



## Beta-Thalassemia

Synonyms: Cooley's Anemia, Mediterranean Anemia

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## Summary

### Clinical characteristics

Beta-thalassemia ( $\beta$ -thalassemia) has two clinically significant forms,  $\beta$ -thalassemia major and  $\beta$ -thalassemia intermedia, caused by absent or reduced synthesis of the hemoglobin subunit beta (beta globin chain).

Individuals with  $\beta$ -thalassemia major present between ages six and 24 months with pallor due to severe anemia, poor weight gain, stunted growth, mild jaundice, and hepatosplenomegaly. Feeding problems, diarrhea, irritability, and recurrent bouts of fever may occur. Treatment with regular red blood cell transfusions and iron chelation therapy allows for normal growth and development and improves prognosis. Long-term complications associated with iron overload include stunted growth, dilated cardiomyopathy, liver disease, and endocrinopathies.

Individuals with  $\beta$ -thalassemia intermedia have a more variable age of presentation due to milder anemia that does not require regular red blood cell transfusions from early childhood. Additional clinical features may include jaundice, cholelithiasis, hepatosplenomegaly, skeletal changes (long bone deformities, characteristic craniofacial features, and osteoporosis), leg ulcers, pulmonary hypertension, extramedullary masses of hyperplastic erythroid marrow, and increased risk of thrombotic complications. Individuals with  $\beta$ -thalassemia intermedia are at risk for iron overload secondary to increased intestinal absorption of iron as a result of dysregulation of iron metabolism caused by ineffective erythropoiesis.

### Diagnosis/testing

The diagnosis of  $\beta$ -thalassemia is established in a proband older than age 12 months by identification of microcytic hypochromic anemia, absence of iron deficiency, anisopoikilocytosis with nucleated red blood cells on peripheral blood smear, and decreased or complete absence of hemoglobin A (HbA) and increased hemoglobin A<sub>2</sub> (HbA<sub>2</sub>) and often hemoglobin F (HbF) on hemoglobin analysis. Identification of biallelic pathogenic variants in *HBB* on molecular genetic testing can establish the diagnosis in individuals younger than age 12 months who have a positive or suggestive newborn screening result and/or unexplained microcytic hypochromic anemia with anisopoikilocytosis and nucleated red blood cells on peripheral blood smear.

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## Management

*Targeted therapies:* For  $\beta$ -thalassemia major, hematopoietic stem cell transplantation (HSCT), cord blood transplantation from a related donor, or autologous HSCT with gene therapy.

*Supportive care:* For  $\beta$ -thalassemia major, regular red blood cell transfusions with iron chelation therapy (e.g., deferoxamine B, deferiprone, deferasirox). Transfusion requirements may be reduced with the use of luspatercept. Anticoagulation for unprovoked venous thromboembolism; cholecystectomy for biliary colic; additional treatments for osteoporosis include hormone replacement therapy, vitamin D supplementation, regular physical activity, and bisphosphonates.

For  $\beta$ -thalassemia intermedia, splenectomy, folic acid supplementation, red blood cell transfusions as needed, and iron chelation. Some individuals can benefit from HbF induction with hydroxyurea. Luspatercept may also be used to ameliorate anemia with variable efficacy. Cholecystectomy for biliary colic; vitamin D supplementation, regular physical activity, and bisphosphonates for osteoporosis; referral for treatment of pulmonary hypertension; anticoagulation for unprovoked venous thromboembolism.

*Surveillance:* For  $\beta$ -thalassemia major, complete blood count every three to four weeks and with illnesses. For  $\beta$ -thalassemia intermedia, complete blood count every three to four months and with illnesses. Additional surveillance in individuals with  $\beta$ -thalassemia major and  $\beta$ -thalassemia intermedia: monitor efficacy and side effects of transfusion therapy and chelation therapy with monthly physical examination; evaluation of growth and development every three months during childhood; ALT and serum ferritin every three months; annual evaluation of eyes, hearing, heart, endocrine function (thyroid, endocrine pancreas, parathyroid, adrenal, pituitary), and myocardial and liver MRI. In adults: bone densitometry to assess for osteoporosis; serum alpha-fetoprotein concentration for early detection of hepatocarcinoma in those with hepatitis C and iron overload.

*Agents/circumstances to avoid:* Alcohol consumption if there is history of liver damage, iron-containing preparations, and exposure to infection.

*Evaluation of relatives at risk:* If the pathogenic variants have been identified in an affected family member, molecular genetic testing of at-risk sibs should be offered to allow for early diagnosis and treatment. Hematologic testing can be used if the pathogenic variants in the family are not known.

*Pregnancy management:* Individuals with  $\beta$ -thalassemia major often require increased red blood cell transfusions during pregnancy. Individuals with  $\beta$ -thalassemia intermedia often have a significant drop in hemoglobin necessitating regular red blood cell transfusions during pregnancy, and those who have never received a red blood cell transfusion or who received minimal transfusions are at risk for severe alloimmune anemia if red blood cell transfusions are required during pregnancy. Iron chelation should not be given during fetal organogenesis and may be started in the second trimester if necessary due to extent of maternal iron overload. Cardiac evaluation including pulmonary hypertension screening is recommended prior to conception.

## Genetic counseling

Beta-thalassemia major and  $\beta$ -thalassemia intermedia are inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *HBB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a (typically) asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. If one parent is known to be heterozygous for an *HBB* pathogenic variant and the other parent is affected with  $\beta$ -thalassemia, each sib of an affected individual has a 50% chance of inheriting biallelic *HBB* pathogenic variants and being affected and a 50% chance of inheriting one *HBB* pathogenic variant and being a (typically) asymptomatic carrier. Carrier testing for at-risk relatives can be done by hematologic and/or molecular genetic testing (if the familial pathogenic variants are known). Once both *HBB*

pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

## GeneReview Scope

Beta-Thalassemia ( $\beta$ -Thalassemia): Included Phenotypes

- Beta-thalassemia major
- Beta-thalassemia intermedia
- Beta-thalassemia minor: heterozygote (carrier) for  $\beta$ -thalassemia

## Diagnosis

### Suggestive Findings

**Beta-thalassemia ( $\beta$ -thalassemia) major should be suspected** in an infant or child younger than age two years with the following clinical and laboratory findings.

- **Clinical findings**
  - Pallor
  - Poor weight gain
  - Stunted growth
  - Mild jaundice
  - Hepatosplenomegaly
- **Laboratory findings**
  - Reduced (or absent) hemoglobin A (HbA) on newborn screening (i.e., through hemoglobin electrophoresis, isoelectric focusing, or high-performance liquid chromatography [HPLC] on newborn blood spots)
  - Increased hemoglobin A<sub>2</sub> (HbA<sub>2</sub>) with or without increased hemoglobin F (HbF) on hemoglobin electrophoresis
  - Absence of iron deficiency
  - Severe microcytic hypochromic anemia with anisopoikilocytosis and nucleated red blood cells on peripheral blood smear

**Beta-thalassemia intermedia should be suspected** in individuals who present after age two years or with less severe but similar findings to  $\beta$ -thalassemia major.

### Establishing the Diagnosis

The diagnosis of  $\beta$ -thalassemia is established in a proband older than 12 months by identification of microcytic hypochromic anemia (see Table 1), absence of iron deficiency, anisopoikilocytosis with nucleated red blood cells on peripheral blood smear, and decreased or complete absence of HbA and increased HbA<sub>2</sub> with or without increased HbF on hemoglobin analysis (see Table 2).

The diagnosis of  $\beta$ -thalassemia is established in a proband younger than age 12 months by identification of either:

- Complete absence of HbA on newborn screening (diagnostic of  $\beta^0$ -thalassemia, in which no beta globin chain is produced; see Genotype-Phenotype Correlations);

OR

- Biallelic pathogenic (or likely pathogenic) variants in *HBB* on molecular genetic testing (see Table 3) in a proband with suggestive laboratory findings.

Note: (1) The reduction of HbA levels in infants with  $\beta^+$ -thalassemia (in which a reduced amount of beta globin chains are produced; see Genotype-Phenotype Correlations) overlaps with the normal range for HbA in healthy infants; therefore, molecular genetic testing is required to diagnose infants younger than age 12 months with  $\beta^+$ -thalassemia. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015].

Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (3) Identification of biallelic *HBB* variants of uncertain significance (or of one known *HBB* pathogenic variant and one *HBB* variant of uncertain significance) does not establish or rule out the diagnosis.

## Hematologic Findings

**Red blood cell indices** show microcytic anemia (see Table 1).

**Table 1.** Red Blood Cell Indices in Beta-Thalassemia

Red Blood Cell Indices	Normal <sup>1</sup>		$\beta$ -Thalassemia Major	$\beta$ -Thalassemia Intermedia	$\beta$ -Thalassemia Minor <sup>2</sup>
	Male	Female			
<b>Mean corpuscular volume (MCV, in fL)</b>	89.1 $\pm$ 5.01	87.6 $\pm$ 5.5	50-70	50-70	55-78
<b>Mean corpuscular hemoglobin (MCH, in pg)</b>	30.9 $\pm$ 1.9	30.2 $\pm$ 2.1	12-20	Decreased	15-25
<b>Hemoglobin (Hb, in g/dL)</b>	15.9 $\pm$ 1.0	14.0 $\pm$ 0.9	<7	7-10	9.5-12.5

1. Galanello et al [1979]

2. Brancaloni et al [2016]

**Peripheral blood smear.** Individuals with  $\beta$ -thalassemia major demonstrate the red blood cell morphologic changes of microcytosis, hypochromia, anisocytosis, poikilocytosis (spiculated teardrop and elongated cells), and nucleated red blood cells (i.e., erythroblasts). The number of erythroblasts is related to the degree of anemia. Peripheral blood smear findings in individuals with  $\beta$ -thalassemia intermedia are similar to those in individuals with  $\beta$ -thalassemia major. Individuals with  $\beta$ -thalassemia minor demonstrate microcytosis, hypochromia, and target cells.

