

## Beta-Thalassemia – an Overview

### Disease Summary

Beta thalassemia is a typically autosomal recessive form of severe anemia. Incidence is estimated at 1:100,000 worldwide and at 1:10,000 in the European Union, reflecting the increased prevalence in Mediterranean populations.<sup>1</sup> Based on disease severity, three types of beta thalassemia are distinguished: Beta thalassemia major (also known as Cooley's anemia), beta thalassemia intermedia, and beta thalassemia minor (also known as beta thalassemia trait). Beta thalassemia minor is mostly asymptomatic, but may be accompanied by mild anemia.<sup>1</sup> In contrast, beta thalassemia major is characterized by infancy-onset severe anemia and requires life-long blood transfusions for survival.<sup>1,2</sup> Additional manifestations of untreated beta thalassemia major are hepatosplenomegaly, jaundice, growth retardation, poor musculature, leg ulcers, development of masses from extramedullary hematopoiesis, and bone deformities that result from expansion of the bone marrow.<sup>1,2</sup> Primary complications of transfusion-treated beta thalassemia major are secondary to transfusion-related iron overload that leads to organ damage, with iron-overload induced dilated or restrictive cardiomyopathy presenting the major cause of death.<sup>1,2</sup> In addition, osteoporosis is common among treated beta thalassemia patients.<sup>1,2</sup>

Manifestations of beta thalassemia intermedia are similar, but less severe, and onset is typically later than in the major form. The intermediate form requires only intermittent blood transfusions for survival.<sup>1,2</sup> Main complications are again due to organ damage secondary to iron over-

load, which in this case may be caused mainly by increased intestinal iron absorption triggered by inefficient erythropoiesis.<sup>1,2</sup> Morbidity and mortality from iron overload can be reduced by use of iron chelating agents.<sup>2</sup> Bone marrow or cord blood transplantation offers a cure, especially if performed before lasting organ damage has developed.<sup>1,2</sup> Early diagnosis allows timely treatment initiation. Distinction between the major and intermediate forms is also important to avoid both unnecessary transfusions and unnecessary delay of required regular transfusions, which can increase the risk that the patient may develop multiple antibodies against donor red blood cells.<sup>1</sup>

Thalassemias are caused by an imbalance of the two types of protein subunits of hemoglobin.<sup>3</sup> In beta thalassemia, mutations in the gene *HBB* lead to reduced production of stable beta globin, one of the two protein components of the adult (ie, postnatal) form of hemoglobin.<sup>3</sup> This results in decreased hemoglobin and excess alpha globin, the second protein component of adult hemoglobin. The excess alpha globin chains form precipitates that damage the developing red blood cells and lead to ineffective erythropoiesis.<sup>1</sup> Mutations in *HBB* that cause complete absence of stable beta globin (eg, nonsense and frameshift) are known as beta<sup>0</sup> mutations.<sup>2</sup> *HBB* mutations that reduce but do not completely abolish production of stable beta globin (eg, promotor or splice-site mutations) are beta<sup>+</sup> mutations.<sup>2</sup>

Beta thalassemia is typically diagnosed based on the presence of microcytic and

hypochromic red blood cells as well as nucleated red blood cells (erythroblasts) in a peripheral blood smear and on reduced levels of adult hemoglobin (HbA).<sup>2</sup> Genetic testing can confirm a diagnosis and help to distinguish the major from the intermediate form of beta thalassemia.<sup>2</sup> Once the mutations causing beta thalassemia in a specific family have been

determined, genetic testing for these mutations can identify presymptomatic individuals among the patient's relatives and help to predict disease severity, facilitating early initiation of the most effective treatment.

For additional information, see Tables 1-2 below and references 1-3.

**Table 1: Disease Facts about Beta-thalassemia (based on references 1-3)**

<b>Disease Fact</b>	<b>Beta thalassemia</b>
<b>MIM* number</b>	141900, 187550, 603902
<b>Estimated Prevalence</b>	1:100,000 worldwide; higher in populations with a high percentage of individuals of Mediterranean origins (eg, 1:10,000 in European Union)
<b>Average Age at Diagnosis</b>	Infancy (beta thalassemia major) Young childhood to adulthood (beta thalassemia intermediate)
<b>Typical Symptoms</b>	<p><b>Presenting symptoms of beta thalassemia major:</b> Feeding problems, diarrhea, irritability, recurrent fever, progressive enlargement of the abdomen caused by splenomegaly, mild jaundice</p> <p><b>Symptoms of untreated beta thalassemia major</b> Growth retardation, pallor, jaundice, brown pigmentation of the skin, poor musculature, genu valgum, hepatosplenomegaly, leg ulcers, masses from extramedullary hematopoiesis, skeletal changes such as deformities of the long bones of the legs and characteristic craniofacial changes, osteoporosis</p> <p><b>Symptoms of transfusion-treated thalassemia major</b> Hypersplenism, venous thrombosis, osteoporosis, complications of transfusion-related iron overload</p> <p><b>Symptoms of beta thalassemia intermedia</b> Pallor, jaundice, cholelithiasis, liver and spleen enlargement, moderate to severe skeletal changes, leg ulcers, extramedullary masses of hyperplastic erythroid marrow, tendency to develop osteopenia and osteoporosis, and thrombotic complications, complications of iron overload from increased gastrointestinal iron absorption</p> <p><b>Complications secondary to iron overload</b> In children : growth retardation, failure of sexual maturation In adults: dilated cardiomyopathy, liver fibrosis and cirrhosis, diabetes mellitus, insufficiency of the parathyroid, thyroid, pituitary, and, less commonly, adrenal glands</p>
<b>Therapy</b>	<p>Blood transfusion</p> <p>Iron chelation to ameliorate transfusion-related iron overload</p> <p>Hydroxyurea</p> <p>Splenectomy</p> <p>Folic acid replacement</p> <p>Bone marrow or cord blood transplantation</p>

\*MIM: Mendelian Inheritance in Man, see <http://www.ncbi.nlm.nih.gov/omim>

**Table 2: Molecular Genetics of Beta thalassemia (based on references 1-3)**

<b>Gene (Protein)</b>	<b>Transmission</b>	<b>Mutation type</b>	<b>Penetrance</b>	<b>Comments</b>
HBB (hemoglobin beta)	Autosomal recessive	Loss-of-function	High, but disease severity may vary based on type of mutation and modifying mutations in other genes	In rare case, inheritance can be dominant.

## References

1. Galanello R and Origa R (2010) Beta-thalassemia. Orphanet Journal of Rare Diseases 5:11
2. Cao A and Galanello R. Beta Thalassemia. GeneReviews. <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gen&part=b-thal> Accessed 080110
3. Thein SW (2005) Genetic modifiers of  $\beta$ -thalassemia. Haematologica 90:649-60.