

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

International Consensus on Differential Diagnosis and Management of Patients With Danon Disease



JACC State-of-the-Art Review

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ABSTRACT

Danon disease is a rare X-linked autophagic vacuolar cardioskeletal myopathy associated with severe heart failure that can be accompanied with extracardiac neurologic, skeletal, and ophthalmologic manifestations. It is caused by loss of function variants in the *LAMP2* gene and is among the most severe and penetrant of the genetic cardiomyopathies. Most patients with Danon disease will experience symptomatic heart failure. Male individuals generally present earlier than women and die of either heart failure or arrhythmia or receive a heart transplant by the third decade of life. Herein, the authors review the differential diagnosis of Danon disease, diagnostic criteria, natural history, management recommendations, and recent advances in treatment of this increasingly recognized and extremely morbid cardiomyopathy. (J Am Coll Cardiol 2023;82:1628-1647) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

In 1981 Morris Danon described 2 patients with severe hypertrophic cardiomyopathy resembling Pompe syndrome but with normal acid maltase levels; unbeknownst to him, he identified the first patient with a disease that would carry his name.¹ Danon disease was soon recognized to be a rare

X-linked cause of cardiac hypertrophy that was strongly associated with various other systemic manifestations, including skeletal myopathy, intellectual disability, and retinal disorders. However, it would be another 20 years before Ichizo Nishino identified the gene that caused Danon disease as *LAMP2*, a



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HIGHLIGHTS

- Danon disease is a rare, X-linked genetic cardiomyopathy in which protein deficiency results in autophagy, accumulation of autophagosomes, defective mitochondria myocyte death, and adverse clinical outcomes.
- Clinical features include myocardial hypertrophy, conduction abnormalities, heart failure, malignant ventricular arrhythmia, and multisystem involvement.
- Understanding the pathophysiology and clinical trajectory of Danon disease may promote earlier diagnosis, risk stratification, and patient selection for medical and gene therapies that may have implications for other genetic cardiomyopathies.

critical regulator of autophagic flux expressed ubiquitously in virtually all multicellular organisms.²

During the past decade, significant insights have been achieved into the pathobiology of Danon disease, primarily because of the development of in vivo and in vitro models of the disease.^{3,4} Furthermore, several retrospective natural history studies have been completed that shed light on the disease progression and emphasize the morbidity and mortality of Danon disease in both sexes.⁵⁻¹⁰ Whereas the current standard of care for the condition has a limited impact on altering the natural history of the disease, promising new therapies are being evaluated in ongoing clinical trials.

Danon disease is one of the most severe and penetrant forms of inherited cardiomyopathy.¹¹ Case reports of male patients with Danon disease describe hearts that are among the largest ever described.^{12,13} Although symptomatic heart failure will develop in these patients irrespective of sex, ventricular arrhythmia, and conduction disturbances, males affected by Danon disease generally present earlier than women. In fact, most male patients will die of heart failure or undergo cardiac transplantation by the third decade of life. Many unanswered questions remain regarding Danon disease, including not only why these patients experience such severe disease but how they manage to survive despite the absence of a protein thought to be critical for cellular homeostasis. Although Danon disease is rare, we believe it merits a comprehensive review because of its

unique pathologic characteristics, severity, and phenotypic similarity to other inherited disorders.

DEFINITION OF DANON DISEASE

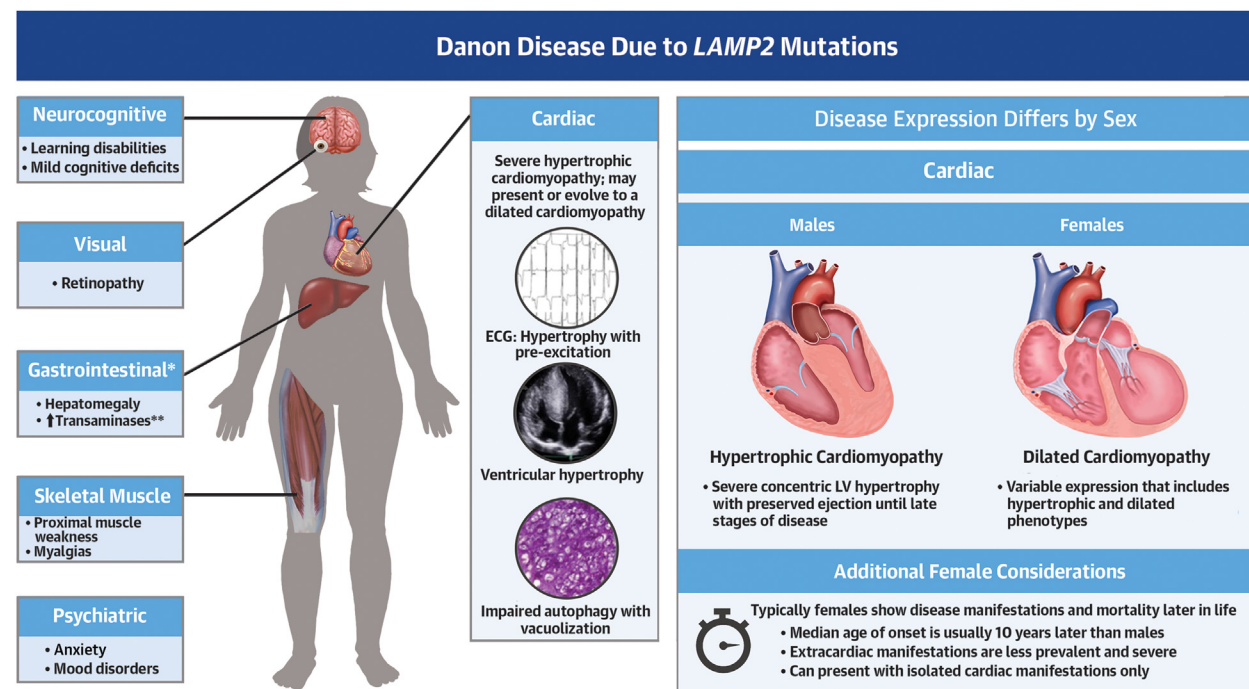
PATHOPHYSIOLOGY. Danon disease is caused by a critical deficiency of expression of the lysosomal-associated membrane 2 (LAMP-2) protein, encoded by the *LAMP2* gene, which is localized to the X-chromosome (Xq24).^{2,14} Deficient production of LAMP-2B results in impaired macroautophagy. Intracellular vacuoles containing glycogen and other cytoplasmic components accumulate, instead of being degraded and recycled for reuse by the cell, resulting in cardiomyocyte hypertrophy.^{15,16} Defective autophagy results in a mismatch between the supply and demand of energy and resources within cells and oxidative stress, causing cell death and diffuse fibrosis, which affects conduction and increases susceptibility to arrhythmias. Although immunohistochemistry and other protein-based studies are feasible, from a practical standpoint the diagnosis of Danon disease is typically made on the basis of suggestive clinical features and detection of a pathogenic or likely pathogenic variant in *LAMP2*. Variants that portend a loss of LAMP-2 protein expression (nonsense, frameshift, and insertion/deletion variants) represent the spectrum of Danon disease-causing genetic findings.¹⁶ *LAMP2* is included in most hypertrophic and dilated cardiomyopathy gene panels. Thus, even if Danon disease is not initially suspected in a patient with cardiomyopathy, the diagnosis of Danon disease may be revealed to clinicians through the results of genetic testing.

CLINICAL MANIFESTATIONS. Clinically, the disease is characterized by the classic triad of severe cardiomyopathy, skeletal myopathy, and cognitive impairment, reflecting the fact that the myocardium, skeletal muscle, and brain have the most abundant expression of LAMP-2 (**Central Illustration**).^{17,18} Cardiac manifestations are usually the most prominent and severe, whereas skeletal muscle and neurologic phenotypes can vary considerably (**Figure 1**).⁵⁻¹⁰ Furthermore, this multisystem disorder can include retinopathy as well as gastrointestinal, hepatic, and pulmonary manifestations (**Table 1**). Although liver enzyme abnormalities and creatine kinase elevation can precede the diagnosis of cardiomyopathy, hepatic and pulmonary symptoms are often sequelae of progressive cardiac disease. Notably, although mild cognitive and muscular impairments may have been

ABBREVIATIONS AND ACRONYMS

- AAV** = adenoassociated viruses
- BNP** = B type natriuretic peptide
- CMR** = cardiac magnetic resonance
- ECG** = electrocardiogram
- GAA** = acid α -glucosidase gene
- ICD** = implantable cardioverter defibrillator
- LAMP-2** = lysosomal-associated membrane 2
- LVH** = left ventricular hypertrophy
- MDs** = mitochondrial diseases
- mtDNA** = mitochondrial DNA

CENTRAL ILLUSTRATION Clinical Presentation of Danon Disease



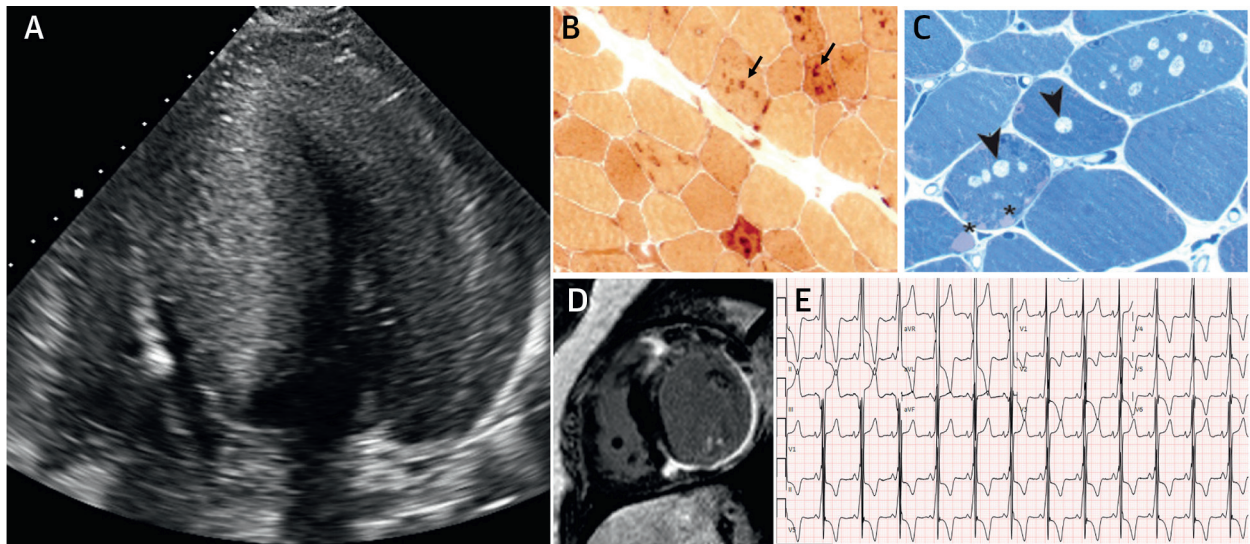
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Due to its X-linked dominant inheritance, disease expression differs by sex. Danon disease in males is characterized by the classical triad of severe cardiomyopathy, skeletal myopathy, and cognitive impairment. Additional extracardiac symptoms include visual, gastrointestinal, and psychiatric manifestations. Females often present with disease later in life and with isolated cardiac manifestations that include hypertrophic and dilated phenotypes. If extracardiac symptoms are present in females, they are often less severe. *Congestive hepatopathy can be seen in patients with advanced heart failure. **Elevated transaminases can be due to skeletal myopathy. ECG = electrocardiogram; LV = left ventricular.

present since childhood, cardiovascular symptoms are often what trigger clinical evaluation. Thus, at the time of diagnosis, simultaneous reporting of all of these symptoms can occur.^{5,19} Owing to its X-linked dominant inheritance, disease expression differs by sex, with female individuals often presenting with disease manifestations later in life and often with isolated cardiac symptoms.^{5-10,15} The clinical presentation and specific cardiac features demonstrate large variability in female individuals, presumably because of different patterns of X chromosome inactivation. Inasmuch as extracardiac manifestations are less prevalent and severe, the diagnosis of Danon disease is more challenging in female individuals and may be an unexpected finding from cardiomyopathy-panel or whole exome-based genetic testing. Although this suggests that surveillance intervals should differ by sex, all *LAMP2* variant carriers should undergo baseline multisystem evaluation to assess for the presence of any symptoms or signs of disease.

