The Thalassemias

Introduction

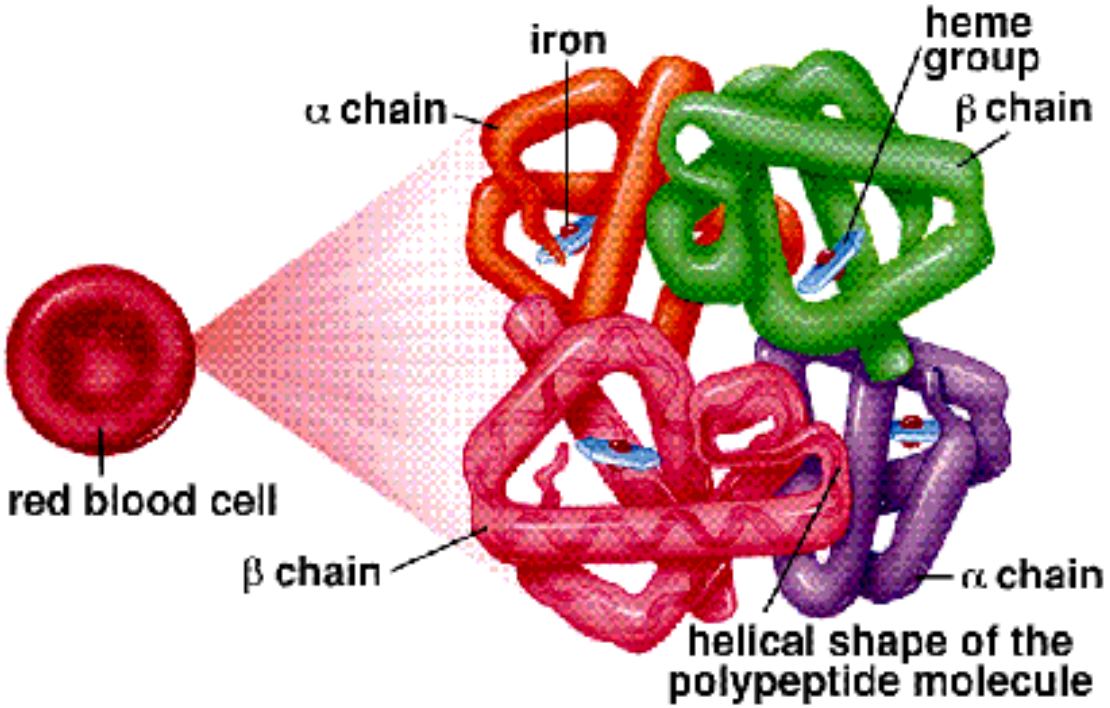
- Heritable, hypochromic anemias-varying degrees of severity
- Genetic defects result in decreased or absent production of mRNA and globin chain synthesis
- At least 100 distinct mutations
- High incidence in Asia, Africa, Mideast, and Mediterrenean countries

Hemoglobin Review

- Each complex consists of :
  - Four polypeptide chains, non-covalently bound
  - Four heme complexes with iron bound
  - Four O2 binding sites

Hemoglobin Structure

- Four subunits
  - two α
  - two β
- Iron
- Heme
- Binds 4 O_2



Globin Chains

- Alpha Globin
  - 141 amino acids
  - Coded for on Chromosome 16
  - Found in normal adult hemoglobin, A1 and A2
- Beta Globin
  - 146 amino acids
  - Coded for on Chromosome 11, found in Hgb A1
- Delta Globin
  - Found in Hemoglobin A2--small amounts in all adults
- Gamma Globin
  - Found in Fetal Hemoglobin
- Zeta Globin
  - Found in embryonic hemoglobin

