Disease 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 patient. Cardiomyopathy, which is almost always present before age five years, is typically dilated cardiomyopathy with or without endocardial fibroelastosis (EFE) or left ventricular noncompaction (LVNC); rarely it is hypertrophic cardiomyopathy (HCM). 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 non-progressive myopathy predominantly affects the proximal muscles, and results in early motor delays. Prepubertal growth delay is followed by a post-pubertal 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 suggested by typical clinical findings, a five- to 20-fold increase in urinary 3-methylglutaconic acid (3-MGC), and moderately increased urinary 3-methylglutaric acid and 2-ethylhydracrylic acid. The diagnosis is established in a male proband with either an increased monolysocardiolipin:cardiolipin ratio (if available) or detection of a TAZ pathogenic variant on molecular genetic testing.

Management. Treatment of manifestations: Standard heart failure medications are used for inpatient and outpatient care. Daily use of aspirin to help prevent clot formation and, thus reduce the risk of stroke in males with severe cardiac dysfunction and/or marked LVNC should be considered. The potential role of prophylactic antiarrhythmic medication or an implantable cardiac defibrillator has not been clarified. Cardiac transplantation has been successful when heart failure is severe and intractable. The treatment of neutropenia can include regular administration of granulocyte colony stimulating factor (G-CSF), administration of G-CSF during times of high risk only (e.g., surgery or infection), prophylactic antibiotics, and other preventative treatment strategies. Uncooked cornstarch given prior to bedtime has been recommended as a means of avoiding muscle protein loss overnight. Excessive fatigue and the specific cognitive profile warrant educational support during the early school-age years.

Prevention of secondary complications: Granulocyte-colony stimulating factor (G-CSF) or antibiotic prophylaxis to prevent recurrent infections can be considered; limiting episodes of necessary fasting (e.g., prior to surgery) and simultaneously providing intravenous glucose; monitoring serum potassium levels for hypokalemia during episodes of diarrhea and for hyperkalemia during administration of intravenous fluids containing potassium.

Surveillance: Monitor height and weight on a regular basis with consideration to Barth syndrome-specific growth patterns; consider at least annual standardized cardiac evaluation including EKG, ECG, and Holter monitoring; assess for a potentially serious arrhythmia in the presence of symptoms (e.g., palpitations, syncope), abnormal screening tests, or a family history of sudden death.

Agents/circumstances to avoid: The use of rectal thermometers in those with neutropenia; the use of succinylcholine, as non-depolarizing neuromuscular blockers could have a prolonged effect.

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.

**Pregnancy management:** Because of the increased risk for prenatal complications (e.g., intrauterine growth restriction, oligohydramnios, intrauterine ventricular dysfunction, hydrops fetalis), it seems prudent to recommend that pregnancies of male fetuses known to have Barth syndrome be managed by a high-risk maternal fetal obstetrician.

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

### Diagnosis

**Suggestive Findings**

Diagnosis of Barth syndrome should be suspected in male children with a combination of any of the following:

- At least one of the following cardiac findings:
  - Dilated cardiomyopathy ± endocardial fibroelastosis (EFE): 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 (LVNC): noncompacted left ventricular myocardium with prominent trabeculations and deep intertrabecular recesses that communicate with the ventricular cavity
  - Hypertrophic cardiomyopathy (HCM) (much less common): characterized by increased ventricular wall thickness
- Neutropenia
  - Defined as:
    - Mild neutropenia. Absolute neutrophil count (ANC) between 1000 and 1500 cells/µL;
    - Moderate neutropenia. ANC between 500 and 1000 cells/µL;
    - Severe neutropenia. ANC<500 cells/µL.
  - In a study of 83 males with Barth syndrome, the median ANC was 1100 cells/µL (range: 140-5400 cells/µL) [Dale et al 2013]. These findings are similar to those of a French cohort in which the median ANC was 1300 cells/µL (range: 0-6400 cells/µL) [Rigaud et al 2013]. In both studies, the ANC fluctuated, but without detectable periodicity.
- 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
- A family history consistent with X-linked inheritance, including recurrent pregnancy loss involving male fetuses [Steward et al 2010]

### Preliminary Testing

**Urine organic acids.** 3-methylglutaconic acid (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 (Table 1).


- In one study all 28 patients ranging in age from ten months to 30 years had elevated urine 3-MGC levels [Vernon et al 2014].
- In contrast, only eight of 16 individuals in a French cohort had elevated 3-MGC levels [Rigaud et al 2013].