Cardiac. Left ventricular hypertrophy (LVH) is the most common cardiac manifestation at presentation for both sexes, although 30% to 50% of female individuals can present with a dilated or hypokinetic nondilated phenotype.⁸ Cardiac magnetic resonance (CMR) can identify varying patterns of hypertrophy and distribution of late gadolinium enhancement in male and female individuals. In male individuals, LVH was typically concentric with normal ejection fraction, whereas female individuals presented with asymmetric LVH, right ventricular hypertrophy, and both hypertrophic and dilated phenotypes.²⁰ Progression of cardiac disease is the greatest cause of morbidity.⁵⁻¹⁰ Oftentimes, children and adolescents can have accelerated hypertrophy of the cardiomyocytes, resulting in severe LVH, which is a distinguishing feature of Danon disease compared with other forms of hypertrophic cardiomyopathy. Defective autophagy impairs crucial biological functions in the relentlessly working cardiac muscle,

FIGURE 1 Clinical Features of Danon Disease



(A) Apical 4-chamber view from a 19-year-old man with *LAMP2* frameshift variant c.420_421insG (p.Leu141ValfsX9), showing severe left ventricular hypertrophy. **(B, C)** Skeletal muscle biopsy specimen with lysosomes (arrows), autophagic vacuoles (arrowheads), and glycogen deposits (*). **(D)** Cardiac MR short-axis view from a 20-year-old male with *LAMP2* splicing variant c.741G>A (p.Lys247=) showing diffuse late gadolinium enhancement that spares the septum. **(E)** Electrocardiogram from same patient as in **A** with pre-excitation, left ventricular hypertrophy with repolarization abnormalities.

leading to ongoing myocardial injury and sustained circulating troponin elevation.²¹ Typically, owing to cardiomyocyte death and progressive fibrosis, the hypertrophic heart becomes hypokinetic, followed by wall thinning and possible dilation. It remains unclear whether the dilated cardiomyopathy in female individuals is part of the continuum of disease that begins as cardiac hypertrophy or whether it represents an independent disease phenotype.²² Although there are case reports of female individuals with early onset of hypertrophy, symptoms, arrhythmia, and an accelerated malignant clinical course, the majority experience milder disease that may delay diagnosis until a later time, when their hearts may have already become hypokinetic and/or dilated.^{19,22}

Electrophysiologic abnormalities and arrhythmias are common in Danon disease. Early manifestations include short PR and/or delta waves, which suggest accelerated atrioventricular nodal conduction and/or accessory pathways, high ECG voltage with repolarization abnormalities, and atrial and ventricular arrhythmias. Supraventricular tachycardias, including atrial flutter and atrial fibrillation, as well as ventricular arrhythmias, are common and occur in approximately 60% of individuals.⁹ Pre-excitation secondary to Wolff-Parkinson-White syndrome or fasciculoventricular pathways, which may be an early marker of

disease, is common in both male (69%) and female individuals (27%) and occurs more frequently in Danon disease than in other forms of hypertrophic heart disease.^{5,6,23} Multiple accessory pathways may coexist. Although the mechanism for pre-excitation in Danon disease is unknown, disruption of the annulus fibrosus that surrounds the atrioventricular node by glycogen-filled myocytes is speculated to be a mechanism for accessory conduction pathways in *PRKAG2* mutations, another disorder associated with glycogen storage and dysfunctional autophagy.^{24,25} High-degree heart block or sinus node dysfunction requiring pacemaker implantation is also highly prevalent and is reported to be between 35% and 50%.¹¹ Bradyarrhythmias may either be present at diagnosis (sometimes concomitantly with pre-excitation) or evolve at a later stage of the disease. Cardiac arrest and sudden arrhythmia death may be the first disease presentation in both sexes. Finally, intraventricular conduction disturbances and malignant ventricular arrhythmia are common and are frequently associated with severe hypertrophy, disease progression, and heart failure.¹⁰

Skeletal muscle. Manifestations of skeletal muscle myopathy are usually mild, with weakness reported predominantly in proximal muscles, including pelvic girdle and axial muscles.²⁶ Additional symptoms can

TABLE 1 Danon Disease Is a Multisystem Disorder With Reported Clinical Dysfunction in Various Physiological Systems

| System | Symptoms and Signs | Diagnostics |
|------------------|--|---|
| Cardiac | <ul style="list-style-type: none"> Severe and progressive cardiac hypertrophy; may present/evolve to dilated, hypokinetic LV Arrhythmias: atrial fibrillation, ventricular tachycardia/fibrillation; pre-excitation; 1st-, 2nd-, and 3rd-degree heart block and sinus node dysfunction | <ul style="list-style-type: none"> Electrocardiogram Echocardiogram CMR Event monitor Laboratory tests: natriuretic peptides, troponin |
| Skeletal | <ul style="list-style-type: none"> Proximal muscle weakness Myalgias | <ul style="list-style-type: none"> Electromyography Functional assessments Timed tests Laboratory tests: CPK, AST, ALT |
| Neurocognitive | <ul style="list-style-type: none"> Learning disabilities Mild cognitive deficits | <ul style="list-style-type: none"> Developmental assessment |
| Psychiatric | <ul style="list-style-type: none"> Anxiety Mood disorders | |
| Visual | <ul style="list-style-type: none"> Retinopathy | <ul style="list-style-type: none"> Ophthalmic and retinal examination Electroretinogram |
| Gastrointestinal | <ul style="list-style-type: none"> Hepatomegaly Elevated liver enzymes | <ul style="list-style-type: none"> Laboratory tests: AST, ALT, GGT, LDH, alkaline phosphatase |

ALT = alanine transaminase; AST = aspartate transferase; CMR = cardiac magnetic resonance; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; HCM = hypertrophic cardiomyopathy; LDH = lactate dehydrogenase; LV = left ventricle.

be nonspecific and include myalgias and decreased exercise capacity. Objective functional assessments, including timed tests, 6-minute walk tests, and cardiopulmonary exercise testing, along with electromyography testing, can be helpful for diagnosis and surveillance. Creatine kinase and transaminase levels are typically elevated in male individuals, suggesting ongoing myocyte injury.⁵ Skeletal muscle manifestations may be aggravated by strenuous exercise, certain drugs, and other myopathic stimuli/conditions.

Cognitive and psychiatric signs and symptoms. Mild cognitive impairment and learning difficulties have been reported in at least 80% of affected male individuals and between 6% and 47% of female patients.^{8,27} Psychiatric disorders can be subtle and range from behavioral abnormalities to mood and anxiety disorders, with 1 case series reporting an incidence of 69%.²⁷ Young individuals with the disease often carry the diagnosis of attention deficit disorder before receiving a definitive diagnosis of Danon disease. Embolic strokes from intracardiac thrombi, in the setting of depressed left ventricular function, apical aneurysms, or atrial fibrillation or flutter can also occur. For these reasons, in cases of acute neurologic changes, neurologic imaging and transthoracic echocardiography with contrast material and/or transesophageal echocardiography should be obtained to rule out intracardiac thrombi.^{28,29}

Retinopathy. Vision impairment, mainly pigmentary retinopathy and myopia, have been classically described in patients with Danon disease, with male individuals disproportionately affected compared with female individuals despite the prevalence of eye abnormalities in Danon disease being highly variable across series.^{8,30} These visual deficits are often of no clinical significance but may be demonstrated by specific testing. The mechanisms for ophthalmologic disease include loss of retinal pigment in the retinal epithelium and cone-rod dystrophy.^{5,8,11,31,32}

Gastrointestinal involvement. Hepatomegaly has been reported and may occur in conjunction with elevated transaminases without hepatic synthetic dysfunction, which may be more indicative of myocyte and skeletal muscle involvement and not hepatocellular injury.¹⁴ Patients with advanced heart failure may experience congestive hepatopathy.

CRITERIA FOR DIAGNOSIS

Family history of a cardiomyopathy with an X-linked hereditary pattern and multiorgan dysfunction that includes neurocognitive deficits, skeletal myopathy, and visual involvement is suggestive of Danon disease. In addition to further phenotypic testing that includes the aforementioned diagnostics, confirmatory genetic testing is critical for diagnosis. Skeletal and myocardial tissue biopsies can be performed in circumstances when variants of unknown significance are identified in genetic testing and there is diagnostic uncertainty. Although not widely available, functional gene protein assays such as flow cytometry testing and immunohistochemistry of peripheral leukocytes and immunofluorescence and western blot on skeletal and myocardial tissue can be used to quantify LAMP-2 protein expression and identify patients for genetic testing.³³⁻³⁵ Additionally, because some rearrangements and copy-number variants in the *LAMP2* gene may be missed by next-generation sequencing, if the result of genetic testing is negative and suspicion for Danon disease persists, then expression of LAMP-2 on leukocytes or on tissue obtained by biopsy should be performed as described earlier.

Given variable age- and sex-dependent penetrance and expressivity of Danon disease, clinical diagnoses should be confirmed by genetic testing (Figure 2). All patients with suspected Danon disease should undergo genetic testing. For individuals who carry pathogenic or likely pathogenic *LAMP2* variants, diagnosis with clinical disease depends on the presence of cardiac, neuromuscular, or cognitive features of disease. Owing to the high penetrance of disease in

FIGURE 2 Diagnostic Algorithm for Clinical Danon Disease

Diagnostic Algorithm for Clinical Danon Disease

LAMP2* mutation (pathogenic or likely pathogenic)

+

Males: A or B or C; Females: A only

A: Objective cardiovascular abnormality defined as any:

- LVH: interventricular septal and posterior wall thickness
 - age <18 y: z-score ≥ 2
 - age ≥ 18 y: ≥ 1.3 cm
- LVEF <50%
- Electrocardiogram abnormalities:
 - history of AF or AFL, VT, VF, or sudden cardiac death
 - repolarization abnormalities, LVH/RVH, AV block
 - pre-excitation pattern due to Wolff-Parkinson-White or fasciculoventricular pathways
- Late gadolinium enhancement on cardiac MRI

B: Muscle abnormalities defined by any:

- Abnormal EMG, functional assessment (CPET, 6MWT), or timed tests
- Elevated CPK, AST, or ALT (>2 SD above the upper limit of normal)

C: Intellectual disability, attention deficit disorder, or developmental delay

The diagnostic algorithm for Danon disease incorporates genetics, sex, and clinical features. *In patients with a *LAMP2* VUS: Cardiovascular abnormality + family history with: 1- presence of autophagic vacuoles with unique sarcolemmal features in myocytes on histology or 2- aberrant *LAMP2* gene expression detected via mRNA or cDNA sequencing or absent/deficient *LAMP2* expression in blood, leukocytes or skeletal/cardiac tissue is suggestive of clinical Danon disease. 6MWT = 6-minute walk test; AF = atrial fibrillation; AFL = atrial flutter; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AV = atrioventricular; CPET = cardiopulmonary exercise test; CPK = creatine phosphokinase; EMG = electromyogram; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging; RVH = right ventricular hypertrophy; VF = ventricular fibrillation; VT = ventricular tachycardia.

male Danon patients with *LAMP2* mutations, extracardiac symptoms in male individuals automatically qualify them as having Danon disease. This is in contrast to female individuals, where penetrance is lower and thus, diagnosis requires the presence of cardiac manifestations. In patients with a *LAMP2* variant of unknown significance, regardless of sex, diagnosis requires RNA analysis to demonstrate radical defects or absence of LAMP-2 protein as determined by either leukocyte flow cytometry or tissue analysis. Supporting evidence includes cellular histologic analysis showing autophagic vacuoles with unique sarcolemmal features, as well as an X-linked inheritance pattern, and confirming a de novo mutation in the absence of a family history of diseases.^{15,24,36,37}

