

# Monozygotic twins with myocarditis and a novel likely pathogenic desmoplakin gene variant

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## Abstract

Myocarditis most often affects otherwise healthy athletes and is one of the leading causes of sudden death in children and young adults. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disorder with increased risk for paroxysmal ventricular arrhythmias and sudden cardiac death. The clinical picture of myocarditis and ARVC may overlap during the early stages of cardiomyopathy, which may lead to misdiagnosis. In the literature, we found several cases that presented with episodes of myocarditis and ended up with a diagnosis of arrhythmogenic cardiomyopathy, mostly of the left predominant type. The aim of this case presentation is to shed light upon a possible link between myocarditis, a desmoplakin (*DSP*) gene variant, and ARVC by describing a case of male monozygotic twins who presented with symptoms and signs of myocarditis at 17 and 18 years of age, respectively. One of them also had a recurrent episode of myocarditis. The twins and their family were extensively examined including electrocardiograms (ECG), biochemistry, multimodal cardiac imaging, myocardial biopsy, genetic analysis, repeated cardiac magnetic resonance (CMR) and echocardiography over time. Both twins presented with chest pain, ECG with slight ST-T elevation, and increased troponin T levels. CMR demonstrated an affected left ventricle with comprehensive inflammatory, subepicardial changes consistent with myocarditis. The right ventricle did not appear to have any abnormalities. Genotype analysis revealed a nonsense heterozygous variant in the desmoplakin (*DSP*) gene [NM\_004415.2:c.2521\_2522del (p.Gln841Aspfs\*9)] that is considered likely pathogenic and presumably ARVC related. There was no previous family history of heart disease. There might be a common pathophysiology of ARVC, associated with desmosomal dysfunction, and myocarditis. In our case, both twins have an affected left ventricle without any right ventricular involvement, and they are carriers of a novel *DSP* variant that is likely associated with ARVC. The extensive inflammation of the LV that was apparent in the CMR may or may not be the primary event of ARVC. Nevertheless, our data suggest that irrespective of a possible link here to ARVC, genetic testing for arrhythmogenic cardiomyopathy might be advisable for patients with recurrent myocarditis associated with a family history of myocarditis.

**Keywords** Myocarditis; Arrhythmogenic cardiomyopathy; Desmoplakin gene

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## Introduction

Myocarditis is defined as an inflammatory disease of the myocardium, mainly caused by viral infections. It mostly affects otherwise healthy athletes, children, and young adults.

Myocarditis is occasionally related to and may be a trigger for arrhythmogenic right ventricular cardiomyopathy (ARVC), and sometimes, these conditions overlap,<sup>1–4</sup> which may lead to misdiagnosis. ARVC is a predominantly genetically determined heart muscle disorder, pathologically characterized by

fibrofatty replacement of the right ventricular myocardium and a high degree of myocardial electrical instability, which significantly increases the risk for ventricular arrhythmias and sudden cardiac death.<sup>5</sup> Despite abnormalities in the right ventricle (RV) being the predominant finding, it has been reported that patients with ARVC may also have left ventricle (LV) involvement, and indeed, severe LV impairment can sometimes be the initial manifestation of the disorder.<sup>6,7</sup> Inflammatory cell infiltrates have been described in patients with ARVC,<sup>8,9</sup> and some patients with ARVC present with signs and symptoms accompanied by electrocardiogram (ECG) changes as well as echocardiography (ECHO) and cardiac magnetic resonance (CMR) findings consistent with myocarditis.<sup>1,9,10</sup>

