Haemoglobinopathies and Thalassaemias

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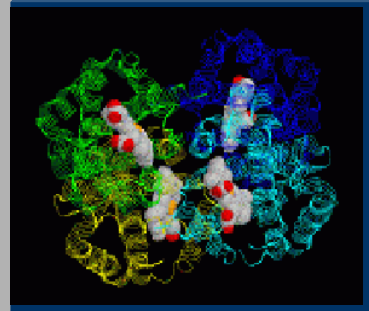
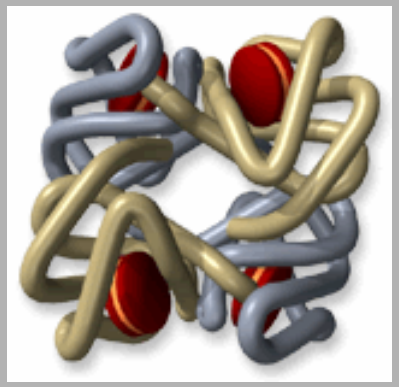


Genetic Disorders of Haemoglobin



Haemoglobin

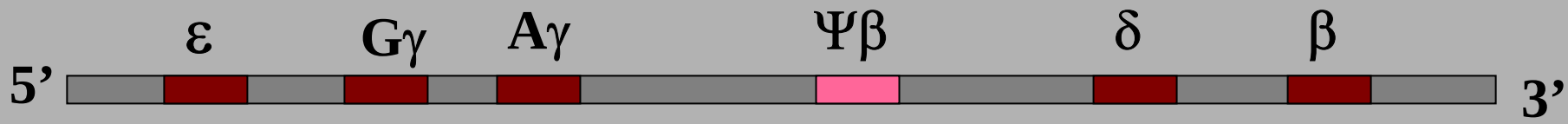
- A conjugated protein consisting of iron-containing heme and protein (globin).
- Globin chains are of different types:
  α-chains and non α -chains.
- Each molecule is a tetramer of two α- and non α -chains.
- Each globin binds a heme in a heme binding site.

Haemoglobin binds and transports oxygen from lungs to the tissues, while it transports CO_2 from tissues to the lungs.

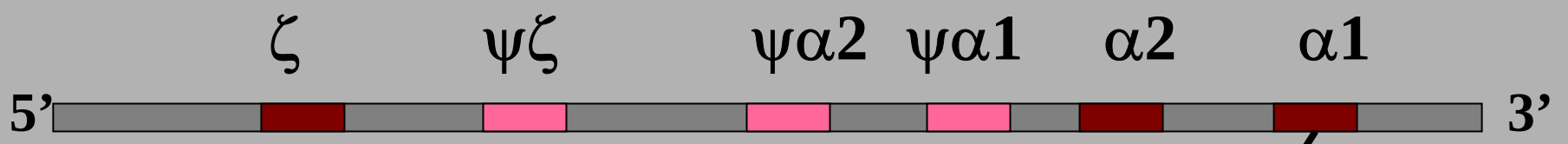
Types of Hemoglobin in adults

Globin genes Chromosome 16	11	Gene product (globin) in RBCs	Tetramers haemoglobin	Name of adult	Conc. in
α	β	α, β-chain	α2 β2	Hb A	96-97
α	δ	α, δ-chain	α2 δ2	Hb A2	2.3-3.5
α	γ	α ,γ-chain	α2 γ2	Hb F	<1.0
α	ε	α ,ε -chain	α2 ε2	Hb-Gower II	0
ζ	ε	ζ, ε -chain	ζ 2 ε2	Hb-Gower I	0
ζ	γ	ζ, γ-chain	ζ2 γ2	Hb-Portland	0