3-methylglutaric acid and 2-ethylhydracrylic acid can be moderately elevated. [Kelley et al 1991].
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 1088 nmol/L ± 435 (range: 393-2326 nmol/L) [Vernon et al 2014]. (See Table 1.)

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

<table>
<thead>
<tr>
<th>Organic Acid</th>
<th>In Urine (μg/mg Cr)</th>
<th>In Plasma (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Barth Syndrome</td>
<td>Control</td>
</tr>
<tr>
<td>3-methylglutaconic acid</td>
<td>Avg: 44.6±25 (SD)</td>
<td>1088±435</td>
</tr>
<tr>
<td></td>
<td>↑5- to 20-fold</td>
<td>0-2y:6.6±2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2-12y:5.3±2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult: 3.7±1.8</td>
</tr>
<tr>
<td>3-methylglutaric acid</td>
<td>Moderately↑</td>
<td>Trace</td>
</tr>
<tr>
<td>2-ethylhydracrylic acid</td>
<td>6.7±25</td>
<td></td>
</tr>
</tbody>
</table>

1. Vernon et al [2013]  
2. Clarke et al [2013]  

Establishing the Diagnosis

The diagnosis of Barth syndrome is established in a proband with either an increased monolysocardiolipin:cardiolipin ratio (if available) or detection of a TAZ pathogenic variant on molecular genetic testing (see Table 2).

Monolysocardiolipin:cardiolipin ratio. Since the protein that is deficient in Barth syndrome is responsible for cardiolipin (CL) remodeling within the inner mitochondrial membrane, affected individuals have (in a variety of tissues):

- Increased monolysocardiolipins (MLCL);
- Decreased cardiolipins (specifically tetrainoleylcardiolipin, L4-CL).

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

Using a screening method in bloodspots, Kulik et al [2008] found that all males with Barth syndrome had an MLCL:CL ratio >0.40 and all controls had a ratio of <0.23. Using a cutoff of 0.30, they reported a sensitivity and specificity of 100%.

- The same group later validated a confirmatory method in cultured fibroblasts, lymphocytes, and skeletal muscle [Houtkooper et al 2009].
- In a 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].

Molecular Genetic Testing

One molecular genetic testing strategy is testing of TAZ, the only gene in which pathogenic variants are known to cause Barth syndrome (Table 2).

An alternative molecular genetic testing strategy is use of a multi-gene panel that includes TAZ and other genes of interest (see Differential Diagnosis). Note: The genes included and the methods used in multi-gene panels vary by laboratory and over time.

Table 2. Summary of Molecular Genetic Testing Used in Barth Syndrome
### Affected Males

<table>
<thead>
<tr>
<th>Method</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence analysis ^2</td>
<td>93.1%</td>
</tr>
<tr>
<td>Deletion/duplication analysis ^7</td>
<td>6.9%</td>
</tr>
</tbody>
</table>

### Heterozygous Females

<table>
<thead>
<tr>
<th>Method</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>91.7%</td>
</tr>
</tbody>
</table>

1. See Table A. Genes and Databases for chromosome locus and protein name. See Molecular Genetics for information on allelic variants.

2. Sequence analysis detects variants that are benign, likely benign, of unknown significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exonic or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

3. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation may require additional testing by deletion/duplication analysis.

4. Based on Stenson et al [2003] and Human Tafazzin (TAZ) Gene Mutation & Variation Database

5. Sequence analysis of genomic DNA cannot detect deletion of one or more exons or the entire X-linked gene in a heterozygous female.

6. These are estimates, as large-scale studies on carrier females have not been carried out.

7. Testing that identifies exonic or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

8. A single affected female was found to have a mosaic ring chromosome X, with a deletion of the Xq28 region containing TAZ.

### Genetically Related (Allelic) Disorders

Isolated left ventricular noncompaction has been associated with various mutations in TAZ [Bleyl et al 1997, Ichida et al 2001, Chen et al 2002]; however, this is a rare occurrence [Kenton et al 2004].

### Clinical Description

#### Natural History

Although Barth syndrome is classically characterized by cardiomyopathy, neutropenia, skeletal myopathy, prepubertal growth delay, and characteristic dysmorphic features, any given patient may not have all of these features.

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 cardiomyopathy 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.

