Case Report

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Clinical cases of biventricular arrhythmogenic cardiomyopathy with a variant in the *DES* gene

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Abstract

Mutations in the *DES* gene, which encodes the desmin protein, are associated with various forms of skeletal and/or cardiac myopathies. Arrhythmogenic cardiomyopathy (ACM) due to a *DES* gene mutation is a rare form of desminopathy. In this article, we describe a familial case of biventricular ACM with early subclinical signs of myogenic involvement in the upper and lower limbs, initially manifesting with ventricular arrhythmias and progressive systolic dysfunction. Genetic analysis revealed a likely pathogenic variant c.358G>C (p.Ala120Pro, rs794728996) in exon 1 of the *DES* gene, located in the N-terminal region of the 1A helix domain. This variant affects filament assembly, leading to cytoplasmic aggregation of desmin, further supporting the functional importance of this region. Early implantation of an implantable cardioverter-defibrillator may contribute to primary prevention of sudden cardiac death in patients carrying this desmin variant. This is the first report of the phenotypic manifestations of the p.Ala120Pro variant in the *DES* gene in 2 patients with biventricular ACM from the same family.

Abbreviations: ACM = arrhythmogenic cardiomyopathy, AV = atrioventricular, CPK = creatine phosphokinase, DCM = dilated cardiomyopathy, ECG = electrocardiogram, EDV = end-diastolic volume, EMG = electroneuromyography, HF = heart failure, HTx = heart transplantation, ICD = implantable cardioverter-defibrillator, LGE = late gadolinium enhancement, LV = left ventricular, LVEF = left ventricular ejection fraction, MRI = magnetic resonance imaging, NGS = next-generation sequencing, RV = right ventricular, SCD = sudden cardiac death, TTE = transthoracic echocardiography, VT = ventricular tachycardia.

Keywords: arrhythmogenic cardiomyopathy, desmin, systolic dysfunction, ventricular arrhythmia

Key Points

1. The presence of a likely pathogenic or pathogenic *DES* gene variant, such as p.Ala120Pro, should prompt early genetic screening in patients with unexplained biventricular cardiomyopathy, particularly when associated with ventricular arrhythmias and conduction disturbances. Early identification enables timely risk stratification and implementation of life-saving interventions such as ICD implantation.
2. Familial evaluation and segregation analysis are critical in the assessment of *DES*-related cardiomyopathy, as phenotypic expression may vary significantly even within the same family—ranging from early-onset, life-threatening arrhythmias to subclinical skeletal muscle involvement in later life.

1. Introduction

Primary cardiomyopathies represent one of the most common hereditary disorders of the cardiovascular system, with a cumulative population prevalence of up to 0.5%.[1] This group of diseases is also characterized by considerable genetic heterogeneity. To date, more than 100 genes have been identified as being responsible for various forms of cardiomyopathies. New classification strategies, based on the genotypic characterization of patients, have led to the recognition of distinct clinical entities, each with unique molecular pathogenesis, clinical course, and prognosis. One such example is desmin-associated cardiomyopathy, caused by mutations in the *DES* gene.

Desmin, encoded by *DES*, is a type III intermediate filament protein expressed in skeletal, smooth, and cardiac muscle cells. It plays an essential role in maintaining mechanical integrity, cellular organization, and intracellular signaling, as well as contributing to mitochondrial

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function. Desmin is more abundantly expressed in cardiac than skeletal muscle, with particularly high expression in the Purkinje conduction system.

A critical function of desmin in the cardiac conduction system stems from its unique ability to form filamentous networks that link and stabilize various cellular structures and organelles, including desmosomes, costameres, Z-discs, the cytoskeleton, mitochondria, and nuclei.[2] In addition, desmin interacts with multiple proteins in cardiomyocytes, modulating diverse signaling pathways[2] essential for maintaining normal cardiomyocyte function. As a result, numerous *DES* gene variants have been reported in the literature in association with a range of cardiac pathologies, including atrial and ventricular arrhythmias, as well as hypertrophic, restrictive, dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ACM), and left ventricular (LV) noncompaction.[3,4]

Over the past 15 years, several DES mutations have been shown to cause both cardiac and skeletal myopathies.[5] In most reported cases, cardiac involvement coexists with skeletal muscle disease. However, in more than 20% of patients with *DES* mutations, isolated cardiac manifestations are observed, without involvement of skeletal muscle.[6]

Desminopathies are relatively prevalent, with an estimated frequency of 1:2,000 individuals.[7] Approximately 80% of cases follow an autosomal dominant inheritance pattern with full penetrance. However, rare cases of incomplete penetrance of dominant mutations, as well as autosomal recessive familial forms with early disease onset and rapid progression, have also been reported.[7]

Clinical cases of desminopathy associated with DCM have been described. For instance, Brodehl et al.[8] reported a heterozygous missense variant (c.407C>T; p.L136P) in *DES*, identified via high-throughput sequencing in a Caucasian patient with DCM.

