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Barth Syndrome

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Abstract

Clinical characteristics

Barth syndrome is characterized in affected males by cardiomyopathy, neutropenia, skeletal myopathy, prepubertal growth delay, and distinctive facial gestalt (most evident in infancy); not all features may be present in a given affected male. Cardiomyopathy, which is almost always present before age five years, is typically dilated cardiomyopathy with or without endocardial fibroelastosis or left ventricular noncompaction; hypertrophic cardiomyopathy can also occur. Heart failure is a significant cause of morbidity and mortality; risk of arrhythmia and sudden death is increased. Neutropenia is most often associated with mouth ulcers, pneumonia, and sepsis. The nonprogressive myopathy predominantly affects the proximal muscles, and results in early motor delays. Prepubertal growth delay is followed by a postpubertal growth spurt with remarkable "catch-up" growth. Heterozygous females who have a normal karyotype are asymptomatic and have normal biochemical studies.

Diagnosis/testing

The diagnosis of Barth syndrome is established in a male proband with either an increased monolysocardiolipin:cardiolipin ratio (if available) or a hemizygous pathogenic variant in *TAFAZZIN* (formerly *TAZ*) identified by molecular genetic testing. The diagnosis of Barth syndrome is usually established in a female proband with suggestive clinical findings and a *TAFAZZIN* pathogenic variant identified by molecular genetic testing.

Management

Treatment of manifestations: Standard treatment of heart failure including careful fluid and volume management and avoidance of overdiuresis and dehydration, standard heart failure medications to improve symptoms, and

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cardiac transplantation when heart failure is severe and intractable; consideration of antiarrhythmic medications or implantable cardiac defibrillator for cardiac arrhythmia; granulocyte colony-stimulating factor for neutropenia; physical therapy for skeletal muscle weakness; standard treatment for talipes equinovarus and/or scoliosis; feeding therapy and consideration of gastrostomy tube for persistent feeding issues; uncooked cornstarch prior to bedtime for hypoglycemia; standard treatment for developmental delay / intellectual disability.

Prevention of secondary complications: Aspirin therapy for prevention of clot formation in those with severe cardiac dysfunction and/or marked left ventricular noncompaction; antibiotic prophylaxis to prevent recurrent infections; limiting fasting or providing intravenous glucose infusion prior to planned procedures; regular monitoring of potassium levels during administration of IV fluids that contain potassium and during episodes of diarrhea; consultation with a nutritionist and/or gastroenterologist to determine optimal caloric delivery.

Surveillance: At least annual electrocardiography with Holter monitor and echocardiography; electrophysiologic study to assess for potentially serious arrhythmia as needed; complete blood count with differential with all febrile episodes and at least semiannually; measurement of height and weight, clinical assessment of strength and for scoliosis, and assessment of developmental progress and educational needs at each visit; formal developmental assessments every three to five years during childhood.

Agents/circumstances to avoid: Prolonged fasting, use of rectal thermometers in those with neutropenia, and use of succinylcholine. Growth hormone is typically discouraged unless growth hormone deficiency is conclusively established, as the majority of affected males will attain normal stature by adulthood. The muscular involvement in Barth syndrome may increase the risk for malignant hyperthermia compared to the general population.

Evaluations of relatives at risk: It is appropriate to evaluate the older and younger brothers of a proband in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

Pregnancy management: Pregnancies of male fetuses known to have Barth syndrome should be managed by a high-risk maternal fetal obstetrician; there are no specific recommendations regarding mode, timing, or location of delivery.

Genetic counseling

Barth syndrome is inherited in an X-linked manner. If a mother has a *TAFAZZIN* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the *TAFAZZIN* pathogenic variant will be affected; females who inherit the *TAFAZZIN* pathogenic variant are typically not affected. Affected males pass the *TAFAZZIN* pathogenic variant to all of their daughters and none of their sons. Testing for at-risk female relatives and prenatal testing for a pregnancy at increased risk are possible if the *TAFAZZIN* pathogenic variant has been identified in an affected family member.

Diagnosis

Formal clinical diagnostic criteria for Barth syndrome have not been established.

Suggestive Findings

Barth syndrome is an X-linked condition in which heterozygous females typically do not express clinical or biochemical features, although rare instances of affected females have been reported.

Barth syndrome **should be suspected** in an individual (typically a male) with the following clinical features, supportive laboratory findings, and family history.

Clinical features

- At least one of the following cardiac findings:
  - Dilated cardiomyopathy ± endocardial fibroelastosis. Ventricular chamber enlargement and contractile dysfunction in the setting of normal left ventricular wall thickness, with or without diffuse thickening of the ventricular endocardium
  - Left ventricular noncompaction. Noncompacted left ventricular myocardium with prominent trabeculations and deep intertrabecular recesses that communicate with the ventricular cavity
  - Hypertrophic cardiomyopathy (less common). Characterized by increased ventricular wall thickness
- Skeletal myopathy or hypotonia
- Prepubertal growth delay
- Typical dysmorphic findings in infants and toddlers including round face, full cheeks, prominent pointed chin, large ears, and deep-set eyes

Supportive laboratory findings

- Lactic acidosis (normal: 0.5-2.2 mmol/L)
- Hypocholesterolemia (total cholesterol <110 mg/dL)
- Neutropenia (absolute neutrophil count <1,500 cells/μL)
- Elevated 3-methylglutaric acid, 3-methylglutaconic acid (3-MGC), and 2-ethylhydracrylic acid on **urine organic acids** analysis
  - 3-MGC is typically increased five- to 20-fold [Clarke et al 2013] with an average value of 44.6±25 SD μg/mg Cr (see Table 1).
  - Note: Urinary 3-MGC levels can be normal on single sample testing [Takeda et al 2011], and may be normal for the first six to 18 months of life [Baban et al 2020].
- Increased **monolysocardiolipin:cardiolipin ratio is a pathognomonic biochemical finding.** Since the protein that is deficient in Barth syndrome is responsible for cardiolipin remodeling within the inner mitochondrial membrane, affected individuals have (in a variety of tissues):
  - Increased monolysocardiolipins;
  - Decreased cardiolipin (specifically tetralinoleylcardiolipin).