## Case presentation

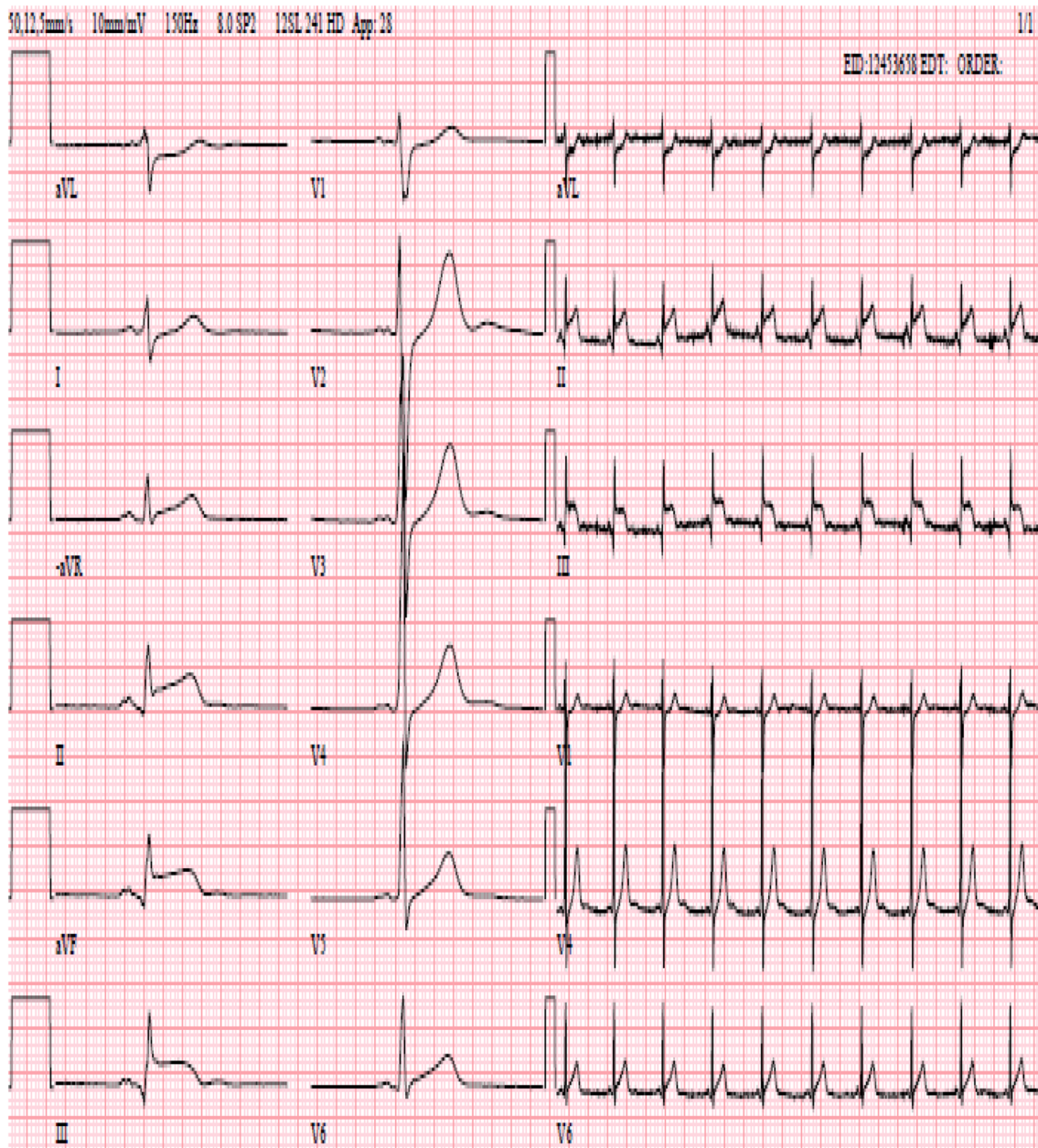
A pair of male monozygotic twins, born in 1998, presented with symptoms and signs of myocarditis at 17 and 18 years of age, respectively. Their parents were second-degree cousins. Our index patient (IV: 1) presented at age 18 with chest pain after having flu-like symptoms. ECG showed slight ST-T elevation inferiorly. Troponin T was elevated to 3600 ng/L (normal < 15 ng/L) and C-reactive protein to 12 mg/L. The ECHO demonstrated an LV with reduced inferolateral wall motion. The LV had normal dimensions with slightly reduced systolic function, with an ejection fraction of 46%. The RV had normal size and function. The CMR imaging showed comprehensive inflammatory, subepicardial changes of the LV in late gadolinium enhancement (LGE) images, consistent with myocarditis. Viral serology was indicative of previous Epstein–Barr virus and cytomegalovirus infections, and rheumatological blood tests were negative. A year later, the index patient (IV: 1) was readmitted at 19 years of age with similar symptoms and imaging findings, consistent with recurrent myocarditis. The CMR did not meet any current Task Force criteria for ARVC<sup>11</sup> as only the LV was affected. During hospitalization, the heart telemetry showed one episode of non-sustained ventricular tachycardia. He was discharged with a beta-blocker and an angiotensin-converting enzyme inhibitor. An endomyocardial biopsy with histochemical and immunohistochemical analysis was performed that did not show any inflammatory changes, granulomas, or signs of infiltrative disease. No convincing interstitial fibrosis was detected, and only subendocardial fibrosis was seen. Cardiac positron emission tomography scan did not depict any sarcoidosis related changes or signs of active inflammation of the myocardium.

