Hb & Hemoglobinopathies

By

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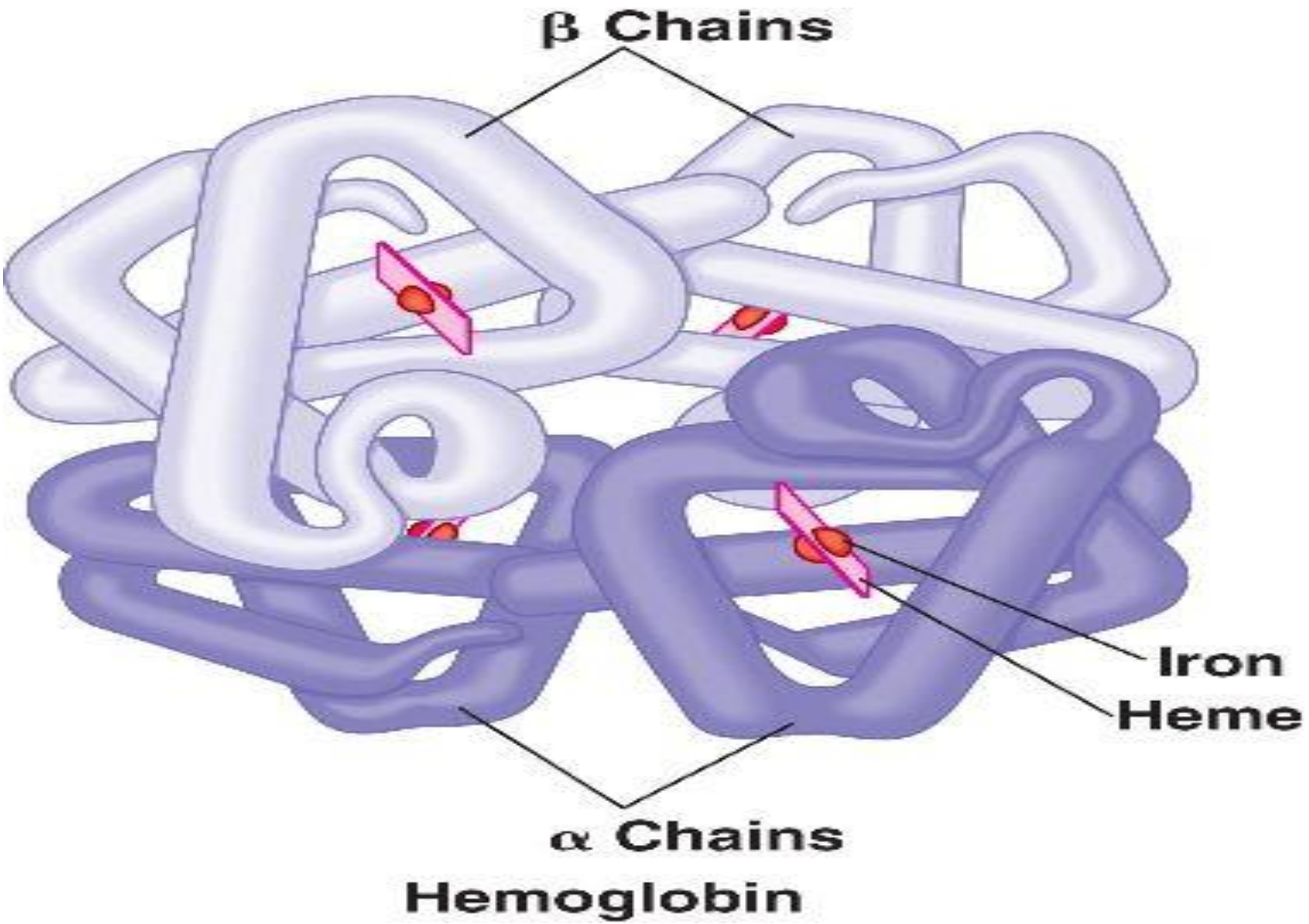
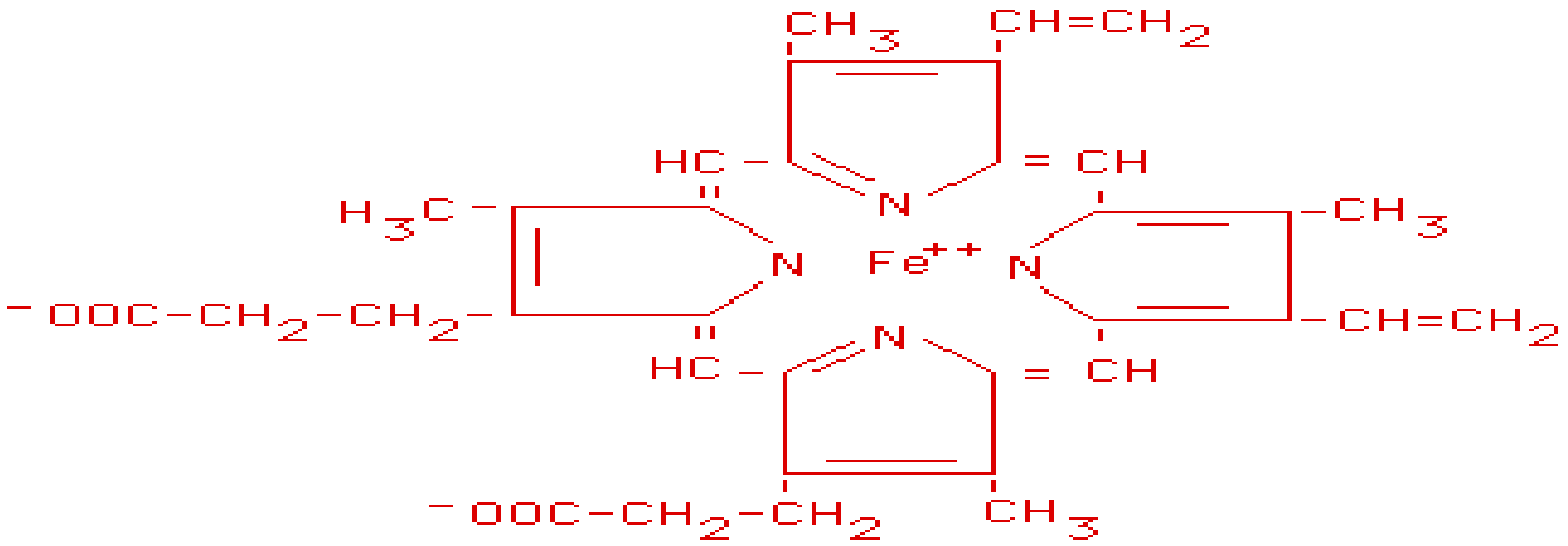


