Hemoglobinopathies

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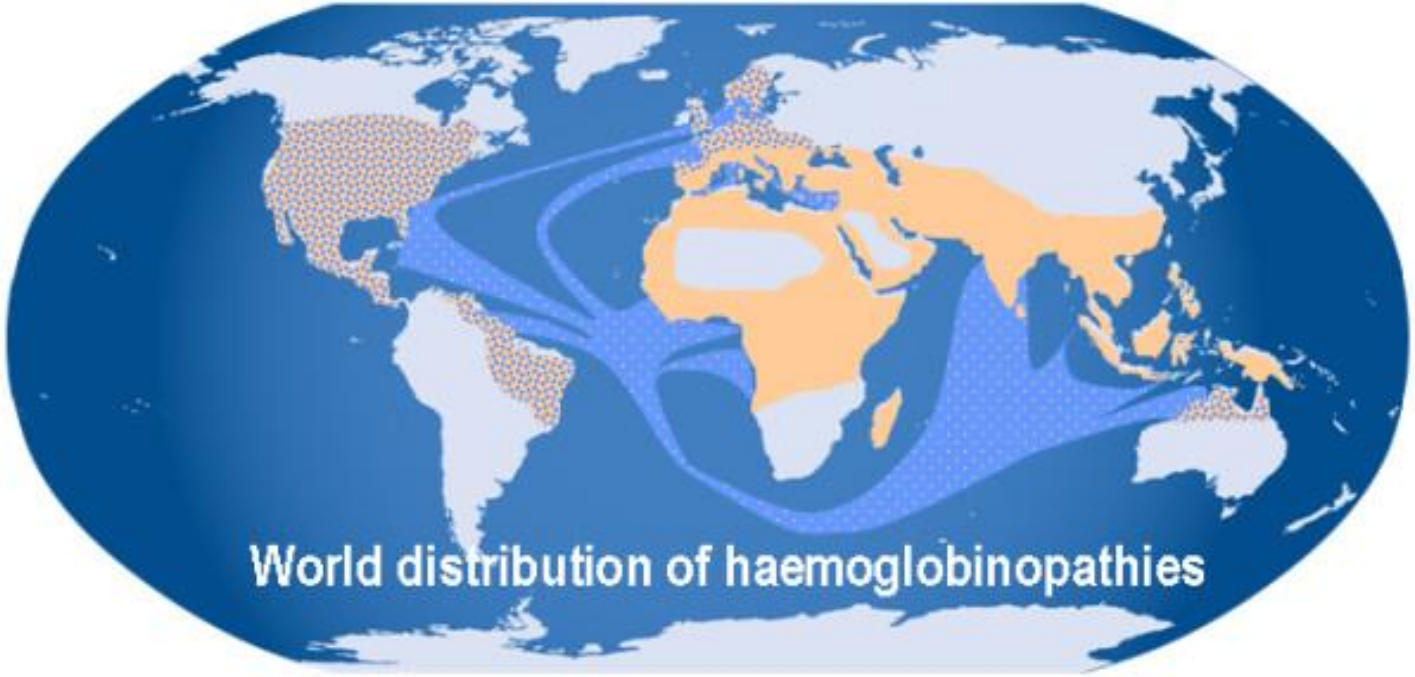
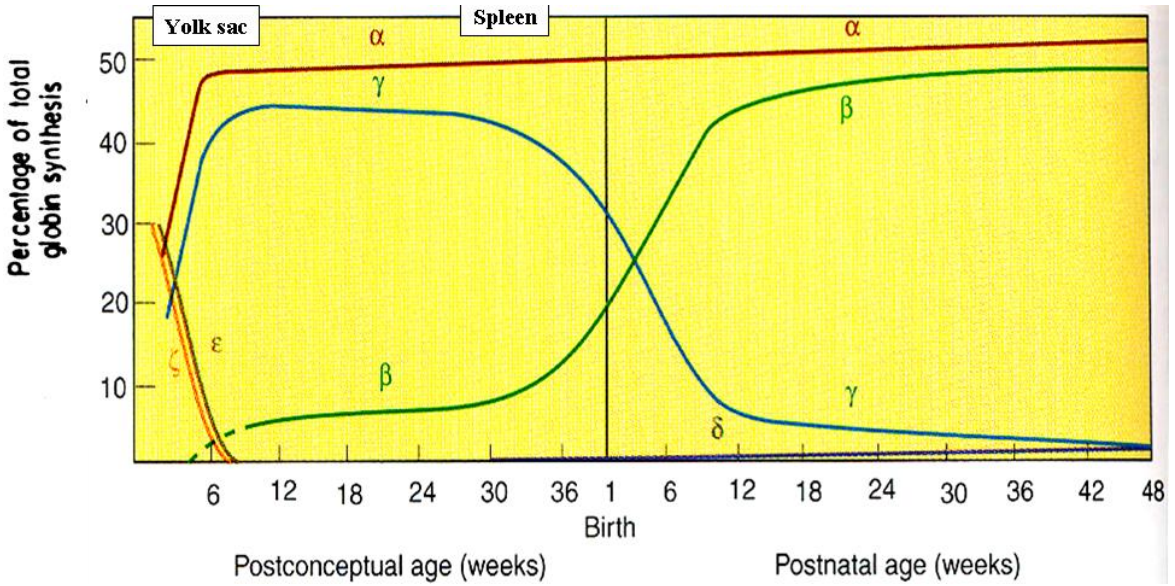
What are hemoglobinopathies?

- Hemoglobinopathies: Disorders of human hemoglobin.
- The most common genetic disease group in the world (5% of people are carriers) with substantial morbidity (about 300,000 born each year).
- Hemoglobin disorders account for 3.4% of deaths in children < 5 years.



Hereditary hemoglobins disorders

- Quantitative abnormalities are abnormalities in the relative amounts of α and β subunits (thalassemias).
- Qualitative abnormalities: mutations resulting in structural variants.
  - Over 800 variants have been identified.
- Hereditary persistence of fetal hemoglobin (HPFH): impairment of the perinatal switch from γ to β globin.