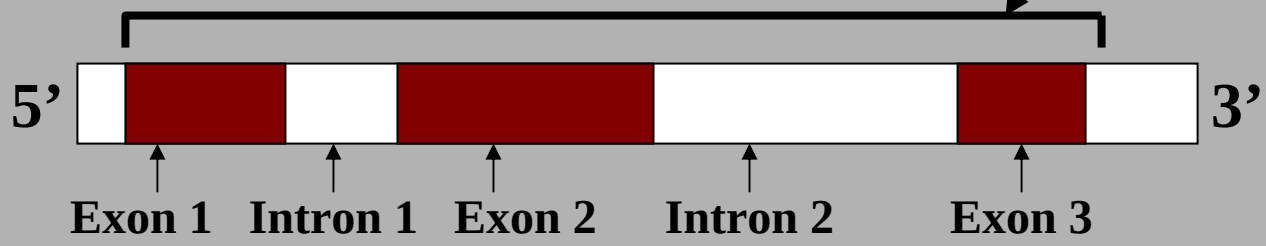
Chromosome 11



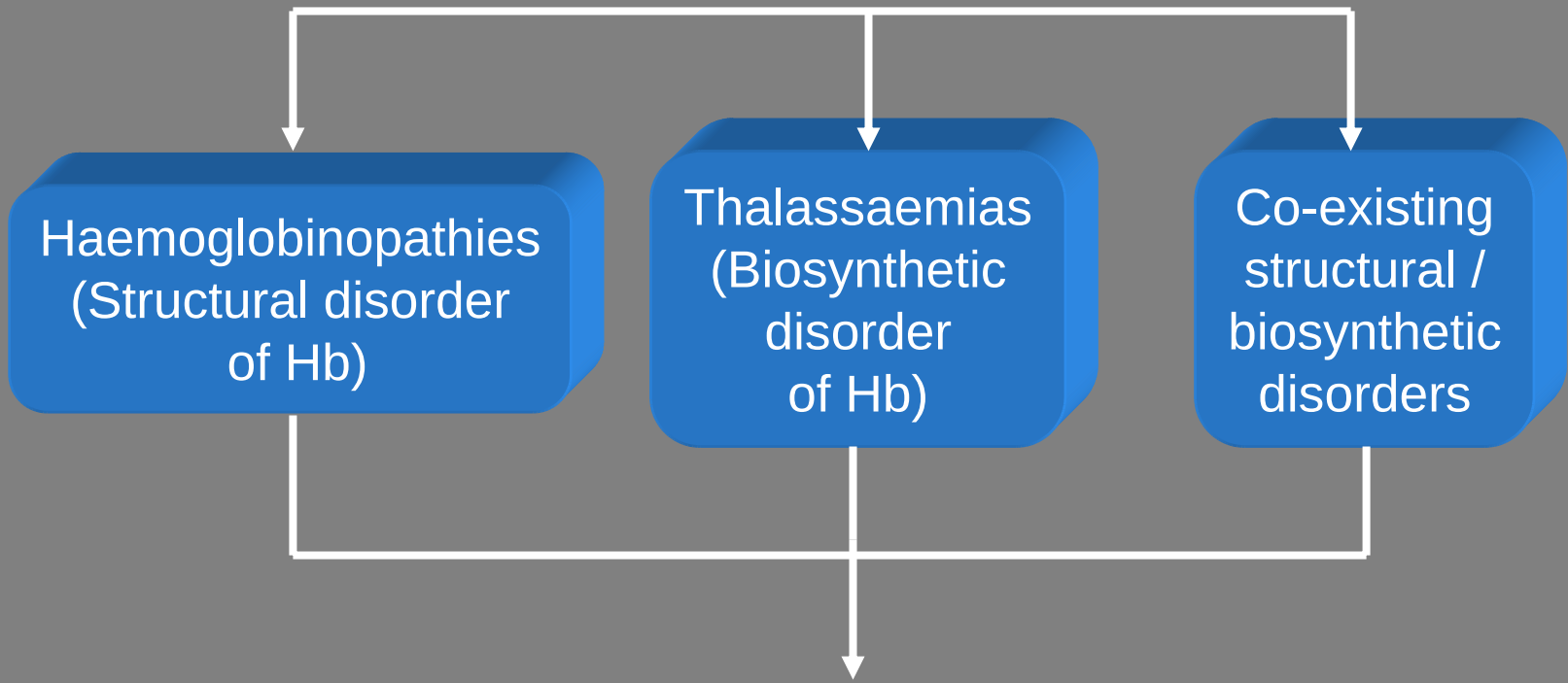
Chromosome 16



Structure of each Globin gene



Disorders of Haemoglobin



Constitute a major health problem in several populations of the world (particularly those residing in malaria endemic region)

Haemoglobinopathies

- Genetic disorder.
- Due to mutation in the globin gene of haemoglobin.
- Mostly autosomal recessive inheritance.
- Result in haemoglobin variants with altered structure and function.
- Altered functions include:
  - Reduced solubility
  - Altered oxygen affinity- increased or decreased
  - Reduced stability
  - Methaemoglobin formation

Abnormalities in Haemoglobin

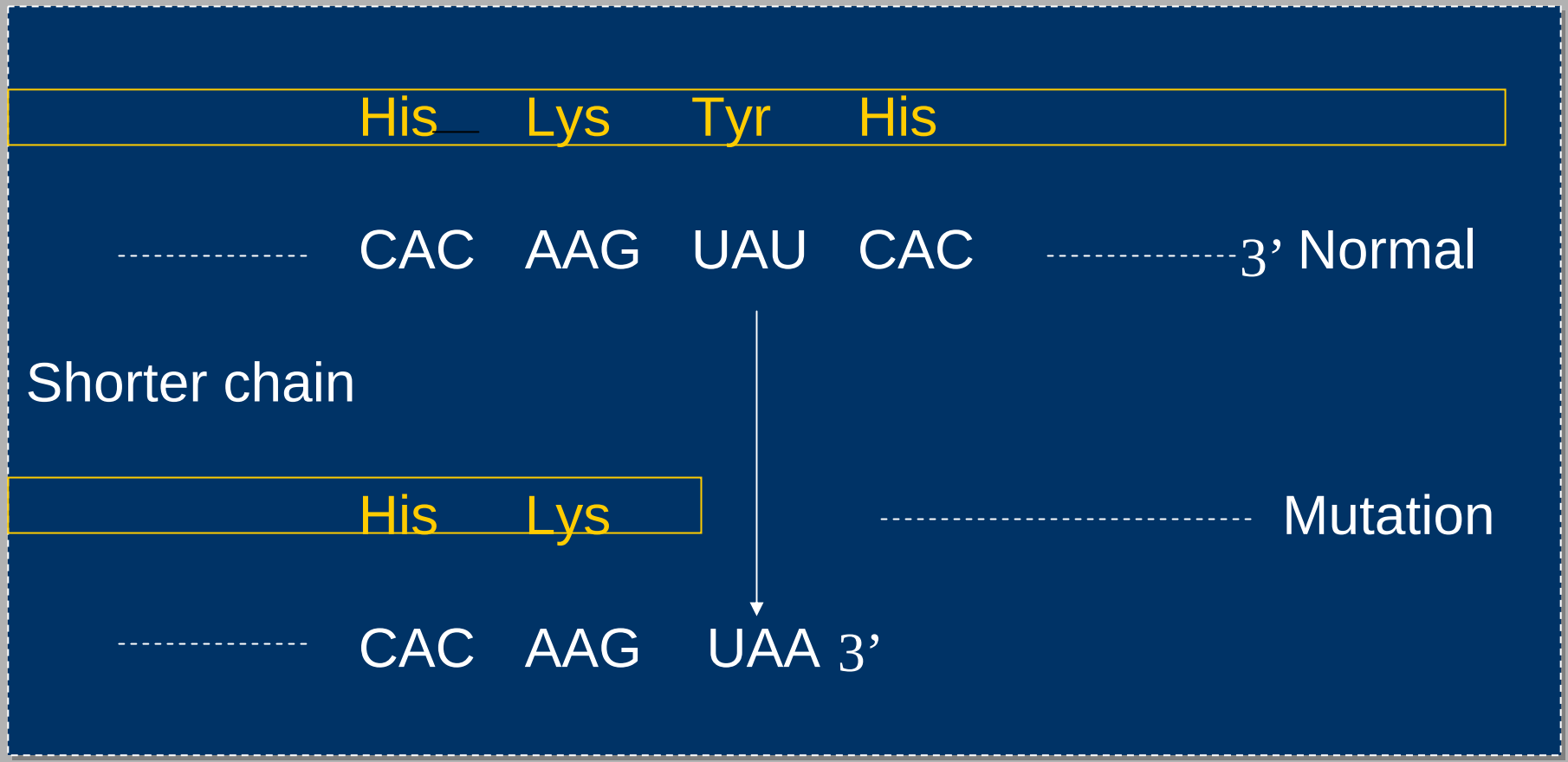
- Point mutation: a change of a single nucleotide base in a DNA giving rise to altered amino acids in the polypeptide chains (e.g. Hb S and Hb C)
- Deletions and additions: Addition and deletion of one or more bases in the globin genes (e.g. Hb-constant spring which is associated with mild α-thalassaemia).
- Unequal crossing over: as in Hb-lepore and Hb-antilepore associated with β-thalassaemias.