In the French study of 11 males with echocardiograms available at diagnosis:
Seven had left ventricular noncompaction,
Six had dilated cardiomyopathy and hypertrophic cardiomyopathy,
Two had dilated cardiomyopathy,
One had hypertrophic cardiomyopathy.

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 French cohort, left ventricular size and mass increased during the first six months of life, then decreased until age two years, and then appeared to stabilize. Data were insufficient to characterize these parameters in older children.

**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 towards 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 French study, 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).

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 patients had normal ejection fraction and left ventricular diastolic volume. However, some patients 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. ECG abnormalities can include repolarization abnormalities and prolonged QTc intervals.

All 20 patients with ECGs 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 five instances of ventricular arrhythmia leading to cardiac arrest or placement of an internal defibrillator [Spencer et al 2005]:

- Five had normal QTc intervals.
- 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.

**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) <500 cells/µL at least once.

*Defined as follows:

- Mild neutropenia. ANC between 1000 and 1500cells/µL
- Moderate neutropenia. ANC between 500 and 1000cells/µL
- Severe neutropenia. ANC<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]. 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 1000 cells/µL could be due to the development of a chronic, substantial monocytosis [Kelley 2002], which has been reported in two recent studies:

- In the French study the median absolute monocyte count (AMC) was 1100 cells/µL (range: 500-4300 cells/µL).
- Vernon et al [2014] reported that the average AMC was 894 ± 449 cells/µL (range: 500-2400 cells/µL), with five of 17 affected males having monocyte counts at or above 1000 cells/µL.

Of note, hematologic parameters neither worsen nor improve with age [Dale et al 2013].

**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].

**Growth delay.** Between ages six and 36 months the 50th percentile for weight 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 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 (BMI) is below the fifth percentile in 44% of males, normal in 48%, and above the 95th percentile in 7%.

In males 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 visuo-spatial skills that is 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 patients 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, pre-term birth from 29 to 36 weeks occurred in nine of 65 males; birth weight was <2.5 kg in nine of 48 males.

In the French study, median birth weight was 2770 g (range: 2180-3730 g) and seven of 22 males had severe intrauterine growth restriction with birth weight below the third percentile.

**Survival.** 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 (the oldest living individual with a confirmed diagnosis) and mention anecdotally two affected males, one in his 40s and one in his 60s.

**Laboratory findings** that may be found in association with Barth syndrome:

- 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 patients 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 alipid 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 do not manifest the disease. Biochemical abnormalities have not been found in eight female carriers [Vernon et al 2014].

It is proposed that female carriers are healthy due to selection against cells with the mutated TAZ allele on the active X chromosome, based on the study of the X-chromosome inactivation pattern in 16 obligate carriers [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) which was not observed in 148 female controls.

The only female reported with Barth syndrome had biallelic changes in TAZ as a result of (1) a complete deletion of the paternal allele (associated with a ring X chromosome with a large deletion that included TAZ) and (2) a deletion of exons 1-5 in the maternal TAZ 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 TAZ allele.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known [Johnston et al 1997, Rigaud et al 2013].

Penetration

Although the question of the penetrance of Barth syndrome has never been formally evaluated, it is thought that males manifest complete penetrance, although with variable expressivity.

Female carriers with a normal 46,XX karyotype do not manifest the disease (see Clinical Description, Female heterozygotes).

Prevalence
As of 2013, 151 males with Barth syndrome were recorded worldwide.

- It is estimated that fewer than ten new patients are diagnosed with Barth syndrome in the United States each year, suggesting an incidence of 1:300,000-1:400,000 births [Kelley 2002].
- Clarke et al [2013] calculated an incidence potentially as high as 1:140,000 live births in South West England and South Wales.
- Rigaud et al [2013] estimated an incidence of 1.5 cases per million births (95% CI: 0.2-2.3) based on data from France between 1995 and 2008; they noted, however, that some patients may have been undiagnosed either due to a mild clinical course or sudden unexplained death.

Barth syndrome shows no ethnic or racial predilection, as it has been described throughout the world.

**Differential Diagnosis**

**Disorders in which excretion of 3-methylglutaconate (3-MGC) 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.

Classification of inborn errors of metabolism with 3-methylglutaconic aciduria as a discriminative feature has recently been updated [Wortmann et al 2013, Wortmann et al 2014] (Table 3).

Clinical features (Table 3) and biochemical findings (Table 4) of the 3-MGCA syndromes vary. Tissues with higher requirements for oxidative metabolism, such as the central nervous system and cardiac and skeletal muscle, are predominantly affected.