Hemoglobin

- The iron atom of heme occupies the central position of the porphyrin ring.
- In Hb iron is in the **ferrous state** (**Fe^{++}**)
- Ferrous iron (Fe^{++}) has 6 valencies.
- Iron carries oxygen.


CH3
CH=CH2
HC
=CH
H3C
N
Fe++
N
CH3
-OOC-CH2-CH2
CH=CH2
N
HC
=CH
-OOC-CH2-CH2
CH3

Heme

Globin

- **Tetramer : 4 polypeptide chains.**
- **Each polypeptide chain is formed of 7 or 8 helices which are termed A-B-C-D…….**
- **There are 4 types of the polypeptide chains that may enter in the formation of Hb (α-β-γ-δ).**

- α –chain → 141 amino acids

(α chain gene is on chromosome 16)

- β-γ-δ chains → 146 amino acids

(β-γ-δ chain genes are on chromosome 11)

- **Hb is composed of 2 α and 2 either β , γ or δ**

Types of Hb

- **Hb A:**

- The Hb of normal adult

- forms about 97-98% of adult Hb

- 2 α and 2 β (α 2 β 2)

- **Hb A1:**

- This is a group of glycated HbA. They are faster than HbA in electrophoresis, and hence the designation A_1 .The most abundant is HbA_{1c} in which glucose is linked to amino groups of the N terminal valine of the β chains. **This glycosylation depends on the blood glucose level .** Since the half -life of the RBCs is about 60 days, Hb A_1 gives an idea about the average blood glucose level over the last 8 weeeks. Normally Hb A_1 forms **4 – 5.6%** of the total Hb . Values higher than 8% indicate poorly controlled diabetes mellitus.