Most abnormal Hbs are produced by mutations in the structural genes which determine the amino acid sequence of the globin chains of the Hb molecule.

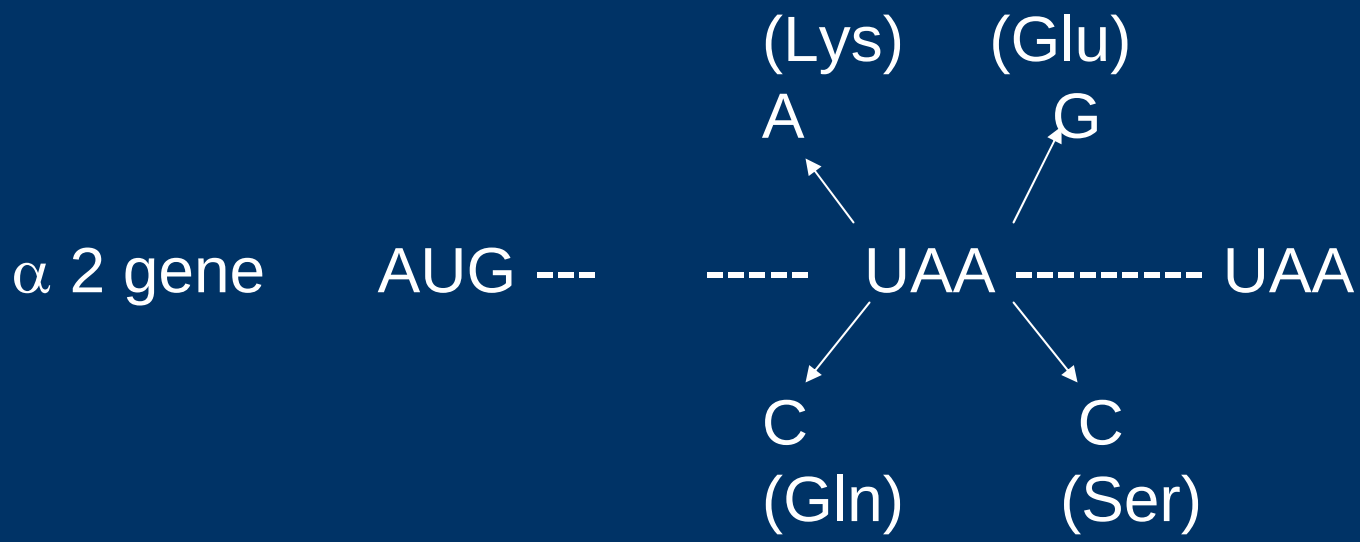
Geographical distribution of common Hb variants

Variant	Occurrence predominantly in:
Hb S (β^{6}Glu$\rightarrow$Val)	Africa, Arabia, Black Americans
Hb C (β^{6}Glu$\rightarrow$lys)	West Africa, China
Hb E (β^{26}Glu$\rightarrow$lys)	South East Asia
Hb D (β^{121}Glu$\rightarrow$Gln)	Asia
Hb O (β^{121}Glu$\rightarrow$Val)	Turkey and Bulgury

Other examples of Haemoglobin variants

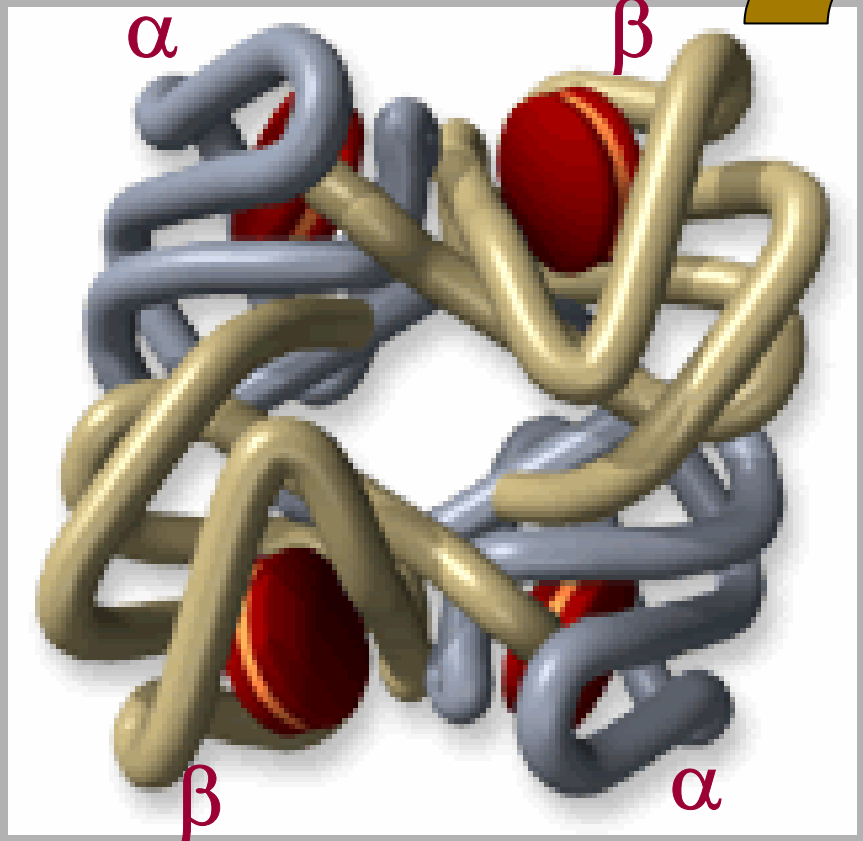


Long chains, e.g.



