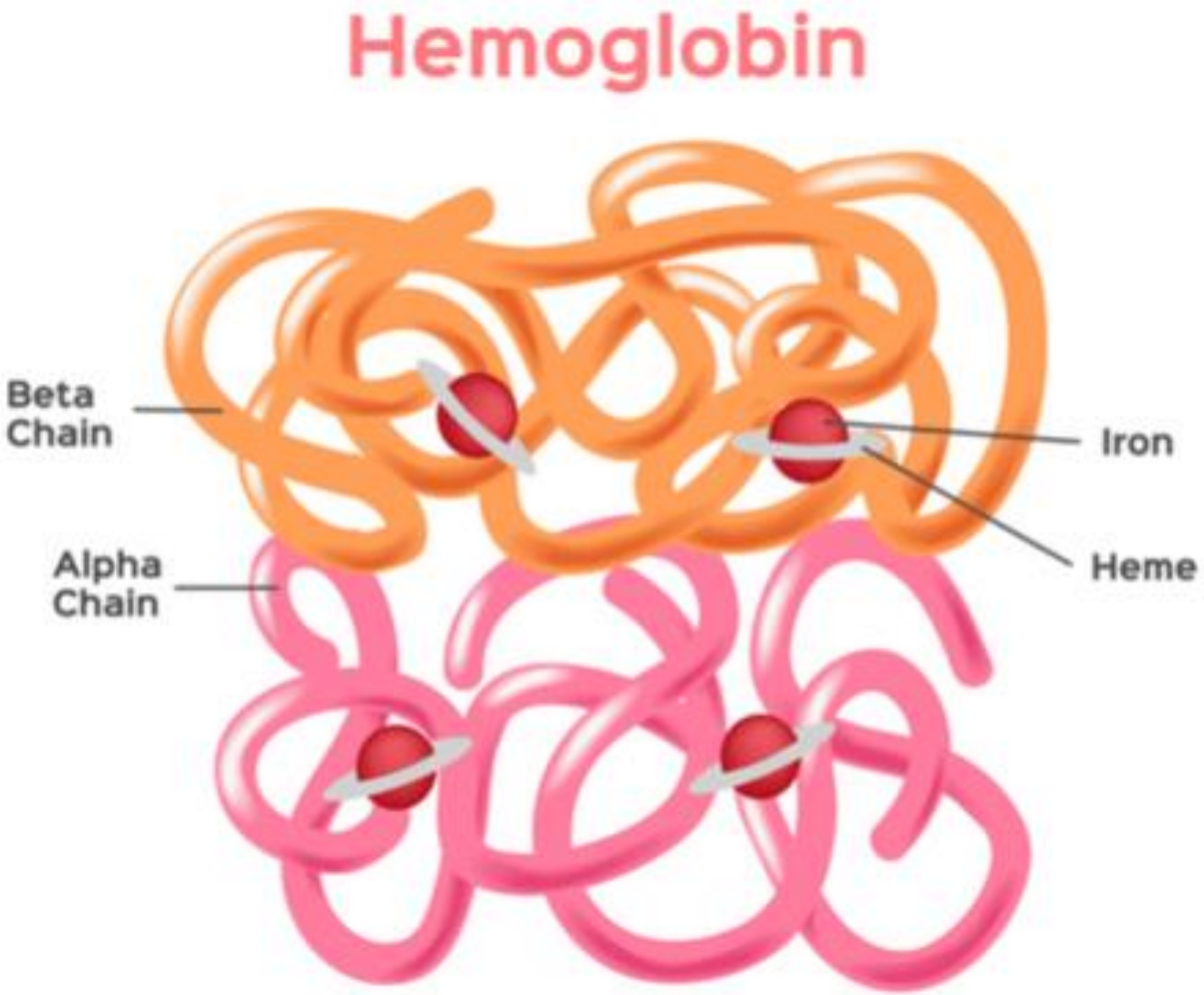
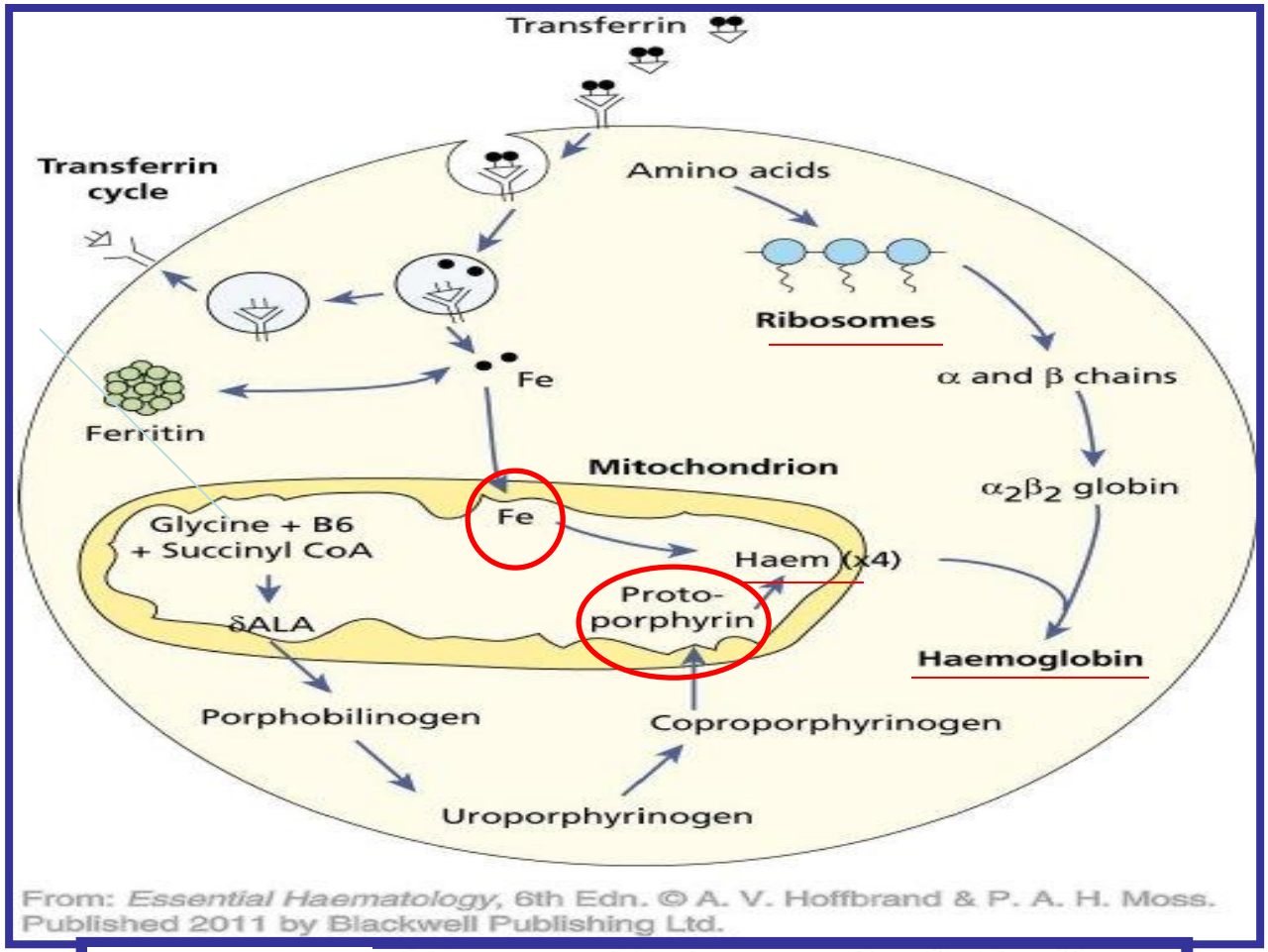
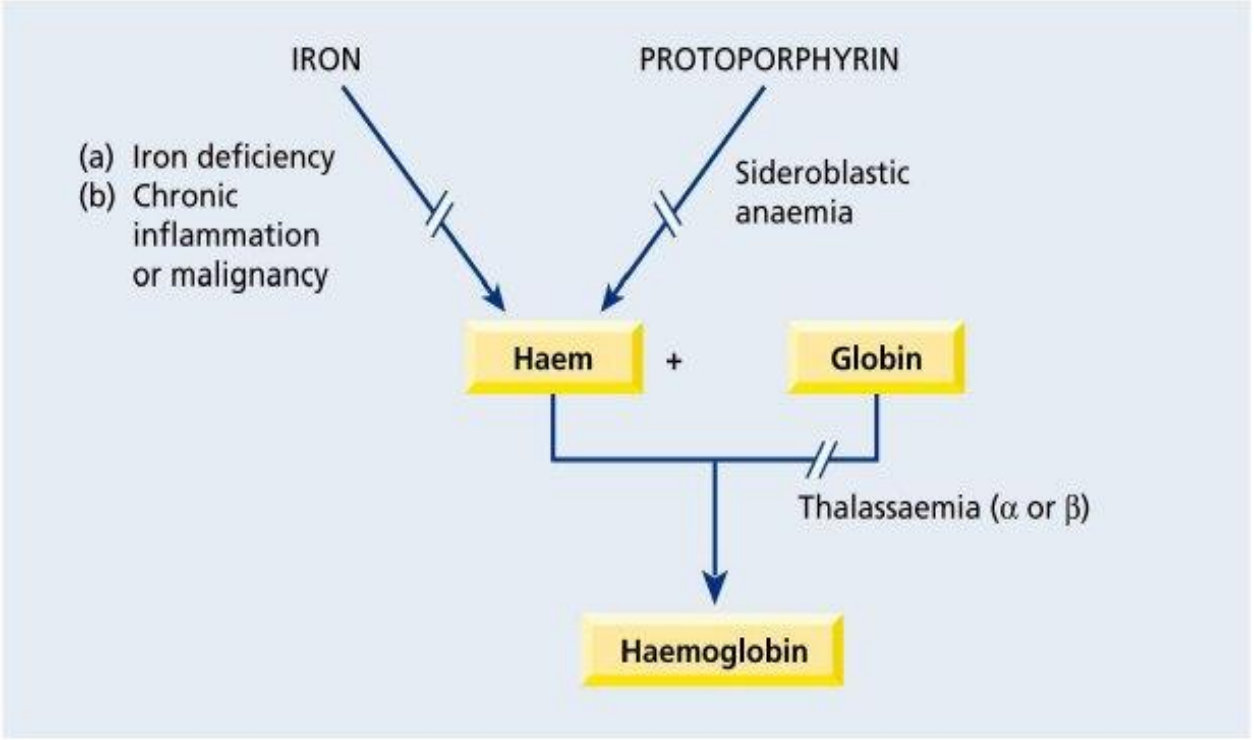
Hemoglobin Structure