**Qualitative and quantitative hemoglobin analysis** (by cellulose acetate electrophoresis and DE-52 microchromatography or HPLC) identifies the amount and type of hemoglobin present. The following hemoglobin types are most relevant to  $\beta$ -thalassemia:

- HbA. Two alpha globin chains and two beta globin chains ( $\alpha_2\beta_2$ )
- HbF. Two alpha globin chains and two gamma globin chains ( $\alpha_2\gamma_2$ )
- HbA<sub>2</sub>. Two alpha globin chains and two delta globin chains ( $\alpha_2\delta_2$ )

The hemoglobin pattern in  $\beta$ -thalassemia varies by  $\beta$ -thalassemia type (see Table 2).

**Table 2.** Hemoglobin Patterns in Beta-Thalassemia (Age >12 Months)

Hemoglobin Type	Normal <sup>1</sup>	$\beta$ -Thalassemia Major <sup>2</sup>	$\beta$ -Thalassemia Intermedia <sup>2</sup>	$\beta$ -Thalassemia Minor <sup>2</sup>
HbA	96%-98%	0%-30% (typically near 0%)	10%-50%	>88%
HbF	<1%	Up to 95%	10%-50%	<5%

Table 2. continued from previous page.

Hemoglobin Type	Normal <sup>1</sup>	$\beta$ -Thalassemia Major <sup>2</sup>	$\beta$ -Thalassemia Intermedia <sup>2</sup>	$\beta$ -Thalassemia Minor <sup>2</sup>
HbA <sub>2</sub>	2%-3%	>5%	>4%	>4%

HbA = hemoglobin A; HbA<sub>2</sub> = hemoglobin A<sub>2</sub>; HbF = hemoglobin F

1. Telen & Kaufman [1999]

2. Brancaleoni et al [2016]

Hemoglobin electrophoresis and HPLC also detect other hemoglobinopathies (S, C, E, O<sub>Arab</sub>, Lepore) that may interact with  $\beta$ -thalassemia.

## Molecular Genetic Testing

The recommended molecular genetic testing approach for  $\beta$ -thalassemia is **single-gene testing** (see Table 3).

Sequence analysis of *HBB* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

Note: Analysis of *HBB* is complicated by the presence of highly homologous gene family members as well as a pseudogene, *HBBP1*; therefore, any assay that examines *HBB* sequence must be validated to ensure specificity to the active gene (see Molecular Genetics).

Note: Targeted analysis for pathogenic variants can be performed first in individuals of specific at-risk populations (see Table 8).

**Table 3.** Molecular Genetic Testing Used in Beta-Thalassemia

Gene <sup>1</sup>	Method	Proportion of Pathogenic Variants <sup>2</sup> Detectable by Method
<i>HBB</i>	Sequence analysis <sup>3</sup>	Almost 100%
	Gene-targeted deletion/duplication analysis <sup>4</sup>	Rare <sup>5</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

5. Hartevelde et al [2005], Shooter et al [2015], Reading et al [2016], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

## Clinical Characteristics

### Clinical Description

Beta-thalassemia ( $\beta$ -thalassemia) has two clinically significant forms,  $\beta$ -thalassemia major and  $\beta$ -thalassemia intermedia, caused by absent or reduced synthesis of the hemoglobin subunit beta (beta globin chain). Individuals with  $\beta$ -thalassemia major usually come to medical attention within the first two years of life; they subsequently require regular red blood cell transfusions to survive. Individuals with  $\beta$ -thalassemia intermedia

have a more variable age of presentation due to milder anemia that does not require regular red blood cell transfusions from early childhood.

## Beta-Thalassemia Major

**Presentation.** Clinical presentation of  $\beta$ -thalassemia major occurs between ages six and 24 months.

- Affected infants have progressive pallor, poor weight gain, and stunted growth.
- Feeding problems, diarrhea, irritability, recurrent fever, and progressive enlargement of the abdomen caused by hepatosplenomegaly may occur.
- If the diagnosis of  $\beta$ -thalassemia major is established by age 24 months and red blood cell transfusions that maintain a minimum hemoglobin concentration of 9.5-10.5 g/dL are initiated, growth and development progress normally until at least age ten to 11 years.

**Complications.** After age ten to 11 years, affected individuals are at risk of developing severe complications related to iron overload, depending on their compliance with iron chelation therapy (see Management). In individuals receiving red blood cell transfusions, iron overload results mainly from transfusions.

Complications of iron overload include the following:

- In children, stunted growth and failure of sexual maturation
- In adults, involvement of the heart (arrhythmias, dilated cardiomyopathy), liver (fibrosis and cirrhosis), and endocrinopathies (resulting in diabetes mellitus and insufficiency of the parathyroid, thyroid, pituitary, and, less commonly, adrenal glands)

Complications of iron chelation include the following:

- Ocular toxicity (primarily with deferoxamine)
- Hearing loss
- Liver injury (primarily with deferasirox)
- Proteinuria (only with deferasirox)
- Impaired renal filtration
- Agranulocytosis (only with deferiprone)
- Injection site reaction (only with deferoxamine)

Other possible complications include the following:

- Hypersplenism
- Chronic hepatitis due to hepatitis B and/or hepatitis C infection acquired from transfusion
- HIV infection acquired from transfusion
- Venous thrombosis, especially in individuals who have undergone splenectomy
- Cholelithiasis due to the formation of pigment gallstones in the setting of chronic hemolysis
- Osteoporosis, a common complication in adults; its origin is multifactorial, making it difficult to manage
- Hepatocellular carcinoma secondary to chronic hepatitis and cirrhosis [Moukhadder et al 2017]

**Prognosis.** The prognosis in individuals with  $\beta$ -thalassemia major has dramatically improved over the past decades with the advent of noninvasive methods to measure liver and cardiac iron accumulation before the appearance of clinical symptoms, improved iron chelators, and decreased risk of infection with red blood cell transfusions. After 2000, these developments led to a significant decrease in cardiac mortality, previously reported to cause 71% of deaths in individuals with  $\beta$ -thalassemia major [Borgna-Pignatti et al 2004, Telfer et al 2006, Modell et al 2008]. Prognosis continues to improve as access to both red blood cell transfusions and iron chelation increases, but life expectancy remains greatly diminished in low-resource settings, with more than half

of individuals dying before age 30 years compared to more than half of individuals living to age 60 years in high-resource settings [Kattamis et al 2020, Taher et al 2021].

**Untreated  $\beta$ -thalassemia major** is presently only seen in low-resource settings in which long-term red blood cell transfusion programs are not available. The most relevant features of untreated or poorly transfused individuals include:

- Stunted growth
- Pallor
- Jaundice
- Poor musculature
- Hepatosplenomegaly
- Leg ulcers, which are thought to reflect a similar physiology to pulmonary hypertension and relate to nitric oxide depletion in the setting of chronic hemolysis
- Development of paraspinous masses from extramedullary hematopoiesis
- Skeletal changes that result from expansion of the bone marrow, including the following:
  - Deformities of the long bones of the legs
  - Typical craniofacial changes (frontal bossing, malar prominence, depressed nasal bridge, tendency toward upslanted palpebral fissures, and hypertrophy of the maxillae, which tends to expose the upper teeth)
  - Osteoporosis

Individuals who do not receive red blood cell transfusions usually die in the first two decades. Individuals who have been poorly transfused are also at risk of complications of iron overload, as are those who do not receive iron chelation.

## Beta-Thalassemia Intermedia

Clinical features of  $\beta$ -thalassemia intermedia include pallor, jaundice, cardiac disease, cholelithiasis, hepatosplenomegaly, moderate-to-severe skeletal changes (long bone deformities, craniofacial changes, and osteopenia/osteoporosis), leg ulcers, pulmonary hypertension (often clinically silent until advanced and much more common than in individuals with  $\beta$ -thalassemia major), extramedullary masses of hyperplastic erythroid marrow, and thrombotic complications [Cappellini et al 2012].

By definition, red blood cell transfusions are not continuously required from childhood, but may become regularly needed over time or due to complications (e.g., pulmonary hypertension, paraspinous extramedullary hematopoiesis).

Iron overload occurs mainly from increased intestinal absorption of iron caused by hepcidin deficiency (a peptide produced by hepatocytes that plays a central role in the regulation of iron homeostasis). Hepcidin deficiency is driven by the elaboration of erythroferrone during ineffective erythropoiesis. The complications of iron overload present later in individuals with  $\beta$ -thalassemia intermedia but may be as severe as those seen in individuals with  $\beta$ -thalassemia major.

## Genotype-Phenotype Correlations

The clinical severity of the  $\beta$ -thalassemia depends on the extent of alpha/non-alpha globin chain imbalance (i.e., ratio of alpha globin chains to beta globin chains or gamma globin chains). The nonassembled alpha globin chains that result from unbalanced alpha/non-alpha globin chain synthesis precipitate in the form of inclusions. These inclusions damage erythroid precursors in the bone marrow and the spleen, causing ineffective erythropoiesis.

**$\beta^0$  variants** (absent hemoglobin subunit beta production) result from *HBB* nonsense, frameshift, and some splicing variants. Biallelic  $\beta^0$  variants typically result in  $\beta$ -thalassemia major.