Gln
Lys
Glu
Ser
142

Sickle Cell Haemoglobin



β^{6} GAG → GTG

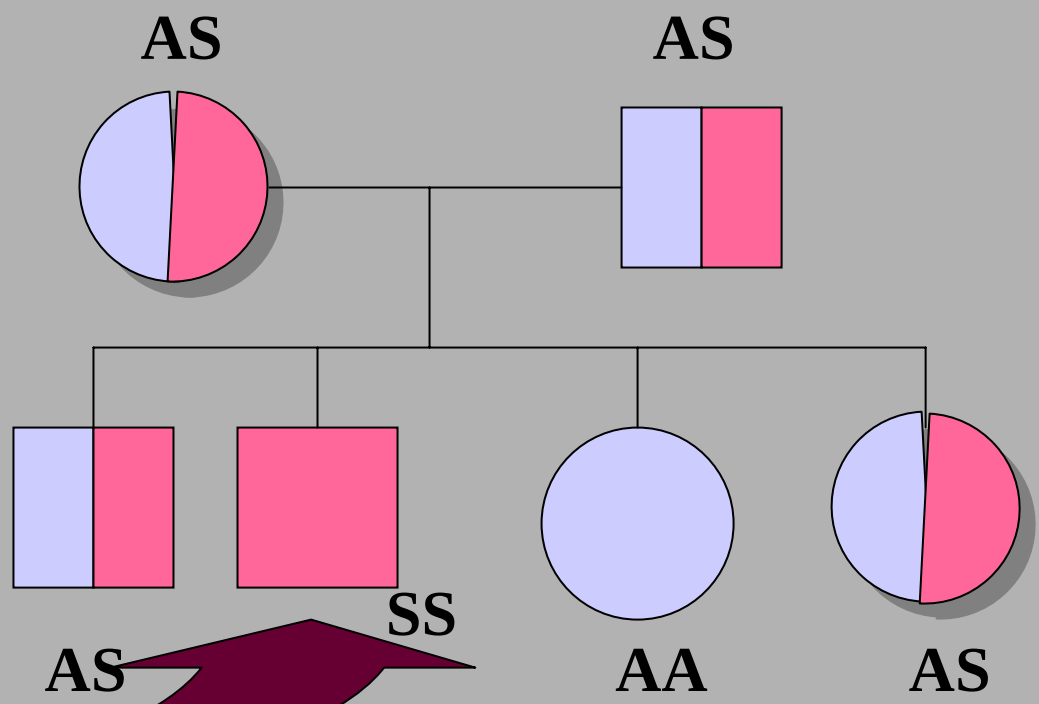
RBC

Sickle Cell

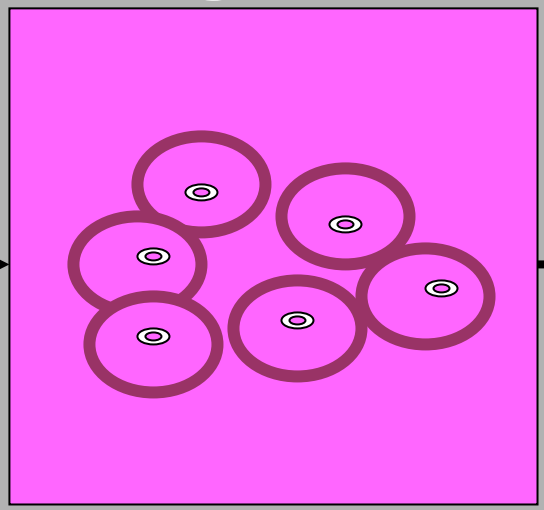
Haemolysis

Inheritance of Sickle Cell Anaemia

AR



Red cell sickling



Lungs
↑ pO_2

Tissues
↓ pO_2

Major abnormalities in SCA

- Sickling of the red cell during deoxygenation, as the HbS has low solubility at low O_2 partial pressure and precipitates.
- Chronic haemolytic anaemia due to repeated sickling in tissues and unsickling in the lungs.
- Plugging of microcapillaries by rigid sickled cells leading to sickle cell crises i.e severe pain and edema. This causes significant damage to internal organs, such as heart, kidney, lungs and endocrine glands.
- Repeated infections.
- Frequent cerebrovascular accidents.
- Hand-foot syndrome.
- Bone deformation – bossing of the forehead.
- Hepato-spleenomegaly.
- Growth retardation.
- Frequent blood transfusion requirements.
- Psychosocial problems.