Haemoglobin synthesis in the developing red cell. The mitochondria are the main sites of protoporphyrin synthesis, iron (Fe) is supplied from circulating transferrin; globin chains are synthesized on ribosomes. δ-ALA, δ-aminolaevulinic acid; CoA, coenzyme A.



Types of normal Hemoglobins

- All Normal Haemoglobins consists of two pairs of globin chains, at the centre of each is one heme group.
- Hb A (Adult Hb) : $\alpha_2 \beta_2$ (~96%).
- HbF (Fetal Hb) : $\alpha_2 \gamma_2$ (0.1-<2.0%).
- Hb A2 (minor Adult Hb) : $\alpha_2 \delta_2$(1.8-3.5%).

Hemoglobinopathies

Disorders of globin synthesis rather than hem synthesis.

Qualitative Disorders

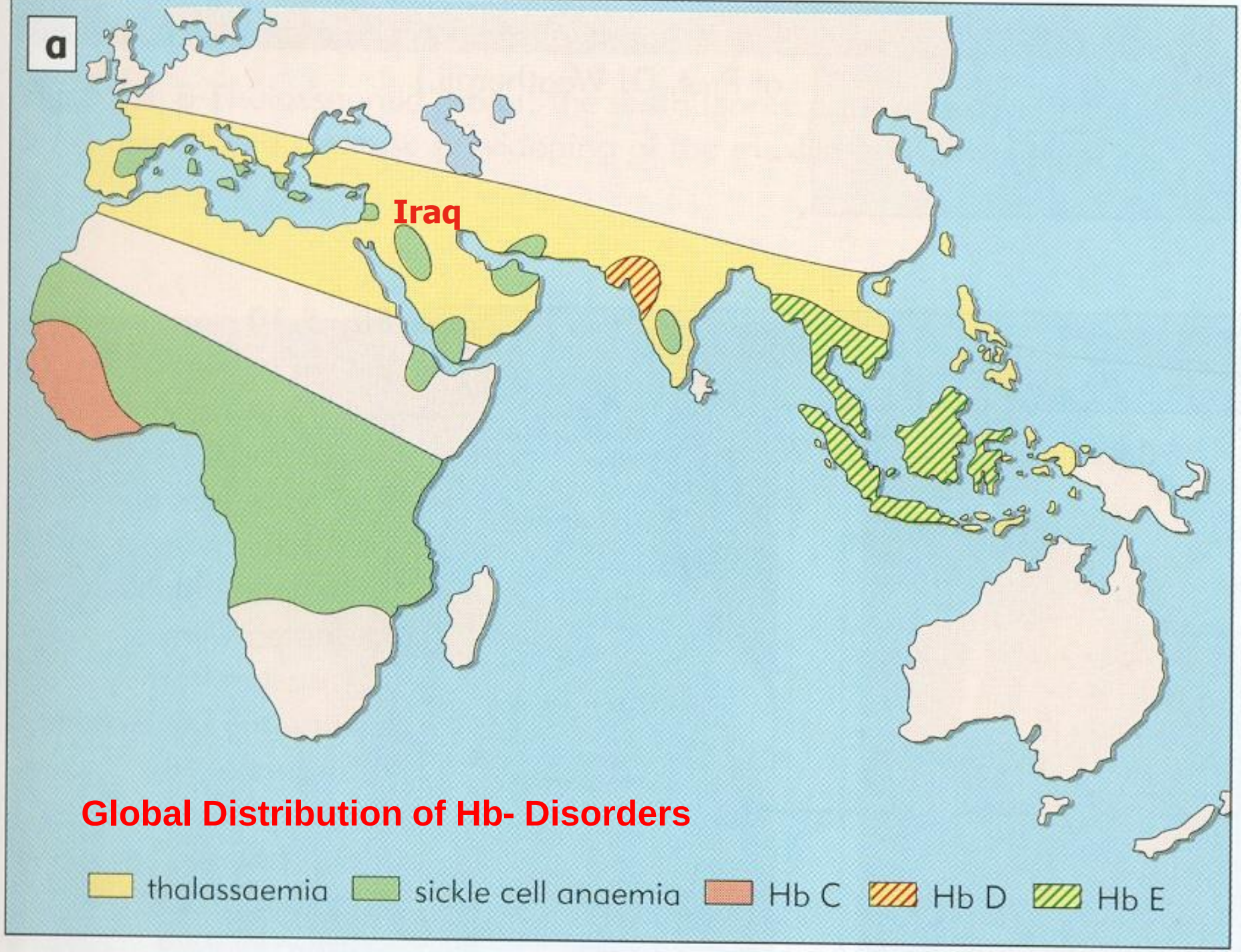
-Abnormal hemoglobins are formed when the sequence of globin chain amino acids is altered. There is usually only a single amino acid substitution in one of the globin (polypeptide) chains.

Quantitative Disorders

-Thalassemia result from a lack of production of globin chains to maintain adequate Hb levels.

β- Thalassaemia

- β-Thalassaemias are inherited defects in the rate of synthesis of β-globin chains of Hb, which are widely distributed throughout the world, with considerable frequencies in certain areas particularly the Mediterranean and Middle Eastern countries, including Kurdistan and Iraq.

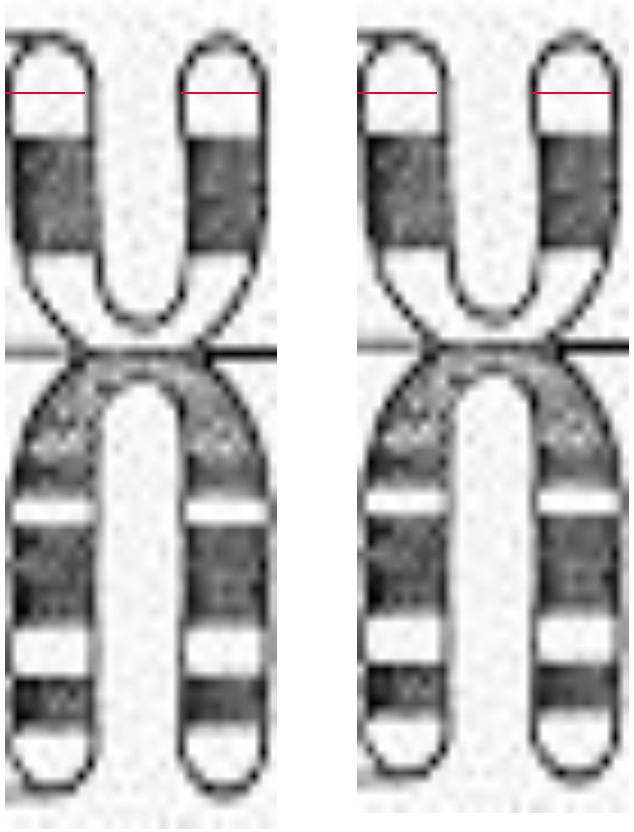

a
Iraq
Global Distribution of Hb- Disorders
thalassaemia
sickle cell anaemia
Hb C
Hb D
Hb E

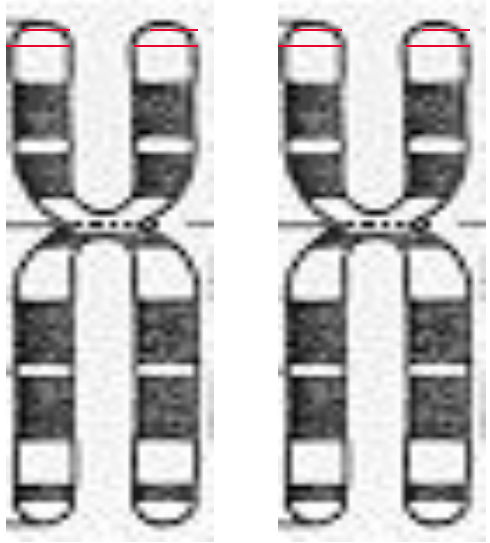
Genetics of β thalassemia

- There is one β- globin gene on each chromosome 11 in human genome.
- This form of thalassaemia is mostly caused by point mutations involving various points in and around the beta globin gene.
- The inheritance of this disorder is autosomal recessive, so that heterozygous are usually symptomless, while homozygotes are severely or moderately affected.
- β0 denotes absent β chain synthesis, while β+ means reduced synthesis of β chain .

