Thalassaemia

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Blood Module
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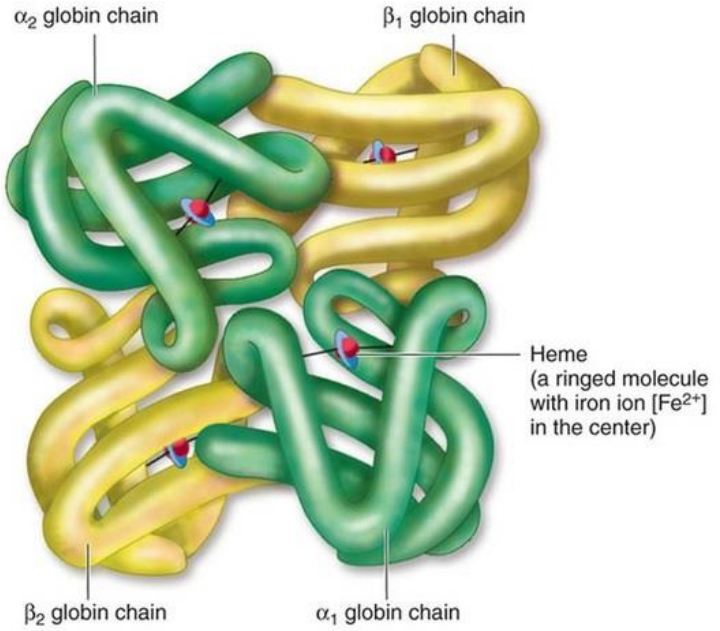
Haemoglobin

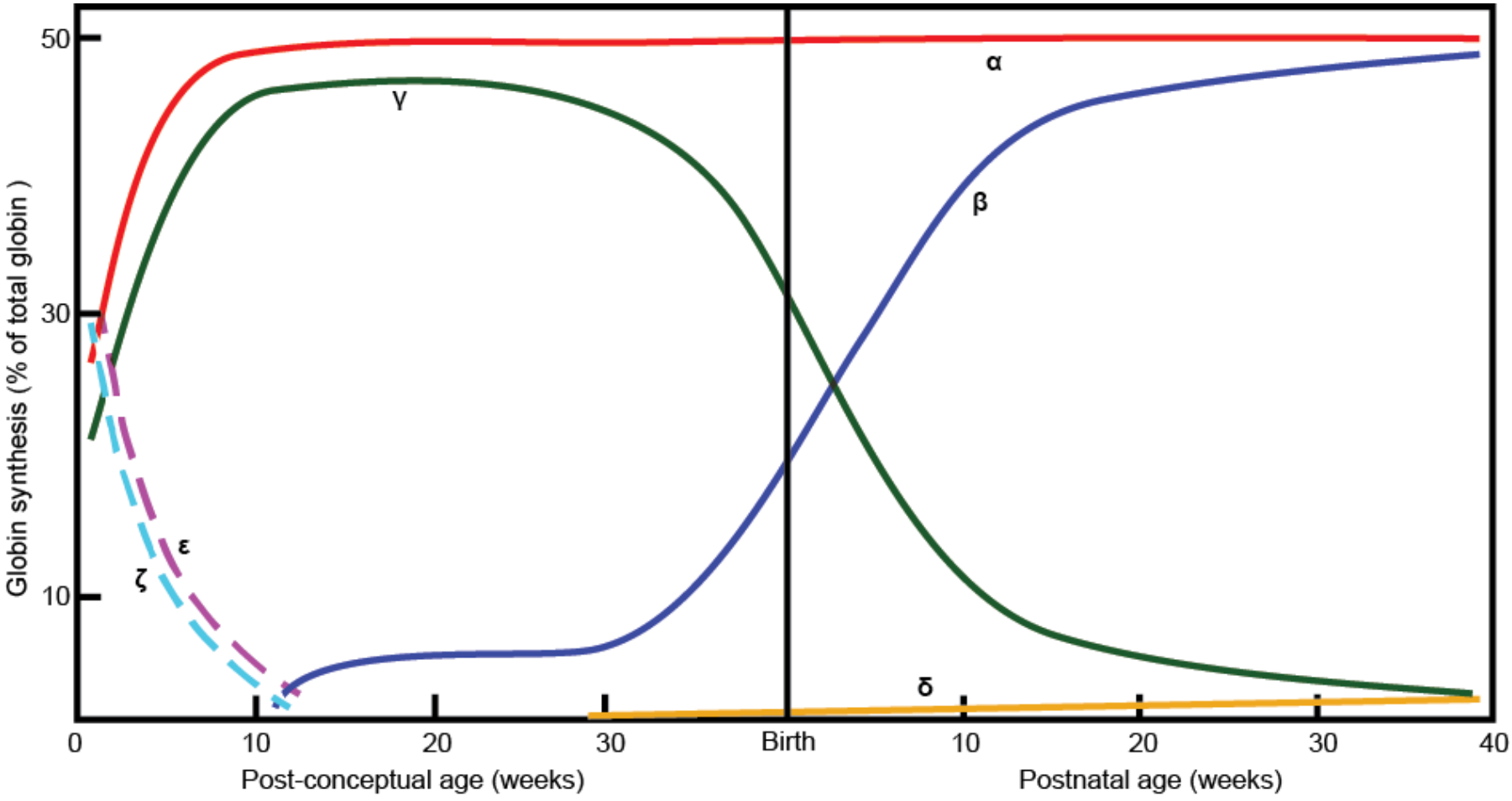
- Heam + Globin
- Haem= iron containing molecule - binds oxygen
- Globins are peptide chains- 4 chains of two types

  ($\alpha_2\beta_2$ in HbA, $\alpha_2\gamma_2$ in HbF)
- Each globin chain binds one molecule of haem (4 haems for each haemoglobin molecule)