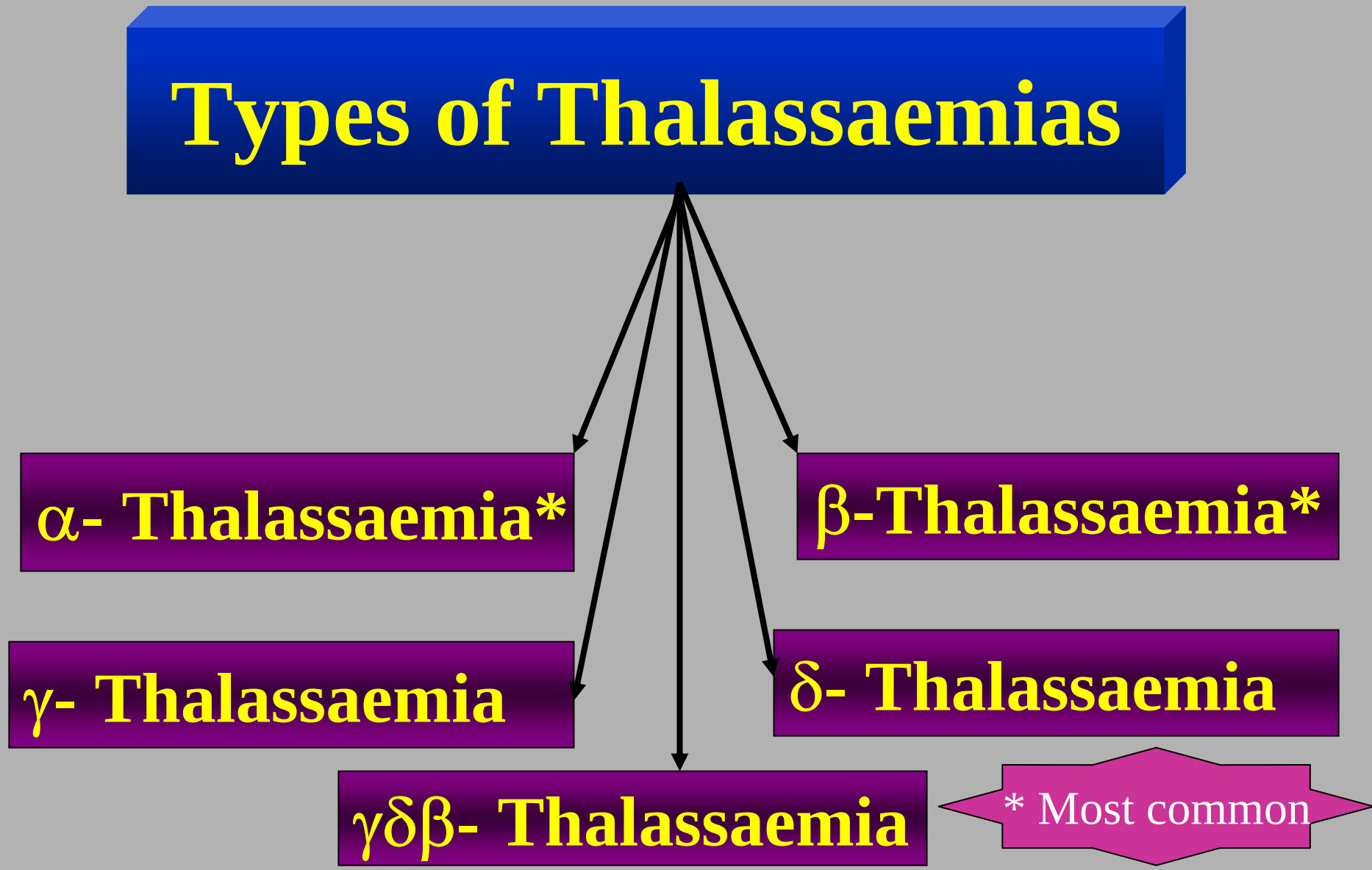
Thalassaemias

Genetic disorders resulting from decreased synthesis of globin chains of haemoglobin.

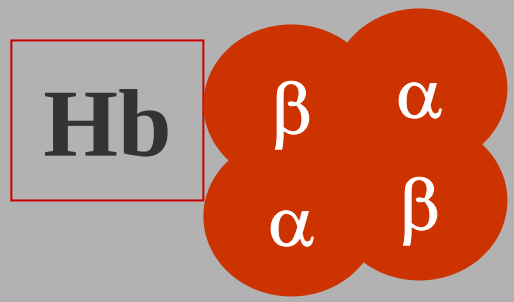
Thalassaemias

- **A group of Genetic defects.**
- **Due to mutations in and around the globin genes.**
- **Decreased production of one or more of the globin chains.**
- Result in an imbalance in the relative amounts of the α- and non α -chains. Altered α/non- α ratio.
- A few rare Hb variants are effectively synthesized but are highly unstable, and thus cause thalassaemias as the α:β chain ratio is altered.
- As a consequences of thalassaemias there is excess production of the other chains, and a decreased over all haemoglobin synthesis.