Table 1. Urine and Plasma Organic Acid Levels in Barth Syndrome

Organic Acid	In Urine (μg/mg Cr)		In Plasma (nmol/L)	
	Barth Syndrome	Control	Barth Syndrome	Control
3-methylglutaconic acid	Avg: 44.6±25 (SD) [1] ↑ 5- to 20-fold [2]	0-2 yrs: 6.6±2.4 2-12 yrs: 5.3±2.4 Adult: 3.7±1.8	1,088±435 (range: 393-2326) [1]	162±68
3-methylglutaric acid	Moderately ↑ [3]			
2-ethylhydracrylic acid	Moderately ↑ [3] 14.4±10 [1]	Trace		

1. Vernon et al [2013]
2. Clarke et al [2013]
3. Kelley et al [1991]

Family history is consistent with X-linked inheritance including recurrent pregnancy loss involving male fetuses [Steward et al 2010]. Note: Absence of a known family history of Barth syndrome or recurrent pregnancy loss involving male fetuses does not preclude the diagnosis.

Establishing the Diagnosis

Male proband. The diagnosis of Barth syndrome **is established** in a male proband with either an increased monolysocardiolipin:cardiolipin ratio (if available) or a hemizygous pathogenic variant in *TAFAZZIN* (formerly *TAZ*) identified by molecular genetic testing (see Table 2).

Female proband. The diagnosis of Barth syndrome **is usually established** in a female proband with suggestive clinical findings and a *TAFAZZIN* pathogenic variant identified by molecular genetic testing (see Table 2).

Note: (1) Females with a heterozygous pathogenic variant in *TAFAZZIN* typically do not express clinical or biochemical features of Barth syndrome (see Clinical Description, Female Heterozygotes). (2) In the rare cases where a female has presented with clinical features of Barth syndrome there has been an additional scientific explanation (i.e., ring X chromosome) or unfavorably skewed X inactivation. Theoretically, a female with 45,X or another structural X-chromosome anomaly may also be symptomatic.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, 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 Barth syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with cardiomyopathy and/or hypotonia are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *TAFAZZIN* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected, particularly in females. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

- **A cardiomyopathy multigene panel** that includes *TAFAZZIN* 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 2).

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by cardiomyopathy and/or hypotonia, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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

Table 2. Molecular Genetic Testing Used in Barth Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TAFAZZIN (formerly TAZ)	Sequence analysis [3]	~92%-93% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	~7%-8% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Based on Stenson et al [2020] and Human Tafazzin Gene Mutation & Variation Database (accessed 10-25-22)
5. A synonymous variant in TAFAZZIN, c.348C>T (p.Gly116=), was shown to cause exon skipping and determined to be causative for Barth syndrome in one person [Ferri et al 2016].
6. 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.

Clinical Characteristics

Clinical Description

Affected Males

To date, more than 200 individuals with Barth syndrome have been identified [Miller et al 2020]. The vast majority of affected individuals are male (see Female Heterozygotes). The following description of the phenotypic features associated with this condition is based on these reports.

Table 3. Select Features of Barth Syndrome

Feature	% of Persons w/Feature [1]	Comment
Skeletal myopathy	97%	6MWT is abnormal in almost all individuals.
Cardiomyopathy [2]	73%	Dilated cardiomyopathy is most common. [2]
Neutropenia	70%-85%	
Prepubertal growth delay	58% [3]	
Prolonged QTc	25%-43%	

Table 3. continued from previous page.

Feature	% of Persons w/Feature [1]	Comment
Arrhythmia	10%-20% [4]	

6MWT = distance walked on six-minute walk test
1. The vast majority of affected individuals are male.
2. At presentation
3. Spencer et al [2006]
4. Based on the study by Kang et al [2016] and Spencer et al [2006]

Most affected individuals with Barth syndrome are male and present in infancy with cardiac issues, specifically dilated cardiomyopathy. In a French study of 22 males with Barth syndrome from 16 families, the median age at which medical care was first sought was 3.1 weeks (range: 0-1.4 years) [Rigaud et al 2013].

In another study of 73 males enrolled in the Barth Syndrome Registry, the age of onset was 0.76±1.6 years and the mean age at diagnosis was 4.04±5.45 years [Roberts et al 2012]. Therefore, there is on average a three-year delay between presentation and diagnosis of Barth syndrome. Cardiomyopathy was the presenting manifestation in 73% and infection was the presenting manifestation in 18%.

Cardiomyopathy in Barth syndrome is usually dilated but can also have features of combined dilated and hypertrophic cardiomyopathy, or isolated hypertrophic cardiomyopathy. Left ventricular noncompaction is also seen in many affected males.

The cardiomyopathy characteristically follows an undulating course in which the cardiac tissue can undergo remodeling, including a transition between hypertrophic and dilated appearances.

Cardiomyopathy almost always presents before age five years [Clarke et al 2013]. In many affected individuals the cardiomyopathy improves and in some it stabilizes after the toddler years. In the study by Rigaud et al [2013], left ventricular size and mass increased during the first six months of life, then decreased until age two years, and then appeared to stabilize. However, data in this study were insufficient to characterize these parameters in older children.

In a study by Kang et al [2016] of 27 individuals with Barth syndrome followed in the United Kingdom, those with normal left ventricular size and function had abnormalities of longitudinal and circumferential strain and reduced apical rotation. This finding led to the suggestion that cardiac medications be continued as long as functional or mechanical abnormalities persist.

Heart failure is a significant cause of morbidity and mortality; however, overall cardiac function varies greatly in individuals with Barth syndrome. Roberts et al [2012] noted that there may be a trend toward decline in cardiac function over time, as data from the Barth Syndrome Registry showed that for each five-year increase in age, ejection fraction z-score decreases on average by 0.6.

In the study by Rigaud et al [2013], out of 54 total hospitalizations for heart failure, 11 were due to worsening of heart failure attributed to infections. In this cohort, nine died from heart failure and two from sepsis. Median age of death was 5.1 months (range: 1.2-30.7 months). In the study by Kang et al [2016] of 27 people with Barth syndrome followed in the United Kingdom, seven underwent cardiac transplantation at a median age of two years, and five died at a median age of 1.8 years. All deaths were reported to be due to cardiomyopathy or the side effects of its management.

The response to medical therapy for cardiac failure is generally good. Spencer et al [2006] observed that with standard cardiac medications for dilated cardiomyopathy more than 16/30 affected males had normal ejection fraction and left ventricular diastolic volume. However, some responded to therapy initially but deteriorated after a period of stability, requiring cardiac transplantation [Adwani et al 1997, Mangat et al 2007].

Arrhythmia. The risk for arrhythmia (including supraventricular and ventricular tachycardia) and sudden death is increased. While arrhythmia has been most often reported in adolescents and young adults, it can occur in children of all ages. EKG abnormalities can include repolarization abnormalities and prolonged QTc intervals.