A1C results and what the numbers mean

Diagnosis*	A1C Level
Normal	below 5.7 percent
Prediabetes	5.7 to 6.4 percent
Diabetes	6.5 percent or above

- **Hb A2:**
- **2-3% of adult Hb**
- **2 α and 2 δ (α 2 δ 2)**
- **Appears in the blood at the age of 3 months.**
- **It increases in β thalassemia.**

- **Hb F:**

- **Normal fetal Hb**
- **2 α and 2 γ (α 2 γ 2)**
- **Has higher affinity for O2 than maternal Hb which allows fetal Hb to take oxygen from maternal blood**
- **Presents during fetal life and disappears gradually after birth and becoms almost completely replaced by Hb A by the age of**

6 months

Difference between oxygenation and oxidation

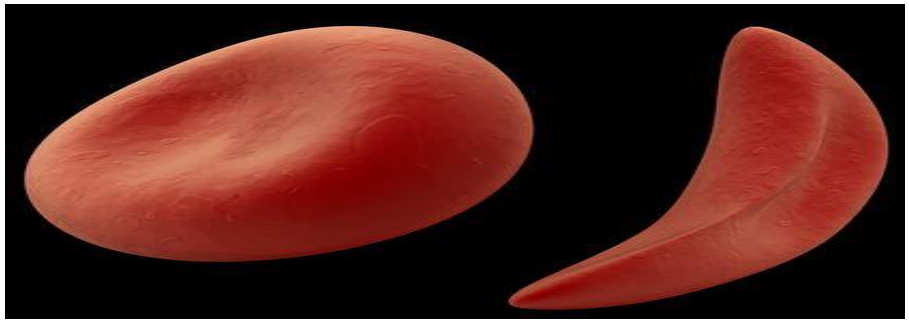
- **When Hb carries oxygen, it is oxygenated and the iron atom is still in the ferrous state**
- **Oxidised Hb is called Met-Hb and the iron atom is present in the ferric state (the oxygen carrying capacity is lost)**

Hemoglobinopathies

- **Abnormalities in the primary sequence of globin chains**

Hemoglobinopathies

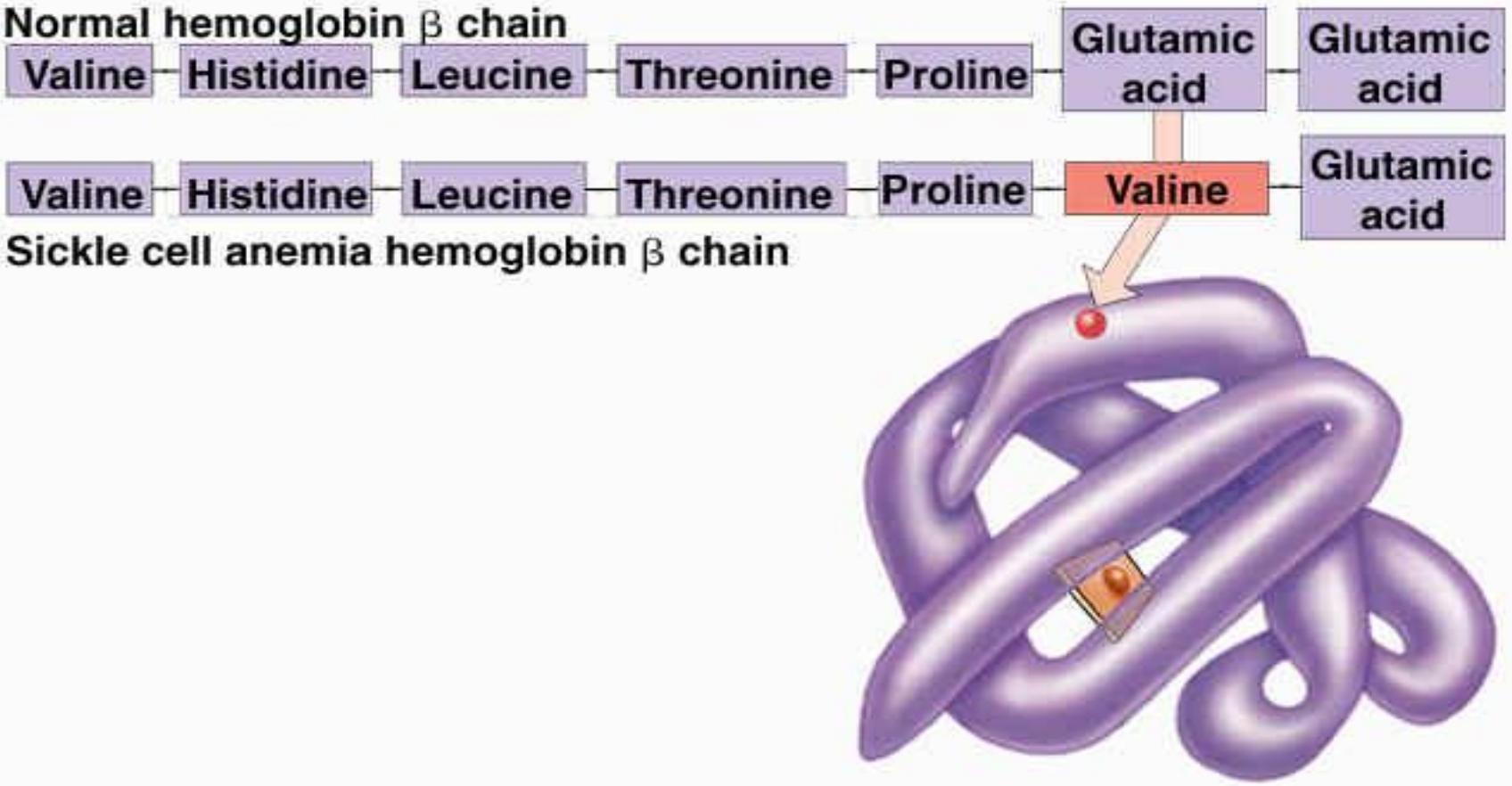
Types :