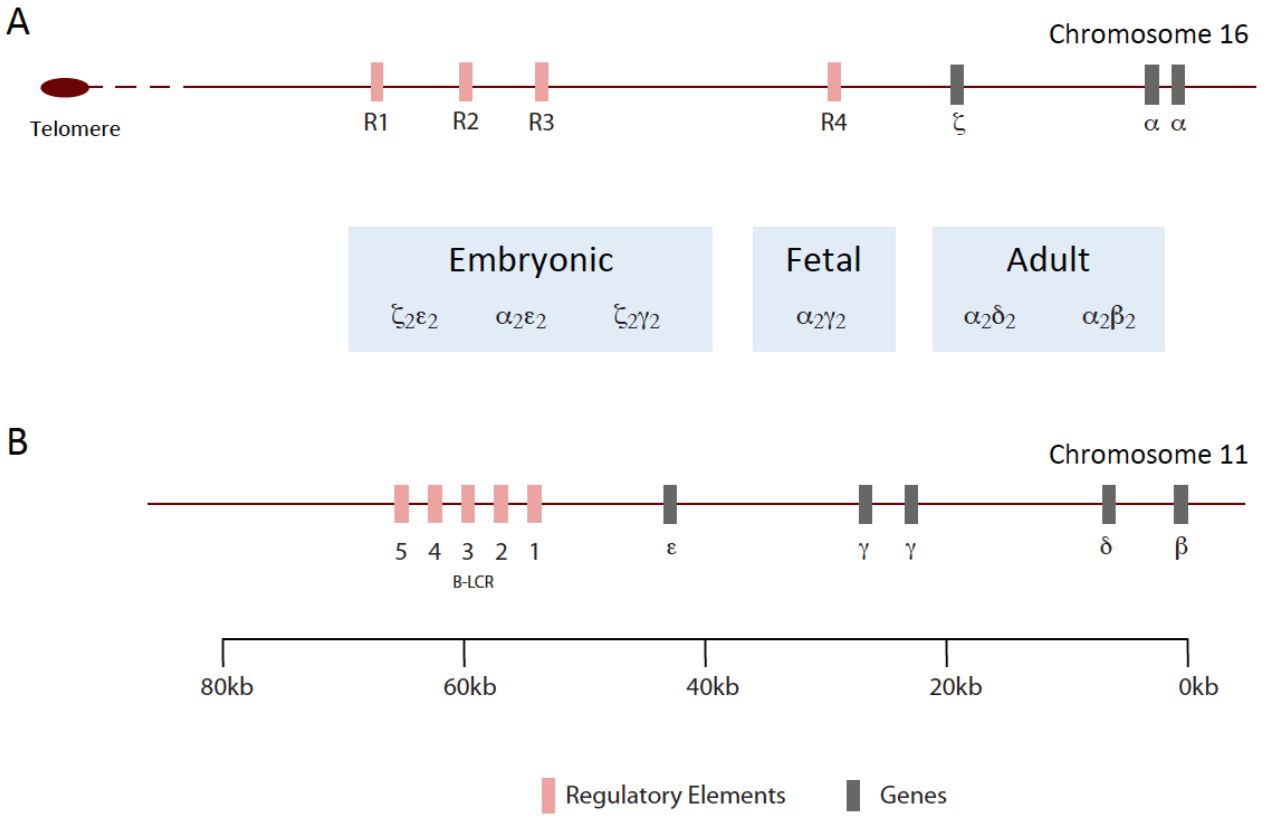
Haemoglobin

- Type of haemoglobin present depends on physiological status
- ie: Embryo has Hb Gower, Hb Portland
- Foetus- Hb F
- Adults- HbA, HbA_2
- synthesis of globin by transcription from globin genes


50
30
10
Globin synthesis (% of total globin)
α
γ
β
ε
ζ
δ
0
10
20
30
Birth
10
20
30
40
Post-conceptual age (weeks)
Postnatal age (weeks)

Globin genes

- α and β globin is produced at equal amounts
- α/β globin ratio is 1:1



Globin genes

- Normal adult has 2 β genes and 4 α genes
- Mutations of the genes results in altered structure(abnormal haemoglobin) or reduced synthesis (thalassaemia)
- Some “abnormal haemoglobins are produced at a reduced rate eg: Hb E

