U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Taylor MRG, Adler ED. Danon Disease. 2020 Mar 5 [Updated 2024 May 23]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Danon Disease

Matthew RG Taylor, MD, PhD[1] and Eric D Adler, MD[2]

Created: March 5, 2020; Revised: May 23, 2024.

Summary

Clinical characteristics

Danon disease is a multisystem condition with predominant involvement of the heart, skeletal muscles, and retina, with overlying cognitive dysfunction. Males are typically more severely affected than females. Males usually present with childhood onset concentric hypertrophic cardiomyopathy that is progressive and often requires heart transplantation. Rarely, hypertrophic cardiomyopathy can evolve to resemble dilated cardiomyopathy. Most affected males also have cardiac conduction abnormalities. Skeletal muscle weakness may lead to delayed acquisition of motor milestones. Learning disability and intellectual disability, most often in the mild range, are common. Additionally, affected males can develop retinopathy with subsequent visual impairment. The clinical features in females are broader and more variable. Females are more likely to have dilated cardiomyopathy, with a smaller proportion requiring heart transplantation compared to affected males. Cardiac conduction abnormalities, skeletal muscle weakness, mild cognitive impairment, and pigmentary retinopathy are variably seen in affected females.

Diagnosis/testing

The diagnosis of Danon disease is established in a proband (male or female) with suggestive findings and/or a hemizygous (in males) or a heterozygous (in females) pathogenic variant in *LAMP2* identified by molecular genetic testing.

Management

Treatment of manifestations: While the age of onset and progression of disease are typically later and slower in females, the management approach in males and females is similar. Standard treatment guidelines for hypertrophic cardiomyopathy and heart failure; consideration of ablation therapy in those with cardiac pre-excitation and arrhythmia; physical therapy for skeletal muscle weakness; standard treatment for developmental delay / intellectual disability; use of low vision aids for those with retinopathy.

Author Affiliations: 1 Adult Medical Genetics Program, University of Colorado Anschutz Medical Campus, Aurora, Colorado; Email: matthew.taylor@cuanschutz.edu. 2 Division of Cardiology, University of California San Diego, San Diego, California; Email: eradler@ucsd.edu.

Surveillance: Electrocardiography at least annually with echocardiography and cardiac MRI at least every one to two years; ambulatory arrhythmia monitoring as needed based on symptoms; annual assessment of strength and for neurologic changes; monitoring of developmental progress, educational needs, and behavior at each visit with formal developmental assessments every three to five years during childhood; ophthalmology evaluation at least every three to five years.

Agents/circumstances to avoid: Avoidance of dehydration or over-diuresis in those with heart failure; in the presence of significant cardiac hypertrophy with obstruction and/or symptomatic arrhythmia, consideration of instituting the guidelines for physical exertion for individuals with sarcomeric hypertrophic cardiomyopathy.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment and surveillance.

Pregnancy management: Management should be guided by the degree of overt disease in the pregnant woman and per guidelines for pregnant women with hypertrophic or dilated cardiomyopathy, depending on their condition.

Genetic counseling

Danon disease is inherited in an X-linked manner. If the mother of the proband has a *LAMP2* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who have a pathogenic variant in *LAMP2* will transmit the pathogenic variant to all of their daughters and none of their sons. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygous and may have features of Danon disease. Once the causative pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing for Danon disease for a pregnancy at increased risk are possible.

Diagnosis

For the purposes of this *GeneReview*, the terms "male" and "female" are narrowly defined as the individual's biological sex at birth as it determines clinical care [Caughey et al 2021].

Danon disease is a multisystem condition with predominant involvement of the heart, skeletal muscles, and retina, with overlying cognitive dysfunction. Formal clinical diagnostic criteria for Danon disease have not been established.

Suggestive Findings

Males

Danon disease **should be suspected in a male** with the following clinical, supportive laboratory, electrophysiologic, imaging, and family history findings.

Clinical findings

- Cardiomyopathy that is predominantly hypertrophic and rapidly progressive
- Mild muscle weakness
- Retinopathy. The most detailed report of retinal findings to date is from a family with four males with Danon disease, two of whom had a classic cone-rod dystrophy [Thiadens et al 2012] including:
  - Progressive visual impairment
  - Severe color vision disturbances

    - Fundus examination revealing a bull's eye maculopathy and diffuse loss of pigment in the retinal pigment epithelium (RPE)
    - Electroretinogram revealing reduced photopic (cone) and scotopic (rod) responses
    - Visual field testing revealing a central scotoma
    - Optical coherence tomography revealing thinning of the retinal outer segments (rods and cones) and RPE
- Mild intellectual disability

Supportive laboratory findings

- Elevated creatine kinase (~5-fold increase)
- Elevated asparate aminotransferase (AST) (~7-fold increase) and alanine aminotransferase (ALT) (~6-fold increase) with preserved hepatic synthetic function
- Muscle biopsy (either skeletal or cardiac) demonstrating a relatively specific vacuolar myopathy on standard histology but best seen by electron microscopy; substantial fibrosis is often present.

