Hemoglobinopathies

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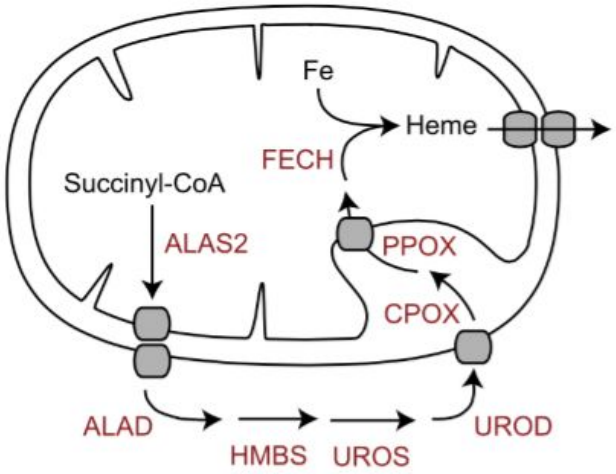
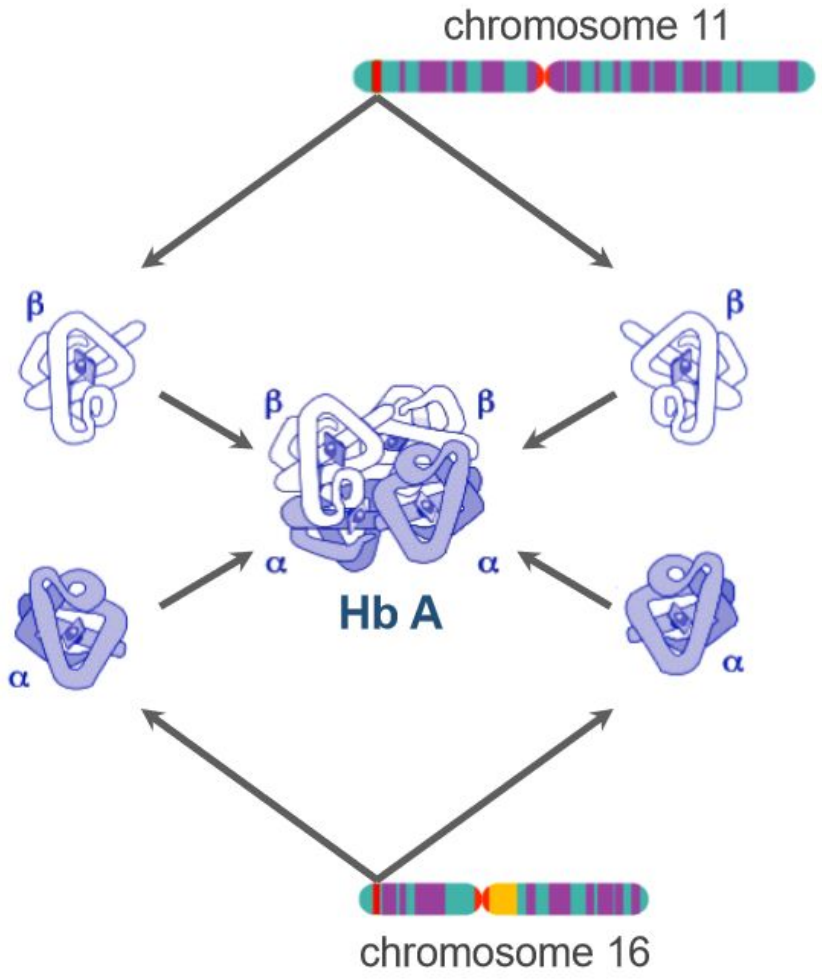
Heme

