


# Danon disease in a Sardinian family: different aspects of the same mutation—a case report

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## Background

Danon disease (DD) is a rare X-linked disorder due to mutations in the lysosome-associated membrane protein 2 gene. It is characterized by a clinical triad of hypertrophic cardiomyopathy, skeletal myopathy, and a variable degree of intellectual disability.

## Case summary

In this case series, we describe a mother and her son affected by DD, highlighting consistent clinical severity despite the expected variability related to gender. The mother (Case 1) presented isolated cardiac involvement, with an arrhythmogenic phenotype that evolved into severe heart failure requiring heart transplantation (HT). Danon disease was diagnosed 1 year after this event. Her son (Case 2) showed an earlier age onset of symptoms with complete atrioventricular block and fast progression of cardiac disease. Diagnosis was established 2 years after clinical presentation. He is currently listed for HT.

## Discussion

In both of our patients, diagnostic delay was extremely long and could have been avoided by emphasizing the relevant clinical red flags. Patients affected by DD may present clinical heterogeneity in terms of natural history, age of onset, and cardiac and extra-cardiac involvement, even in the same family. Early diagnosis that phenotypic sex differences may impact is a crucial factor in managing patients with DD. Considering the rapid progression of cardiac disease and the poor prognosis, early diagnosis is important and close surveillance should be mandatory during follow-up.

## Keywords

Danon disease • LAMP-2 (lysosome-associated membrane protein 2) gene • Hypertrophic cardiomyopathies • Phenocopy • Case report

## ESC Curriculum

6.5 Cardiomyopathy • 6.2 Heart failure with reduced ejection fraction • 6.1 Symptoms and signs of heart failure • 5.10 Implantable cardioverter defibrillators

## Learning points

- Danon disease is a rare X-linked disorder due to a mutation in the lysosome-associated membrane protein 2 gene, characterized by a clinical triad of hypertrophic cardiomyopathy, skeletal myopathy, and a variable degree of intellectual disability. Diagnostic delay is common despite typical clinical red flags.
- Danon disease presents clinical heterogeneity among sexes in terms of age of onset, cardiac and extracardiac involvement, and natural history, even in the same family. Prognosis remains poor.

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## Introduction

Danon disease (DD) is a rare multisystemic disorder usually characterized by a classical clinical triad of hypertrophic cardiomyopathy (HCM), skeletal myopathy, and a variable degree of intellectual disability.<sup>1</sup> First described by Danon et al.<sup>2</sup> in 1981, DD is an inherited dominant X-linked condition due to mutations in the lysosome-associated membrane protein 2 (LAMP-2) gene.<sup>3</sup> Originally postulated to be a glycogen storage defect, DD has recently been shown to be due to primary deficiency of LAMP-2 leading to impaired autophagosome/lysosome function, resulting in an autophagy disorder with accumulation of glycogen granules and intracytoplasmic vacuoles containing autophagic material.<sup>4</sup>

In the general population, the clinical suspicion of DD should be high in young patients presenting HCM or dilated cardiomyopathy (DCM), myopathy, several degrees of cognitive impairment, electrocardiogram (ECG) abnormalities such as ventricular pre-excitation or atrioventricular block (AVB), or a family history of sudden cardiac death (SCD). Diagnosis can be complex and needs to be confirmed by the presence of suggestive clinical features and/or pathogenic (or likely pathogenic) variants in the LAMP-2 gene.<sup>5</sup>

The prevalence of DD is unknown but is generally estimated at 5% of all cases of paediatric HCM<sup>6</sup> and 0.7% among adult patients presenting a HCM phenotype, according to a recent Italian study.<sup>7</sup> To date, about 500 cases of affected patients and a hundred different pathogenic variants of the LAMP-2 gene have been described.<sup>4</sup> Male patients typically present a more severe phenotype characterized by earlier onset and rapid progression of heart failure (HF), death, or the need for heart transplantation (HT), typically in the second or third decade of life.<sup>6</sup> Female patients usually manifest a milder phenotype, with a later onset and isolated cardiac involvement,<sup>1,8</sup> although some authors have reported the occurrence of cardiac death even at a young age.<sup>9,10</sup>

Furthermore, female carriers may develop DCM.<sup>11</sup> The mean age of diagnosis is  $13 \pm 9$  and  $36 \pm 15$ , respectively, in men and women, while the mean age of death is  $23 \pm 19$  among men and  $45 \pm 18$  in women, suggesting rapid progression of cardiac impairment. Leading causes of death in DD are HF (59%), SCD (18%), stroke, and other minor causes.<sup>12</sup> Our understanding of the complexity and variety in the phenotypic manifestations and clinical course of DD is still limited. In this paper, we describe a family in which a mother and her son, originating from Sardinia, were both diagnosed with DD and referred to our Heart Failure and Transplant Unit.