**$\beta^+$  variants** (reduced hemoglobin subunit beta production) result from pathogenic *HBB* variants located in introns, promoters, the polyadenylation signal, and the 5' or 3' untranslated region, as well as some splicing variants.

- Some  $\beta^+$  variants have been classified as mild or silent (see Table 8).
- Biallelic  $\beta^+$  variants can be associated with  $\beta$ -thalassemia intermedia or  $\beta$ -thalassemia minor.
- $\beta^+$  variants can be associated with  $\beta$ -thalassemia major when compound heterozygous with a  $\beta^0$  variant.
- $\beta^+$  silent variants can result in a mild phenotype when compound heterozygous with a  $\beta^0$  variant.
- Biallelic  $\beta^+$  silent variants are associated with normal hematologic findings and only a mildly unbalanced alpha/beta globin chain synthesis ratio; silent variants occur in the distal CACCC box, the 5' unbalanced region, the polyadenylation signal, and some splice sites (see Table 8).

Note: The clinical severity associated with  $\beta^0$  and  $\beta^+$  variants is variable and may be modified if ameliorating genetic factors are present.

## Heterozygous *HBB* Pathogenic Variants

Heterozygous *HBB* pathogenic variants can be associated with autosomal dominant  $\beta$ -thalassemia intermedia.

- Heterozygosity for some *HBB* pathogenic variants results in hyper-unstable hemoglobins, which precipitate in the red cell membrane together with unassembled alpha globin chains and lead to markedly ineffective erythropoiesis. Most of these *HBB* pathogenic variants are located in exon 3 and lead to the production of a markedly unstable hemoglobin protein often not detectable in peripheral blood.
- Double heterozygosity for an *HBB* pathogenic variant associated with  $\beta$ -thalassemia and an *HBA1* or *HBA2* duplication ( $\alpha\alpha\alpha/\alpha\alpha$  or  $\alpha\alpha\alpha/\alpha\alpha\alpha$  or  $\alpha\alpha\alpha\alpha/\alpha\alpha$ ) increases the imbalance in the ratio of alpha/non-alpha globin chains. Duplications of the entire alpha globin gene cluster have been reported to cause  $\beta$ -thalassemia intermedia in heterozygotes [Harteveld et al 2008, Sollaino et al 2009, Origa et al 2014].

Clinical presentation in individuals with compound heterozygosity for a  $\beta$ -thalassemia-related *HBB* variant and c.79G>A (p.Glu27Lys) (hemoglobin E [HbE] allele) is usually comparable to  $\beta$ -thalassemia intermedia. Homozygosity for HbE usually has a milder phenotype comparable to  $\beta$ -thalassemia minor (see Genetically Related Disorders).

## Ameliorating Genetic Factors

Clinical severity of  $\beta$ -thalassemia may be ameliorated by coinheritance of pathogenic variants in *HBA1* or *HBA2* (associated with [alpha-thalassemia](#)), which reduce alpha globin expression, thereby decreasing the alpha/non-alpha globin chain imbalance.

The coinheritance of some genetic determinants able to sustain a continuous production of gamma globin chains (hereditary persistence of fetal hemoglobin [HPFH]) in adult life may also reduce the extent of alpha/non-alpha globin chain imbalance and may result in a milder phenotype.

- *HBB* pathogenic variants that increase gamma globin chain (fetal hemoglobin, or HbF) output:
  - $\delta\beta^0$ -Thalassemia caused by deletions of variable size in the *HBB* gene cluster
  - Deletions that remove only the 5' region of the *HBB* promoter, which also results in high levels of HbA<sub>2</sub>
- HPFH due to single-nucleotide variants in *HBG2* (hemoglobin G $\gamma$  promoter) or *HBG1* (hemoglobin A $\gamma$  promoter) (most commonly NM\_000184.33:c.-211C>T in *HBG2* and NM\_000559.3:c.-170G>A in *HBG1*) [Ali et al 2015].



- The NM\_000559.3:c.-249C>T *HBG1* variant in *cis* with *HBB* variant p.Gln40Ter has been identified in individuals of Sardinian ancestry with milder  $\beta$ -thalassemia (Sardinian  $\delta\beta^0$ -thalassemia) [Mingoia et al 2021].

Other genetic loci not linked to the *HBB* gene cluster have been reported to have ameliorating effects on of the severity of  $\beta$ -thalassemia, including other genetic variants resulting in HPFH.

- The *BCL11A* intronic variant NM\_022893.3:c.386-24278G>A was strongly associated with HbF levels. The c.386-24278G allele was significantly more common in individuals homozygous for *HBB* variant p.Gln40Ter with a mild  $\beta$ -thalassemia phenotype [Lettre et al 2008, Uda et al 2008].
- *HBSIL-MYB* intergenic variants contain regulatory sequences controlling *MYB* expression. Coinheritance of these HPFH determinants and  $\alpha$ -thalassemia contribute to amelioration of  $\beta$ -thalassemia major, accounting for 75% of difference in clinical severity [Galanello et al 2009].

A study of 890 individuals with  $\beta$ -thalassemia reported that three factors – the type of pathogenic variant in *HBB*; *HBA1* and *HBA2* pathogenic variants; and HbF production modulators (c.-211C>T in *HBG2*, c.386-24278G>A in *BCL11A*, *HBSIL-MYB* intergenic variants) could be combined to predict transfusion-free survival and the age at which the individual started regular red blood cell transfusions [Danjou et al 2015].

## Nomenclature

Beta-thalassemia includes three main forms:

- Beta-thalassemia major, also referred as Cooley's anemia, Mediterranean anemia, or transfusion-dependent thalassemia (TDT);
- Beta-thalassemia intermedia; and
- Beta-thalassemia minor, also called  $\beta$ -thalassemia carrier,  $\beta$ -thalassemia trait, or heterozygous  $\beta$ -thalassemia.

Non-transfusion-dependent thalassemia (NTDT) is a term used to designate individuals with thalassemia (alpha or beta) who do not require regular red blood cell transfusions for survival; NTDT encompasses  $\beta$ -thalassemia intermedia, hemoglobin E/ $\beta$ -thalassemia (mild and moderate forms), and  $\alpha$ -thalassemia intermedia (hemoglobin H disease). Some individuals with NTDT develop complications that necessitate initiating regular red blood cell transfusions and are then characterized as having TDT. Note: Individuals with  $\beta$ -thalassemia major by definition have TDT.

## Prevalence

Beta-thalassemia is more prevalent in populations from the Mediterranean, the Middle East, Central and Southeast Asia, and the Indian subcontinent. It is also common in populations of African descent. The highest incidences are reported in Cyprus (14%), Sardinia (12%), and Southeast Asia. The increased frequency of  $\beta$ -thalassemia in these regions is most likely related to selective pressure from malaria. This distribution is quite similar to that of endemic *Plasmodium falciparum* malaria. However, because of population migration,  $\beta$ -thalassemia can be found around the world.

## Genetically Related (Allelic) Disorders

**Sickle cell disease (SCD)** encompasses a group of disorders characterized by the presence of at least one hemoglobin S allele (HbS; p.Glu6Val in *HBB*) and a second *HBB* pathogenic variant resulting in abnormal hemoglobin polymerization. Hb S/S (homozygous p.Glu6Val in *HBB*) accounts for the majority of SCD. Other forms of SCD result from compound heterozygosity for HbS with other *HBB* pathogenic variants (e.g., sickle-

hemoglobin C disease [Hb S/C], sickle beta-thalassemia [Hb S/ $\beta^+$ -thalassemia and Hb S/ $\beta^0$ -thalassemia], Hb S/D, Hb S/O<sub>Arab</sub>, Hb S/E; see [globin.bx.psu.edu](http://globin.bx.psu.edu)).

**Hemoglobin E (HbE) thalassemia.** Individuals homozygous for *HBB* variant c.79G>A (p.Glu27Lys) have mild hemolytic microcytic anemia. This nucleotide substitution activates a cryptic donor splice site.

## Differential Diagnosis

**Beta-thalassemia ( $\beta$ -thalassemia) associated with additional hematologic and/or nonhematologic features.**

In rare instances, the molecular etiology in an individual with characteristic hematologic features of  $\beta$ -thalassemia does not lie in *HBB* or in the beta globin gene cluster. In instances in which the  $\beta$ -thalassemia phenotype is associated with additional features, the genetic alteration has been found either in *ERCC2* (which encodes a subunit of the transcription factor TFIIF) or *GATA1*.

- ***ERCC2*-related xeroderma pigmentosum** is characterized by acute sun sensitivity with marked freckle-like pigmentation of the face before age two years; sunlight-induced ocular involvement; and a greatly increased risk of sunlight-induced cutaneous neoplasms within the first decade of life.
- ***ERCC2*-related trichothiodystrophy** (OMIM 601675) is associated with a variable phenotype including photosensitivity, ichthyosis, brittle hair, intellectual impairment, short stature, microcephaly, brain dysmyelination, characteristic facial features, and a 20-fold increased risk of death before age ten years, primarily from infections.
- ***GATA1*-related cytopenia** is characterized by thrombocytopenia and/or anemia ranging from mild to severe. Thrombocytopenia typically presents in infancy as a bleeding disorder with easy bruising and mucosal bleeding (e.g., epistaxis). Anemia ranges from minimal (mild dyserythropoiesis) to severe (hydrops fetalis requiring in utero transfusion). Some affected individuals have neutropenia and/or splenomegaly. Cryptorchidism and hypospadias have been reported.

Few conditions share similarities with  $\beta$ -thalassemia major and  $\beta$ -thalassemia intermedia.