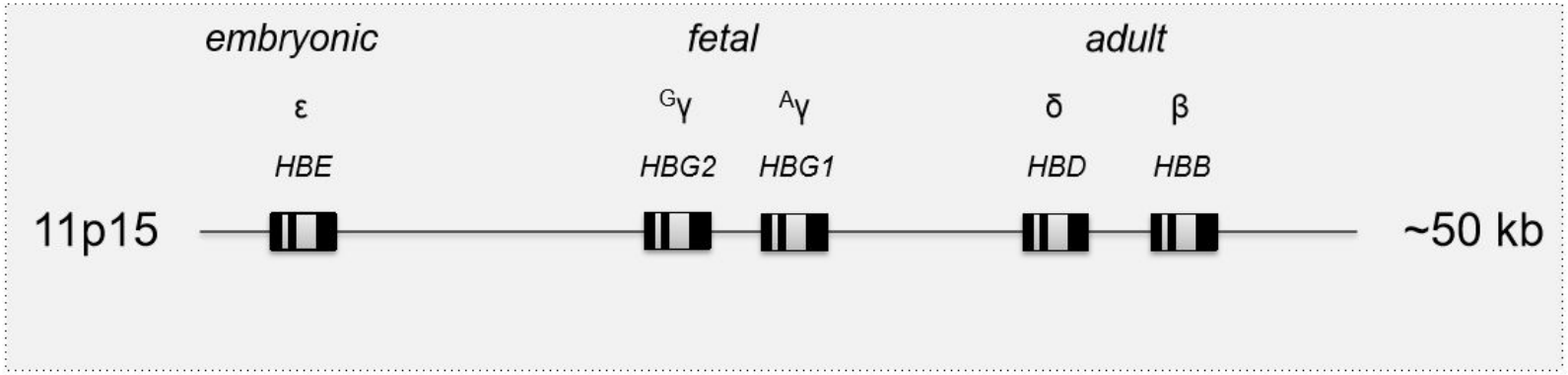


8 genes
7 chromosomes

Globin



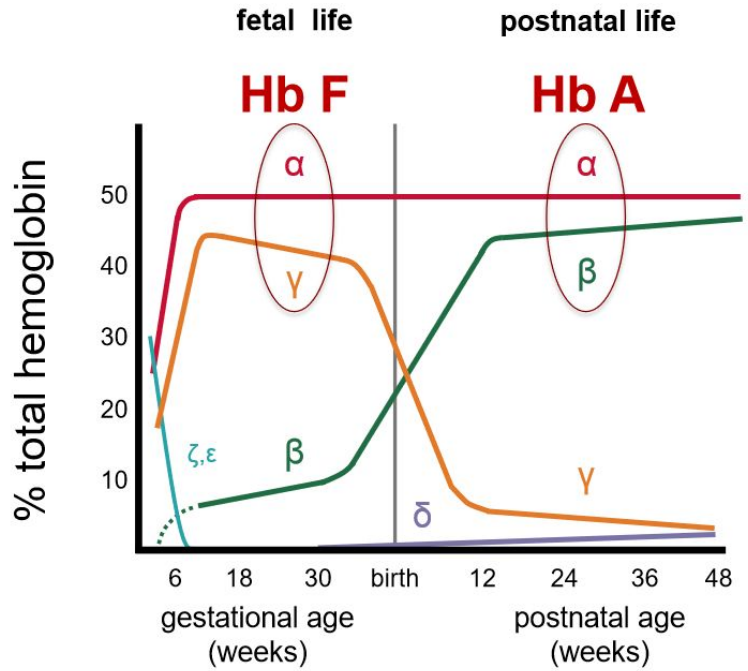
coding genes of the β-globin cluster



2: β/β
4: αα/αα

coding genes of the α-globin cluster

Hemoglobins Throughout Development



