

# THALASSEMIA


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## Definition

Thalassemias are inherited hemoglobin disorders caused by mutations in globin genes that lead to decreased synthesis of either  $\alpha$ -globin or  $\beta$ -globin chains.

 Key idea:


Reduced synthesis of one globin chain causes:

- ↓ Hemoglobin formation
- ↑ Excess unpaired normal globin chains → toxic intracellular precipitates → Red cell damage, hemolysis, and ineffective erythropoiesis 

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## EPIDEMIOLOGY & EVOLUTIONARY ASPECT

- Common in Mediterranean, African, and Asian regions

- Areas where falciparum malaria is endemic
  - Like HbS, thalassemia mutations are believed to confer partial protection against malaria, explaining their high prevalence 
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## GENETIC BASIS (PATHOGENESIS)

- Autosomal codominant inheritance
- Adult hemoglobin (HbA) =  $\alpha_2 \beta_2$

### Globin Gene Locations

- $\alpha$ -globin genes:
  - 2 genes on each chromosome 16 → 4 total
- $\beta$ -globin gene:
  - 1 gene on chromosome 11 → 2 total (one from each parent)

 Clinical severity depends on:

- Which globin chain is affected
- Number of affected genes

- Type of mutation inherited
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## $\beta$ -THALASSEMIA

### Types of $\beta$ -Globin Mutations



Mutations fall into two major categories:

#### 1) $\beta^0$ mutation

- No  $\beta$ -globin synthesis
- Severe functional deficit

#### 2) $\beta^+$ mutation

- Reduced but detectable  $\beta$ -globin synthesis
- Milder effect

 More than 100 different mutations identified  Most are single-base substitutions

📌 Important contrast:

Unlike  $\alpha$ -thalassemia, gene deletions are rare in  $\beta$ -thalassemia.

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## CLINICAL FORMS OF $\beta$ -THALASSEMIA

$\beta$ -Thalassemia Minor (Trait) 😊

- One abnormal  $\beta$ -globin allele
  - Usually asymptomatic or mildly symptomatic
  - Mild microcytic anemia
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$\beta$ -Thalassemia Major 




- Two  $\beta^0$  or  $\beta^0/\beta^+$  alleles
  - Severe disease
  - Presents in infancy
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$\beta$ -Thalassemia Intermedia 

- Usually at least one  $\beta^+$  allele
  - Severity between minor and major
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## MOLECULAR MECHANISMS OF DISEASE

$\beta$ -globin mutations impair synthesis via:


-  Abnormal RNA splicing (most common)
-  Defective gene promoter  $\rightarrow$   $\downarrow$  transcription
-  Coding region mutations  $\rightarrow$   $\downarrow$  translation

 The mutation type determines whether the allele is  $\beta^0$  or  $\beta^+$

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## MECHANISMS OF ANEMIA IN $\beta$ -THALASSEMIA

### Defective Hemoglobin Formation

- $\downarrow$  HbA production  $\rightarrow$  Microcytic, hypochromic red cells 

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## 2 Toxic Accumulation of $\alpha$ -Globin Chains ☠️

- Excess unpaired  $\alpha$ -chains
- Form insoluble precipitates
- Damage:
  - RBC membranes
  - Erythroid precursors

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## Ineffective Erythropoiesis 🧠🦴

- Severe damage to erythroid precursors
- → Apoptosis within bone marrow
- → Few RBCs released into circulation
- → Shortened lifespan of circulating RBCs

📌 This phenomenon is called ineffective erythropoiesis

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## IRON OVERLOAD IN $\beta$ -THALASSEMIA ⚠️

Despite anemia:

- Dietary iron absorption increases

Why?

- ↓ Plasma hepcidin
- Hepcidin normally inhibits iron absorption
- Low hepcidin → uncontrolled iron uptake

→ Leads to secondary iron overload, even without transfusions

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## PATHOPHYSIOLOGY OF $\beta$ -THALASSEMIA MAJOR

Normal globin synthesis ↓ → Reduced  $\beta$ -globin production → Relative excess of  $\alpha$ -globin chains → Insoluble  $\alpha$ -globin aggregates form → Membrane damage in erythroblasts & RBCs



Two parallel consequences:

## 1] Ineffective erythropoiesis

Most erythroblasts → Die in bone marrow (apoptosis)  
→ ↓ Effective RBC production → Severe anemia



Tissue hypoxia → ↑ Erythropoietin → Marrow expansion → Skeletal deformities 🦴

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## 2] Extravascular hemolysis

