

Genetics of Barth Syndrome

Gene Responsible for Barth syndrome:	Tafazzin (<i>TAZ</i> or <i>G4.5</i>)
Mode of Inheritance:	X-linked recessive
Diagnostic Genetic Test available:	Yes

Inside the cells

Every cell in the body contains 46 chromosomes, each of which is made up of hundreds or thousands of genes. The chromosomes are organized into 23 pairs, one chromosome of each pair coming from each parent. The two chromosomes of each pair have the same size and contain the same number of genes in both men and women for the first 22 pairs, but the 23rd pair, the “sex chromosomes,” is different. For this pair, females have two equally matched “X” chromosomes, whereas males have one X chromosome and a much smaller “Y” chromosome, which contains only a few of the genes on the paired X-chromosome plus a few genes that only occur on the Y-chromosome. The gene for Barth syndrome is located at the Xq28 position on the long arm of the X-chromosome, which does not have a matching region on the Y chromosome. This gene is called “*Tafazzin*” (“*TAZ*” or “*G4.5*”) and serves as the code for making *Tafazzin* protein. Mutations in the *TAZ* gene lead to alterations in the structure and function of *Tafazzin* protein or in the amount of protein produced. Although we do not know all of the functions of *Tafazzin* protein, it is clear that mutations that alter the *Tafazzin* protein can cause Barth syndrome.

Inheritance

The inheritance of Barth syndrome follows an “X-linked” (or “sex-linked”) recessive pattern ^{Figure 1}, in which females can be carriers of a *TAZ* mutation but only males will have the disease. Because females have two copies of the X chromosome, they also have two copies of every gene on the X chromosome. Because *TAZ* mutations are very rare, a female who inherits one chromosome carrying a mutation of the gene for Barth syndrome from one parent will almost always inherit a normal X chromosome from the other parent. In all Barth mothers who carry a *TAZ* mutation on one of their two X-chromosomes, the normal *TAZ* gene on the other X chromosome provides enough *TAZ* function to prevent any disease. For this reason, a *TAZ* mutation in a female is termed a “recessive” mutation. In other words, although the female who carries a recessive *TAZ* mutation can pass the abnormal *TAZ* gene on to her children, she will not show any symptoms of Barth syndrome because of the protective effect of the normal *TAZ* gene on the other X-chromosome.

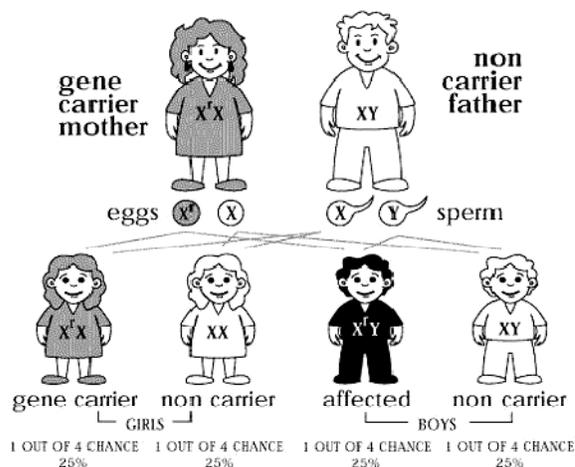


Figure 1

Unlike females who carry two copies of *TAZ* on their matched X-chromosomes, males have only one copy of the *TAZ* gene because they have only one X-chromosome. This is because a male who inherits from his mother an X-chromosome with one *TAZ* gene inherits from his father a shorter Y chromosome that lacks a copy of the *TAZ* gene. With no normal *TAZ* gene on the Y chromosome to compensate for a *TAZ* mutation inherited on the mother’s X chromosome, all males with a *TAZ* mutation will have clinical signs of Barth syndrome.

