Hemoglobinopathies

⚖️ Types of Hereditary Hemoglobin Disorders

Type	Description
1. Quantitative abnormalities	• Abnormalities in the relative amounts of α and β subunits. → **Thalassemias.**
2. Qualitative abnormalities	• Structural variants caused by mutations altering amino acid sequence of globin chain. → >800 variants identified.
3. Hereditary persistence of fetal hemoglobin (HPFH)	• Impairment of the switch from γ-globin → β-globin after birth. • Fetal Hb ($\alpha_2\gamma_2$) has higher O_2 affinity than adult Hb ($\alpha_2\beta_2$). • Persistence of HbF → mild or no symptoms.

🫁 Thalassemias Overview

| Definition |

Most common single-gene disorder (either α or β).Caused by reduced synthesis of α or β chains → imbalanced α:β ratio.

| Main consequences |

• Imbalance in chain production → precipitation of excess unpaired chains → RBC destruction → anemia.

| Types |

α-Thalassemia: reduced α-chain synthesis.

β-Thalassemia: reduced β-chain synthesis.

🌿 Alpha-Thalassemia

| Definition |

Reduced or absent synthesis of α-globin chains.Mainly due to deletion mutations that inactivate α-globin genes.

| Genetic basis |

• 4 α-globin genes total (2 per chromosome 16).

• Severity depends on number of genes deleted (1–4).

| Mechanism |

↓ α-chain synthesis → excess β or γ chains → formation of unstable tetramers (β_4 or γ_4).

| Pathophysiology |

Unstable Hb (HbH or Hb Bart's) → high O_2 affinity → poor O_2 release → tissue hypoxia → hemolysis.

🩸 Subtypes of α-Thalassemia

Subtype	Genes Deleted	Main Hb Formed	Clinical Features
α^0-Thalassemia (Hydrops fetalis / Hb Bart's)	4/4	Hb Bart's (γ_4)	• Very high O_2 affinity (cannot release O_2). • Severe anemia, edema (hydrops fetalis). • Stillbirth or death soon after birth.
α^{+}-Thalassemia (HbH disease)	3/4	HbH (β_4)	• β-chain tetramers with high O_2 affinity, unstable → Heinz bodies. • Mild–moderate (sometimes severe) hemolytic anemia. • May need transfusions; not fatal.
α^{++}-Thalassemia trait	2/4	—	• Mild microcytic anemia. • Clinically mild.
α^{+}-Thalassemia (Silent carrier)	1/4	—	• No symptoms, clinically silent.

🧾 Summary of α-Thalassemia Severity

Deleted genes	Type	Main Hb formed	Severity
4	α^0 (Hydrops fetalis)	Hb Bart's (γ_4)	Lethal
3	α^{+} (HbH disease)	HbH (β_4)	Mild–moderate anemia
2	α^{++} (Trait)	—	Mild microcytic anemia
1	α^{+} (Silent carrier)	—	Asymptomatic

🔬**Beta-Thalassemia**

| Definition |

Reduced (β^+) or absent (β^0) synthesis of β-globin chains.Caused mainly by point mutations in β-globin gene on chromosome 11.

| Mechanism |

↓ β-chain → excess α-chain → precipitation → RBC membrane damage → hemolysis.

| Main mutation type |

Point mutations (not deletions).

| Result |

Imbalanced α:β chain ratio → ineffective erythropoiesis and anemia.

🧪 Types of β-Thalassemia

Type	Genetic basis	Clinical severity
β^0-Thalassemia	No β-chain synthesis	Severe
β^+-Thalassemia	Reduced β-chain synthesis	Mild–moderate
β-Thalassemia major (Cooley's anemia)	Both β genes defective	Severe anemia; requires lifelong transfusion
β-Thalassemia intermedia	Partial β production	Moderate anemia; occasional transfusion
β-Thalassemia minor (trait)	One gene defective	Mild microcytic anemia; often asymptomatic

🧠 Pathophysiology of β-Thalassemia

Defect	Effect
↓ β synthesis	→ Excess α-chains precipitate in RBCs.
Precipitated α-chains	→ Damage RBC membrane → intramedullary destruction.
Ineffective erythropoiesis	→ Bone marrow expansion (especially in skull/face).
Compensatory mechanisms	→ Extramedullary hematopoiesis → splenomegaly.
Iron overload	→ From transfusions + ↑ absorption → hemosiderosis.
Clinical findings	Anemia, bone deformities, hepatosplenomegaly, growth retardation.