- **Hemoglobin S (HbS) / sickle cell hemoglobin:**

Genetic disease caused by: Replacement of glutamic acid in the 6th position of beta chain by valin.

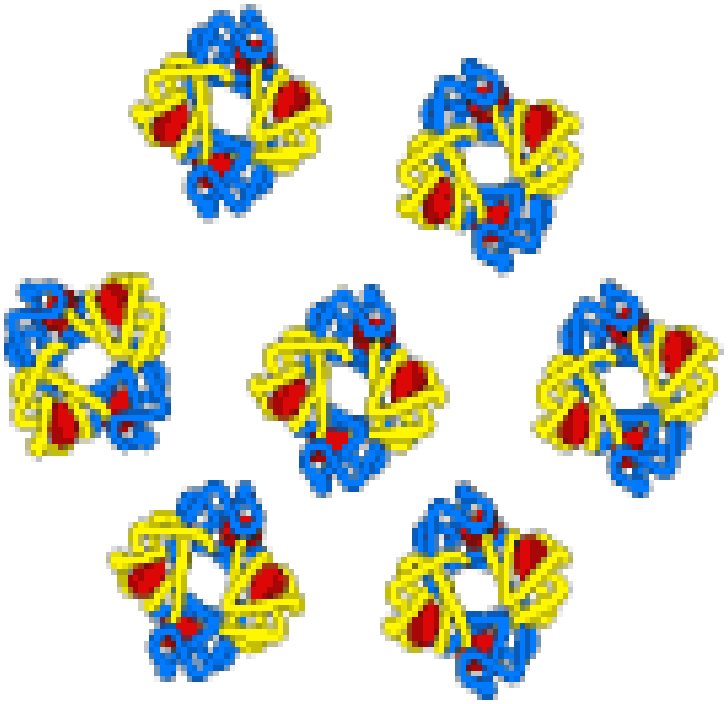
Effect of Amino Acid Change—Sickle Cell Anemia