## Timeline

Case	Age	Events
Case 1	40 years old	Supraventricular tachyarrhythmias; pre-excitation pattern; electrophysiological study
	47 years old	Ventricular fibrillation episodes interrupted by implantable cardioverter defibrillators
	48 years old	Advanced heart failure (HF) requiring heart transplantation (HT) listing
	49 years old	Heart transplantation

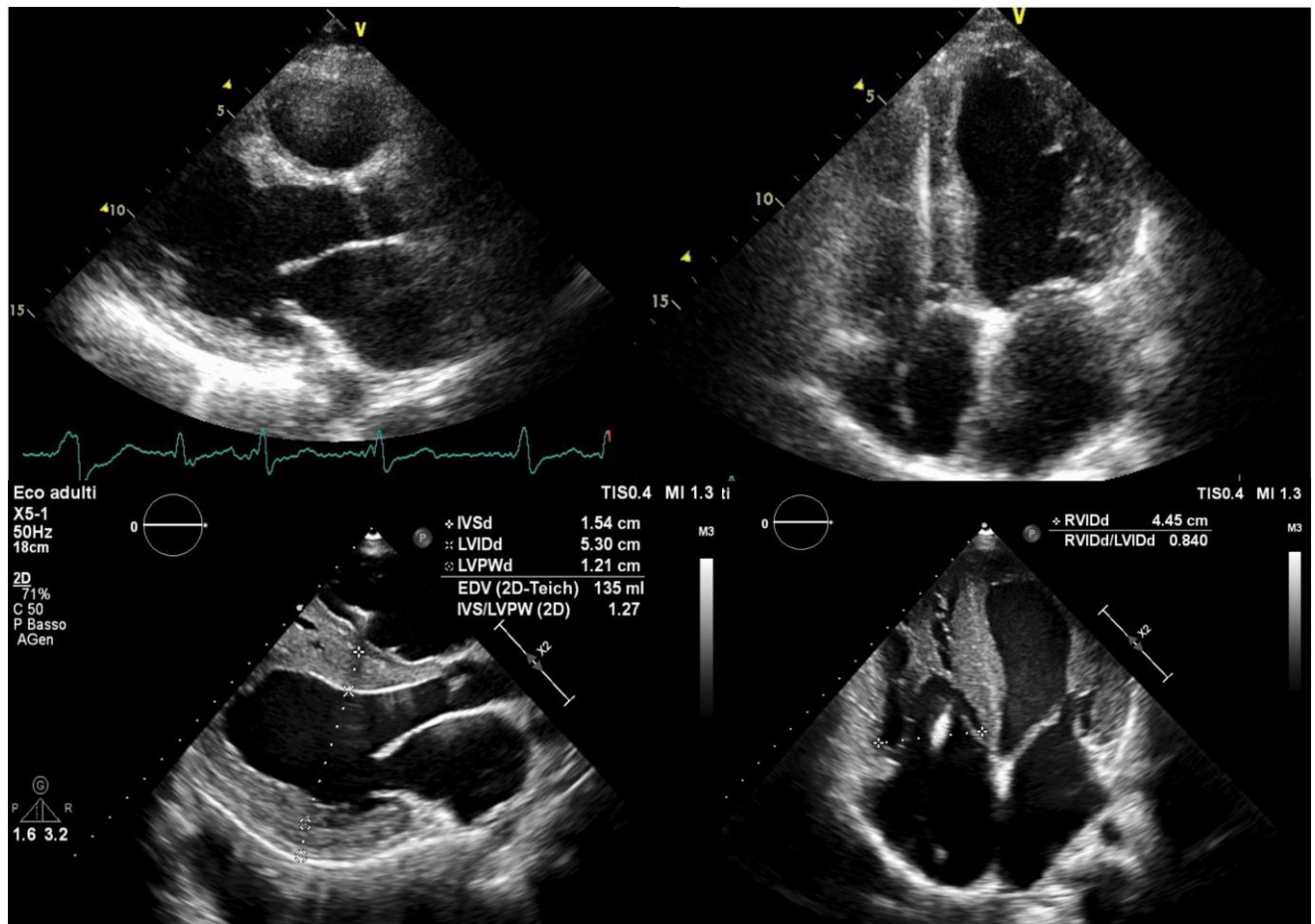
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### Continued