Note: (1) Muscle biopsy is not required to make the diagnosis; (2) tissue staining demonstrating absence of the LAMP-2 protein can confirm the diagnosis, although this assay is not widely available on a clinical basis.

Electrophysiologic findings

- Severe cardiac hypertrophy with or without evidence of outflow obstruction
- Wolff-Parkinson-White syndrome with pre-excitation on surface electrocardiogram
- Ventricular arrhythmias and atrial tachyarrhythmias

Imaging. Late gadolinium enhancement on cardiac MRI

Family history is consistent with X-linked inheritance (male relatives with more severe hypertrophic cardiomyopathy or female relatives with either hypertrophic or dilated cardiomyopathy). Absence of a family history of cardiomyopathy does not preclude the diagnosis.

Females

Danon disease **should be suspected in a female** with the following clinical, suggestive laboratory, and family history findings.

Clinical findings

- Either dilated or hypertrophic cardiomyopathy
- Retinal changes reminiscent of, but not as severe as, those seen in affected males

Laboratory findings

- Normal or mildly increased creatine kinase
- Normal or mildly increased AST and ALT with preserved hepatic synthetic function

Family history is consistent with X-linked inheritance (male relatives with more severe hypertrophic cardiomyopathy or female relatives with either hypertrophic or dilated cardiomyopathy). Absence of a family history of cardiomyopathy does not preclude the diagnosis.

Establishing the Diagnosis

Male proband. The diagnosis of Danon disease **is established** in a male with suggestive findings by identification of a hemizygous pathogenic (or likely pathogenic) variant in *LAMP2* on molecular genetic testing (see Table 1).

Female proband. The diagnosis of Danon disease **is usually established** in a female proband with cardiac pre-excitation and cardiomyopathy (either hypertrophic or dilated) by identification of a heterozygous pathogenic (or likely pathogenic) variant in *LAMP2* on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *LAMP2* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Danon disease is broad, individuals with the distinctive features described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Danon disease has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of Danon disease, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *LAMP2* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A cardiomyopathy or myopathy multigene panel** that includes *LAMP2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of Danon disease is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Danon Disease

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
LAMP2	Sequence analysis [3]	~95% [4]
	Gene-targeted deletion/duplication analysis [5, 6]	~5% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Nishino et al [2000], Dougu et al [2009], D'Souza et al [2014]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. The vast majority of pathogenic variants reported to date are nonsense, frameshift, splicing, and small insertion-deletion variants. A minority of pathogenic variants are due to large gene deletions, duplications, or rearrangements.

Clinical Characteristics

Clinical Description

Danon disease is an X-linked condition in which males are often more severely affected than females. A total of 146 molecularly confirmed affected individuals (90 males and 56 females) with Danon disease have been reported in the literature and the information below summarizes the findings in these individuals [Brambatti et al 2019] and in others who did not undergo clinical genetic testing.

Table 2. Features of Danon Disease

Feature	% of Males w/Feature	% of Females w/Feature	Comment
Hypertrophic cardiomyopathy	96%	30%-70%	Cardiomyopathy in females, when present, is less likely to be hypertrophic than in males.
Dilated cardiomyopathy	4%	30%-50%	In males, dilated cardiomyopathy may develop later as hypertrophic cardiomyopathy progresses; this does not appear to be the case in females.
Cardiac conduction abnormalities	>80%	60%-100%	
Skeletal muscle weakness	80%-90%	12%-50%	Typically not progressive in females
Intellectual disability (typically mild)	~80%	~10%	Intellectual disability is usually mild but can be of variable degree, particularly in females.
Retinopathy	~20%	~20%	The % of individuals w/visual impairment may be higher for both males & females, as formal ophthalmology examinations are not always reported.

Males

Males with Danon disease often present with the triad of severe cardiomyopathy, skeletal myopathy, and mild intellectual disability. Penetrance for cardiomyopathy approaches 100% in males, with 80%-90% of affected individuals experiencing some degree of skeletal muscle weakness and more than 70% experiencing some degree of cognitive impairment [D'Souza et al 2014].

Cardiac. The most striking and apparent clinical findings involve childhood onset of cardiomyopathy, arrhythmias, and the progressive development of heart failure. Males are affected earlier (average age of first symptom 12.1 years) than females (average age of first symptom 19.0 years), although females show a wider phenotypic spectrum (see Females). Limited data are available on presenting clinical symptoms, although chest pain and palpitations have been reported as common symptoms at the time of diagnosis [Boucek et al 2011].