- The genetic sideroblastic anemias are easily differentiated from  $\beta$ -thalassemia because of ring sideroblasts in the bone marrow and variably elevated serum concentration of erythrocyte protoporphyrin. They do not result in increased hemoglobin A<sub>2</sub> (HbA<sub>2</sub>) or hemoglobin F (HbF). Sideroblastic anemia is most often due to pathogenic variants in genes involved in the heme biosynthetic pathway (e.g., *ALAS2*).
- Congenital dyserythropoietic anemias do not have high HbA<sub>2</sub> or HbF and have other distinctive features, such as multinuclearity of the red blood cell precursors (see [Congenital Dyserythropoietic Anemia Type I](#)).
- A few acquired conditions associated with high HbF (juvenile chronic myeloid leukemia, aplastic anemia) may be mistaken for  $\beta$ -thalassemia, even though they have very characteristic hematologic features.
- Rarely, severe iron deficiency can be mistaken for  $\beta$ -thalassemia intermedia due to microcytosis. This should be readily distinguishable by both the lack of hemolysis and laboratory evidence of iron deficiency such as decreased ferritin.

## Management

Comprehensive reviews of the management of beta-thalassemia ( $\beta$ -thalassemia) major and  $\beta$ -thalassemia intermedia have been published by the Thalassemia International Federation [Cappellini et al 2021, Taher et al 2023] and are available at the TIF [website](#).

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with  $\beta$ -thalassemia, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 4.** Beta-Thalassemia: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
<b>Hematologic</b>	<ul style="list-style-type: none"> <li>Hemoglobin electrophoresis</li> <li>Molecular analysis to determine globin genotype</li> </ul>	
	Hb level x 2 (drawn $\geq 2$ wks apart)	
	Clinical assessment for manifestations of $\beta$ -thalassemia major: <ul style="list-style-type: none"> <li>Facial changes</li> <li>Stunted growth</li> <li>Fractures</li> <li>Hepatosplenomegaly</li> </ul>	<ul style="list-style-type: none"> <li>To determine if person has <math>\beta</math>-thalassemia major or <math>\beta</math>-thalassemia intermedia</li> <li>Those w/Hb <math>&lt; 7</math> g/dL (excluding all other contributory causes, e.g., infections), or presence of manifestations of <math>\beta</math>-thalassemia major, regardless of Hb level, are diagnosed w/thalassemia major</li> </ul>
<b>Genetic counseling</b>	By genetics professionals <sup>1</sup>	To inform affected persons & their families re nature, MOI, & implications of $\beta$ -thalassemia to facilitate medical & personal decision making

Hb = hemoglobin; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

## Treatment of Manifestations

### Targeted Therapies

*In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED*

### Beta-Thalassemia Major

**Hematopoietic stem cell transplant (HSCT)** represents an alternative to red blood cell transfusions and iron chelation therapy. If HSCT is successful, iron overload may be reduced by repeated phlebotomy, thus eliminating the need for iron chelation.

- The ideal donor is a human leukocyte antigen (HLA)-matched sib. Individuals without an HLA-matched sib could also benefit from haploidentical mother-to-child transplantation, the results of which appear encouraging [Sodani et al 2011, Anurathapan et al 2016].
- The outcome of HSCT is related to pretransplantation clinical manifestations (presence of hepatomegaly, extent of liver fibrosis, and magnitude of cardiac and liver iron accumulation). In children who lack these pretransplantation risk factors, the disease-free survival rate is greater than 90%. Adults with  $\beta$ -thalassemia are at increased risk for transplant-related toxicity due to an advanced phase of the disease and have a two-year overall survival rate of 80% and a two-year event-free survival rate of 76% with current treatment protocols [Baronciani et al 2016].
- Individuals with limited iron overload who receive HSCT from an unrelated donor selected based on stringent criteria of HLA compatibility have results that are comparable to HSCT from an HLA-matched sib donor [La Nasa et al 2005, Gaziev et al 2013].
- Severe acute graft-versus-host disease (GVHD) may occur in 9% of individuals, with a lower risk observed in those with an HLA-matched sib donor.
- Cord blood transplantation remains an alternative for individuals seeking curative therapy without other donor options. Treatment with related donor cord blood was associated with a low risk of GVHD and a good chance of cure [Orofino et al 2003, Pinto & Roberts 2008]. Unrelated cord blood transplantation in

35 individuals with  $\beta$ -thalassemia resulted in an overall survival rate of 88% and a  $\beta$ -thalassemia-free survival rate of 74% [Jaing et al 2012].

**Gene therapy** is an emerging alternative to HSCT for curative therapy. Essentially a genetically modified autologous HSCT, stem cells are collected from an affected individual, and gene-editing techniques are used to modify the stem cells *ex vivo*. Individuals then undergo conditioning chemotherapy before infusion of genetically modified stem cells. Gene editing can either introduce a functional beta globin chain or silence *BCL11A* to induce gamma globin chain production.

- **Betibeglogene autotemcel (beti-cel)**, a gene addition via a lentiviral vector, was recently approved by the FDA. Beti-cel has been shown to yield transfusion independence in 91% of individuals who are *not* homozygous for  $\beta^0$  alleles [Locatelli et al 2022b]. Response rates for  $\beta^0/\beta^0$  individuals was slightly lower, at 86%, although sample size was small [Langer & Esrick 2021]. Individuals who achieved transfusion independence were eventually able to stop iron chelation and sustain a normal iron profile [Thompson et al 2021]. Acute myeloid leukemia (AML) was diagnosed in two individuals with sickle cell disease who received beti-cel, raising concerns of potential toxicity, but neither case was caused by insertional mutagenesis. Myelodysplastic syndrome or AML have not been reported in any individuals with  $\beta$ -thalassemia treated with gene therapy, including beti-cel [Hsieh et al 2020].
- **Exagamglogene autotemcel (exa-cel)**, a *BCL11A* knockdown using CRISPR, was recently approved by the FDA. Exa-cel has shown promise with transfusion independence in more than 95% of individuals reported thus far [Frangoul et al 2021, Locatelli et al 2022a].

## Supportive Care

### Beta-Thalassemia Major

**Red blood cell transfusions**, usually every two to four weeks with a pretransfusion hemoglobin (Hb) concentration goal of 9.5-10.5 g/L, are needed to correct the anemia, suppress ineffective erythropoiesis, and inhibit increased gastrointestinal absorption of iron.

Before starting red blood cell transfusions, the following are recommended: hepatitis B vaccination; extensive red blood cell antigen typing, including Rh, Kell, Kidd, and Duffy; and serum immunoglobulin determination, which detects individuals with IgA deficiency, who need special (repeatedly washed) blood unit preparation before each transfusion.

**Chelation therapy** can prevent transfusional iron overload.

- **Deferoxamine B (DFO)** is administered five to seven days a week by 12-hour continuous subcutaneous infusion via a portable pump. Recommended dosage depends on the individual's age, transfusion volume, and the serum ferritin concentration. Young children start with 20-30 mg/kg/day, increasing to up to 40 mg/kg/day after age five to six years. The maximum dose is 50 mg/kg/day after growth is completed. The dose may be reduced if serum ferritin concentration is low. By maintaining the total body iron stores below critical values (i.e., hepatic iron concentration <7.0 mg per gram of dry weight liver tissue), long-term organ damage can be prevented. Ascorbate repletion (daily dose  $\leq$ 100-150 mg) increases the amount of iron removed after DFO administration. Side effects of DFO are more common in the presence of relatively low iron burden and include ocular and auditory toxicity, growth restriction, and, rarely, kidney impairment and interstitial pneumonitis. DFO also increases susceptibility to *Yersinia* infections. The major drawback of DFO is difficulty with adherence to subcutaneous administration, which can be particularly difficult with younger children.
- **Deferiprone**, an oral chelator, is administered in a dose of 75-100 mg/kg/day. The main side effects of deferiprone include arthropathy, gastrointestinal symptoms, and, above all, neutropenia and

agranulocytosis [Galanello & Campus 2009], which demand close monitoring. A prospective study showed that deferiprone is more cardioprotective than DFO; compared to those treated with DFO, individuals treated with deferiprone have better myocardial MRI pattern and less probability of developing (or worsening pre-existing) cardiac disease [Pennell et al 2006]. Different formulations exist for administration two or three times per day, with the older and more readily available formulation requiring three times per day administration. Frequency of administration can be a barrier to adherence.

- **Deferasirox (DFX)** is a once-daily oral monotherapy for the treatment of transfusional iron overload. It is effective in adults and children and has a defined safety profile that is clinically manageable with appropriate monitoring. The most common treatment-related adverse events are abdominal pain, nausea, vomiting, diarrhea, and a mild, nonprogressive increase in serum creatinine concentration [Cappellini 2008]. Monitoring for proteinuria is required. Kidney failure, liver failure, and gastrointestinal hemorrhage have been reported. Provided adequate doses are given, there is a good response to DFX across the full range of baseline liver iron concentration values. Prospective data demonstrate the efficacy of DFX in improving myocardial  $T_2^*$  and in maintaining a normal left ventricle ejection fraction [Pennell et al 2012, Pennell et al 2014]. DFX has not been evaluated in formal trials for affected individuals with symptomatic heart failure or low left ventricle ejection fraction.
- **Combination therapies.** The combination of DFO and deferiprone has been effective in individuals with severe iron overload. Retrospective, prospective, and randomized clinical studies have shown that iron chelation with combined DFO and deferiprone rapidly reduces myocardial iron deposition, improves cardiac and endocrine function, reduces liver iron and serum ferritin concentration, reduces cardiac mortality, and improves survival; toxicity is manageable [Tanner et al 2007, Galanello et al 2010].