Case	Age	Events
Case 2	50 years old	Genetic diagnosis of Danon disease (DD) (pathogenic frameshift variant c.103_104delGA;p.Asp35Phefs*20 in the lysosome-associated membrane protein 2 gene); histopathological confirmation
	26 years old	Pre-syncope due to complete atrioventricular block requiring a pacemaker
	28 years old	Advanced HF requiring listing for HT and genetic confirmation of DD

## Case summaries

The proband (Case 1) is a Caucasian female from Sardinia (Italy) with a familiar history of four SCD. A routine ECG performed during pregnancy at 30 years of age revealed a ventricular pre-excitation pattern. She suffered from a transient ischaemic attack (TIA) at the age of 35 years old. Due to recurrent palpitations, at the age of 40 years old, she underwent her first electrophysiological study (EPS), where no accessory pathways were identified. At that time, an echocardiographic exam showed mild concentric hypertrophy of the left ventricle (LV), with an interventricular septum (IVS) of 13 mm and preserved left ventricular ejection fraction (LVEF 60%). In the following years, palpitations recurred due to atrial fibrillation (AF), requiring two more transcatheter (TC) ablation treatments. Further echocardiographic examinations during follow-up showed a progressive LV dilatation and dysfunction up to LVEF 25% with mild LV hypertrophy (Figure 1A and B). A coronary angiogram excluded significant coronary artery disease, and a biventricular defibrillator [cardiac resynchronization therapy-defibrillator (CRT-D)] was implanted for primary prevention. After two subsequent episodes of ventricular fibrillation (VF) interrupted by the device, she was referred to our Heart Failure Unit (HFU) at the age of 48 years. During our first evaluation, she presented mild tachypnoea at rest but was haemodynamically stable in New York Heart Association (NYHA) Class II-III. She was oriented to time and to situations, with no neurological symptoms. Echocardiographic evaluation showed a mildly dilated LV with preserved wall thickness, severe systolic dysfunction (LVEF 22%), and diastolic dysfunction of Grade 2, normal right ventricular (RV) function, and moderate pulmonary hypertension. She underwent right heart catheterization (RHC) that showed a reduced cardiac index (CI 1.79 L/min/m<sup>2</sup>) with a mean pulmonary artery pressure (mPAP) of 36 mmHg, pulmonary capillary wedge pressure (PCWP) of 27 mmHg, and pulmonary vascular resistance (PVR) of 3.3  $\mu$ W, consistent with combined post-capillary and pre-capillary pulmonary hypertension (Cpc-PH). During outpatient clinic follow-up, she experienced rapid clinical deterioration and worsening of HF symptoms, to NYHA Class III-IV, not responsive to optimal medical treatment, for which she was hospitalized several times. For this reason, at 48 years of age, she was listed for HT with a non-specific diagnosis of hypokinetic cardiomyopathy. Heart transplantation was performed a year later without complications. In the following years, she remained clinically stable. Genetic testing was proposed a few years later, and a pathogenic frameshift variant (c.103\_104delGA;p.Asp35Phefs\*20) in the LAMP-2 gene (NM\_002294.3) predicted to cause truncation of the protein was detected in a heterozygous state, consistent with DD. A cascade clinical and genetic screening was proposed to her first-degree family members