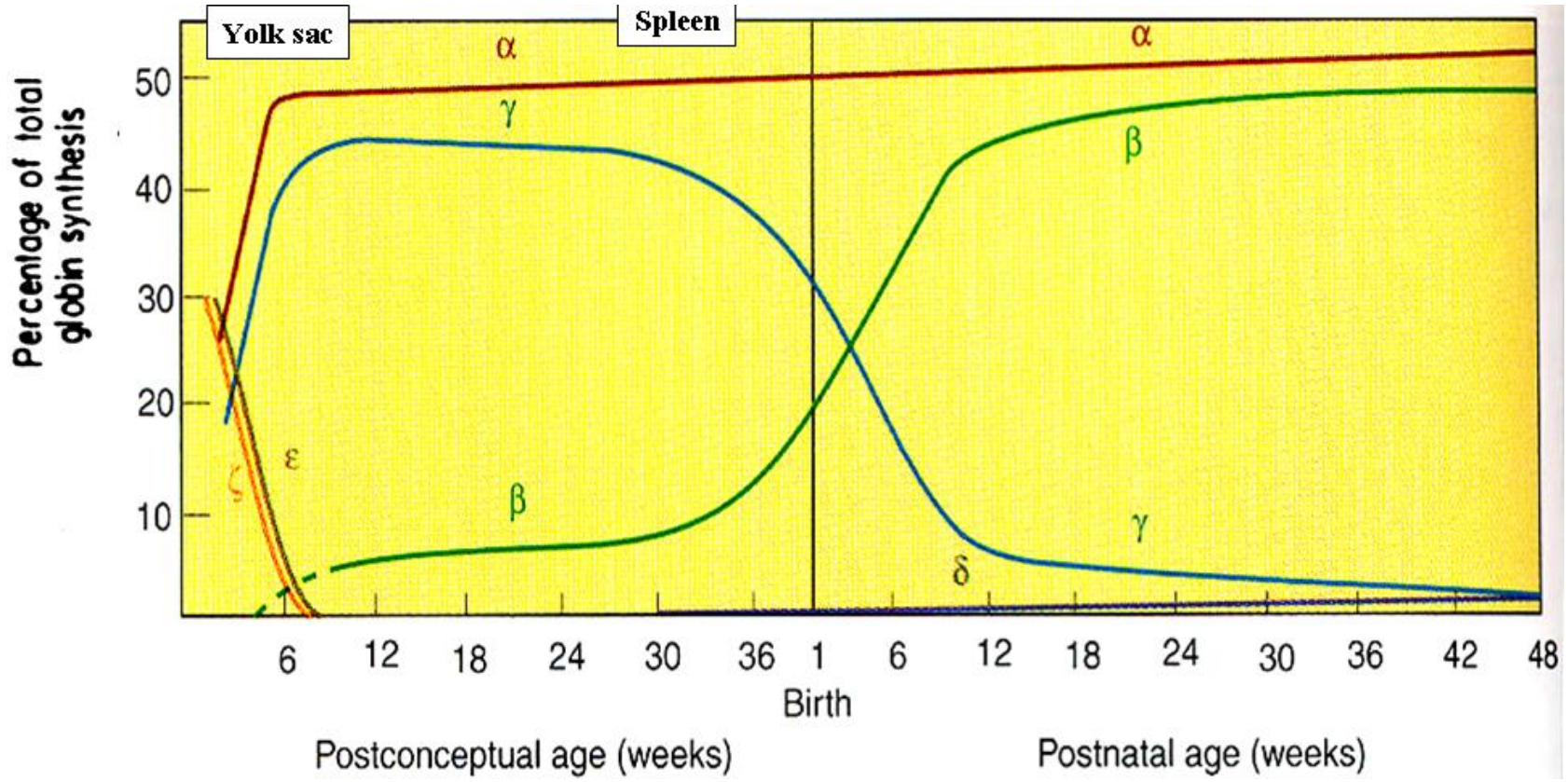
Quantitative abnormalities (Thalassemias)

Thalassemias

- Thalassemias: the most common human single-gene disorder.
- They are caused by a reduced amount of either the α or β protein, which alters the ratio of the α:β ratio.

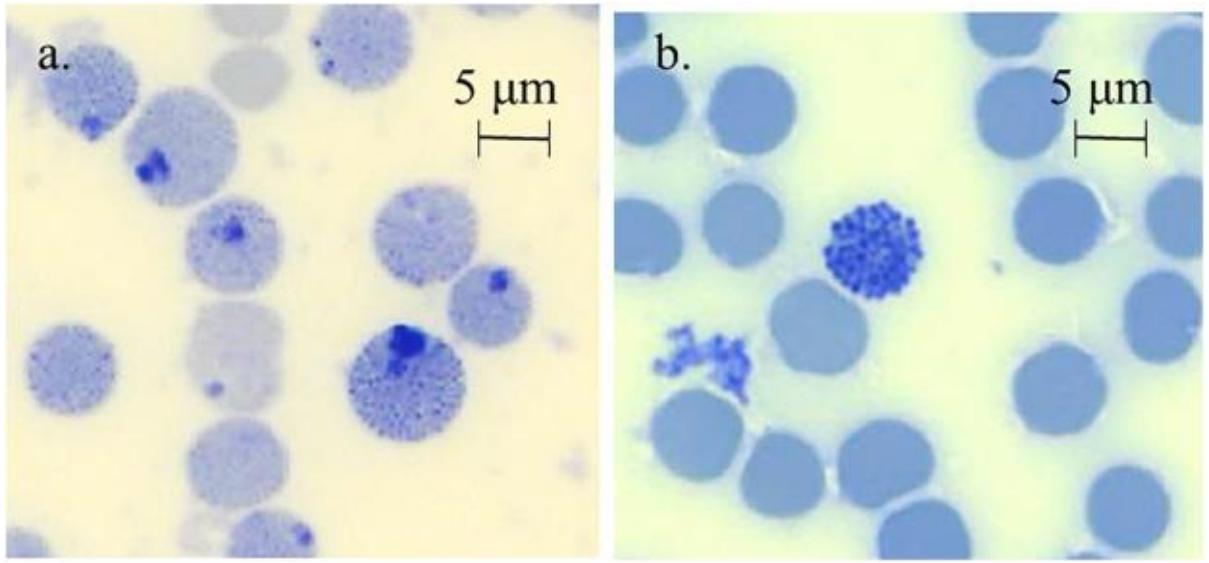
The Alpha-Thalassemias

- Alpha-thalassemia: underproduction of the α-globin chains.
- HbA ($\alpha 2\beta 2$), HbF ($\alpha 2\gamma 2$), and HbA2 ($\alpha 2\delta 2$) are all affected in α-thalassemia.



