HBA1/HBA2 Genes and Alpha Thalassemia

Description

Alpha thalassemia is an inherited blood disorder that reduces the production of hemoglobin and affects the blood's ability to carry oxygen. Hemoglobin is the protein in red blood cells that carries oxygen to cells throughout the body. **There are two types of alpha-thalassemia that cause health problems; - hemoglobin H (HbH) disease and hemoglobin Bart hydrops fetalis (Hb Bart) syndrome.**

HbH disease is the milder type and affected individuals experience mild to moderate anemia (too few red blood cells) that causes pale skin, yellowing of the eyes and skin (jaundice), weakness, fatigue, spleen and liver problems. Some affected individuals also have characteristic bone changes such as overgrowth of the upper jaw and an unusually prominent forehead or upper jaw. Symptoms typically appear in childhood and survival is into adulthood. Some individuals with HbH disease may not require any special medical treatment and some may require regular blood transfusions.

The more severe type, Hb Bart syndrome is characterized by hydrops fetalis and is generally diagnosed during pregnancy because it causes fluid to build up in the body before birth.

Additional signs and symptoms can include severe anemia, an enlarged liver and spleen (hepatosplenomegaly), heart defects, and abnormalities of the urinary system or genitalia. As a result of these serious health problems, most babies with this condition are stillborn or die soon after birth. Hb Bart syndrome can also cause serious complications for women during pregnancy, including dangerously high blood pressure with swelling (preeclampsia), premature delivery, and abnormal bleeding.

Alpha-thalassemia is caused by pathogenic variants on the HBA1 and HBA2 genes.

Frequency - How Often Does Alpha Thalassemia Occur?

Alpha thalassemia is a fairly common blood disorder worldwide. **Alpha-thalassemia is most frequent in Southeast Asian populations,** where the incidence of HbH disease is between 4 and 20 per 1000 births, and the incidence of Hb Bart syndrome is between 0.5 and 5 per 1000 births. Alpha thalassemia also occurs frequently in people from Mediterranean countries, Africa, the Middle East, India, and Central Asia.

Normal Function of the HBA1 and HBA2 Genes And Genetic Changes

Alpha thalassemia typically results from deletions involving the HBA1 and HBA2 genes. Both of these genes provide instructions for making a protein called alpha-globin, which is a component (subunit) of hemoglobin.

Each person has two copies of the HBA1 gene and two copies of the HBA2 gene in each cell. Each copy is called an allele. For each gene, one allele is inherited from a person's father, and the other is inherited from a person's mother. As a result, there are four alleles that produce alpha-globin. The different types of alpha thalassemia result from the loss of some or all of these alleles.

Hb Bart syndrome, the most severe form of alpha thalassemia, results from the loss of all four alpha-globin alleles. **HbH disease is caused by a loss of three of the four alpha-globin alleles.** In these two conditions, a shortage of alpha-globin prevents cells from making normal hemoglobin. Instead, cells produce abnormal forms of hemoglobin called

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hemoglobin Bart (Hb Bart) or hemoglobin H (HbH). These abnormal hemoglobin molecules cannot effectively carry oxygen to the body's tissues. The substitution of Hb Bart or HbH for normal hemoglobin causes anemia and the other serious health problems associated with alpha thalassemia.

Two additional variants of alpha thalassemia are related to a reduced amount of alpha-globin. Because cells still produce some normal hemoglobin, these variants tend to cause few or no health problems. A loss of two of the four alpha-globin alleles results in alpha thalassemia trait. People with alpha thalassemia trait may have unusually small, pale red blood cells and mild anemia. A loss of one alpha-globin allele is found in alpha thalassemia silent carriers. These individuals typically have no thalassemia-related signs or symptoms.

Pattern of Inheritance - How Is Alpha Thalassemia Inherited?

The inheritance of alpha thalassemia is complex. Alpha-thalassemia is inherited in an autosomal recessive manner. Normally two alpha hemoglobin genes are inherited from each parent, one HBA1 gene and one HBA2 gene, for a total of four alpha hemoglobin genes. **If a parent is missing one or two of these genes or if both parents are missing at least one alpha-globin allele, then their children are at risk of having Hb Bart syndrome, HbH disease, or alpha thalassemia trait. The precise risk depends on how many alleles are missing and which combination of the HBA1 and HBA2 genes is affected.** HbH disease results from inheriting only one good alpha hemoglobin gene. Hb Bart syndrome results from inheriting no alpha hemoglobin genes.

What Does It Mean To Be A Carrier?

Carriers of alpha-thalassemia may have mild anemia or no medical issues. The risk of having a child affected with alpha-thalassemia is increased; however, the severity varies based on the type of pathogenic variants present. Testing of reproductive partners with consideration to their ethnicity is recommended for carriers of alpha-thalassemia.

Carrier Rates

Ethnicity	Detection Rate	Carrier Frequency
African/African American	>99%	1 in 1000
East Asian	>99%	1 in 16
General Population	>99%	1 in 1000
Northern European Caucasian	>99%	1 in 1000
South Asian	>99%	1 in 2
Southeast Asian	>99%	1 in 7

Clinician References

OMIM [Alpha-thalassemia: 604131] (http://www.ncbi.nlm.nih.gov/omim)

Gene Reviews: Alpha-thalassemia (http://www.ncbi.nlm.nih.gov/books/NBK1116/)

Patient and Family Resources

Genetics Home Reference: Alpha-thalassemia (http://ghr.nlm.nih.gov/)

Genetic Alliance: Alpha-thalassemia (http://www.diseaseinfosearch.org/)