An open-label single-arm prospective Phase II study evaluated combination DFX-DFO in individuals with severe transfusional myocardial iron deposition followed by optional switch to DFX monotherapy when achieving myocardial  $T_2^* > 10$  ms; this approach rapidly decreased liver iron accumulation in individuals with high liver iron load and decreased myocardial iron overload in one third of individuals [Aydinok et al 2015].

While large-scale studies have not been conducted, the combination of DFX and deferiprone has been shown to be safe and effective in repeated case series [Berdoukas et al 2010, Farmaki et al 2011, Voskaridou et al 2011, Elalfy et al 2015, Karami et al 2017].

**Luspatercept** is a transforming growth factor beta (TGF- $\beta$ ) superfamily ligand trap. Inhibition of TGF- $\beta$  reduced Smad 2/3 signaling, resulting in reduced ineffective erythropoiesis and apoptosis and increased survival of erythroid precursors. Luspatercept reduced transfusion volume by at least 33% in 21.4% of individuals with transfusion-dependent thalassemia (TDT) compared to 4.5% for placebo [Cappellini et al 2020]. Common side effects included transient arthralgias and headaches. A small incidence (3.6%) of both arterial and venous thrombosis was reported, exclusively in individuals with prior splenectomy. While this reflects an exciting breakthrough as the first therapy to reduce the frequency of red blood cell transfusions, the inability to eliminate the need for transfusions, low response rate, and subcutaneous administration every three weeks, which may not align with the individual's transfusion schedule, has resulted in limited uptake in clinical practice. Selected individuals with TDT benefit from a trial of luspatercept, though lack of response should prompt discontinuation.

**Venous thromboembolism (VTE)** occurs at an increased rate in  $\beta$ -thalassemia major even in spleen-intact individuals, but splenectomy is an additional significant risk factor [Cappellini et al 2000]. Indefinite anticoagulation at prophylactic dosing after an initial therapeutic course is indicated in individuals with unprovoked VTE. Individuals with provoked VTE can be considered for discontinuation, but the significant baseline risk should be considered even in individuals with provoked clot.

**Cholelithiasis.** Cholecystectomy should be performed in those with biliary colic. Symptoms will not resolve without surgery, and individuals will be more difficult to manage if they develop cholecystitis, as this will likely also worsen hemolysis and anemia concurrently.

**Osteoporosis** treatment includes hormonal replacement, red blood cell transfusions and iron chelation, vitamin D supplementation, and regular physical activity. Sufficient evidence exists to support the use of bisphosphonates in the management of  $\beta$ -thalassemia-associated osteoporosis (to prevent bone loss and improve bone mineral density). Further research is warranted to establish anti-fracture efficacy and long-term safety of bisphosphonates [Giusti 2014]. Denosumab and strontium ranelate have each been evaluated in only a single study, and there are no data on the effects of anabolic agents [Chavassieux et al 2014, Yassin et al 2014]. Since the origin of bone disease in  $\beta$ -thalassemia is multifactorial and some of the underlying pathogenic mechanisms are still unclear, further research in this field is needed to allow for the design of optimal therapeutic measures [Skordis & Toumba 2011, Dede et al 2016].

### **Beta-Thalassemia Intermedia**

The need for and timing of **splenectomy** is highly variably. Many individuals will not develop significant splenomegaly until adolescence or adulthood. Indications for splenectomy include the severity of anemia (e.g., splenectomy to avoid initiation of transfusions) and symptoms from the mass effect of splenomegaly. For individuals with other indications to initiate red blood cell transfusions, splenectomy may not be needed or preferred. Deferring splenectomy during early childhood is recommended, if the degree of anemia allows, due to the increased risk of infection and sepsis in infants and young children. Splenectomy also increases the risk of venous thromboembolism and pulmonary hypertension. The decision to proceed to splenectomy should be made with a clinician experienced in  $\beta$ -thalassemia management and alternative approaches.

**Folic acid supplementation** is recommended.

**Luspatercept** is not yet FDA approved for individuals with non-transfusion-dependent thalassemia (NTDT) (including  $\beta$ -thalassemia intermedia) at the time of writing. However, clinical trial data has shown that 77% of individuals given luspatercept had a rise of at least 1 g/dL of Hb [Taher et al 2022]. For individuals with symptomatic anemia, this may become a therapeutic option in the near future.

Development of **extramedullary erythropoietic masses** is an indication to initiate chronic red blood cell transfusion therapy, as suppression of ineffective erythropoiesis is paramount. Alternative approaches such as radiotherapy may transiently ameliorate a mass effect but will not address the underlying cause nor prevent future growth of erythropoietic masses. Extramedullary erythropoietic masses are usually paraspinal, and the risk of nerve impingement and neurologic damage requires long-term control.

**Hydroxyurea** has a limited treatment role in individuals with  $\beta$ -thalassemia intermedia. It may increase Hb levels by increasing hemoglobin F (HbF) [Levin & Koren 2011]. However, few individuals derive significant benefit. A retrospective study found no pulmonary hypertension in 50 individuals with  $\beta$ -thalassemia intermedia treated with hydroxyurea for seven years [Karimi et al 2009, Taher et al 2010]. Individuals who are compound heterozygous for a  $\beta$ -thalassemia *HBB* variant and hemoglobin E (HbE) are more likely to benefit, with a clinically meaningful rise in Hb (estimated 1.3 g/dL rise in 40% of individuals) [Singer et al 2005, Algiraigri & Kassam 2017].

Individuals with  $\beta$ -thalassemia intermedia may develop **iron overload** from increased gastrointestinal absorption of iron or from occasional transfusions; chelation therapy with deferasirox has been demonstrated to be safe and effective in persons age ten years or older with a liver iron concentration  $\geq 5$  mg per gram of dry weight liver tissue or serum ferritin  $\geq 800$  ng/mL (thresholds after which the risk of serious iron-related morbidity is increased) [Taher et al 2012]. The need for chelation therapy is often intermittent due to slowly progressive iron loading or after periods of intensive transfusion such as prolonged infection or pregnancy.

**Cardiac disease.** For individuals with evidence of iron loading in the liver, MRI to assess myocardial iron deposition and assessment of cardiac function is vital. Iron chelation should be initiated or increased when cardiac iron deposition is identified. Deferiprone is especially effective in chelating cardiac iron and should be used alone or in combination with another chelator depending on the extent of iron loading [Belmont & Kwiatkowski 2017]. If cardiac iron deposition is rapidly addressed, preserved cardiac function is expected. If cardiac iron is controlled or prevented, additional cardiac therapy is not needed for thalassemia.

**Cholelithiasis** is common due to the formation of pigment gallstones in the setting of chronic hemolysis. Cholecystectomy is common and should not be deferred if biliary colic is present. There is no expectation of resolution without surgery, and individuals will be more difficult to manage if they develop cholecystitis, as this will likely also worsen hemolysis and anemia concurrently.

**Osteoporosis** treatment includes hormonal replacement, red blood cell transfusions and iron chelation, vitamin D supplementation, and regular physical activity. Sufficient evidence exists to support the use of bisphosphonates in the management of  $\beta$ -thalassemia-associated osteoporosis (to prevent bone loss and improve bone mineral density). Further research is warranted to establish the anti-fracture efficacy and long-term safety of bisphosphonates [Giusti 2014]. Denosumab and strontium ranelate have each been evaluated in only a single study, and there are no data on the effects of anabolic agents [Chavassieux et al 2014, Yassin et al 2014]. Since the origin of bone disease in  $\beta$ -thalassemia is multifactorial and some of the underlying pathogenic mechanisms are still unclear, further research in this field is needed to allow for the design of optimal therapeutic measures [Skordis & Toumba 2011, Dede et al 2016].

**Leg ulcers.** Red blood cell transfusion will help in healing. Recurrent leg ulcers are an indication for chronic transfusion therapy. Emerging therapies to raise hemoglobin may be attempted as an alternative.

**Pulmonary hypertension** is a vital consideration in  $\beta$ -thalassemia intermedia, especially for asplenic individuals. If pulmonary pressures are elevated or ambiguous on transthoracic echocardiogram, referral to a pulmonary hypertension specialist and initiation of chronic red blood cell transfusions is recommended [Fraidenburg & Machado 2016, Pinto et al 2022].

**Venous thromboembolism (VTE)** occurs even in spleen-intact individuals, but splenectomy is an additional significant risk factor [Cappellini et al 2000]. Indefinite anticoagulation at prophylactic dosing after an initial therapeutic course is indicated in individuals with unprovoked VTE. Individuals with provoked VTE can be considered for discontinuation of anticoagulation, but the significant baseline risk of VTE should be considered even in individuals with a provoked clot.

## Surveillance

Recommendations for clinical and laboratory evaluations for individuals with  $\beta$ -thalassemia major have been provided by the Thalassemia International Federation [Cappellini et al 2014] and are available at the TIF [website](#). To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations in Table 5a (for  $\beta$ -thalassemia major) and Table 5b (for  $\beta$ -thalassemia intermedia) are recommended.

**Table 5a.** Beta-Thalassemia Major: Recommended Surveillance

System/Concern	Evaluation	Frequency
<b>Hematologic</b>	CBC	Every 3-4 wks & w/illness
<b>General</b>	Physical exam by physician familiar w/affected person & manifestations of $\beta$ -thalassemia major	Monthly
<b>Growth</b>	Assess growth & development	Every 3 mos throughout childhood

Table 5a. continued from previous page.