All 20 affected males with EKGs in the French cohort had a normal sinus rhythm. Repolarization abnormalities (including ST flattening and T-wave inversion) were seen in 17. Five had QTc values within the normal range (QTc <420 ms), and five had QTc greater than 460 ms. The median QTc was 440 ms (range: 360-530 ms). In the study by Kang et al [2016], nine of 21 affected individuals had prolonged QTc of greater than 460 ms and three had borderline QTc prolongation between 450 and 460 ms.

In five instances of ventricular arrhythmia leading to cardiac arrest or placement of an internal defibrillator [Spencer et al 2005]:

- All five individuals had normal QTc intervals;
- All five had a history of recurrent vasovagal symptoms including postural dizziness, nausea, and pallor suggestive of autonomic instability;
- Four had only mild LV dilatation and low normal to mildly depressed LV function; only one had poor but stable LV function prior to cardiac arrest;
- Three showed inducible ventricular arrhythmias on electrophysiologic testing;
- Two (and possibly 3) had a family history of sudden death in a brother suspected of having Barth syndrome; of note, no genotype-phenotype correlations predicted increased risk for arrhythmia;
- One had a normal Holter monitor study; one had only repolarization abnormalities at higher heart rates;
- One had both ventricular and supraventricular tachycardia.

In the study by Kang et al [2016], 42 Holter recordings were performed in 16 affected individuals, and none had sustained tachyarrhythmia. Two had loop recorder implantation and brief atrial tachycardia was identified in one. One affected individual was noted to have broad complex tachycardia lasting five beats during an echocardiogram, correlating with symptoms.

Neutropenia and infections. In the Barth Syndrome Registry study, self-reported data revealed that neutropenia * was present in 69.1% at some point, a number similar to that from the French study, in which 16 of 22 males had a median absolute neutrophil count (ANC) of fewer than 500 cells/μL at least once.

- In a study of 83 males with Barth syndrome, the median ANC was 1,100 cells/μL (range: 140-5,400 cells/μL) [Dale et al 2013].
- These findings are similar to those of the French cohort, in which the median ANC was 1,300 cells/μL (range: 0-6,400 cells/μL) [Rigaud et al 2013]. In both studies, the ANC fluctuated, but without detectable periodicity.
- In another report of 88 individuals with Barth syndrome, 84% had at least one ANC below 1,500 cells/μL [Steward et al 2019].

* Defined as follows:

- Mild neutropenia: ANC between 1,000 and 1,500 cells/μL
- Moderate neutropenia: ANC between 500 and 1,000 cells/μL
- Severe neutropenia: ANC below 500 cells/μL

In the original description of the syndrome by Barth et al [1983] three of seven males with a known cause of death died from infection; however, such high mortality from infection was not observed in subsequent publications. In fact, the effects of neutropenia are more often limited to mild involvement, such as persistent oral infections [Barth et al 1999]. However, significant complications can occur. A recent review of the UK NHS Barth Syndrome Service documented infections in 35 affected individuals prior to the introduction of G-CSF therapy: two had complications of acute tubular necrosis secondary to streptococcal septicemia; one developed

renal failure requiring transplant due to haemophilus septicemia; two had osteomyelitis; one had septic arthritis; three had soft tissue abscesses; five had cellulitis; two had balanitis; four had lobar consolidation/pneumonia; two had gingivitis; and one had a urinary tract infection [Steward et al 2019]. In the more recent Barth Syndrome Registry study, 60.2% of affected males had mouth ulcers, 28% had pneumonia, and 10% had blood infections.

This relatively low incidence of bacterial infections despite an ANC persistently below 1,000 cells/μL could be due to the development of a chronic, substantial monocytosis [Kelley 2002], which has been reported in two studies:

- In the French study the median absolute monocyte count (AMC) was 1,100 cells/μL (range: 500-4,300 cells/μL)
- Vernon et al [2014] reported an average AMC of 894±449 cells/μL (range: 500-2,400 cells/μL), with five of 17 affected males having monocyte counts at or above 1,000 cells/μL.
- In a report of 88 individuals with Barth syndrome [Steward et al 2019], monocyte counts greater than 1,000 cells/μL were observed at least once in 75%.

Of note, hematologic parameters neither worsen nor improve with age [Dale et al 2013]. Patterns of neutropenia seen in people with Barth syndrome can vary between intermittent and unpredictable, chronic and severe, or cyclical with a predictable pattern [Steward et al 2019].

Skeletal myopathy, which predominantly affects the proximal muscles, is non-progressive during childhood [Clarke et al 2013]. Frequently, affected children are diagnosed with hypotonia.

- In the Barth Syndrome Registry study it was observed that the myopathy led to developmental motor delay: 44 of 67 children showed a delay in sitting up, and 48 of 67 showed a delay in walking. Of note, 34% of affected males reported the use of foot and/or ankle orthoses, walkers, or wheelchairs at some point in their lives.
- In the French study the median age for walking was 19 months (range: 12-24 months).

Some males with Barth syndrome were born with talipes equinovarus, indicating a possible prenatal onset of hypotonia [Adès et al 1993, Gedeon et al 1995].

Of note, the exercise intolerance seen in males with Barth syndrome is due to both cardiac impairment and decreased skeletal muscle oxygen utilization [Spencer et al 2011].

In a study of individuals with Barth syndrome, six-minute walk test (6MWT) distance was abnormal in 33/34 individuals compared to controls [Thompson et al 2016]. In a study of functional exercise capacity and strength in 31 individuals with Barth syndrome [Hornby et al 2019], participants with Barth syndrome demonstrated abnormal 6MWT, increased five times sit-to-stand time (5XSST), and decreased knee extensor strength compared to controls.

Growth delay. Between ages six and 36 months the 50th percentile for length for boys with Barth syndrome is roughly equivalent to the third percentile in the standard curve; between ages 27 and 36 months, the 50th percentile for weight is roughly equal to the third percentile in the standard curve [Roberts et al 2012].

- Roberts et al [2012] published specific growth curves for boys with Barth syndrome [Roberts et al 2012; see Figure 1a-d].
- Spencer et al [2006] found that males with Barth syndrome show a delayed post-pubertal growth spurt with remarkable "catch-up" growth.

In males younger than age 18 years:

- Mean weight is in the 15th percentile (range: <1-66), with 15 of 26 males below the fifth percentile. Mean height is in the eighth percentile (range: <1-38), with 15 of 26 males at or below the fifth percentile.
- Body mass index is below the fifth percentile in 44% of males, normal in 48%, and above the 95th percentile in 7%.

In males older than age 18 years, mean weight was in the 13th percentile (range: <1-63) and mean height in the 50th percentile (range: 8-90).