- **Cardiomyopathy.** The typical early cardiac finding is concentric hypertrophy with persevered ejection fraction and normal heart cavity dimensions.
  - Hypertrophic cardiomyopathy is present in 70%-88% of affected males [Boucek et al 2011, Brambatti et al 2019].
  - In contrast to many other forms of hypertrophic cardiomyopathy, progression to severe hypertrophy, heart failure, and an almost certain need for transplantation in the second and third decades of life is typically seen in Danon disease.
  - Reported ages of cardiac transplantation and death in males are 33.7 and 34.5 years, respectively [Boucek et al 2011].
  - In a minority of affected males the cardiac features evolve to resemble dilated cardiomyopathy [D'Souza et al 2014], although in rare affected males dilated cardiomyopathy may be the initial presentation without an apparent hypertrophic phase [López-Sainz et al 2019].
- **Electrophysiology.** Pre-excitation findings on EKG are present in more than 80% of affected males. Atrial and ventricular arrhythmias may also be detected.
  - Arrhythmias may cause clinical symptoms of palpitations or syncope.
  - Pre-excitation, including Wolff-Parkinson-White syndrome, is the most common finding on EKG [D'Souza et al 2014], seen in approximately 48% of males at presentation [Brambatti et al 2019].
  - In some instances a pre-excitation, Wolff-Parkinson-White pattern on electrocardiography may precede overt cardiomyopathy.
- **Cardiac imaging** most commonly involves echocardiography.
  - Left-ventricular outflow obstruction is present in some individuals on exercise testing.
  - Increasingly, cardiac MRI is proving to be a useful tool to characterize hypertrophy and quantify the presence of late gadolinium enhancement as a measure of cardiac fibrosis.

Neuromuscular. Skeletal muscle myopathy most often presents as slowly progressive proximal muscle weakness in the neck, shoulders, and legs [D'Souza et al 2014]. Affected males have varying degrees of functional impairment due to muscle weakness and underlying deficits in muscle activation [Stevens-Lapsley et al 2010].

- Although progression may occur, weakness is not typically disabling and most men retain the ability to ambulate. Because of this, the rehabilitation outcomes for men who undergo cardiac transplantation are generally good, although profound muscle weakness after cardiac transplantation has been rarely described [D'Souza et al 2014, Brambatti et al 2019].
- Creatine kinase (CK) levels are elevated in most males (mean 944 U/L) [Boucek et al 2011]. It is unknown if elevated CK levels are present in affected males at birth or if they slowly increase over time as the disease develops.
- Delayed motor milestones are reported in approximately 20% of affected males [Boucek et al 2011, Brambatti et al 2019]. These deficits have not been well described in terms of gross and fine motor impairment or ages of onset.
- Dysmetria unrelated to muscle weakness has rarely been reported [Lacoste-Collin et al 2002].

Cognitive delays and behavioral issues. Clinical cognitive issues (learning disability or intellectual disability) probably affect close to 100% of males but have not been well characterized. Intellectual disability, most often in the mild range, has been reported in about 80% of affected males. Speech and language delays are common. Most affected males are able to [D'Souza et al 2014]:

- Learn to read
- Have a job
- Live independently
- Take part in a relationship

Other neuropsychiatric issues that have been reported primarily in case reports or as part of small case series of affected individuals include [Hatz et al 2010, D'Souza et al 2014]:

- Attention deficit disorder
- Behavior problems
- Psychiatric issues (e.g., severe depression, psychosis)

Due to the small number of individuals reported with these particular features, it is unclear whether these issues are directly related to Danon disease.

Retinopathy. The retinopathy described in variable detail in earlier reports (see commentary by Brodie [2012]) appears to be consistent with the cone-rod dystrophy described by Thiadens et al [2012] (see also Suggestive Findings).

- The severity varies even among males in the same family [Schorderet et al 2007, Thiadens et al 2012].
- While details regarding rate of vision decline in males are not available in the limited number of published reports in Danon disease, Brambatti et al [2019] reported the risk of "vision abnormalities" from "retinopathy" as 10.9% in the 129 males and females on whom data were available.

Gastrointestinal. Gastrointestinal/hepatic disease is suspected in a majority of affected males [D'Souza et al 2014]. Features may include:

- Hepatomegaly
- Elevated liver enzymes without hepatic synthetic dysfunction; however in many instances the elevated transaminases are suspected to be of skeletal muscle origin.

Respiratory disease is present in about half of affected males, with shortness of breath, chest tightness, coughing, and/or wheezing being reported most frequently [D'Souza et al 2014]. Respiratory muscle insufficiency and airway disease have not been characterized in detail.

Females

Overall, the phenotypic spectrum in females appears to be broader and more variable [Brambatti et al 2019]. Females develop symptoms later than males and are more apt to have a cardiac-restricted phenotype. Onset of symptoms in females is about ten to 15 years later than in affected males, with average age of onset of first symptom 19.0 years, average age of cardiac transplant 33.7 years, and average age of death 34.6 years [D'Souza et al 2014]. The proportion of heterozygous females who have evidence of cardiomyopathy is reported to be between 61% and 100%, whereas 12%-50% of heterozygous females are reported to have some degree of skeletal muscle weakness, and between 6% and 47% have been reported to have some degree of cognitive issues [D'Souza et al 2014]. Although some females appear to be nearly as severely affected as typically affected males, the average age of diagnosis in females is reported to be 27.9 years.

Cardiac features predominate in females with a heterozygous pathogenic variant in *LAMP2*, although some have no discernable clinical features [Stevens-Lapsley et al 2010].