Thalassaemia

- Reduced rate of synthesis of normal haemoglobin

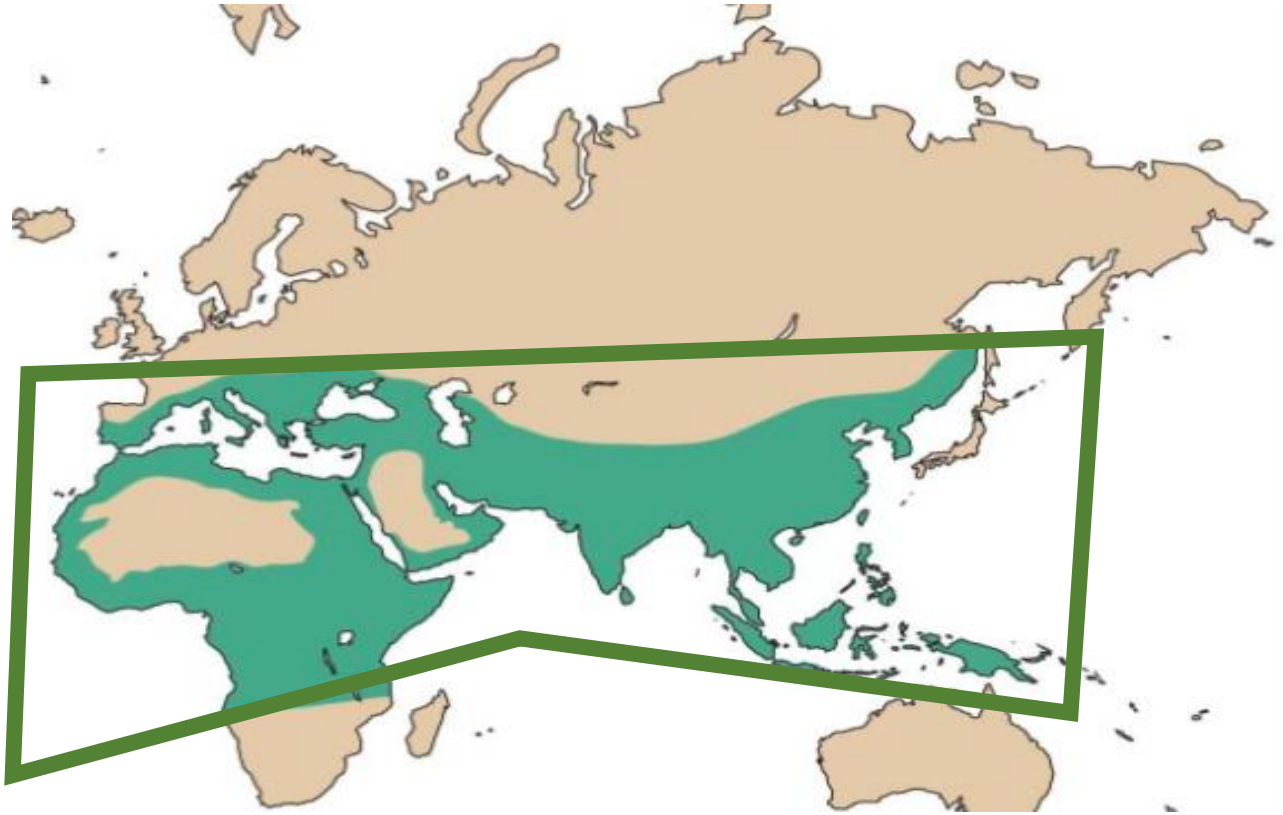
- α-thalassaemia-

  reduced production of α–chains
- β-thalassaemia-

  reduced production of β–chains
- (δ,γ $\delta\beta$, $\gamma\delta\beta$ thalassaemia)

Thalassaemia- World Map

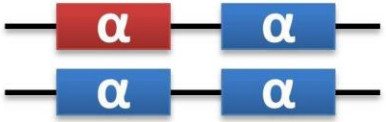
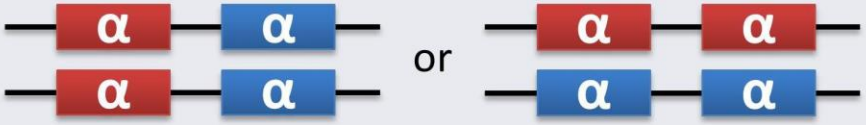
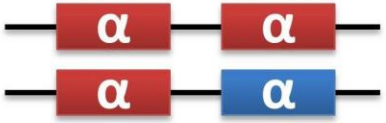
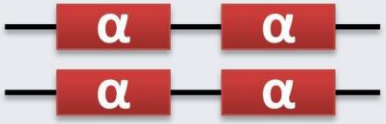
- One of the most common genetic disorders
- 70,000 children are born each year



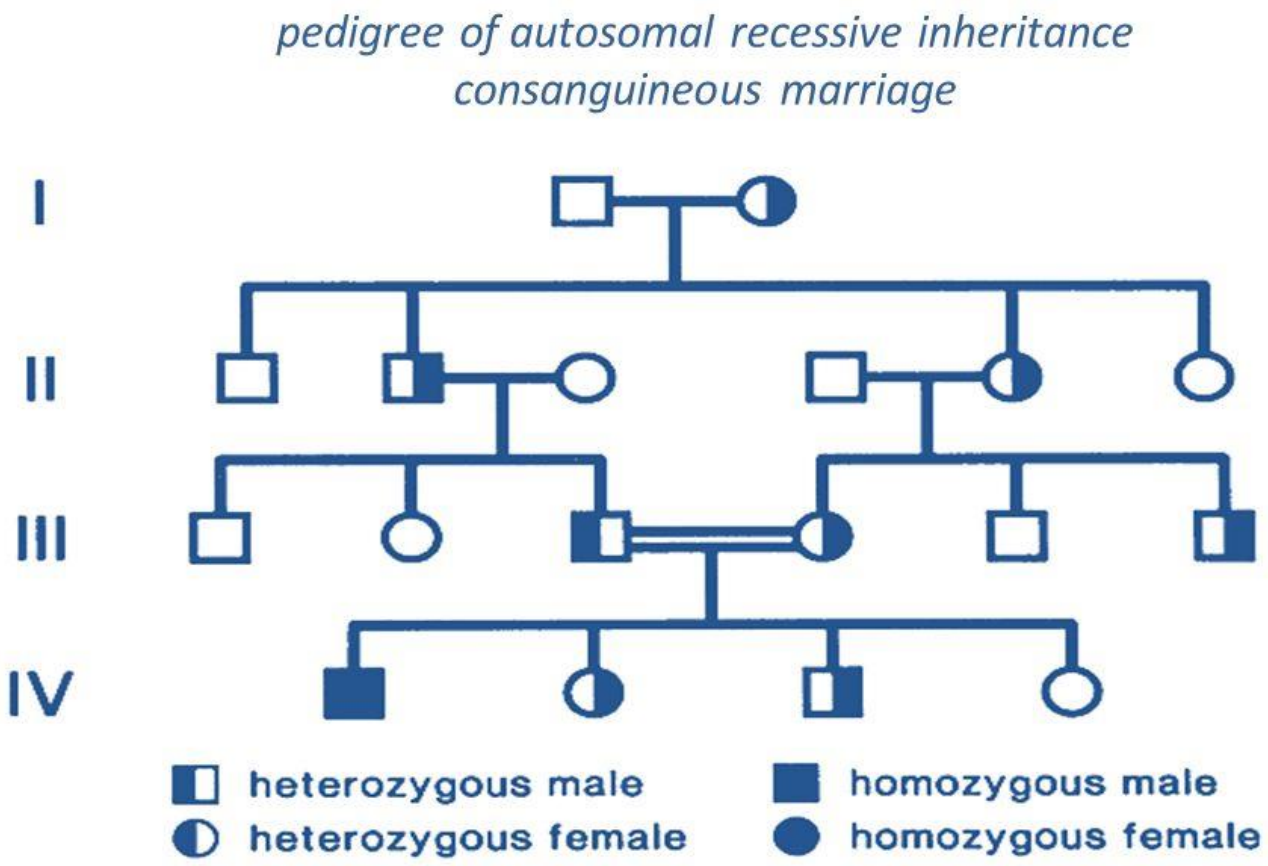
Ref: Higgs et al. *Lancet* 2012,
Weatherall *Blood* 2010