Dysmorphology. Younger males with Barth syndrome have a characteristic facial gestalt that is most evident during infancy, characterized by a tall and broad forehead, round face, full cheeks, prominent pointed chin, large ears, and deep-set eyes. This appearance persists through childhood, becoming less obvious following puberty. The ears tend to remain prominent and the eyes deep-set.

At this point and after the late pubertal period of "catch-up" growth the most striking feature is that of gynoid fat distribution [Hastings et al 2009].

Intellectual development. Cognition in boys with Barth syndrome is characterized by age-appropriate vocabulary and basic reading skills, but a below-average performance in mathematics and selective difficulties in visuospatial skills that are not due to impaired motor functioning from myopathy [Mazzocco et al 2007]. Math difficulties are not evident in preschool but appear to emerge in kindergarten [Raches & Mazzocco 2012].

In the Barth Syndrome Registry study, 30 of 60 males older than age three years reported delay either in first words or in putting words together; 31 of 67 participated in speech therapy. Twenty-two of 46 males older than age seven years reported some form of "learning disability."

Sensory issues related to feeding and eating are common, and many affected males have a strong preference for salty, cheesy, and spicy foods while having an overall restricted repertoire of foods. Some issues such as a strong gag reflex manifest early in development [Reynolds et al 2012].

Psychosocial functioning. Boys with Barth syndrome experience lower quality of life than both healthy controls and boys with cardiac disease alone [Storch et al 2009]. Nine of 34 children were being monitored by a school psychologist, and eight of 34 children had close contact with a school counselor.

Acute decompensation. An acute metabolic presentation with metabolic acidosis, elevated plasma lactate, elevated transaminases, hypoglycemia, and hyperammonemia has been reported [Donati et al 2006]. Of note, this presentation has been described even in the setting of largely preserved cardiac function [Yen et al 2008, Steward et al 2010]. All four males reported to date with this metabolic presentation had onset of symptoms during the neonatal period (between days 1 and 13). Their subsequent course is not known to differ from that of other males with Barth syndrome.

Other. Based on data collected by the Barth Syndrome Registry study, other observed findings were:

- Delayed bone age (in 58%);
- Scoliosis (in 20%);
- Supplemental feeds via either gastrostomy tube or nasogastric tube (in 23 of 70 individuals).

Perinatal. In 19 families with Barth syndrome, Steward et al [2010] found that six had serious perinatal issues including male fetal loss, nine stillbirths, and severe neonatal illness or death. The authors noted that Barth syndrome may be an under-recognized cause of male fetal loss. Others have described characteristic cardiac pathology of Barth syndrome (endocardial fibroelastosis and subendocardial vacuolization of myocytes) as early as 18 weeks' gestation [Brady et al 2006].

In the Barth Syndrome Registry study, preterm birth from 29 to 36 weeks occurred in nine of 65 males; birth weight was below 2.5 kg in nine of 48 males.

In the French study, median birth weight was 2.77 kg (range: 2.18-3.73 kg) and seven of 22 males had severe intrauterine growth restriction with birth weight below the third percentile.

Prognosis. The two factors that correlate with survival are severe neutropenia at the time of diagnosis and birth year (before 2000 or in/after 2000) [Rigaud et al 2013].

- Males with an ANC <500 cells/µL at the time of diagnosis have a one-year survival rate of 25% compared to 68% for those with an ANC >500 cells/µL.
- Males born before 2000 had a five-year survival rate of 22% compared to 70% in those born in or after 2000. This finding is likely related to the better management of heart failure in more recent years.

In the French study, the five-year survival rate was 51%, with no deaths reported in males age three years or older; thus, the risk for early mortality appears to peak in the first few years of life.

Ronvelia et al [2012] report a man age 51 years with Barth syndrome, while Mazar et al [2019] reported seven individuals ages 37.2 to 58.6 years (the latter the oldest living individual with a confirmed diagnosis). Two affected males in their 60s are known [Author, personal observation].

Laboratory findings that may be associated with Barth syndrome include the following.

Plasma 3 methylglutaconic acid (3-MGC). In a single study, 28 of 28 affected individuals ranging in age from ten months to 30 years had elevated plasma 3-MGC levels, with an average of 1,088 nmol/L ± 435 (range: 393-2,326 nmol/L) [Vernon et al 2014] (see Table 1). In contrast, only eight of 16 individuals in the French cohort had elevated 3-MGC levels [Rigaud et al 2013].

Monolysocardiolipin:cardiolipin ratio. Using high-performance liquid chromatography-mass spectrometry (HPLC-MS), van Werkhoven et al [2006] measured monolysocardiolipin (MLCL) and cardiolipin (CL) levels from cultured fibroblasts of males with Barth syndrome and controls. They found that the range of MLCL:CL ratios was 5.41–13.83 in Barth syndrome and 0.03–0.12 in controls.

Using a screening method in bloodspots, Kulik et al [2008] found that all males with Barth syndrome had an MLCL:CL ratio greater than 0.40 and all controls had a ratio of lower than 0.23. Using a cutoff of 0.30, they reported a sensitivity and specificity of 100%. Males with classic Barth syndrome tend to have ratios greater than 1 but those with an intermediate form or atypical phenotype (mild cardiac involvement, good exercise tolerance, mild/no neutropenia) can have ratios lower than this but greater than 0.4. It is important that the MLCL:CL ratio is used for diagnosis, rather than CL content alone, as false negative results can result for atypical phenotypes if only tetralinoleoyl cardiolipin is measured. [Bowron et al 2015]. It is also advised to confirm the results from MLCL:CL either through molecular genetic testing or with a repeat sample, ideally in a different medium.

- A confirmatory method in cultured fibroblasts, lymphocytes, and skeletal muscle has also been validated [Houtkooper et al 2009].
- In the French study, all 16 affected males had an elevated MLCL:CL ratio: in fibroblasts (14 individuals); in lymphoblasts (1 individual); and in platelets (1 individual) [Rigaud et al 2013].
- Lactic acidosis. Blood lactate ranges from normal to well above normal related to both cardiac and metabolic status (normal: 0.5-2.2 mmol/L).
- Plasma amino acids
  - In a French study in which plasma amino acid levels were available for eight affected males, all showed lower arginine levels than controls [Rigaud et al 2013].
  - This finding was reproduced in 28 males with Barth syndrome (mean arginine level: 43 µmol/L) vs controls (70 µmol/L) with a statistically significant p-value [Vernon et al 2014]. These 28 males also showed significantly higher proline levels (291 µmol/L) than controls (165 µmol/L).

