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HEART FAILURE AND CARDIOMYOPATHIES

CLINICAL CASE

A Novel Homozygous Mutation of the Desmoplakin Gene With Biventricular Arrhythmogenic Cardiomyopathy

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ABSTRACT

BACKGROUND A 23-year-old male with arrhythmic syncope and a presumed diagnosis of COVID-19 myocarditis was ultimately diagnosed with biventricular arrhythmogenic cardiomyopathy based on cardiac magnetic resonance imaging (MRI) and genetic testing (next-generation sequencing).

CASE SUMMARY The patient presented with recurrent syncope, frequent ventricular ectopics, and reduced left ventricular ejection fraction. Cardiac MRI revealed biventricular dysfunction and nonischemic late gadolinium enhancement with ring-like pattern. Genetic analysis identified a novel homozygous desmoplakin (DSP) mutation. He was treated with heart failure therapy and received an implantable cardioverter-defibrillator due to high arrhythmic risk. Family screening revealed heterozygous carriers among his relatives.

DISCUSSION This case underscores the importance of integrating advanced imaging with genetic testing in early-onset cardiomyopathies and expands the phenotype of DSP-related disease. (JACC Case Rep. 2025;30:103688)

HISTORY OF PRESENT ILLNESS

A 23-year-old man who had been initially evaluated at the emergency department (ED) of the University of Pisa was admitted to our hospital, Fondazione Toscana G. Monasterio, for a diagnostic workup after 2 recent episodes of syncope preceded by palpitations while he was driving a car and a motorbike, respectively. At the ED he had been found positive for SARS-CoV-2 infection and showed paroxysmal atrial fibrillation, ventricular ectopics on the electrocardiogram (ECG), and mild left ventricular systolic dysfunction (left ventricular ejection fraction [LVEF] 48%) at echocardiography, associated with a slight elevation of both high-sensitivity troponin T (up to 86 ng/L; upper reference limit <14 ng/L) and N-terminal pro-B-type natriuretic peptide (NT-proBNP 619 ng/L).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

DSP = desmoplakin

ECG = electrocardiogram

ED = emergency department

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LV = left ventricle

LVEF = left ventricular ejection fraction

MRI = magnetic resonance imaging

NSVT = nonsustained ventricular tachycardia

RV = right ventricle

SCD = sudden cardiac death

PAST MEDICAL HISTORY

The patient's past medical history was completely negative apart from paroxysmal palpitations of short duration from adolescence. The presumed diagnosis proposed at the ED was COVID-19-related myocarditis.

INVESTIGATIONS

The 12-lead ECG showed fragmented QRS, negative T waves in the V_2-V_5 leads, and ectopics with right bundle branch block morphology and superior axis (**Figure 1**). The baseline echocardiography showed a 38% LVEF with normal left ventricular volumes and no pericardial effusion. Cardiac magnetic resonance imaging (MRI) evidenced a global disfunction (LVEF 31%, right ventricular ejection fraction 40%) with biventricular regional wall motion abnormalities (Video 1). T2-weighted sequences were negative for myocardial edema whereas postcontrast images revealed a nonischemic late gadolinium enhancement (LGE) with a ringlike pattern and subepicardial/intramyocardial extension involving all LV segments and part of the RV free wall (**Figure 2**).

Holter ECG monitoring showed sinus rhythm (normal heart rate and standard deviation of RR intervals), frequent ventricular ectopics (8,518 per 24 hours), and nonsustained ventricular tachycardia (NSVT) (up to 12 beats, heart rate 185 beats/min). Coronary angiography was not performed given the clinical presentation (young age, syncope, no chest pain) and the clearly nonischemic pattern of LGE on cardiac MRI. The MRI imaging was initially interpreted as possibly associated with hypokinetic nondilative cardiomyopathy.

The molecular basis of the disease was identified for the proband with next-generation sequencing technology using Illumina's Trusight Cardio sequencing panel covering 174 genes clinically relevant to cardiac diseases. The genetic analysis revealed a missense variant in the desmoplakin gene (*DSP* NM_004415.4: c.6328 G>C, p.Ala2110Pro; chr6-7583823-G-C [GRCh37/hg19]). The proband was homozygous for this variant, which was initially classified as a variant of unknown significance (VUS) according to American College of Medical Genetics criteria.[1] The variant is extremely rare, appearing once in the heterozygous state in gnomAD v4.0 (chr6-7583590-G-C [GRCh38/hg38]) in an individual of European (non-Finnish) ancestry (allele frequency 3.98e-6; PM2 criterion). Computational prediction tools suggest a deleterious effect (REVEAL score 0.91; PP3 criterion).