DIFFERENTIAL DIAGNOSIS. Danon disease is part of the differential diagnosis in conditions exhibiting early-onset cardiac hypertrophy (Table 2). In male patients, the severity of LVH in children and adolescents, as well as the prominent extracardiac

phenotype, may strongly guide clinical suspicion toward the diagnosis. By contrast, women may present with an isolated cardiomyopathy that includes pre-excitation arrhythmias and resembles either a sarcomeric hypertrophic or a dilated phenotype.⁸ In the absence of an affected male in the family, misdiagnoses may occur in the absence of genetic testing. The evaluation of suspected Danon disease should, as with other cardiomyopathies, include a detailed family history (Figure 3). Clues to a Danon disease diagnosis include X-linked dominant transmission and male individuals being generally more severely affected than female individuals. Although de novo *LAMP2* mutations may occur, resulting in no contributory family history, male-to-male transmission or female-to-all-offspring patterns suggestive of mitochondrial disease should prompt consideration of other diagnoses. Differential diagnoses should include the following:

PRKAG2-related disease. *PRKAG2* (gamma-2 regulatory subunit of AMP-activated protein kinase)

TABLE 2 Differential Diagnosis of Danon Disease vs Other Diseases With Hypertrophic Phenotype

| Disease | Genetic Variant | Cardiac Features | ECG | Extracardiac Features | Treatment | Differences From Danon Disease |
|-------------------|---|--|--|--|---|--|
| Sarcomeric HCM | <ul style="list-style-type: none"> Sarcomeric protein gene variants <ul style="list-style-type: none"> MYH7: most common in infant/childhood MYBPC3: most common in adulthood Autosomal dominant Onset: infancy, childhood, adulthood | <ul style="list-style-type: none"> Left ventricular hypertrophy: <ul style="list-style-type: none"> Asymmetric septal Apical Concentric Left ventricular outflow tract obstruction (up to two thirds of patients) Mitral valve abnormalities: <ul style="list-style-type: none"> Elongated anterior leaflet Papillary muscles abnormalities Accessory and slack mitral valve chords Hypercontractility Anatomically narrowed left ventricular outflow tract Atrial fibrillation Ventricular arrhythmias Persistent natriuretic and/or troponin elevation may be detected | <ul style="list-style-type: none"> LVH pattern with repolarization changes T wave inversion Left anterior fascicular block Q waves | None | <ul style="list-style-type: none"> Left ventricular outflow tract obstruction: <ul style="list-style-type: none"> Medications: beta-blockers, non-dihydropyridine calcium-channel blockers, disopyramide, mavacamten Septal reduction therapies: myectomy and alcohol septal ablation. Supportive care | <ul style="list-style-type: none"> Pattern of hypertrophy usually asymmetric Ventricular pre-excitation is rare Slower disease progression |
| PRKAG2 | <ul style="list-style-type: none"> Pathogenic variants in the <i>PRKAG2</i> gene that encode the adenosine monophosphate-activated protein kinase gamma 2 regulatory subunit Autosomal dominant Onset: childhood, adulthood | <ul style="list-style-type: none"> Left ventricular hypertrophy Atrial fibrillation AV block | <ul style="list-style-type: none"> High QRS voltage Repolarization abnormalities Ventricular pre-excitation Bundle branch blocks | <ul style="list-style-type: none"> CPK may be slightly increased Myopathy seldom reported | Supportive care | <ul style="list-style-type: none"> AV block is more common compared with Danon disease Less severe left ventricular hypertrophy |
| Friedreich ataxia | <ul style="list-style-type: none"> Large triplet expansion in intron 1 of the human <i>FRDA</i> gene (<i>FXN</i>) Autosomal recessive Onset: childhood, adulthood | <ul style="list-style-type: none"> Left ventricular concentric hypertrophy Atrial arrhythmias Progressive heart failure | <ul style="list-style-type: none"> Left ventricular hypertrophy T wave inversion Pathological Q waves | <ul style="list-style-type: none"> Progressive ataxia Spasticity Sensory neuropathy Scoliosis Foot deformity (pes cavus) Diabetes mellitus Dysarthria Muscle weakness in lower limbs | Supportive care | <ul style="list-style-type: none"> Different extracardiac manifestations Less severe left ventricular hypertrophy |
| Pompe disease | <ul style="list-style-type: none"> Pathogenic variants in acid α-glucosidase leading to lysosomal glycogen accumulation Autosomal recessive Onset: infancy, childhood, adulthood | <ul style="list-style-type: none"> In infancy: <ul style="list-style-type: none"> Severe left ventricular hypertrophy Left ventricular outflow tract obstruction Heart failure associated with hypokinetic hypertrophic cardiomyopathy Milder phenotypes in childhood and adulthood onset | <ul style="list-style-type: none"> High QRS voltage Repolarization abnormalities Ventricular pre-excitation Bundle branch blocks AV block | <ul style="list-style-type: none"> In infants: <ul style="list-style-type: none"> Muscular hypotonia (floppy baby) Macroglossia Hepatomegaly Delayed motor milestones Frequent respiratory infections In adults proximal muscle weakness (limb girdle dystrophy) Increased serum AST, ALT, CPK, LDH | <ul style="list-style-type: none"> Enzyme replacement therapy Supportive care | <ul style="list-style-type: none"> Infant onset have severe cardiac and extracardiac involvement Childhood and adulthood onset have a less severe cardiomyopathy |

Continued on the next page

mutations can cause dysregulation of adenosine monophosphate kinase, which eventually leads to myocyte hypertrophy and the accumulation of vacuoles with glycogen stores.³⁸ The inheritance pattern in *PRKAG2* families is autosomal dominant. However, the combination of early-onset cardiac hypertrophy

and pre-excitation makes *PRKAG2* disease relevant to the differential diagnosis of Danon disease.

In a recent multicenter study, 90 patients with *PRKAG2* genetic variants, including 24 nonaffected carriers, were described.³⁹ Among the affected patients, 56% were male, the median age at first

TABLE 2 Continued

| Disease | Genetic Variant | Cardiac Features | ECG | Extracardiac Features | Treatment | Differences From Danon Disease |
|------------------------|--|---|--|--|---|---|
| Mitochondrial diseases | <ul style="list-style-type: none"> Pathogenic variants in mtDNA or nuclear DNA encoding mitochondrial proteins Inheritance: <ul style="list-style-type: none"> mtDNA: matrilinear Nuclear DNA: variable Onset: infancy, childhood, adulthood | <ul style="list-style-type: none"> Left ventricular hypertrophy Evolution to systolic dysfunction more common compared with sarcomeric HCM Dilated cardiomyopathy (less common) | <ul style="list-style-type: none"> Short PR or pre-excitation Left ventricular hypertrophy Repolarization abnormalities WPW syndrome AV block | <ul style="list-style-type: none"> Bilateral sensorineural deafness Retinitis pigmentosa/optic atrophy Diabetes mellitus Palpebral ptosis Lactic acidosis Increased CPK, AST, ALT, LDH, lactate | <ul style="list-style-type: none"> Dietary supplements: carnitine, thiamine, Q10 enzyme Supportive care | <ul style="list-style-type: none"> Different extracardiac manifestations Less severe left ventricular hypertrophy |
| Rasopathies | <ul style="list-style-type: none"> Pathogenic variants in genes encoding proteins involved in the RAS/mitogen-activated protein kinase (MAPK) pathway Autosomal dominant Onset: infancy | <ul style="list-style-type: none"> Pulmonary valve stenosis Atrioventricular septal defect Atrial septal defect Left ventricular hypertrophy Left ventricular outflow tract obstruction due to: <ul style="list-style-type: none"> Displaced papillary muscles Longer anterior mitral valve leaflet Anomalous insertion of mitral chordae Hyperdynamic left ventricle Subaortic fibrous tissue Right ventricular hypertrophy Right ventricular outflow tract obstruction Coronary artery abnormalities Diastolic dysfunction Atrial arrhythmias | <ul style="list-style-type: none"> Extreme right-axis deviation Bundle branch blocks Prolonged QT T-wave inversion | <ul style="list-style-type: none"> Short stature Facial abnormalities: <ul style="list-style-type: none"> Short and depressed nasal root Low-set ears Hypertelorism Dermatological abnormalities: <ul style="list-style-type: none"> Lentigines (Noonan syndrome with multiple lentigines, LEOPARD syndrome) Café-au-lait spots Hematopoietic, gastrointestinal, neurologic, and endocrine involvement Sensorineural deafness | Supportive care | Frequently associated with congenital heart disease and left ventricular outflow tract obstruction |
| Fabry disease | <ul style="list-style-type: none"> Pathogenic variants in the GLA gene encoding α-galactosidase A gene causing accumulation of glycolipids X-linked Onset: childhood, adulthood | <ul style="list-style-type: none"> Cardiac hypertrophy after 3rd-4th decade <ul style="list-style-type: none"> Concentric (most common) Asymmetric septal Apical AV block Atrial and ventricular arrhythmias Microvascular angina | <ul style="list-style-type: none"> Left ventricular hypertrophy Short PR Right bundle branch block ST-segment depression and T-wave inversion | <ul style="list-style-type: none"> Neuropathic pain Febrile crisis Gastrointestinal: <ul style="list-style-type: none"> Diarrhea Constipation Angiokeratomas Ophthalmologic: <ul style="list-style-type: none"> Cornea veritcillata Cataracts Hypo/ hyperhidrosis Fatigue Neurological: <ul style="list-style-type: none"> Stroke White matter lesions Hearing loss Renal: <ul style="list-style-type: none"> Microalbuminuria, proteinuria, chronic kidney disease | <ul style="list-style-type: none"> Enzyme replacement therapy Chaperone therapy | <ul style="list-style-type: none"> Adult-onset cardiomyopathy Different extracardiac involvement |

AV = atrioventricular; mtDNA = mitochondrial DNA; WPW = Wolff-Parkinson-White; other abbreviations as in Table 1.

evaluation was 37 years (IQR: 18-50 years), and LVH was significant, with a mean myocardial wall thickness of 20 ± 8 mm. Sixty-four percent had LVH on ECG, and 32% had left or right bundle branch block. This condition was associated with a high prevalence of arrhythmias, with 57% of patients having a pre-

excitation pattern or requiring accessory pathway ablation, and 14% experienced atrial fibrillation with a prevalence of 29% after 6 years (IQR: 2.3-13.9 years) of follow-up care, with a median age at onset of 43 years. Nineteen percent had a pacemaker implanted at first evaluation, and 15 patients (21%) required an

implant during follow-up care, with a median age at implantation of 36 years and a final prevalence of 35%. Twenty-five percent of patients had received an implantable cardioverter-defibrillator (ICD) at last evaluation, 5 of them for secondary prevention. The disease progression of this condition was milder and less abrupt than that of Danon disease, with 15% experiencing systolic dysfunction with an ejection fraction <50%, 4% requiring heart transplantation, and 6% dying of sudden cardiac death or end-stage heart failure. Patients with greater baseline mean wall thickness and lower left ventricular ejection fraction were at higher risk for adverse events. Unlike in Danon disease, muscle weakness or myalgia was seldom reported in PRKAG2 (2% of patients), although 21% had mildly elevated creatine kinase levels. Additionally, PRKAG2 disease does not cause retinal disease or intellectual impairment.