Chromosomal location of globin genes

11p15.5



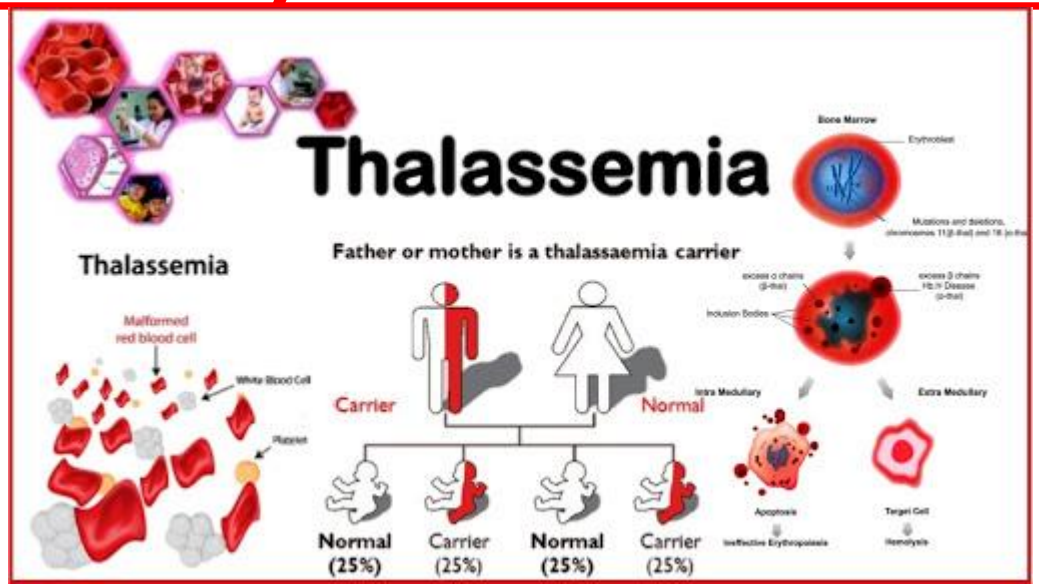


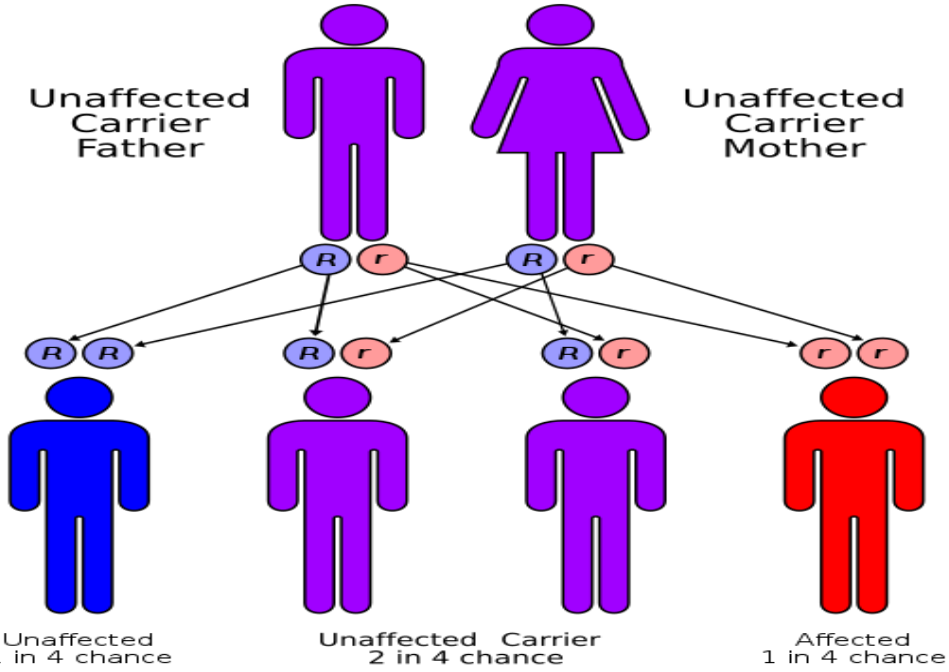
16p13.3

Beta cluster

Alpha cluster

Recessively Inherited Diseases





Clinically β thalassaemia could be classified into :

- β Thalassemia Major :

  Severe clinical manifestations presenting before the age of 2 years, usually transfusion dependent. Due usually to homozygosity to β thalassemia gene defect (β0 β0, β+ β+, β0 β+) .

- β Thalassemia minor :

  Mild or no clinical manifestations, usually does not require specific management. Due usually to heterozygosity to β thalassemia gene defect($\beta^0\beta$ or β^+ β) .

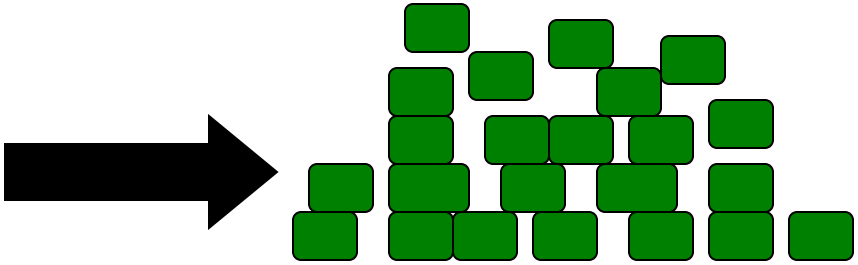
- β Thalassemia Intermedia :

  Moderate manifestations, intermediate between major and minor.

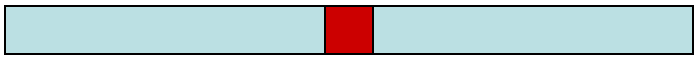
Simplified diagram of types of Beta thal. Genetic defect & relevance of Beta chain production