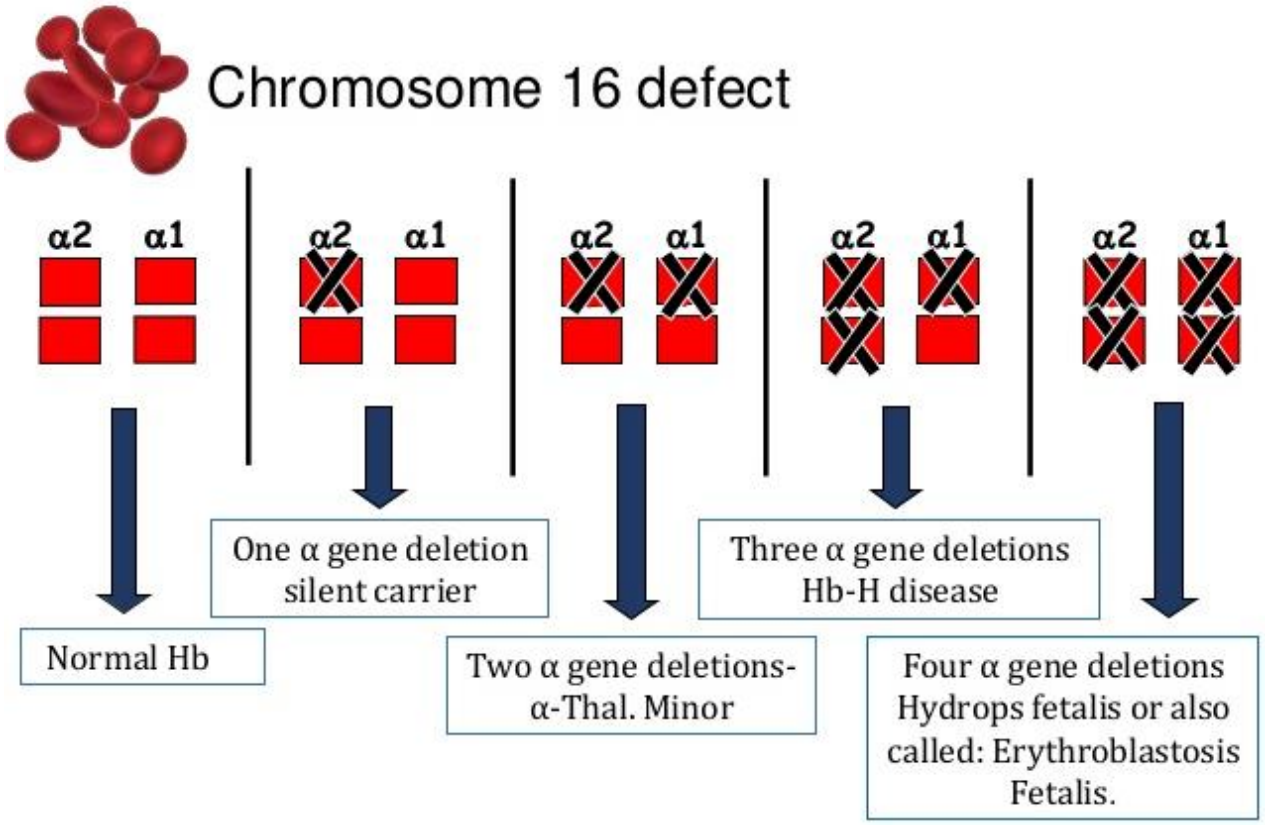
HbH

- With the reduction of α chain production, and β-chain production is established, homotetramers of β (β4 or HbH) are formed.
- The HbH tetramers have a high affinity towards oxygen and are highly unstable (meaning that they denature, aggregate and precipitate resulting in the formation of Heinz bodies).
- The main type of mutation is gene deletion



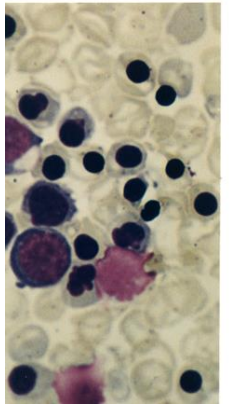
Variable severity

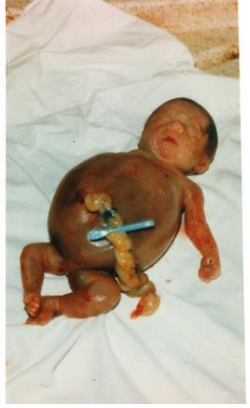
- With α-thalassemia, the level of α-globin production can range from none to very nearly normal levels.
- This is due to the fact that each individual has 4 genes.



α-thalassemia major

Hydrops fetalis

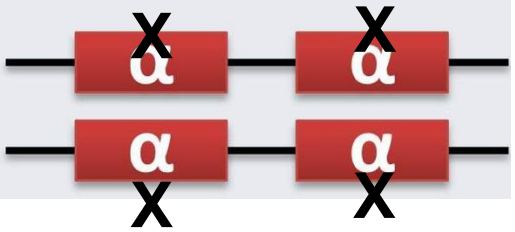




- 4 of 4 genes are deleted.
- The predominant fetal hemoglobin is a tetramer of γ-chains.
- γ4 or Hb Bart: a homotetramer of γ.
- Hb Bart has a <u>high</u> affinity towards oxygen.
- This condition is called hydrops fetalis.
- Stillbirth or death shortly after birth occurs.