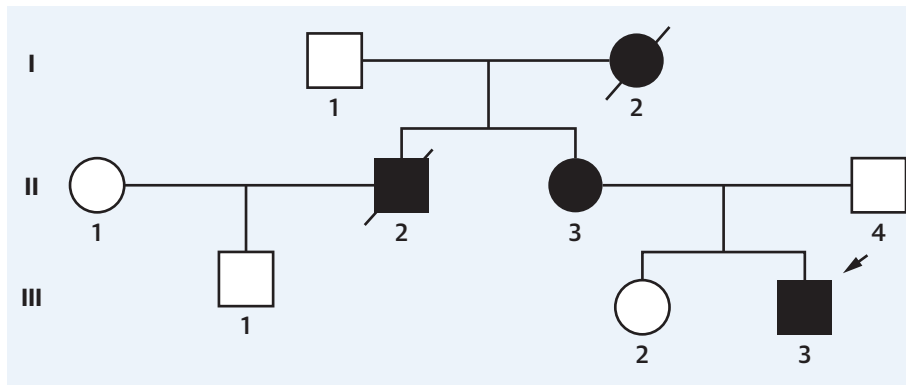
Pompe disease. Pompe disease is an autosomal recessive genetic disorder caused by pathogenic variants in the gene encoding acid α -glucosidase (GAA), leading to lysosomal glycogen accumulation mostly in skeletal and cardiac muscles. The phenotypic expression depends on the residual enzymatic activity, which is low in patients presenting at infancy and higher in patients presenting later in life.⁴⁰ The infantile form is characterized by muscular hypotonia (floppy baby), macroglossia, hepatomegaly, and severe LVH that may be associated with left ventricular outflow tract obstruction. On ECG, high QRS voltage, pre-excitation patterns, repolarization abnormalities, bundle branch blocks, and atrioventricular blocks may be present. Childhood-onset patients present with a phenotype characterized by muscle weakness and a less severe form of cardiomyopathy, compared with adult-onset patients, where cardiac involvement is infrequent and manifestations are predominantly progressive skeletal and respiratory muscular failure.⁴¹ The disease course is favorably influenced by enzyme replacement therapies, and novel gene-therapy approaches are being explored.

Mitochondrial cardiomyopathy. Mitochondrial diseases (MDs) are heterogeneous conditions that affect mainly tissues that demand high energy, such as the nervous system, myocardium, skeletal muscles, kidneys, and endocrine system. Pathogenic variants in mitochondrial genes, encoded by mitochondrial or nuclear DNA, may be responsible for its phenotype.⁴² Mitochondrial DNA (mtDNA) is transmitted in a matrilineal pattern; therefore, wild-type and mutant mtDNA may coexist in the same tissue, a condition termed heteroplasmy. The mutant mtDNA load may vary between organs, explaining the high degree of

clinical variability. Although the degree of heteroplasmy in female cardiomyocytes can be hypothesized to influence clinical cardiac severity in female individuals, this concept has not been well studied or confirmed with formal biopsy studies. Cardiac hypertrophy is a common cardiac phenotype manifestation, present in $\leq 40\%$ of patients, and the evolution to systolic dysfunction is not infrequent.⁴³ On ECG, short PR or pre-excitation patterns, signs of LVH, and repolarization abnormalities may be found. Arrhythmic complications include Wolff-Parkinson-White syndrome (around 15% of patients with mitochondrial encephalopathy lactic acidosis and stroke-like episodes and myoclonic epilepsy with ragged-red fibers syndromes) and atrioventricular conduction disease, mostly in Kearns-Sayre syndrome.⁴³ Pediatric patients with cardiac involvement have an unfavorable prognosis, with a mortality rate of nearly 80% by 16 years of age.⁴⁴ Conversely, in a cohort of 260 adults, only 5% had a major adverse cardiac event after a mean of 7 years of follow-up care, including sudden death, resuscitated cardiac arrest, death due to heart failure, or heart transplantation.⁴⁵ This suggests that age-related penetrance is related to disease severity and outcomes. As with Danon disease, patients with MDs may have cognitive impairment, although often more severe than that of Danon disease. Treatments include dietary supplementation and supportive care.

Friedreich ataxia. Friedreich ataxia is an autosomal recessive, multisystem disease, with the clinical picture dominated by progressive ataxia, spasticity, and sensory neuropathy, followed by diabetes and hypertrophic cardiomyopathy. It is due to GAA sequence expansion in the *FXN* gene, encoding frataxin, a mitochondrial protein. Impaired frataxin leads to impaired mitochondrial oxidative phosphorylation, deficient iron-sulfur cluster enzymes, and mitochondrial iron overload. In a cohort of 78 children with Friedreich ataxia-associated hypertrophic cardiomyopathy, the mean age at diagnosis was 10 ± 3 years and concentric LVH was present, with a mean left ventricular wall thickness of 12.8 ± 2.6 mm. On ECG, 64% had LVH, 73% had T-wave inversions, and 27% had pathological Q waves. After a median follow-up period of 5.1 years (IQR: 2.4-7.3 years), 16% had atrial arrhythmias and 11% died, although none had died of sudden cardiac death. Freedom from death or transplantation at 5 and 10 years was 97% and 81% respectively, comparable with that of nonsyndromic hypertrophic cardiomyopathy.⁴⁶ In a cohort of 138 adult patients with Friedreich ataxia (mean age: 31 ± 10 years), survival after 20 years of follow-up care was approximately 80%, with a mean age at

FIGURE 3 Pedigree of Family With a Pathogenic Variant in *LAMP2* Gene



Pedigree of 3 generations of a family with Danon disease that demonstrates its X-linked dominant inheritance pattern. Black symbols indicate affected subjects; white symbols indicate unaffected subjects. III-3 is the proband (arrow) for this family. Slashed figures indicate deceased individuals.

death of 39 years. The most common cause of death was progressive heart failure. Predictors of mortality included length of GAA repeats, left ventricular ejection fraction, and mass index. Twenty-one percent of patients belonged to a high-risk group with progressive systolic dysfunction.⁴⁷

Rasopathies. Rasopathies are caused by mutations in genes encoding proteins involved in the RAS/mitogen-activated protein kinase pathway. The most common conditions include Noonan syndrome, cardiofaciocutaneous syndrome, Noonan syndrome with multiple lentigines (previously called LEOPARD syndrome [lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness]), and Costello syndrome. Rasopathies are characterized by multisystemic involvement and may present with facial dysmorphism, short stature, dermatologic alterations (eg, café-au-lait spots, lentigines), genitourinary abnormalities (eg, cryptorchidism), and hematopoietic, gastrointestinal, neurologic, and endocrine diseases. The most frequent cardiovascular manifestations include congenital heart disease (pulmonary valve stenosis, atrioventricular septal defect, atrial septal defect) and cardiac hypertrophy diagnosed during infancy (mean age at diagnosis: 6 months).⁴⁸ The prevalence of hypertrophic cardiomyopathy is 80% in Noonan syndrome with multiple lentigines, 65% in Costello syndrome, 40% in cardiofaciocutaneous syndrome, and 20% to 25% in Noonan syndrome. In rasopathies, left ventricular outflow tract obstruction is common and is associated with multiple

cardiovascular abnormalities including displaced papillary muscles, longer anterior mitral valve leaflet, anomalous insertion of mitral chordae, hyperdynamic left ventricle, and subaortic fibrous tissue. Patients may also present with biventricular hypertrophy, right ventricular outflow tract obstruction, and coronary artery abnormalities. On ECG, extreme right-axis deviation, bundle branch blocks, prolonged QT, T-wave inversion, and atrial arrhythmias may be seen. In a small subset of patients (5% to 10%), the presentation is severe heart failure, and in other cases clinical status may improve over time with progressive reduction of LVH and lower risk of sudden cardiac death compared with sarcomeric hypertrophic cardiomyopathy.⁴⁹

Fabry disease. Cardiac hypertrophy due to Fabry disease, caused by genetic defects resulting in deficiency of α -galactosidase A enzyme activity (*GLA* gene Xq22.1), is rare in children and adolescents, in whom extracardiac manifestations like febrile crisis, gastrointestinal symptoms, hypo/hyperhidrosis, and neuropathic pain predominate.⁵⁰ Cardiac involvement appears in the third to fourth decades and later, with a hypertrophic phenotype characterized by biventricular hypertrophy that involves the papillary muscles, valvular thickening, and diastolic dysfunction.⁵¹ As such, Fabry disease, which also displays X-linked inheritance, can be considered in a differential diagnosis with Danon disease in male individuals. Cardiac complications include heart failure, microvascular angina, atrial or ventricular arrhythmias, atrioventricular conduction disease, and chronotropic incompetence.⁵¹ Renal impairment

and angiokeratoma corporis diffusum are also frequently detected in adult male individuals with Fabry disease.

Sarcomeric hypertrophic cardiomyopathy. Sarcomeric hypertrophic cardiomyopathy has an age-related penetrance with 3 peaks in age at onset, the first in infancy (<1 year), the second in the teenage and early adulthood years, and the third in mid-adulthood. Although the onset of the phenotype may occur in a relatively short time, progression toward massive LVH and systolic dysfunction is uncommon (<10%) and should raise suspicion of a rare genocopy such as Danon disease. The disease phenotype ranges from mild to extreme LVH at any age and is only partially explained by genotypic variability, inasmuch as phenotypic variance is observable also among the same mutation carriers within the same family.⁵² Data from the Sarcomeric Human Cardiomyopathy Registry show that patients receiving a diagnosis during infancy present a higher risk of morbidity and mortality than do patients receiving a diagnosis in childhood (1-18 years); however, surviving patients with infant-onset hypertrophic cardiomyopathy had a lower risk of adverse events (heart failure, ventricular arrhythmias, atrial fibrillation) than did those receiving a diagnosis in childhood. Furthermore, patients with childhood-onset hypertrophic cardiomyopathy showed a higher risk of life-threatening ventricular arrhythmias (HR: 1.36; 95% CI: 1.03-1.8) and need for advanced heart failure therapy (transplantation, ventricular assist device; HR: 1.99; 95% CI: 1.23-3.23) compared with patients receiving a diagnosis as adults. Patients receiving a diagnosis in adulthood were less likely to have a pathogenic/likely pathogenic variant and had a greater risk for the development of atrial fibrillation than did patients receiving a diagnosis as children.⁵³ The rate of adverse events in patients receiving a diagnosis in childhood was 2% per year; early events included mostly ventricular arrhythmias, and later events were more frequently related to heart failure and atrial fibrillation. Notably, the ECG does not invariably show striking abnormalities, as in Danon disease, and instead may only be mildly abnormal. Additionally, pre-excitation is rare and bradyarrhythmias are less frequent in hypertrophic cardiomyopathy.

GENETIC DIAGNOSIS. Candidate gene testing of a panel of cardiomyopathy genes is an integral part of evaluating the condition of individuals with hypertrophic and other forms of nonischemic cardiomyopathy.^{54,55}

Genetic testing for pediatric patients. Genetic testing should be strongly considered for any individuals in a pediatric clinical setting who meet

clinical diagnostic criteria suggestive of Danon disease (Table 3). The presence of ≥ 1 of the commonly associated clinical features, such as hypertrophic cardiomyopathy or pre-excitation, muscle weakness, or elevation in creatinine phosphokinase and transaminases, cognitive or intellectual impairment, and an observed X-linked inheritance pattern, should increase suspicion for Danon disease. Because of skewed X-inactivation, female individuals are less likely to display the characteristic phenotypic features of this disorder; despite this, a significant number of affected female individuals have been reported in the literature.^{8,25,56,57} For this reason, female sex should not be a factor that precludes an individual who meets the appropriate clinical criteria from genetic analysis.

Genetic testing for adult patients. The estimated prevalence of individuals with hypertrophic cardiomyopathy who have an identifiable likely pathogenic or pathogenic variant in the *LAMP2* gene is 1% to 4%.^{11,58} Notably, the prevalence of Danon disease increases to 17% in individuals with both hypertrophic cardiomyopathy and pre-excitation.⁵⁹ *LAMP2* defects rarely mimic dilated cardiomyopathy, especially in women.^{33,60} This reinforces the inclusion of *LAMP2* on multigene panels for common inherited cardiomyopathy for both adult and pediatric populations.

Familial cascade testing. Genetic testing for relatives of an individual affected by Danon disease is imperative for proper risk assessment and determination of recurrence risk. For male individuals identified to have a pathogenic or likely pathogenic variant in the *LAMP2* gene, only genetic testing of the patient's mother is required because the affected X chromosome is inherited maternally. Negative maternal genetic test results in these cases are most compatible with a de novo mutation in the affected son, although a residual risk of maternal germline mosaicism may exist. This is not the case for affected female individuals, and both parents should be tested once a pathogenic variant is identified in the affected proband. Testing for the affected individual's female parent is imperative, regardless of the sex of the affected individual, to determine her carrier status and/or risk for health complications secondary to an identified disease-causing variant. Mothers who are identified to carry the same pathogenic variant will have a 50% chance of passing on this variant to existing or future offspring. Male individuals with Danon disease could theoretically pass a *LAMP2* mutation to all their daughters. However, in practical terms, male individuals with Danon disease are often too medically sick to father children.