Aggregate-containing RBCs → Destroyed by splenic macrophages → Splenomegaly → Worsening anemia

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## Iron Dysregulation Pathway 🇨🇪

Ineffective erythropoiesis → ↑ Erythroferrone →  
Suppression of hepcidin → ↑ Intestinal iron absorption  
PLUS → Repeated blood transfusions 🩸



Systemic iron overload (secondary hemochromatosis)

→ Iron deposition in:

- Liver
  - Heart 
  - Endocrine organs
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Summary 

$\beta$ -Thalassemia is an autosomal codominant disorder caused by reduced or absent  $\beta$ -globin synthesis, leading to microcytic hypochromic anemia, ineffective erythropoiesis, hemolysis, and iron overload due to low hepcidin levels.

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$\alpha$ -THALASSEMIA 

Basic Concept

Unlike  $\beta$ -thalassemia,  $\alpha$ -thalassemia is caused predominantly by gene deletions involving one or more  $\alpha$ -globin genes on chromosome 16.

 Key principle:

Disease severity is directly proportional to the number of  $\alpha$ -globin genes deleted


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## $\alpha$ -GLOBIN GENE DELETIONS & CLINICAL CORRELATION

Each person normally has 4  $\alpha$ -globin genes (2 on each chromosome 16).

Deletion Pattern  $\rightarrow$  Clinical Outcome

- 1 gene deleted ( $-\alpha / \alpha \alpha$ )  $\rightarrow$  Silent carrier state  $\rightarrow$  No anemia, clinically normal
- 2 genes deleted ( $-\alpha / -\alpha$  or  $-- / \alpha \alpha$ )  $\rightarrow$   $\alpha$ -thalassemia trait  $\rightarrow$  Mild microcytic, hypochromic anemia

- 3 genes deleted ( $--/-\alpha$ )  $\rightarrow$  HbH disease  $\rightarrow$  Moderate anemia
  - 4 genes deleted ( $--/--$ )  $\rightarrow$  Hydrops fetalis (Hb Bart syndrome)  $\rightarrow$  Lethal in utero 
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## PATHOGENESIS OF $\alpha$ -THALASSEMIA

### Effect of Progressive $\alpha$ -Globin Loss

Loss of  $\alpha$ -globin genes  $\rightarrow$   $\downarrow$   $\alpha$ -chain synthesis  $\rightarrow$   
Relative excess of:

- $\beta$ -globin chains (later life)
  - $\gamma$ -globin chains (fetal life)
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## ABNORMAL HEMOGLOBINS FORMED

- Excess  $\beta$ -globin  $\rightarrow$   $\beta_4$  tetramers = HbH
- Excess  $\gamma$ -globin  $\rightarrow$   $\gamma_4$  tetramers = Hb Bart

 These tetramers are:

- Relatively stable
  - Cause less membrane damage than free  $\alpha$ -chains seen in  $\beta$ -thalassemia  $\rightarrow$  Ineffective erythropoiesis is less severe in  $\alpha$ -thalassemia 👍
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## WHY HbH & Hb BART ARE FUNCTIONALLY INEFFECTIVE 🚫🫁

Despite being stable, both HbH and Hb Bart have:

- Very high oxygen affinity
- Poor oxygen unloading in tissues

➡ Oxygen remains bound

➡ Tissue hypoxia despite normal or near-normal Hb levels


📌 Exam phrase:

“Functionally ineffective hemoglobin due to increased oxygen affinity”

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## CLINICAL FEATURES

### $\alpha$ -Thalassemia Trait & $\beta$ -Thalassemia Trait

- Usually asymptomatic
- Mild microcytic, hypochromic anemia
- Normal life expectancy
- Iron deficiency anemia must be excluded by iron studies 

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### HbH Disease

- Moderate anemia
- More effective erythropoiesis than  $\beta$ -thalassemia major
- Usually no transfusion dependence
- Iron overload is uncommon

## Hydrops Fetalis (Hb Bart Syndrome) 🚨


- Absence of functional hemoglobin
  - Severe hypoxia in utero
  - Incompatible with life
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## $\beta$ -Thalassemia Major ⚠️

- Manifests postnatally as HbF synthesis declines
- Severe anemia in infancy
- Growth retardation
- Skeletal deformities due to marrow expansion 🦴

## Management

- Regular blood transfusions
- Iron chelation therapy essential 🧲
- Without chelation:
  - Secondary hemochromatosis
  - Cardiac failure 💔

- Hematopoietic stem cell transplantation  
→ Treatment of choice when feasible 
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## IRON OVERLOAD MECHANISM IN THALASSEMIA