Incompatible with Life

Hydrops Fetalis



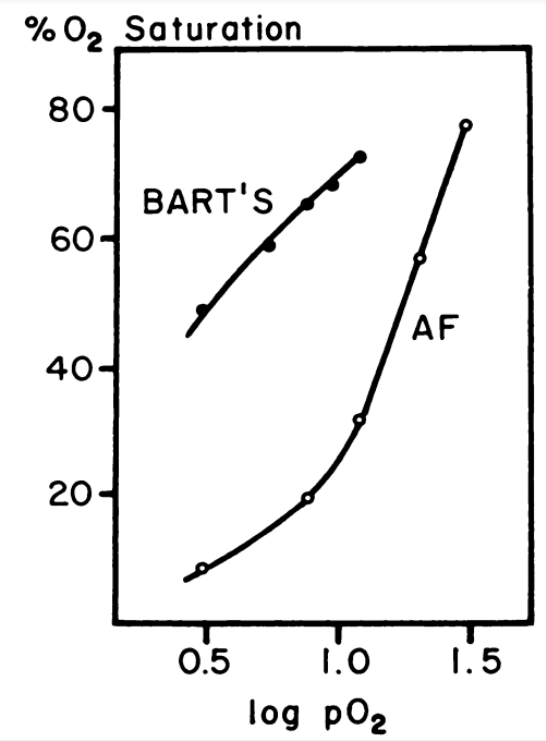


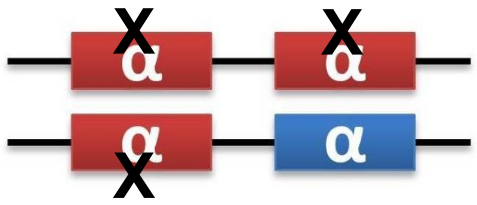
Fig. 4.—Oxygen dissociation curves. of the hemoglobin components of cord blood: Hb-Bart's and the Hb-A and F mixture.

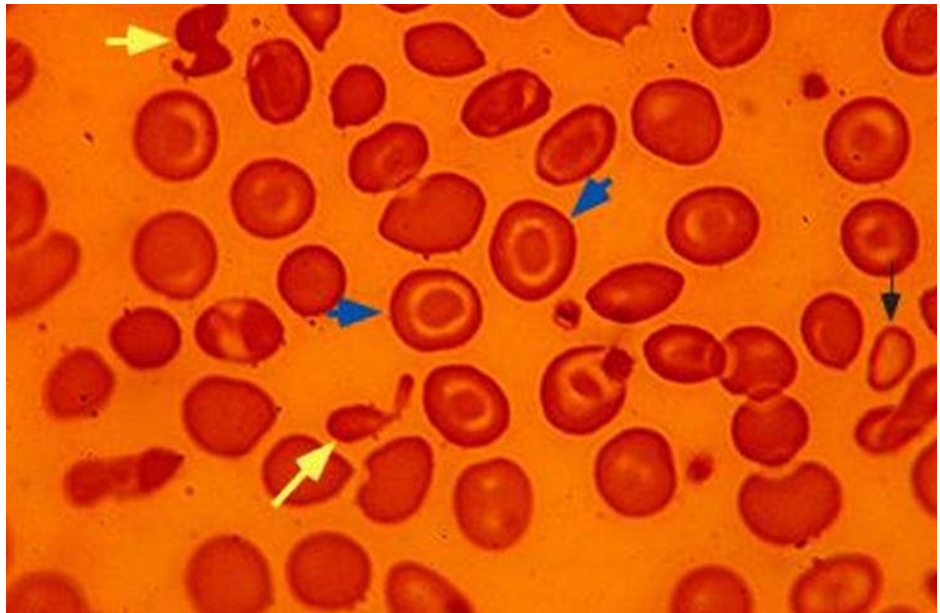
α-thalassemia intermedia

Hemoglobin H disease

- 3 of 4 genes deleted.
- Mild to moderate hemolytic anemia in adults.
- A high level of β4 tetramer is present.
- Clinically, it is known as hemoglobin H disease.
- The disease is not fatal, but symptomatic.

Hb H Disease: Symptomatic
Hemolytic and Microcytic anemia
Splenomegaly



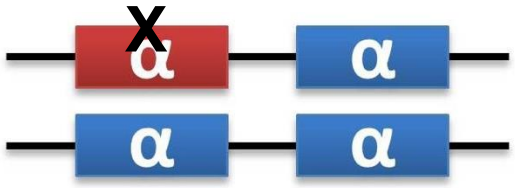


α-thalassemia minor and silent carrier

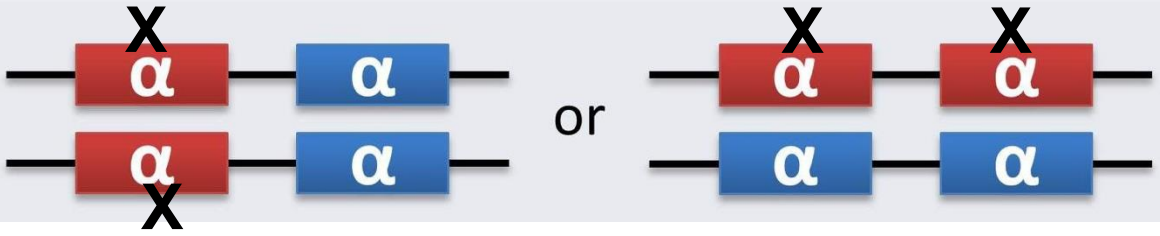
- α-Thalassemia trait: If 2 of the 4 genes are inactivated.
  - The individuals are generally asymptomatic.

- Silent carrier: 1 of 4 genes deleted.
  - Individuals are completely asymptomatic.

Carrier: Asymptomatic
No abnormalities



α-thal minor: Asymptomatic
Mild microcytic anemia



The beta-thalassemias

- β-globins are deficient and the α-globins are in excess and will form α-globin homotetramers.
- The main type of mutation is point mutations (a change in one nucleotide of the DNA sequence within the gene)
- The α-globin homotetramers are extremely insoluble, which leads to premature red cell destruction in the bone marrow and spleen.

β-thalassemia major and minor

β-thalassemia major

- A complete lack of a normal HbA gene is denoted as β^0-thalassemia or β-thalassemia major.
- Affected individuals suffer from severe anemia beginning in the first year of life and need blood transfusions.
  - Long-term transfusions lead to the accumulation of iron in the organs, particularly the heart, liver and pancreas and, finally, death in the teens to early twenties.