Individuals may be identified to be affected by Danon disease as the result of a de novo pathogenic variant in the *LAMP2* gene, meaning that neither parent was found to carry the same disease-causing variant. The estimated de novo rate for this condition is high ($\leq 40\%$), reflecting its malignant nature and a negative effect on reproduction. Cases of germline mosaicism have also been described.^{2,15,34}

Improvements to treatment and management, especially for male individuals affected by Danon disease, mean that the reproductive risk for patients should be addressed. Genetic counseling should be offered to all affected families to ensure they are aware of the inheritance pattern, reproductive risks, and technologies available to those who wish to pursue further testing before, during, and after pregnancy. This risk for other relatives within a proband's family is largely determined by the genetic testing status of the proband's parents.

Recommended genetic testing panel(s). The majority of reported cases of Danon disease are associated with nonsense, frameshift, splicing, and small indel variants detected in the *LAMP2* gene, accounting for approximately 95% of all pathogenic and likely pathogenic variants detected.^{5,34} A small proportion of affected individuals have copy number variants, which include the *LAMP2* gene in the form of large deletions, duplications, and structural rearrangements.^{12,61-64} Emerging literature reports suggest that the number of copy number variants detected in association with Danon disease may appear to be lower because of under-testing of female patients as well as those with large deletions including many genes that may result in a more severe clinical phenotype.⁶⁵

Given the high genetic testing yield in the *LAMP2* gene for individuals who meet the clinical diagnostic criteria for Danon disease, sequencing of this gene alone may seem sufficient to achieve a diagnosis. However, it is imperative that clinicians also consider the less common copy number variants, which may be causative, and ensure that gene targeted deletion/duplication analysis is also performed. Sequencing with deletion/duplication analysis is the industry standard for most commercial laboratories at this time. A multigene next-generation sequencing panel is the rule when an individual's disease presentation is atypical, especially when one presents with isolated hypertrophic cardiomyopathy at <15 years of age. Inclusion of other common causes of hypertrophic cardiomyopathy, such as sarcomere genes (eg, *MYH7*, *MYBPC3*, *TNNT2*, *TNNI3*) and syndromic genocopies of hypertrophic cardiomyopathy (as

TABLE 3 Clinical "Red Flags" That Should Raise Suspicion of Danon Disease in an Individual With HCM

| | |
|--|--|
| Extracardiac | |
| | X-linked inheritance |
| | Developmental delay |
| | Pigmentary retinopathy |
| | Skeletal myopathy |
| | Elevated serum CK |
| Cardiac | |
| ECG | Short PR interval/ventricular pre-excitation |
| | AV block |
| | Voltage criteria for extreme LVH |
| Echocardiography | Extreme LVH |
| | Concentric distribution of LVH (especially in male individuals) |
| | Concomitant RVH |
| | Rapid progression (including progression to hypokinetic dilated phase) |
| CMR | Extensive LGE with sparing of the midseptum |
| Adapted from Rapezzi et al. ⁷¹ | |
| CK = creatine kinase; CMR = cardiac magnetic resonance; ECG = electrocardiogram; LGE = late gadolinium enhancement; LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy; other abbreviations as in Tables 1 and 2. | |

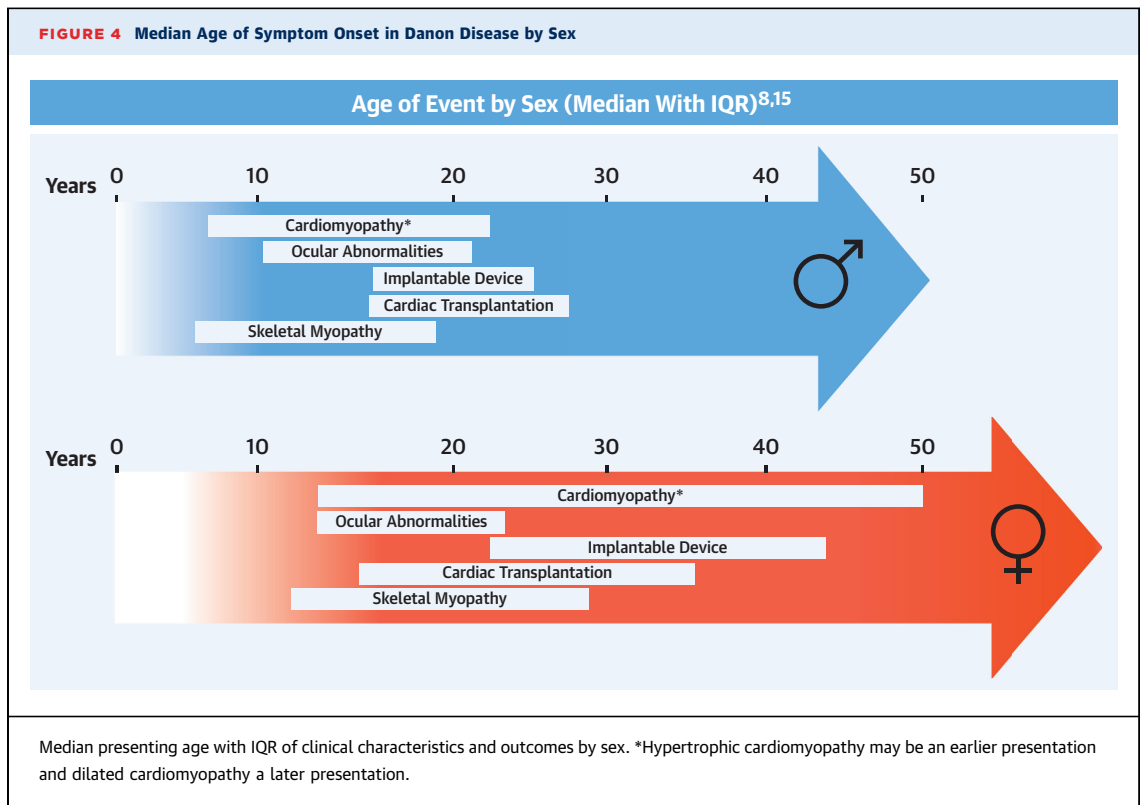
mentioned earlier) is a common practice, especially if diagnostic criteria are not definitively met in an affected individual.

NATURAL HISTORY

PENETRANCE. Disease penetrance is likely 100% in both sexes. However, because female individuals are heterozygous for the mutation, whereas male individuals are hemizygous, the disease ordinarily manifests at an earlier age in male than in female individuals (Figure 4). Furthermore, disease expression is also less predictable in female individuals, with cardiac manifestations making up the dominant disease features and extracardiac involvement being more variable. Heterogenous penetrance and expressivity in female individuals is thought to be due to skewed X-chromosome inactivation and functional mosaicism of *LAMP-2* expression.^{14,66} Additionally, more than one third of Danon disease cases are de novo mutations.

SEX DIFFERENCES IN CLINICAL COURSE AND OUTCOME.

Male individuals with Danon disease experience symptoms approximately 15 years earlier than do female individuals, with diagnosis occurring in their childhood or adolescence.⁶⁻¹⁰ Male individuals typically manifest with a severe hypertrophic cardiomyopathy that progresses to end-stage in the second or third decade of life, whereas female individuals can present with either a hypertrophic or



dilated cardiomyopathy that progresses more slowly, reaching the end stage a full decade or later than in male individuals.^{7,8,67}

Interestingly, although male individuals experience heart failure decades before female individuals do, a recent international registry of Danon patients who had undergone transplantation found early and equivalent ages at time of transplantation for both sexes.^{6-10,68} Specifically, the median age for transplantation in this cohort was 20.2 years.⁶⁸ In an unpublished subanalysis of the same data that stratified by transplantation age groups <25 years old and ≥25 years old, comparison of median age in these 2 groups revealed 2 separate age cohorts in female individuals who had undergone transplantation: those with a median age of 16.9 years and those with a median age of 36.6 years (personal communication, September 2021). This finding is consistent with prior descriptions of a fulminant female phenotype with a disease course that more closely resembles male patients with Danon disease.^{19,22,25,69}

Regarding musculoskeletal symptoms, male individuals are more likely to have symptomatic muscle involvement with associated AST/ALT, LDH or CPK abnormalities.⁷ Although the prevalence and severity of cognitive delay and psychiatric comorbidities, including attention-deficit/hyperactivity disorder,

anxiety, and mood disorders, are greater in male individuals, female individuals could also be affected. Vision abnormalities, such as retinopathy and myopia, occur equally in both sexes.^{6,27}

INITIAL EVALUATION, TREATMENT, AND MANAGEMENT

DANON DISEASE IN CURRENT HYPERTROPHIC CARDIOMYOPATHY GUIDELINES. Danon disease represents a small proportion of patients included in historical hypertrophic cardiomyopathy cohorts and has a very distinct clinical profile. Therefore, it is likely inappropriate to apply hypertrophic cardiomyopathy guidelines to patients with Danon disease.^{54,70} There are currently no consensus clinical practice guidelines and assessment, and management is largely based on expert opinion and extrapolation from hypertrophic cardiomyopathy guidelines. Neither the 2014 European Society of Cardiology guidelines on hypertrophic cardiomyopathy⁷⁰ nor the 2020 American Heart Association/American College of Cardiology guidelines on hypertrophic cardiomyopathy⁵⁴ contain any specific recommendations for the evaluation and treatment of patients with Danon disease, although both highlight the importance of clinical “red flags” suggestive of Danon disease

TABLE 4 Diagnostic Test, Typical Findings, and Surveillance Recommended in Patients With Danon Disease

| | Typical Findings | Frequency During Follow-Up Care |
|---------------------------|--|--|
| Initial evaluation | | |
| Blood tests | Raised NT-proBNP/troponin CK, AST, ALT, LDH | Yearly |
| Cardiac tests | | |
| ECG | Pre-excitation, ventricular hypertrophy, extreme voltage, repolarization abnormalities, conduction disease | Yearly |
| 24-h Holter | Atrial fibrillation, ventricular arrhythmias Atrioventricular block | Yearly Every 6 mo if enlarged atria |
| Echocardiography | Extreme hypertrophy 25% LVOTO | Yearly |
| CMR | Apical sparing strain pattern Extensive and diffuse LGE with midseptal sparing Increased T1 and ECV | Every 2-3 y |
| Extracardiac tests | | |
| Neurologic evaluation | Proximal muscle weakness | Yearly if symptoms, otherwise, every 3-4 y |
| Development evaluation | Intellectual disability | At baseline and if new manifestations appear |
| Ophthalmologic evaluation | Cone-rod dystrophy Peripheral pigmentation | Every 3-5 y |
| Genetic counseling | Cascade screening Family planning | At diagnosis and when needed |

CMR = cardiac magnetic resonance; ECV = extracellular volume; LVOTO = left ventricular outflow tract obstruction; NT-proBNP = N-terminal pro-B type natriuretic peptide; other abbreviations as in Tables 1 and 3.

(Table 3) and of considering genetic testing for *LAMP2* variants in those patients with a clinical suspicion.⁷¹ A recent position statement from the Italian Society of Cardiology and the Italian Society of Paediatric Cardiology provided specific recommendations for the treatment of individuals with hypertrophic cardiomyopathy associated with Danon disease, specifically in relation to primary preventive implantation of an ICD, consideration of cardiac transplantation, and catheter ablation of atrioventricular re-entry tachycardia.⁷²

INITIAL WORK-UP AND ROUTINE FOLLOW-UP CARE FOR DANON DISEASE. The initial work-up in an individual with Danon disease should include an assessment of cardiac and extracardiac features.⁵ It is recommended that patients with Danon disease be assessed and receive follow-up care at referral centers where a multidisciplinary team can provide a comprehensive management strategy. Table 4 summarizes tests that should be performed at baseline evaluation and the recommended follow-up care.

