

Thalassemia

Thalassemia is an inherited blood related disorder due to absent or reduced production of hemoglobin, a protein present in red blood cells responsible for carrying oxygen through the body. Each red blood cell may contain between 240 and 300 million molecules of hemoglobin. A hemoglobin molecule has two sub-units commonly referred to as alpha and beta. Both sub-units are necessary to bind oxygen and deliver it to cells and tissues in the body. The gene locus controlling the production of alpha chains is called the alpha globin gene cluster, and similarly the beta globin gene cluster produces beta chains. A lack of a particular subunit determines the type of the resulting thalassemia (alpha or beta).

Thalassemia is derived from the Greek word "*thalassa*" meaning "the sea" because the condition was first described in populations living near the Mediterranean Sea. However, it is now very well known that alpha- and beta-thalassemia are the most common inherited single-gene disorders in the world with the highest prevalence in areas where malaria was or still is endemic (Mediterranean Basin, Australasia, the Americas, and Africa). In many parts of the world, thalassemia still represents a major public health concern.

In alpha-thalassemia, mutations in alpha-globin genes can give rise to a range of clinical presentations. The loss of one gene diminishes the production of the alpha chain only slightly. The loss of two genes produces a condition with small red blood cells, and at most a mild anemia. This is, in all circumstances, compatible with life. The loss of three alpha genes results in HbH disease characterized by anemia, liver and spleen enlargement, mild jaundice, and sometimes bone deformities. The loss of all four alpha genes produces Hemo-

globin Barts Hydrops Fetalis, a condition that is incompatible with life leading to fetal death.

In beta-thalassemia, symptoms occur starting from six to 24 months of age. The severity of the damage depends on the type of the mutation. Some mutations (beta-zero) prevent any formation of beta chains; others (beta-plus) allow some beta chain formation to occur. In the severe form of the disease, the bone marrow expands as it attempts to keep pace with the perceived need for new red blood cells, setting the stage for moderate-to-severe skeletal deformities and pain. If left untreated, affected infants fail to thrive and become progressively pale. Feeding problems, diarrhea, irritability, recurrent bouts of fever, leg ulcers, osteoporosis, thrombotic complications, and progressive expansion of the abdomen caused by liver and spleen enlargement may occur.

Risk Factors

People with Mediterranean (including North African), Middle Eastern, or Southeast Asian ancestry are at higher risk of being carriers of alpha- or beta-thalassemia than are other populations.

Beta-thalassemia, in most cases, requires inheriting two defective beta-globin genes from parents to trigger the disease. If only one defective copy of the beta-globin gene is inherited, no symptoms may appear; this condition is called beta-thalassemia minor or beta-thalassemia trait. The inheritance of alpha-thalassemia, however, is more complex because of the involvement of one or more genes. A positive family history of alpha- or beta-thalassemia is an important indication for an individual to seek consultation as he/she might be at high risk of carrying the disease.

Diagnosis and Management

Diagnosis of thalassemia can be made as early as 9-11 weeks in pregnancy using procedures such as chorionic villi sampling. Analyzing the amniotic fluid may be carried out at 16-20 weeks of pregnancy. Individuals can also be tested for thalassemia through routine blood counts.

Early treatment of beta-thalassemia has proved to be very effective in improving the quality of life of patients. Long term transfusion support is the conservative approach for beta-thalassemia patients to alleviate anemia. Frequent blood transfusions usually lead to iron overload that is countered by iron chelation therapy to prevent damage to the internal organs. In recent years, bone marrow transplantation has shown promise in many patients, where a successful transplant can eliminate their dependency on blood transfusions.

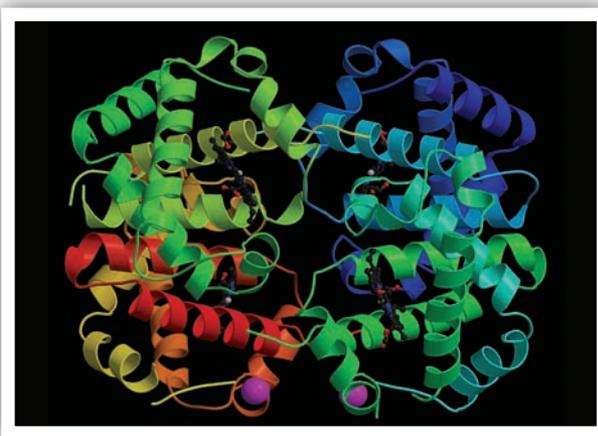
Untreated beta thalassemia eventually leads to death usually by heart failure; therefore, genetic testing, counseling, and prenatal diagnosis are very important in the prevention, management, and treatment of this disease. In some Mediterranean countries, such as Cyprus, long-established control programs have achieved 80-100% prevention of newly affected births.

Thalassemia in Arab Populations

Alpha- and beta-thalassemia are endemic in almost all Arab countries probably due to the historical presence of malaria in the region and the high level of consanguinity. Carrier frequencies of beta-thalassemia vary from 1% to 5% while prevalence data for alpha-thalassemia are scant. However, a recent genetic study in the United Arab Emirates estimates that alpha-thalassemia carrier rate may be as high as 49%.

The molecular basis of beta-thalassemia has been extensively studied in various Arab countries. A total of more than 60 mutations in the beta-globin gene have been reported in Arab patients with beta-thalassemia. A recent genetic study in Dubai demonstrated the presence of 50 mutations in the UAE population. As expected, each Arab country has its own characteristic spectrum of mutations. While some mutations appear in most countries, others seem to be regionally restricted paving the way to studies on their historical origins.

Extensive efforts have been taken to reduce the rates of thalassemia in Arab populations. Screening of newborns, children, and obligatory screening of couples before their marriage have been very effective. In Palestine, for instance, adoption of obligatory screening of couples for beta-thalassemia before the issue of a marriage certificate has decreased the number of marriages of carrier couples, which in turn has led to a reduction in the birth of children with this disease. In the Emirate of Dubai, the launch of a prenatal diagnosis program in 2005 has been extremely successful and resulted in a dramatic reduction in the birth of affected babies with beta-thalassemia major.



3-D Structure of Hemoglobin.