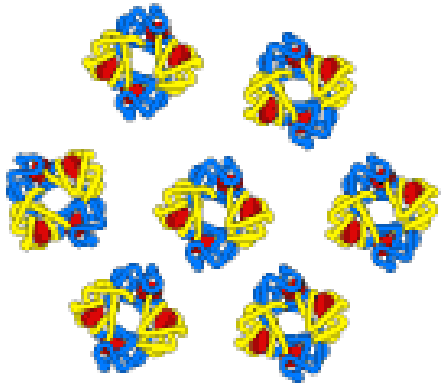
β-thalassemia minor

- Individuals with one normal β-globin gene and a mutated gene are termed β-thalassemia minor.
- Individuals with beta-thalassemia minor are generally asymptomatic.

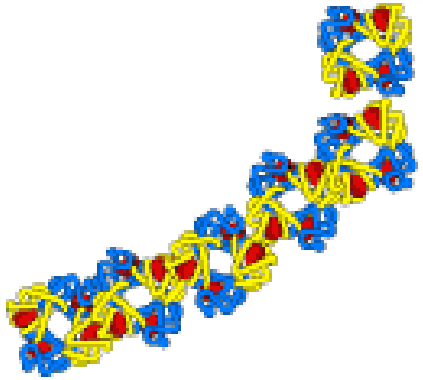
Qualitative abnormalities

Sickle cell hemoglobin (HbS)

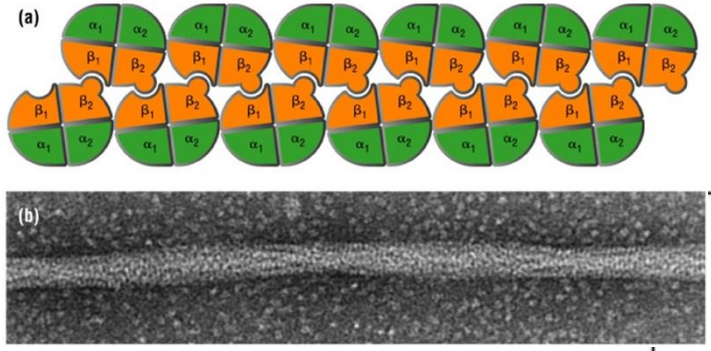
- It is caused by a change of amino acids in the 6th position of β globin (Glu to Val).
- The hemoglobin is designated α2βs2 or HbS.
- The hemoglobin tetramers aggregate into arrays upon deoxygenation in the tissues.
- This aggregation leads to deformation of the red blood cell.
- It can also cause hemolytic anemia (life span of RBCs is reduced from 120 days to <20 days).

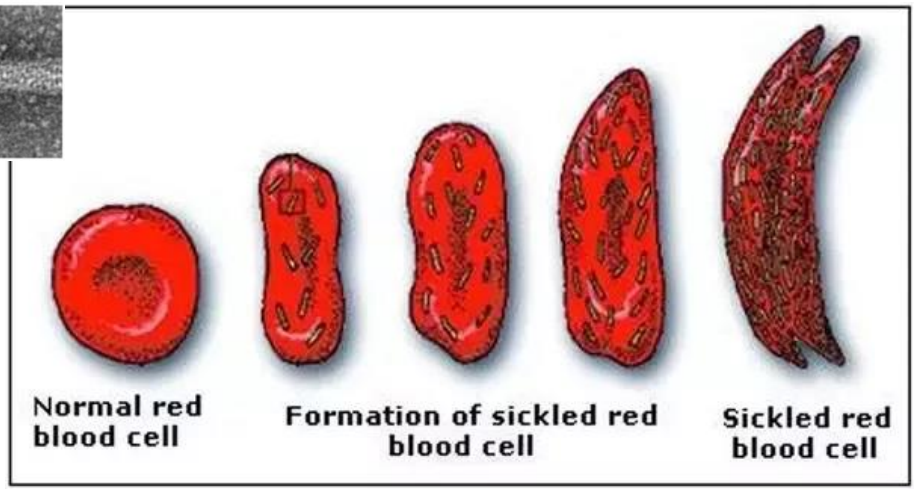


NORMAL HEMOGLOBIN



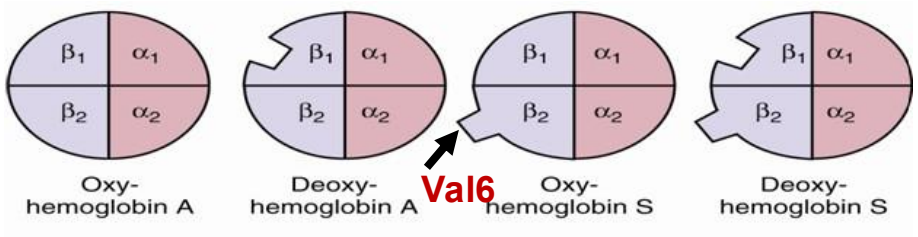
CLUMPED HEMOGLOBIN

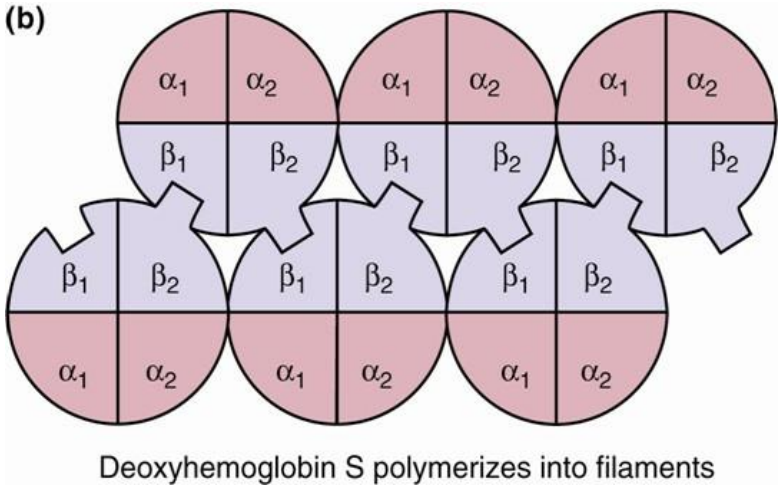


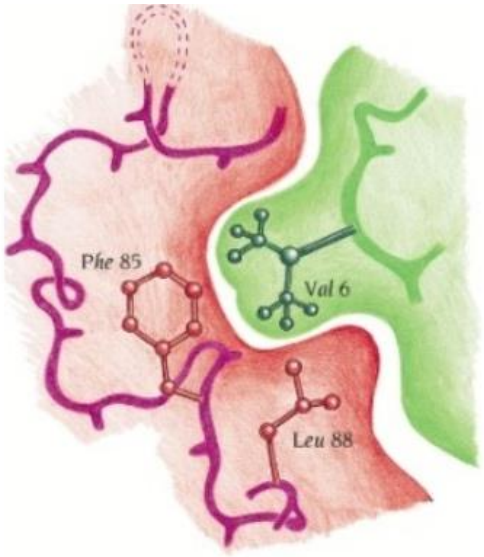


How does the fiber form?