CARDIAC EVALUATION AT BASELINE. All individuals with a diagnosis of Danon disease should undergo a resting 12-lead ECG, echocardiogram, ambulatory Holter monitoring, and serum N-terminal pro-B-type natriuretic peptide (or B-type natriuretic peptide [BNP]) levels at baseline. One of the frequent ECG findings is pre-excitation or Wolff-Parkinson-White

syndrome, which is observed in almost one-half of patients, sometimes preceding overt hypertrophy.^{8,9,15} A recent study showed that potentially malignant extranodal accessory pathways are frequent among these patients,⁷³ and consequently electrophysiological studies and ablation should be considered in patients with pre-excitation.⁷⁰ Frequent 24-h Holter monitoring (at least yearly or every 6 months if the left atrium is dilated) or even the consideration of implantable loop recorders is recommended based on the high incidence of atrial fibrillation and advanced atrioventricular bloc.^{8,9} The incidence of nonsustained ventricular arrhythmia and its role as a predictor of sudden cardiac death is unknown. In the experience of this panel, nonsustained ventricular tachycardia is not rare in Danon disease. Again, in patients with unexplained syncope or presyncope, an implantable loop recorder or direct implantation of an ICD seems reasonable (see sudden cardiac death prevention, later).^{54,70} BNP has been found to be elevated in progressive Danon disease, suggesting a benefit^{74,75} in monitoring wall stress biomarkers such as N-terminal pro-B-type natriuretic peptide and/or BNP levels in these patients.⁶⁷

CMR imaging is a useful tool to evaluate cardiac hypertrophy; furthermore, late gadolinium enhancement may provide additional morphologic and functional information on myocardial involvement, as well as an assessment of the presence and degree of

myocardial fibrosis. In Danon disease, late gadolinium enhancement is frequently present with extensive patchy and diffuse patterns.⁸ A recent study in a small cohort of patients showed that the mid-interventricular septum is spared, suggesting this pattern might be specific for Danon disease.²⁰ We recommend that CMR imaging be repeated every 2 to 3 years to monitor progression of fibrosis. In cases of marked fibrosis (>15%), consideration for sudden cardiac death prevention and for heart transplantation referral should be made.⁷⁶

Echocardiography is the imaging test of choice because of its availability for baseline and follow-up imaging. Extreme concentric LVH (>30 mm) is an echocardiographic hallmark of Danon disease, but it is important to realize that only a minority of patients (more frequently male individuals) will exhibit this degree of hypertrophy.⁹ It is important to consider that left ventricular outflow tract obstruction can be present in one quarter of patients with Danon disease and should be actively searched for in patients with dyspnea.⁸ Decreased longitudinal strain with sparing of the apex, similar to cardiac amyloidosis, has recently emerged as a new echocardiographic feature. Furthermore, reduced global longitudinal strain values seem to predict worse outcomes.^{77,78} It is critical to keep in mind that even though cardiac hypertrophy is the most frequent cardiac manifestation, as mentioned previously, a dilated phenotype can be present, usually in female individuals in the third or fourth decade of life.^{8,9,15}

Exercise testing with the use of treadmill ergometry or cardiopulmonary exercise testing is useful for risk stratification and to provide guidance about physical activity. Although exercise testing has not been formally evaluated in individuals with Danon disease, it may be helpful for providing objective evidence of symptoms and risk stratifying for cardiac transplantation.⁷⁹ Beyond general recommendations, follow-up care should be tailored to patients' needs and clinical status. Closer follow-up care is required in advanced stages when cardiopulmonary exercise testing and right heart catheterization should be scheduled to guide optimal timing for heart transplantation. Degree of skeletal myopathy will determine cardiopulmonary exercise testing modality (ie, treadmill vs cycle ergometry).

There are no guidelines specific to Danon disease to guide the frequency of follow-up care, but given the potential for rapid disease progression and the high risk of ventricular arrhythmia and heart failure complications, it is reasonable to recommend clinical

cardiologic follow-up with 12-lead ECG, echocardiogram, and ambulatory Holter monitoring at least annually.

EXTRACARDIAC EVALUATION AT BASELINE. Although extracardiac involvement is more frequent and severe in male individuals, female individuals can also manifest mild or subclinical extracardiac features that support a multidisciplinary approach in both sexes.^{5,14} Neuromuscular involvement is frequent in male individuals and presents as progressive proximal muscle weakness. Although they are usually mild, delayed motor milestones can affect 1 in 5 male individuals.⁸ Neuromuscular examination to assess for signs of skeletal myopathy at initial evaluation and during follow-up visits is recommended for all patients.^{8,15,30} Ophthalmologic assessment for evidence of pigmentary retinopathy is recommended at initial evaluation and during follow-up care in all patients.^{8,15,30} Comprehensive developmental assessment with a view to initiating early educational support and interventions should be performed in all male individuals with Danon disease and in female individuals as clinically indicated. Last, 2 life milestones should guide genetic counseling. First, cascade genetic screening of relatives should be recommended at the time of diagnosis; second, family planning strategies should be introduced when a patient reaches reproductive age.¹⁴ Ideally, integrated multidisciplinary assessment and follow-up care should be organized for these challenging patients, along the model suggested for Fabry disease.

FOLLOW-UP CARE OF GENOTYPE-POSITIVE, PHENOTYPE-NEGATIVE INDIVIDUALS. Given that sex is a major determinant of age at disease onset, surveillance of at-risk individuals (healthy carriers) differs for male and female individuals. The median age at onset in male individuals is approximately 14 years, whereas in female individuals it ranges between 17 and 35 years.^{8,9} Nevertheless, very early onset in the first year of life has been described in both sexes, although mainly in male infants.^{5,15} Consequently, although both sexes should be screened during infancy (first year of life), yearly multidisciplinary follow-up care is recommended to begin at that time in boys, whereas girls can start annual follow-up visits around the age of 6 years. From the cardiac perspective, laboratory tests, 12-lead ECG, and echocardiography should detect early stages of involvement. CMR imaging might be helpful in identifying mild phenotypes and should be used upon clinical suspicion or when adequate echocardiographic images are not attainable.

CONSIDERATIONS FOR SUDDEN CARDIAC DEATH RISK ASSESSMENT. Existing strategies for stratifying risk in patients with hypertrophic cardiomyopathy are based on the presence of clinical markers of increased ventricular arrhythmia risk, either as a cumulative approach⁵⁴ or in the context of individualized risk prediction models.⁸⁰⁻⁸² Importantly, neither approach has been validated in individuals with Danon disease. Nevertheless, currently available data support a low threshold for consideration of ICD implantation in patients with Danon disease who have severe LVH, unexplained syncope, and/or non-sustained ventricular tachycardia.⁷²

A subcutaneous device should be considered in young individuals who do not require pacing, to minimize the long-term risk of infection and vascular complications with procedures. Defibrillation threshold testing should be considered in individuals with massive hypertrophy. And last, education to avoid strenuous physical activity and competitive sports is important to decrease the risk of stress-provoked arrhythmia in those without an ICD and the risk of arrhythmic storm in those considered to be protected (by an ICD).

MEDICAL THERAPY. Currently, there are no available therapies to specifically treat Danon disease. A multidisciplinary care approach, including a cardiology, neurology, genetics, ophthalmology, rehabilitation medicine and physical therapy, should be used to alleviate the multisystem effects of the disease.⁵ For the treatment of heart disease, clinical signs and symptoms should guide the use of medications for congestive heart failure and arrhythmias, such as diuretics and antiarrhythmics, with beta blockers as first line therapies. Physical therapy and educational support are also recommended for skeletal myopathy and cognitive impairment, respectively.

Inasmuch as cardiomyopathy in Danon disease is characterized by progressive fibrosis and an inadvertent loss of systolic function, one should consider therapies to attenuate cardiac remodeling (ie, renin-angiotensin-aldosterone system inhibition and β -adrenergic blockers). Although no proof of efficacy exists in Danon disease, a similar approach to prevent the development of systolic dysfunction is a prevailing practice in another X-linked malignant cardiomyopathies, including Duchenne muscular dystrophy caused by Duchenne muscular dystrophy mutations.⁸³

As in any pre-existing cardiac pathologic process involving a compromise in mitochondrial function, patients with Danon disease are expected to have

poor tolerance to hypertension, tachycardia, and anemia. Cardiotoxic medications and stimulants should be avoided.

Finally, lifestyle modifications may have a role in delaying disease progression and may have a unique role in the vulnerable myocardium of *LAMP2* mutation carriers. Instructions on healthy lifestyle and avoidance of smoking, excess alcohol consumption, and substance abuse should be communicated to prevent additional damage. Stimuli activating autophagy such as strenuous physical activity and diet therapy should be decreased because of a risk of enhancing disease progression in a *LAMP-2*-deficient heart.⁸⁴

HEART TRANSPLANTATION. Cardiac transplantation may be required for those in whom end-stage cardiomyopathy develops. Post-transplantation survival in patients with Danon disease appears to be similar to that in patients with other cardiomyopathies.⁶⁸ In the largest cohort (n = 38) of patients with Danon disease who have undergone transplantation, the post-transplant 5-year survival was 87.1%, which supports the allocation of donor organs to this population.⁶⁸ The prognosis is especially favorable in women. Despite the presence of extracardiac involvement including skeletal muscle disease, which may limit rehabilitation, post-transplantation outcomes are good. Specific considerations include the use of steroid-sparing immunosuppressive agents to mitigate the risk of myopathy.⁶⁸ Furthermore, there is a theoretical risk of increased cellular autophagy with sirolimus, an mTOR inhibitor, which can worsen muscle weakness; however, this has not been observed thus far in contemporary cohorts.⁶⁸

FUTURE DIRECTIONS: GENETIC THERAPIES AND OTHER APPROACHES

Therapies that target the underlying genetic or molecular mechanisms of monogenic cardiomyopathies are appealing in that they offer a therapeutic approach that is directed to the fundamental abnormality.⁸⁵ Initial approaches using gene therapy to treat heart failure that focused on common pathophysiologic derangements considered to be central to the disease process (as opposed to correction of a driving genetic abnormality) had limited success.^{86,87} However, the development of more efficient viral capsids (ie, adeno-associated viruses [AAV]) that improve the transduction of genes into striated muscle, and various new gene therapy strategies such

as genome editing, exon skipping, allele-specific silencing, spliceosome-mediated RNA trans-splicing, and gene replacement, have revitalized the field.^{88,89}

Use of cardiotropic vectors such as AAV9 have been shown to improve uptake of genetic material into the heart while minimizing uptake in other organs. Clinical trials have begun to evaluate the efficacy of this AAV9 gene therapy in Danon disease after preclinical studies in mice suggested improved survival and cardiac function after treatment with LAMP2B/AAV9 gene therapy.^{4,90} Preliminary phase 1 clinical trial data in pediatric and adult patients have shown encouraging results, including evidence of LAMP2B protein expression, significant vacuole clearance at the tissue level, trends toward reduction in cardiac biomarkers (ie, troponin and BNP), and improvements in functional (NYHA functional classification) and quality-of-life assessments (Kansas City Cardiomyopathy Questionnaire). Whereas gene therapy may ameliorate cardiac symptoms, extracardiac symptoms including skeletal myopathy, retinal impairment, and intellectual disability will be largely unaffected by this therapy. Furthermore, additional challenges with gene therapy include efficiency issues due to pre-existing antibodies or robust immune responses that require immunosuppressive therapy, inability to retreat patients if therapy fails over time, and safety concerns about potential off-target effects.^{91,92}

CONCLUSIONS

Although Danon disease is rare, it is arguably the most severe and highly penetrant of the monogenic cardiomyopathies. Its severity underscores the importance of LAMP-2 and its role in autophagy, which maintains cardiac homeostasis. This is particularly relevant, given the numerous drugs associated with impaired autophagic flux and cardiomyopathies, such as hydroxychloroquine and anthracyclines.