System/Concern	Evaluation	Frequency
<b>Cardiac</b>	Cardiologist visit	Annually starting in childhood
	Myocardial MRI to assess iron overload	Every 1-2 yrs starting either in childhood or when liver iron concentration is 1st ↑
<b>Liver</b>	<ul style="list-style-type: none"> <li>Serum ALT</li> <li>Serum ferritin <sup>1</sup></li> </ul>	Every 3 mos
	Liver MRI to assess iron overload	Annually starting in childhood
	<ul style="list-style-type: none"> <li>Liver ultrasound</li> <li>Serum alpha-fetoprotein for early detection of hepatocarcinoma</li> </ul>	Annually in adults w/hepatitis C &/or iron overload
<b>Endocrine</b>	Laboratory eval of thyroid, endocrine pancreas, parathyroid, adrenal, & pituitary function per endocrinologist	Annually starting in childhood
<b>Eyes</b>	Ophthalmology exam	Annually in those treated w/iron chelation
<b>Hearing</b>	Audiology exam	
<b>Side effects of specific iron chelation therapies</b>	<ul style="list-style-type: none"> <li>Serum creatinine, creatinine clearance, &amp;/or plasma cystatin C levels</li> <li>Urine protein</li> </ul>	In persons on deferasirox: prior to therapy, weekly in 1st mo after initiation or modification of therapy, & monthly thereafter
	Laboratory assessment of hepatic function	In persons on deferasirox: before initiation of treatment, every 2 wks during 1st mo, & monthly thereafter
	Neutrophil count	In persons on deferiprone: weekly & in those w/signs/symptoms of infection
<b>Venous thrombosis</b>	Assess for leg swelling or pain, unexplained dyspnea, pleuritic chest pain	At each visit
<b>Cholelithiasis</b>	Assess for postprandial abdominal pain	
<b>Orthopedic</b>	Bone densitometry to assess for osteoporosis	Every 1-5 yrs in adults

ALT = alanine transaminase; CBC = complete blood count

1. Serum ferritin is not always reliable for evaluating iron burden because it is influenced by other factors, the most important being the extent of liver damage.

Table 5b. Beta-Thalassemia Intermedia: Recommended Surveillance

System/Concern	Evaluation	Frequency
<b>Hematologic</b>	CBC	Every 3-12 mos & w/illness
<b>General</b>	Physical exam by physician familiar w/affected person & manifestations of $\beta$ -thalassemia minor	At each visit in early childhood; then annually
<b>Growth</b>	Assess growth & development	Every 3 mos throughout childhood
<b>Cardiac</b>	Cardiologist visit	Annually starting in childhood
	Myocardial MRI to assess iron overload	Every 1-2 yrs starting either in childhood or when liver iron concentration is 1st ↑
<b>Pulmonary hypertension</b>	Transthoracic echocardiogram	Every 2-5 yrs



Table 5b. continued from previous page.

System/Concern	Evaluation	Frequency
<b>Liver</b>	<ul style="list-style-type: none"> <li>Serum ALT</li> <li>Serum ferritin <sup>1</sup></li> </ul>	Every 3 mos
	Liver MRI to assess iron overload	Annually starting in childhood
	<ul style="list-style-type: none"> <li>Liver ultrasound</li> <li>Serum alpha-fetoprotein for early detection of hepatocarcinoma</li> </ul>	Annually in adults w/hepatitis C &/or iron overload
<b>Endocrine</b>	Laboratory eval of thyroid, endocrine pancreas, parathyroid, adrenal, & pituitary function per endocrinologist	Annually starting in childhood
<b>Orthopedic</b>	Bone densitometry to assess for osteoporosis	Every 1-5 yrs in adults
<b>Eyes</b>	Ophthalmology exam	Annually in those treated w/iron chelation
<b>Hearing</b>	Audiology exam	
<b>Side effects of specific iron chelation therapies</b>	Laboratory assessment of hepatic function (liver function tests)	In persons on deferasirox: before initiation of treatment, every 2 wks during 1st mo, & monthly thereafter
	<ul style="list-style-type: none"> <li>Serum creatinine, creatinine clearance, &amp;/or plasma cystatin C levels</li> <li>Urine protein</li> </ul>	In persons on deferasirox: prior to therapy, weekly in 1st mo after initiation or modification of therapy, & monthly thereafter
	Neutrophil count	In persons on deferiprone: weekly & in those w/signs/symptoms of infection
<b>Venous thrombosis</b>	Assess for leg swelling or pain, unexplained dyspnea, pleuritic chest pain	At each visit
<b>Cholelithiasis</b>	Assess for postprandial abdominal pain	

ALT = alanine transaminase; CBC = complete blood count

1. Serum ferritin is not always reliable for evaluating iron burden because it is influenced by other factors, the most important being the extent of liver damage.

## Agents/Circumstances to Avoid

The following should be avoided:

- Alcohol consumption, which in individuals with liver disease has a synergistic effect with iron-induced liver damage
- Iron-containing preparations
- Exposure to infection

## Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of an affected individual as early as possible. Early detection allows prompt, appropriate treatment and monitoring.

- For newborn sibs, *HBB* molecular genetic testing (if the familial *HBB* pathogenic variants are known) can allow the diagnosis of  $\beta$ -thalassemia to be made at birth without waiting for the shift in globin chain transcription.\*
- For sibs older than 12 months in whom absent or reduced hemoglobin A (HbA) was not detected on newborn screening\* (or who did not undergo newborn screening), initial screening can be quickly accomplished with a complete blood count, as the absence of microcytosis rules out all forms of  $\beta$ -

thalassemia. Sibs with microcytosis should have a hemoglobin electrophoresis and may merit additional testing (e.g., *HBB* molecular genetic testing) depending on the results and the extent of anemia.

\* In the United States, infants with biallelic  $\beta^0$  variants may be diagnosed by complete absence of HbA on newborn screening. Sibs with  $\beta$ -thalassemia who do not have biallelic  $\beta^0$  variants may not be diagnosed until age six to 12 months, when the switch from gamma globin to beta globin production reveals insufficient beta globin function.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

Pregnancy in women with  $\beta$ -thalassemia usually has a favorable outcome in those followed by a multidisciplinary team but requires collaboration and preparation to avoid complications [Savona-Ventura & Bonello 1994, Virot et al 2022]. While hypogonadotropic hypogonadism remains a common condition in  $\beta$ -thalassemia major, gonadal function is usually intact. Assisted reproduction with induced ovulation or egg retrieval and in vitro fertilization is usually successful. Screening and management should be up to date prior to pursuing pregnancy. Iron chelation cannot be used during the first trimester and ought to be deferred until late in the second trimester if the degree of iron overload permits this delay. Assuring good control of iron overload prior to pregnancy is ideal. Additionally, screening for cardiac dysfunction and pulmonary hypertension prior to conception is strongly recommended, as the risks of pregnancy increase substantially if either is present.

Women with  $\beta$ -thalassemia intermedia who had never previously received a red blood cell transfusion or who had received a minimal quantity of blood are reported to be at risk of alloimmunization anemia if red blood cell transfusions are required during pregnancy and therefore are also at increased risk for hemolytic disease of the fetus and newborn [Origa et al 2010].

## Therapies Under Investigation

Therapeutic strategies aimed at improving iron dysregulation such as minihepcidin, TMPRSS6, and ferroportin inhibitors are showing promise [Ramos et al 2012, Casu et al 2016, Casu et al 2020]. The first clinical trials are ongoing [Richard et al 2020].

**Pyruvate kinase activators** (e.g., mitapivat, etavopivat) are in Phase II and III clinical trials for both TDT and NTDT [Lal et al 2021, Kuo et al 2022]. They aim to improve anemia and decrease hemolysis.

Preliminary results for **ST-400**, a zinc finger nuclease that disrupts the *BCL11A* enhancer, have been disappointing, as initial increase in HbF was followed by a steady decline requiring resumption of transfusion in all five of the initial individuals enrolled, though only preliminary results have been reported thus far [Walters et al 2021].

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) in Europe for information on clinical studies for a wide range of diseases and conditions.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

Beta-thalassemia ( $\beta$ -thalassemia) major and  $\beta$ -thalassemia intermedia are inherited in an autosomal recessive manner.

## Risk to Family Members

### Parents of a proband

- The parents of an individual with  $\beta$ -thalassemia are typically heterozygous for one *HBB* pathogenic variant. Alternatively, it is possible that one or both parents have biallelic *HBB* pathogenic variants and are affected.
- Evaluation of the parents is recommended to determine their genetic status and to allow reliable recurrence risk assessment.
  - If both *HBB* pathogenic variants have been identified in the proband, molecular genetic testing can be used to determine the genetic status of the parents.
  - If the *HBB* pathogenic variants have not been identified in the proband, hematologic analysis can be used (see Population Screening for pitfalls in carrier identification by hematologic testing).
- If an *HBB* pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as the result of a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are typically clinically asymptomatic but have microcytosis and either mild anemia or no anemia. Carriers are often referred to as having  $\beta$ -thalassemia minor.
  - Rarely, a heterozygous *HBB* pathogenic variant is associated with  $\beta$ -thalassemia (see Genotype-Phenotype Correlations, Heterozygous *HBB* Pathogenic Variants).