- Hypocholesterolemia (total cholesterol <110 mg/dL). Described in six of 25 affected individuals tested [Spencer et al 2006]. In another study, only two of 28 were found to be hypocholesterolemic, with a mean cholesterol level of 137±26 mg/dL [Vernon et al 2014].
- Hypoglycemia. Although not a common finding, hypoglycemia has been described occasionally [Kelley et al 1991, Christodoulou et al 1994] and in at least one case was the presenting complaint [Rigaud et al 2013].
- Creatine kinase. Mild elevations ranging from 192 to 397 mg/dL have been reported in three of 20 males tested [Spencer et al 2006].
- Prealbumin. Low prealbumin (<20 mg/dL) has been described in 15 of 19 males tested [Spencer et al 2006]. In a separate study 13 of 18 affected males showed decreased prealbumin levels with a mean of 16.9±4.0 mg/dL [Vernon et al 2014].

Respiratory chain studies reveal decreased activity of complex III and IV in skeletal muscle [Barth et al 1983] and fibroblasts [Barth et al 1996].

Pathology

- Skeletal muscle. Accumulation of lipid droplets within type I muscle fibers and nonspecific mitochondrial abnormalities have been described [Barth et al 1983, Ino et al 1988, Kelley et al 1991]. In at least one case the initial presentation was a lipid storage myopathy [Takeda et al 2011].
- Liver. Lipid storage in the liver has also been described [Ino et al 1988, Kelley et al 1991, Donati et al 2006].
- Bone marrow
  - A maturation arrest at the myelocyte stage was noted in the original description of the disease [Barth et al 1983].
  - More recently, in a French cohort in which five bone marrow smears were available, two showed promyelocyte-myelocyte maturation arrest, and the samples without a complete arrest showed an increased proportion of promyelocytes with a greatly decreased proportion of myelocytes, metamyelocytes, and neutrophils [Rigaud et al 2013].

Female Heterozygotes

Heterozygous females typically do not manifest the disease. Biochemical abnormalities have not been found in eight heterozygous females [Vernon et al 2014].

It is proposed that heterozygous females are asymptomatic due to selection against cells with the mutated *TAFAZZIN* (formerly *TAZ*) allele on the active X chromosome, based on a study of the X-chromosome inactivation pattern in 16 obligate heterozygotes [Orstavik et al 1998]. In this study, six of the 16 had an extremely skewed pattern of X-chromosome inactivation (≥95:5) and five had a skewed pattern (80:20≤95:5) that was not observed in 148 female controls.

Two females with Barth syndrome have been reported:

- One had biallelic pathogenic variants in *TAFAZZIN* as a result of (1) a complete deletion of the paternal allele (associated with a ring X chromosome with a large deletion that included *TAFAZZIN*) and (2) a deletion of exons 1-5 in the maternal *TAFAZZIN* allele [Cosson et al 2012]. Analysis of lymphocyte and fibroblast cultures showed monosomy X with mosaicism for the ring X chromosome; thus, at least in lymphocytes, she lacked a normal *TAFAZZIN* allele.
- A second affected female with pathogenic *TAFAZZIN* variant c.253insC (p.Arg85ProfsTer54) in exon 3 had left ventricular noncompaction and hypotonia. Skewed X inactivation (presumably where the X chromosome with the nonmutated *TAFAZZIN* was preferentially inactivated) was identified in her blood [Avdjieva-Tzavella et al 2016].

Genotype-Phenotype Correlations

In general, genotype-phenotype correlations have not been found [Johnston et al 1997, Rigaud et al 2013].

Prevalence

As of 2020, an estimated 230-250 males have been identified with Barth syndrome worldwide [Miller et al 2020]. Estimates of the prevalence of Barth syndrome range from 1:140,000 live births in South West England and South Wales [Clarke et al 2013] to 1:300,000-1:400,000 based on new diagnoses in the United States each year [Kelley 2002], to 1.5 cases per million births (95% CI: 0.2-2.3) based on data from France between 1995 and 2008 [Rigaud et al 2013]. A Bayesian analysis to estimate Barth syndrome prevalence based on subsets of individuals with Barth syndrome included in publications describing the incidence and prevalence of cardiomyopathy and neutropenia estimates the prevalence of Barth syndrome at 1 per million males [Miller et al 2020].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TAFAZZIN* (formerly *TAZ*).

Differential Diagnosis

Disorders in which excretion of 3-methylglutaconate is increased. Increased urinary excretion of the branched-chain organic acid 3-methylglutaconate (3-MGC) is a relatively common finding in children investigated for suspected inborn errors of metabolism [Gunay-Aygun 2005]. 3-MGC is an intermediate of leucine degradation and the mevalonate shunt pathway that links sterol synthesis with mitochondrial acetyl-CoA metabolism.

A classification of inborn errors of metabolism with 3-methylglutaconic aciduria (3-MGCA) as the discriminative feature was published by Wortmann et al [2013a] and Wortmann et al [2013b]. Clinical features (see Table 4) and biochemical findings of syndromes associated with 3-MGCA vary. Tissues with higher requirements for oxidative metabolism, such as the central nervous system and cardiac and skeletal muscle, are predominantly affected.

Table 4. Inborn Errors of Metabolism with 3-Methylglutaconic Aciduria as a Discriminative Feature

Gene	MOI	Disorder	Key Clinical Characteristics (in addition to 3-MGCA)
AGK	AR	Sengers syndrome (See Mitochondrial DNA Maintenance Defects Overview.)	• Cataracts; cardiomyopathy • DD [1]
ATAD3A	AD AR	Harel-Yoon syndrome (OMIM 617183)	DD; hypotonia; optic atrophy; axonal neuropathy; hypertrophic cardiomyopathy [2]
AUH	AR	*AUH* defect (OMIM 250950)	Adult-onset progressive spasticity & dementia w/ characteristic slowly developing radiologic picture of extensive leukoencephalopathy [3, 4]
CLPB	AR	CLPB deficiency	• Cataracts; central hypopnea; DD & ID; movement disorder; neutropenia • Epilepsy [1]
DNAJC19	AR	*DNAJC19* defect (DCMA syndrome) (OMIM 610198)	Characteristic combination of childhood-onset dilated cardiomyopathy, nonprogressive cerebellar ataxia, testicular dysgenesis, & growth failure

Table 4. continued from previous page.