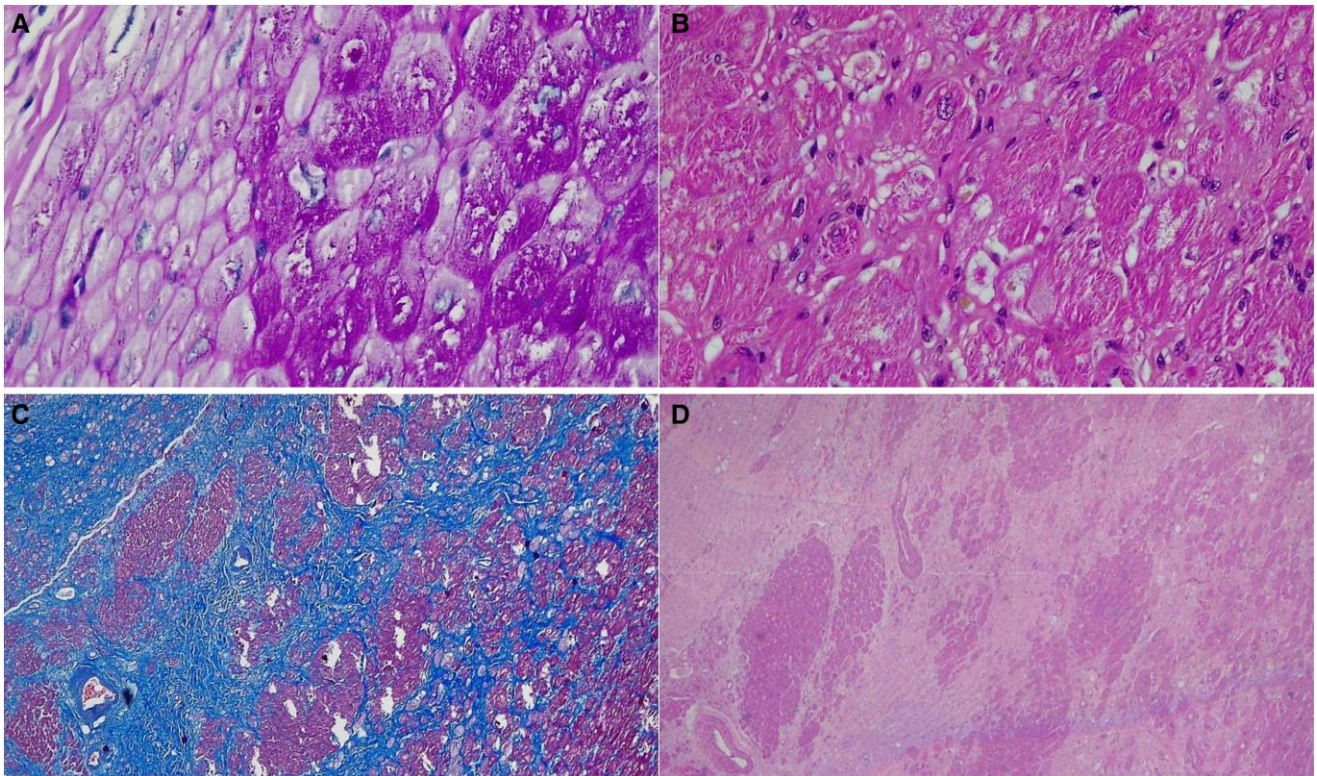
**Figure 1** Echocardiographic evaluation at listing for heart transplantation. (A and B) Case 1 [(A) Lax view; (B) 4ch view]. (C and D) Case 2 [(C) Lax view; (D) 4ch view].

but initially refused. The explanted heart was recently histologically re-examined, showing multiple prominent foci of myocardial scarring extensively involving mid-ventricular layers of the anterior, lateral, and posterior LV walls. Cardiomyocytes were hypertrophic with prominent sarcoplasmic vacuoles filled with Periodic Acid–Schiff (PAS)-positive granules. In the area of replacement fibrosis, there was partial remodelling of intramural coronary arterioles with variable degrees of intimal thickening and perivascular fibrosis (Figure 2).

A few years later, the proband's son (Case 2) was referred to our centre due to advanced HF. He had been previously assessed at another centre due to a pre-syncope episode when he was 26 years old. On admission, his ECG showed third-degree AVB. Echocardiography revealed a HCM pattern with preserved EF (60%) and severe diastolic impairment. In light of familial sudden cardiac deaths and echocardiographic findings, an implantable cardioverter defibrillator (ICD) was implanted. A couple of months later, he was re-admitted because of AF and underwent two TC ablations in rapid succession.