The pathophysiology and extracardiac manifestations of Danon disease distinguish it from sarcomeric

hypertrophic cardiomyopathy and other phenocopies. Although the condition is currently considered to be ultra-rare (2 in 100,000), the number of patients with diagnoses may increase as genetic testing becomes more commonly available and therapies become available.

Since its first discovery as a unique autophagic vacuolar myopathy, much has been learned regarding its pathobiology and natural history of disease. Nonetheless, critical questions remain regarding its clinical trajectory and management. As reviewed, it is unclear how to evaluate the risk of sudden cardiac death, whether goal-directed medical therapy is beneficial, and the natural history of the disease in women. In addition, trials are ongoing to evaluate gene therapy in Danon disease—the first attempts at gene therapy for a monogenic cardiac disorder. Nonetheless, without clarity regarding the natural history of the disease, it may be challenging to identify appropriate surrogates of mortality or design a trial in female individuals. In summary, although a potential cure for Danon disease is on the horizon, further investigations are urgently needed.

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REFERENCES

- Danon MJ, Oh SJ, DiMauro S, et al. Lysosomal glycogen storage disease with normal acid maltase. *Neurology*. 1981;31(1):51-57. <https://doi.org/10.1212/wnl.31.1.51>
- Takahashi M, Yamamoto A, Takano K, et al. Germline mosaicism of a novel mutation in lysosome-associated membrane protein-2 deficiency (Danon disease). *Ann Neurol*. 2002;52(1):122-125. <https://doi.org/10.1002/ana.10235>
- Del Favero G, Bonifacio A, Rowland TJ, et al. Danon disease-associated LAMP-2 deficiency drives metabolic signature indicative of mitochondrial aging and fibrosis in cardiac tissue and hiPSC-derived cardiomyocytes. *J Clin Med*. 2020;9(8):2457. <https://doi.org/10.3390/jcm9082457>
- Manso AM, Hashem SI, Nelson BC, et al. Systemic AAV9.LAMP2B injection reverses metabolic and physiologic multiorgan dysfunction in a murine model of Danon disease. *Sci Transl Med*. 2020;12(535):eaax1744. <https://doi.org/10.1126/scitranslmed.aax1744>
- D'souza RS, Levandowski C, Slavov D, et al. Danon disease: clinical features, evaluation, and management. *Circ Heart Fail*. 2014;7(5):843-849. <https://doi.org/10.1161/CIRCHEARTFAILURE.114.001105>

6. Cenacchi G, Papa V, Pegoraro V, Marozzo R, Fanin M, Angelini C. Review: Danon disease: review of natural history and recent advances. *Neuropathol Appl Neurobiol*. 2020;46(4):303-322. <https://doi.org/10.1111/nan.12587>
7. Boucek D, Jirikowic J, Taylor M. Natural history of Danon disease. *Genet Med*. 2011;13(6):563-568. <https://doi.org/10.1097/GIM.0b013e31820ad795>
8. Brambatti M, Caspi O, Maolo A, et al. Danon disease: gender differences in presentation and outcomes. *Int J Cardiol*. 2019;286:92-98. <https://doi.org/10.1016/j.ijcard.2019.01.020>
9. López-Sainz Á, Salazar-Mendiguchía J, García-Álvarez A, et al. Clinical findings and prognosis of Danon disease: an analysis of the Spanish Multi-center Danon Registry. *Rev Esp Cardiol (Engl Ed)*. 2019;72(6):479-486. <https://doi.org/10.1016/j.rec.2018.04.035>
10. Lotan D, Salazar-Mendiguchía J, Mogensen J, et al. Clinical profile of cardiac involvement in Danon disease: a multicenter European registry. *Circ Genom Precis Med*. 2020;13(6):e003117. <https://doi.org/10.1161/CIRCGEN.120.003117>
11. Yang Z, McMahon CJ, Smith LR, et al. Danon disease as an underrecognized cause of hypertrophic cardiomyopathy in children. *Circulation*. 2005;112(11):1612-1617. <https://doi.org/10.1161/CIRCULATIONAHA.105.546481>
12. Bui YK, Renella P, Martínez-Agosto JA, Verity A, Madikians A, Alejos JC. Danon disease with typical early-onset cardiomyopathy in a male: focus on a novel LAMP-2 mutation. *Pediatr Transplant*. 2008;12(2):246-250. <https://doi.org/10.1111/j.1399-3046.2007.00874.x>
13. Wang Y, Jia M, Guo Y, Zhang T, Ning B. Case report: Danon disease: six family members and literature review. *Front Cardiovasc Med*. 2022;9:842282. <https://doi.org/10.3389/fcvm.2022.842282>
14. Taylor MR, Adler ED. Danon Disease. 2020. <https://www.ncbi.nlm.nih.gov/books/NBK554742/>
15. Sugie K, Komaki H, Eura N, et al. A nationwide survey on Danon disease in Japan. *Int J Mol Sci*. 2018;19(11):3507. <https://doi.org/10.3390/ijms19113507>
16. Endo Y, Furuta A, Nishino I. Danon disease: a phenotypic expression of LAMP-2 deficiency. *Acta Neuropathol*. 2015;129(3):391-398. <https://doi.org/10.1007/s00401-015-1385-4>
17. Nishino I, Fu J, Tanji K, et al. Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). *Nature*. 2000;406(6798):906-910. <https://doi.org/10.1038/35022604>
18. Hong KN, Brambatti M, John S, et al. Recommendations and guidance on the diagnosis and management of Danon disease. *Expert Opin Orphan Drugs*. 2021;9(1):25-33. <https://doi.org/10.1080/21678707.2021.1882994>
19. Hedberg Oldfors C, Máthé G, Thomson K, et al. Early onset cardiomyopathy in females with Danon disease. *Neuromuscul Disord*. 2015;25(6):493-501. <https://doi.org/10.1016/j.nmd.2015.03.005>
20. Rigolli M, Kahn AM, Brambatti M, Contijoch FJ, Adler ED. Cardiac magnetic resonance imaging in Danon disease cardiomyopathy. *J Am Coll Cardiol* *Imag*. 2021;14(2):514-516. <https://doi.org/10.1016/j.jcmg.2020.08.011>
21. Alcalai R, Arad M, Wakimoto H, et al. LAMP2 cardiomyopathy: consequences of impaired autophagy in the heart. *J Am Heart Assoc*. 2021;10(17):e018829. <https://doi.org/10.1161/JAHA.120.018829>
22. Samad F, Jain R, Jan MF, et al. Malignant cardiac phenotypic expression of Danon disease (LAMP2 cardiomyopathy). *Int J Cardiol*. 2017;245:201-206. <https://doi.org/10.1016/j.ijcard.2017.06.031>
23. Jhaveri S, Herber J, Zahka K, Boyle GJ, Saarel E v, Aziz PF. Arrhythmias and fasciculoventricular pathways in patients with Danon disease: a single center experience. *J Cardiovasc Electrophysiol*. 2019;30(10):1932-1938. <https://doi.org/10.1111/jce.14049>
24. Taylor MRG, Ku L, Slavov D, et al. Danon disease presenting with dilated cardiomyopathy and a complex phenotype. *J Hum Genet*. 2007;52(10):830-835. <https://doi.org/10.1007/s10038-007-0184-8>
25. Bottillo I, Giordano C, Cerbelli B, et al. A novel LAMP2 mutation associated with severe cardiac hypertrophy and microvascular remodeling in a female with Danon disease: a case report and literature review. *Cardiovasc Pathol*. 2016;25(5):423-431. <https://doi.org/10.1016/j.carpath.2016.07.005>
26. Stevens-Lapsley JE, Kramer LR, Balter JE, Jirikowic J, Boucek D, Taylor M. Functional performance and muscle strength phenotypes in men and women with Danon disease. *Muscle Nerve*. 2010;42(6):908-914. <https://doi.org/10.1002/mus.21811>
27. Yardeni M, Weisman O, Mandel H, et al. Psychiatric and cognitive characteristics of individuals with Danon disease (LAMP2 gene mutation). *Am J Med Genet A*. 2017;173(9):2461-2466. <https://doi.org/10.1002/ajmg.a.38320>
28. Spinazzi M, Fanin M, Melacini P, Nascimbeni AC, Angelini C. Cardioembolic stroke in Danon disease. *Clin Genet*. 2008;73(4):388-390. <https://doi.org/10.1111/j.1399-0004.2008.00971.x>
29. Tsuda T, Shillingford AJ, Vetter J, Kandula V, Jain B, Temple J. Transient ischemic attack and ischemic stroke in Danon disease with formation of left ventricular apical thrombus despite normal systolic function. *Case Rep Pediatr*. 2017;2017:6576382. <https://doi.org/10.1155/2017/6576382>
30. Prall FR, Drack A, Taylor M, et al. Ophthalmic manifestations of Danon disease. *Ophthalmology*. 2006;113(6):1010-1013. <https://doi.org/10.1016/j.ophtha.2006.02.030>
31. Fukushima M, Inoue T, Miyai T, Obata R. Retinal dystrophy associated with Danon disease and pathogenic mechanism through LAMP2-mutated retinal pigment epithelium. *Eur J Ophthalmol*. 2020;30(3):570-578. <https://doi.org/10.1177/1120672119832183>
32. Kousal B, Majer F, Vlskova H, et al. Pigmentary retinopathy can indicate the presence of pathogenic LAMP2 variants even in somatic mosaic carriers with no additional signs of Danon disease. *Acta Ophthalmol*. 2021;99(1):61-68. <https://doi.org/10.1111/aos.14478>
33. Gurka J, Piherova L, Majer F, et al. Danon disease is an underdiagnosed cause of advanced heart failure in young female patients: a LAMP2 flow cytometric study. *ESC Heart Fail*. 2020;7(5):2534-2543. <https://doi.org/10.1002/ehf2.12823>
34. Hashida Y, Wada T, Saito T, Ohta K, Kasahara Y, Yachie A. Early diagnosis of Danon disease: flow cytometric detection of lysosome-associated membrane protein-2-negative leukocytes. *J Cardiol*. 2015;66(2):168-174. <https://doi.org/10.1016/j.jjcc.2014.09.011>
35. Majer F, Vlskova H, Krol L, et al. Danon disease: a focus on processing of the novel LAMP2 mutation and comments on the beneficial use of peripheral white blood cells in the diagnosis of LAMP2 deficiency. *Gene*. 2012;498(2):183-195. <https://doi.org/10.1016/j.gene.2012.02.004>
36. Ng KM, Mok PY, Butler AW, et al. Amelioration of X-linked related autophagy failure in Danon disease with DNA methylation inhibitor. *Circulation*. 2016;134(18):1373-1389. <https://doi.org/10.1161/CIRCULATIONAHA.115.019847>
37. Fanin M, Nascimbeni AC, Fulizio L, Spinazzi M, Melacini P, Angelini C. Generalized lysosome-associated membrane protein-2 defect explains multisystem clinical involvement and allows leukocyte diagnostic screening in Danon disease. *Am J Pathol*. 2006;168(4):1309-1320. <https://doi.org/10.2353/ajpath.2006.050646>
38. Porto AG, Brun F, Severini GM, et al. Clinical spectrum of PRKAG2 syndrome. *Circ Arrhythm Electrophysiol*. 2016;9(1):e003121. <https://doi.org/10.1161/CIRCEP.115.003121>
39. Lopez-Sainz A, Dominguez F, Lopes LR, et al. Clinical features and natural history of PRKAG2 variant cardiac glycogenosis. *J Am Coll Cardiol*. 2020;76(2):186-197. <https://doi.org/10.1016/j.jacc.2020.05.029>
40. Teener JW. Late-onset Pompe's disease. *Semin Neurol*. 2012;32(5):506-511. <https://doi.org/10.1055/s-0033-1334469>
41. Limongelli G, Fratta F. S1.4 Cardiovascular involvement in Pompe disease. *Acta Myologica*. 2011;30(3):202-203.
42. El-Hattab AW, Scaglia F. Mitochondrial cardiomyopathies. *Front Cardiovasc Med*. 2016;3:25. <https://doi.org/10.3389/fcvm.2016.00025>
43. Limongelli G, Masarone D, Pacileo G. Mitochondrial disease and the heart. *Heart*. 2017;103(5):390-398. <https://doi.org/10.1136/heartjnl-2015-308193>
44. Scaglia F, Towbin JA, Craigen WJ, et al. Clinical spectrum, morbidity, and mortality in 113 pediatric patients with mitochondrial disease. *Pediatrics*. 2004;114(4):925-931. <https://doi.org/10.1542/peds.2004-0718>
45. Wahbi K, Bougouin W, Béhin A, et al. Long-term cardiac prognosis and risk stratification in 260 adults presenting with mitochondrial diseases. *Eur Heart J*. 2015;36(42):2886-2893. <https://doi.org/10.1093/eurheartj/ehv307>
46. Norrish G, Rance T, Montanes E, et al. Friedreich's ataxia-associated childhood hypertrophic cardiomyopathy: a national cohort study. *Arch Dis*