ACM due to *DES* mutations is a much rarer entity. In a recent study of 138 probands with ACM who lacked variants in canonical ACM-associated genes, a novel missense variant (p.Leu115Ile) in *DES* was identified. This variant was associated with disease in 3 unrelated British families of Caucasian origin.[9] All affected individuals exhibited a mixed biventricular ACM/DCM phenotype. Prominent features of this phenotype included enhanced arrhythmogenesis, LV dysfunction, and subepicardial myocardial fibrosis.

In this article, we report a familial case of biventricular ACM with early subclinical signs of myogenic involvement of the upper and lower limbs, early-onset disease manifestation, progressive systolic dysfunction, and life-threatening arrhythmias.

2. Clinical case report

Patient Sh. (male, 15 years old) was referred from the Pediatric Cardiac Surgery Center to the Republican Scientific and Practical Center "Cardiology" for further evaluation, including cardiac magnetic resonance imaging (MRI), with a preliminary diagnosis of DCM. At the time of genetic evaluation, the patient was 15 years old, with an asthenic body habitus (height 178 cm, weight 52 kg, BMI 16.4 kg/m²). He was not engaged in intense physical activity, maintaining a moderate level of exercise. Medical history revealed that at the age of 6 years, the patient exhibited frequent ventricular ectopic beats (burden 5.8%). By age 9, a 12-lead electrocardiogram (ECG) showed left axis deviation and repolarization abnormalities in precordial leads V4-V6. He was prescribed metoprolol at a dose of 12.5 mg twice daily. At 13 years of age, transthoracic echocardiography (TTE) demonstrated reduced left ventricular ejection fraction (LVEF) of 45%, LV dilation, and diffuse hypokinesis of the LV walls. At age 15, the patient was hospitalized at the Pediatric Cardiac Surgery Center with a preliminary diagnosis of DCM.

Physical examination upon admission revealed no pathological findings; resting pulse rate was 59 bpm. A 12-lead ECG showed low QRS voltage with minimal R wave progression in leads V1-V3 and T-wave inversion in leads V4–V6 (Fig. 1A). Twenty-four-hour Holter monitoring revealed isolated and paired polymorphic premature ventricular contractions (burden 3.54%) and episodes of nonsustained ventricular tachycardia (VT) (Fig. 1B). TTE confirmed LV dilation (end-diastolic diameter 62 mm; indexed end-diastolic volume [iEDV] 110 mL/m²), systolic dysfunction of both the left (LVEF 26%) and right ventricles (right ventricular [RV] fractional area change 29%, tricuspid annular plane systolic excursion 21 mm), and diffuse LV hypokinesis (wall motion score index 2.25).

Cardiac MRI with late gadolinium enhancement (LGE) revealed findings consistent with cardiomyopathy: marked LV dilation (EDV 283 mL), moderate RV dilation (EDV 167 mL), reduced systolic function (LVEF 34%, RVEF 31%), and eccentric LV hypertrophy. LGE imaging demonstrated extensive areas of subepicardial, linear intramural, and transmural nonischemic fibrosis involving multiple LV segments, the anterolateral papillary muscle, RV trabeculae and papillary muscles, and localized fibrosis of the RV posterior wall (Fig. 2).

A single-chamber implantable cardioverter-defibrillator (ICD) was implanted. Continued treatment with beta-blockers (metoprolol 25 mg twice daily) was recommended.

Neurological examination revealed no abnormalities. Serum creatine phosphokinase (CPK) levels were within reference range (38 U/L; normal 24–195 U/L). The patient declined electroneuromyography (EMG) due to the implanted ICD.

Family history was negative for sudden cardiac death (SCD) or cardiovascular mortality. The patient's 51-year-old father had frequent polymorphic premature ventricular contractions (burden 15.66%), episodes of nonsustained VT, and second-degree atrioventricular (AV) block, Mobitz type I, as revealed by 24-hour Holter ECG monitoring (Fig. 3). A 12-lead ECG showed low QRS voltage in standard leads and poor R wave progression in leads V1-V3.