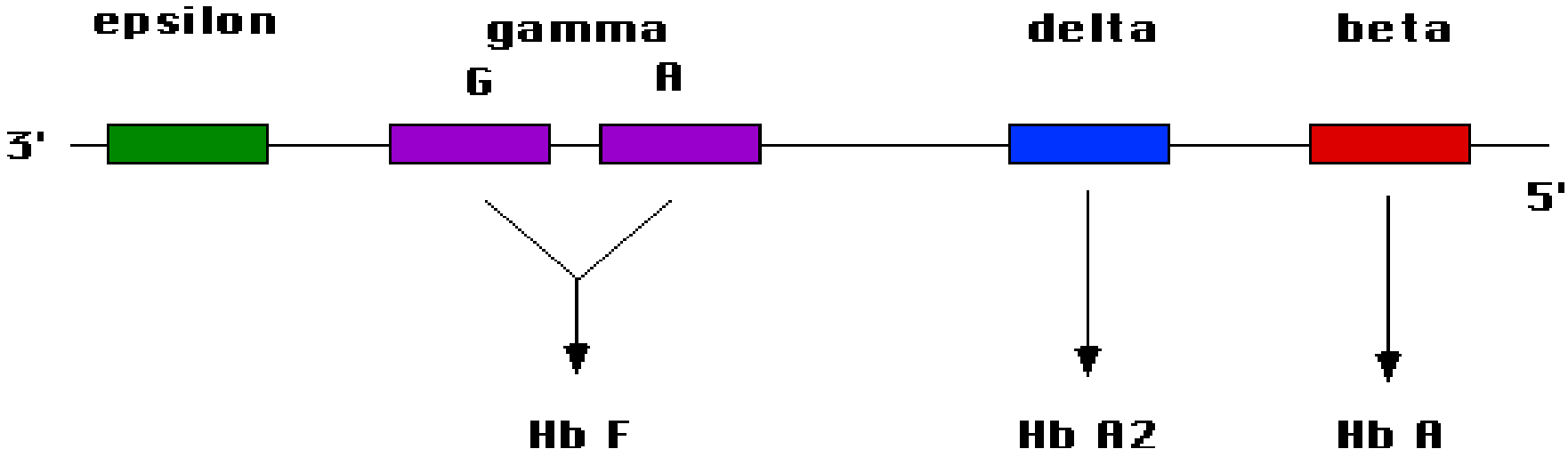
Hemoglobin Types

Hemoglobin Type	Globin Chains
• Hgb A1—92%---------	$\alpha_2\beta_2$
• Hgb A2—2.5%--------	$\alpha_2\delta_2$
• Hgb F — <1%---------	$\alpha_2\gamma_2$
• Hgb H ----------	β_4
• Bart's Hgb----------	γ_4
• Hgb S----------	$\alpha_2\beta_{26}^{glu\rightarrow val}$
• Hgb C----------	$\alpha_2\beta_{26}^{glu\rightarrow lys}$

Genetics

- Alpha globins are coded on chromosome 16
  - Two genes on each chromosome
  - Four genes in each diploid cell
  - Gene deletions result in Alpha-Thalassemias
- Also on chromosome 16 are Zeta globin genes—Gower's hemoglobin (embryonic)
- Beta globins are coded on chromosome 11
  - One gene on each chromosome
  - Two genes in each diploid cell
  - Point mutations result in Beta-Thalassemias
- Also on chromosome 11 are Delta (Hgb A2) and Gamma (Hgb F) and Epsilon (Embryonic)

Beta Globin Gene Cluster
Chromosome 11



Alpha Globin Gene Cluster
Chromosome 16

Alpha Thalassemias

- Result from gene deletions
- One deletion—Silent carrier; no clinical significance
- Two deletions—α Thal trait; mild hypochromic microcytic anemia
- Three deletions—Hgb H; variable severity, but less severe than Beta Thal Major
- Four deletions—Bart's Hgb; Hydrops Fetalis; In Utero or early neonatal death

Alpha Thalassemias

- Usually no treatment indicated
- 4 deletions incompatible with life
- 3 or fewer deletions have only mild anemia

Beta Thalassemias

- Result from Point Mutations on genes
- Severity depends on where the hit(s) lie
  - β^0-no β-globin synthesis;
  - β^+ reduced synthesis
- Disease results in an overproduction of α-globin chains, which precipitate in the cells and cause splenic sequestration of RBCs
- Erythropoiesis increases, sometimes becomes extramedullary

β-Thal--Clinical

- β-Thalassemia Minor
  - Minor point mutation
  - Minimal anemia; no treatment indicated
- β-Thalassemia Intermedia
  - Homozygous minor point mutation or more severe heterozygote
  - Can be a spectrum; most often do not require chronic transfusions
- β-Thalassemia Major-Cooley's Anemia
  - Severe gene mutations
  - Need careful observation and intensive treatment

Beta Thalassemia Major

- Reduced or nonexistent production of β-globin
  - Poor oxygen-carrying capacity of RBCs
    - Failure to thrive, poor brain development
  - Increased alpha globin production and precipitation
    - RBC precursors are destroyed within the marrow
- Increased splenic destruction of dysfunctional RBCs
  - Anemia, jaundice, splenomegaly
- Hyperplastic Bone Marrow
  - Ineffective erythropoiesis—RBC precursors destroyed
    - Poor bone growth, frontal bossing, bone pain
  - Increase in extramedullary erythropoiesis
- Iron overload—increased absorption and transfusions
  - Endocrine disorders, Cardiomyopathy, Liver failure

β-Thalassemia Major—Lab findings

- Hypochromic, microcytic anemia
  - Target Cells, nucleated RBCs, anisocytosis
- Reticulocytosis
- Hemoglobin electrophoresis shows
  - Increased Hgb A2—delta globin production
  - Increased Hgb F—gamma globin production
- Hyperbilirubinemia
- LFT abnormalities (late finding)
- TFT abnormalities, hyperglycemia (late endocrine findings)

β-Thalassemia Major--Treatment

- Chronic Transfusion Therapy
  - Maximizes growth and development
  - Suppresses the patient's own ineffective erythropoiesis and excessive dietary iron absorption
  - PRBC transfusions often monthly to maintain Hgb 10-12
- Chelation Therapy
  - Binds free iron and reduces hemosiderin deposits
  - 8-hour subcutaneous infusion of deferoxamine, 5 nights/week
  - Start after 1year of chronic transfusions or ferritin>1000 ng/dl
- Splenectomy--indications
  - Trasfusion requirements increase 50% in 6mo
  - PRBCs per year >250cc/kg
  - Severe leukopenia or thrombocytopenia

β-Thalassemia Major Complications and Emergencies

- Sepsis—Encapsulated organisms
  - Strep Pneumo
- Cardiomyopathy—presentation in CHF
  - Use diuretics, digoxin, and deferoxamine
- Endocrinopathies—presentation in DKA
  - Take care during hydration so as not to precipitate CHF from fluid overload

Anticipatory Guidance and Follow Up

- Immunizations—Hepatitis B, Pneumovax
- Follow for signs of diabetes, hypothyroid, gonadotropin deficiency
- Follow for signs of cardiomyopathy or CHF
- Follow for signs of hepatic dysfunction
- Osteoporosis prevention
  - Diet, exercise
  - Hormone supplementation
  - Osteoclast-inhibiting medications
- Follow ferritin levels

On The Horizon

- Oral Chelation Agents
- Pharmacologically upregulating gamma globin synthesis, increasing Hgb F
  - Carries O2 better than Hgb A2
  - Will help bind α globins and decrease precipitate
- Bone Marrow transplant
- Gene Therapy
  - Inserting healthy β genes into stem cells and transplanting