals diagnosed with DCM in life had pathological features consistent with ACM at autopsy. This highlights



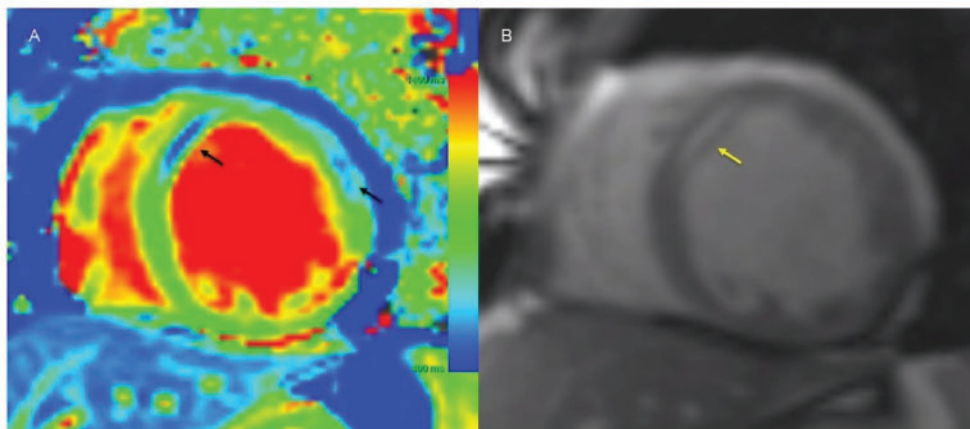
**Video 3** Axial balanced steady-state free precession (bSSFP) cine demonstrating dyskinesia of basal right ventricular free wall (red arrow) and the distal lateral wall (blue arrow).



**Figure 2** (A; top row) Axial HASTE demonstrating myocardial fatty infiltration (blue arrows) of the mid to distal lateral wall and septum and (B; bottom row) corresponding areas of suppressed myocardial fatty infiltration on axial T1 Dixon fat saturation sequences (red arrows).



**Figure 3** Short axis phase sensitive inversion recovery late gadolinium enhanced images demonstrating (A) late gadolinium epicardial enhancement of the mid-inferolateral wall and (B) mid-myocardial enhancement of the distal septal wall (yellow arrows).



**Figure 4** (A) Native T1 map (SHMOLLI) demonstrating reduced global T1 relaxation time ( $T1 = 827$  ms) with focal, very reduced T1 relaxation time (black arrows) of the mid-myocardial basal anteroseptal wall ( $T1 = 495$  ms) and epicardial basal anterolateral wall ( $T1 = 562$  ms); the basal infero-septum (green) had a T1 relaxation time =  $922 \pm 42.9$  ms, which was within our institution's normal range of T1 relaxation time (normal myocardial  $T1 = 945\text{--}965$  ms). (B) T2 map demonstrating mid-myocardial fatty infiltration of the basal anteroseptal wall (yellow arrow).

the difficulty in distinguishing DCM from ACM clinically using traditional diagnostic tools such as the 2010 modified International Task Force (ITF) diagnostic criteria, which often under-recognizes left-dominant or isolated LV ACM.<sup>3,9</sup> Moreover, differentiating the two diseases can be further challenging based on genotyping alone, as desmosomal gene mutations have been associated with both ACM and DCM.<sup>10</sup> The reason why particular desmosomal gene mutations have the potential to cause different cardiomyopathy phenotypes is not fully understood. Many have hypothesized that the cause is likely due to interacting final common pathways leading to a spectrum of phenotypes. Based on the known overlap, several authors have proposed shifting the current ACM classification which is based on phenotypic findings to a pathogenic categorization under a broad category of ACM.<sup>7</sup>