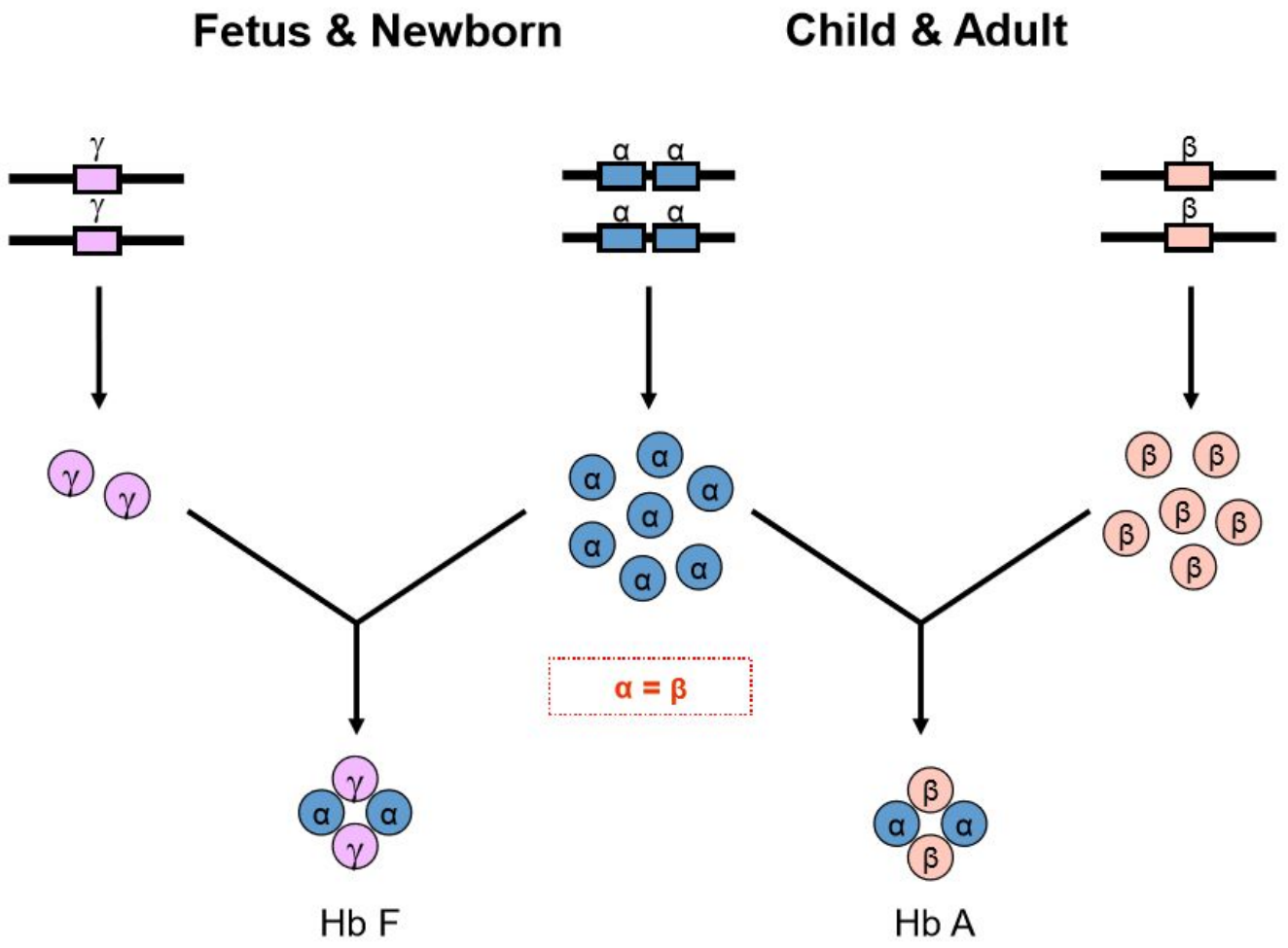
Name	Description	Formula
Hb A	Adult Hb	$\alpha_2\beta_2$
Hb A_2	Minor adult Hb	$\alpha_2\delta_2$
Hb F	Fetal Hb	$\alpha_2\gamma_2$
Hb Barts	Abnormal Hb	γ_4
Hb H	Abnormal Hb	β_4