Alpha-thalassaemia –genetic basis

Alpha-thalassemia Genetics and Clinical Consequences

Normal	
Carrier: Asymptomatic No abnormalities Mild microcytic anaemia	
α-thal minor: Asymptomatic Mild microcytic anemia	
Hb H Disease: Symptomatic Hemolytic and Microcytic anemia Splenomegaly	
Incompatible with Life Hydrops Fetalis	

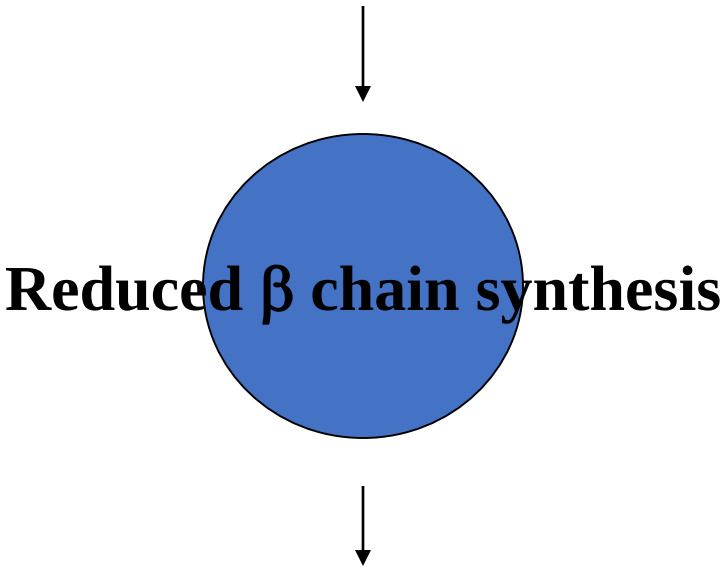
β–thalassaemia Inheritance



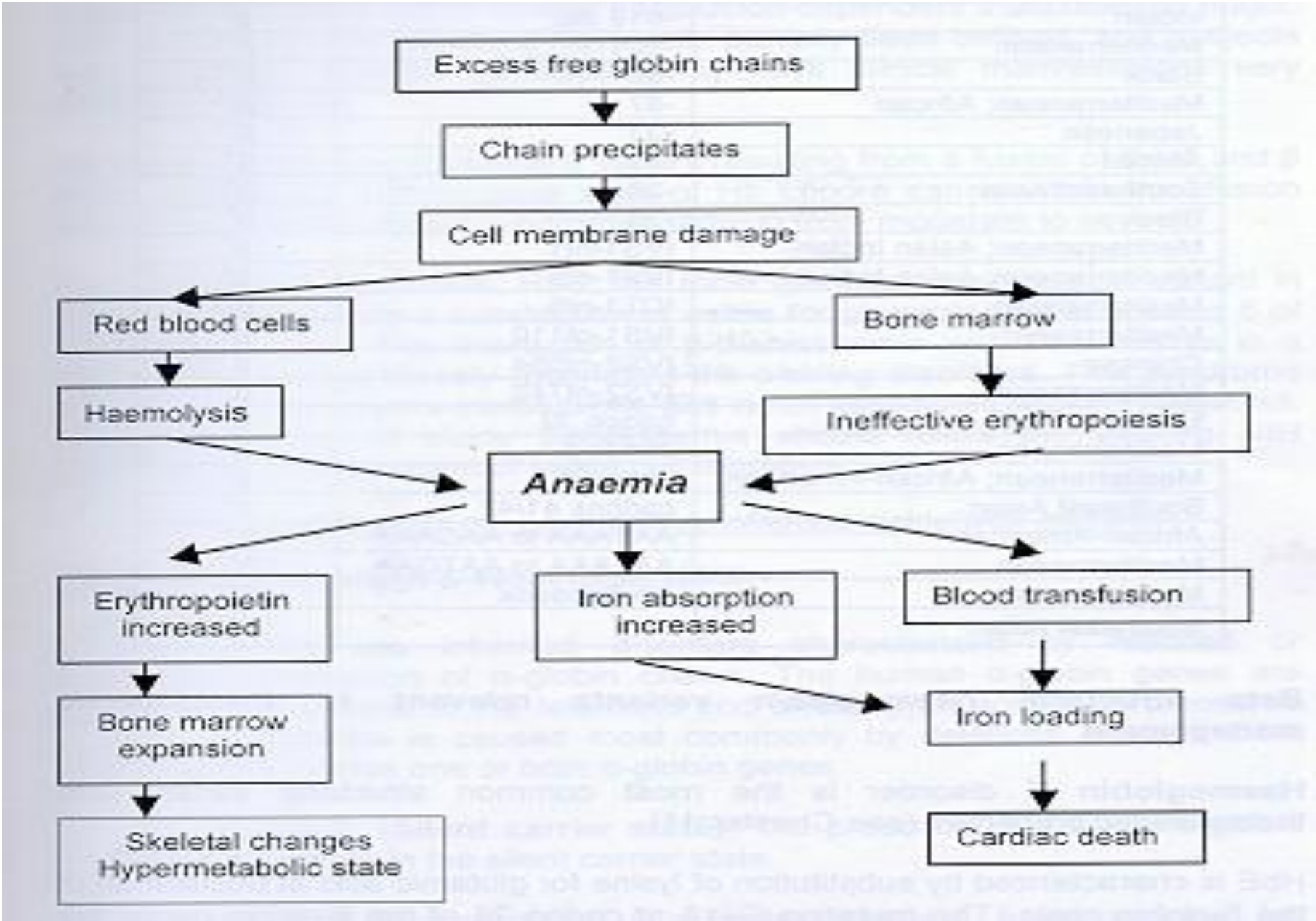
Thalassaemia- pathogenesis

- Altered ratio of α/β synthesis

In β- thalassaemia



β–thalassaemia - pathophysiology



Clinical features β–thalassaemia major

- Presents at 2nd 6 months of infancy with features of progressive chronic haemolytic anaemia including mild jaundice & failure to thrive
- Progressively enlarging spleen and liver
- Skeletal deformities
- Features of iron overload