At age 28 years, he was hospitalized for acute HF with severe systolic dysfunction, fluid overload, and anasarca. At first presentation, he suffered from dyspnoea, tachycardia, restlessness, and mild confusion. Examination revealed a respiratory rate of 28, a heart rate of 120, and an oxygen saturation of 87% on room air. After clinical stabilization, he was transferred to our department. At echocardiography (Figure 1C and D), we found a hypertrophic LV with severe systolic

and diastolic dysfunction (LVEF 25%, E/A > 2, E/e' 20). The RV was of normal size but with reduced systolic function [tricuspid annular plane systolic excursion (TAPSE) 9 mm, area fractional change 24%, free wall S' wave 5], and both atria were enlarged. We performed RHC, demonstrating a reduced CI (1.82 L/min/m<sup>2</sup>) with a mPAP of 40 and a PCWP of 32 mmHg. During follow-up, he remained in NYHA Class III–IV despite optimal medical treatment and was listed for HT. The patient is still on the HT waiting list, undergoing periodic cardiological evaluations. Genetic testing revealed that he inherited the pathogenic variant from his mother. For both patients, cardiac and extracardiac findings are summarized (Tables 1 and 2). Our patients' pathogenic variant was previously reported in France by Echaniz-Laguna *et al.*<sup>13</sup> in a Sardinian family with a history of cardiomyopathy. About 10 years before, SCD associated with a 'DD-like syndrome' had been described in Sardinia by Muntoni *et al.*<sup>14</sup> Investigation of our patients' familial background revealed an extended pedigree, which included both the families described by Echaniz-Laguna *et al.*<sup>13</sup> and Muntoni *et al.*<sup>14</sup>, encompassing what is, to the best of our knowledge, the largest family affected by DD published to date (Figure 3). Family tree analysis showed the striking impact of DD on familial members of both sexes. Most male patients died at a young age with cardiac and extracardiac disease manifestations; but mortality was elevated (even though less premature) also in women, unless HT was performed.



**Figure 2** Anatomopathological findings of the explanted heart (Case 1). (A)  $\times 40$  Periodic Acid-Schiff. The vacuoles in cardiac myocytes contain Periodic Acid-Schiff-positive granules. (B)  $\times 40$  Em-Eosin. Cardiac myocytes with prominent sarcoplasmic vacuoles and nuclear hypertrophy. (C)  $\times 4$  Masson trichrome stain. Left ventricular free wall shows multiple foci of mid-ventricular scarring and remodelling of intramyocardial arterioles associated with replacement fibrosis. (D)  $\times 4$  Em-Eosin. Left ventricular free wall shows multiple foci of mid-ventricular scarring.

## Discussion

Danon disease is a rare multisystemic X-linked dominant disorder with a poor prognosis, mostly due to cardiac involvement; diagnosis can be challenging, and genetic confirmation is mandatory. In both of our patients, diagnostic delay was extremely long and could have been avoided if the important clinical red flags had raised clinical suspicion. Considering X-linked transmission, DD is expected to be more severe in male patients. In line with other similar cardiomyopathies with the same transmission (e.g. Fabry disease),<sup>15</sup> males suffered from a broad range of clinical manifestations. The main feature of our report is the different behaviour in terms of age of onset, natural history, and cardiac and extracardiac manifestations according to sex that is associated with the same disease-causing mutation (Tables 1 and 2).

The first clinical presentation of the proband was palpitations due to atrial tachycardia with a ventricular pre-excitation pattern, requiring an EPS that excluded an anterograde AV conducting accessory pathways. An association between this disease and ventricular pre-excitation has been described in 68% of males and 27% of females.<sup>9</sup> The mechanism of ventricular pre-excitation is unclear but is supposed to result from the disruption of the annulus fibrosus, which normally insulates the ventricles from the atria, by glycogen-filled myocytes.<sup>4</sup> The patient experienced VF appropriately interrupted by CRT-D before her first hospitalization for HF. Data on fatal arrhythmias are unclear and reported in both sexes up to 26% in a Spanish registry.<sup>12,16</sup> According to other clinical reports,<sup>10</sup> DD patients might present a severe arrhythmic phenotype, which, in women, might anticipate HF.