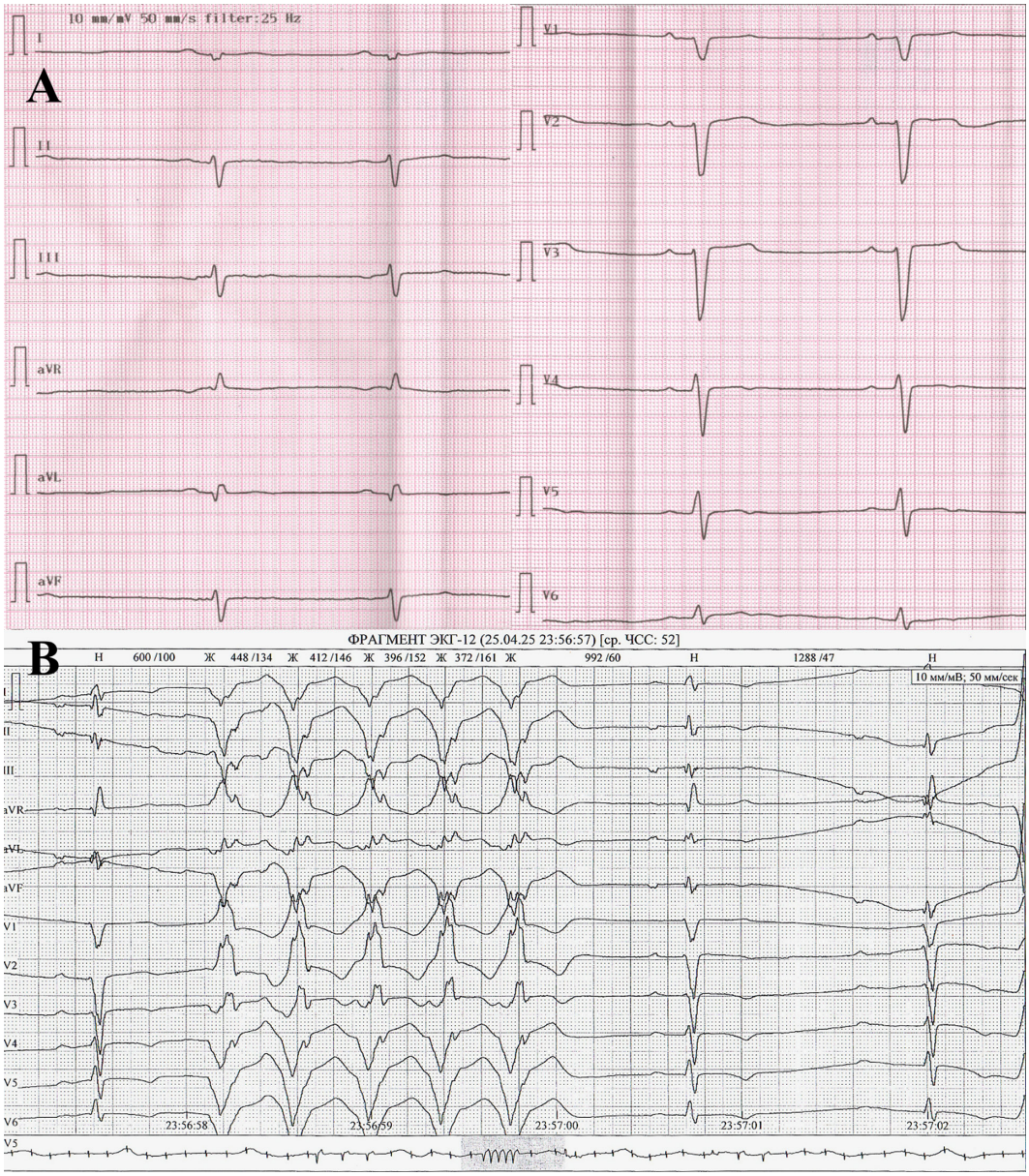

Figure 1. Twelve-lead electrocardiogram and 24-hour Holter monitoring. (A) Resting 12-lead ECG demonstrating sinus rhythm with low QRS voltage in limb leads and T-wave inversion in precordial leads V4–V6. (B) Fragment of 24-hour Holter monitoring showing a wide-complex tachycardia consistent with ventricular tachycardia morphology, likely originating from the left ventricle. ECG = electrocardiogram.

Like his son's, the father's serum CPK level was within the reference range (94 U/L). Needle EMG detected mild signs of moderate myogenic involvement in both upper and lower limbs without clinical symptoms.

TTE in the father revealed no evidence of ventricular dilation or dysfunction (LVEF 72%, LV end-diastolic diameter 53 mm, iEDV 64 mL/m²), and no signs of LV hypertrophy (IVS 9 mm, PW 9 mm, LV mass index 79 g/m²).

Cardiac MRI revealed a phenotype consistent with biventricular ACM based on one major Padua criterion (intramural LV myocardial fibrosis) and 3 minor MRI criteria (1. regional akinesis/dyskinesis of the RV free wall; 2. global LV systolic dysfunction with LVEF of 49% without LV dilation; 3. regional hypokinesis/akinesis of the LV free wall and interventricular septum), as well as one minor International Task Force (2010) criterion (RVEF 44%). LGE imaging showed nonischemic intramural fibrosis of the LV myocardium in a stria-like pattern in ≥ 1 segment of the LV free wall and interventricular septum (Fig. 4). Given the positive family history, MRI findings consistent with biventricular ACM, ECG abnormalities, and documented ventricular tachyarrhythmias, the father was diagnosed with biventricular ACM.