Beta Thalassemia Major – bone changes

Skeletal deformities

- skull bossing
- prominent maxilla
- flat nasal bridge
- malocclusion of teeth
- bone tenderness and fractures
- deformities in legs similar to rickets

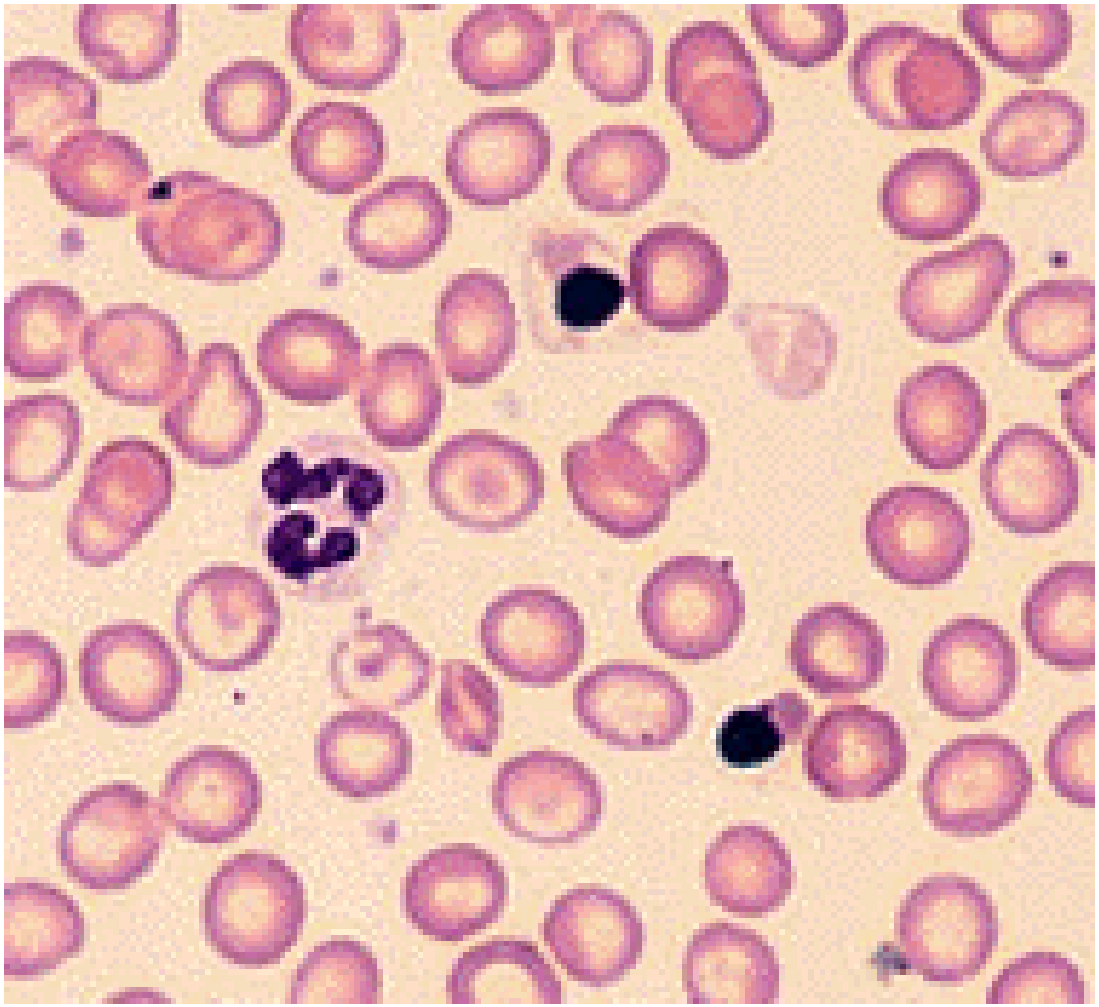
Clinical features of β– thalassaemia major

- Untransfused or inadequately transfused develop major health problems
- Heart failure, growth retardation,facial changes,fractures, leg ulcers, organomegaly, hypersplenism
- death occurs very early (before 10yrs)

Diagnosis

- Clinical features
- FBC- Hypochromic microcytic anaemia
- Blood Picture -
- Hb electrophoresis/ HPLC- very high HbF levels (>90%)
- Family studies (screen both parents)

Thalassaemia blood picture



HPLC / electrophoresis

- HbF ~70% at birth
- By 6-12 months only traces are present
- Normal child - HbA 98%, HbF traces, HbA_2 2%

Management of thalassaemia
(transfusion dependent thalassaemia)

- Regular blood transfusions
- Iron chelation therapy
- Management of complications
- Genetic counselling
- Prevention
- HSCT
- Emerging therapies

RBC Transfusion

- Usually commences around 6 months of age- When Hb <7g/dl

- Before the first transfusion
  - Establish accurate diagnosis
  - Extended phenotyping of RBC antigens (minor blood groups)

- Aims of Transfusions
  - Promotes normal growth
  - Allows normal physical activities
  - Adequately suppresses bone marrow activity
  - While minimizing transfusional iron accumulation

RBC Transfusion (cont.)

- Leukoreduced packed RBCs (Reduction to $<10^6$ leucocytes per unit) – reduce risk of febrile non-haemolytic reactions
- In patients with severe allergic reactions – washed RBC
- Ideally all patients with thalassaemia should receive ABO, Rh(C, c, D, E, e) and Kell compatible blood
- Use as fresh blood as possible (<2 weeks old)

RBC Transfusion (cont.)