- **Cardiomyopathy.** Cardiomyopathy affects more than 70% of females, with dilated cardiomyopathy being present in 30%-50% of females and hypertrophic cardiomyopathy in the remaining [Boucek et al 2011,

Brambatti et al 2019]. In most instances a dilated cardiomyopathy is the presenting finding and evidence of preceding hypertrophic cardiomyopathy (that then converted to a dilated phenotype) is lacking.

Of the heterozygous females who develop cardiomyopathy, about 18% receive a cardiac transplantation, compared to almost all affected males [D'Souza et al 2014]. However, as most data reported are cross-sectional, the prevalence of heart transplant in females may rise with age.

- **Electrophysiology.** Conduction abnormalities have been reported in 60% to 100% of women with a heterozygous pathogenic variant in *LAMP2* [D'Souza et al 2014, Brambatti et al 2019].
  - Pre-excitation with Wolff-Parkinson-White is identified in 32% of females at presentation [Brambatti et al 2019].
  - With time, however, the prevalence of cardiac disease in females approaches that of males, with one comprehensive study of published case reports noting a composite outcome (death, heart transplant, or ventricular assist device) occurring in 37% of males and 37% of females [Brambatti et al 2019].
- **Cardiac imaging** most commonly involves echocardiography. In females with cardiac hypertrophy, imaging modalities and findings are similar to those in males, although the findings may be less severe in females (see Males, **Cardiac imaging**).

Neuromuscular. Skeletal muscle weakness is reported in 12%-50% of females with a heterozygous pathogenic variant in *LAMP2* and appears to be milder than that of males [Boucek et al 2011, Brambatti et al 2019].

- Skeletal muscle weakness is not known to be progressive.
- Some females with a heterozygous pathogenic variant in *LAMP2* develop minimal clinical muscle abnormalities in the fourth decade as their only symptom [Stevens-Lapsley et al 2010].
- Creatine kinase (CK) levels are usually normal in females (mean 106 U/L) [Boucek et al 2011].

Cognitive delays. Some form of intellectual impairment has been reported in between 6% and 47% of affected females. Details on the definition or degree of intellectual impairment are largely lacking. The authors' collective experience is that females with Danon disease generally do not meet a formal definition of intellectual disability as defined by an IQ <70.

Eye. Retinal findings in females that are similar to but milder than those observed in males have been reported [Prall et al 2006, Schorderet et al 2007, Taylor et al 2007, Brambatti et al 2019]. It is unclear if Danon disease leads to legal blindness in females or to what degree the ocular phenotypes are progressive. Ophthalmic findings include changes to the peripheral retinal pigment epithelium that could lead to:

- Near-loss of visible pigment
- Abnormal electroretinogram
- Impaired vision

Gastrointestinal and respiratory symptoms have been reported in females but are not well characterized to date (see information pertaining to Males).

Genotype-Phenotype Correlations

To date, no specific genotype-phenotype correlations for pathogenic loss-of-function variants have been confirmed.

A small number of pathogenic missense variants and pathogenic variants confined to exon 9B of the LAMP-2B protein isoform have been reported in association with mild or atypical phenotypes [Nishino et al 2000, Musumeci et al 2005, van der Kooi et al 2008, Hong et al 2012, D'Souza et al 2014]. In some cases the onset of cardiac features is later in males (e.g., after the 4th decade) and rare males have been reported without overt

hypertrophic or dilated cardiomyopathies. Data convincingly showing a deficiency or functional abnormality of LAMP-2 protein have not been widely reported with variants in this genomic region.

Penetrance

The penetrance in Danon disease is age dependent and has not been well studied in the literature. Given the severity of the cardiac phenotype, the penetrance is estimated as high or nearly complete in males by the second decade. Females appear to also have a high cardiac penetrance that is later in onset compared to males.

Nomenclature

Outdated terms for Danon disease represented in the literature:

- X-linked vacuolar cardiomyopathy and myopathy
- Glycogen storage disease IIb
- X-Linked pseudoglycogenosis II
- Antopol disease
- Lysosomal glycogen storage disease without acid maltase deficiency

Prevalence

Danon disease is rare; measures of the general population prevalence are not known. Among individuals with hypertrophic cardiomyopathy (which has an overall prevalence of ~1:500 persons) the prevalence of those with a pathogenic *LAMP2* variant has been reported as 1%-4% [Charron et al 2004, Yang et al 2005].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *LAMP2*.

Differential Diagnosis

The disorders listed in Table 3 have cardiac and/or skeletal muscle findings that may be similar to those in Danon disease. However, unlike Danon disease, these disorders are not known to be associated with intellectual disability or retinal disease.