A marked discrepancy is observed between the LVEF values obtained by TTE (72%, April 2024) and by MRI (49%, April 2025). Given the 1-year interval between the examinations, the reduction in LVEF detected by MRI may reflect progression of structural and functional myocardial alterations consistent with the natural course of the disease.

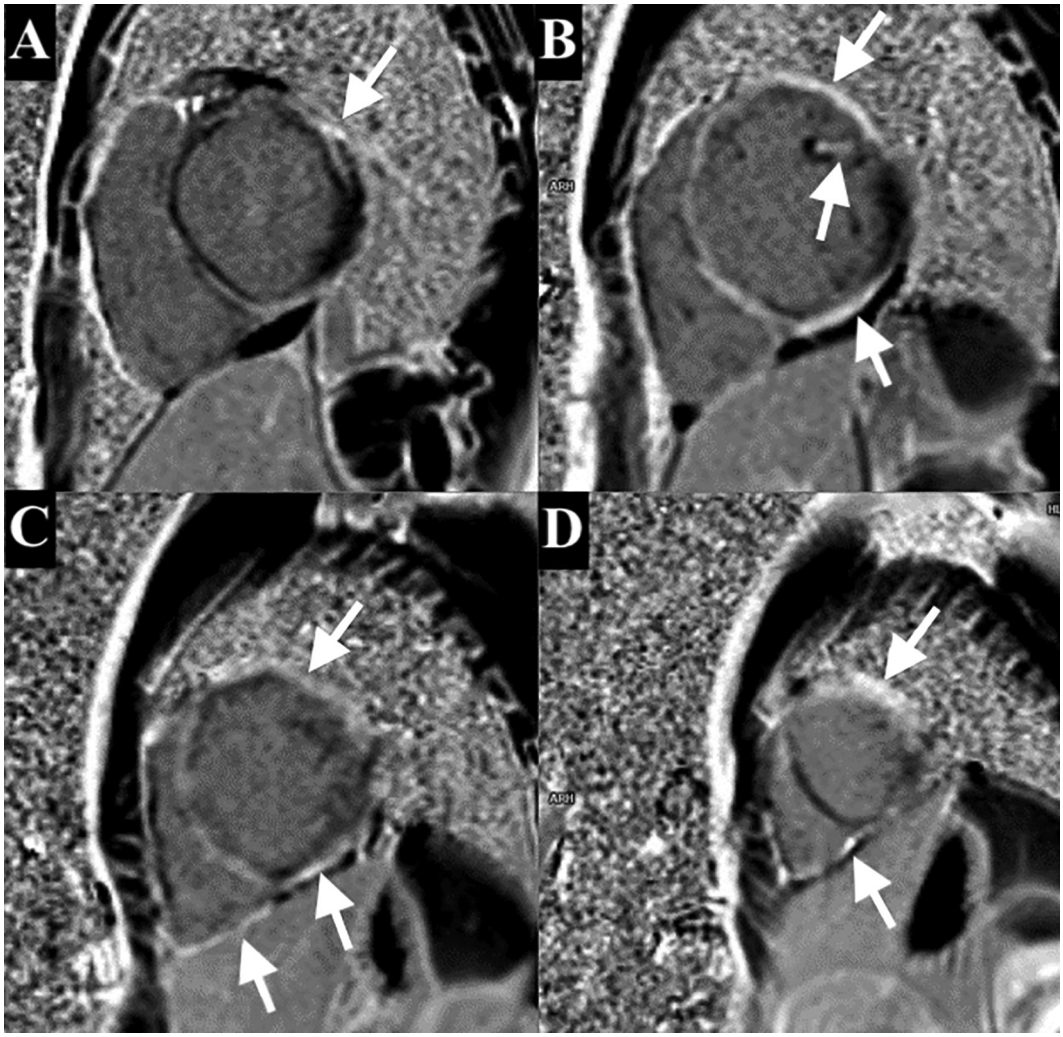

Figure 2. Cardiac MRI of patient Sh. Late gadolinium enhancement in the short-axis view during end-diastole at the basal (A), mid-ventricular (B, C), and apical (D) segments of the left ventricle: multisegmental nonischemic fibrosis with subepicardial, linear intramural, and transmural distribution in the LV myocardium, involving the anterolateral papillary muscle of the LV, trabeculae and papillary muscles of the right ventricle, and localized areas of the posterior RV wall (white arrows). LV = left ventricular, MRI = magnetic resonance imaging.