TAKE-HOME MESSAGES

- Multimodal imaging, genetic testing, and cascade family screening are crucial in suspected arrhythmogenic cardiomyopathy cases to optimize risk stratification and management.
- This case highlights the importance of integrating advanced imaging techniques with genetic analysis in cardiomyopathies with unusual clinical presentation (ie, early onset biventricular arrhythmogenic cardiomyopathy).
- In high-risk patients, a more aggressive treatment strategy, including pharmacologic and device interventions, should be considered, going beyond standard thresholds (ie, left ventricular ejection fraction) commonly used for decision making.

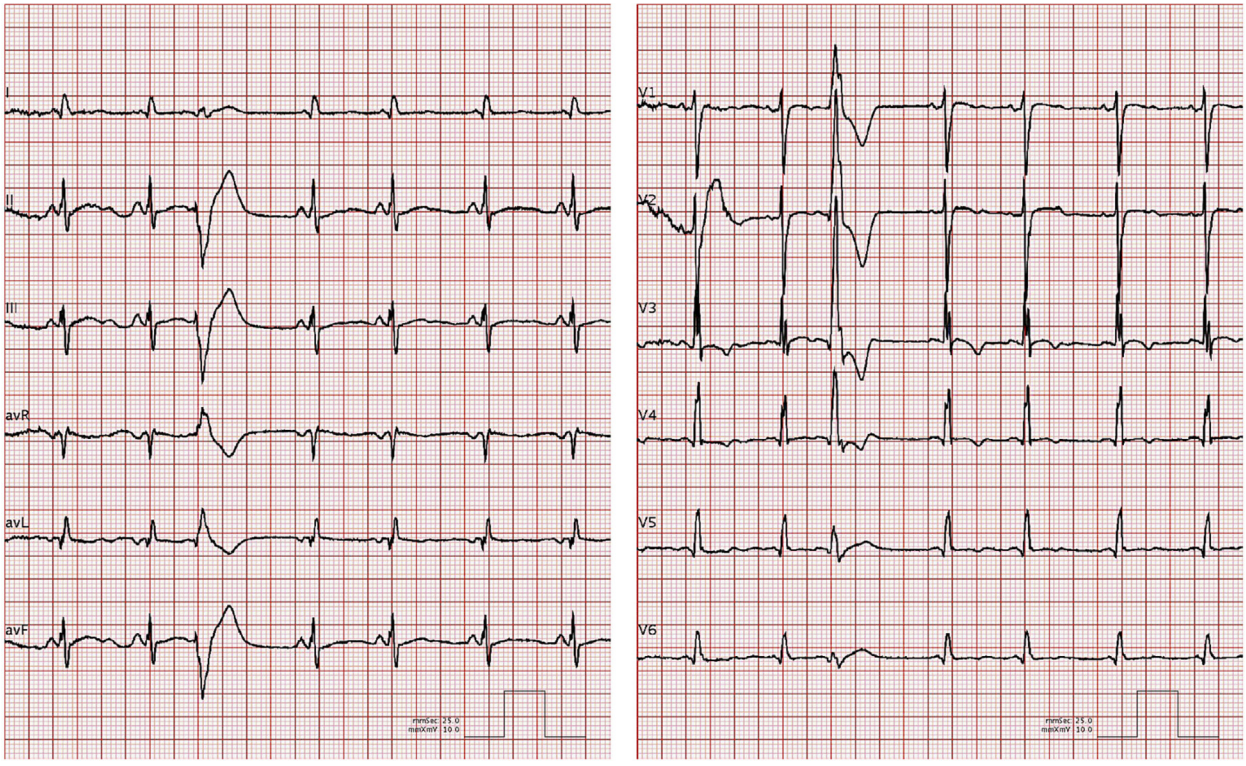
MANAGEMENT

Considering the syncope of arrhythmic origin, extensive ventricular fibrosis, left ventricular dysfunction, and NSVT, he was implanted with a transvenous single-chamber defibrillator (ICD). A transvenous ICD was chosen due to the relevant septal fibrosis and the risk of conduction defects. He was discharged with the diagnosis of hypokinetic nondilative cardiomyopathy and with the following treatment: bisoprolol (7.5 mg once daily), sacubitril-valsartan (49/51 mg twice daily), eplerenone (25 mg once daily), and dapagliflozin (10 mg once daily). Bisoprolol and sacubitril-valsartan were then uptitrated at the maximum recommended dosage.