- Fiber formation only occurs in the deoxy- or T-state.
- The mutated valine of the β2 chain is protruded and inserted into a hydrophobic pocket on the surface of β1 chain.



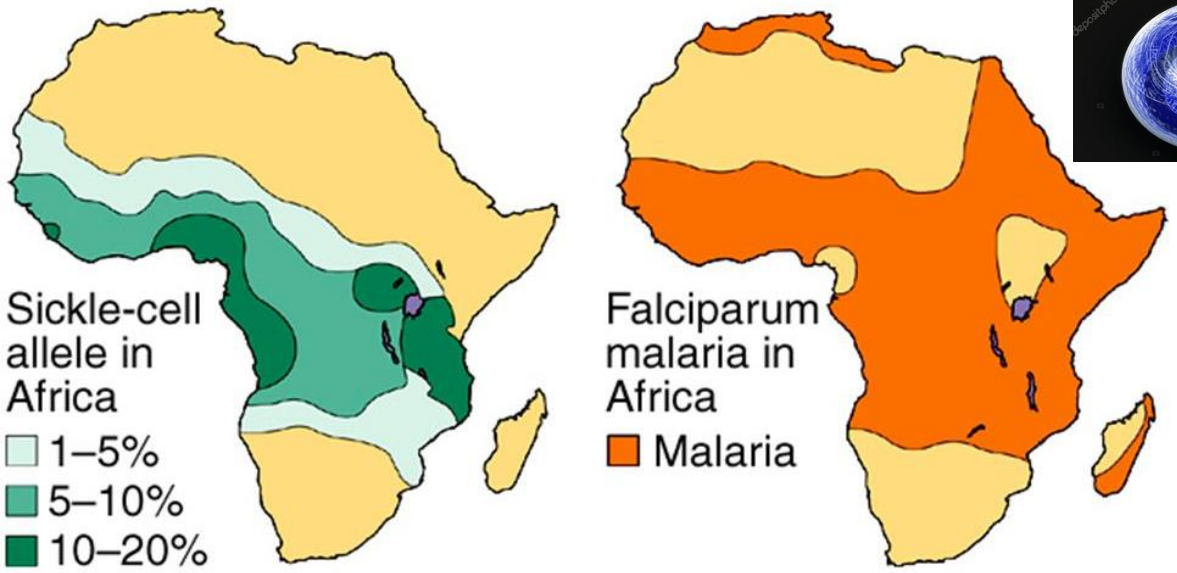


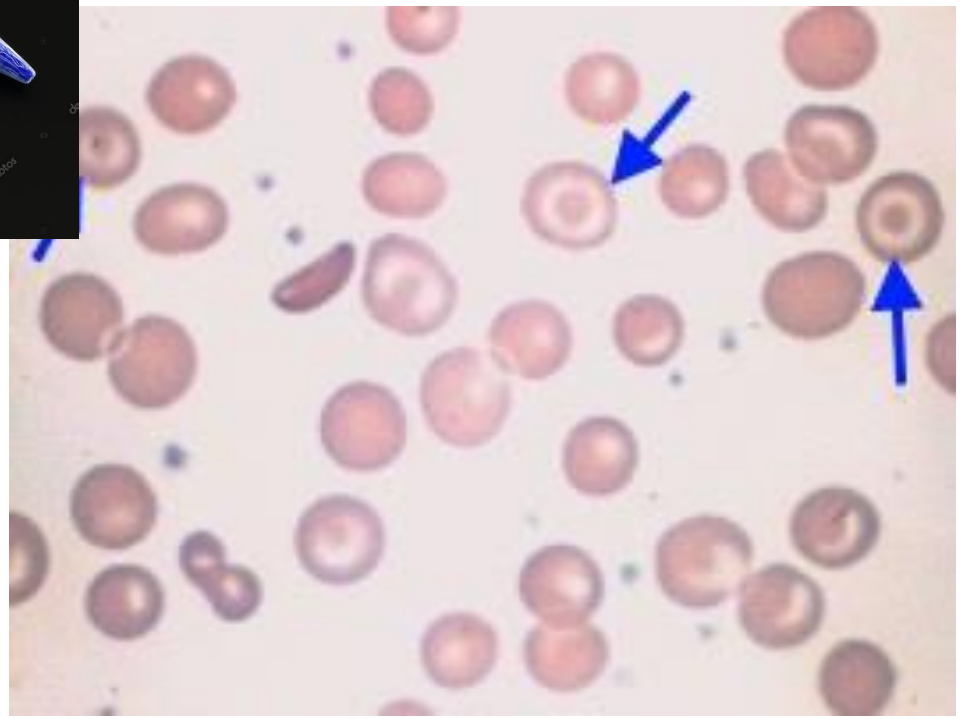


Sickle cell trait

- Advantage: selective advantage from plasmodium falciparum that causes malaria. Why?