Table 3. Selected Genes of Interest in the Differential Diagnosis of Danon Disease

Gene(s)	Disorder	MOI	Cardiomyopathy	Skeletal Muscle
GAA	Pompe disease	AR	Severe early-onset hypertrophic cardiomyopathy	Rapidly progressive muscle weakness (infantile form only)
MYBPC3 *MYBPC3* *TNNI3* *TNNT2* (>30 genes) [1]	Hypertrophic cardiomyopathy	AD	Hypertrophic cardiomyopathy	Normal
PRKAG2	Familial Wolff-Parkinson White syndrome (OMIM 194200) [2]	AD	• Wolff-Parkinson White syndrome w/or w/o hypertrophic cardiomyopathy • Vacuolar cardiomyopathy & ↑ myocardial glycogen (in severe congenital cases; see OMIM 261740)	Normal

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Cardiomyopathy	Skeletal Muscle
VMA21	X-linked myopathy w/ excessive autophagy [3] (OMIM 310440)	XL	Hypertrophic cardiomyopathy (mild) in a minority of cases	• Hypotonia & muscle atrophy • ↑ creatine kinase • Autophagocytic vacuoles on muscle biopsy

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked
1. Listed genes represent the most common genes known to be associated with hypertrophic cardiomyopathy. See Phenotypic Series: Familial hypertrophic cardiomyopathy for additional genes associated with this phenotype in OMIM.
2. Mutation of *PRKAG2* is also known to be associated with hypertrophic cardiomyopathy.
3. X-linked myopathy w/excessive autophagy is also associated with scoliosis and has extraocular muscle involvement.

Management

Suggested treatment guidelines for Danon disease were reported by D'Souza et al [2014]; however, consensus management guidelines have not been published and evaluation and management is typically based on expert opinion. Although the age of onset and progression of disease are typically later and slower in females, the management approach in males and females is similar.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Danon disease, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Danon Disease: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Cardiac	Electrocardiography	To evaluate for hypertrophy, arrhythmia, & conduction abnormalities
	Echocardiography	Incl eval for left-ventricular outflow tract obstruction
	Cardiac MRI	Late gadolinium enhancement indicates fibrosis & likely ↑ arrhythmia risk.
	Cardiopulmonary exercise testing	Has not been formally studied in persons w/Danon disease
	Brain natriuretic peptide level	As a baseline
Neuromuscular	Neurologic exam for signs of muscle disease	
Development	Developmental assessment in males (& as indicated clinically in females)	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention/special education
Retinopathy	Retinal exam for evidence of cone-rod dystrophy	To incl: • BCVA • Refractive error • Color vision testing • Full-field ERG • Spectral-domain optical coherence tomography
Gastrointestinal	Liver function tests [1]	To incl AST, ALT, & LDH

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling

Adapted from D'Souza et al [2014]
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BCVA = best corrected Snellen visual acuity; ERG = electroretinogram; LDH = lactate dehydrogenase
1. If results are strikingly abnormal, evaluation of liver synthetic function (e.g., total protein, albumin) and evaluation for other causes of abnormal liver function may be considered.

Treatment of Manifestations

Table 5. Danon Disease: Treatment of Manifestations

Manifestation/ Concern	Treatment	Considerations/Other
Hypertrophic cardiomyopathy	• Institute hypertrophic cardiomyopathy guidelines [1] for those w/cardiac hypertrophy & preserved left-ventricular ejection fraction. • Timely consideration of implantable cardiac defibrillators	The benefit of negative inotropes or myomectomy for cardiac obstruction has not been established.
Heart failure	Standard treatment, [2] incl careful fluid & volume mgmt & avoidance of over-diuresis & dehydration	The benefit of neurohormonal [3] therapy has not been established.
	Timely consideration of cardiac transplantation in those w/ progressive symptoms or significant ↓ in left-ventricular ejection fraction	Durable mechanical circulatory support should be used w/caution given biventricular involvement of disease.
Cardiac pre-excitation & arrhythmia	• Consideration of electrophysiologic studies & ablation therapy • Timely consideration of implantable cardiac defibrillators	Efficacy of ablations for accessory pathways & arrhythmia foci may be ↓ in those w/Danon disease.
Skeletal muscle weakness	Physical therapy	
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Retinopathy	Use of low vision aids [4]	Consultation w/agencies for the visually impaired [5]
Family/ Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Consider involvement in adaptive sports or Special Olympics.

DD = developmental delay; ID = intellectual disability
Adapted from D'Souza et al [2014]
1. Gersh et al [2011] (full text)
2. See Bozkurt et al [2016] (full text)
3. Neurohormonal therapy includes drugs that target the sympathetic nervous system (beta-blockers, alpha-blockers) and the renin-angiotensin system (ACE inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists).
4. Low vision aids such as magnifiers and closed circuit television may provide useful reading vision for individuals with reduced central acuity and constricted visual fields.
5. In the US, publicly funded agencies at the state level provide services for the blind or those with progressive eye disorders; services include vocational training, mobility training, and skills for independent living.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction. Physical therapy is recommended to maximize mobility.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Social/Behavioral Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Surveillance