FOLLOW-UP

One year after hospitalization, the patient was reassessed and found to be clinical stable (no other syncopal events), with positive remodeling (LVEF 45% at echocardiography) and slightly decreased ventricular ectopics (5,001 per 24 hours, 2 NSVT episodes) on Holter ECG. A diagnosis-directed physical examination revealed palmoplantar keratoderma, which was confirmed by a dermatologist (**Figure 3**). No curly hair (only fine hair) or significant nail or dental abnormalities were observed. Two cardiopulmonary exercise tests showed a good functional capacity (peak oxygen consumption 21.9 and 24.1 mL/kg/min) with ubiquitous ventricular ectopics and without sustained or nonsustained ventricular tachycardias. One year after the index event, his high-sensitivity

FIGURE 1 12-Lead Electrocardiogram at Admission



The 12-lead electrocardiogram shows QRS fragmentation, inverted T-waves in V_3-V_5 leads, and ectopics with right bundle branch block morphology and superior axis.

troponin T was normal (7.2 ng/L), and NT-proBNP was halved (305 ng/L).

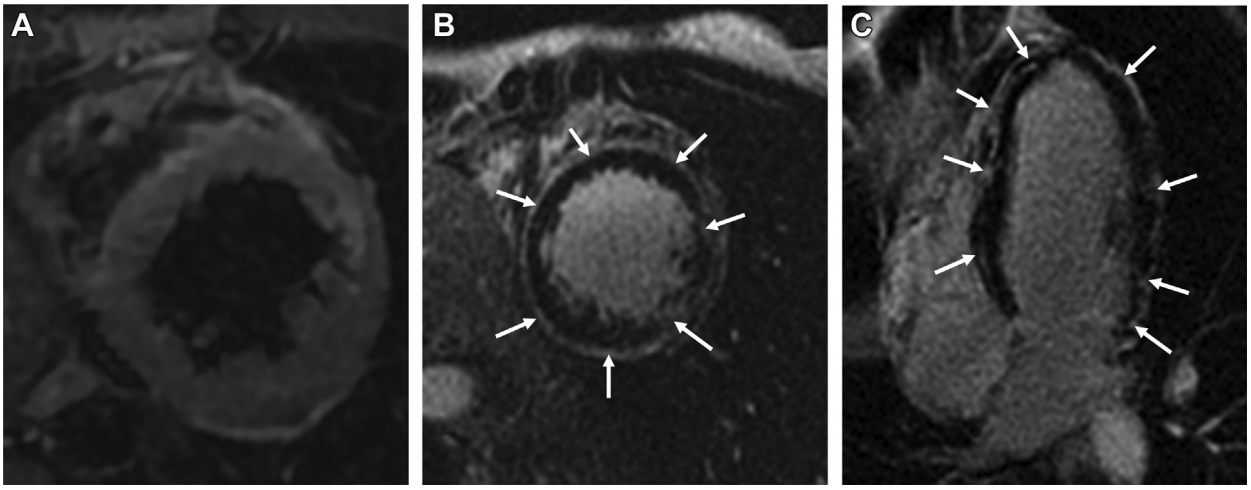
Both parents underwent DSP genetic testing by targeted Sanger sequencing and were found to be heterozygous for p.Ala2110Pro. Moreover, cascade genetic analysis showed the presence in heterozygosis of the same variant in a brother (II-1) of the proband. Following these genetic results and a more in-depth second interview, the parents (I.1 and I.2) revealed that they both originated from the same Albanian village and are consanguineous. This consanguinity provides additional context for the inheritance pattern of the homozygous variant (Figure 4).

All members of the family had undergone clinical evaluation with ECG and echocardiography. The echography displayed normal systolic function in proband's relatives, except for II-1 and II-2 (sister without the mutation) who showed hyperkinetic global left function. Additionally, I-1 and I-2 presented mild mitral insufficiency. Their ECG recordings were normal. Cardiac MRI was normal in the brother with the mutation. The father showed preserved biventricular function with regional RV wall motion abnormalities (hypokinesia of the lateral wall) and an irregular RV epicardial contour. The mother had normal biventricular volumes and function, with an RV "India ink" sign in the lateral wall suggesting fatty infiltration and nonischemic LGE in the left ventricle (subepicardial/intramyocardial pattern in the inferolateral wall). Considering that they were totally asymptomatic and without arrhythmias at Holter ECG, they were advised to avoid excessive physical efforts including competitive sports, and they were directed to follow-up evaluations.