In the family history, the twin brother (IV: 2) also had had an episode of myocarditis. He presented at age 17 with chest pain while he was playing football, after having tonsillitis. He had inferior ECG changes (*Figure 1*) and troponin T levels up to 6000 ng/L, and the CMR demonstrated extensive subepicardial non-ischæmic scars of the LV with

inflammation (*Figure 2*) and an LV ejection fraction of 52%. He had a normal-sized RV with normal systolic function.

The father of the twins, who was also a cousin to their mother, died in his forties due to diabetic complications. Their paternal grandfather died due to a severe infection at old age. There was no family history of heart disease. Their remarkable clinical picture motivated a genetic evaluation. Next-generation sequencing was performed with a gene panel including 80 genes associated with inherited cardiac disease (*Table 1*). The genotype analysis revealed a novel nonsense heterozygous variant in the desmoplakin (*DSP*) gene [NM\_004415.2:c.2521\_2522del, (p.Gln841Aspfs\*9)] that is considered likely pathogenic in the heterozygous state, according to the American College of Medical Genetics and Genomics criteria.<sup>12</sup> This specific genetic variant creates a frame shift starting at codon Gln841 and a premature stop nine nucleotides downstream, which should cause loss of protein function thus likely a disease-causing variant, although not earlier described. The variant is absent from controls in the Exome Sequencing Project and more than 251 400 alleles have been sequenced in gnomAD for this position. Genetic variants in *DSP* are mainly linked to ARVC, but may also be a cause of dilated cardiomyopathy and cutaneous manifestations such as palmoplantar keratoderma or woolly hair, typically seen in Naxos disease,<sup>13</sup> but none of the boys had any such manifestations. The 40-year-old mother of the twins (III: 1) is also a carrier of the *DSP* variant, but she has not experienced any cardiac symptoms. Although her ECG and ECHO findings are within normal ranges, the CMR depicted a discrete LV wall motion disturbance anteroseptally and a thin focal scar, reminiscent of that seen following myocarditis. The LV ejection fraction was 55%. The RV was normal in size and function. The maternal grandparents of the twins (II: 1 and II: 2) were also tested, but none of them carry this specific *DSP* variant. Quantitative fluorescence polymerase chain reaction with short tandem repeat markers was used to confirm their parenthood and the monozygotic status of the twins. All nine siblings (III: 2–10) to the mother (III: 1) have also undergone genetic testing without being carriers. Thus, the detected *DSP* variant is a ‘de novo’ variant that has occurred in the mother of the twins. The twins’ younger brother (IV: 3) is not a carrier (*Figure 3*).

Both twins are on clinical follow-up every 6 months, nearly 3 years now after the first admission, with no apparent further medical complications and no arrhythmias either during regular Holter monitoring or exercise test. Their ECGs are completely normal without any repolarization or conduction abnormalities. Control ECHO, in both twins, demonstrated a completely normal RV and LV with ejection fraction around 53%, without any remaining hypokinesia. CMR during follow-up still depicts extensive subepicardial scars of the LV but no myocardial oedema. Both patients are receiving beta-blockers and are discouraged from participating in competitive sports.

**Figure 1** The electrocardiogram of the IV: 2 twin with ST-elevation in inferior leads.

## Discussion

We describe a family with a novel de novo *DSP* genetic variant, which segregates with myocarditis and is considered likely pathogenic and a risk factor for ARVC as it creates a premature stop codon that should cause a loss of function of the desmoplakin protein. A recent published study demonstrated that de novo variants in ARVC are rare.<sup>14</sup> Increasing evidence supports the hypothesis that myocardial injury from myocarditis contributes to the onset of ARVC,<sup>1–4,9,10,15,16</sup> and hence,

myocarditis may be part of the clinical presentation of ARVC. An inflammatory process secondary to infection or immune mechanism has been postulated to be the trigger for myocardial injury in ARVC, in so called hot phases of the disease. It has also been reported<sup>17</sup> that cardiotropic viruses (e.g. enterovirus and adenovirus) are identified more frequently in patients with ARVC than in control subjects.