Gene	MOI	Disorder	Key Clinical Characteristics (in addition to 3-MGCA)
HTRA2	AR	MGCA8 (OMIM 617248)	Cataracts; central hypopnea; DD & ID; epilepsy; movement disorder; neutropenia
MICOS13 (*C19orf70*, *QIL1*)	AR	Combined oxidative phosphorylation deficiency 37 (OMIM 618329)	Hypotonia; failure to thrive; neurodegeneration w/loss of developmental milestones; liver dysfunction
OPA3	AR	Costeff syndrome	Optic atrophy; movement disorder (ataxia or extrapyramidal disorder)
SERAC1	AR	MEGDEL syndrome (SERAC1 defect)	• DD & ID; deafness; movement disorder • Epilepsy & optic atrophy [1]
TAFAZZIN (formerly TAZ)	**XL**	**Barth syndrome (topic of this GeneReview)**	**In males, cardiomyopathy (left ventricular noncompaction), neutropenia, myopathy, typical facial features, hypocholesterolemia, & a cognitive phenotype**
TIMM50	AR	MGCA9 (OMIM 617698)	DD & ID; epilepsy
TMEM70	AR	*TMEM70* defect	• Typically neonatal onset w/muscular hypotonia, hypertrophic cardiomyopathy, psychomotor disability, hyperammonemia, & lactic acidosis • Children surviving neonatal period later show DD; phenotypic spectrum is variable.

3-MGCA = 3-methylglutaconic aciduria; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

Adapted from Table 1 in Kovacs-Nagy et al [2018]

1. Seen in some individuals

2. Harel et al [2016]

3. Wortmann et al [2010]

4. AUH defect is the only one of the five inborn errors of metabolism with 3-MGA-uria with a distinct biochemical finding: elevated urinary excretion of 3-hydroxyisovaleric acid (3-HIVA).

Cardiomyopathy. Left ventricular noncompaction (LVNC) is seen in other genetic syndromes as an isolated finding or associated with other congenital cardiac malformations.

Other genes in which pathogenic variants can lead to isolated cardiomyopathy with left ventricular noncompaction include: *LDB3*, *ACTC1*, *MYH7*, *MIB1*, *PRDM16*, *TNNT2*, *TPM1*, and *MYBPC3* (OMIM PS604169). Given the considerable phenotypic overlap, it can be quite difficult to differentiate the phenotypes on the basis of specific genetic cause. However, as none of these other genes is on the X chromosome, a family history suggestive of X-linked inheritance (i.e., affected males related through unaffected females) can point to Barth syndrome. Often, the most efficient way to determine the responsible gene is through molecular genetic testing using a multigene panel.

LVNC and skeletal myopathy can be seen in Duchenne muscular dystrophy, with a prevalence as high as 28% [Statile et al 2013]. However, in Duchenne muscular dystrophy (in contrast to Barth syndrome) the LVNC tends to worsen over time.

Neutropenia. The differential for isolated neutropenia is wide and includes several notable genetic conditions:

- *ELANE*-related neutropenia is an autosomal dominant disorder associated with either congenital neutropenia or cyclic neutropenia, both of which are primary hematologic disorders characterized by recurrent fever, skin and oropharyngeal inflammation (i.e., mouth ulcers, gingivitis, sinusitis, and pharyngitis), and cervical adenopathy.

- Kostmann syndrome (OMIM 610738) is an autosomal recessive form of severe congenital neutropenia. Klein et al [2007] identified homozygous pathogenic variants in *HAX1* (encoding HCLS1-associated protein X-1) in several individuals with Kostmann syndrome.
- Mutation of *G6PC3* (encoding glucose-6-phosphate 3) results in an autosomal recessive form of severe congenital neutropenia [Klein 2011]. (See G6PC3 Deficiency.)
- Benign familial neutropenia is an autosomal dominant form of congenital neutropenia with milder neutropenia and less severe symptoms.

Management

Consensus clinical management recommendations for Barth syndrome have not been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in a male diagnosed with Barth syndrome, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Note: In the very rare event that a heterozygous female has signs and/or symptoms of Barth syndrome, evaluation and treatment should follow what is recommended for affected males.

Table 5. Recommended Evaluations Following Initial Diagnosis in a Male with Barth Syndrome

System/Concern	Evaluation	Comment
Cardiac	Electrocardiography	To evaluate for hypertrophy, QTc, & arrythmia
	Echocardiography	To evaluate for cardiac muscle structure (size/noncompaction) strain & function
Immune	Complete blood count w/differential	To evaluate for neutropenia
Neuromuscular	Neurologic exam for signs of muscle weakness & hypotonia	
Constitutional	Measurement of growth parameters	Consider plotting on the Barth syndrome specific growth charts. [1]
Gastrointestinal	Gastroenterology / nutrition / feeding team eval	- To incl eval of weight gain & nutritional status - Consider eval for gastric tube placement in those w/poor weight gain.
Development	Developmental assessment	- To incl motor, adaptive, & cognitive assessments - Eval for early intervention/special education based on age
Genetic counseling	By genetics professionals [2]	To inform affected males & families re nature, MOI, & implications of Barth syndrome to facilitate medical & personal decision making
Family support & resources		Assess need for: - Community or online resources such as Parent to Parent; - Social work involvement for parental support.

MOI = mode of inheritance
1. Derived from Roberts et al [2012; see Figure 1a-d]
2. Medical geneticist, certified genetic counselor, or certified advanced genetics nurse

Treatment of Manifestations

Table 6. Treatment of Manifestations in Individuals with Barth Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Heart failure	Standard treatment [1] incl careful fluid & volume mgmt & avoidance of overdiuresis & dehydration	
	Standard HF medications are used to improve symptoms, effect reverse remodeling of the ventricle, & improve ventricular function as measured by EF. [2]	• ACE inhibitors & beta blockers for typical outpatient mgmt [3] • IV inotropes incl milrinone for in-patient mgmt of acute decompensation
	Cardiac transplantation has been successful when HF is severe & intractable. [4]	Given the natural history of improving ventricular function after infancy, cardiac transplantation should be carefully considered.
Cardiac arrhythmia	Consideration of antiarrhythmic medications or implantable cardiac defibrillator	Use of these therapies prophylactically for prevention of primary arrhythmia has not been clarified. Long-term implantable cardiac monitoring devices can be considered for those at risk.
Neutropenia	G-CSF of 2-3 μg/kg/dose w/frequency of administration ranging from 2x/wk to every other day [5, 6, 7]	• Consider regular administration of G-CSF (i.e., not only during times of high risk, e.g., surgery or infection). • Consider prophylactic antibiotics (see Prevention of Secondary Complications).
Skeletal muscle weakness	PT	To aid in attainment of developmental milestones & functional outcomes while monitoring cardiovascular status [8]
Talipes equinovarus &/or scoliosis	Standard treatment per orthopedist	
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval when showing poor weight gain
Hypoglycemia/ Nutrition	Uncooked cornstarch given prior to bedtime	• To avoid muscle protein loss overnight • Specific dosing by age & weight can be obtained from the Barth Syndrome Foundation. [9]
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
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.