DISCUSSION

This case describes a previously unreported homozygous variant of the *DSP* gene in a patient with biventricular arrhythmogenic cardiomyopathy. The literature predominantly has described truncating or heterozygous missense variants with dominant inheritance and LV-predominant phenotypes,[2,3] and homozygous missense variants are exceptionally rare. Desmoplakin, an essential component of the desmosome in epithelial cells and cardiomyocytes,

FIGURE 2 Cardiac Magnetic Resonance Imaging at Admission

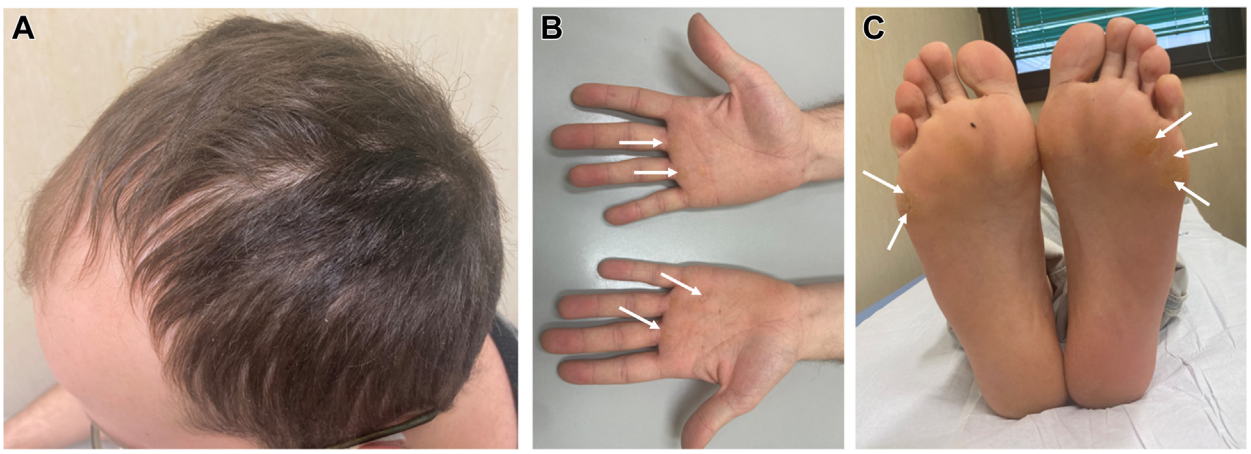


(A) T2-weighted midventricular short axis image without evidence of myopericardial inflammation. (B) Midventricular short axis postcontrast image with nonischemic pattern of ringlike late gadolinium enhancement (LGE) and (C) 4-chamber postcontrast image with evidence of LGE also of the right ventricle lateral basal wall. LGE is highlighted by white arrows.

maintains intercalated disc function; its alterations lead to cardiomyocyte inflammation and fibrosis. *DSP* variants typically cause arrhythmogenic cardiomyopathy through loss-of-function mechanisms inherited in an autosomal dominant pattern, and recessive forms are typically reported in cardiocutaneous Carvajal syndrome.[3-5]

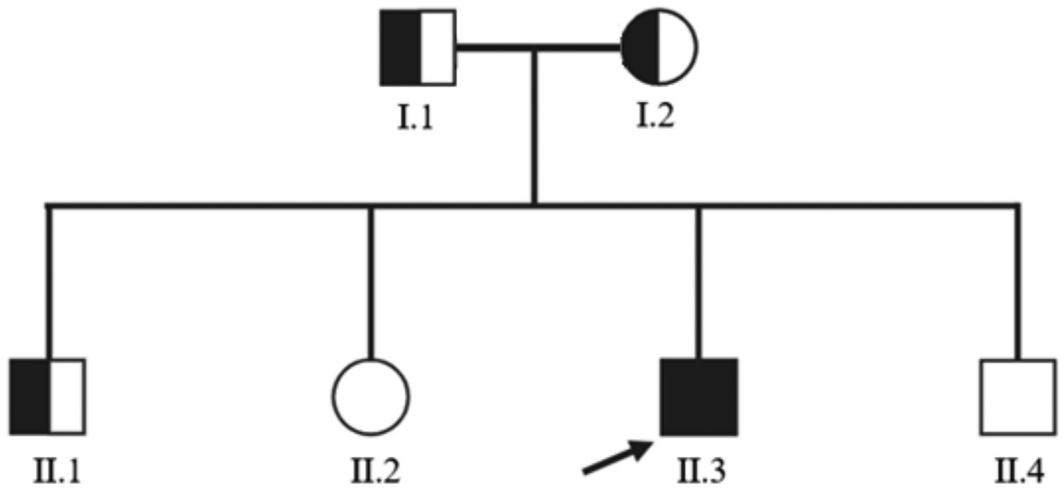
Our patient's variant (p.Ala2110Pro) is located in the PRD-A domain of DSP's C-terminal portion, which comprises 3 plakin repeat domains with distinct roles: PRD-A initiates intermediate filament binding and junction assembly, PRD-B provides core stability, and PRD-C reinforces these connections. This represents only the second reported homozygous missense

FIGURE 3 Clinical Manifestations



The patient did not display wooly hair as described in other patients carrying a desmoplakin mutation (A), but he showed a mild form of palmoplantar keratoderma (B and C, white arrows).