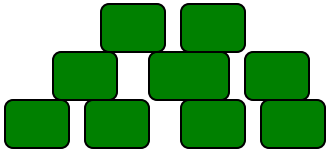
Normal β chain production

Normal β gene



β^+ thal. Gene defect



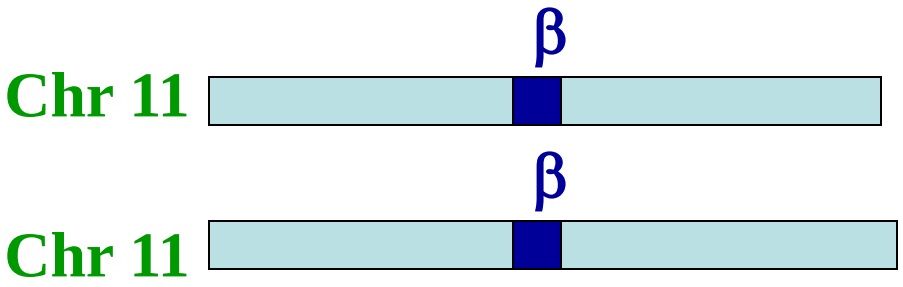


reduced β chain production

β^o thal. Gene defect

No β chain production

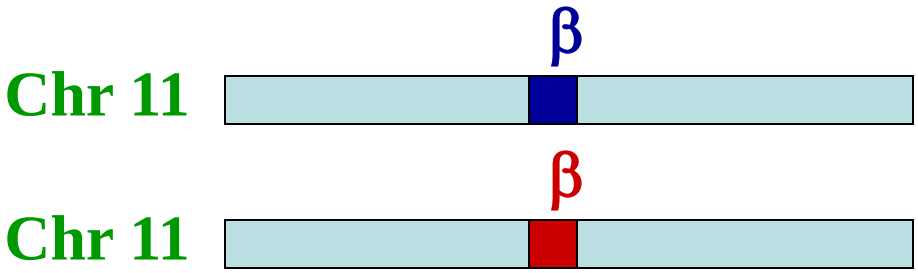
Courtesy of professor Nasir Al Allawi



Normal beta genes

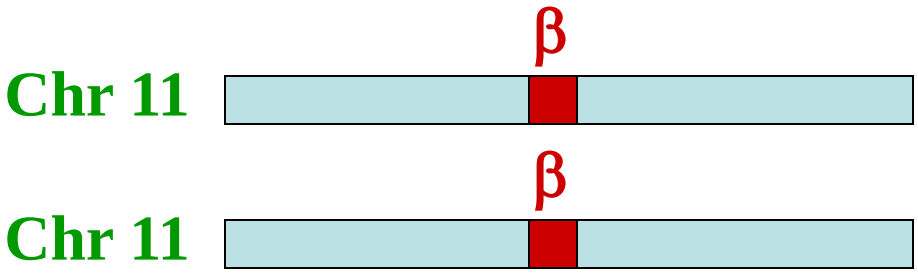
Defective β gene

Normal β gene



Heterozygous to beta thalassemia genetic defect

→ ***Thalassamia Minor***



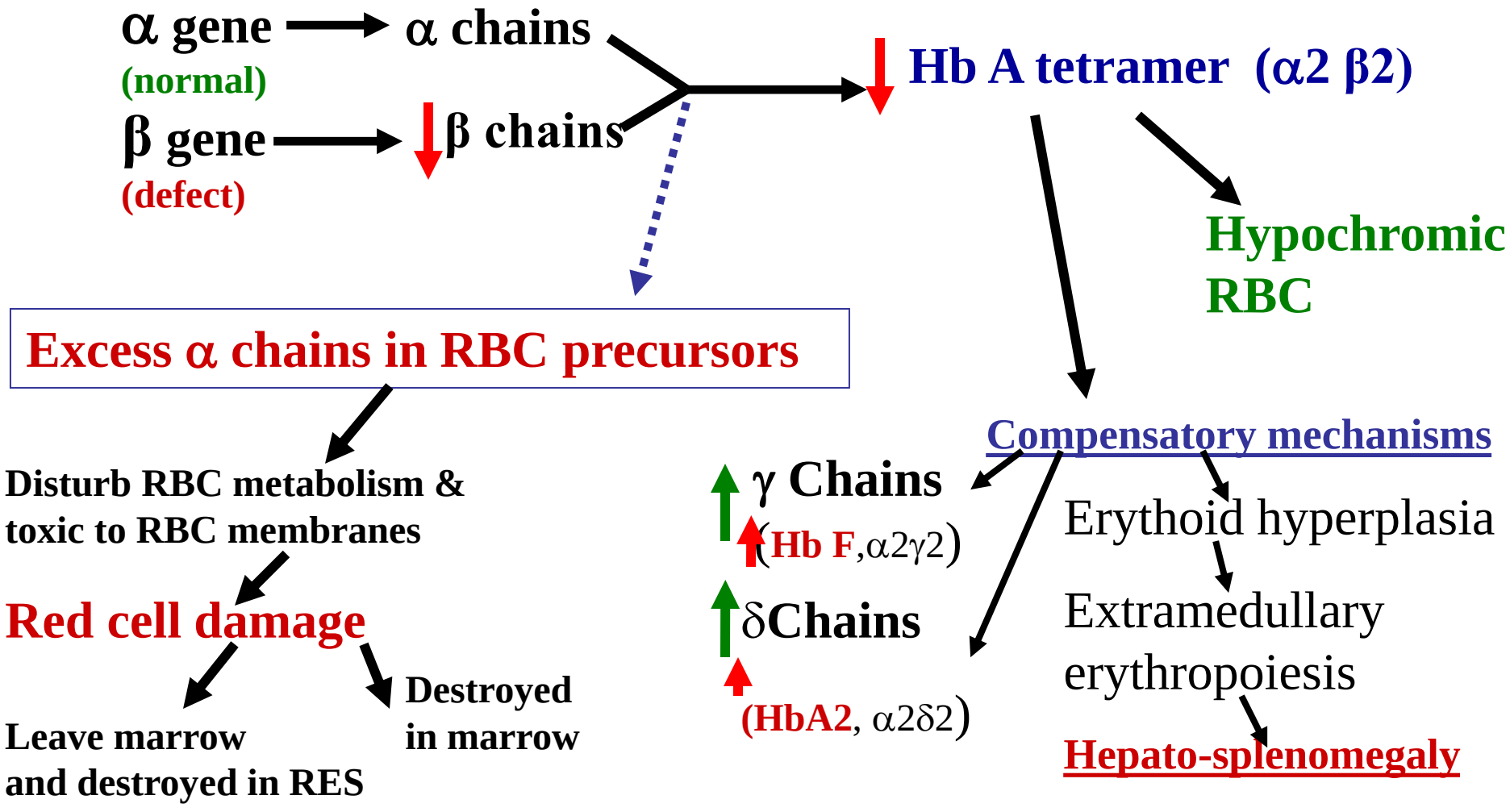
Homozygous to beta thalassemia genetic defect

→ ***Thalassamia Major***

Courtesy of professor Nasir Al Allawi

Pathophysiology of β thalassemia major

Courtesy of professor Nasir Al Allawi



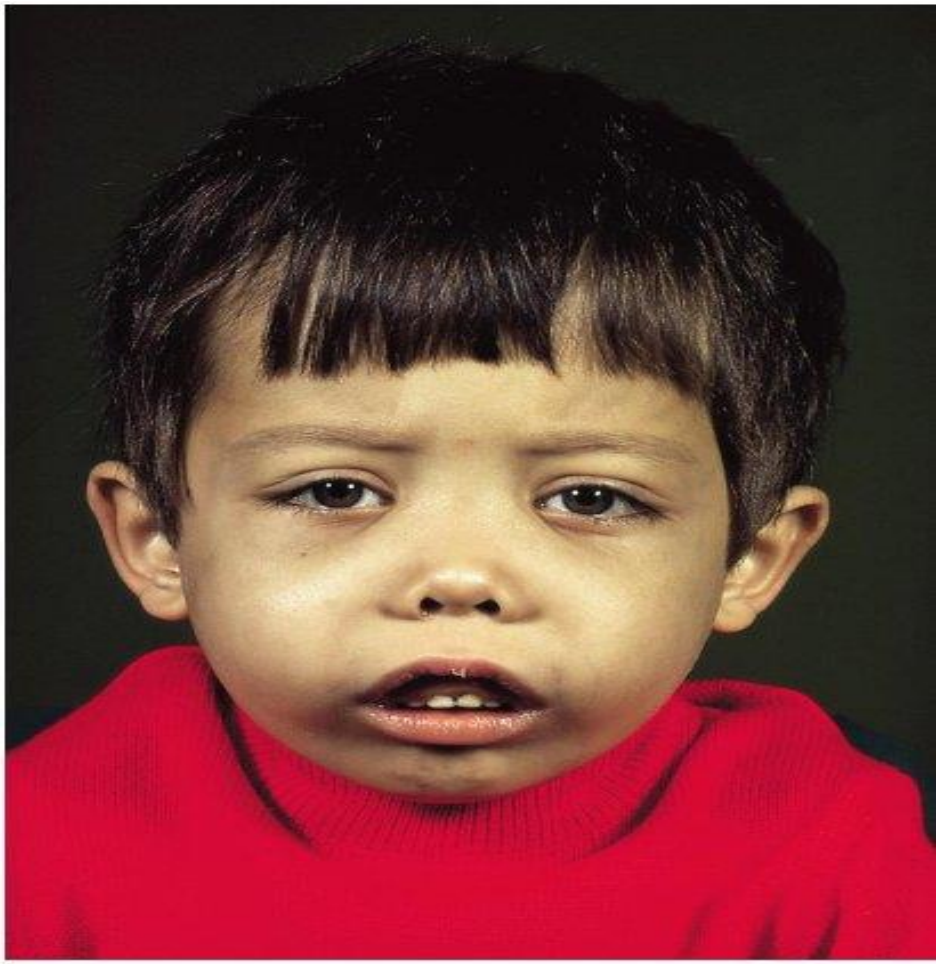
Clinical features of β thalassaemia Major

- First diagnosis between age of 6 months and 2 years.

- Presentation usually with pallor, poor feeding, failure to thrive , abdominal swelling (due to hepato-splenomegaly) and sometimes Jaundice.

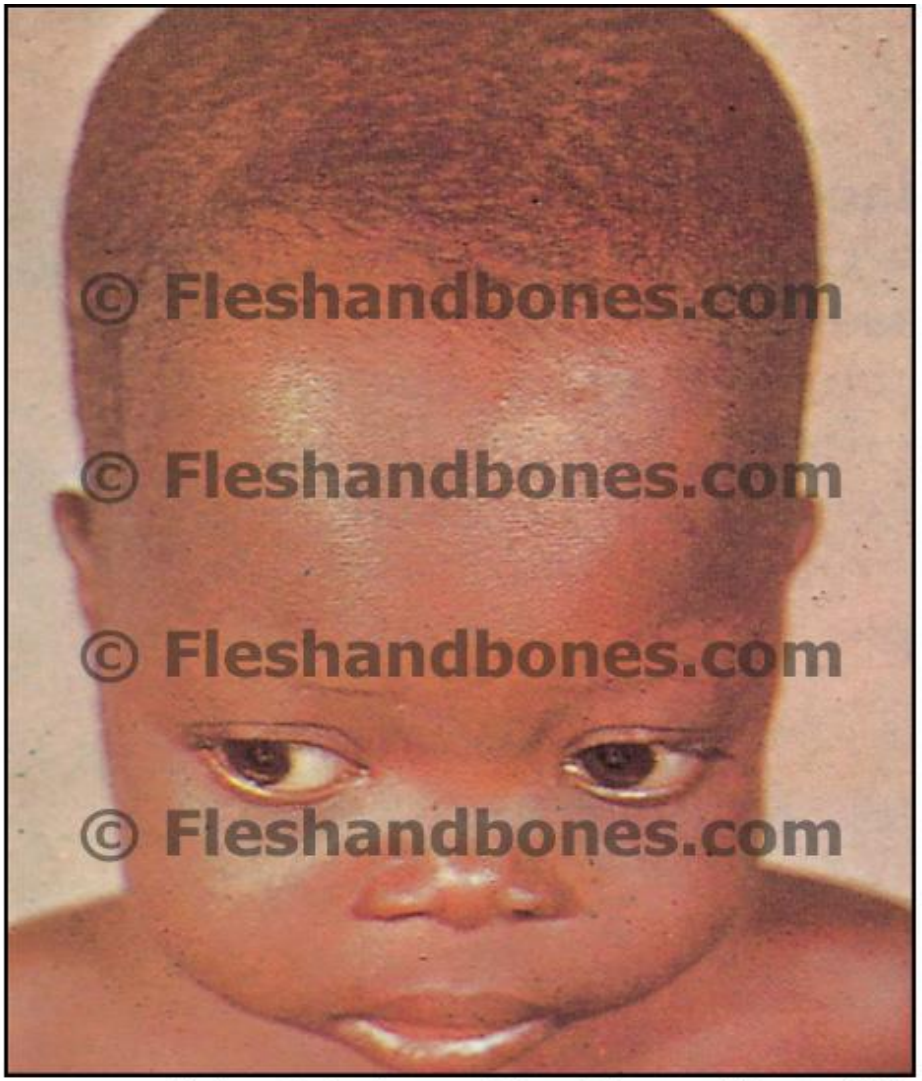
- Deformities in the skull due to bone marrow expansion (Bossing , and mongoloid facies; hair-on-end appearance on skull X-ray).