Other cardiac conditions, such as cardiac sarcoidosis and inflammatory myocarditis, can mimic the clinical findings of genetic ACM. Cardiac sarcoidosis usually is distinguished from ACM by the presence of conduction abnormalities (such as high-grade AV block), extra-cardiac symptoms (such as fever, weight loss, changes in vision), and extra-cardiac findings (such as hilar lymphadenopathy).<sup>11,12</sup> Myocarditis is often more challenging to differentiate from ACM, as inflammatory myocarditis is thought to be part of the pathogenesis of ACM and often the first clinical presentation of genetic ACM. Targeted genetic testing is usually needed to differentiate myocarditis from early left-dominant ACM.<sup>13</sup>

The gap in knowledge in diagnosing left-dominant or isolated LV ACM was addressed by a recent European Society of Cardiology expert report. In the report, authors suggested several distinctive

criteria for detecting LV involvement in ACM, including the presence of inverted inferolateral T waves on ECG, monomorphic VT with RBBB morphology on cardiac monitoring, and a significant non-ischaemic pattern of mid-myocardial/epicardial LGE in multiple LV segments on CMR. In left-dominant or biventricular forms of ACM, demonstrating RV involvement or pathogenic mutation related to ACM were proposed as important distinguishing factors in differentiating left-dominant ACM from DCM.<sup>6</sup> CMR detection of significant non-ischaemic epicardial/mid-myocardial myocardial fatty infiltration—which is a common CMR morphological feature associated with left-dominant ACM<sup>3</sup>—was excluded as a possible diagnostic criterion.<sup>3,6</sup>

In our patient, her clinical presentation and findings were not suggestive of inflammatory conditions such as sarcoidosis or myocarditis and she was found to have a likely pathogenic variant related to ACM in exon 15 of the DSG-2 gene. A 'likely pathogenic' variant is defined by the American College of Medical Genetics and Genomics (ACMG) as a variant that has >90% certainty of being disease-causing and can be used in clinical decision-making when combined with clinical evidence of the disease.<sup>14</sup> Nonetheless, identifying a likely pathogenic gene associated with ACM was insufficient to fulfil the ITF criteria for the diagnosis of ARVC, despite meeting one major criterion (identification of a gene mutation likely associated with ACM) and one minor criterion (>500 PVCs detected on 24 Holter). Furthermore, although our patient had focal dyskinesia involving her RV free wall, she failed to meet specific echocardiographic- or CMR-related ITF diagnostic structural criteria for the diagnosis of ACM because her RV cavity size and RVEF were preserved.<sup>3</sup> The patient's ACM diagnosis was confirmed after CMR imaging found significant fibrofatty myocardial infiltration in a non-ischaemic pattern causing epicardial contour irregularities ('rat-bite sign'), focal areas of extremely low myocardial T1 relaxation times consistent with focal myocardial fatty infiltration, and regional biventricular dyskinesia not clearly observed on echocardiographic imaging. These characteristic CMR findings were frequently found in a recent series of patients with left-dominant ACM.<sup>15</sup>

It is important to note that in DSG-2 gene mutation carriers, significant LV involvement with no significant RV involvement has been previously reported in members of two families with established DSG-2 mutations and ACM.<sup>2</sup> In another more recent series from France, LV dysfunction was found in more than 50% of patients with DSG-2 mutations and associated with a higher likelihood of developing end-stage heart failure compared to patients with the more common PKP-2 gene mutation.<sup>4</sup>

Our case highlights the importance of a comprehensive clinical assessment in the evaluation of patients who have unexplained DCM associated with ventricular arrhythmias or a family history of malignant arrhythmias/SCA. It also demonstrates the urgent need to establish specific left-dominant ACM imaging criteria incorporating characteristic CMR imaging discoveries published in the past decade, including the presence of a unique pattern of subepicardial fatty infiltration and LGE not explained by other disease processes.

## Lead author biography



Nicole Lao is a resident physician at the Internal Medicine Department of Cleveland Clinic Akron General in Akron City, Ohio. Currently, she is doing research focused on heart failure and cardiovascular imaging under the guidance of Dr Adeeb Al-Quthami and Dr Zenab Laiq of the Heart, Thoracic and Vascular Institute.

## 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 report including images and associated text has been obtained from the patient in line with COPE guidance.

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