Several publications have demonstrated the presence of active myocarditis in ARVC patients. Bauce *et al.*<sup>15</sup> first described clinical myocarditis in two siblings with ARVC

**Figure 2** Cardiac magnetic resonance of the IV: 2 twin with subepicardial late gadolinium enhancement (LGE) in the inferolateral and anteroseptal wall of the left ventricle, (arrows).



**Table 1** Genes associated with sudden cardiac death and inherited cardiac diseases used in the NGS 80 gene-panel

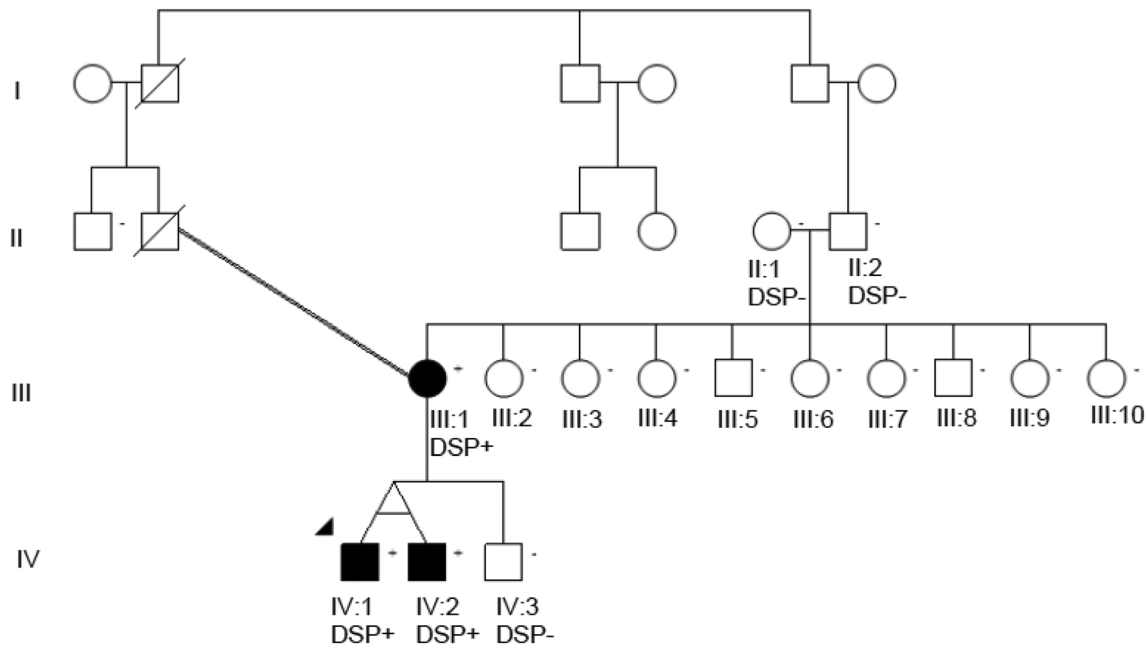
ABCC9	COL3A1	GLA	LDLRAP1	PKP2	TGFBR1
ACTA2	COL5A1	GPD1L	LMNA	PLN	TGFBR2
xACTC1	COL5A2	JUP	MYBPC3	PRKAG2	TMEM43
ACTN2	CSRP3	KCNE1	MYH11	RBM20	TMPO
AKAP9	DES	KCNE2	MYH6	RYR2	TNNC1
ANK2	DMD	KCNE3	MYH7	SCN1B	TNNI3
ANKRD1	DSC2	KCNH2	MYL2	SCN3B	TNNT2
APOb	DSG2	KCNJ2	MYL3	SCN4B	TPM1
BAG3	DSP	KCNJ5	MYLK	SCN5A	TTN
CACNA1C	EMD	KCNJ8	MYLK2	SMAD3	TTR
CACNA2D1	FBN1	KCNQ1	MYOZ2	SNTA1	
CACNB2	FBN2	LAMP2	NEBL	TAZ	
CASQ2	FHL1	LDB3	NEXN	TCAP	
CAV3	FHL2	LDLR	PCSK9	TGFB3	