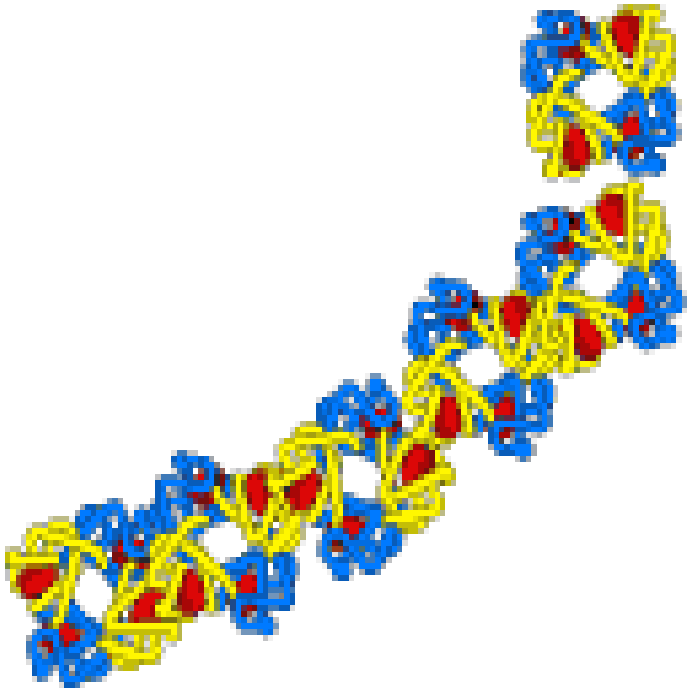
- **Solubility of HbS in the deoxygenated form is 50 times less than oxygenated form leading to crystallization.**

- **HbS polymerize when deoxygenated leading to the formation of a fibrous precipitate in the RBCs which collapes and aquire the shape of a sickle.**

- **Thus the red blood cells become sickled in the peripheral circulation and reaquire the normal shape in the lungs. After repeated sickling and unsickling the red cells become permanently sickled.**