- Child.* 2022;107(5):450-455. <https://doi.org/10.1136/archdischild-2021-322455>
47. Pousset F, Legrand L, Monin ML, et al. A 22-year follow-up study of long-term cardiac outcome and predictors of survival in Friedreich ataxia. *JAMA Neurol.* 2015;72(11):1334-1341. <https://doi.org/10.1001/jamaneurol.2015.1855>
48. Lioncino M, Monda E, Verrillo F, et al. Hypertrophic cardiomyopathy in RASopathies. *Heart Fail Clin.* 2022;18(1):19-29. <https://doi.org/10.1016/j.hfc.2021.07.004>
49. Delogu AB, Limongelli G, Versacci P, et al. The heart in RASopathies. *Am J Med Genet C Semin Med Genet.* 2022;190(4):440-451. <https://doi.org/10.1002/ajmg.c.32014>
50. Germain DP. Fabry disease. *Orphanet J Rare Dis.* 2010;5:30. <https://doi.org/10.1186/1750-1172-5-30>
51. Pieroni M, Moon JC, Arbustini E, et al. Cardiac involvement in Fabry disease: JACC review topic of the week. *J Am Coll Cardiol.* 2021;77(7):922-936. <https://doi.org/10.1016/j.jacc.2020.12.024>
52. Norrish G, Field E, Kaski JP. Childhood hypertrophic cardiomyopathy: a disease of the cardiac sarcomere. *Front Pediatr.* 2021;9. <https://doi.org/10.3389/fped.2021.708679>
53. Marston NA, Han L, Olivetto I, et al. Clinical characteristics and outcomes in childhood-onset hypertrophic cardiomyopathy. *Eur Heart J.* 2021;42(20):1988-1996. <https://doi.org/10.1093/eurheartj/ehab148>
54. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol.* 2020;76(25):3022-3055.
55. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol.* 2022;79(17):e263-e421.
56. Stack-Pyle TJ, Shah J, Stack L, Arcara V. Dilated cardiomyopathy and systolic heart failure in a female patient with Danon disease. *Cureus.* 2022;14(10):e30803. <https://doi.org/10.7759/cureus.30803>
57. Mulder BA, Hoedemaekers YM, van den Berg MP, et al. Three female patients with Danon disease presenting with predominant cardiac phenotype: a case series. *Eur Heart J Case Rep.* 2019;3(3):ytz132. <https://doi.org/10.1093/ehjcr/ytz132>
58. Charron P. Danon's disease as a cause of hypertrophic cardiomyopathy: a systematic survey. *Heart.* 2004;90(8):842-846. <https://doi.org/10.1136/hrt.2003.029504>
59. Arad M, Maron BJ, Gorham JM, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med.* 2005;352(4):362-372. <https://doi.org/10.1056/NEJMoa033349>
60. Cardiovascular Genomics and Precision Medicine Group. The Atlas of Cardiac Genetic Variation: Dilated Cardiomyopathy - DCM. London: Institute of Medical Sciences.
61. Lines MA, Hewson S, Halliday W, et al. Danon disease due to a novel LAMP2 microduplication. *JIMD Rep.* 2013;14:11-16. https://doi.org/10.1007/8904_2013_277
62. Majer F, Kousal B, Dusek P, et al. *Alu*-mediated *Xq24* deletion encompassing *CUL4B*, *LAMP2*, *ATP1B4*, *TMEM255A*, and *ZBTB33* genes causes Danon disease in a female patient. *Am J Med Genet A.* 2020;182(1):219-223. <https://doi.org/10.1002/ajmg.a.61416>
63. Yang Z, Funke BH, Cripe LH, et al. LAMP2 microdeletions in patients with Danon disease. *Circ Cardiovasc Genet.* 2010;3(2):129-137. <https://doi.org/10.1161/CIRCGENETICS.109.901785>
64. Regelsberger G, Höftberger R, Pickl WF, et al. Danon disease: case report and detection of new mutation. *J Inher Metab Dis.* 2009;32(S1):115-122. <https://doi.org/10.1007/s10545-009-1097-9>
65. Majer F, Piherovala L, Reboun M, et al. LAMP2 exon-copy number variations in Danon disease heterozygote female probands: infrequent or underdetected? *Am J Med Genet A.* 2018;176(11):2430-2434. <https://doi.org/10.1002/ajmg.a.40430>
66. Mehta A, Beck M, Sunder-Plassmann G. *Fabry Disease: Perspectives from 5 Years of FOS.* Oxford Pharmagenesis; 2006.
67. D'souza RS, Mestroni L, Taylor MRG. Danon disease for the cardiologist: case report and review of the literature. *J Community Hosp Intern Med Perspect.* 2017;7(2):107-114. <https://doi.org/10.1080/20009666.2017.1324239>
68. Hong KN, Battikha C, John S, et al. Cardiac transplantation in Danon disease. *J Card Fail.* 2022;28(4):664-669. <https://doi.org/10.1016/j.cardfail.2021.11.007>
69. Miani D, Taylor M, Mestroni L, et al. Sudden death associated with Danon disease in women. *Am J Cardiol.* 2012;109(3):406-411. <https://doi.org/10.1016/j.amjcard.2011.09.024>
70. Elliott PM, Anastakis A, Borger MA, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J.* 2014;35(39):2733-2779. <https://doi.org/10.1093/eurheartj/ehu284>
71. Rapezzi C, Arbustini E, Ceforino ALP, et al. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. a position statement from the ESC working group on myocardial and pericardial diseases. *Eur Heart J.* 2013;34(19):1448-1458. <https://doi.org/10.1093/eurheartj/ehs397>
72. Limongelli G, Adorisio R, Baggio C, et al. Diagnosis and management of rare cardiomyopathies in adult and paediatric patients. a position paper of the Italian Society of Cardiology (SIC) and Italian Society of Paediatric Cardiology (SICP). *Int J Cardiol.* 2022;357:55-71. <https://doi.org/10.1016/j.ijcard.2022.03.050>
73. Darden D, Hsu JC, Tzou WS, et al. Fasciculoventricular and atrioventricular accessory pathways in patients with Danon disease and preexcitation: a multicenter experience. *Heart Rhythm.* 2021;18(7):1194-1202. <https://doi.org/10.1016/j.hrthm.2021.03.024>
74. Geske JB, McKie PM, Ommen SR, Sorajja P. B-type natriuretic peptide and survival in hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2013;61(24):2456-2460. <https://doi.org/10.1016/j.jacc.2013.04.004>
75. Minami Y, Haruki S, Kanbayashi K, Maeda R, Itani R, Hagiwara N. B-type natriuretic peptide and risk of sudden death in patients with hypertrophic cardiomyopathy. *Heart Rhythm.* 2018;15(10):1484-1490. <https://doi.org/10.1016/j.hrthm.2018.04.030>
76. Fontana M, Martinez-Naharro A, Chacko L, et al. Reduction in CMR derived extracellular volume with patsiran indicates cardiac amyloid regression. *J Am Coll Cardiol Img.* 2021;14(1):189-199. <https://doi.org/10.1016/j.jcmg.2020.07.043>
77. Bui QM, Hong KN, Kraushaar M, et al. Myocardial strain and association with clinical outcomes in Danon disease: a model for monitoring progression of genetic cardiomyopathies. *J Am Heart Assoc.* 2021;10(23):e022544. <https://doi.org/10.1161/JAHA.121.022544>
78. Bui QM, Hong KN, Kraushaar M, et al. Apical sparing strain pattern in Danon disease: insights from a global registry. *J Am Coll Cardiol Img.* 2020;13(12):2689-2691. <https://doi.org/10.1016/j.jcmg.2020.05.027>
79. Crespo-Leiro MG, Metra M, Lund LH, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2018;20(11):1505-1535. <https://doi.org/10.1002/ehf.1236>
80. O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J.* 2014;35(30):2010-2020. <https://doi.org/10.1093/eurheartj/ehu439>
81. Norrish G, Ding T, Field E, et al. Development of a novel risk prediction model for sudden cardiac death in childhood hypertrophic cardiomyopathy (HCM risk-kids). *JAMA Cardiol.* 2019;4(9):918-927. <https://doi.org/10.1001/jamacardio.2019.2861>
82. Miron A, Lafreniere-Roula M, Steve Fan CP, et al. A validated model for sudden cardiac death risk prediction in pediatric hypertrophic cardiomyopathy. *Circulation.* 2020;142(3):217-229. <https://doi.org/10.1161/CIRCULATIONAHA.120.047235>
83. Kamdar F, Garry DJ. Dystrophin-deficient cardiomyopathy. *J Am Coll Cardiol.* 2016;67(21):2533-2546. <https://doi.org/10.1016/j.jacc.2016.02.081>
84. Yadin D, Petrover Z, Shainberg A, et al. Autophagy guided interventions to modify the cardiac phenotype of Danon disease. *Biochem Pharmacol.* 2022;204:115229. <https://doi.org/10.1016/j.bcp.2022.115229>
85. Repetti GG, Toepfer CN, Seidman JG, Seidman CE. Novel therapies for prevention and

early treatment of cardiomyopathies. *Circ Res*. 2019;124(11):1536-1550. <https://doi.org/10.1161/CIRCRESAHA.119.313569>

86. Greenberg B, Butler J, Felker GM, et al. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. *Lancet*. 2016;387(10024):1178-1186. [https://doi.org/10.1016/S0140-6736\(16\)00082-9](https://doi.org/10.1016/S0140-6736(16)00082-9)

87. Hammond HK, Penny WF, Traverse JH, et al. Intracoronary gene transfer of adenylyl cyclase 6 in patients with heart failure: a randomized clinical trial. *JAMA Cardiol*. 2016;1(2):163-171. <https://doi.org/10.1001/jamacardio.2016.0008>

88. Ylä-Herttuala S, Baker AH. Cardiovascular gene therapy: past, present, and future. *Mol Ther*. 2017;25(5):1095-1106. <https://doi.org/10.1016/j.ymthe.2017.03.027>

89. Prondzynski M, Mearini G, Carrier L. Gene therapy strategies in the treatment of hypertrophic cardiomyopathy. *Pflugers Arch*. 2019;471(5):807-815. <https://doi.org/10.1007/s00424-018-2173-5>

90. Gene therapy for male patients with Danon disease (DD) using RP-A501; AAV9.LAMP2B. ClinicalTrials.gov identifier: NCT03882437. Accessed March 5, 2023. <https://www.clinicaltrials.gov/search?term=NCT03882437%20>

91. Tuohy CV, Kaul S, Song HK, Nazer B, Heitner SB. Hypertrophic cardiomyopathy: the future of treatment. *Eur J Heart Fail*. 2020;22(2):228-240. <https://doi.org/10.1002/ejhf.1715>

92. Rossano J, Taylor M, Lin K, et al. Abstract 11117: Phase 1 Danon disease results: the first single dose intravenous (IV) gene therapy (RP-A501) with recombinant adeno-associated virus (AAV9:LAMP2B) for a monogenic cardiomyopathy. *Circulation*. 2022;146(suppl 1).

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