ACE = angiotensin-converting enzyme; DD = developmental delay; EF = ejection fraction; G-CSF = granulocyte colony-stimulating factor; HF = heart failure; ID = intellectual disability; IV = intravenous; PT = physical therapy

1. See Kirk et al [2014] for pediatric heart failure management and Yancy et al [2017] for adult heart failure management guidelines.

2. Although no studies are available to evaluate the effectiveness of medical therapy in males with Barth syndrome, when medications are stopped a decline in heart function is often observed. However, this can sometimes be difficult to distinguish from the natural fluctuations of the clinical phenotype (Clinical Description, **Heart failure**).

3. Therapy received by 22 individuals in the French cohort [Rigaud et al 2013] included: 16/22 beta blockers, 9/22 beta blockers, 11/22 digoxin, 17/22 diuretics, 5/22 anticoagulants, and 5/22 aspirin.

4. Mangat et al [2007], Roberts et al [2012]

5. Clarke et al [2013]

6. In 83 affected males, 42 of whom had been treated with G-CSF, the median dose was 2.78±0.78 μg/kg/dose (range: 0.45-12.8 μg/kg/ dose) [Dale et al 2013]. On average, G-CSF was begun at age 5.8 years, with an average exposure of 7.3 years; none developed acute myeloid leukemia, and treatment responses to G-CSF were maintained long-term.

7. Although neutropenia appears to improve with G-CSF treatment, in the French cohort in which six affected males were actively treated with G-CSF, two developed a severe infection, including one episode of septic shock [Rigaud et al 2013].

8. Jarvis et al [2001]

9. Avery [2006]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / learning 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 and special educators. 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, or social 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.

- 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.
- The excessive fatigue that boys with Barth syndrome experience and the characteristic cognitive phenotype (see Clinical Description) warrant educational support during the early school-age years [Mazzocco et al 2007] with particular attention to mathematics [Raches & Mazzocco 2012].
- 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 adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Gross Motor Dysfunction

Physical therapy is recommended to maximize strength.

Social/Behavioral Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, when necessary.

Prevention of Secondary Complications

Table 7. Prevention of Secondary Complications in Males with Barth Syndrome

Manifestation/Concern	Preventive Measure	Considerations/Other
Blood clot formation	Aspirin therapy - 5 mg/kg daily for children - 81-325 mg daily for adults	For prevention of clot formation (& thus ↓ in risk for stroke) in males w/severe cardiac dysfunction &/or marked LVNC
Infections	Antibiotic prophylaxis [1]	To prevent recurrent infections
Hypoglycemia	Episodes of fasting (e.g., prior to surgery) should be as short as possible & accompanied by IV glucose infusion.	Schlame [2013]
Hyperkalemia	Regular monitoring of potassium levels during administration of IV fluids that contain potassium	Affected males lack normal muscle "reservoir" for potassium & can rapidly develop hyperkalemia when given IV fluids containing potassium.
Hypokalemia	Regular monitoring of potassium levels during episodes of diarrhea	Affected males can rapidly become potassium depleted during a GI illness due to marked muscular hypoplasia. [2]

Table 7. continued from previous page.

Manifestation/ Concern	Preventive Measure	Considerations/Other
Chronic diarrhea induced by overfeeding	Consultation w/nutritionist/gastroenterologist to determine optimal caloric delivery	• Males w/Barth syndrome have lower-than-normal caloric requirements. [2] • Attempts to induce growth by overfeeding can lead to chronic diarrhea.

GI = gastrointestinal; IV = intravenous; LVNC = left ventricular noncompaction
1. In the French study of 22 affected males, four received antibiotic prophylaxis [Rigaud et al 2013].
2. Kelley [2002]

Surveillance

Table 8. Recommended Surveillance for Males with Barth Syndrome

System/Concern	Evaluation	Frequency
Cardiac [1]	Electrocardiography w/Holder monitoring	At least annually
	Echocardiography	At least annually or more frequently depending on clinical status
	Electrophysiologic study to assess for a potentially serious arrhythmia	As needed & for eval of symptoms incl palpitations & syncope, abnormal arrhythmia screening tests, or family history of sudden death
Immune	Complete blood count w/differential	With all febrile episodes & semi-annually (or more frequently based on history & symptoms)
Neuromuscular	Clinical assessment of strength & for scoliosis	At each visit
Constitutional	Measurement of height & weight [2]	
Neurocognitive	Monitor developmental progress & educational needs.	
	Formal developmental assessments	Every 3-5 yrs during childhood
Miscellaneous/ Other	Assess family need for social work support (e.g., respite care, home nursing, other local resources) & care coordination.	At each visit

1. Spencer et al [2005]
2. Consideration of Barth syndrome-specific growth patterns [Roberts et al 2012].

Agents/Circumstances to Avoid

Avoid the following:

- Prolonged fasting because of a predisposition to hypoglycemia
- The use of rectal thermometers in those with neutropenia
- The use of succinylcholine, as nondepolarizing neuromuscular blockers could have a prolonged effect [Schlame 2013]

The use of human growth hormone is usually discouraged, as the majority of affected males will attain normal stature by adulthood.

Although the use of sevoflurane has been reported without adverse effects, the muscular involvement in Barth syndrome may increase the risk for malignant hyperthermia compared to the general population [Schlame 2013].

Evaluation of Relatives at Risk

It is appropriate to evaluate the older and younger brothers of a proband in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

- If the *TAFAZZIN* (formerly *TAZ*) pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk male sibs.
- If the *TAFAZZIN* pathogenic variant in the family is not known, testing by means of monolysocardiolipin:cardiolipin (MLCL:CL) ratio (if available) can be used to clarify the genetic status of at-risk male sibs. Note: MLCL:CL measurement is not appropriate for evaluation of the genetic status of females.
- If MLCL:CL ratio is not available, a combination of urine organic acid analysis, complete blood count with differential, and echocardiogram may be able to clarify the genetic status of at-risk male sibs. However, such testing cannot exclude a diagnosis of Barth syndrome.

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

Pregnancy Management

Given that Barth syndrome has been variably associated with different prenatal complications including intrauterine growth restriction, oligohydramnios, intrauterine ventricular dysfunction, and hydrops fetalis [Cardonick et al 1997, Steward et al 2010], it appears prudent to recommend that pregnancies of male fetuses known to have Barth syndrome be managed by a high-risk maternal fetal obstetrician. Of note, there are no specific recommendations regarding mode, timing, or location of delivery.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Pantothenic acid. The original report of successful treatment of Barth syndrome with pantothenic acid [Ostman-Smith et al 1994] was not substantiated by later reports [Kelley 2002, Rugolotto et al 2003].