When a mother is a carrier of a *TAZ* mutation on one of her two X chromosomes, there is a 50% chance in any pregnancy that she will pass the X-chromosome with the *TAZ* mutation onto the child. If the child who inherits the *TAZ* mutation is a girl, she will be a carrier of Barth syndrome, and, like her mother, be able to pass the *TAZ* mutation on to her own children. However, also like her mother, she will not show symptoms of Barth syndrome. If the child is a boy, there is a 50% chance he will inherit *TAZ* mutation and have Barth syndrome and a 50% chance he will inherit only the X chromosome with the normal *TAZ* gene and, therefore, not have Barth syndrome. If the male inherits the *TAZ* mutation and has Barth syndrome, all of his daughters will be carriers, but

none of his sons will have Barth syndrome. This is because the X- and Y-chromosomes are the sex-determining chromosomes, and all children who inherit his Y-chromosome (with no *TAZ* gene) from him will be boys, and all children who inherit the X-chromosome with a *TAZ* mutation will be girls. A genetic counselor can assist families in understanding these potential outcomes.

Possible pregnancy outcomes:

A new mutation:

When a *TAZ* mutation for Barth syndrome cannot be detected in either parent, this is considered a new mutation. New mutations can be sporadic or they can be a result of “gonadal mosaicism.” Gonadal mosaicism is the rare occurrence of a genetic mutation in a proportion of the eggs or sperm of an individual as a result of a random mutation that occurs during the development of eggs and sperm. The individual does not have any signs of the disorder, and the mutation would not be detected by a blood test because it is in only the egg or sperm cells. However, if one of the egg or sperm cells is used to conceive a child, that child will have the mutation in all cells.

Definitions:

Cell: The smallest unit of living organism from which all tissues are made. Except for mature red cells, all cells contain complete copies of all 46 chromosomes. Cells are highly variable and specialize into many different types of cells and tissues, but all cells must at some stage use genes as instructions to make essential proteins.

Chromosome: The genetic structure of cells that contains the DNA. Each chromosome is a single strand of DNA that encodes from hundreds to thousands of separate genes. All 23 pairs of chromosomes reside in the cell nucleus.

Gene: The physical and functional unit of heredity located in a specific position on a particular chromosome. Most human genes are given a letter name, such as “*TAZ*,” and written by convention in italics.

Genetic counselor: A person who will gather genetic and medical information about a family using a pedigree and will help the family learn about potential risks for others to inherit the gene for Barth syndrome. This is done by taking an in depth interview and creation of a family pedigree. A genetic counselor can also help the family understand and handle the many psychosocial issues surrounding a genetic diagnosis in a family.

Geneticist: A physician trained to identify and diagnose genetic conditions. A geneticist will obtain a complete medical history, conduct a thorough physical examination, and recommend testing to identify or confirm a genetic diagnosis. A geneticist will help identify other family members at risk of being a carrier or affected by Barth syndrome. This information can be used to help a high-risk obstetrician provide appropriate pregnancy monitoring and arrange for delivery of an affected boy at a high-risk neonatal center.

Mutation: A heritable change in the structure of a gene.

Pedigree: A record of ancestral lines. A medical pedigree includes medical history and information about inheritance of a genetic disorder. Below is an example of a pedigree for an X-linked recessive condition, like Barth syndrome, highlighting several carriers and affected individuals. ^{Figure 2}

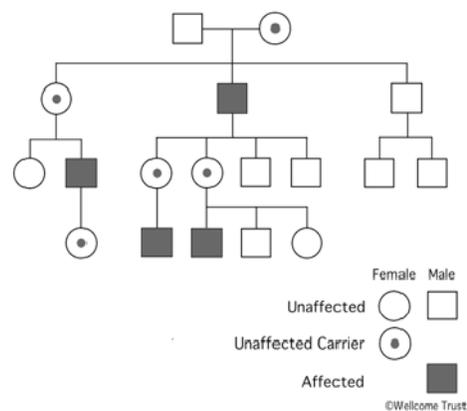


Figure 2

Genetics Fact Sheet

The Barth Syndrome Foundation (www.barthsyndrome.org)

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