### Sibs of a proband

- If both parents are known to be heterozygous for an *HBB* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being a (typically) asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- If one parent is known to be heterozygous for an *HBB* pathogenic variant and the other parent is affected with  $\beta$ -thalassemia, each sib of an affected individual has a 50% chance of inheriting biallelic *HBB* pathogenic variants and being affected and a 50% chance of inheriting one *HBB* pathogenic variant and being a (typically) asymptomatic carrier.
- The clinical severity of  $\beta$ -thalassemia in sibs who inherit biallelic *HBB* pathogenic variants is influenced by a range of factors including:
  - The familial pathogenic variants segregating in the family (see Genotype-Phenotype Correlations);
  - The presence of ameliorating genetic factors.
- Heterozygotes (carriers) are typically clinically asymptomatic but occasionally slightly anemic. Carriers are often referred to as having  $\beta$ -thalassemia minor.
  - Rarely, a heterozygous *HBB* pathogenic variant is associated with  $\beta$ -thalassemia (see Genotype-Phenotype Correlations, Heterozygous *HBB* Pathogenic Variants).

**Offspring of a proband.** If the reproductive partner of an individual with  $\beta$ -thalassemia:

- Does not have an *HBB* pathogenic variant (or variants), offspring will be heterozygous for an *HBB* pathogenic variant;
- Is heterozygous for an *HBB* pathogenic variant,\* offspring will have a 50% chance of having  $\beta$ -thalassemia and a 50% chance of being heterozygous for an *HBB* pathogenic variant;
- Is also affected with  $\beta$ -thalassemia,\* all offspring will have biallelic *HBB* pathogenic variants and be affected.

\* Beta-thalassemia can be found around the world but is more prevalent in populations from the Mediterranean, the Middle East, Central and Southeast Asia, and the Indian subcontinent. It is also common in populations of African descent (see Prevalence). If the reproductive partner of an individual with  $\beta$ -thalassemia is from a population with a higher frequency of  $\beta$ -thalassemia, the likelihood that the reproductive partner will have a heterozygous *HBB* pathogenic variant or biallelic *HBB* pathogenic variants is increased (see Population Screening).

**Other family members.** If both parents of the proband are heterozygous for an *HBB* pathogenic variant, each sib of the proband's parents is at a 50% risk of being a carrier of an *HBB* pathogenic variant.

## Carrier Detection

Carrier testing for at-risk relatives can be done by hematologic and/or (if the pathogenic variants have been identified in an affected family member) molecular genetic testing.

See Population Screening for review of hematologic and molecular approaches to carrier testing.

## Population Screening

Population screening relies on hematologic analysis. When the hematologic analysis indicates a  $\beta$ -thalassemia carrier state, molecular genetic testing of *HBB* can be performed to identify a pathogenic variant. If both partners of a couple have an *HBB* pathogenic variant, each of their offspring has a 25% risk of being affected. Through genetic counseling and the option of prenatal testing, such a couple can opt to bring to term only those pregnancies in which the fetus is unaffected or be better prepared for care during infancy and childhood.

Individuals who should be considered for carrier detection:

- Family members (See Risk to Family Members.)
- Gamete donors
- Members of populations with a higher prevalence of  $\beta$ -thalassemia (See Table 8.)

Of note, the American College of Medical Genetics and Genomics includes  $\beta$ -thalassemia among those disorders for which carrier screening should be offered to all individuals who are pregnant or planning a pregnancy [Gregg et al 2021].

## Hematologic Testing

Carriers are often identified by analysis of red blood cell indices (see Table 6), which shows microcytosis (low mean corpuscular volume) and reduced content of hemoglobin (Hb) per red blood cell (low mean corpuscular hemoglobin), and normal iron studies; and by quantitative Hb analysis (see Table 7), which shows hemoglobin A<sub>2</sub> (HbA<sub>2</sub>) greater than 3.5%.

**Table 6.** Hematologic Findings in individuals with Beta-Thalassemia Minor (Carrier)

Red Blood Cell Indices	Normal		$\beta$ -Thalassemia Minor (Carrier)	
	Male	Female	Male	Female
Hemoglobin (Hb, in g/dL)	15.9 $\pm$ 1.0	14.0 $\pm$ 0.9	11.5-15.3	9.1-14

Table 6. continued from previous page.

Red Blood Cell Indices	Normal		$\beta$ -Thalassemia Minor (Carrier)	
	Male	Female	Male	Female
Mean corpuscular volume (MCV, in fL)	89.1 $\pm$ 5.01	87.6 $\pm$ 5.5	<79	
Mean corpuscular hemoglobin (MCH, in pg)	30.9 $\pm$ 1.9	30.2 $\pm$ 2.1	<27	

Adapted from Galanello et al [1979]

Table 7. Hemoglobin Analysis in Beta-Thalassemia Minor (Carrier)

Hemoglobin Type	Normal <sup>1</sup>	$\beta$ -Thalassemia Minor (Carrier)
HbA	96%-98%	92%-95%
HbF	<1%	0.5%-4%
HbA <sub>2</sub>	2%-3%	>3.5%

HbA = hemoglobin A; HbA<sub>2</sub> = hemoglobin A<sub>2</sub>; HbF = hemoglobin F  
I. Telen & Kaufman [1999]

### Pitfalls in carrier identification by hematologic testing:

- Coinheritance of [alpha-thalassemia](#) ( $\alpha$ -thalassemia) may normalize the red blood cell indices. However, in  $\alpha$ -thalassemia and  $\beta$ -thalassemia double heterozygotes, the HbA<sub>2</sub> concentration remains in the  $\beta$ -thalassemia carrier range and thus is of diagnostic value.
- Coinheritance of delta-thalassemia ( $\delta$ -thalassemia), which reduces to normal the increased HbA<sub>2</sub> levels typical of the  $\beta$ -thalassemia carrier state. Double heterozygosity for  $\delta$ -thalassemia and  $\beta$ -thalassemia can be distinguished from the most common  $\alpha$ -thalassemia carrier state by hemoglobin electrophoresis or *HBB* molecular testing. Often hemoglobin F (HbF) is elevated, which is not present with  $\alpha$ -thalassemias, and is highly suggestive in the setting of red blood cell indices compatible with thalassemia minor.
- Confusion of  $\alpha$ -thalassemia carriers with  $\beta$ -thalassemia carriers can occur, resulting from microcytosis and hypochromia. However,  $\alpha$ -thalassemia carriers are easily distinguished by normal HbA<sub>2</sub> levels (see [Alpha-Thalassemia](#)).
- $\beta^+$  silent variants (see Table 8) are associated with consistent residual output of beta globin chains, normal red blood cell indices, and normal or borderline HbA<sub>2</sub>.

## Molecular Genetic Testing

When the hematologic analysis is abnormal, molecular genetic testing of *HBB* may be performed to identify the underlying pathogenic variants, including mild and silent  $\beta$ -thalassemia pathogenic variants.

## 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.

A thorough overview of the issues involved in  $\beta$ -thalassemia prevention is provided in *Prevention of Thalassaemias and other Haemoglobin Disorders Volume 1* [Angastiniotis et al 2013] and *Volume 2* [Old et al 2012].

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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.** Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

Once both *HBB* pathogenic variants have been identified in an affected family member or – in the context of population screening, the couple at risk – prenatal and preimplantation genetic testing are possible. Prenatal testing is available not only in cases of high-risk pregnancies but also in indeterminate-risk pregnancies.

An indeterminate-risk pregnancy is one in which:

- One parent is a definite heterozygote, and the other parent has a  $\beta$ -thalassemia-like hematologic picture, but no *HBB* pathogenic variant has been identified by molecular analysis;
- The mother is a known heterozygote, and the clinical/genetic status of the father is unknown or the father is unavailable for testing, especially if the father belongs to a population at risk.

Options for noninvasive prenatal testing:

- **Analysis of fetal DNA in maternal plasma** for the presence of the father's pathogenic variant may lead to prenatal exclusion of homozygous  $\beta$ -thalassemia. Sufficient DNA may not be available.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## 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](#).*

- **Cooley's Anemia Foundation**  
Phone: 212-279-8090  
[Thalassemia](#)
- **MedlinePlus**  
[Beta thalassemia](#)
- **Thalassaemia International Federation (TIF)**  
Cyprus  
Phone: +357 22 319129  
Fax: +357 22 314552  
Email: [thalassaemia@cytanet.com.cy](mailto:thalassaemia@cytanet.com.cy)  
[www.thalassaemia.org.cy](http://www.thalassaemia.org.cy)
- **Newborn Screening in Your State**  
Health Resources & Services Administration  
[www.newbornscreening.hrsa.gov/your-state](http://www.newbornscreening.hrsa.gov/your-state)
- **National Haemoglobinopathy Registry**  
United Kingdom

**Phone:** 0161 277 7917

**Email:** support@mdsas.com

[www.nhr.nhs.uk](http://www.nhr.nhs.uk)

## 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.** Beta-Thalassemia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>HBB</i>	11p15.4	Hemoglobin subunit beta	HBB @ LOVD HbVar: A Database of Human Hemoglobin Variants and Thalassemias (HBB)	HBB	HBB

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for Beta-Thalassemia ([View All in OMIM](#))

<a href="#">141900</a>	HEMOGLOBIN--BETA LOCUS; HBB
<a href="#">613985</a>	BETA-THALASSEMIA

## Molecular Pathogenesis

*HBB*, which spans 1.6 kb, contains three exons and both 5' and 3' untranslated regions. *HBB* is regulated by an adjacent 5' promoter, which contains TATA, CAAT, and duplicated CACCC boxes, and an upstream regulatory element dubbed the locus control region (LCR). A number of transcription factors regulate the function of *HBB*, the most important of which is the erythroid Kruppel-like factor (EKLF), which binds the proximal CACCC box. *HBB* is contained within the *HBB* gene cluster, which includes *HBD*, *HBG1*, *HBG2*, and an *HBB* pseudogene, *HBBP1*. *HBB* encodes hemoglobin subunit beta. The heterodimeric protein hemoglobin A (HbA) is made up of two alpha globin chains and two beta globin chains.