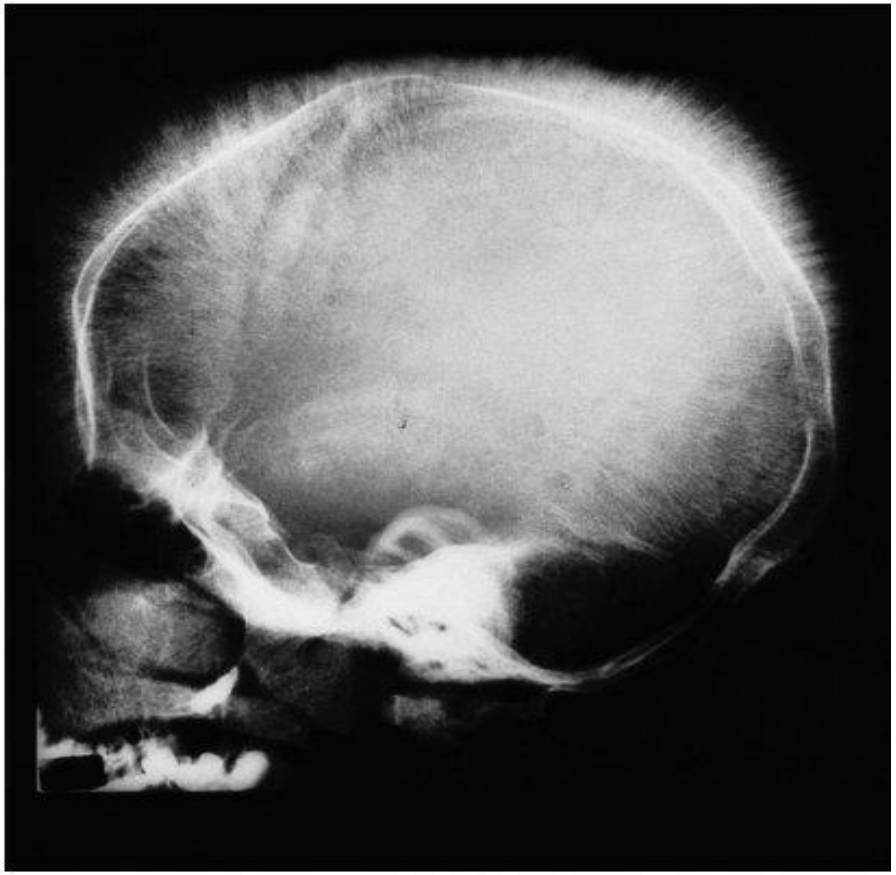
- Increased frequency of infections.



The facial appearance of a child with β-thalassaemia major. The skull is bossed with prominent frontal and parietal bones; the maxilla is enlarged.

Bossing of the skull



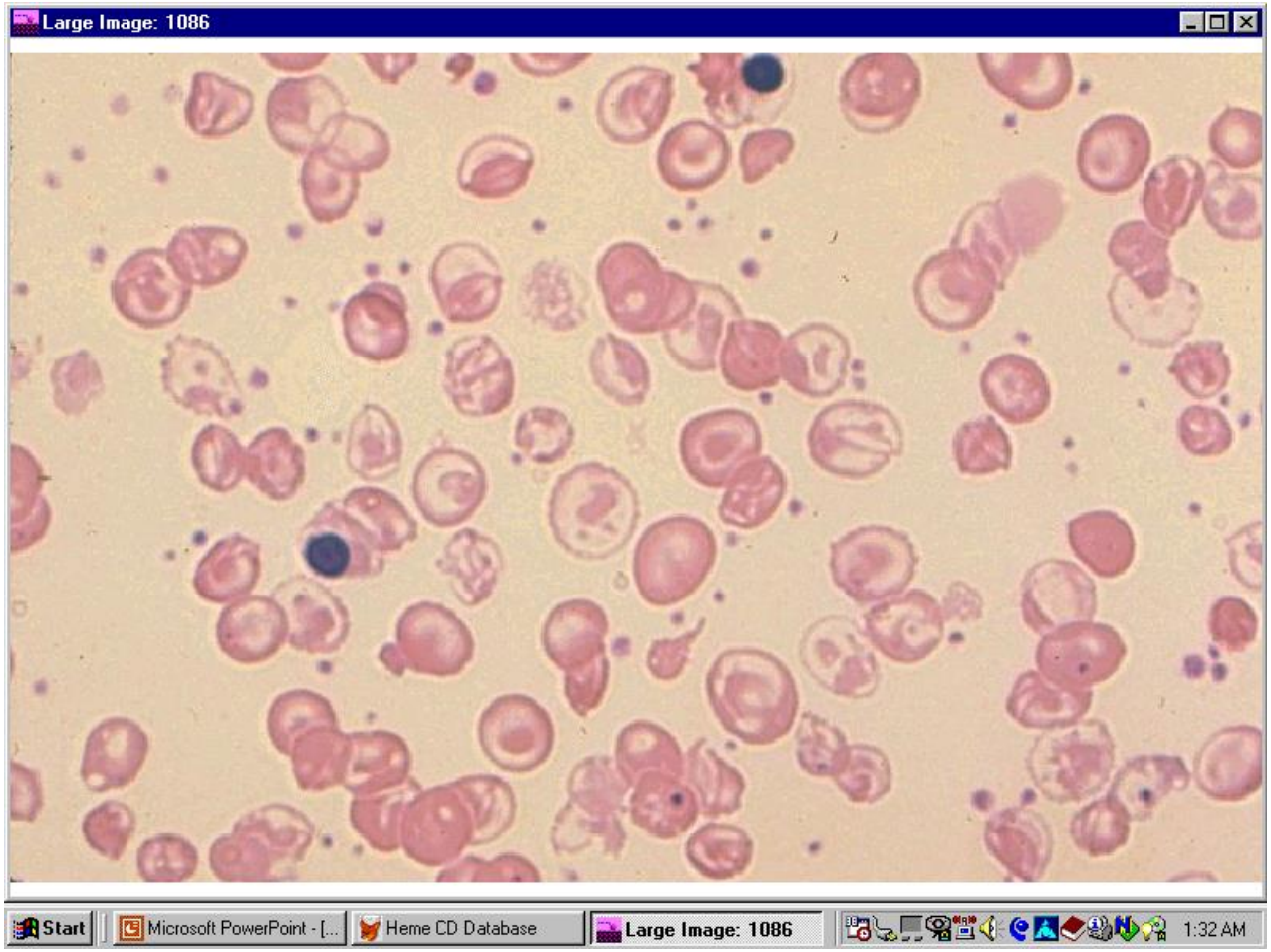


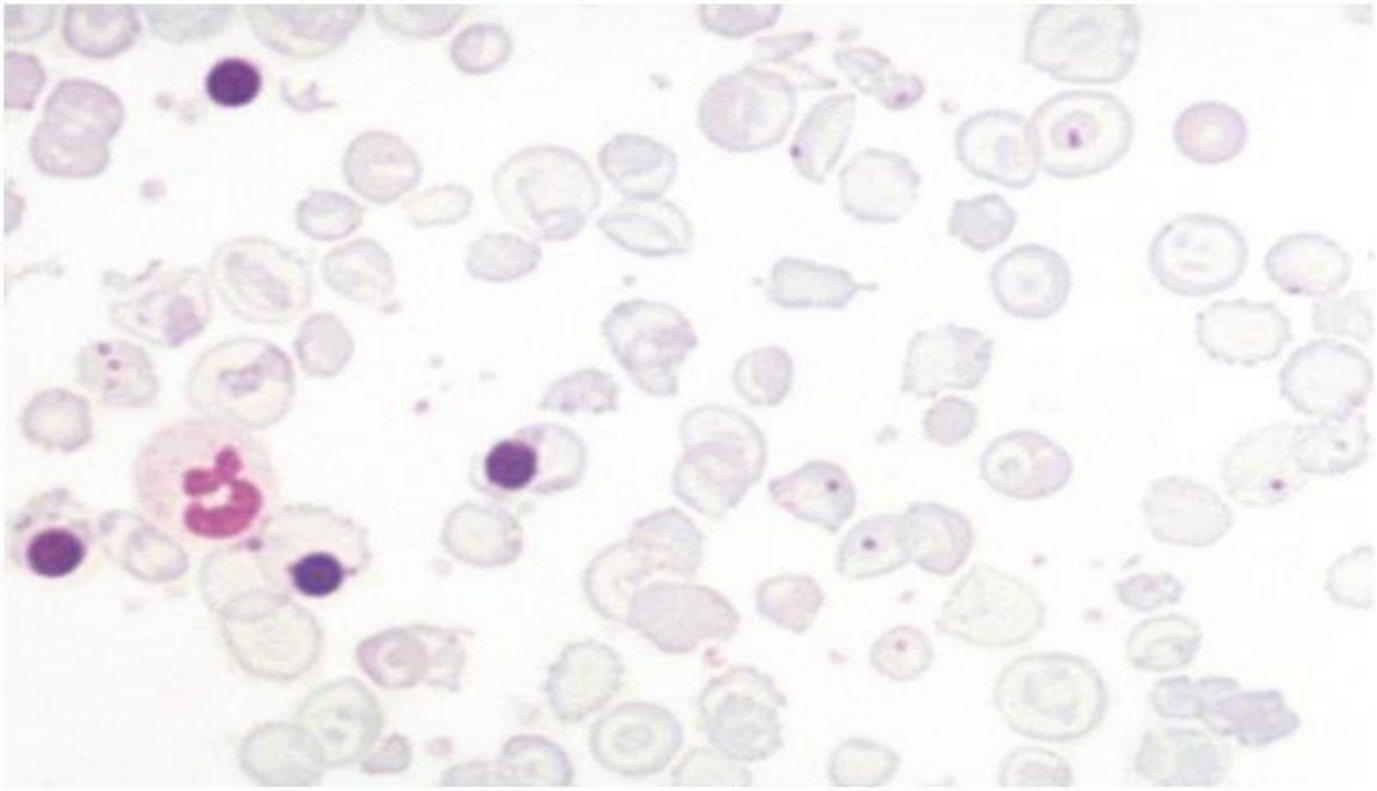
The skull X-ray in β-thalassaemia major. There is a 'hair-on-end' appearance as a result of expansion of the bone marrow into cortical bone.