No abnormalities were detected on TTE or Holter ECG monitoring in the patient's mother or older sister (age 19).

As part of the genetic analysis conducted at the Institute of Genetics and Cytology of the National Academy of Sciences of Belarus, the proband underwent next-generation sequencing (NGS) targeting 174 genes associated with cardiovascular diseases (Illumina platform), including both desmosomal and nondesmosomal genes implicated in ACM. This analysis identified a nucleotide variant, c.358G>C (p.Ala120Pro, rs794728996), located in exon 1 of the *DES* gene, which encodes the desmin protein (Fig. 5). According to ACMG criteria, the p.Ala120Pro variant is classified as "likely pathogenic" based on in vitro functional studies,[10] its absence in population databases, and segregation with the disease in multiple affected family members carrying the variant (criteria PS3, PM2, PP1).[11] No other potentially pathogenic variants in the genes included in this panel were identified.

In silico analysis predicts that p.Ala120Pro is likely to damage the structure/function of the protein. This amino acid position is highly conserved among existing vertebrate species. Furthermore, p.Ala120Pro has not been observed in individuals of European or African American descent, indicating that it is not a common benign variant in these populations.

Another variant, c.359C>A (p.Ala120Asp, rs195-4373010), which affects the same amino acid, has been identified in association with DCM and SCD, further supporting the functional importance of this site.[5] The p.Ala120Pro variant was also identified in the proband's father using Sanger sequencing (Fig. 5). As expected, the sister did not carry this variant. Given the family history, the MRI findings were consistent with biventricular ACM (2 major and 3 minor Padua 2020 criteria), the presence of ECG abnormalities and ventricular tachyarrhythmias, as well as the genetically identified *DES* gene variant, the proband's diagnosis of "dilated cardiomyopathy" was revised to "biventricular arrhythmogenic cardiomyopathy."