NORMAL
HEMOGLOBIN

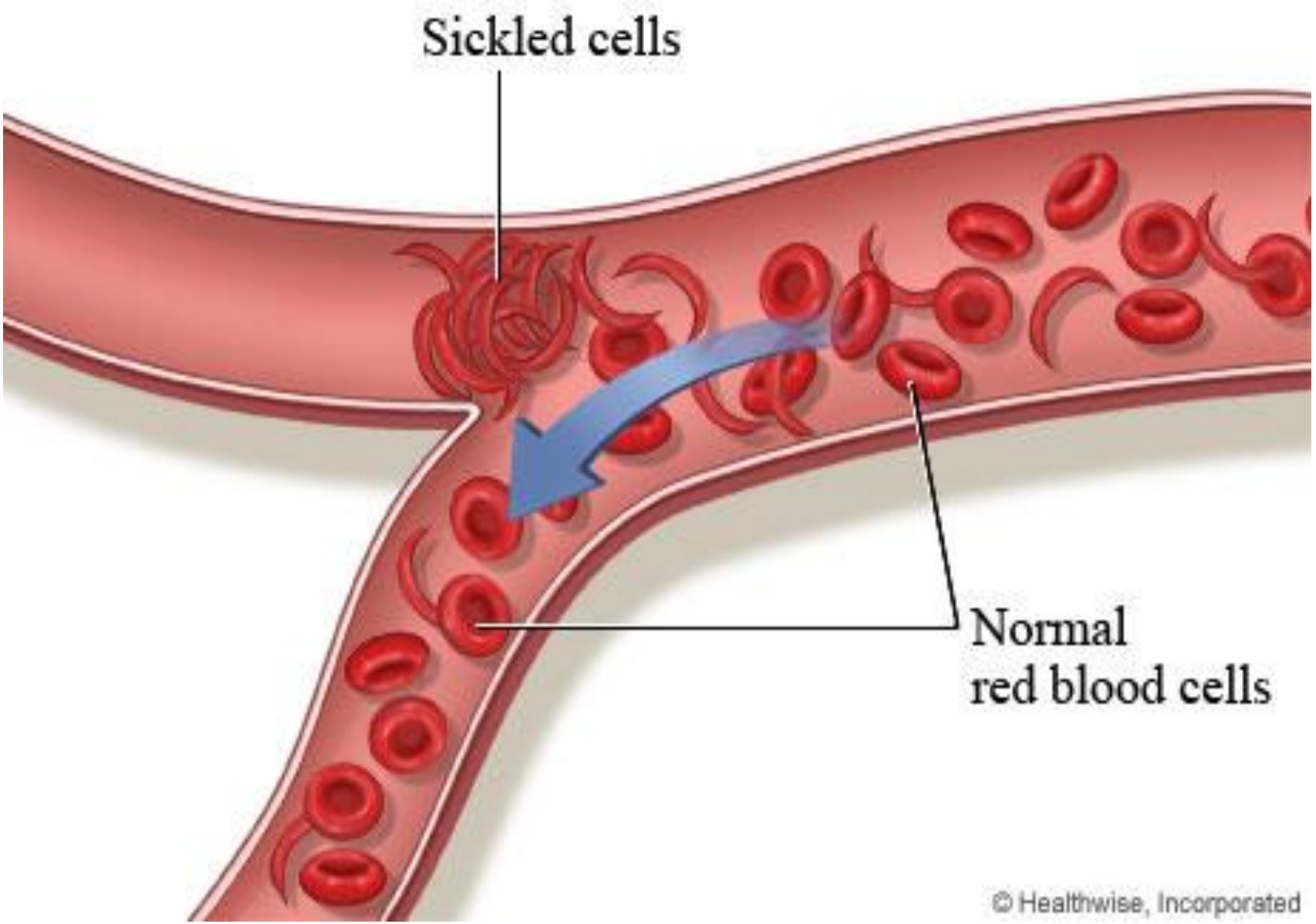


CLUMPED
HEMOGLOBIN

- **Sickle cells aggregate in microcirculation and may occlude it leading to infarctions in different organs (crisis in the form of sever pain)**

- **The spleen removes sickle cells at a faster rate than normal cells leading to hemolytic anemia.**

- **HbS is slower than HbA in electrophoresis.**


Sickled cells
Normal
red blood cells
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- **Individual who is heterozygous for HbS do not acquire the symptoms of the sickle cell disease, they have both HbA and HbS in their blood cells. They are only carriers (sickle cell trait).**
- **They are resistant to parasites that causes malaria**
- **These parasites do not survive in erythrocytes containing HbS because these cells have shorter life span than normal cells so the parasite can not complete its development.**
- **Also the infected cells require larger amounts of oxygen than uninfected ones so cells tend to be sickled sooner and thus be removed from circulation.**

Hemoglobin C :

- Genetic disease caused by replacement of glutamic acid in the 6^{th} position of beta chain of HbA by lysine.

- Homozygotes suffer from mild hemolytic anemia

Thalassemias

- **Group of diseases characterized by reduced formation of the α- or the β- globin chains.**

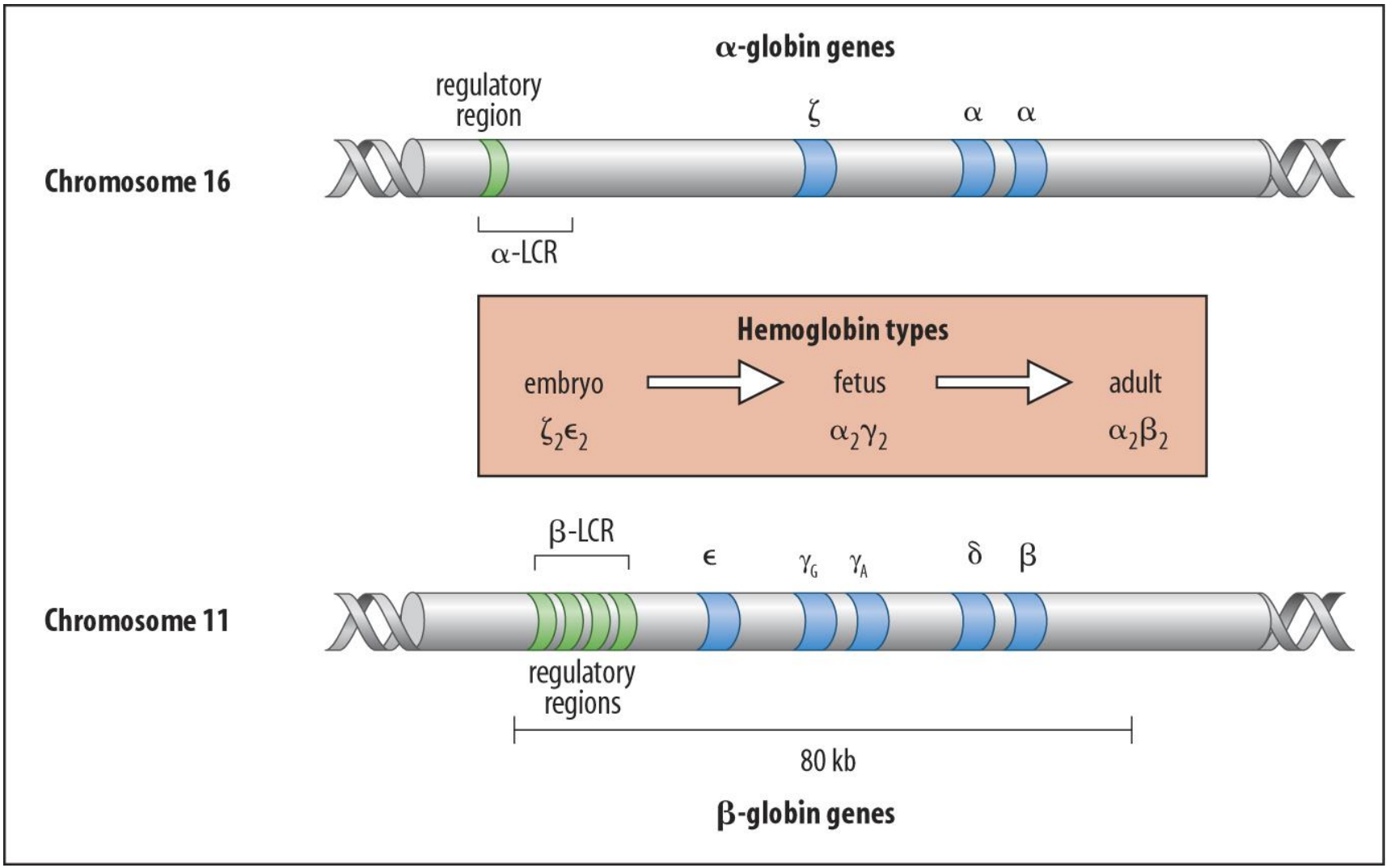
- **It is due to mutations in the genes responsible for the synthesis of the globin chain producing abnormal Hb with impaired oxygen binding properties.**