The proband's son presented with pre-syncope due to third-degree AVB requiring pacemaker implantation. Also, bradi-arrhythmias are common in both sexes, according to large DD registries.<sup>12</sup> In both of our patients, a cardiac defibrillator was implanted in primary prevention. Both patients experienced progression of systolic dysfunction, with mild LV dilatation in the mother, while the son presented a suggestive restrictive phenotype. Both conditions resulted in progressive myocardial fibrosis, which might be a predictor of prognosis.<sup>17</sup> Unfortunately, cardiac magnetic resonance before transplantation was not performed due to the presence of a device but fibrosis was confirmed in the proband by post-HT examination of the heart (Figure 2).

Cardiac transplantation is the gold standard therapy for DD patients developing advanced HF. A large multicentre study on 38 transplanted patients with DD (19 for each sex) reported a 5-year survival rate of 87.1% for both sexes.<sup>18</sup> After 7 years of follow-up, our transplanted patient is alive with optimal quality of life.

## Conclusion

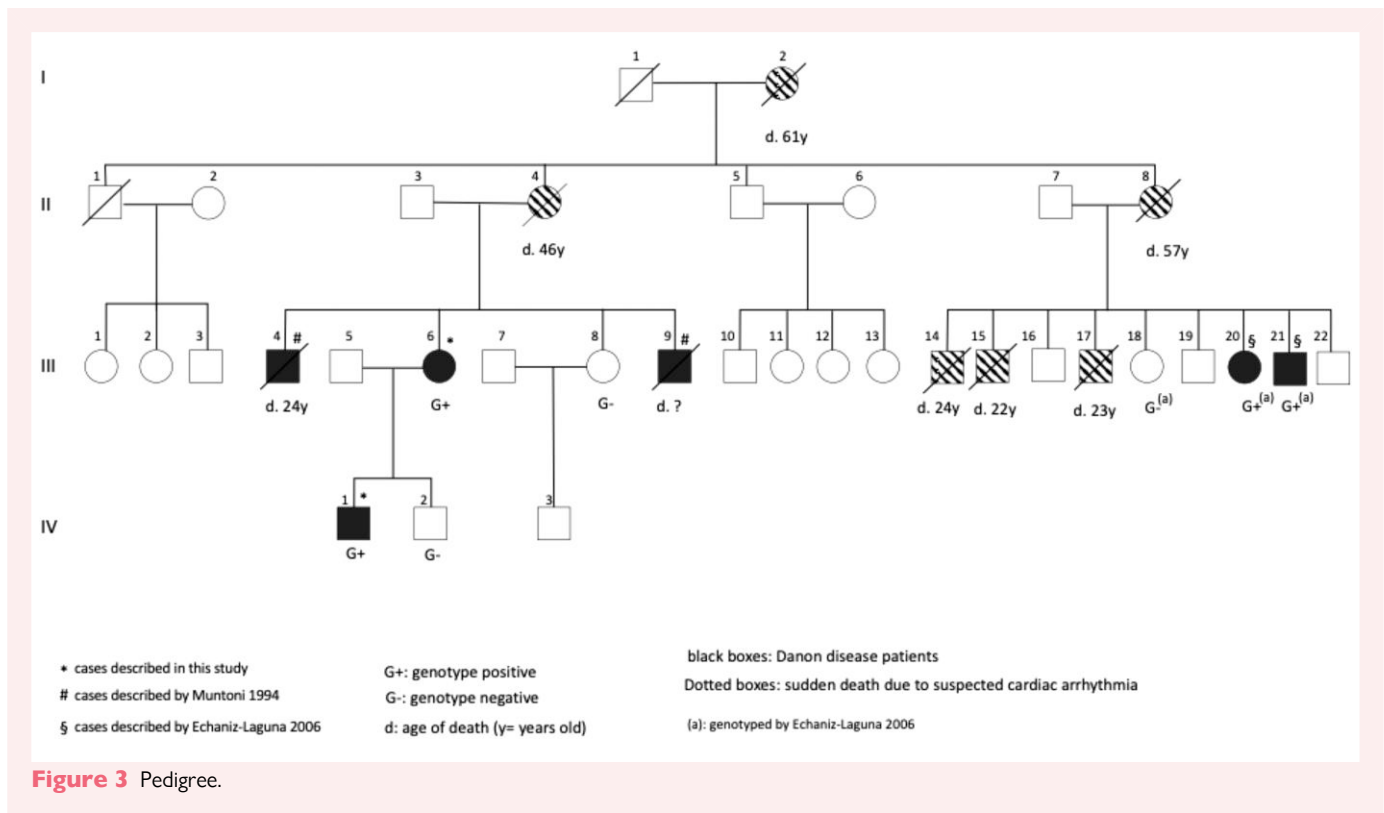
In this paper, we describe a case series of a mother and her son affected by DD that we retrospectively connected with a previously reported case series of members of the same extended family. Similarities and differences exist among sexes; nevertheless, in all cases, genetic testing is mandatory for diagnosis as delay may lead to inappropriate management of the patients. Considering the rapid progression of cardiac