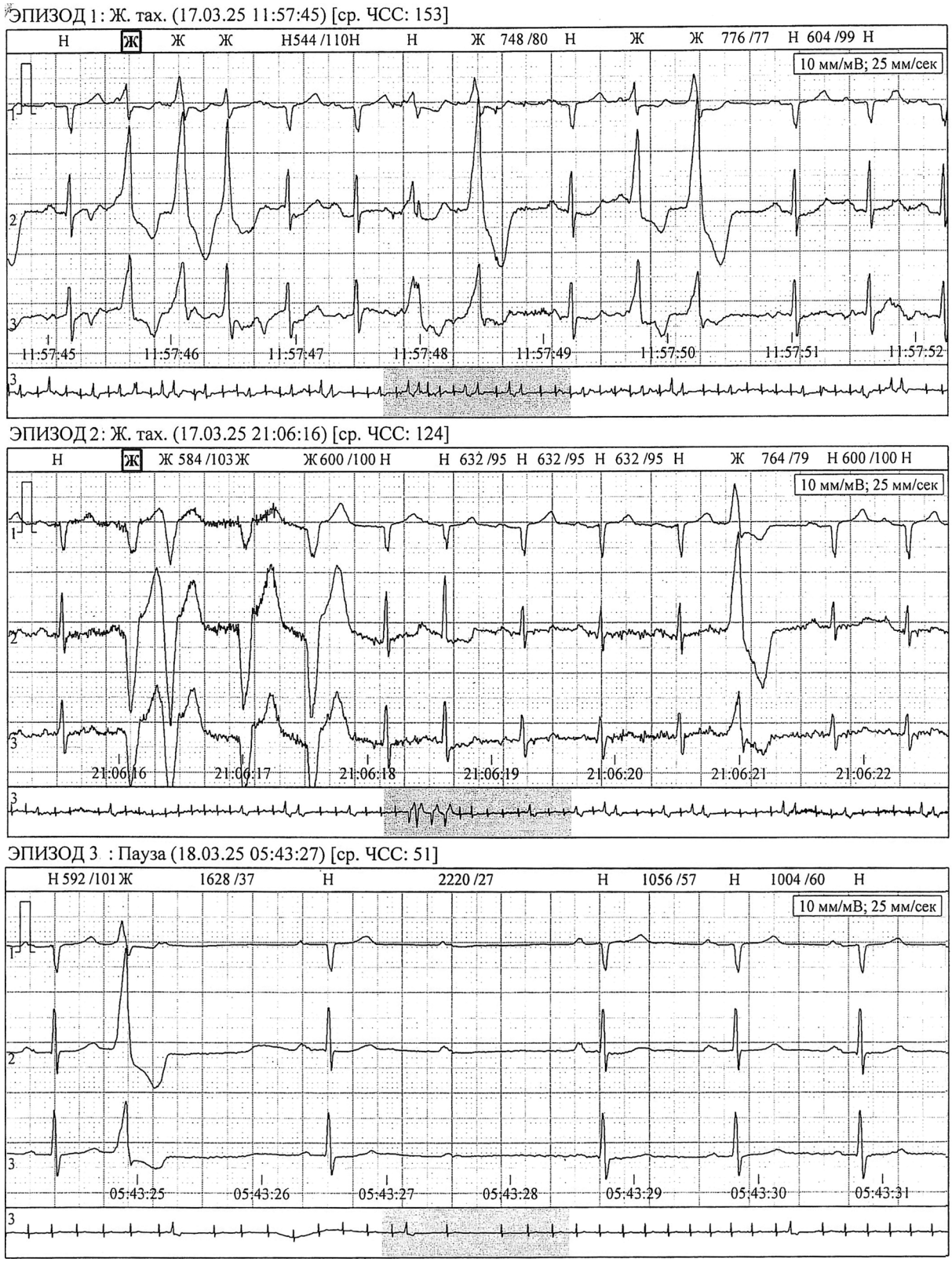

Figure 3. Twenty-four-hour Holter monitoring of the proband's father. Single and paired ventricular premature complexes with episodes of nonsustained ventricular tachycardia. Episode of second-degree atrioventricular block, Mobitz type I (the PQ interval following the dropped QRS complex is shorter than the PQ interval preceding the dropped complex).

3. Discussion

In this article, we describe a familial case of biventricular ACM with early subclinical signs of myogenic involvement in the upper and lower limbs, progressive ventricular systolic dysfunction, and ventricular tachyarrhythmia requiring implantable ICD implantation.