Hemoglobinopathies

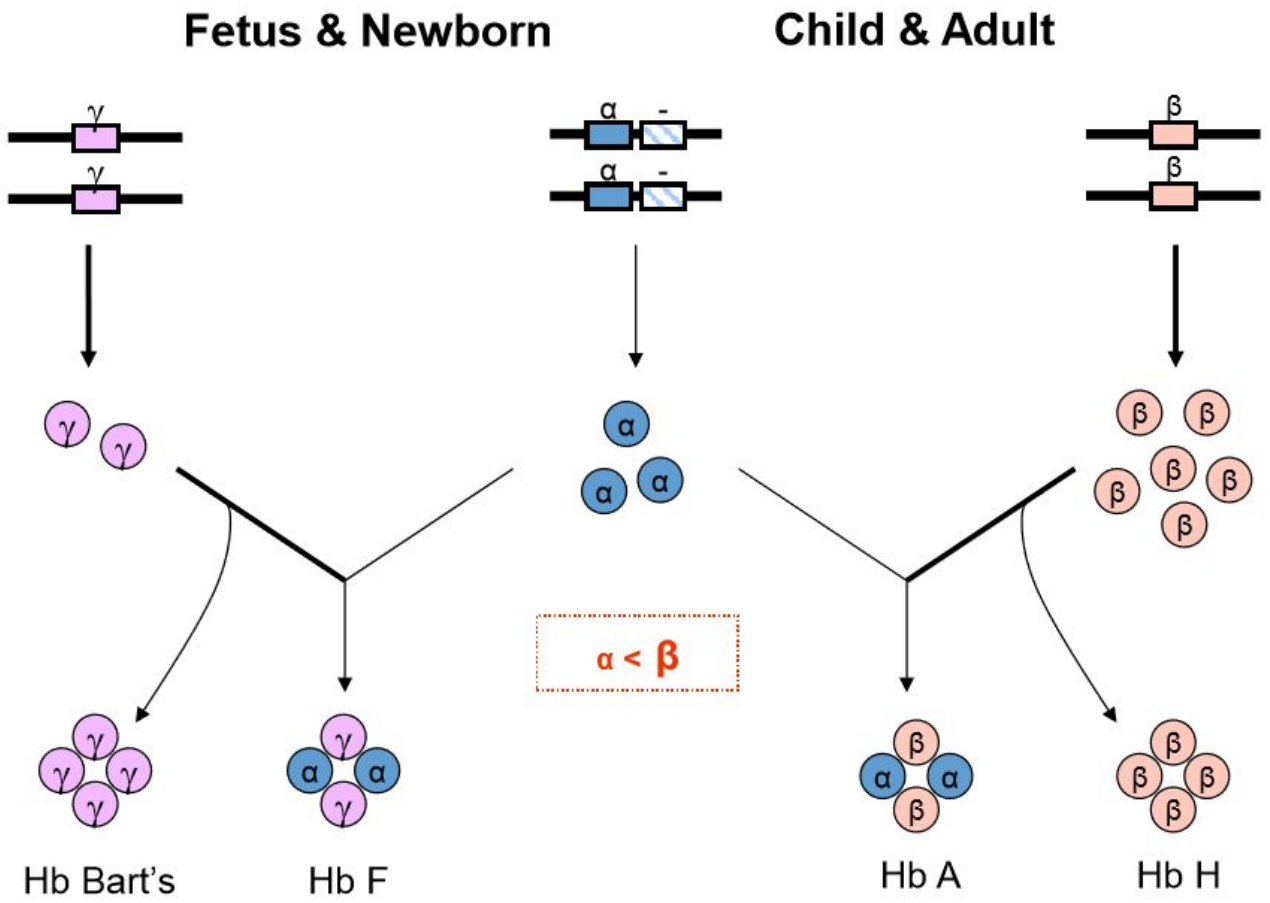
Quantitative aka thalassemia.

Qualitative.

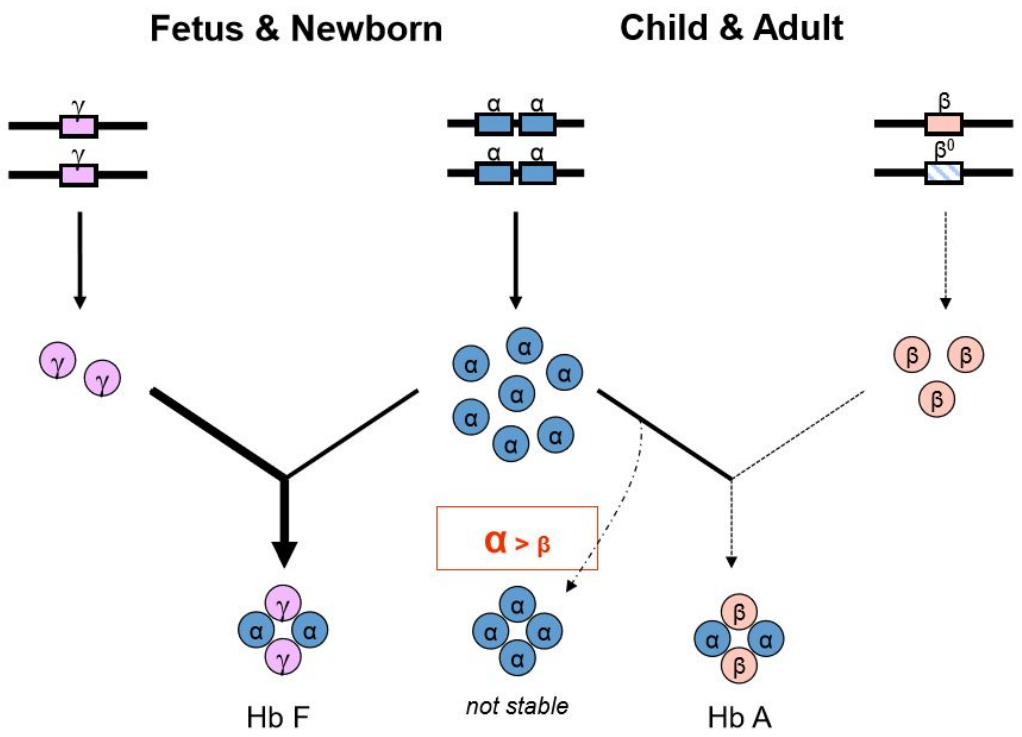
Normal State



Alpha Thalassemia



Beta Thalassemia



no HbH equivalent

Consequences of thalassemia.