**Table 3. New Classification for Inborn Errors of Metabolism with 3-Methylglutaconic Aciduria as Discriminative Feature**
### 3-Methylglutaconic Aciduria: OMIM Phenotypic Series

**Disorder** | **Urinary Excretion** | **3-Hydroxyisovaleric Acid (3-HIV)**
---|---|---
3-methylglutaconyl-CoA hydratase deficiency | 500 to 1000 | Increased
TAZ defect (Barth syndrome) | Mild to moderate | Normal
OPA3 defect (Costeff syndrome) | 9-187 | Normal
DNAJC19 defect (DCMA syndrome) | Moderate | Normal
NOS 3-MGA-uria | Elevated to variable degrees | Normal
Normal controls | 3.2-7 | NA

1. The urinary excretion of 3-methylglutaric acid (3-MGA) correlates with protein intake, whereas in most individuals with other types of 3-MGCA the amount of 3-MGC in urine is not dependent on dietary leucine [Sweetman & Williams 2001].

2. Less than ten times the upper limit of normal

3. In 39 individuals [Elpeleg et al 1994]

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From Wortmann et al [2013]

DCMA = Dilated cardiomyopathy with ataxia; NOS= Not otherwise specified

1. In addition to 3-MGA-uria

See 3-Methylglutaconic Aciduria: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.
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 mutations can lead to isolated cardiomyopathy with left ventricular noncompaction include: *LDB3, ACTC1, MYH7, MIB1, PRDM16, TNNT2, TPM1,* and *MYBPC3*. 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 with a clear X-linked pattern of inheritance can point to Barth syndrome. Often, the most efficient way to determine the responsible gene is through molecular genetic testing using a multi-gene panel.

Left ventricular noncompaction 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 is an autosomal recessive form of severe congenital neutropenia. Klein et al [2007] identified homozygous mutations in *HAX1* (encoding HCLS1-associated protein X-1) in several individuals with Kostmann syndrome.
- Mutations in *G6PC3* (encoding glucose-6-phosphate 3) result in an autosomal recessive form of severe congenital neutropenia [Klein 2011].
- Benign familial neutropenia is an autosomal dominant form of congenital neutropenia with milder neutropenia and less severe symptoms.

**Note to clinicians:** For a patient-specific ‘simultaneous consult’ related to this disorder, go to [SimulConsult®](#), an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

### Management

#### Evaluations Following Initial Diagnosis

To establish the extent of disease and medical needs in an individual diagnosed with Barth syndrome, the following evaluations are recommended:

- Complete blood count and differential
- Echocardiogram
- ECG
- Plasma amino acids
- Medical genetics consultation

#### Treatment of Manifestations

**Management of heart failure.** There is no specific treatment for cardiac dysfunction or arrhythmia in Barth syndrome. Standard heart failure (HF) medications are used to improve symptoms, effect reverse remodeling of the ventricle, and improve ventricular function as measured by ejection fraction (EF).

These medications include ACE-inhibitors, beta blockers, and digoxin for typical outpatient management, and intravenous inotropes, including milrinone for inpatient management of acute decompensation.


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 (see Clinical Description, Natural History, Heart failure).

Aspirin should be considered for prevention of clot formation (and thus reduction in the risk for stroke) in males with severe cardiac dysfunction and/or marked LVNC. Suggested aspirin dose is 5 mg/kg daily for children and 81 to 325 mg daily for adults.

The potential role of prophylactic antiarrhythmic medication or implantable cardiac defibrillator for primary arrhythmia prevention has not been clarified.

Cardiac transplantation has been successful when heart failure is severe and intractable [Mangat et al 2007, Roberts et al 2012]; however, given the natural history of improving ventricular function after infancy, cardiac transplantation should be carefully considered.

Management of neutropenia. The treatment of neutropenia in children with Barth syndrome varies, including regular administration of granulocyte colony stimulating factor (G-CSF), administration of G-CSF during times of high risk only (e.g., surgery or infection), prophylactic antibiotics, and other preventative treatment strategies.

Early on, it was suggested that the administration of G-CSF during times of suspected or known bacterial infection may be effective in reducing the incidence of severe infections [Cox et al 1995]. The usual starting dose of G-CSF is 2-3 μg/kg/dose with a frequency of administration ranging from twice a week to every other day [Clarke et al 2013].