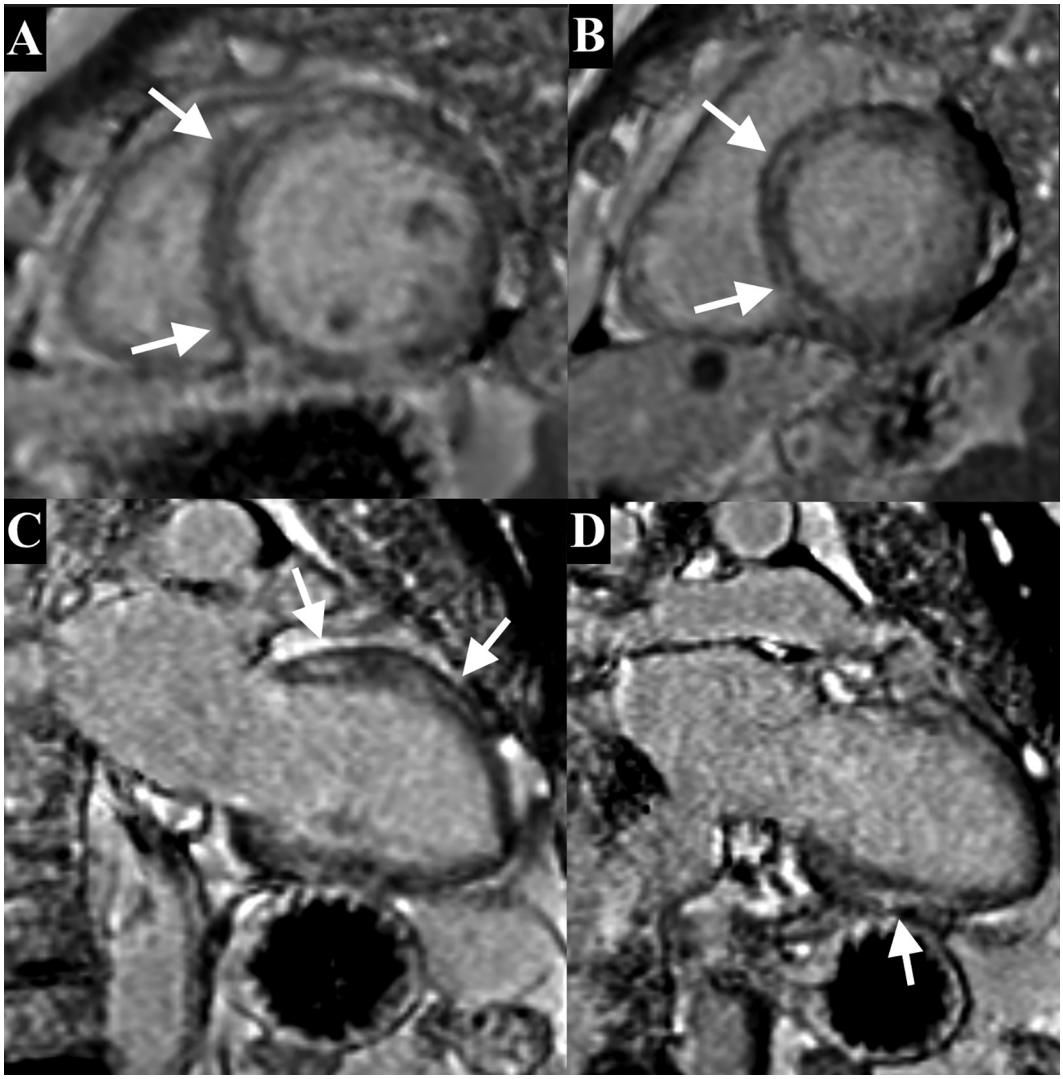

Figure 4. Cardiac MRI of the proband's father. Late gadolinium enhancement in the short-axis view during end-diastolic phase at the mid-ventricular (A) and apical (B) segments of the left ventricle, and in the 2-chamber view (C, D): nonischemic intramural myocardial fibrosis of the left ventricle, displaying a stria-like pattern in ≥ 1 segment of the LV free wall and interventricular septum. LV = left ventricular, MRI = magnetic resonance imaging.

The literature reports various phenotypes of isolated ACM characterized by ventricular arrhythmias and AV conduction disorders in patients carrying *DES* gene variants. In a study by Protonotarios et al., a novel *DES* variant—previously considered a variant of uncertain significance—was identified in 3 unrelated families with biventricular ACM. Although some clinical features typically seen in desminopathy were absent, the p.Leu115Ile variant was implicated in the biventricular ACM phenotype.[9]

The concept of ACM reflects the evolving spectrum of myocardial disease definitions.[12] The classical understanding of ACM has been expanded to include RV-dominant, LV-dominant, and biventricular forms.[13] Previous studies have described the phenotypic variability in desminopathies, including involvement of skeletal muscle, the myocardium, or combined forms, presenting as dilated, hypertrophic, restrictive, or arrhythmogenic cardiomyopathies, as well as myofibrillar myopathy, distal muscular dystrophy, and other desmin-related syndromes.[14] In 2009, the p.Ser13Phe variant in *DES* was first identified in 5 Dutch families and was associated with an ACM phenotype in 13% of cases, in addition to other forms of cardiomyopathy.[4] In smaller case series (ranging from 1 to 5 cases), additional missense variants in *DES* have also been reported in association with various cardiomyopathies. For example, Bermudez-Jimenez et al.[15] described a cardiomyopathy phenotype with repolarization abnormalities, subepicardial fibrosis, and ventricular arrhythmia in a patient carrying the p.Glu401Asp variant.

A recent study by Bermudez-Jimenez et al.[16] presented phenotypic data and clinical outcomes for 16 families with *DES*-related ACM from 10 European centers. Among 82 patients (54% male, median age 36 years), 11 died of SCD (SCD, $n = 7$) or heart failure (HF)/heart transplantation (HTx, $n = 4$) before clinical evaluation. Of the 68 surviving patients, 59 (86%) showed signs of cardiomyopathy,