- Anemia.
- Bone marrow expansion
- Extramedullary hematopoiesis.
- Increased intestinal iron absorption.

Clinical phenotype

Minor	Minor: mild anemia, asymptomatic trait state.
Moderate	Intermedia: moderate anemia, intermittent transfusion.
Major	Major: severe anemia, transfusion-dependent.

Overview of Alpha Thalassemia

Common (Classical) Genotypes

Genotype	α genes	Name	
αα / αα	4	Normal	
αα / α–	3	Silent carrier	
– – / αα	2	Thalassemia trait	minor
α– / α–	2		
– – / α–	1	Hgb H disease	intermedia
– – / $\alpha^{CS}\alpha$	1	Hgb H-Constant Spring	
– – / – –	0	Hydrops fetalis	major

Older terms:
α-thalassemia-2: α –
α-thalassemia-1: – –

α-/α-
trans "African" genotype

	α–	α–
α–	α–/α–	α–/α–
α–	α–/α–	α–/α–

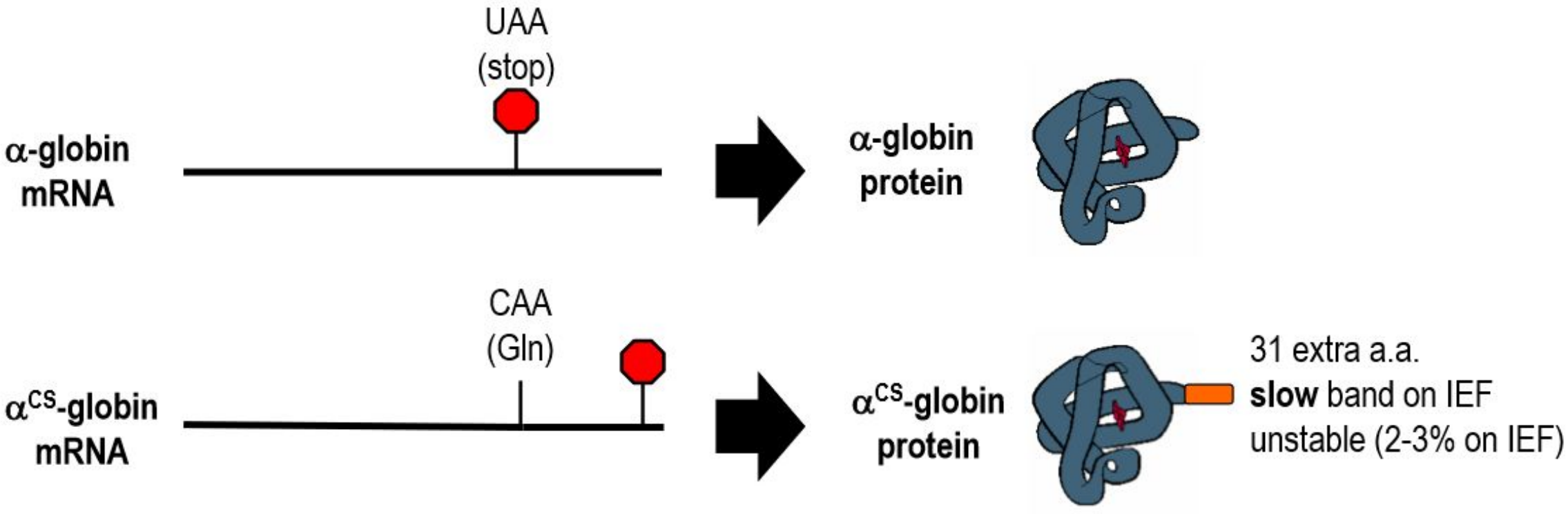
No thalassemia major

--/αα
cis "Asian" genotype

	––	αα
––	––/––	––/αα
αα	αα/––	αα/αα

25% thalassemia major

Hb Constant Spring (CS)