Coenzyme Q$_{10}$. The rationale behind the use of coenzyme Q$_{10}$ is based on the fact that both coenzyme Q$_{10}$ and 3-methylglutaconic acid (3-MGC) can be produced from dimethylallyl pyrophosphate (DMAPP), an intermediate in the synthesis of cholesterol. Thus, if coenzyme Q$_{10}$ production is impaired, more DMAPP could potentially be shunted toward the production of 3-MGC [Costeff et al 1998]. However, no formal study has been undertaken to prove the efficacy of coenzyme Q$_{10}$ therapy in males with Barth syndrome. In a study of 15 males with Barth syndrome, three took coenzyme Q$_{10}$ [Spencer et al 2011].

Carnitine. Although early reports claimed significant benefit from carnitine supplementation in males with Barth syndrome [Ino et al 1988], subsequent reports identified rapid deterioration in cardiac function in some cases with carnitine supplementation [Ostman-Smith et al 1994, Kelley 2002]. Thus, unless plasma carnitine levels are low, its supplementation has no role in the treatment of Barth syndrome.

Arginine. Because lower plasma arginine levels detected in males with Barth syndrome [Rigaud et al 2013, Vernon et al 2014] could contribute to growth delay and cardiac abnormalities by impairing protein synthesis, it has been proposed that oral arginine supplementation be used. Improvements in ventricular function have also been noted concurrently with normalization of the amino acid profile [R Kelley, personal communication]. However, to date no formal assessments of the efficacy of this treatment have been published.

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

Barth syndrome 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 *TAFAZZIN* (formerly *TAZ*) 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 *TAFAZZIN* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. Germline mosaicism has been reported in two families with Barth syndrome [Chang et al 2010, Momoi et al 2012, Rigaud et al 2013].
- 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 TAFAZZIN* pathogenic variant, in which case the mother is not a heterozygote. In the experience of one laboratory, the son's pathogenic variant was not identified in the leukocyte DNA of five of 42 mothers of boys with Barth syndrome [Kirwin et al 2007].

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

- If the mother of the proband has a *TAFAZZIN* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and are typically not affected (see Clinical Description, Female Heterozygotes).
- If a male proband represents a simplex case (i.e., a single occurrence in a family) and if the *TAFAZZIN* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is greater than that of the general population because of the possibility of maternal germline mosaicism [Chang et al 2010, Momoi et al 2012, Rigaud et al 2013].

Offspring of a male proband. Affected males transmit the *TAFAZZIN* pathogenic variant to:

- All of their daughters, who will be heterozygotes and will typically not be affected;
- None of their sons.

Other family members. The proband's maternal aunts may be at risk of being heterozygotes and the aunts' offspring, depending on their sex, may be at risk of being heterozygotes or of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo TAFAZZIN* pathogenic variant arose, information that could help determine genetic risk status of the extended family. One laboratory reported that *de novo* mutation of *TAFAZZIN* occurs more frequently in a male ancestor than in a female ancestor [Kirwin et al 2007].

Heterozygote Detection

Identification of female heterozygotes requires either (1) prior identification of the *TAFAZZIN* pathogenic variant in the family or, (2) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and then, if no pathogenic variant is identified, by deletion/duplication analysis. Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Heterozygous females typically do not manifest the disease. In Barth syndrome, heterozygous females often demonstrate skewed X-chromosome inactivation due to preferential inactivation of the X chromosome with the *TAFAZZIN* pathogenic variant [Orstavik et al 1998]. To date, two females with Barth syndrome have been reported (see Clinical Description, Female Heterozygotes).

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, clarification of genetic status, 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, are heterozygous, or are at risk of being heterozygous.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *TAFAZZIN* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for Barth syndrome 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.

- **Barth Syndrome Foundation**
  PO Box 618
  Larchmont NY 10538
  Phone: 850-273-6947
  Fax: 518-213-4061
  Email: bsfinfo@barthsyndrome.org
  www.barthsyndrome.org

- **Organic Acidemia Association**
  Phone: 763-559-1797
  Fax: 866-539-4060 (toll-free)
  Email: kstagni@oaanews.org; menta@oaanews.org
  www.oaanews.org

- **European Society for Immunodeficiencies (ESID) Registry**
  Email: esid-registry@uniklinik-freiburg.de
  ESID Registry

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. Barth Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TAFAZZIN	Xq28	Tafazzin	TAZbase: Mutation registry for Barth syndrome Human Tafazzin Gene Variants Database TAZ database	TAFAZZIN	TAFAZZIN

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 Barth Syndrome (View All in OMIM)

300394	TAFAZZIN, PHOSPHOLIPID-LYSOPHOSPHOLIPID TRANSACYLASE; TAFAZZIN
302060	BARTH SYNDROME; BTHS

Molecular Pathogenesis

TAFAZZIN (formerly *TAZ*) encodes tafazzin, a transacylase located on the inner mitochondrial membrane. Tafazzin catalyzes the remodeling of the acyl chains of immature cardiolipin to a mature, predominantly tetralinoleylcardiolipin. Cardiolipin is important for high energy-requiring tissues such as cardiac muscle; in Barth syndrome, less mature cardiolipin is produced [Schlame et al 2002, Valianpour et al 2005]. The exact mechanism by which decreased tetralinoleylcardiolipin leads to the pathophysiology of Barth syndrome is unclear. However, cardiolipin is involved in maintaining mitochondrial structure and organizing mitochondrial super complexes and has an important role in apoptosis [Koshkin & Greenberg 2002, Brandner et al 2005, Gonzalvez & Gottlieb 2007].

Almost 45% of the genomic sequence of *TAFAZZIN* is represented by interspersed repeated sequences (SINES and LINES) and 76% of these (accounting for 35% of the *TAFAZZIN* genomic sequence) are *Alu* sequences [Ferri et al 2013]. Ferri et al [2013] postulate that because of the high content of repeat sequences in this gene, *TAFAZZIN* rearrangements (which may appear to be similar in different patients on the basis of deleted exons) may actually be recurrent *de novo* pathogenic variants.

Mechanism of disease causation. Loss of function

Table 9. Notable *TAFAZZIN* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000116.5 NP_000107.1	c.348C>T	p.Gly116= [1]	Causes exon skipping; infantile onset [Ferri et al 2016]. See Table 2.
	c.253insC	p.Arg85ProfsTer54	In a female w/Barth syndrome; see Female Heterozygotes [Avdjieva-Tzavella et al 2016]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Denotes silent (no change) in the amino acid

Chapter Notes

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