Lecture_5

Hemoglobinopathies

Thalassaemia

fourth year students

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BASICS - 3 types of Hb

1. Hb A

- 2 α and 2 β chains forming a tetramer
- 97% adult Hb
- Postnatal life Hb A replaces Hb F by 6 months

2. Fetal Hb F

- (2α and 2γ) chains
- 1% of adult Hb
- 70-90% at term.
- Falls to 25% by 1st month and progressively

3. Hb A2

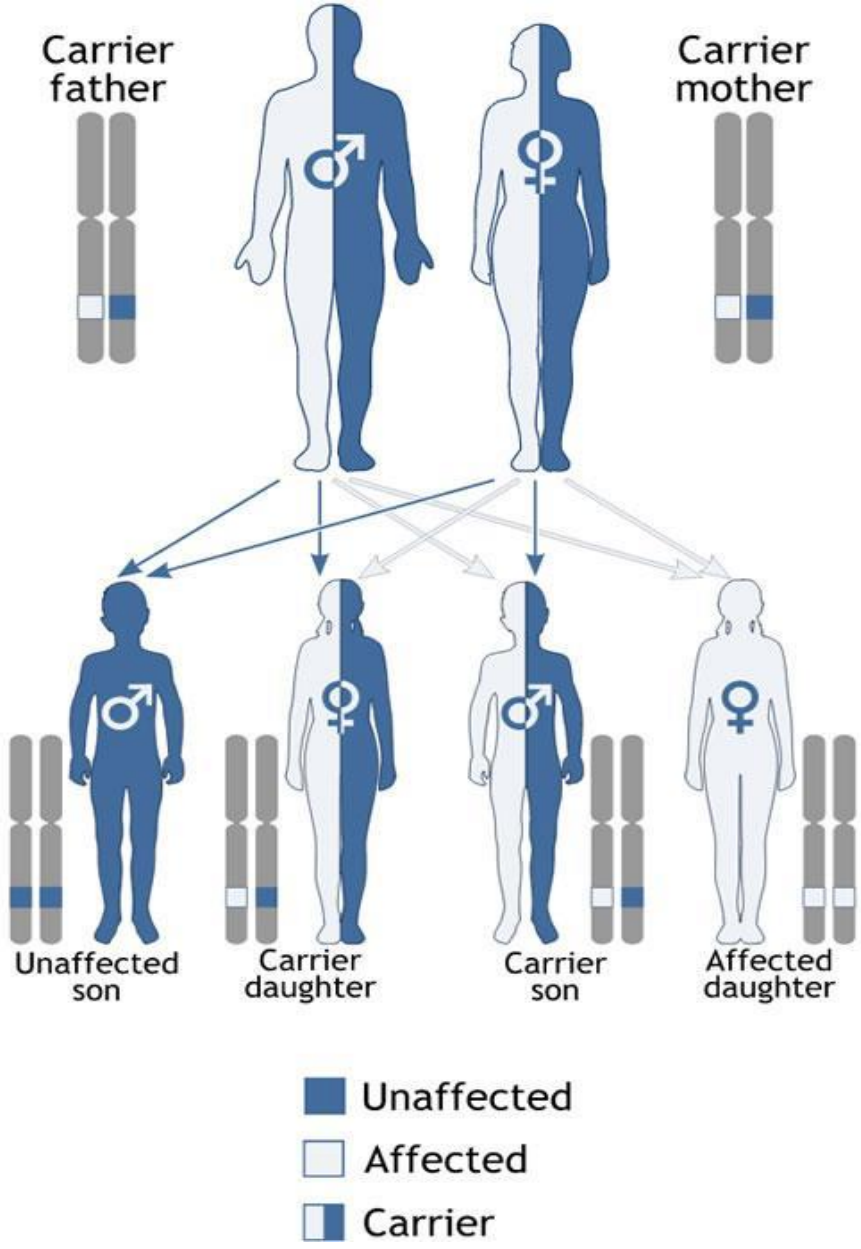
- Consists of 2 α and 2 δ chains
- 1.5 – 3.0% of adult Hb

Thalassaemia

- Thalassemias are inherited , autosomal recessive diseases characterized by:

A failure to produce hemoglobin.