secondary to a variant in the *DSP* gene, and they highlighted that left ventricular involvement is not a rare feature of the disease in *DSP* mutation carriers. Of 42 patients with left-dominant arrhythmogenic cardiomyopathy (AC), described by Sen-Chowdhry *et al.*<sup>7</sup> four patients had a prior diagnosis of myocarditis. Lopez-Ayala *et al.*<sup>2</sup> analysed the genetic basis of myocarditis in ARVC-affected patients and unaffected mutation-carrying relatives. Seven patients (3.5%) in their cohort presented with myocarditis: two with classic ARVC, four with left-dominant AC, and

one was a gene-positive, phenotype-negative daughter of a patient with left-dominant AC. These episodes of acute myocarditis were recurrent in four cases. Myocarditis was the first clinical presentation in six of the seven cases, and it clustered in families bearing *DSP* gene variants. Reichl *et al.*<sup>1</sup> reported a case of a 24-year-old man with acute myocarditis as the first presentation of AC, and a novel *DSP* variant was reported. Navarro-Manchón *et al.*<sup>18</sup> described a case of a Spanish family, where a 36-year-old male presented with atypical chest pain and CMR findings suggestive of myocarditis. He was admitted 1 year later with poorly tolerated sustained monomorphic ventricular tachycardia. The cardiological and genetic testing diagnosed arrhythmogenic left ventricular cardiomyopathy in the proband and a family member, carrying a novel mutation in the *DSP* gene. An endomyocardial biopsy revealed interstitial fibrosis and myocyte loss < 30% without fatty infiltration, highlighting that cases of myocarditis can trigger episodes of ARVC activity and that the absence of typical ARVC histological data does not rule out the diagnosis. Most of these publications are in favour of the concept that inflammatory myocarditis is part of the natural history of AC where it has a genetic rather than an infective basis. Additionally, focal lymphocyte infiltrates and myocyte necrosis consistent with myocarditis occur in up to 67% of ARVC hearts on post-mortem examination.<sup>8</sup>



**Figure 3** The pedigree of the family. Circles denote women, squares men. A crossed-over symbol indicates that this individual has died. The arrow points out the index patient with two episodes of myocarditis. Consanguinity between the parents of the twins is indicated with a double horizontal line. The genetic variant *DSP* c.2521\_2522del (p.Gln841Aspfs\*9) is indicated with a '+' sign if the individual is a carrier. The *DSP* variant is a de novo variant in the mother (III: 1) of the monozygotic twins (IV: 1 and IV: 2) as none of her parents (II:1 and II:2) and none of her nine siblings (III: 2, 3, 4, 5, 6, 7, 8, 9, 10) is a carrier. The twins' younger brother (IV: 3) is not a carrier of the *DSP* variant.



On the contrary, interpreting the results of our case, we might speculate that *DSP* mutation carriers have an increased susceptibility for myocarditis, without necessarily developing signs of cardiomyopathy. Poller *et al.*<sup>19</sup> described a case of two brothers with recurrent fulminant myocarditis who were carriers of a truncating mutation of *DSP*, but none of them showed histological anomalies or CMR features associated with ARVC. Lopez *et al.*<sup>2</sup> tried also to evaluate the prevalence of myocarditis in a subset of non-affected gene-positive carriers to determine whether they would reveal an initial ARVC phenotype. Only one patient suffered an episode of chest pain and elevated troponin that was not associated with a later change in ECG, Holter monitoring, or imaging.