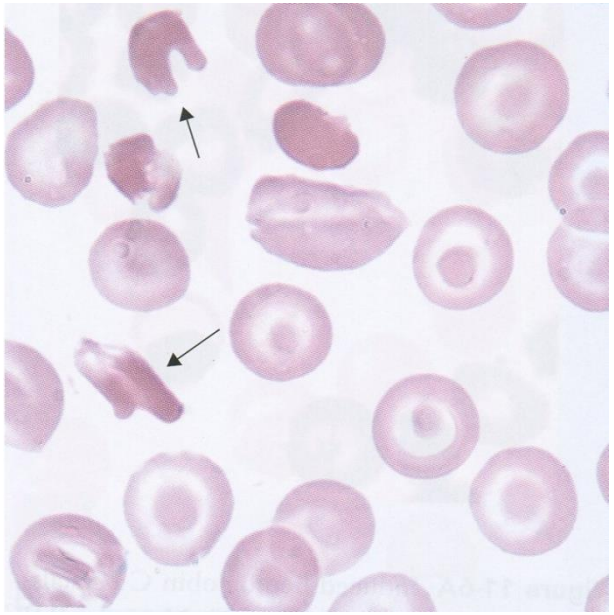
- It occurs in heterozygotes (individuals with both HbA and HbS), who are clinically normal, but their cells sickle when subjected to low oxygen.





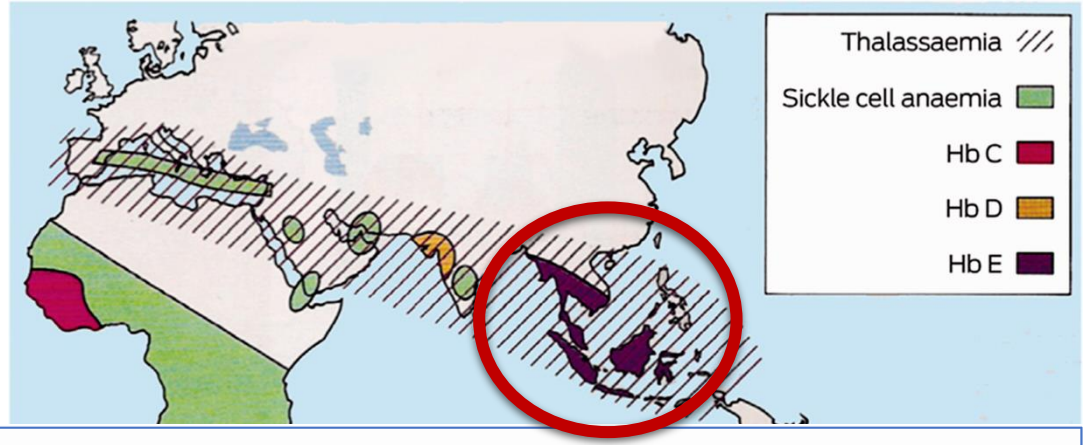
Hemoglobin C (HbC)

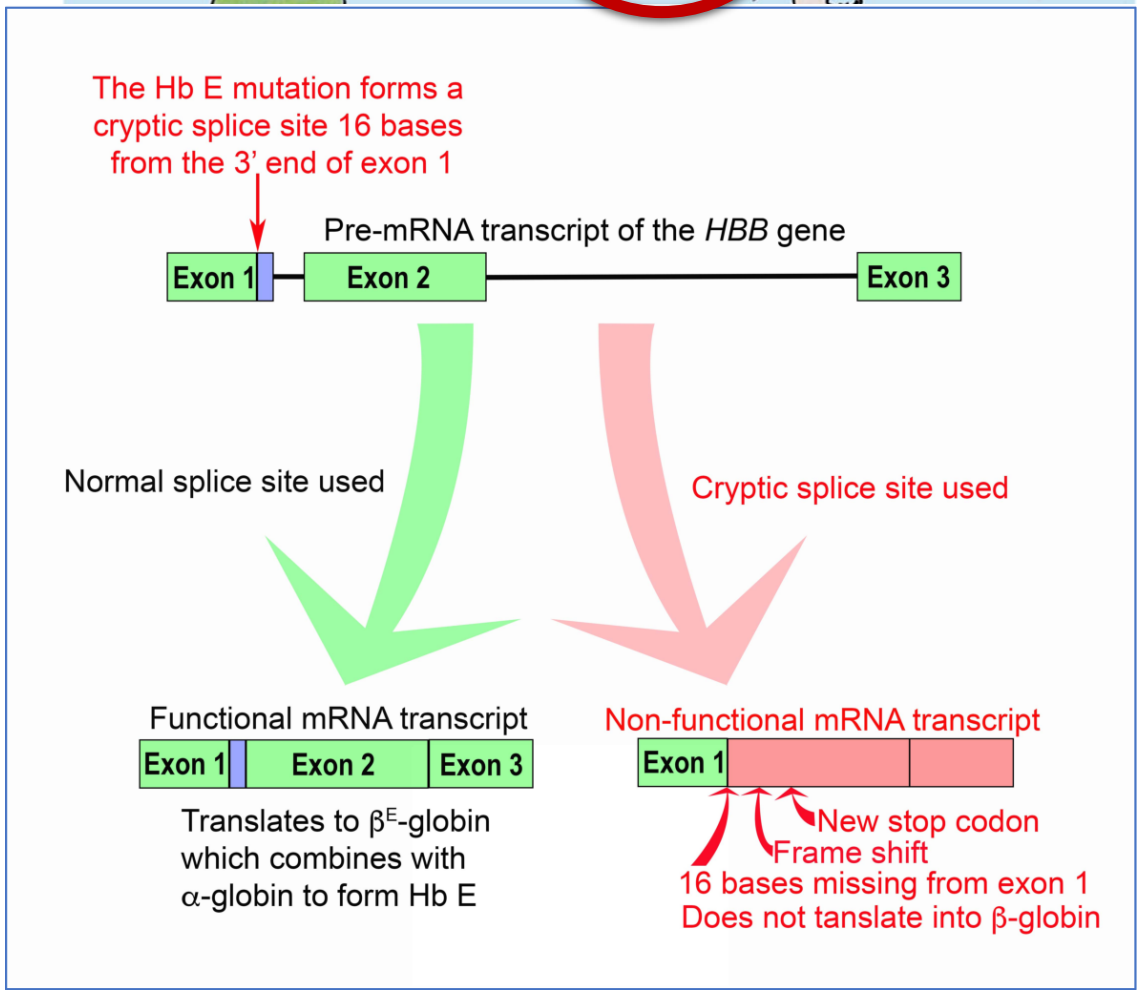
- (HbC) is also due to a change at the 6th position of β globin replacing the glutamate with lysine (designated as βc).
- This hemoglobin is less soluble than HbA so it crystallizes in RBCs reducing their deformability in capillaries.
- HbC also leads to water loss from cells leading to higher hemoglobin concentration.
- This problem causes only a minor hemolytic disorder.