  - o Beta-thalassemia
  - o Alpha-thalassemia



Thalassaemia

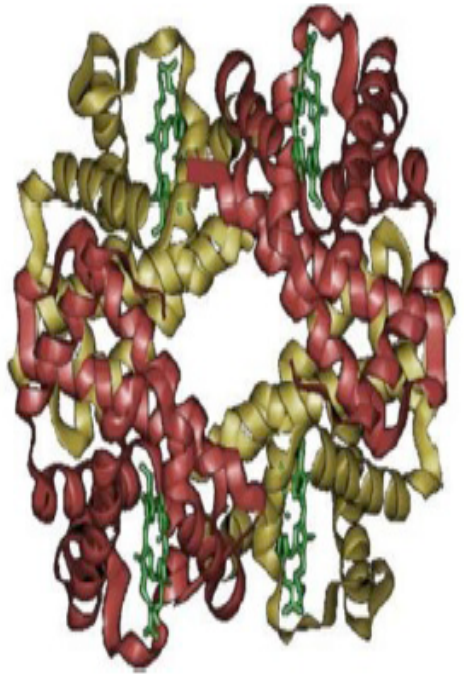
- Autosomal recessive

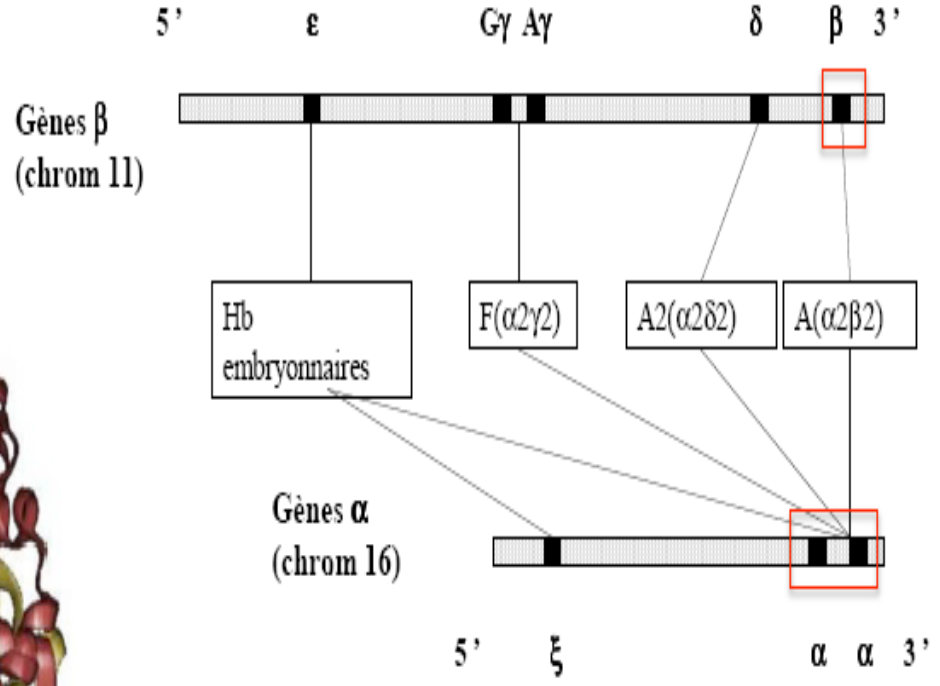
Beta thal –

- point mutations on chromosome **11**

Alpha thal –

- gene deletions on chromosome **16**



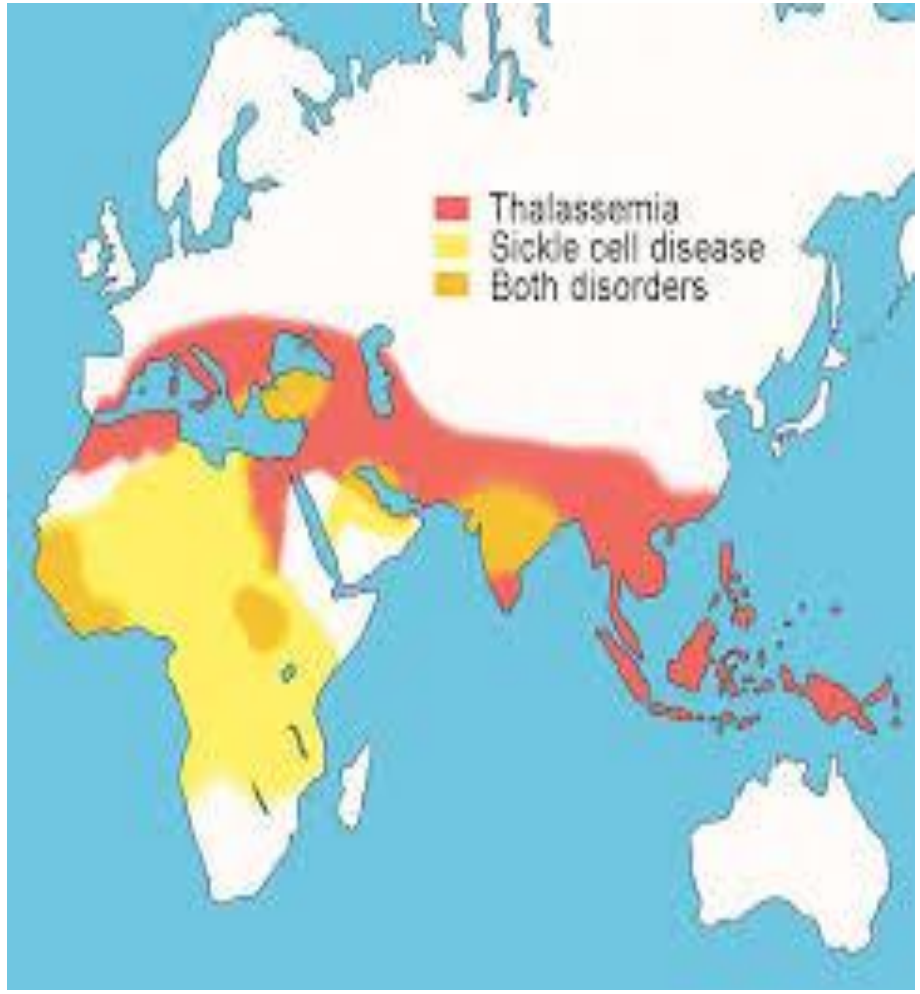


Genetic defect in the production of the alpha or beta globin chain

Quantitative Hemoglobinopathy

Beta-thalassemia

- Failure to synthesise beta chains of the Hb
- is the most common type of thalassaemia