Hoorntje *et al.*<sup>5</sup> proposed the pathophysiological model shown by experimental models of Basso *et al.*<sup>20</sup> where the penetrance of the underlying ARVC genetic variants could be triggered or modified not only by myocarditis, physical activity, and male gender but also by a gene-dosage effect. In consequence, several factors might contribute to the clinical presentation of ARVC.<sup>5,20</sup> Apparently, the very similar clinical course of disease in both monozygotic twins supports a hypothesis that the combination of myocarditis and the finding of a putatively ARVC-causing genetic variant is highly relevant and not just a coincidence. Considering the extreme rarity of disease-causing *DSP* variants in the population and the low incidence of myocarditis, which is usually estimated between 10 to 20 cases per 100,000 persons, the likelihood of such a

coincidence in two people, even if monozygotic twins living in the same family, must be extremely low. Consequently, we conjecture that the supposedly ARVC-disposing *DSP* variant might render the myocardium prone to myocarditis. The diversity of imaging phenotypes in this family demonstrated by the widespread CMR findings of left ventricular fibrosis measured by CMR-LGE in the boys and the discrete scar pattern on the CMR of their mother would also suggest a negative impact of intense physical activity. Both twins had been participating in sports, mostly football, whereas their mother was not actively exercising. It has been advocated earlier that endurance sport training and myocarditis contribute to the onset and the disease progression of ARVC.<sup>21</sup>

Overall, the twins did not meet the revised 2010 Task Force criteria for the diagnosis of ARVC, because the CMR demonstrated only left ventricular engagement. Corrado *et al.*<sup>22</sup> point out that, in the absence of clinically detectable RV involvement, demonstration of a pathogenic mutation in an ARVC-related gene, such as *DSP*, *FLNC*, and *PLN* gene, may support the diagnosis of left-dominant variant of ARVC. The non-sustained ventricular tachycardia in the index patient (IV: 1) could be caused by the acute phase of myocarditis but could also be part of ensuing cardiomyopathy. The endomyocardial biopsy performed in one of the boys turned out to be normal; however, only part of the RV was examined and not the diseased LV. The index patient was referred for genetic testing based on the widespread LGE pattern in the

LV identified by the CMR, the recurrent episode of myocarditis, and the family history. Pathogenic variants in *DSP* may cause recurrent myocarditis,<sup>2,19</sup> and mutation screening enables early detection of high-risk patients with similar phenotypes. The presence of recurrent myocarditis as well as a positive family history of myocarditis or cardiomyopathy should alert clinicians to look for cardiomyopathy genes. Phenotype/genotype studies<sup>15,23,24</sup> suggest that *DSP* mutations are associated with a severe ARVC phenotype, with a higher risk of ventricular arrhythmias and sudden cardiac death and a high level of LV involvement, particularly in patients with truncating *DSP* mutations. The same studies would also indicate a higher incidence of myocarditis in *DSP* mutation carriers affected by the left dominant type of ARVC. The 2010 Task Force criteria for the diagnosis of ARVC are not reliable in these patients. CMR imaging and genetic testing are the keys for their evaluation.

In summary, we describe for the first time a pair of monozygotic twins carrying a likely pathogenic *DSP* variant and presenting with signs of myocarditis, extensive LGE pattern in the LV on the CMR without any RV involvement. We may speculate that this *DSP* variant increases the myocardial susceptibility to viral infection as well as the risk of left dominant type of ARVC, in which case the episodes of myocarditis may be part of the clinical presentation as a superimposed phenomenon during the natural history of the cardiomyopathy.

## Conclusions

Acute myocarditis may reflect an active phase of ARVC and act as the initial trigger for the disease. The challenging question is whether the myocarditis episodes described here are signs of ARVC, or whether ARVC and myocarditis are mimicking disorders. Future studies using a panel of genes associated with cardiomyopathy and also genes that regulate inflammation and susceptibility to viruses associated with myocarditis might provide the missing answer. Nevertheless, based on this case, genetic screening of cardiomyopathy

genes may be recommended for patients with recurrent myocarditis, especially if there is a family history of myocarditis or cardiomyopathy. In the current case, the monozygotic twins both have an affected LV without any RV involvement, and they are carriers of a *DSP* variant that is likely associated with ARVC. If not a coincidence, the *DSP* variant seems to render the myocardium prone to myocarditis, which might or might not represent an active inflammatory phase of the ARVC disease process.

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## Conflict of interest

None declared.

## Ethical approval

The study was approved by an Ethics Committee Dnr: 2016/389–31, and all individuals gave informed consent prior to enrolment. The study complies with the ethical guidelines of the 1975 Declaration of Helsinki.

## Consent for publication

Participants in the present case have signed an informed consent to participate in the study.

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