Types of Thalassaemias



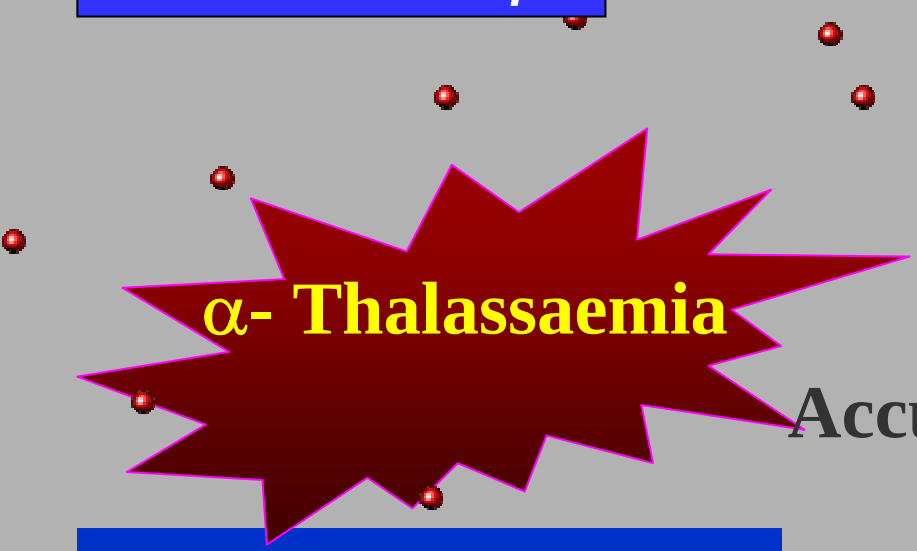
α- Thalassaemia

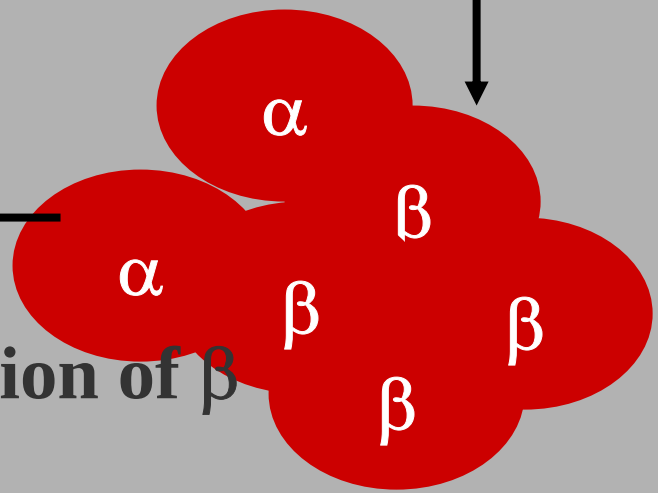


In α- Thalassaemia

Decreased production of α- chains

Normal α= β



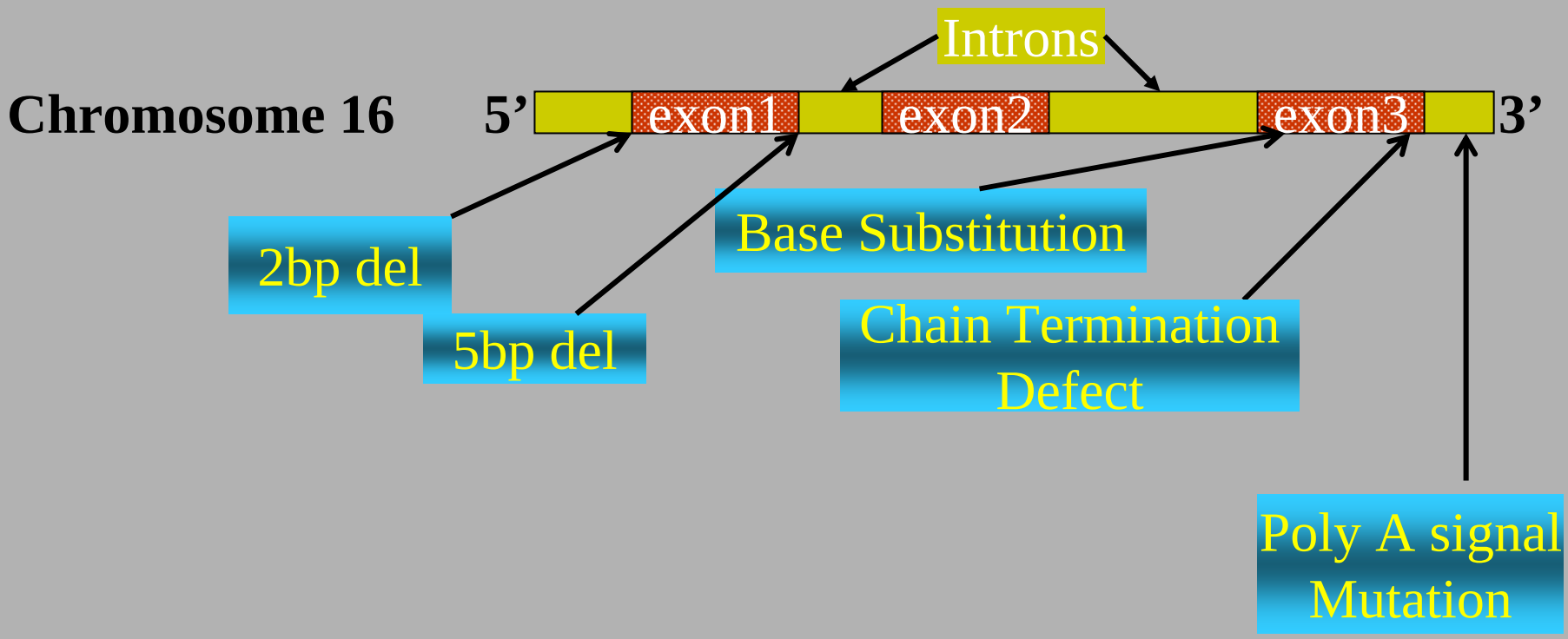


Accumulation of β

- Decreased α/β ratio

Point Mutation producing α- Thalassaemia

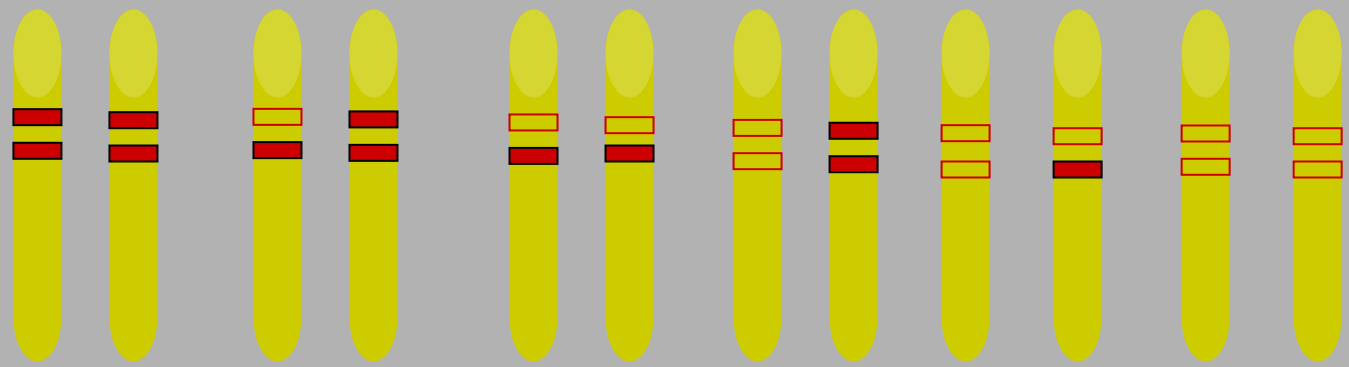
Less Frequent



Mutations Producing α- Thalassaemia

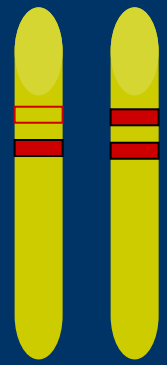
Deletions → Most frequent:

Chromosome 16

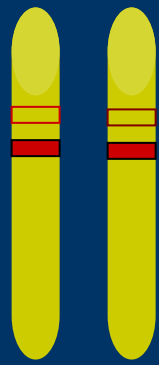


αα/αα	-α/αα	-α/-α	--/αα	--/-α	--/--
Normal	α-thal 2 hetero	α-thal 2 homo	α-thal 1 hetero	HbH Disease	Hydrops fetalis

α-thalassaemia -2

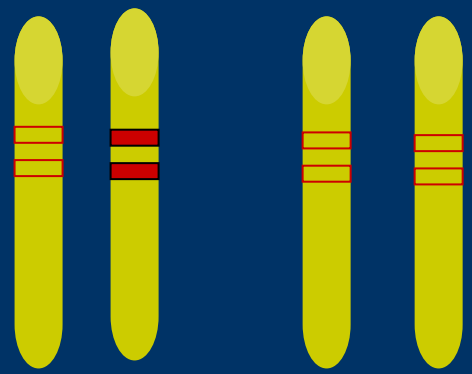


- One α -gene deletion.
- α-chain production is only about 75% of normal.
- May be homo- (- α/- α) or heterozygous (- α/ αα)



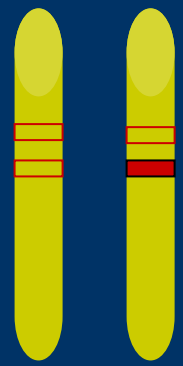
- The patient usually shows a normal phenotypic appearance but there might be mild thalassaemia symptoms.
- Hypochromic-microcytic RBC's due to partial reduction of α-chain.