- Mainly affects people from around the *Mediterranean sea , the Middle East , Asia (China, India, Vietnam ,Thailand) and sub saharian Africa*



- **ß-thalassemia**

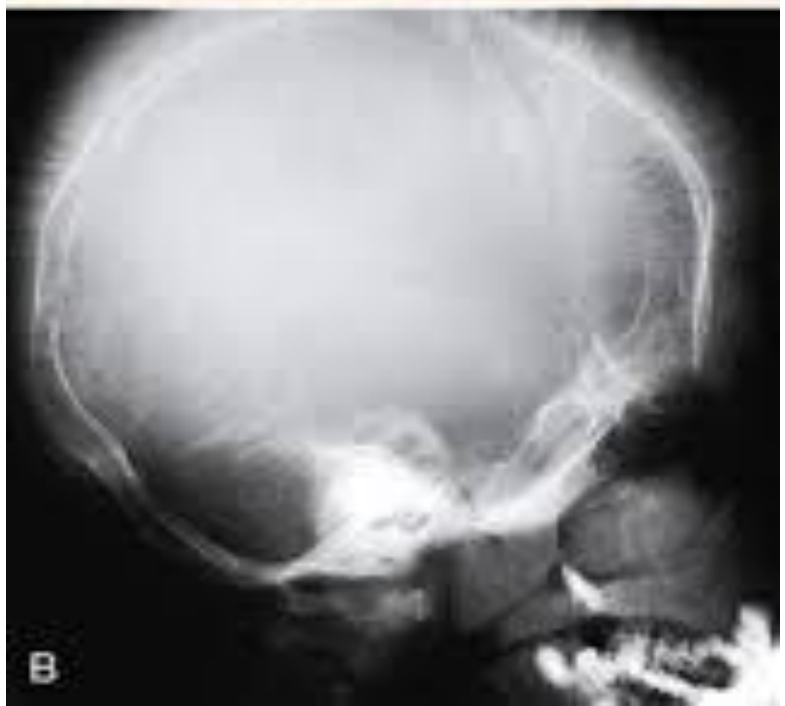
- Whether the production of beta globin chains is absent or only reduced, we distinguish:
  - ß-thalassemia major (Cooley’s anemia)
  - ß-thalassemia intermedia
  - ß-thalassemia minor

CLASSIFICATION OF β THALASSEMIA

CLASSIFICATION	GENOTYPE	CLINICAL SEVERITY
β thal minor/trait	β/β+, β/β0	Silent
β thal intermedia	β+ /β+, β+/β0	Moderate
β thal major	β0/ β0	Severe

Beta-thalassaemia major (homozygotes)