Expanded erythroblast mass → ↑ Erythroferrone secretion → Suppression of hepatic hepcidin → ↑ Iron absorption from gut → Iron overload even without transfusions

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## DIAGNOSIS OF THALASSEMIAS

### $\beta$ -Thalassemia Major

- Hb electrophoresis:
    - ↓ or absent HbA
    - ↑ HbF
    - Normal or ↑ HbA<sub>2</sub>
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## $\beta$ -Thalassemia Minor

- $\downarrow$  HbA ( $\alpha_2 \beta_2$ )
  - $\uparrow$  HbA<sub>2</sub> ( $\alpha_2 \delta_2$ )
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## HbH Disease

- Detection of  $\beta_4$  tetramers (HbH) on electrophoresis
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## Prenatal Diagnosis

- DNA-based testing
  - Thalassemia was the first disease diagnosed using molecular diagnostics
  -  Classic Robbins line - very exam friendly
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## Summary

$\alpha$ -Thalassemia is caused by deletions of  $\alpha$ -globin genes, with disease severity proportional to the number of genes lost. Excess  $\beta$ - or  $\gamma$ -globin chains form HbH or Hb Bart, which have high oxygen affinity and impaired tissue oxygen delivery.

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## MORPHOLOGY OF THALASSEMIA

### Overview

The morphologic spectrum in thalassemia is wide and depends on the specific molecular defect and disease severity.

 Key concept:

 Mild forms  $\rightarrow$  changes limited to peripheral blood



 Severe forms  $\rightarrow$  profound marrow, skeletal, and organ involvement

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## Peripheral Blood Findings

### Mild End of Spectrum

#### $\beta$ -Thalassemia minor & $\alpha$ -thalassemia trait

- Changes confined to peripheral blood
- Red cells are:
  - Microcytic  (small size)
  - Hypochromic  (pale)
  - Regular in shape

### Characteristic Cell Type

- Target cells 
  - Increased surface area-to-volume ratio
  - Cytoplasm pools centrally → dark red “bull’s-eye” appearance



 Exam tip:

Target cells = thalassemia, liver disease, HbC, post-splenectomy

## Severe End of Spectrum

### $\beta$ -Thalassemia major

Peripheral smear shows:

- Marked microcytosis
- Severe hypochromia
- Poikilocytosis → variation in shape 
- Anisocytosis → variation in size 
- Nucleated red cells (normoblasts) → Reflect intense erythropoietic drive

 Presence of nucleated RBCs = severe marrow stress

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## Intermediate Forms

### $\beta$ -Thalassemia intermedia & HbH disease

- Smear findings lie between minor and major
- Moderate microcytosis and hypochromia
- Fewer nucleated RBCs than major

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## Bone Marrow & Skeletal Changes 🦴🧬

### Pathologic Basis

- Ineffective erythropoiesis + hemolysis
- → Massive stimulation of erythroid lineage

### Bone Marrow Findings

- Striking erythroid hyperplasia
- Shift toward early erythroid precursors
- Marrow expansion may:
  - Fill entire intramedullary cavity
  - Invade bony cortex
  - Impair normal bone growth

➔ Leads to skeletal deformities (especially skull and facial bones) 🦴⚠️

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## Extramedullary Hematopoiesis 🩸➔🧠

Expanded marrow capacity exceeded

→ Hematopoiesis resumes in:

- Spleen
- Liver
- Lymph nodes

Results in:

- Splenomegaly  
  - Hepatomegaly
  - Lymphadenopathy
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Systemic Effects of Ineffective Erythropoiesis  

- Erythroid precursors consume:
  - Nutrients
  - Energy
- Yet fail to produce effective RBCs

 Leads to:


- Growth retardation

- Cachexia
  - Wasting similar to cancer-associated cachexia
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## Iron Overload (Hemosiderosis)

Unless prevented:

- Progressive iron accumulation over years
- Affects:
  - Liver
  - Heart
  - Endocrine organs

 Results in secondary hemochromatosis, a major cause of death in untreated patients

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## Comparison Note

- HbH disease &  $\beta$ -thalassemia intermedia:
  - Splenomegaly present

- Erythroid hyperplasia present
  - Growth retardation possible
  - BUT less severe than  $\beta$ -thalassemia major
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## Summary

Thalassemia shows a spectrum of morphologic changes ranging from mild microcytic hypochromic anemia with target cells to severe poikilocytosis, nucleated red cells, massive marrow expansion, skeletal deformities, extramedullary hematopoiesis, and secondary iron overload.

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-> The End <-