- Aim – Pre-transfusion Hb 9 -10g/dl
- We generally aim for a post transfusion Hb of 14 g/dl

- Amount of blood to be transfused
  - (Desired – actual Hb) x body weight x 3/haematocrit of transfused unit = ml to be transfused

- Transfuse every 2-5 weekly

Complications of blood transfusion

- Iron overload
- Transfusional reactions
- Transfusion transmitted infections

Iron overload

- As a result of regular blood transfusions (500 ml of blood will give 200 mg of iron)

- Increased intestinal absorption of iron due to anaemia

Features of iron overload

- **Liver:** Organomegaly, hepatic fibrosis, cirrhosis
- **Heart:** Cardiomegaly, Cardiomyopathy, CCF & Arrythmias
- **Endocrine organs :**

Pancreas	- Diabetes mellitus
Thyroid	- hypothyroidism
Parathyroid	- Hypoparathyroidism
Pituitary failure	- growth failure and delayed puberty

Investigations to assess iron overload

- **Liver** – Liver functions

  (derangement may be due to transfusion transmitted hepatitis, iron chelation related side effects, etc)

  - **Ferriscan/ MRI**
  - **Liver biopsy** – invasive
  - **SQUID**

- **Heart :**

  - 2D ECHO : To assess ejection fraction and chamber size
  - T2* MRI

Investigations to assess iron overload

- **Endocrine organs :**
  - -RBS/FBS
  - -Thyroid functions
  - -S Ca/ PTH
  - -GH assay
  - -FSH/LH

Iron chelation

- First Chelator – Desferrioxamine

- Three iron chelators:
  - ***Desferrioxamine***
  - ***Deferasirox***
  - ***Deferiprone***

- Starts when serum ferritin is >1000ng/dl
- Aim is to maintain serum ferritin between 500 - 1000ng/dl

Comparison between iron chelators

	Desferrioxamine	*Deferasirox*	*Deferiprone*
Route	s.c or i.v.	oral	oral
Frequency	8-12 hours 5 days/week	Once daily	tds
Recommended dose mg/kg/d	30-60 5-7 x/week	20-40 once daily	75-100 in 3 divided doses
Route of iron excretion	Urinary and faecal	faecal	Urinary
Main Adverse effects	Ocular, auditory, bone growth retardation local reactions, allergy	Gastrointestinal, increased creatinine, increased hepatic enzymes	Gastrointestinal, arthralgia, agranulocytosis/ neutropenia
Advantages	Extensive experience Low cost Better Availability	Better compliance	Chelates cardiac iron more efficiently
Disadvantages	Poor compliance	Limited safety data	

Iron chelation - Monotherapy

- Deferasirox (monotherapy) – Standard first line
  - taken orally as a suspension in water once daily, and preferably before a meal
  - starting dose of 20 mg/kg is recommended
  - Recommended to use in children over 2 years
  - DFX is contraindicated in patients with renal failure or significant renal dysfunction
  - Caution is recommended for patients with advanced liver disease and hepatic decompensation.

Iron chelation – Monotherapy (cont.)

- Desferrioxamine (monotherapy) –
  - ➢Was the standard first line for years
  - ➢Has been replaced by Deferasirox
  - ➢We used only if there are
    - ✓Contraindications / Cautions for Deferasirox
    - ✓Very young age group (Below 20 months)

- Deferiprone (monotherapy) –
  - ➢Not recommended

Iron chelation – Combination therapy

- Deferasirox + Desferrioxamine
  - Commonly used
  - When monotherapy failed to control iron overload

- Deferiprone + Desferrioxamine
  - Commonly used
  - Specially when high cardiac iron

- Deferasirox + Deferiprone
  - Not well studied

Splenectomy

Only Limited Indications

- Annual transfusion requirement

  > 200-250 ml/kg/yr

- Hypersplenesm
- Massive splenomegally

Delayed until 5 years

Allogenic Bone Marrow/ Stem Cell Transplantation

- Only available cure at the moment
- First BMT for thalassaemia – 1982
- Thus far over 3000 BMT have been performed

- Indication – Transfusion dependency (for patients with well-matched donor)
- When - as soon as possible; first years of life before iron-related complications have developed

- Disease free survival ~ 80%

Allogenic Bone Marrow/ Stem Cell Transplantation

- Donors
  - HLA identical sibling
  - HLA well match unrelated donor
  - HLA matched unrelated cord blood
  - HLA mismatch related donor

- Predictors of better survival
  - Younger age (<14 years)
  - Regular Chelation
  - Absence of hepatomegaly
  - Absence of liver fibrosis

Allogenic Bone Marrow/ Stem Cell Transplantation

- Challenges
  - Donor Availability
  - Transplant related mortality (~5-10%)
  - Graft rejection
  - Alloimmunization due multiple transfusions - high risk of graft rejection
  - End organ damage from iron overload increases risk of toxicity from conditioning regimens
  - Cost – 4.2 million LKR