Overview of Beta Thalassemia

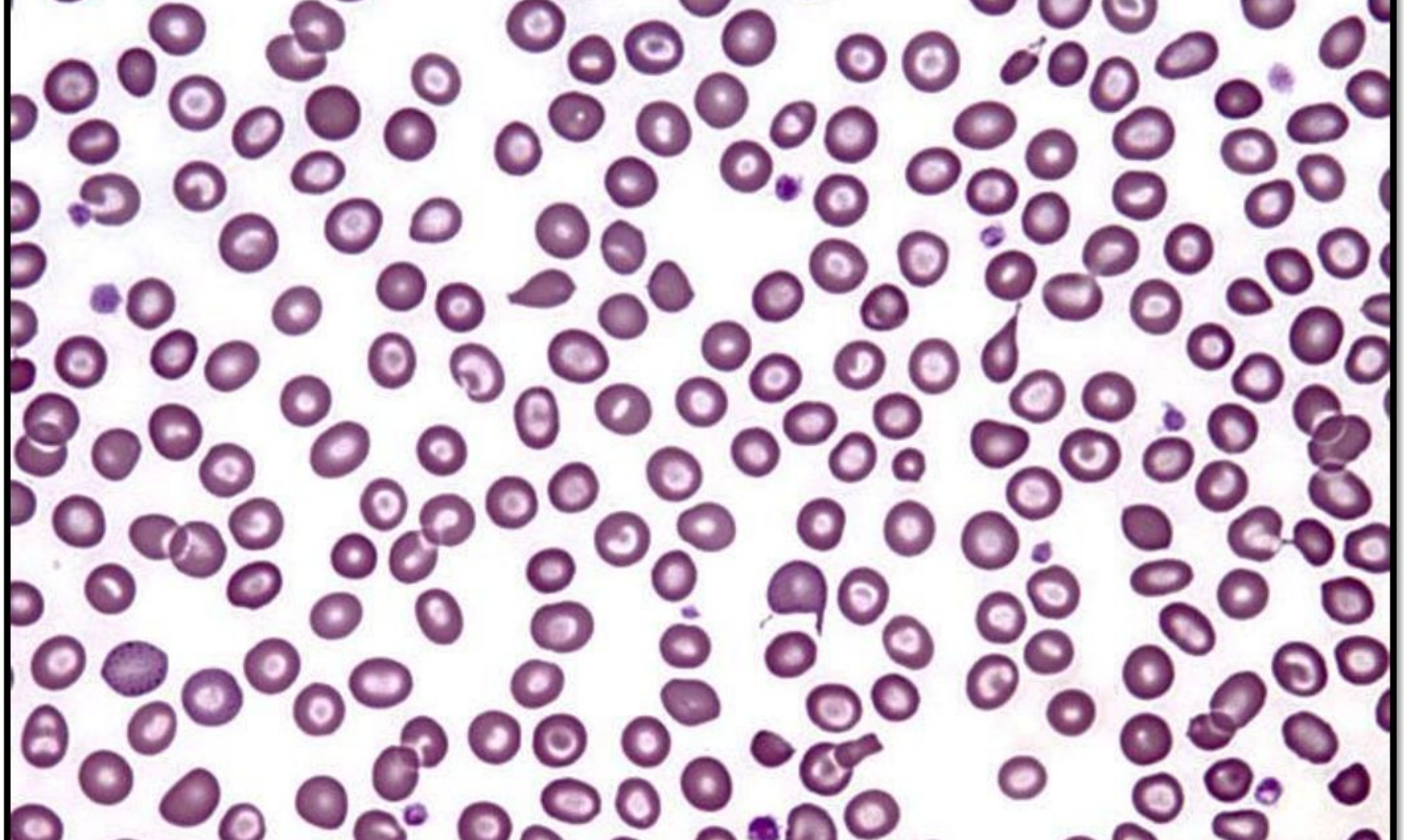
Common (Classical) Genotypes

Genotype	Description
β / β	Normal
β / β^0 β / β^+	Beta thalassemia trait (minor)
β^+ / β^+ β^+ / β^0 β^E / β^+ β^E / β^0	Beta thalassemia intermedia
β^0 / β^0	Beta thalassemia major (Cooley's Anemia)

Production of β-globin:
β^+ = decreased
β^0 = absent

Clinical Spectrum of Hb E Disorders

Name	Main Hbs Present	Clinical features (generalization)
Hb E trait	A > E	Microcytosis, target cells
Hb E disease	E	Mild microcytic anemia, target cells
Hb E / β^{+} -thalassemia	E > A	β-thalassemia minor to intermedia
Hb E / β^{0} -thalassemia	E	β-thalassemia intermedia to major

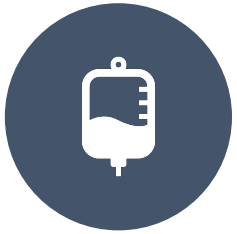


Condition	Hgb F	Hgb A_2
Beta thalassemia trait	Normal or Increased (1 – 10%)	Increased (3 – 10%)
Alpha thalassemia trait	Normal (0 – 2%)	Normal or Decreased (0 – 2.5%)
Iron deficiency anemia	Normal (0 – 2%)	Normal or Decreased (0 – 2.5%)

Normal Hgb F: ≈ 0 – 2%* Normal Hgb A_2: ≈ 2 – 3%*

Treatment of thalassemia

DEPENDS ON THE PHENOTYPE.