Almost 300 *HBB* pathogenic variants associated with beta-thalassemia ( $\beta$ -thalassemia) have been characterized ([globin.bx.psu.edu](http://globin.bx.psu.edu)). The large majority are missense, nonsense, or frameshift variants. Rarely,  $\beta$ -thalassemia is the result of a large *HBB* deletion. Classes of pathogenic variants include the following:

- $\beta^0$ -thalassemia alleles (complete absence of hemoglobin subunit beta production) resulting from nonsense, frameshift, or (sometimes) splicing variants
- $\beta^+$ -thalassemia alleles (residual output of beta globin chains) resulting from pathogenic variants in introns, the promoter area (either the CACCC or TATA box), the polyadenylation signal, the 5' or 3' untranslated region, or splicing abnormalities
- Complex  $\beta$ -thalassemias (delta-beta-thalassemia and gamma-delta-beta-thalassemia) resulting from various contiguous deletions within the *HBB* gene cluster [Rooks et al 2005]
- Beta-thalassemia caused by deletion of the LCR (leaving *HBB* intact but blocking transcription) [Joly et al 2011]

Population-specific pathogenic variants are common (see Table 8), with four to six variants often accounting for most of the *HBB* pathogenic variants within a population.

**Table 8.** *HBB* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change (Alias <sup>1</sup> )	Predicted Protein Change <sup>2</sup> (Alias <sup>1</sup> )	Comment [Reference]
NM_000518.5	c.-151C>T (-101C>T)	--	Silent $\beta^+$ variant (See Genotype-Phenotype Correlations.)
	c.-142C>T (-92C>T)	--	
	c.-140C>T (-90C>T)	--	Mild $\beta^+$ variant (See Genotype-Phenotype Correlations.)
	c.-138C>A (-88C>A)	--	
	c.-138C>T (-88C>T)	--	<ul style="list-style-type: none"> <li>Mild <math>\beta^+</math> variant (See Genotype-Phenotype Correlations.)</li> <li>One of 6 common pathogenic variants in African &amp; African American populations <sup>3</sup></li> </ul>
	c.-137C>A (-87C>A)	--	Mild $\beta^+$ variant (See Genotype-Phenotype Correlations.)
	c.-137C>G (-87C>G)	--	
	c.-137C>T (-87C>T)	--	
	c.-136C>G (-86C>G)	--	<ul style="list-style-type: none"> <li>Mild <math>\beta^+</math> variant (See Genotype-Phenotype Correlations.)</li> <li>One of 6 common pathogenic variants in Mediterranean population <sup>4</sup></li> </ul>
	c.-136C>T (-86C>T)	--	Mild $\beta^+$ variant (See Genotype-Phenotype Correlations.)
	c.-81A>G (-31A>G)	--	
	c.-80T>A (-30T>A)	--	
	c.-79A>G (-29A>G)	--	<ul style="list-style-type: none"> <li>Mild <math>\beta^+</math> variant (See Genotype-Phenotype Correlations.)</li> <li>One of 6 common pathogenic variants in African &amp; African American populations <sup>3</sup></li> </ul>
	c.-78A>G (-28A>G)	--	<ul style="list-style-type: none"> <li>One of 4 common pathogenic variants in Chinese population <sup>4</sup></li> <li>One of 6 common pathogenic variants in Taiwanese population <sup>4</sup></li> </ul>
	c.-50A>C (+1A>C)	--	Silent $\beta^+$ variant (See Genotype-Phenotype Correlations.)
	c.-41del>T (+10delT)	--	Mild $\beta^+$ variant (See Genotype-Phenotype Correlations.)
	c.-29G>A (+22G>A)	--	
c.-18C>G (+33C>G)	--		
	--		



Table 8. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Alias <sup>1</sup> )	Predicted Protein Change <sup>2</sup> (Alias <sup>1</sup> )	Comment [Reference]
NM_000518.5 NP_000509.1	c.20delA	p.Glu7GlyfsTer13 (Glu6GlyfsTer12)	Mild $\beta^0$ variant (See Genotype-Phenotype Correlations.)
	c.25_26delAA	p.Lys9ValfsTer14 (Lys8ValfsTer13)	<ul style="list-style-type: none"> <li>Mild <math>\beta^0</math> variant (See Genotype-Phenotype Correlations.)</li> <li>One of 6 common pathogenic variants in Middle Eastern population <sup>4</sup></li> </ul>
	c.27dupG	p.Ser10ValfsTer14 (Ser9ValfsTer13)	One of 6 common pathogenic variants in Middle Eastern population <sup>4</sup>
	c.52A>T	p.Lys18Ter (Lys17Ter)	<ul style="list-style-type: none"> <li>One of 4 common pathogenic variants in Chinese population <sup>4</sup></li> <li>One of 6 common pathogenic variants in Taiwanese population <sup>4</sup></li> </ul>
	c.59A>G	p.Asn20Ser (Asn19Ser)	<ul style="list-style-type: none"> <li>Hb Malay</li> <li>Mild <math>\beta^+</math> variant (See Genotype-Phenotype Correlations.)</li> <li>One of 6 common pathogenic variants in Taiwanese population <sup>4</sup></li> </ul>
NM_000518.5	c.75T>A (IVS1-18T>A)	See footnote 5.	<ul style="list-style-type: none"> <li>Mild <math>\beta^+</math> variant (See Genotype-Phenotype Correlations.)</li> <li>One of 6 common pathogenic variants in African &amp; African American populations <sup>3</sup></li> </ul>
NM_000518.5 NP_000509.1	c.82G>T	p.Ala28Ser (Ala27Ser)	<ul style="list-style-type: none"> <li>Hb Knossos</li> <li>Silent <math>\beta^+</math> variant (See Genotype-Phenotype Correlations.)</li> </ul>
NM_000518.5	c.93-21G>A (IVS1-21G>A)	--	One of 6 common pathogenic variants in Mediterranean population <sup>4</sup>
	c.92+1G>A (IVS1+1G>A)	--	
	c.92+5G>C (IVS1+5G>C)	--	<ul style="list-style-type: none"> <li>One of 6 common pathogenic variants in African &amp; African American populations <sup>3</sup></li> <li>One of 6 common pathogenic variants in Middle Eastern &amp; Taiwanese populations <sup>4</sup></li> </ul>
	c.92+6T>C (IVS1+6T>C)	--	<ul style="list-style-type: none"> <li>Mild <math>\beta^+</math> variant (See Genotype-Phenotype Correlations.)</li> <li>One of 6 common pathogenic variants in Mediterranean population <sup>4</sup></li> </ul>
NM_000518.5 NP_000509.1	c.118C>T	p.Gln40Ter (Gln39Ter)	One of 6 common pathogenic variants in Mediterranean & Middle Eastern populations <sup>4</sup>
	c.126_129delCTTT	p.Phe42LeufsTer19	<ul style="list-style-type: none"> <li>One of 4 common pathogenic variants in Chinese population <sup>4</sup></li> <li>One of 6 common pathogenic variants in Taiwanese population <sup>4</sup></li> </ul>
	c.135delC	p.Phe46LeufsTer16 (Phe45LeufsTer15)	One of 6 common pathogenic variants in Middle Eastern population <sup>4</sup>

Table 8. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Alias <sup>1</sup> )	Predicted Protein Change <sup>2</sup> (Alias <sup>1</sup> )	Comment [Reference]
NM_000518.5	c.316-197C>T (IVS2+654C>T)	--	<ul style="list-style-type: none"> <li>One of 4 common pathogenic variants in Chinese population <sup>4</sup></li> <li>One of 6 common pathogenic variants in Taiwanese population <sup>4</sup></li> </ul>
	c.316-106C>G (IVS2+745C>G)	--	One of 6 common pathogenic variants in Mediterranean population <sup>4</sup>
	c.316-7C>G (IVS2-7C>G)		Mild $\beta^+$ variant (See Genotype-Phenotype Correlations.)
	c.316-2A>G (IVS2-2A>G)	--	One of 6 common pathogenic variants in African & African American populations <sup>3</sup>
	c.316-2A>C (IVS2-2A>C)	--	
	c.315+1G>A (IVS2+1G>A)	--	One of 6 common pathogenic variants in Middle Eastern population <sup>4</sup>
	c.*6C>G	--	Silent $\beta^+$ variant (See Genotype-Phenotype Correlations.)
	c.*110T>C	--	Mild $\beta^+$ variant (See Genotype-Phenotype Correlations.)
	c.*111A>G	--	
c.*113A>G	--	Silent $\beta^+$ variant (See Genotype-Phenotype Correlations.)	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

2. Variant nomenclature following current guidelines has been provided. However, because the initiation methionine is not part of the mature beta globin protein, the long-standing convention of numbering the amino acids is to begin with the next amino acid (Val). For consistency with the literature and the Globin Gene Server ([globin.bx.psu.edu](http://globin.bx.psu.edu)), the traditional amino acid numbering has been provided.

3. *HBB* pathogenic variants included in Table 8 account for 75%-80% of pathogenic variants in this population.

4. *HBB* pathogenic variants included in Table 8 account for 91%-95% of pathogenic variants in this population.

5. Nucleotide substitution activates a splice site.

## Chapter Notes

### Author Notes

Arielle L Langer, MD, MPH, is the director of the Thalassemia Program at Brigham and Women's Hospital and Dana Farber Cancer Institute. Her research interests include the impact of thalassemia on pregnancy.

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