FIGURE 4 Genetic Family Tree



Solid-filled symbols stand for patients carrying homozygous desmoplakin variant (DSP.c6328 G>C), and half-filled symbols represent patients with the same variant but in heterozygosis.

variant in the literature in the PRD-A domain, following the homozygous variant (p.Gly2056Arg) reported by Christensen et al[6] in a patient from a consanguineous Danish family who presented with left ventricular involvement, mild palmar keratoderma, and no woolly hair.

Other homozygous variants exhibit variable phenotypes: p.G2375R in the B domain causes biventricular Carvajal syndrome[7] whereas p.S2859LfsX5 results in lethal arrhythmogenic cardiomyopathy with epidermolysis bullosa simplex.[8] By contrast, the p.S299R variant shows dominant inheritance but with variable cardiac manifestations in heterozygous carriers.[9] The phenotypic variability between these cases suggests that different missense variants, even within similar functional domains, can lead to distinct clinical presentations. Furthermore, other homozygous missense variants in desmosomal genes (DSG2:p.Thr335Ala and p.Phe531Cys) have been linked to early-onset biventricular disease, reinforcing the pattern of severe phenotypes in homozygous carriers.[10,11]

The heterozygous carriers in the family exhibited subtle yet suggestive features: RV wall motion abnormalities with preserved global function (father) and RV India ink sign with LV nonischemic LGE (mother). Although heterozygous DSP variants typically present with LV involvement,[2,3] these findings broaden the known phenotypic spectrum of desmosomal disease patterns, even though not fulfilling recognized diagnostic criteria.[4,5]

Multiple lines of evidence support the likely pathogenicity of the DSP:p.Ala2110Pro variant: its extreme rarity, computational predictions, early-onset disease, characteristic imaging findings, and family segregation, all of which demonstrate a clear phenotypic gradient between heterozygous and homozygous carriers. Although immunohistochemical studies on myocardial and skin biopsy could have provided further pathogenic confirmation, these were not performed because they would not have altered clinical management.

This case emphasizes the importance of integrating advanced cardiac MRI phenotyping with genetic analysis in complex cases,[12] particularly given the frequent association of homozygous mutations with atypical and aggressive phenotypes,[13] as testified by the young age of the patient and the unusual biventricular involvement. Additionally, this case perfectly summarizes the therapeutic management suggested by the European Society of Cardiology guidelines on ventricular arrhythmias and sudden cardiac death (SCD), which suggest implanting an ICD in patients with borderline LVEF and supplemental SCD risk factors (history of syncope, wide LGE at cardiac MRI, genetic mutation associated with arrhythmic phenotypes, Class IIa, Level of Evidence: C).[14]

Finally, as suggested by the guidelines, we want to highlight the importance of implementing a lifesaving therapy with the 4 pillars of heart failure with reduced ejection fraction management—β-blockers, angiotensin-converting enzyme inhibitor/

angiotensin receptor neprilysin inhibitor, mineralocorticoid receptor blockers, and sodium-glucose cotransporter 2 inhibitors—which notably all have positive effects for SCD as well.[15]

CONCLUSIONS

In conclusion, we suggest to always thinking about arrhythmogenic cardiomyopathy (left dominant and biventricular) in cases of

- Early presentation with syncope and frequent ectopics, especially when a specific ECG pattern (right bundle branch block and superior axis) is present.
- Disproportion between LV volume (only mildly increased) and function at echocardiography.
- Inverse correlation between LV function and the extent of LGE, especially if LGE is epicardial and intramyocardial and is associated with sign of fatty replacement (India ink sign).
- Genetic analysis supports the diagnosis with desmosomal mutations, with co-segregation in the family members of the proband.

In such cases, an early referral to ICD implantation and a full spectrum of drugs with prognostic and antiarrhythmic effects should always be considered.

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KEY WORDS biventricular arrhythmogenic cardiomyopathy, desmoplakin, next-generation sequencing

APPENDIX For supplemental video, please see the online version of this paper.