Types of thalassemia:

- α- thalassemia
- β- thalassemia

The α- gene family

- This family is present on chromosome 16.
- It contains a number of genes for α- globin-like chains .
- It includes 2 α-genes and one ζ-gene(zeta-gene). The zeta-gene is expressed during embryonic life. It stops working by the end of the first 3 months of pregnancy, its function being gradually replaced by the α- genes.


α-globin genes
regulatory region
ζ
α
α
Chromosome 16
α-LCR
Hemoglobin types
embryo
ζ2ε2
fetus
α2γ2
adult
α2β2
β-LCR
ε
γG
γA
δ
β
Chromosome 11
regulatory regions
80 kb
β-globin genes

The β- gene family

- This family is present on chromosome 11.
- It contains a number of genes for β-globin-like chains.
- These include the β-gene, the γ-genes, the δ-gene, and the ε-gene (epsilon-gene). the ε-gene, like the ζ-gene, is expressed during embryonic life. It stops working by the end of the first 3 months of pregnancy, its function being gradually replaced by the γ - genes.
- Thus by the end of the first 3 months of pregnancy **HbF** is the major Hb in the blood of the fetus.

α- thalassemia

- **Results from mutations in one or more of the 4 α- chain genes.**
- **The α- globin genes are duplicated (four) so one to four α- globin genes may be mutated:**

1-patients deficient in one α- globin gene are completely normal and are only **carriers of α- thalassemia.**

2- patients deficient in 2 α- globin genes are said to have **α- thalassemia trait** with **mild anemia**

3- patients deficient in 3 α- globin genes are said to have α- thalassemia major with sever anemia that is present since birth due to deficient formation of HbF.

4- patients deficient in the four α- globin genes are said to have homozygous α-thalassemia . They usually die soon after birth or in the uterus as HbF can not be synthesized we get hydrops fetalis.