**Table 1** Cardiac features

	Case 1	Case 2
<b>Clinical findings</b>		
Sex	Female	Male
Genotype	LAMP-2 (NM_002294.3): c.103_104delGA; p.Asp35Phefs*20 in a heterozygous state	LAMP-2 (NM_002294.3): c.103_104delGA; p.Asp35Phefs*20 in a hemizygous state
Age of first cardiac symptom	40	26
Symptoms and clinical onset	Palpitations	Pre-syncope
ECG presentation	Supraventricular tachyarrhythmias	Atrio-ventricular block III degree
Age of diagnosis	50	28
Age of listing	48	28
Age of transplantation	49	—
NYHA class at evaluation	III	III
<b>EPS abnormalities</b>		
Ventricular pre-excitation	Yes	No
AVB	No	Yes, III degree AVB
AF	Yes	Yes
VF/arrest	Yes	No
Device therapy	CRT-D	ICD
<b>Echocardiography at listing</b>		
Maximum LV wall thickness (mm)	13	17
LV diastolic diameter (mm)	58	45
LVEF (%)	22	25
Pericardial effusion	None	None
Left atrium area (cm <sup>2</sup> )	19	19
RV diastolic diameter (mm)	40	36
TAPSE	12	9
RV-posterior wall S' wave (cm/s)	10	5
Fractional area change (%)	27	24
Pulmonary artery pressures (mmHg)	40	35
<b>Cath lab at listing</b>		
mPAP (mmHg)	36	40
Wedge pressure (mmHg)	27	32
PVR (μW)	3.3	2.9
Cardiac index (L/min/m <sup>2</sup> )	1.79	1.82
Cardiac output (L/min)	2.69	2.76

**Table 2** Extracardiac involvement

	Case 1	Case 2
<b>Neurologic</b>	TIA	Mild cognitive impairment
<b>Ocular</b>	No	Chorioretinitis and high-grade myopia
<b>Musculoskeletal</b>	No	Asymptomatic myopathy
<b>Other symptoms</b>		
Symptomatic respiratory disease	No	No
Symptomatic gastro intestinal disease	No	No
<b>Laboratory values at listing</b>		
Creatine phosphokinase (U/L)	73	1254
Aspartate transaminase–alanine transaminase (U/L)	80–52	592–373
Lactate dehydrogenase (U/L)	468	1088
Total bilirubin (mg/dL)	1.70	2.40
Creatinine (mg/dL)	0.88	0.70
Brain natriuretic peptide (pg/L)	357	1321
High sensitive troponin I (ng/L)	35	84



**Figure 3** Pedigree.

disease, close surveillance should be offered in both sexes since HT is the only available therapy for advanced disease. Hope is now coming from gene therapy, which is still in its early days of investigation. Sudden cardiac death is the second cause of death. In the absence of prediction models to guide ICD implantation, arrhythmic risk should be assessed at diagnosis and reevaluated during follow-up.

## Lead author biography



Dr Daniele Pasqualucci received his MD from the University of Cagliari, Italy, in 2006. He became a cardiologist in 2011, and since then, he has been working in the Department of Cardiology, ARNAS ‘G. Brotzu’, Cagliari. His studies and clinical practice are focused on heart failure, heart transplantation, cardiomyopathies, and genetics. His studies are specifically interested in cardiomyopathies evolving in advanced heart failure.

## Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

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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:** In accordance with COPE guidelines, the authors confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patients.

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## Data availability

The data underlying this article are available in the article and in its online [Supplementary material](#).

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