TRANSFUSION THERAPY.

CHELATION THERAPY.

SPLENECTOMY.

STEM CELL TRANSPLANT.

δβ-thalassemia (Simplified)

Normal β-globin locus:

$(\delta\beta)^0$-thalassemia:

High Hb F
Low Hb A_2

$(\delta\beta)^+$-thalassemia:
(Hb Lepore)

High Hb F
Low Hb A_2
Hb Lepore (7-15%)

Qualitative disorders

- Unstable hemoglobins: Hb Koln.
- Decreased solubility: Hb S (sickle) and Hb C.
- Decreased (Hb Kansas) or increased (Hb Syracuse) affinity to oxygen.
- Abnormal heme oxidation as methemoglobin.

Sickle cell disease

Pathophysiology

Incidence of complications differs by genotype

Complication	Beta Globin Genotype			
	SS	$S\beta^0$	SC	$S\beta^+$
Painful Episodes	80	100	4	4
Acute Chest Syndrome	12.8	9.4	5.2	3.9
Stroke	0.6	0.1	0.2	0.1

All rates expressed per 100 patient-years.
Data from the Cooperative Study of Sickle Cell Disease (CSSCD).

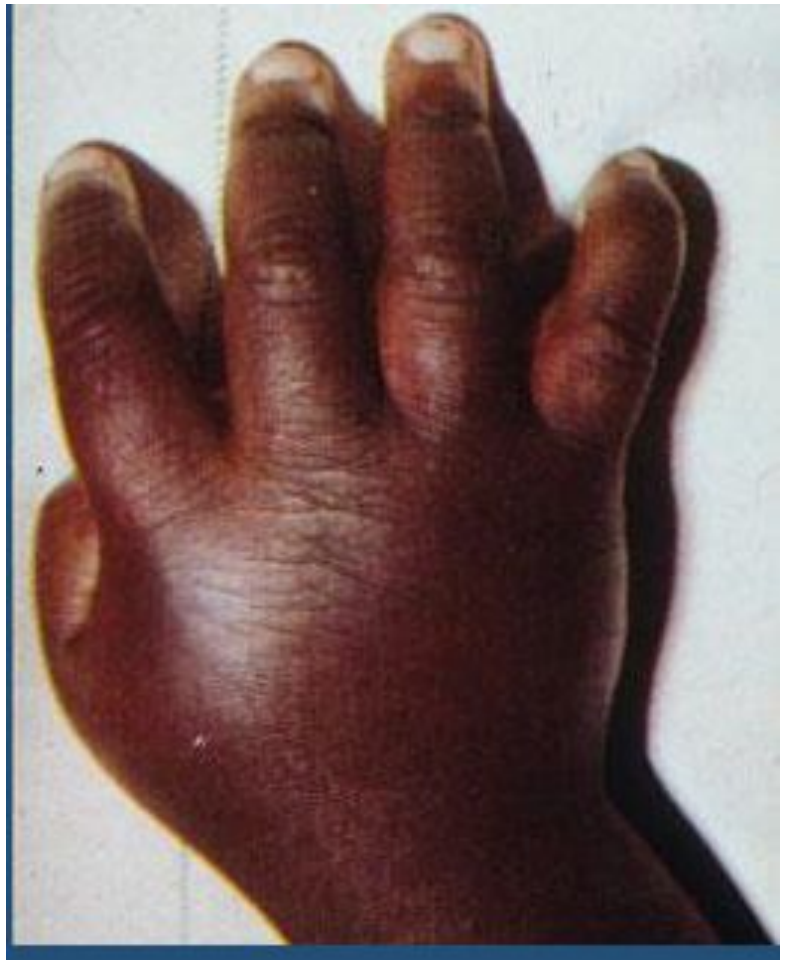
Presentation

Chronic hemolytic anemia: Jaundice, pallor, fatigue, parvovirus aplastic crisis, cholelithiasis.

Acute complications: Pain, dactylitis, acute chest syndrome, splenic sequestration, Overt stroke

Chronic organ damage: Spleen, brain, kidneys, lung, bones, eyes

Susceptibility to infection



Management of SCD

- Early identification: universal newborn screening, ongoing (lifelong) education.

- Prevention and screening: prophylactic penicillin, Immunizations, screening TCD.