Blood Picture in βThalassaemia Major

- Complete Blood Picture (CBP)
- Moderate to sever hypochromic microcytic anemia, with marked anisopoikylocytosis.
- HCT is evidently reduced.
- MCV and MCH are both reduced.
- Leucocytes : Maybe normal or increased.
- Platelets : may be normal or increased.
- Reticulocytes : usually range 2-8%.
- Hb electrophoresis: increased Hb F very high. Hb A2 is variable.
- Ferritin ????

Blood film in βThalassaemia Major





Prognosis of β -Thalassaemia Major

- If no Transfusions, death usually occurs in the first few years of life.

- If iron overload is allowed to occur then death in 2nd or early third decade, most commonly due to progressive cardiac damage due to iron deposition, with heart failure or arrhythmias, often precipitated by infections.

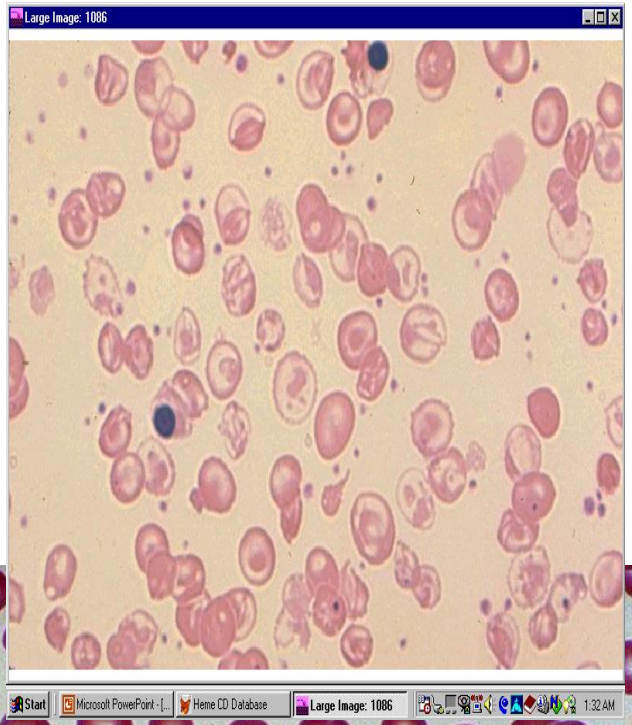
- However, if measures to prevent iron overload by iron chelation are instituted early on, with the transfusion, Iron overload consequences maybe limited, although delayed puberty and stunted growth may still be encountered, but otherwise patients may develop normally.

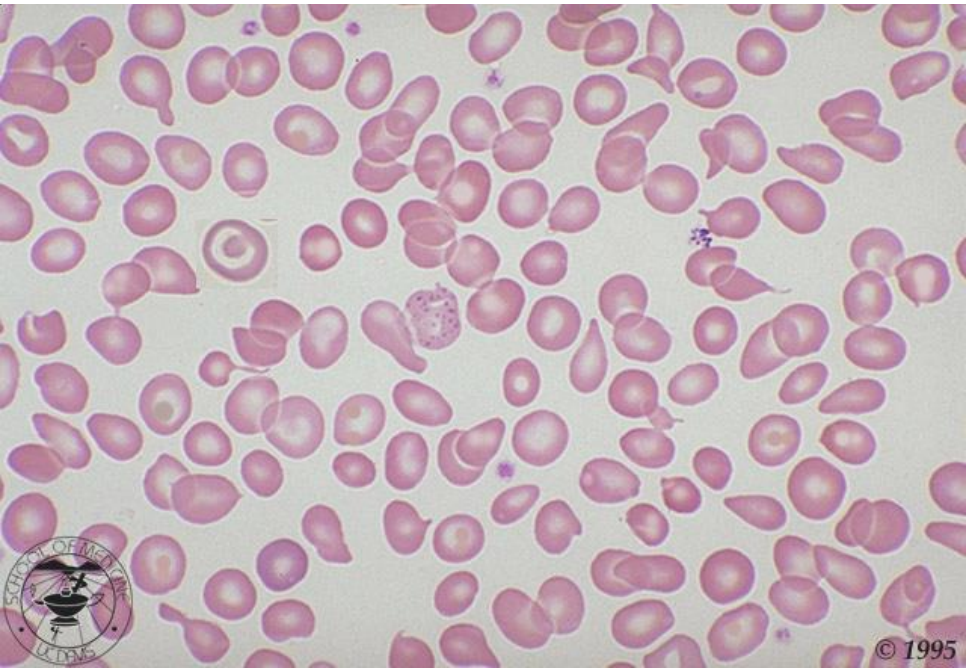
Blood picture of β-Thalassemia Minor

- Hb is usually reduced 1-2 g/dl less than normal for age and sex.
- MCH and MCV are reduced.
- RBC count is > 5 x 10^{12}/L in 85% of cases.
- Reticulocyte count is slightly increased or normal.
- Blood film : slight hypochromia, anisocytosis, poikiocytosis, microcytosis, tear drop cells and target cells.

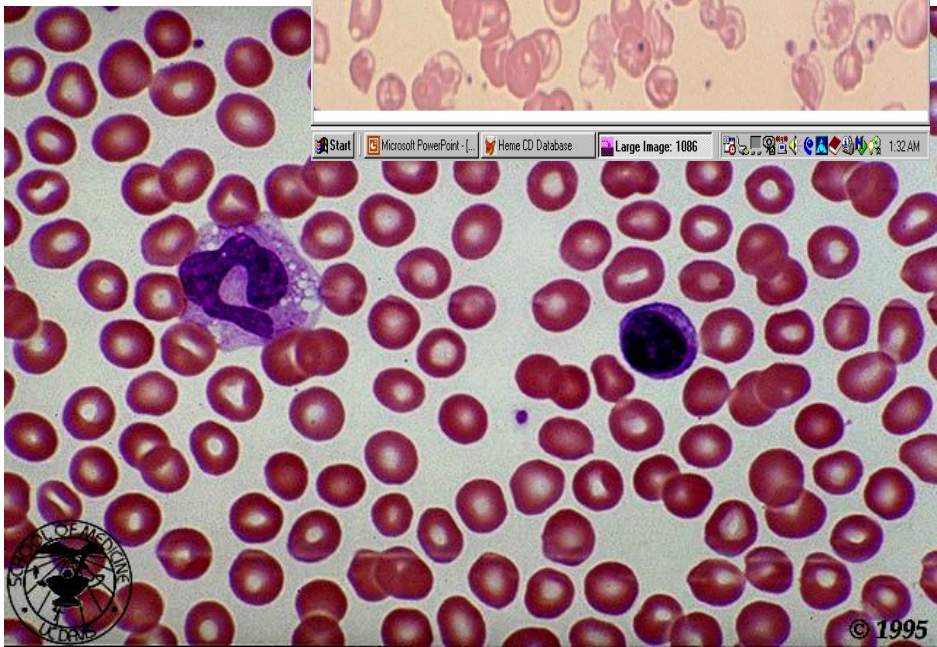
Blood Film in β thal minor

Thalassemia Major





Thalassemia minor



Normal blood film

Diagnostic tests in β-Thal Minor:

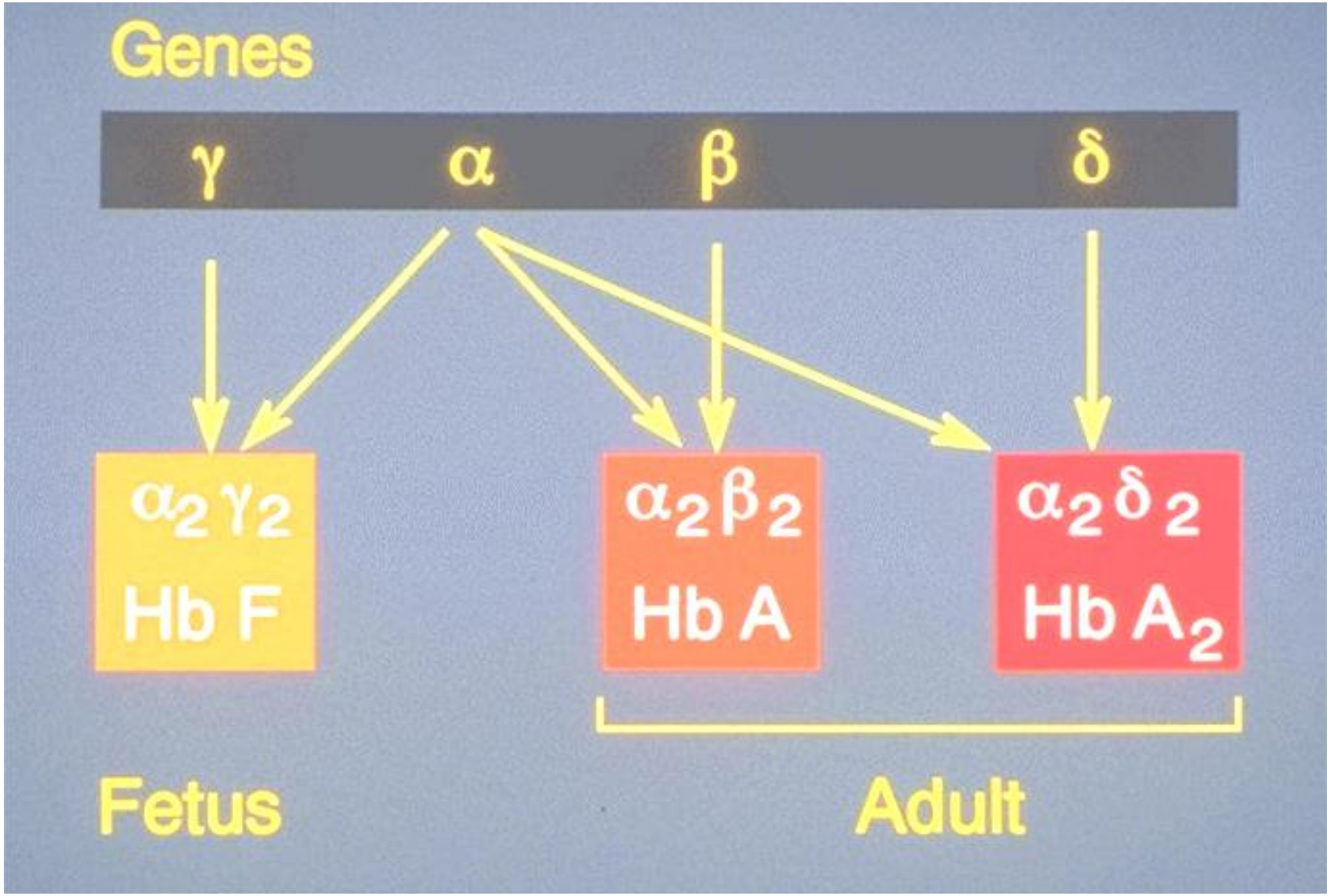
- Increase in Hb A2 : Normal range of Hb A2 is 1.8-3.5%, in Beta thalassemia minor it is increased to 4-7% .
- Increased Hb A2 is considered diagnostic of Beta thalassemia minor.
- S. Transferrin saturation(S.Iron/TIBC) is usually normal or upper normal.

Alpha thalassaemias

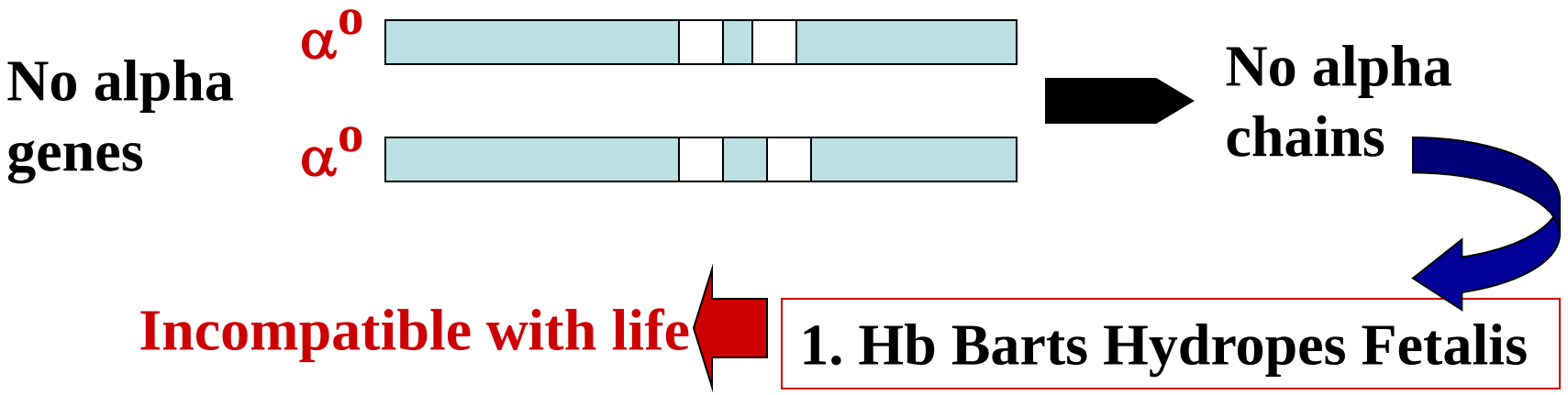
- Much less common in our country than Beta thalassemia, and of much less clinical significance.

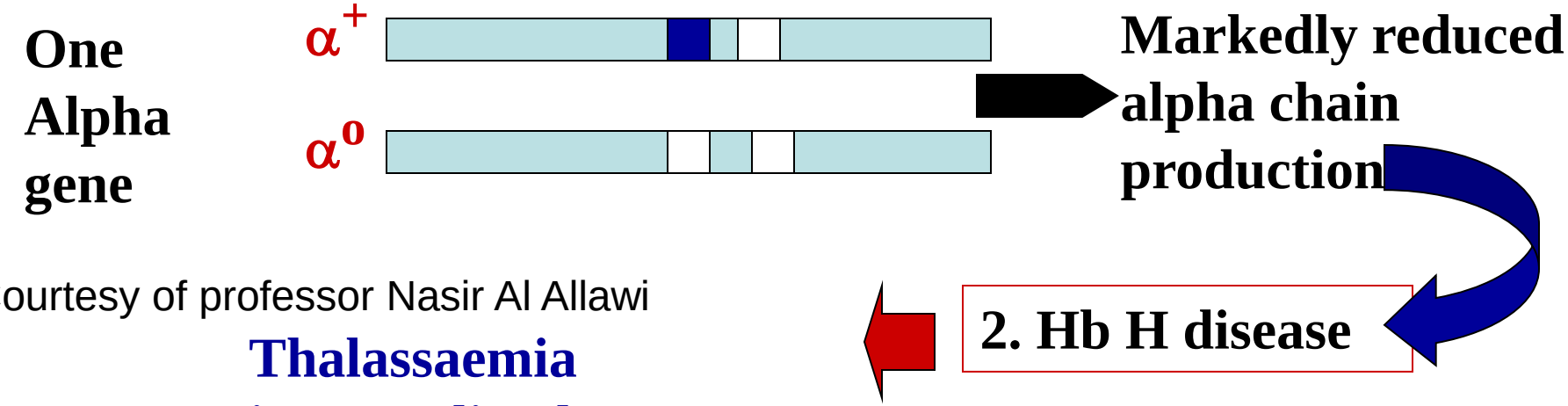
- Due to reduced or absent synthesis of alpha (α) globin chains of hemoglobin.

- (Alpha (α) chains are constituents of all three normal Hb A, A2 and F).


Genes
γ
α
β
δ
α2γ2
Hb F
α2β2
Hb A
α2δ2
Hb A2
Fetus
Adult

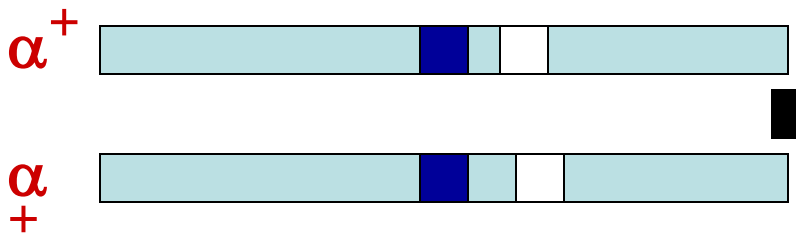
Clinical Phenotypes of Alpha thalassaemia (relevant to number of alpha genes remaining):