In 83 patients, 42 of whom had been treated with G-CSF, the median dose was 2.78 ± 0.78 (SEM) 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.

Of note, 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].

Nutrition. Uncooked cornstarch given prior to bedtime has been recommended as a means of avoiding muscle protein loss overnight. Specific dosing according to age and weight can be obtained from the Barth Syndrome Foundation [Avery 2006].

Educational support in school. 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].

Physical therapy. The goal should be attainment of development milestones and functional outcomes while at the same time monitoring cardiovascular status [Jarvis et al 2001].

Prevention of Secondary Complications

Antibiotic prophylaxis has been used to prevent recurrent infections. In the French study of 22 patients, four received antibiotic prophylaxis [Rigaud et al 2013].

As males with Barth syndrome may be predisposed to hypoglycemia, episodes of fasting (such as prior to surgery) should be as short as possible and accompanied by intravenous glucose infusion [Schlame 2013].

Potassium issues:

- Increased risk for hypokalemia. Because males with Barth syndrome can rapidly become potassium-depleted during a gastrointestinal illness (as would anyone with marked muscular hypoplasia) [Kelley 2002], serum potassium levels should be monitored during episodes of diarrhea.

- Increased risk for hyperkalemia. Because males with Barth syndrome lack normal muscle “reservoir” for potassium, they can rapidly develop hyperkalemia when given intravenous fluids containing potassium [Kelley 2002]; thus, serum potassium levels should be monitored during the administration of intravenous fluids.
Because of their growth delay, males with Barth syndrome have lower than normal caloric requirements, and attempts to induce growth by overfeeding can lead to chronic diarrhea [Kelley 2002].

**Surveillance**

Height and weight should be monitored on a regular basis with consideration of Barth syndrome-specific growth patterns [Roberts et al 2012].

Standardized cardiac evaluation including echocardiogram, ECG, and Holter monitoring should be considered at least yearly [Spencer et al 2005].

A low threshold for performing an electrophysiologic study to assess for a potentially serious arrhythmia is appropriate, especially in the presence of symptoms such as palpitations and syncope, abnormal arrhythmia screening tests, or a family history of sudden death [Spencer et al 2005].

**Agents/Circumstances to Avoid**

Avoid the following:

- The use of rectal thermometers in those with neutropenia
- The use of succinylcholine, as non-depolarizing 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 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 TAZ pathogenic variant in the family is not known, testing by means of MLCL:CL ratio (if available) can be used to clarify the genetic status of at-risk male sibs.
- 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 completely 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 seems 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 for access to 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
Coenzyme Q10. The rationale behind the use of coenzyme Q10 is based on the fact that both coenzyme Q10 and 3-methylglutaconic acid (3-MGC) can be produced from dimethylallyl pyrophosphate (DMAPP), an intermediate in the synthesis of cholesterol. Thus, if coenzyme Q10 production is impaired, more DMAPP could potentially be shunted towards the production of 3-MGC [Costeff et al 1998]. However, no formal study has been undertaken to prove the efficacy of coenzyme Q10 therapy in males with Barth syndrome. In a study of 15 males with Barth syndrome, three took coenzyme Q10 [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 low 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face 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 proband

- The father of an affected male will not have Barth syndrome nor will he be a carrier of the TAZ pathogenic variant.
- In a family with more than one affected individual, the mother of an affected male is an obligate carrier. Note: If a woman has more than one affected child and no other affected relatives and if the TAZ pathogenic variant cannot be detected in her leukocyte DNA, she 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 carrier or the TAZ mutation in the affected male may have occurred de novo, and, thus, the mother is not a carrier. In the experience of one laboratory, five of 42 mothers of boys with Barth syndrome were found not to carry their son’s pathogenic variant in their leukocyte DNA [Kirwin et al 2007].

Sibs of a proband

- The risk to sibs depends on the carrier status of the mother.
- If the mother of the proband has a TAZ pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the TAZ pathogenic variant will be affected; females who inherit the TAZ pathogenic variant will be carriers and will not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the TAZ pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of maternal germline mosaicism.
Offspring of a male proband. Affected males pass the TAZ pathogenic variant to all of their daughters and none of their sons.

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

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the TAZ pathogenic variant in the family.

Note: (1) Carriers are females who are heterozygotes for this X-linked disorder and usually do not develop clinical findings related to the disorder (see Clinical Description, Natural History, Female heterozygotes). (2) Identification of female heterozygotes requires either (a) prior identification of the TAZ pathogenic variant in the family or, (b) 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.