Table 6. Danon Disease: Recommended Surveillance

System/Concern	Evaluation	Frequency
Cardiac	Electrocardiography	At least annually
	Echocardiography	At least every 1-2 yrs, transitioning to every 6 mos once hypertrophy becomes moderate or if hypertrophy is rapidly progressive
	Cardiac MRI	Consider every 1-2 yrs to evaluate progression of fibrosis.
	Ambulatory arrhythmia monitoring	As needed for eval of symptoms consistent w/bypass track (e.g. palpitations, pre-syncope)
Neuromuscular	Clinical assessment: • Of strength, incl consideration of 6-min walking test [1] • For neurologic changes	Annually
Neurocognitive	Monitor developmental progress & educational needs.	At each visit
	Formal developmental assessments	Every 3-5 yrs during childhood
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive behavior	At each visit
Retinopathy	Exam by ophthalmologist for evidence of cone-rod dystrophy: best corrected visual acuity, color vision testing, visual field testing	Every 3-5 yrs or as needed based on concerns about visual acuity, visual field deficits, &/or color vision (as an indicator of cone function) [2]
Miscellaneous/ Other	Assess family need for social work support (e.g., respite care, home nursing, other local resources) & care coordination.	At each visit

Adapted from D'Souza et al [2014]

1. Six-minute walking test has not been formally studied as a means of assessing weakness in individuals with Danon disease.

2. Impact on vision and rate of progression of retinal disease is not well understood.

Agents/Circumstances to Avoid

Dehydration and over-diuresis should be avoided in those with heart failure.

No specific guidelines exist for individuals with non-sarcomeric cardiomyopathy. However, in the presence of significant cardiac hypertrophy with obstruction and/or symptomatic arrhythmia, instituting the guidelines for physical exertion for individuals with sarcomeric hypertrophic cardiomyopathy could be considered [Gersh et al 2011].

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

There are no published guidelines on pregnancy management in women with Danon disease. Management should be guided based on the degree of overt disease in the pregnant woman and as per guidelines for pregnant women with hypertrophic or dilated cardiomyopathy, depending on their condition.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Gene therapy was first offered through a clinical trial in 2019. The ongoing clinical trial (NCT03882437) is currently enrolling males with Danon disease who will receive one of two recombinant adeno-associated serotype 9 gene therapies to introduce the LAMP-2B isoform. Results from this study have not yet been published.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Danon disease is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *LAMP2* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *LAMP2* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. Germline mosaicism for *LAMP2* pathogenic variants has been described but the frequency of mosaicism is currently unknown [Takahashi et al 2002, Hashida et al 2015].
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo LAMP2* pathogenic variant, in which case the mother is not a heterozygote. In one study, the frequency of *de novo* pathogenic variants was estimated at 40% [Sugie et al 2018].

Parents of a female proband

- A female proband may have inherited the *LAMP2* pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*.
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother (and possibly the father, or subsequently the father) can determine if the pathogenic variant was inherited.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *LAMP2* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Both males and females who inherit the pathogenic variant will be affected although the phenotype in females is broader and more variable than in males and onset of symptoms in females is later than in affected males [Boucek et al 2011, Brambatti et al 2019].
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *LAMP2* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of maternal germline mosaicism.

Sibs of a female proband. The risk to sibs depends on the genetic status of the parents:

- If the mother of the proband has a *LAMP2* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Both males and females who inherit the pathogenic variant will be affected, although the phenotype in females is broader and more variable than in males and onset of symptoms in females is later than in affected males [Boucek et al 2011, Brambatti et al 2019].
- If the father of the proband has a *LAMP2* pathogenic variant, he will transmit it to all his daughters and none of his sons.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *LAMP2* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism.

Offspring of proband

- Affected males transmit the *LAMP2* pathogenic variant to:
  - All of their daughters, who will be heterozygotes and have a range of clinical manifestations (see Clinical Description, Females);
  - None of their sons.
- Women with a *LAMP2* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child:
  - Daughters who inherit the pathogenic variant will be heterozygotes and have a range of clinical manifestations (see Clinical Description, Females).
  - Sons who inherit the pathogenic variant will be affected.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or are heterozygotes, or who are at increased risk of being heterozygous and affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *LAMP2* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for Danon disease are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **DanonDisease.org**
  12700 East 19th Avenue
  F442, Room 8022
  Aurora CO
  Phone: 303-724-1400
  www.danondisease.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Danon Disease: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
LAMP2	Xq24	Lysosome-associated membrane glycoprotein 2	LAMP2 homepage - Leiden Muscular Dystrophy pages	LAMP2	LAMP2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Danon Disease (View All in OMIM)

300257	DANON DISEASE
309060	LYSOSOME-ASSOCIATED MEMBRANE PROTEIN 2; LAMP2

Molecular Pathogenesis

Introduction. Danon disease is caused by a deficiency of LAMP-2 (*l*ysosome-*a*ssociated *m*embrane *p*rotein 2) [Nishino et al 2000]. The condition was originally described as a glycogen storage disease due to similarities noted on pathologic studies, however LAMP-2 does not appear to have enzymatic activity nor directly affect glycogen storage or degradation. Three isoforms, LAMP-2A, LAMP-2B, and LAMP-2C, are created by alternative splicing of the terminal exon 9, each with varying roles in autophagy. Most pathogenic variants detected affect all three isoforms, although several reported pathogenic variants appear to affect only the LAMP-2B isoform (see Genotype-Phenotype Correlations).