Courtesy of professor Nasir Al Allawi

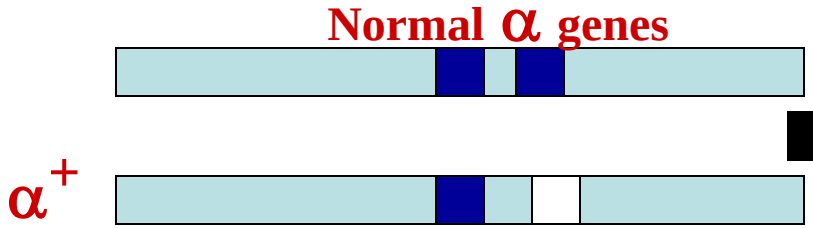
Two alpha genes



Moderately reduced Alpha chains

3. α Thalassemia minor

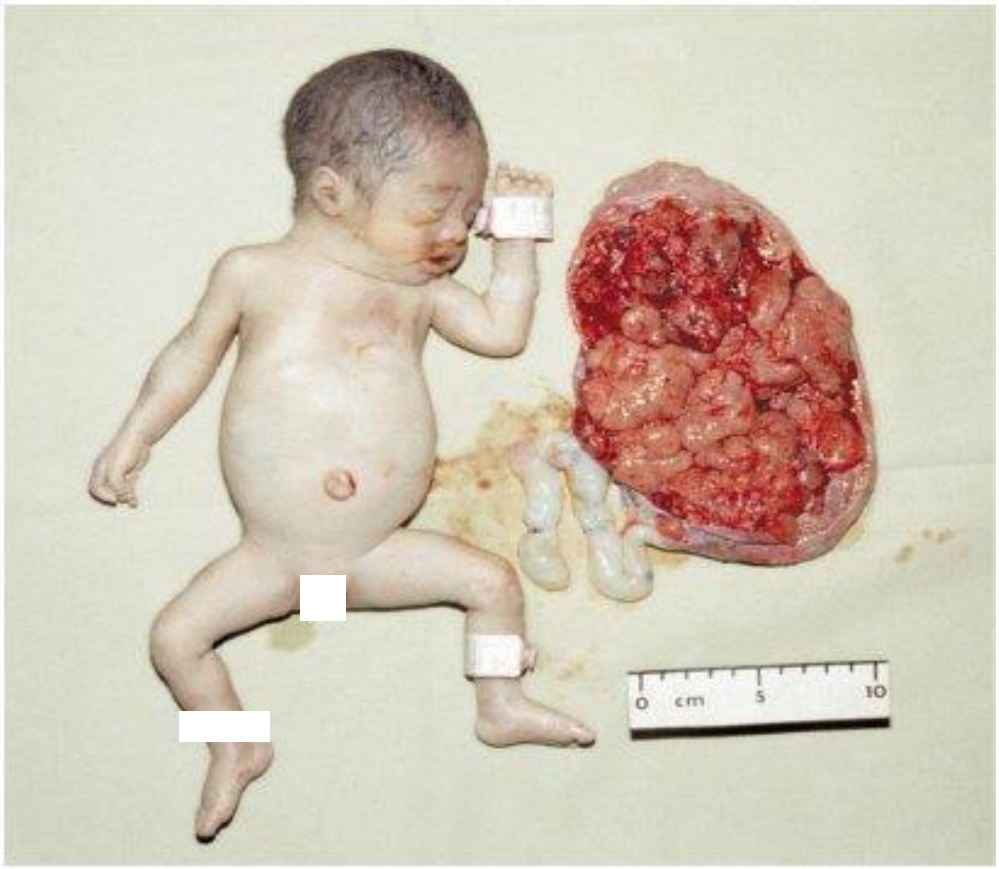
Three Alpha genes



Minimally reduced Alpha chains

4. Silent α thal. carrier state

Courtesy of professor Nasir Al Allawi



α-Thalassaemia: hydrops fetalis, the result of deletion of all four α-globin genes (homozygous α^0-thalassaemia). The main haemoglobin present is Hb Barts (γ_4). The condition is incompatible with life beyond the fetal stage. (Courtesy of Professor D. Todd)

Hemoglobin H disease

- Common in Southeast Asia, less so in Mediterranean countries. Sporadic in Iraq.
- The only clinical phenotype of alpha thalassemia of clinical significance.
- Due to deletion of three of the four normal alpha genes. So, only one functional alpha gene is left with associated marked reduction in alpha chain production.

Clinical Features

- Very variable, variable pallor.
- Variable degrees of splenomegaly.
- Sometimes Jaundice.
- Most unusual to see severe thalassemic skeletal changes or growth retardation.
- Usually survive to adult life.
- Anemia aggravated by infections, oxidant drugs.

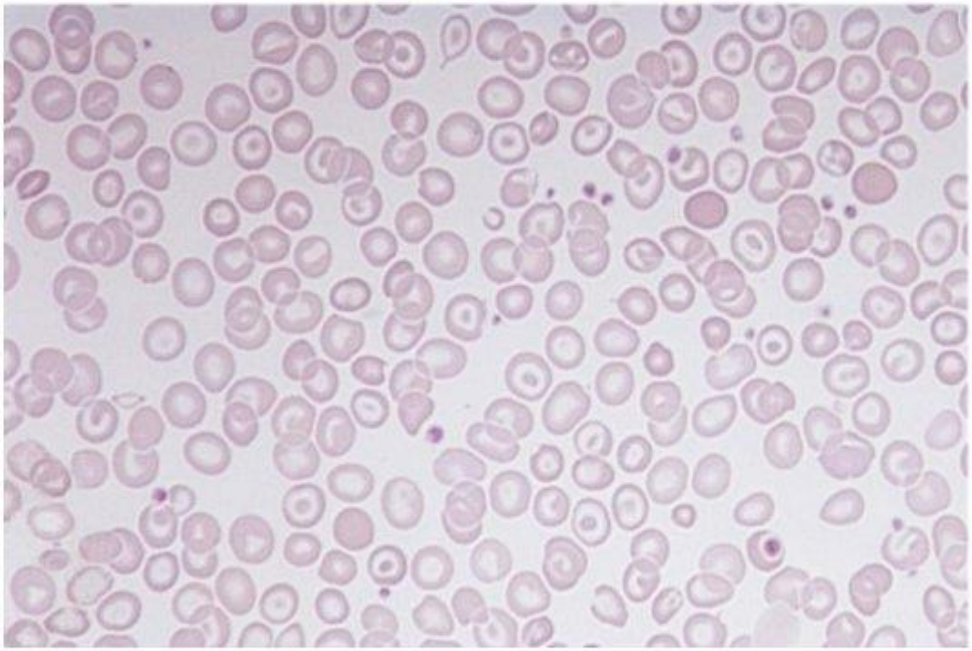
CBP

Sever hypochromic anemia with marked aniso-poikylocytosis.

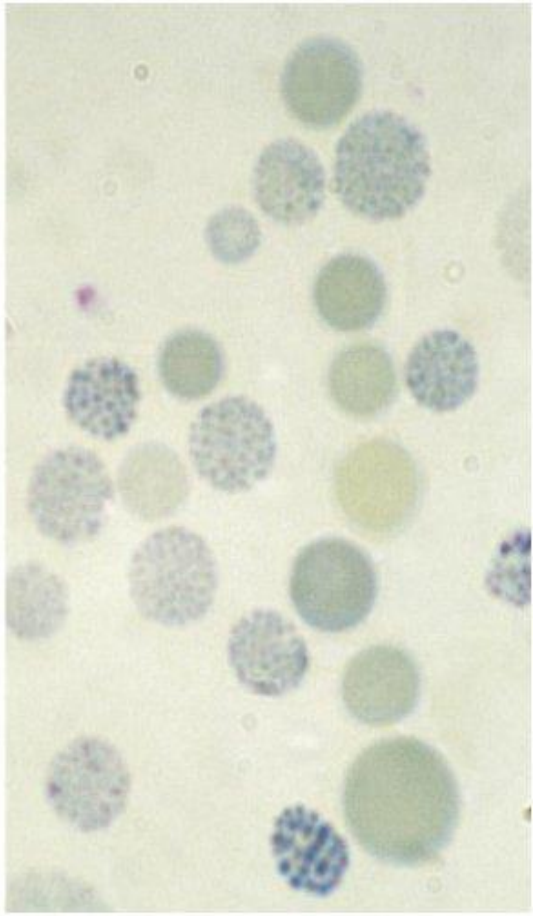
- Electrophoresis :

  ~ Shows Hb A with 5-40% Hb H.

- On modification of the retics stain : characteristic Hb H inclusions could be seen in RBCs(Golf ball appearance).



(a)



(b)

α-Thalassaemia: haemoglobin H disease (three α-globin gene deletion). The blood film shows marked hypochromic microcytic cells with target cells and poikilocytosis. **(b)** α-Thalassaemia: haemoglobin H disease. Supravital staining with brilliant cresyl blue reveals multiple fine, deeply stained deposits ('golf ball' cells) caused by precipitation of aggregates of β-globin chains. Hb H can also be detected as a fast-moving band on haemoglobin electrophoresis (Fig. 7.12).

Alpha thalassemia minor

- Due to deletion of two alpha genes, leaving only two alpha genes, so only moderate reduction of alpha chain production.
- Clinical and blood picture, the same as beta thalassemia minor.
- Hb electrophoresis shows Hb A, with normal or reduced Hb A2 and normal Hb F.

Thalassaemia Intermedia
Clinical Features

TI has an extraordinarily wide clinical spectrum, unlike TM, which presents with severe anaemia requiring frequent blood transfusions

Mild TI
Completely asymptomatic until adulthood

Severe TI
Presentation between 2 and 6 years
Retarded growth and development

Cappellini N, et al, eds. Thalassaemia International Federation; 2010.

Thalassaemia Prevention

First step - Premarital Screen : to identify couples at risk of bearing affected children, depending on red cells indices, followed by the estimation of HbA2 and HbF levels, in addition to sickling test.

Second Step - Genetic Counseling : to allow the couples at risk to take an informed decision.

Third step - Prenatal Diagnosis : to detect any affected fetus in early gestation in couples at risk and allow the partners the choice of termination.

Thank you