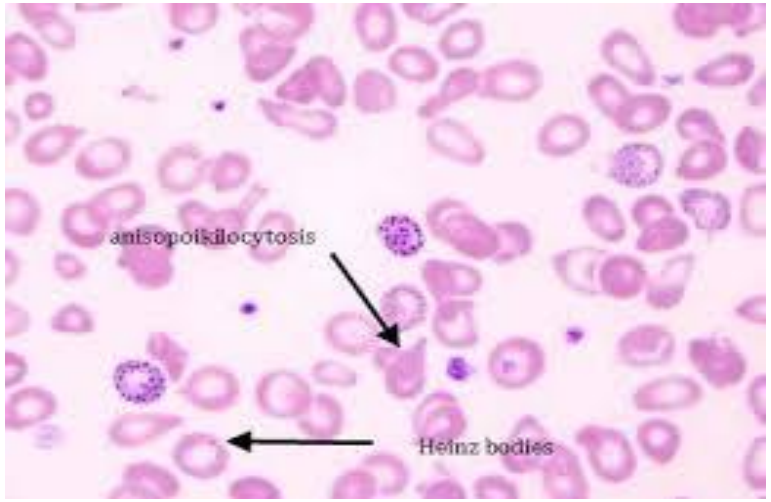
- Profound hypochromic anaemia
- Absence or gross reduction of the amount of HbA
- Raised levels of Hb F
- To compensate a massive hemolysis, erythropoiesis is increased in bone leading to bone deformities
- In children facial bones thicken (deformation of the jaws, flattening of the root of the nose, excessive spacing of the eyes)



- Secondary complications of *B*-thalassaemia major are due to **iron overload** consecutive to hemolysis / continuous transfusion
  - Endocrine and metabolic disorders
    - Hypogonadism 40-55%
    - Stunting 33%
    - Diabetes 6-13%
    - Hypothyroidism 10%
  - Cardiac complications
    - Heart failure (hemosiderosis)
    - Arrythmias
  - Cholelithiasis

Diagnosis of ß-thalassemia major:

- **Clinical suspicion** (signs, symptoms, origin…)
- **Blood smear** :
  - microcytic hypochromic anemia, anisopoikilocytosis, target cells, nucleated RBC, leptocytes, basophilic stippling, tear drop cells
  - cytoplasmic incl bodies in α thal
  - Post splenectomy : Howell-Jolly and Heinz bodies
  - Reticulocyte count increased (up to 10%)
- **Biochemistry:**
  - Hemolysis increased (indirect bilirubin , LDH) and (decreased Haptoglobin
  - Increased (Serum iron, ferritin)
- **Electrophoresis of hemoglobin**
  - (increased **HbA2 3.5-8**% , increased **HbF 1-2**%)



Treatment:

1. Erythropoietic failure
    - Allogeneic HSCT from HLA-compatible sibling
    - Transfusion to maintain Hb > 10 g/dL
    - Folic acid 5 mg daily
2. Iron overload
    - Iron therapy contraindicated
    - Iron chelation therapy
3. Splenomegaly causing mechanical problems, excessive transfusion needs
    - Splenectomy

β-thalassemia intermedia

- Moderate pallor, usually maintains Hb >6gm%
- Anemia worsens with pregnancy and infections (erythroid stress)
- Less transfusion dependant
- Skeletal changes present, progressive splenomegaly
- Growth retardation less
- Longer survival than Thal major

ß-thalassemia minor

- is caused by the mutation of one of the two beta genes.
- Beta-thalassaemia minor (heterozygotes)
- Mild anaemia
- Microcytic hypochromic erythrocytes (not iron-deficient)
- Some target cells
- Punctate basophilia
- Raised Hb A2 fraction

Alpha-thalassaemia

- Reduced or absent alpha-chain synthesis is common in Southeast Asia
- There are two alpha gene on chromosome 16 and therefore each individual carries 4 alpha gene alleles

NO. OF GENES PRESENT	GENOTYPE	CLINICAL CLASSIFICATION
4 genes	αα/αα	Normal
3 genes	αα/- α	Silent carrier
2 genes	- α/- α or αα/- -	α thalassemia trait
1 gene	-α/- -	Hb H Ds
0 genes	- -/- -	Hb Barts / Hydrops fetalis

Haemoglobin H

formed from the excess of beta chains, which is functionally useless, so that patients rely on their low levels of HbA for oxygen transport.

Treatment of Hb H disease is similar to that of beta-thalassaemia of intermediate severity, involving folic acid transfusion if required and avoidance of iron therapy

Hb Bart

Very severe. The fetus cannot live once outside the uterus and may not survive gestation: most such infants are stillborn with hydrops fetalis, and those who are born alive die shortly after birth.