The specific mechanism of disease remains uncertain, though studies of animal models of Danon as well as pluripotent stem cell derived from affected individuals suggest that the absence of LAMP-2, and more specifically the LAMP-2B isoform, results in impaired macro autophagic and subsequent mitochondrial dysfunction [Hashem et al 2015, Hashem et al 2017, Chi et al 2019].

Given all of the above, Danon disease is now considered a condition of pathologic autophagy with histologic features of abnormal cytoplasmic trafficking manifest with vacuolar myopathy and elevated glycogen staining.

Mechanism of disease causation. The majority of *LAMP2* pathogenic variants are loss-of-function alterations that predict an absence or severe reduction in LAMP-2 proteins. As the different LAMP-2 protein isoforms are due to alternative splicing of only the terminal *LAMP2* exon 9, the majority of pathogenic variants abrogate production of all three LAMP-2 protein isoforms.

Chapter Notes

Author Notes

Ongoing Danon Disease research through the Danon Disease Registry is accessible by contacting Matthew Taylor (matthew.taylor@cuanschutz.edu) or visiting DanonDisease.org.

Revision History

- 23 May 2024 (ma) Revision: Nishino et al [2000] added
- 5 March 2020 (ma) Review posted live
- 25 July 2019 (mrgt) Original submission

References

Literature Cited

Boucek D, Jirikowic J, Taylor M. Natural history of Danon disease. Genet Med. 2011;13:563-8. PubMed PMID: 21415759.

Bozkurt B, Colvin M, Cook J, Cooper LT, Deswal A, Fonarow GC, Francis GS, Lenihan D, Lewis EF, McNamara DM, Pahl E, Vasan RS, Ramasubbu K, Rasmusson K, Towbin JA, Yancy C, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: A scientific statement from the American Heart Association. Circulation. 2016;134:e579-e646. PubMed PMID: 27832612.

Brambatti M, Caspi O, Maolo A, Koshi E, Greenberg B, Taylor MRG, Adler ED. Danon disease: Gender differences in presentation and outcomes. Int J Cardiol. 2019;286:92-8. PubMed PMID: 30857840.

Brodie S. Cone-rod dystrophy in Danon disease. Graefes Arch Clin Exp Ophthalmol. 2012;250:633. PubMed PMID: 22407291.

Caughey AB, Krist AH, Wolff TA, Barry MJ, Henderson JT, Owens DK, Davidson KW, Simon MA, Mangione CM. USPSTF approach to addressing sex and gender when making recommendations for clinical preventive services. JAMA. 2021;326:1953-61. PubMed PMID: 34694343.

Charron P, Villard E, Sebillon P, Laforet P, Maisonobe T, Duboscq-Bidot L, Romero N, Drouin-Garraud V, Frebourg T, Richard P, Eymard B, Komajda M. Danon's disease as a cause of hypertrophic cardiomyopathy: a systematic survey. Heart. 2004;90:842-6. PubMed PMID: 15253947.

Chi C, Leonard A, Knight WE, Beussman KM, Zhao Y, Cao Y, Londono P, Aune E, Trembley MA, Small EM, Jeong MY, Walker LA, Xu H, Sniadecki NJ, Taylor MR, Buttrick PM, Song K. LAMP-2B regulates human cardiomyocyte function by mediating autophagosome-lysosome fusion. Proc Natl Acad Sci U S A. 2019;116:556-65. PubMed PMID: 30584088.

Dougu N, Joho S, Shan L, Shida T, Matsuki A, Uese K, Hirono K, Ichida F, Tanaka K, Nishino I, Inoue H. Novel LAMP-2 mutation in a family with Danon disease presenting with hypertrophic cardiomyopathy. Circ J. 2009;73:376-80. PubMed PMID: 19057086.

D'Souza RS, Levandowski C, Slavov D, Graw SL, Allen LA, Adler E, Mestroni L, Taylor MR. Danon disease: clinical features, evaluation, and management. Circ Heart Fail. 2014;7:843-9. PubMed PMID: 25228319.

Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW, et al. 2011 College of Cardiology Foundation/American Heart Association guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2011;142:e153-203. PubMed PMID: 22093723.

Hashem SI, Murphy AN, Divakaruni AS, Klos ML, Nelson BC, Gault EC, Rowland TJ, Perry CN, Gu Y, Dalton ND, Bradford WH, Devaney EJ, Peterson KL, Jones KL, Taylor MRG, Chen J, Chi NC, Adler ED. Impaired mitophagy facilitates mitochondrial damage in Danon disease. J Mol Cell Cardiol. 2017;108:86-94. PubMed PMID: 28526246.

Hashem SI, Perry CN, Bauer M, Han S, Clegg SD, Ouyang K, Deacon DC, Spinharney M, Panopoulos AD, Izpisua Belmonte JC, Frazer KA, Chen J, Gong Q, Zhou Z, Chi NC, Adler ED. Brief report: oxidative stress mediates cardiomyocyte apoptosis in a human model of Danon disease and heart failure. Stem Cells. 2015;33:2343-50. PubMed PMID: 25826782.