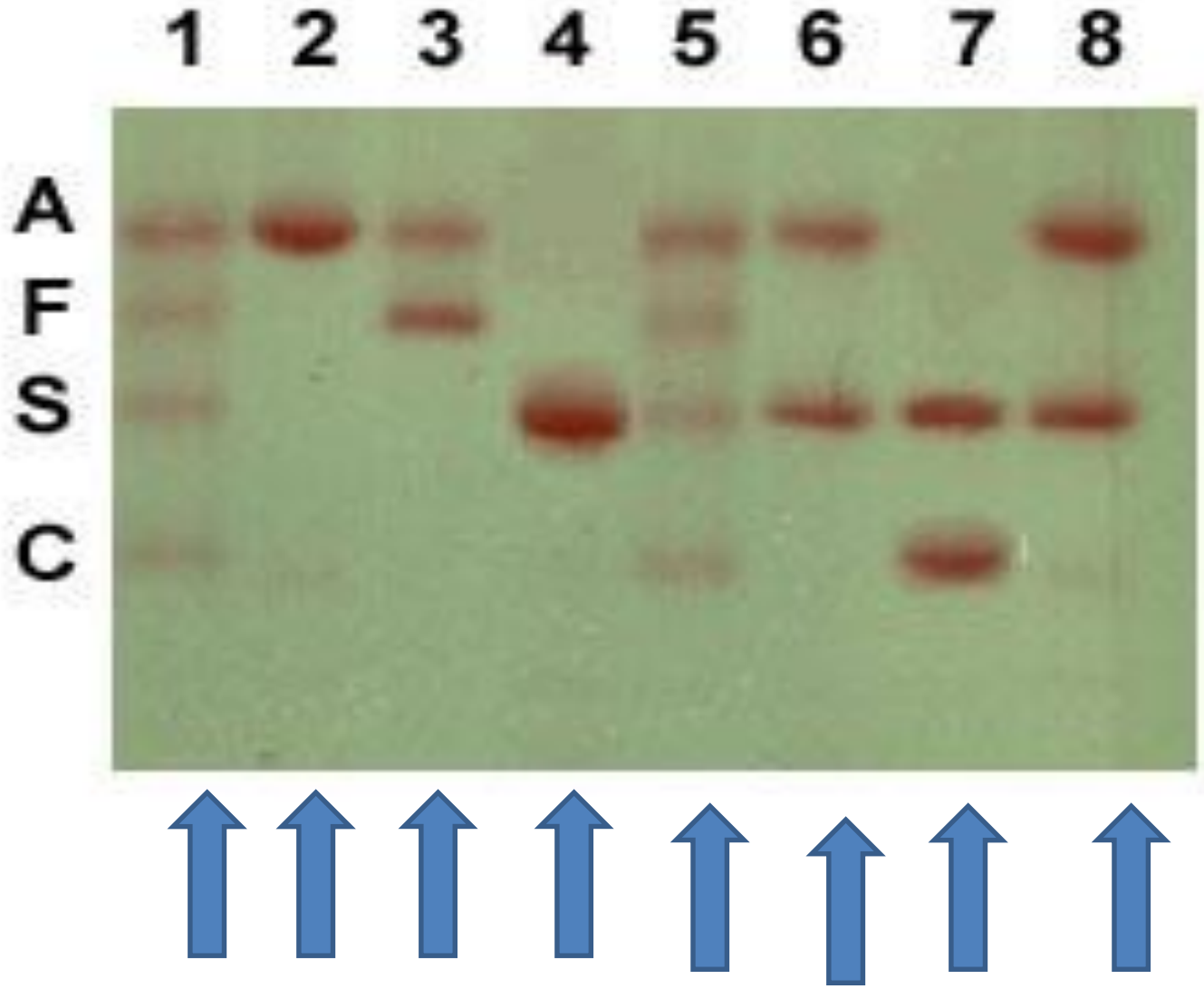
β - thalassemia

- **Results from mutations in one or the 2 β- chain genes.**
- **If only one gene is defective we get β – thalassemia trait or β – thalassemia minor with mild anemia**
- **If the 2 genes are defective we get β – thalassemia major with sever anemia. They rarely live to adulthood.**
- **The fetus appears normal at birth because HbF is formed at the normal rate.**

Normal and abnormal hemoglobins can be identified by electrophoresis:

The arrangement of hemoglobins , fastest to slowest , is A, F, S and C. HbA_2 runs with HbC

Hb electrophoresis



Hemoglobin derivatives

- **Oxyhemoglobin**: carries oxygen present in arterial blood.
- **Reduced hemoglobin**: present in venous blood.
- **Carboxyhemoglobin**: carries carbon monoxide which is toxic.
- **Methemoglobin**: can not carry oxygen because iron is present in ferric state.

Bilirubin Metabolism