In Barth syndrome female carriers usually demonstrate skewed X-chromosome inactivation due to preferential inactivation of the X-chromosome with the TAZ pathogenic variant. Thus, if the family-specific TAZ pathogenic variant cannot be detected or if molecular genetic testing of TAZ is not clinically available, X-chromosome inactivation studies may be helpful in determining if an at-risk female relative is a carrier; however, the finding of random X-chromosome inactivation does not rule out carrier status.

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 carrier status, and discussion of the availability of prenatal 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 carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

If the TAZ pathogenic variant has been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing for this disease/gene or custom prenatal testing.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be an option for some families in which the TAZ pathogenic variant has been identified.

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:** bsinfo@barthsyndrome.org
  www.barthsyndrome.org

- **Save Babies Through Screening Foundation, Inc.**
  P. O. Box 42197
  Cincinnati OH 45242
  **Phone:** 888-454-3383
  **Email:** email@savebabies.org
  http://www.savebabies.org/

- **Organic Acidemia Association**
  PO Box 1008
  Pinole CA 94564
  **Phone:** 510-672-2476
  **Fax:** 866-539-4060 (toll-free)
  **Email:** carolbarton@oaanews.org
  www.oaanews.org

- **European Society for Immunodeficiencies (ESID) Registry**
  Dr. Gerhard Kindle
  University Medical Center Freiburg Centre of Chronic Immunodeficiency
  UFK, Hugstetter Strasse 55
  79106 Freiburg
  Germany
  **Phone:** 49-761-270-34450
  **Email:** registry@esid.org
  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**

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Chromosomal Locus</th>
<th>Protein Name</th>
<th>Locus Specific</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAZ</td>
<td>Xq28</td>
<td>Tafazzin</td>
<td>TAZbase: Mutation registry for Barth syndrome Resource of Asian Primary Immunodeficiency Diseases (TAZ) Human Tafazzin (TAZ) Gene Mutation &amp; Variation Database TAZ database</td>
<td>TAZ</td>
</tr>
</tbody>
</table>

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) to which links are provided, click here.

**Table B. OMIM Entries for Barth Syndrome (View All in OMIM)**

- 300394 TAFAZZIN; TAZ
- 302060 BARTH SYNDROME; BTHS

**Gene structure.** The longest transcript variant of *TAZ* (NM_000116.3) (previously known as G4.5, EFE2) contains 11 exons. For a detailed summary of gene and protein information, see Table A, **Gene Symbol**.
Alternative splicing produces a number of different mRNAs [Bione et al 1996, Vaz et al 2003]. These include the full-length isofrom (NM_000116.3, the canonical/reference sequence), isoforms that are missing exon 5, exon 7, and both exons 5 and 7, and other less well described isoforms.

The isoform missing only exon 5 (Δexon 5) was found to be functional in yeast complementation studies [Vaz et al 2003]. The Δexon 5 variant is the major product of tafazzin expression in humans [Lu et al 2004, Gonzalez 2005].

Interestingly, almost 45% of the genomic sequence of TAZ is represented by interspersed repeated sequences (SINES and LINES) and 76% of these (accounting for 35% of the TAZ 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, TAZ rearrangements (which may appear to be similar in different patients on the basis of deleted exons) may actually be recurrent de novo mutations.

Initially, when mutations in TAZ were implicated as the cause of Barth syndrome, it was suggested that it encoded several different proteins depending on which 5’ end and which of the differentially spliced exons were in the transcript [Bione et al 1996]. In particular, it was thought that initiation of transcription was upstream of exons 1 and 3, leading to the hypothesis that mutations in exons 1 or 2 would produce a normal “short” mRNA and, thus, a milder phenotype. However, subsequent studies revealed only one site for initiation of transcription [Gonzalez 2005], and no significant difference in the phenotype with exon 1 or 2 pathogenic variants from that of pathogenic variants elsewhere [Spencer et al 2006].

Normal gene product. 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 tetrailinoleylcardiolipin. The full-length tafazzin protein contains 292 amino acids (NP_000107.1) and has a molecular weight of 33459 daltons. It contains a transmembrane domain located at amino acids 15-35, and a phosphate acyltransferase domain at amino acids 63-217 [UniProt Consortium 2014; full text].

Abnormal gene product. 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 tetrailinoleylcardiolipin 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].

References

Literature Cited


Chapter Notes

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