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;66:168-74. PubMed PMID: 25458169.

Hatz DE, Sharma A, Germer KE, Rolfsmeyer EA, Bowen JM. Psychosis in a patient with Danon cardiomyopathy. Gen Hosp Psychiatry. 2010;32:328-9. PubMed PMID: 20430238.

Hong D, Shi Z, Wang Z, Yuan Y. Danon disease caused by two novel mutations of the LAMP2 gene: implications for two ends of the clinical spectrum. Clin Neuropathol. 2012;31:224-31. PubMed PMID: 22541782.

Lacoste-Collin L, Garcia V, Uro-Coste E, Arné-Bes MC, Durand D, Levade T, Delisle MB. Danon's disease (X-linked vacuolar cardiomyopathy and myopathy): a case with a novel Lamp-2 gene mutation. Neuromuscul Disord. 2002;12:882-5. PubMed PMID: 12398843.

López-Sainz Á, Salazar-Mendiguchía J, García-Álvarez A, Campuzano Larrea O, López-Garrido MÁ, García-Guereta L, Fuentes Cañamero ME, Climent Payá V, Peña-Peña ML, Zorio-Grima E, Jordá-Burgos P, Díez-López C, Brugada R, García-Pinilla JM, García-Pavía P. Clinical findings and prognosis of Danon disease. An analysis of the Spanish Multicenter Danon Registry. Rev Esp Cardiol (Engl Ed). 2019;72:479-86. PubMed PMID: 30108015.

Musumeci O, Rodolico C, Nishino I, Di Guardo G, Migliorato A, Aguennouz M, Mazzeo A, Messina C, Vita G, Toscano A. Asymptomatic hyperCKemia in a case of Danon disease due to a missense mutation in Lamp-2 gene. Neuromuscul Disord. 2005;15:409-11. PubMed PMID: 15907287.

Nishino I, Fu J, Tanji K, Tamada T, Shimojo S, Koori T, Mora M, Riggs JE, Oh JS, Koga Y, Sue CM, Yamamoto A, Murakami N, Shanske S, Byrne E, Bonilla E, Nonaka I, DiMauro S, Hirano M. Primary LAMP-2 deficiency cases X-linked vacuolar cardiomyopathy and myopathy (Danon disease). Nature. 2000; 406:906-10. PubMed PMID: 10972294.

Prall FR, Drack A, Taylor M, Ku L, Olson JL, Gregory D, Mestroni L, Mandava N. Ophthalmic manifestations of Danon disease. Ophthalmology. 2006;113:1010-3. PubMed PMID: 16751040.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Schorderet DF, Cottet S, Lobrinus JA, Borruat FX, Balmer A, Munier FL. Retinopathy in Danon disease. Arch Ophthalmol. 2007;125:231-6. PubMed PMID: 17296900.

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;42:908-14. PubMed PMID: 21104865.

Sugie K, Komaki H, Eura N, Shiota T, Onoue K, Tsukaguchi H, Minami N, Ogawa M, Kiriyama T, Kataoka H, Saito Y, Nonaka I, Nishino I. A nationwide survey on Danon disease in Japan. Int J Mol Sci. 2018;19:3507. PubMed PMID: 30413001.

Takahashi M, Yamamoto A, Takano K, Sudo A, Wada T, Goto Y, Nishino I, Saitoh S. Germline mosaicism of a novel mutation in lysosome-associated membrane protein-2 deficiency (Danon disease). Ann Neurol. 2002;52:122-5. PubMed PMID: 12112061.

Taylor MR, Ku K, Slavov D, Cavanaugh J, Boucek M, Zhu X, Graw S, Carniel E, Barnes C, Quan D, Prall R, Lovell MA, Mierau G, Ruegg P, Mandava N, Bristow MR, Towbin JA, Mestroni L. Danon disease presenting with dilated cardiomyopathy and a complex phenotype. J Hum Genet. 2007;52: 830-5. PubMed PMID: 17899313.

Thiadens AA, Slingerland NW, Florijn RJ, Visser GH, Riemslag FC, Klaver CC. Cone-rod dystrophy can be a manifestation of Danon disease. Graefes Arch Clin Exp Ophthalmol. 2012;250:769-74. PubMed PMID: 22290069.

van der Kooi AJ, van Langen IM, Aronica E, van Doorn PA, Wokke JH, Brusse E, Langerhorst CT, Bergin P, Dekker LR, dit Deprez RH, de Visser M. Extension of the clinical spectrum of Danon disease. Neurology. 2008;70:1358-9. PubMed PMID: 18413590.

Yang Z, McMahon CJ, Smith LR, Bersola J, Adesina AM, Breinholt JP, Kearney DL, Dreyer WJ, Denfield SW, Price JF, Grenier M, Kertesz NJ, Clunie SK, Fernbach SD, Southern JF, Berger S, Towbin JA, Bowles KR, Bowles NE. Danon disease as an underrecognized cause of hypertrophic cardiomyopathy in children. Circulation. 2005;112:1612-7. PubMed PMID: 16144992.

License