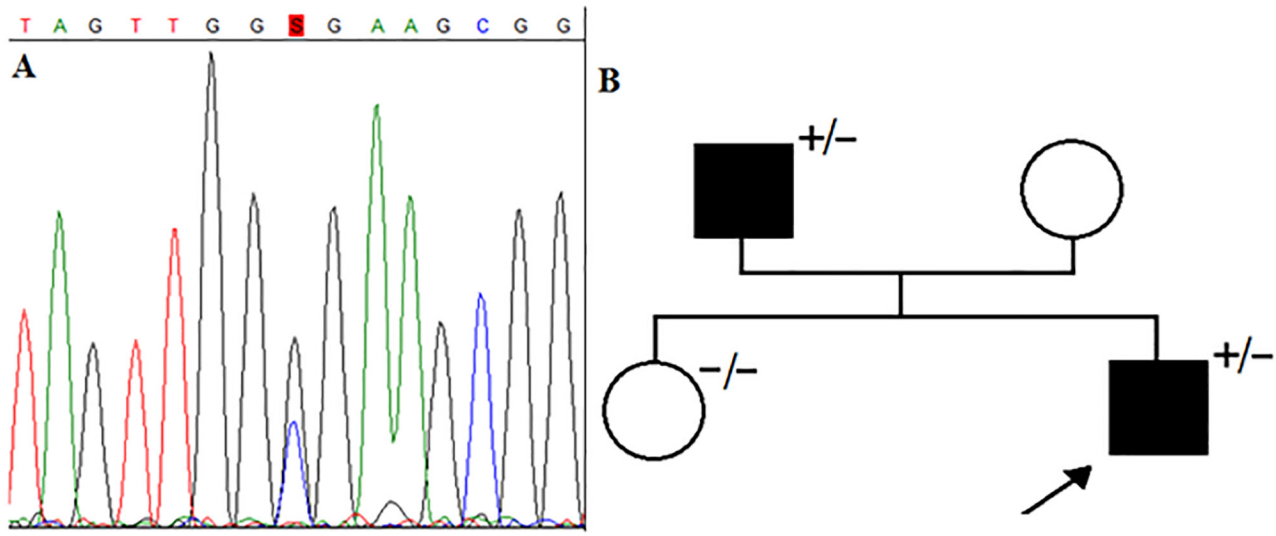

Figure 5. Results of molecular genetic analysis. (A) A fragment of the nucleotide sequence of exon 1 of the *DES* gene showing the c.358G>C (p.Ala120Pro) variant in a heterozygous state in both the proband and his father. (B) Pedigree of the proband's family carrying the heterozygous *DES* gene variant p.Ala120Pro. The proband is indicated by a filled square (male). ○ indicates no signs of disease; ■ indicates diagnosed ACM; **+/–** indicates the presence of a likely pathogenic variant in the *DES* gene in the heterozygous state; **–/–** indicates the absence of a likely pathogenic variant in the *DES* gene. ACM = arrhythmogenic cardiomyopathy.

predominantly LV involvement (50%) or biventricular forms (34%). The mean LVEF was 51% ± 13%; LGE was observed in 36 of 53 patients, with a ring-like fibrosis pattern in 49%. Over a median follow-up of 6.73 years (interquartile range: 3.55–9.52 years), the composite endpoint (sustained VT, aborted SCD, ICD therapy, HF, HTx) occurred in 15 additional patients: 5 experienced HF/HTx, and 10 had SCD/aborted SCD/ICD/sustained VT.

The p.Ala120Pro variant in the *DES* gene, identified in proband Sh., was first described by Brodehl et al.,[10] who conducted a functional in vitro study of this and other variants in the N-terminal portion of the coil 1A domain of desmin—a recognized mutational hotspot. The p.Ala120Pro variant was shown to impair filament assembly and lead to abnormal cytoplasmic aggregation of desmin.[10]

Our study is the first to report the phenotypic expression of the p.Ala120Pro *DES* variant in 2 patients with biventricular ACM from the same family. The proband presented with early-onset at age 15 and a severe clinical phenotype, including progressive systolic dysfunction and life-threatening ventricular arrhythmias, requiring ICD implantation. In contrast, the proband's father developed the ACM phenotype at a later age (51 years), accompanied by rhythm and conduction disturbances, including paroxysmal nonsustained VT and Mobitz type I second-degree AV block. The proband showed no neurological symptoms, whereas the father exhibited mild signs of myogenic involvement of the upper and lower limb muscles, without overt clinical manifestations.

4. Conclusion

Genetic testing should be considered in patients presenting with early-onset cardiac arrhythmias and progressive cardiomyopathy. The presence of a pathogenic variant in the *DES* gene in such a phenotype should serve as a "red flag" when evaluating the need for SCD prevention strategies, as it is frequently associated with a progressive and severe biventricular ACM phenotype. This condition is often characterized by a high incidence of ventricular tachyarrhythmias, AV conduction disturbances, and an elevated risk of SCD. ICD therapy may significantly improve clinical outcomes in patients harboring a pathogenic *DES* variant.

5. Study limitations

The proband's refusal to undergo EMG due to the presence of an ICD, despite normal CPK levels, limits the ability to reliably exclude subclinical myopathy. As part of further clinical follow-up, the use of alternative diagnostic modalities such as skeletal muscle MRI as well as renewed counseling regarding the feasibility of EMG should be considered.

Acknowledgements

Not applicable.

Ethical statement

Written informed consent was obtained from all participants in accordance with institutional guidelines and the study was approved by the Institutional Review Board of State Institution Republican Scientific and Practical Centre "Cardiology" (the approval number 9, dated on July 5, 2022).

Conflicts of interest statement

The authors have no conflicts of interest to disclose.

Funding source

Not applicable.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Svetlana M. Komissarova and Nadiia M. Rineiska developed the article concept. The methodology was designed by Svetlana M. Komissarova and Nadiia M. Rineiska. Genetic analysis was conducted by Natallia N. Chakova and Svetlana S. Niyazova. Patient selection was managed by Svetlana M. Komissarova and Nadiia M. Rineiska. The original draft was written by Svetlana M. Komissarova, Nadiia M. Rineiska, and Natallia N. Chakova. The review and editing of the manuscript was done by Nadiia M. Rineiska. MRI visualization was handled by Iryna K. Haidzel. All authors reviewed and approved the final version of the manuscript.

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