- Disease-modifying therapy: hydroxyurea, chronic transfusion, stem cell transplantation.

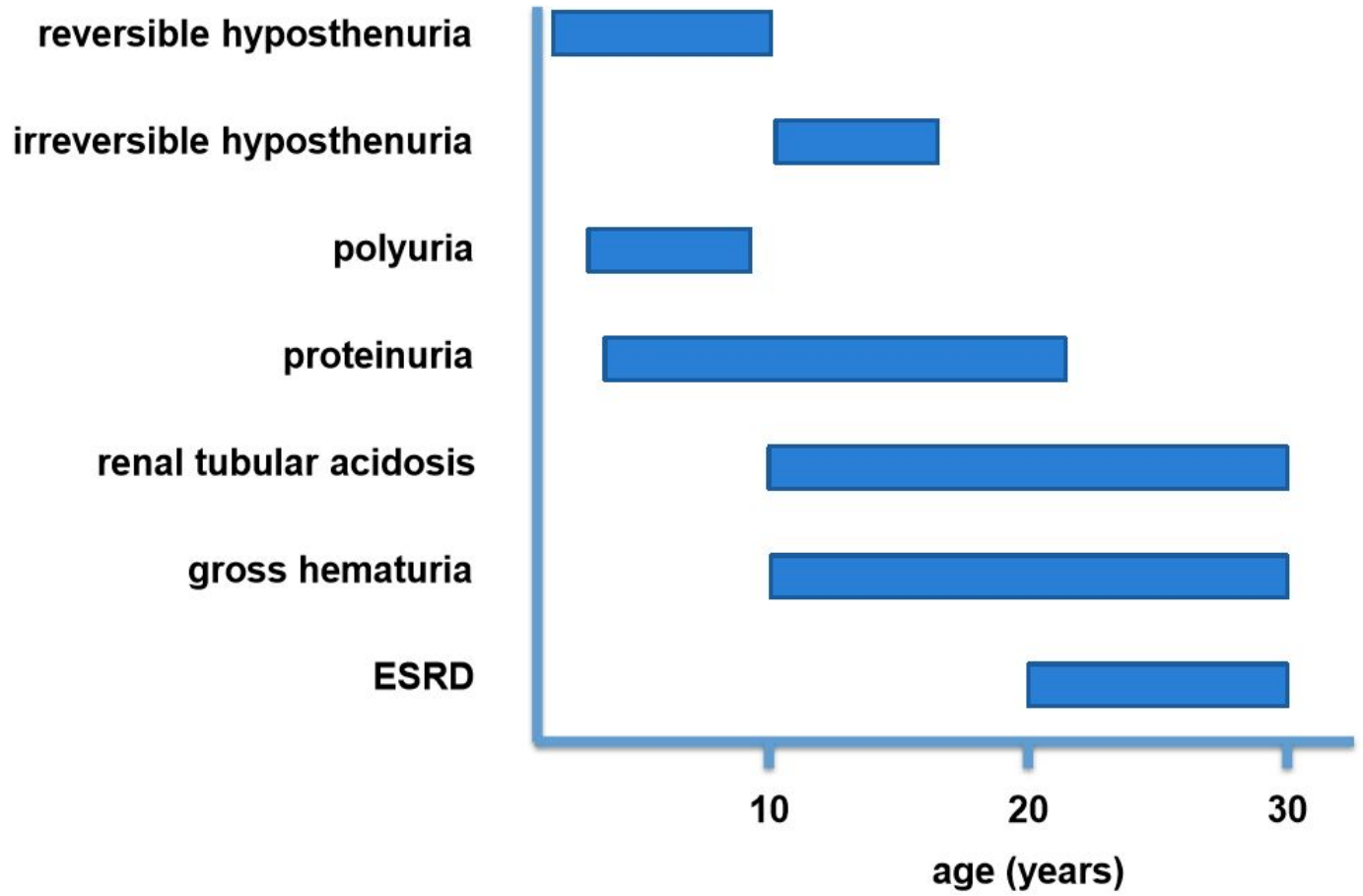
- Management of acute complications.

Complications

- Splenic Complications.
- Acute anemia.
- Fever, sepsis.
- Pain crisis.
- Acute chest syndrome.
- Stroke.
- Priapism.

Renal Complications of SCD

by age of onset



Complications

- Retinopathy.
- Avascular necrosis.
- Cardiomyopathy.
- Pulmonary hypertension.
- Chronic lung disease.
- Renal insufficiency / failure.
- Progressively severe anemia.

Iron Overload