α-thalassaemia- 1



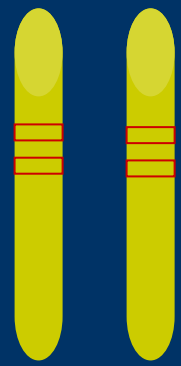
- Two α -genes deletion- (α^o)thal.
- The patient synthesizes α-chain but it is decreased to about 50% of normal.
- Anaemic symptoms- hypochromic microcytic anaemia.
- May be homozygous (- -/- -) or heterozygous(--/ αα). If the patient is homozygous than there is no α-chain synthesis, and if heterozygous than there is decreased synthesis of the α-chain to half normal level.

Hb H Disease



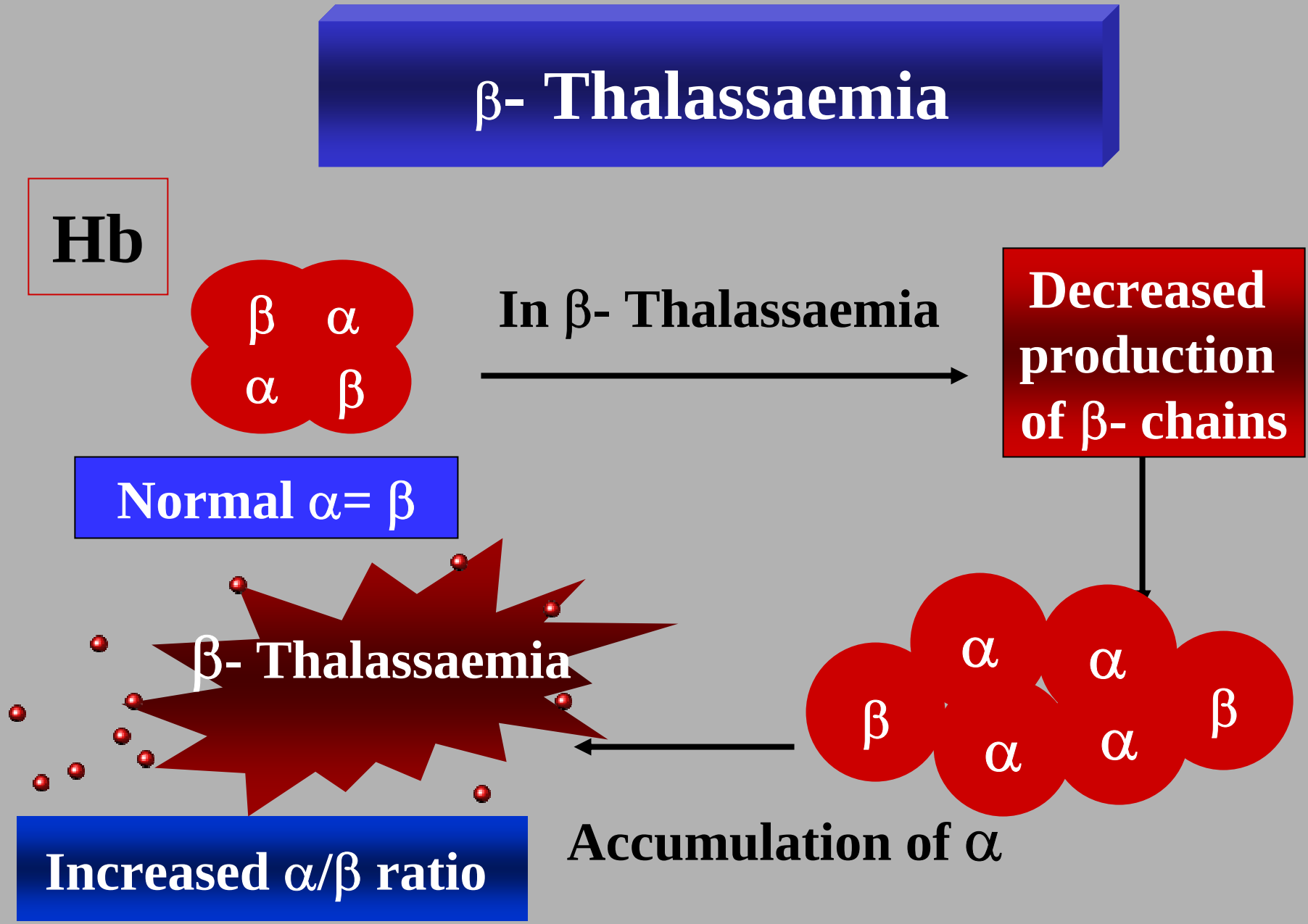
- Three α-gene deletion.
- The Hb present during foetal life is “Hb Bart’s” (γ_4), while during adulthood the Hb present is “Hb H” (β_4).
- Some of the symptoms include: hepatosplenomegally, impairment of erythropoisis, and hypochromoc-microcytic haemolytic anaemia.

Hydrops foetalis



- Homozygous α^{o}-thalassaemia.
- There is a complete absence of α-chain (all α-genes are deleted).
- The Hb produced at birth is Hb Barts (γ_4).
- Hydrops foetalis is lethal and the baby is born dead.
- Symptoms include: Hepatosplenomegaly, severe hypochromic- microcytic anaemia.

β- Thalassaemia



β-Thalassaemia

- It is characterized by either no β-chain synthesis (i.e. β^o) or decreased synthesis of β-chain (β+).
- Excess α-chains precipitate in RBC's causing severe ineffective erythropoiesis and haemolysis.
- The greater the α-chains, the more severe the anaemia.
- Production of γ-chains helps to remove excess α-chains and to improve the β-thalassaemia. Often HbF level is increased.
- Majority of β-thalassaemia is due to point mutation.