Hemoglobin E

- It is common in Southeast Asia
- It has both quantitative and qualitative characteristics.
- It is caused by a mutation that changes glutamic acid to lysine producing either a less efficient hemoglobin or a shorter-than-normal protein.
- Mild disease

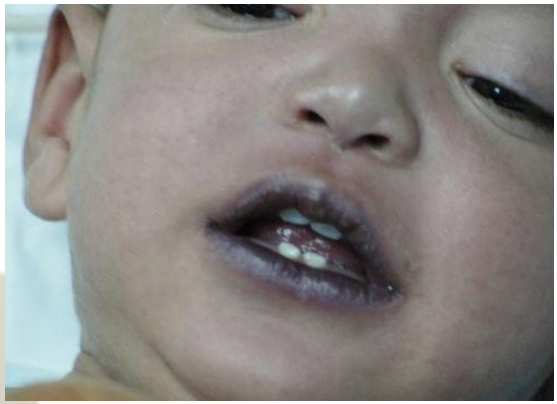


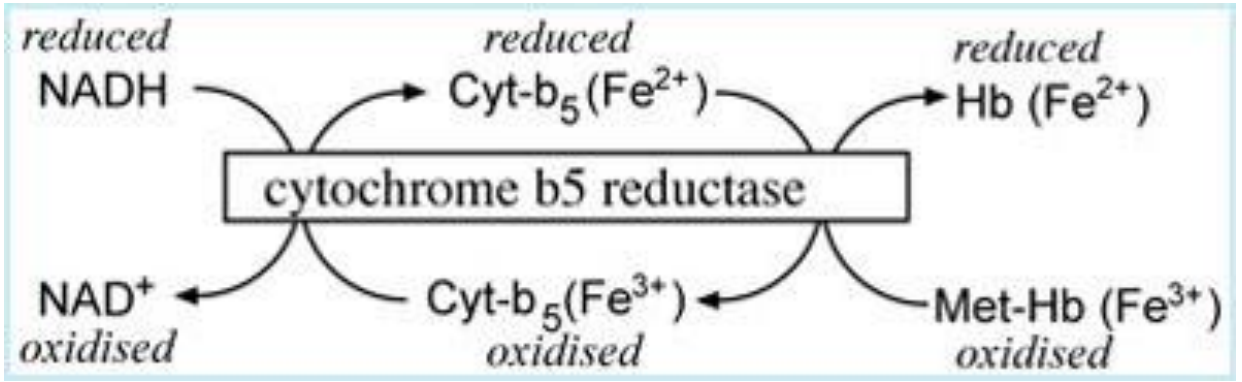


Altered Oxygen Transport

Methemoglobin (HbM)

- Hemoglobin can be reversibly oxygenated because iron remains in the reduced (ferrous, Fe^{+2}) state. Why?
- Oxygen release may cause the oxidation of Fe^{+2} to Fe^{+3}, forming methemoglobin (HbM), except that the enzyme methemoglobin reductase reduces iron back.
- If not, a condition known as methemoglobinemia develops.





Methemoglobin reductase AKA
NADH-Cytochrome b5 reductase

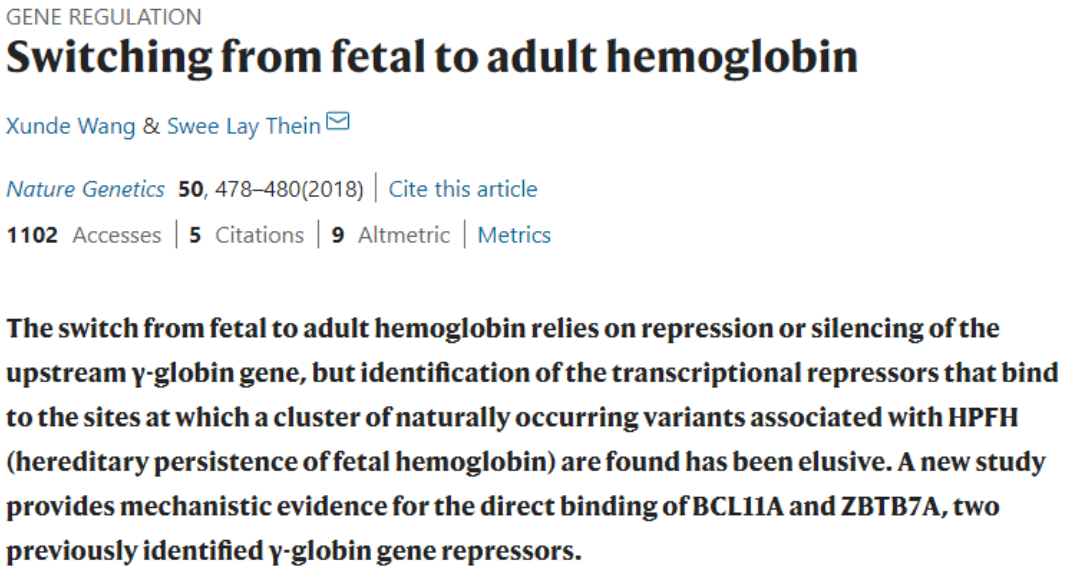
Normal Blood

Chocolate Brown coloured Blood

Hereditary persistence of fetal hemoglobin (HPFH)

- Persons with HPFH continue to make HbF as adults.
- Because the syndrome is benign most individuals do not even know they carry a hemoglobin abnormality.
- There is no deletion of the fetal globin genes.

- Think: treatment for β-thalassemia!!!!



GENE REGULATION

Switching from fetal to adult hemoglobin

Xunde Wang & Swee Lay Thein

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The switch from fetal to adult hemoglobin relies on repression or silencing of the upstream γ-globin gene, but identification of the transcriptional repressors that bind to the sites at which a cluster of naturally occurring variants associated with HPFH (hereditary persistence of fetal hemoglobin) are found has been elusive. A new study provides mechanistic evidence for the direct binding of BCL11A and ZBTB7A, two previously identified γ-globin gene repressors.