Hemoglobin Structure

Hemoglobin (Hb) is synthesized in a complex series of steps. The heme part is synthesized in a series of steps in the mitochondria and the cytosol of immature red blood cells, while the globin protein parts are synthesized by ribosomes in the cytosol.
Heme synthesized by mitochondria, fixed with iron

Heme then surrounded by “globin” proteins that surround and “protect” the heme

Each single Hemoglobin molecule has two globin chains, each with its own heme protein attached

One globin chain is alpha

One is “non-alpha”

Two hemoglobin molecules combine to produce functional hgb tetramer
- Alpha globin genes coded on Chrom 16

  Each Chrom 16 has 2 alpha gene loci

  four total per cell

- Non alpha globin genes on Chrom 11

  Arranged from embryonic expression to adult expression

  (epsilon, gamma, delta, beta)

  Adult chromosome has one copy of beta gene

  Two per cell
Chromosome 11
β globin gene

Chromosome 16
α globin gene
Chromosome 16

Alpha  Alpha
Alpha  Alpha

Chromosome 11

Gamma  Gamma  Delta  Beta
Gamma  Gamma  Delta  Beta

97% = Hemoglobin A

1% = Hemoglobin F (Fetal)

2% = Hemoglobin A2
Hemoglobin Abnormalities

There are 3 main categories of inherited Hemoglobin abnormalities:

- **Structural or qualitative**: The amino acid sequence is altered because of incorrect DNA code (HBs).
- **Quantitative**: Production of one or more globin chains is reduced or absent (Thalassemia).
- **Hereditary persistence of Fetal Hemoglobin (HPFH)**: Complete or partial failure of γ globin to switch to β globin.
Laboratory Methods to evaluate Hemoglobin

Red cell morphologies:
HbS: Sickle cells
Red cell morphologies:
HbS: Sickle cells
HbC: Target cells, crystals after splenectomy
Red cell morphologies:

HbS: Sickle cells
HbC: Target cells, crystals after splenectomy
Thalassemias: Microcystosis, target cells, basophilic stippling
Thalassemia

Variety of genetic defects in globin chain synthesis – decreased or absent

Classified according to globin chain that is affected – e.g. β-thalassemia vs. α thalassemia

Heterozygous: minor

Homozygous: major

The name is derived from the Greek words Thalasso = Sea" and "Hemia = Blood" in reference to anemia of the sea.
Pathophysiology

- If α chain is affected, excess of β chains produced. If β chain is affected, excess of α chains produced

- Imbalance in chain synthesis causes
  - Decrease in total hemoglobin production
  - Ineffective erythropoiesis
  - Chronic hemolysis

- Excess α chains are unstable – precipitate within cell – precipitates bind to cell membrane, causing membrane damage
Excess $\beta$ chains combine to form Hb H
- High oxygen affinity
- poor oxygen transporter
- unstable
Genetics of β thalassemia

- Monogenic disorder: a single gene disorder
- β thalassemia result from over 150 mutations of the β globin genes that result in the absence or a reduction of the β globin chains
Transmission of β thalassemia

If a carrier (thalassemia minor) marries a non-carrier, on average half of their children will be carriers, but none will develop thalassemia major.
Transmission $\beta$ of thalassemia - Cont

- However if two carriers marry, in each pregnancy there is a 25% chance of a non-carrier child, a 50% chance of a carrier child (thalassemia minor), and a 25% chance of a child with thalassemia major.
β- thalassemia Major – Cooley’s Anemia

Homozygous ($\beta^+/$ $\beta$ or $\beta 0/$ $\beta 0$) or double heterozygous ($\beta^+/$ $\beta 0$) inheritance

Pathophysiology: dramatic reduction or complete absence of $\beta$ chain synthesis

– Symptoms begin to manifest at age 6 months
- Increase in non $\beta$ containing hemoglobins
- Excess $\alpha$ chains precipitate in cells
- hemolysis
Pathophysiology

- $\gamma$
  - $\alpha_2 \gamma_2$
    - hb F
      - level of hb F of RBC
        - High O2 affinity
  - excess
    - dest of RBC
      - hemolysis
        - Splenomegaly
          - Anemia
            - tissue hypoxia
              - Epo
                - ineff erythropoiesis

- $\alpha$
  - hemolysis

- $\beta$
  - ineff erythropoiesis

Hi O2 affinity
anemia

EPO

Marrow expansion

Skeletal def.
Inc. metabolic rate
Gout

Folate def.

Inc. Fe absorption

Fe overload

endocrine def.
cardiac f
LC

transfusion

anemia
Clinical Symptoms

- First observed in infants – irritability, pallor, failure to thrive
- Enlarged abdomen
- Sever anemia - cardiac failure in first decade of life
- Growth is retarded; brown pigmentation of skin
- Bone changes – facial deformities
- Splenomegaly – extramedullary hematopoiesis
Gallstones – due to increased intravascular and extravascular hemolysis
-Skeletal abnormalities – expansion of bone marrow
-Pathological fractures – thinning of calcified bone
-Iron toxicity – multiple transfusions
Laboratory Findings of tha.major

Hemoglobin as low as 2-3 g/dL
- Markedly microcytic/hypochromic
- Marked anisocytosis and poikilocytosis
- Basophilic stippling and polychromasia
- Hemoglobin electrophoresis – 90% Hb F and increased Hb A2
- Increased bilirubin, decreased haptoglobin
- Increased serum iron and decreased TIBC
Thalassemia carriers (trait):

Usually no signs or symptoms are apparent, except for a mild anemia.

Carriers are usually initially detected through screening, or when performing routine CBC. Later it can be confirmed using hemoglobin electrophoresis.
Alpha Thalassemias

There are two α genes on each of two chromosome 16 structures (four α genes in the diploid state)

Mutations can affect one or more of the α genes resulting in four levels of severity

- When all four genes deleted – no α chains, hydrops fetalis or α-thalassemia major
- 3 of the four deleted, hemoglobin H Disease
- 2 of the 4 deleted, α-thalassemia minor
- 1 deletion, silent carrier
Classification & Terminology

Alpha Thalassemia

- $\alpha\alpha/\alpha\alpha$  Normal •
- $\alpha/\alpha\alpha$  Silent carrier •
- $-\alpha/-\alpha$  Minor •
- $/--/\alpha\alpha$  
- $--/-\alpha$  Hb H disease •
- $--/--$  Barts hydrops fetalis •