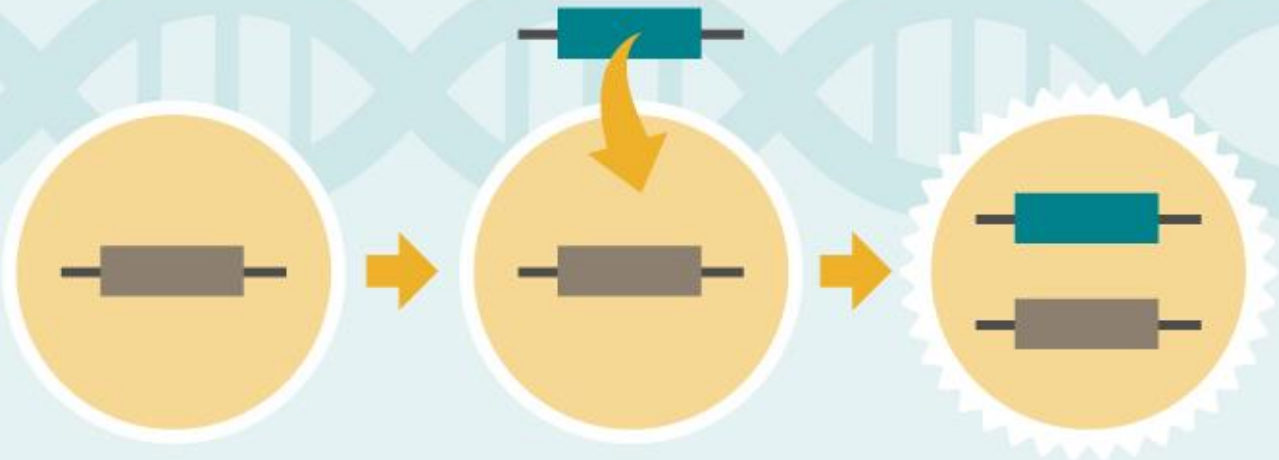
Emerging Therapies

Pharmacological Therapies

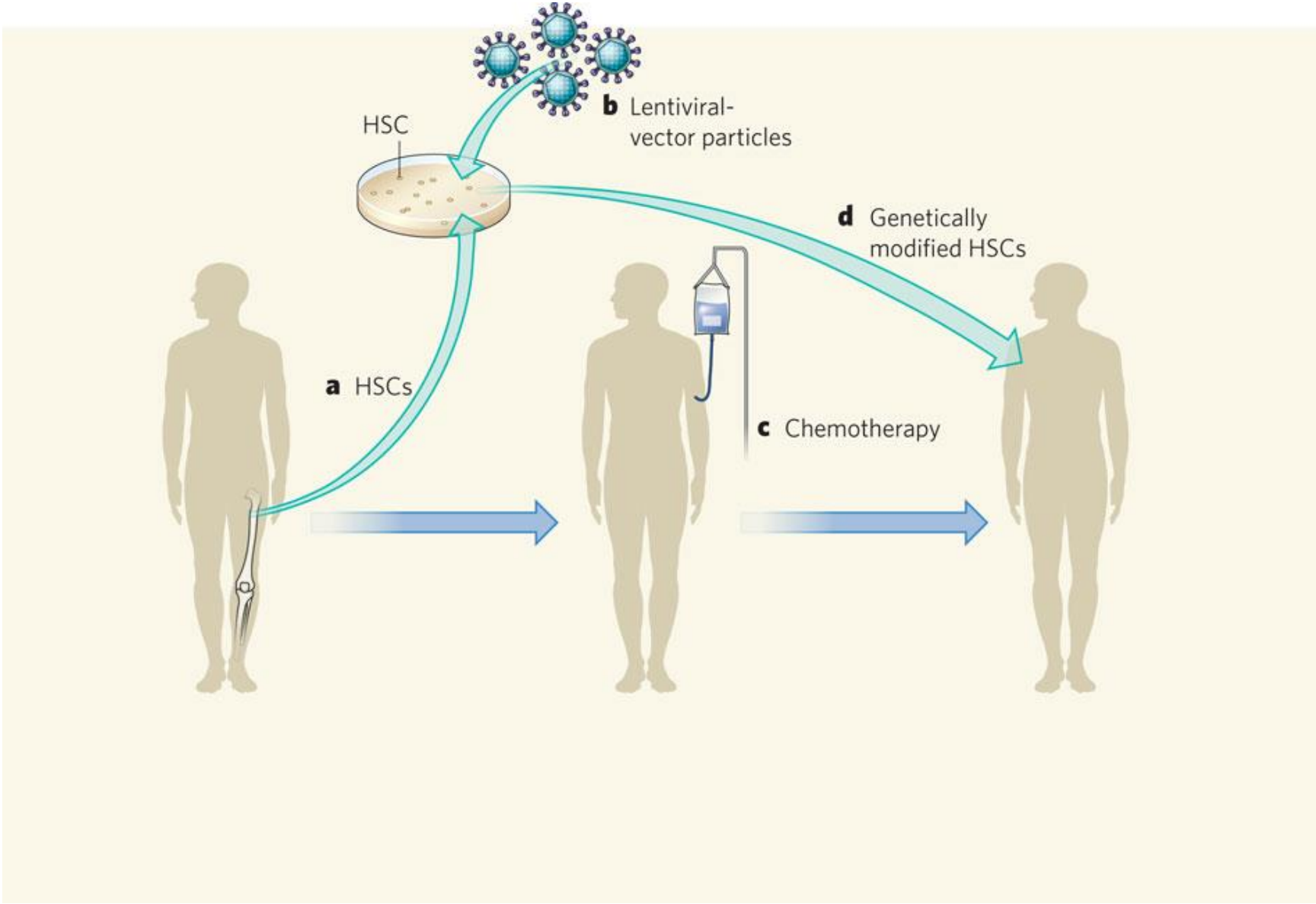
Gene/cell based Therapies

What is Gene Therapy?

Gene therapy gives patients a healthy version of a defective gene



Gene Therapy – Principle and Workflow



β-thalassemia trait

- Essentially asymptomatic, often detected incidentally.
- Hb ranges from 8.5g/dl to 12g/dl
- MCV, MCH, MCHC reduced
- Hypochromic microcytic red cells
- HbA_2 raised (>3.5%)
- Screen partner before marriage/conception
- Reassure
- Hb may drop during pregnancy etc.