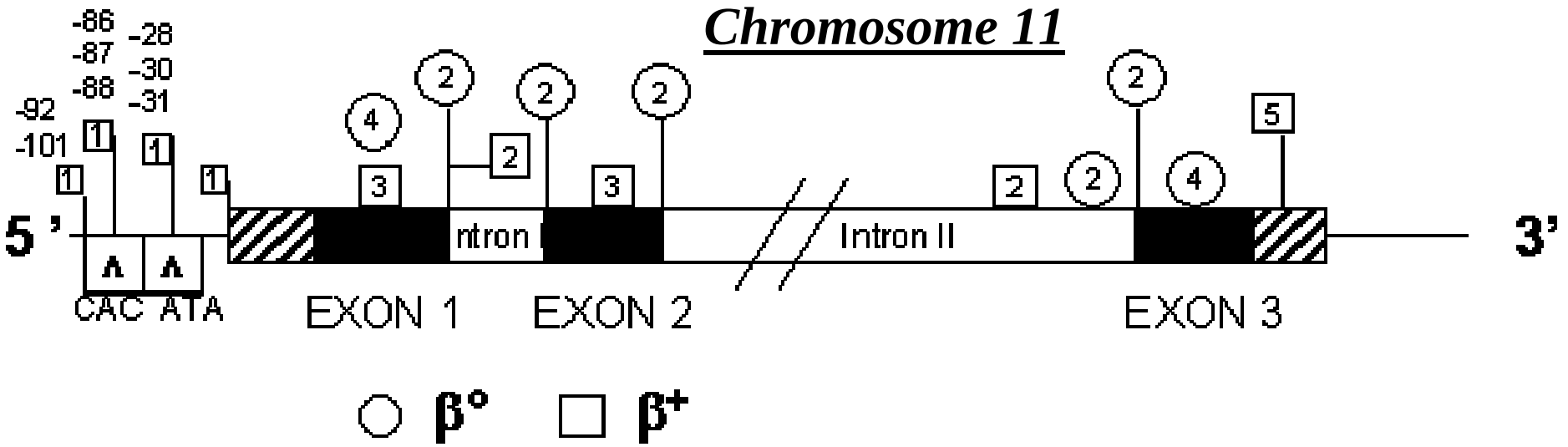
β^o-Thalassaemia

- The β-chain is totally absent.
- There is increase in HbF with absence of HbA and HbA2.
- This is combined with ineffective erythropoisis.
- In majority of the cases, β-gene is present but there is complete absence of mRNA.
- Characteristics of this disorder are:
  - Skeletal deformities (e.g. enlargement of upper jaw, bossing of skull and tendency of bone fractures).
  - Severe hypochromic- microcytic anaemia.
  - Survival depends on regular blood transfusion.
  - This leads to iron overload (iron accumulates in the blood and tissues, causing tissue damage).
  - Death usually occurs in the 2nd decade of life (i.e. at age of about 20 years) if measures are not taken to avoid iron overload by chelation therapy.

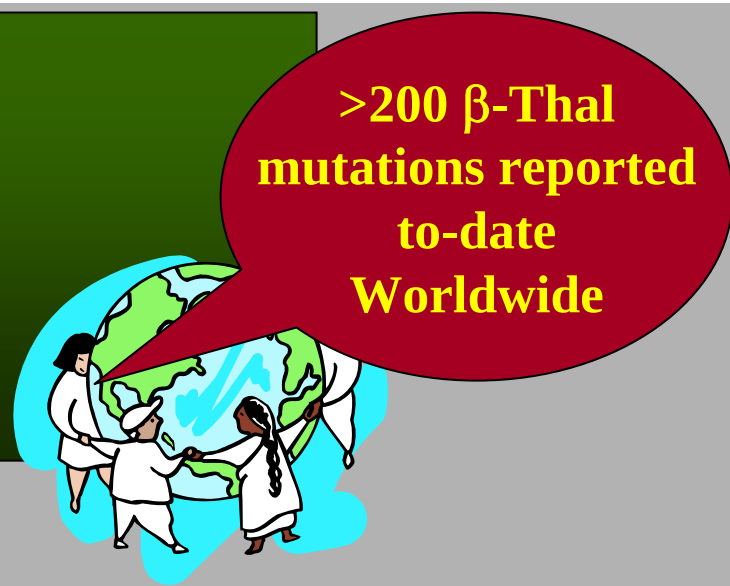
β^+-Thalassaemia

- There is a variable amount of β-chain production.
- There is decreased HbA level, and increased HbA_2, level with normal or increased HbF level (and there is an increased number of α-chains in the free form).
- The β-chain is present but there is decreased numbers of mRNA or there is an abnormality in the mRNA.

Mutations affecting the β-Globin gene.



1. Mutations affecting transcription initiation
2. Mutations affecting RNA splicing
3. Mutations affecting translation initiation
4. Non-sense Mutations.
5. Mutations of polyadenylation site.



Clinical Classification of Thalassaemias

1. Thalassaemia major:

   The patient depends on blood transfusions especially if he is homozygous.

2. Thalassaemia intermediate:
   - Homozygous mild β^+-thalassaemia.
   - Co-inheritance of α-thalassaemia.
   - Heterozygous β-thalassaemia.
   - Co-inheritance of additional α-globin genes.
   - $\delta\ \beta$-thalassaemia and hereditary persistence of foetal Hb
   - Homozygous Hb lepore
   - Hb H disease.

3. Thalassaemia minor (trait):
   - β^o-thalassaemia trait.
   - β^+-thalassaemia trait.
   - Hereditary persistence of foetal Hb only.
   - $\delta\beta$-thalassaemia trait.
   - α^o- and α^+-thalassaemia trait.

Hb-Lepore

- This is an abnormal Hb due to unequal crossing-over of the β- and δ-genes to produce a polypeptide chain consisting of the δ- chain at its amino end and β- chain at its carboxyl end.
- The δβ-fusion chain is synthesized inefficiently and normal δ and β-chain production is abolished.
- The homozygotes show thalassaemia intermediate and heterozygotes show thalassaemia trait.
- Unequal crossing-over can be explained as crossing over between similar DNA sequence that are misaligned resulting in sequences with deletions or duplications of DNA segments; a cause of a number of genetic variants.
- The adjacent δ and β-genes differ at only 10 of their 146 a.a. residues, if mispairing occurs followed by intergenic crossing over, two hybrid genes result: one with a deletion of part of each locus (lepore gene) and one with a corresponding duplication (anti-lepore gene).

Persistence of foetal Hb

A group of disorders due to deletions or cross over abnormalities which affect the production of β and γ chains in non-deletion forms to point mutations upstream from the γ-globin genes.

Double heterozygous indicates the presence of combinations of the following:

- Hb S + β^{O}-thalassaemia.
- Hb S + β^{-}-thalasaemia.
- Hb S + α-thalasaemia.
- Hb S + HbC disease
- Hb S + HbE disease