⚖️ Comparison: α-Thalassemia vs β-Thalassemia

Feature	α-Thalassemia	β-Thalassemia
Defective chain	α-chain	β-chain
Mutation type	Deletion	Point mutation
Excess unpaired chain	β or γ → form β_4, γ_4	α-chains precipitate
Major Hb abnormality	Hb Bart's or HbH	↓ HbA, ↑ HbA_2, ↑ HbF
Severity depends on	Number of genes deleted	β^0 vs β^+ mutation
Main mutation location	Chromosome 16 (α gene cluster)	Chromosome 11 (β gene)
Pathophysiology	Unstable tetramers	Ineffective erythropoiesis
Mutation effect	Quantitative defect	Quantitative defect

🧩 Qualitative Abnormalities (Structural Variants)

| Definition |

Structural variants of Hb caused by point mutations that alter amino acid sequence → change in solubility, stability, or O_2 affinity.

| Categories |

A. Mutations in surface residues

B. Mutations in internal residues

C. Mutations at α1-β2 contacts

D. Mutations stabilizing methemoglobin

| Total variants |

> 800 hemoglobin variants known.

A.

Mutations in Surface Residues – Hemoglobin C (HbC)

| Mutation |

β6 Glutamic acid → Lysine

| Effect |

Replacement of negatively charged residue by positive → promotes Hb crystallization.

| Clinical features |

Mild chronic hemolytic anemia (less severe than sickle cell).

| Heterozygotes (HbA/HbC) |

Usually asymptomatic.

B.
Mutations in Internal Residues – Hemoglobin E (HbE)
| Mutation |
β26 Glutamic acid → Lysine
| Effect |
Occurs near splice site → abnormal splicing → ↓ β-chain synthesis.
| Nature of defect |
Both qualitative and quantitative (like mild thalassemia).
| Clinical |
Mild anemia, common in Southeast Asia.

C.
Mutations at α1-β2 Contacts – Hemoglobin S (HbS)
| Mutation |
β6 Glutamic acid → Valine
| Effect |
Valine (nonpolar) interacts hydrophobically with adjacent Hb → polymerization in deoxy state.
| Result |
RBCs deform (sickle shape) → vaso-occlusion, hemolysis, ischemia.

D.
Mutations Stabilizing Methemoglobin – Hemoglobin M
| Mutation site |
Near heme pocket (e.g., His → Tyr).
| Effect |
Stabilizes Fe^{3+} (ferric state) → cannot bind O_2.
| Clinical |
Methemoglobinemia → cyanosis, usually mild symptoms.

🩺 **Sickle Cell Disease (HbS)**

| Genetic mutation |

Point mutation in β-globin gene: Glu6Val (Valine replaces Glutamic acid).

| Mechanism |

• Valine forms hydrophobic patch → polymerization of deoxy-HbS → sickled RBCs.

| Factors promoting sickling |

↓ O_2, dehydration, high Hb concentration, low pH.

| Reversibility |

Sickling is initially reversible with oxygenation, but repeated cycles cause membrane damage → irreversible sickle cells.

| Clinical features |

• Hemolytic anemia• Painful vaso-occlusive crises• Splenic infarction → autosplenectomy• Increased risk of infection by encapsulated bacteria• Bone and organ infarctions

| Sickle cell trait (HbA/HbS) |

Heterozygous; mostly asymptomatic; protection against Plasmodium falciparum malaria.

| Sickle cell disease (HbS/HbS) |

Homozygous; severe anemia, chronic crises, organ damage.

| Treatment |

• Hydroxyurea (↑ HbF production)

• Transfusions, folic acid, infection control• Bone marrow transplantation (curative in some).

👶 **Hereditary Persistence of Fetal Hemoglobin (HPFH)**

| Definition |

Genetic condition with continued synthesis of γ-globin after birth.

| Mechanism |

Mutation in β-globin gene cluster → failed switch from γ → β production.

| Effect |

Elevated HbF ($\alpha_2\gamma_2$) levels in adults.

| Clinical significance |

• Benign; usually asymptomatic.

• In β-thalassemia or sickle cell → HbF presence lessens symptoms (because HbF inhibits polymerization of HbS).