Prevention

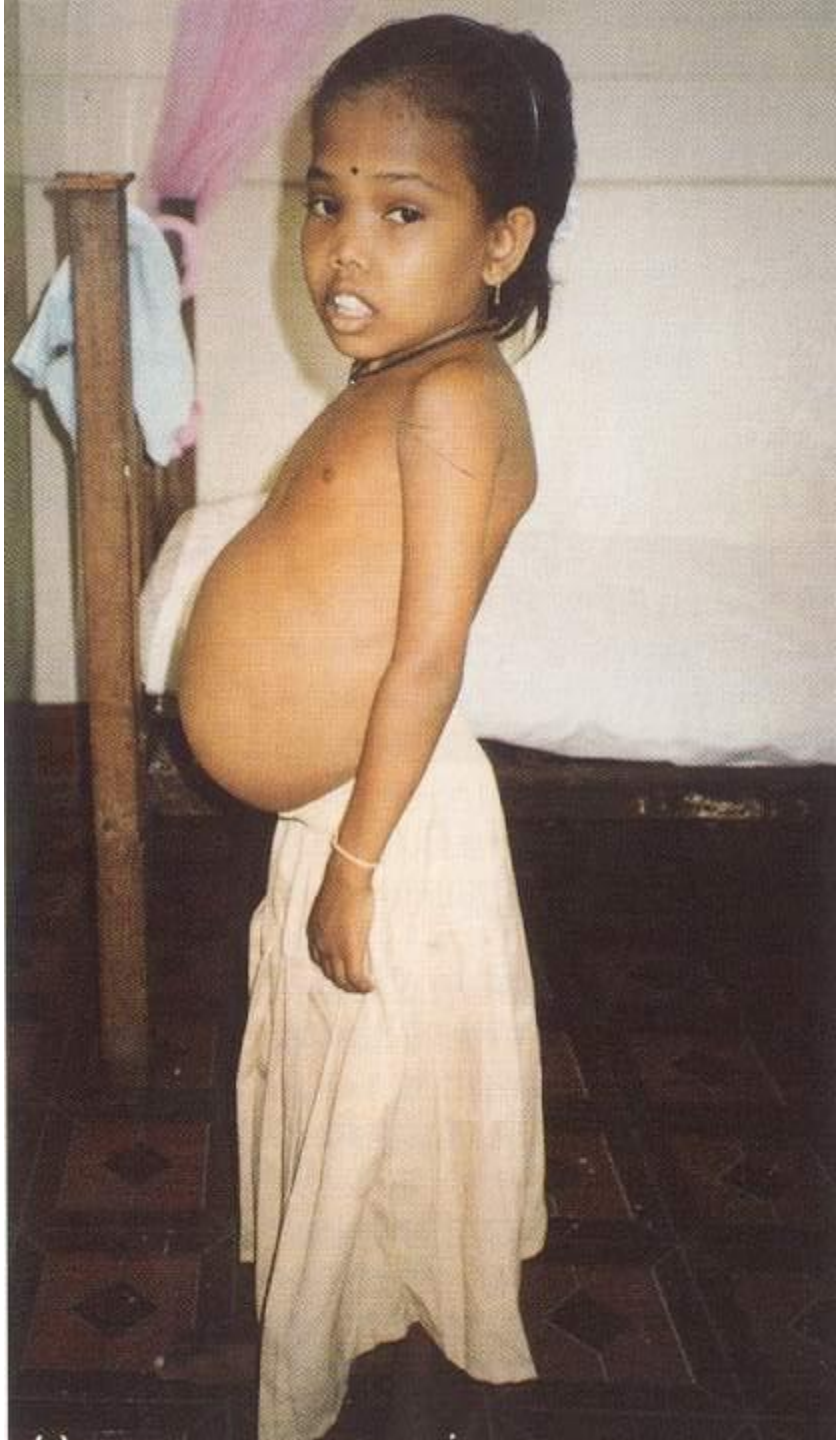
- Education
- Population screens?
- Prenatal diagnosis?
- Abortion of affected foetuses?
- Experience in Cyprus, Sardinia

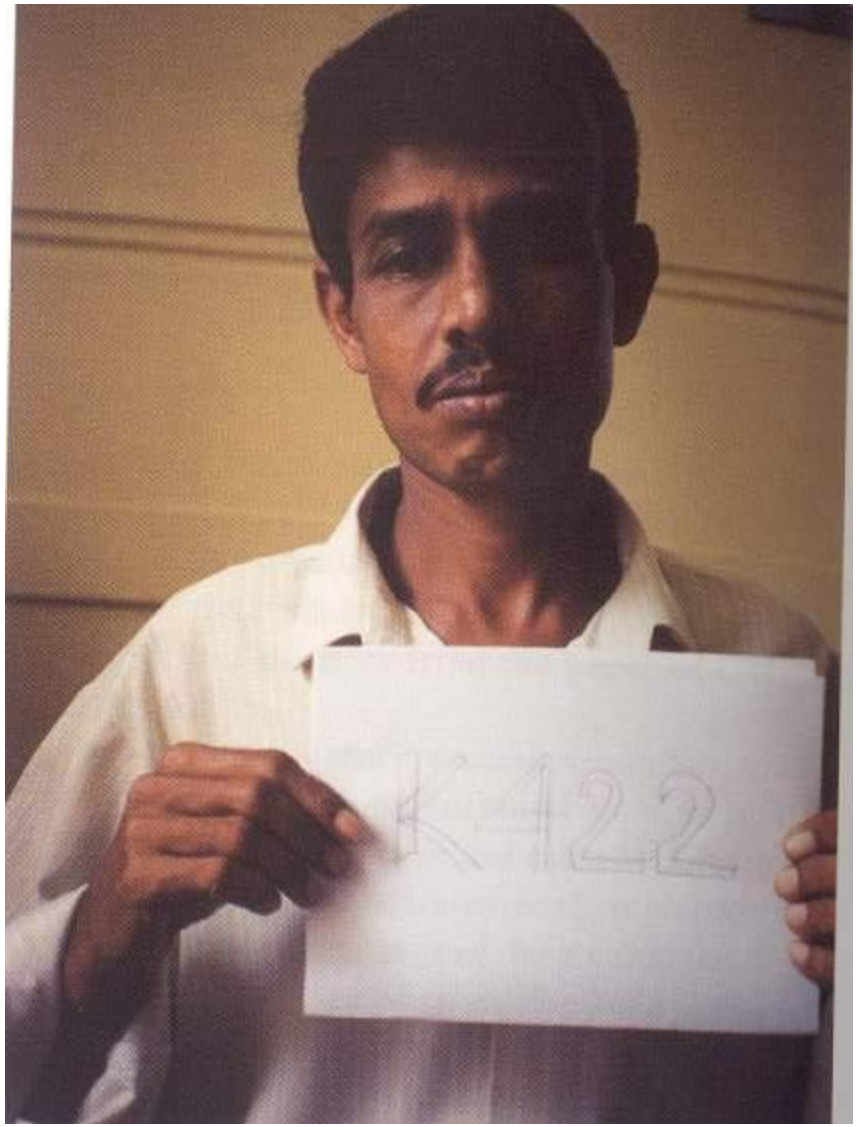
Thalassaemia Intermedia

- Patients who have “intermediate severe” disease compared to trait and major
- Very variable presentaion
- different causes BUT in Sri Lanka the most important cause is Haemoglobin E- β thalassaemia
- 30% patients with “severe thalassaemia” have Hb E- b thalassaemia

Haemoglobin E- β thalassaemia

- Very variable clinical presentation
- Age of presentation from 8months to 55 years!!
- No single transfusion policy
- More work necessary
- Chelation still necessary

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