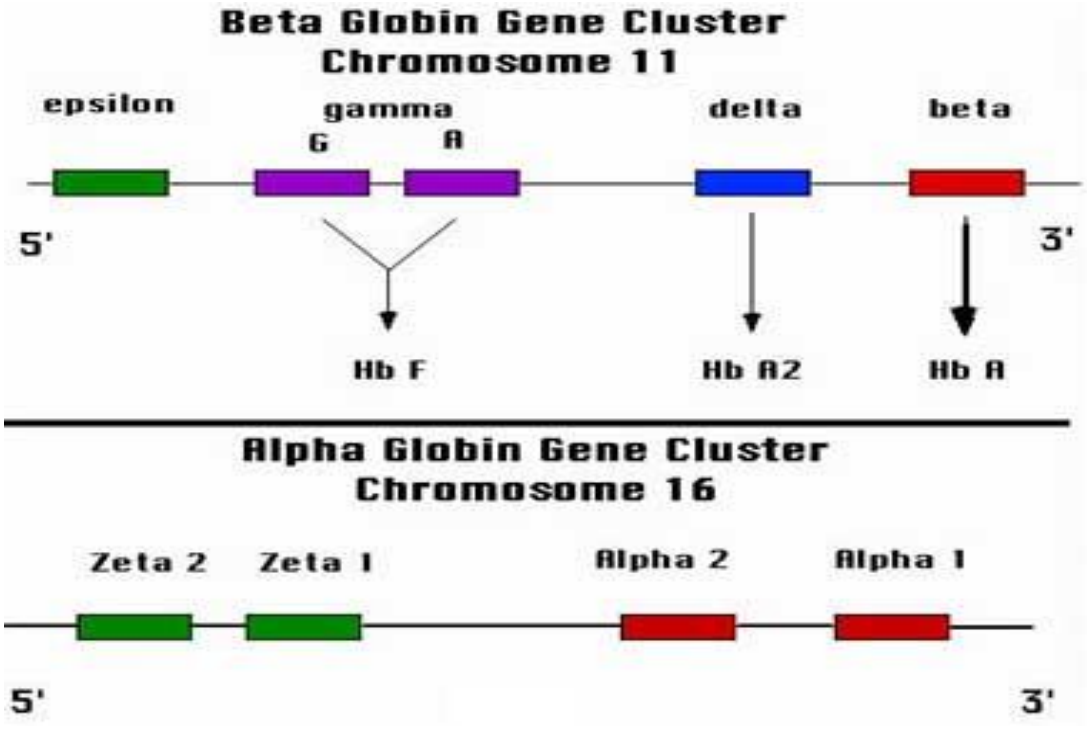
# ***Thalassamia***

## Hemoglobin Types

**Hemoglobin Type** **Globin Chains**

- Hgb A—92%--------- α2β2
- Hgb A2—2.5%-------- α2δ2
- Hgb F — <1%--------- α2γ2
- Hgb H ---------- β4
- Bart's Hgb---------- γ4
- Hgb S---------- α2β2 **6** $^{\text{glu}\rightarrow\text{val}}$
- Hgb C---------- α2β2 **6** $^{\text{glu}\rightarrow\text{lys}}$



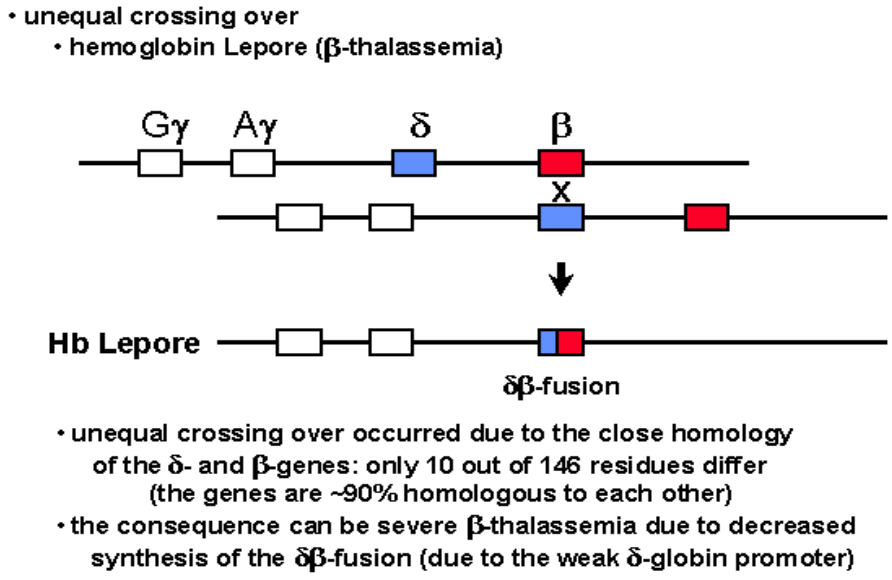
# Other genetic variants of β thalassamia

## 1-Haemoglobin Lepore

- unequal crossing over between the beta (β) gene and the delta (δ) gene.

- Crossing over produced a delta-beta fusion gene, which may well be functional, but is expressed at very low levels because it is controlled by the very weak delta gene promoter.

- This event gave rise to hemoglobin Lepore, which is a beta-thalassemia
- It has the same E/P mobility as Hb S , **D.D:** by acid ph



## Genetic variants & clinical presentation:

**Homozygous:**

(δβ) lepore/(δβ) lepore

Hb A : 0

Hb A2: 0

Hb F : 70-92%

Hb lepore : 8-30%

**Clinically :**

Thalassamia major

**Heterozygous:**

β/(δβ) lepore

Hb A: 80-90 %

Hb A2: ↓

Hb F : 1-3%

Hb lepore : 5-15 %

**Clinically :**

Thalassamia minor

**Double Heterozygous:**

β+/(δβ) lepore

βo/(δβ) lepore

Hb A: 0 in βo , present e' variable amount in β+

Hb A2: ↓

Hb F : ↑

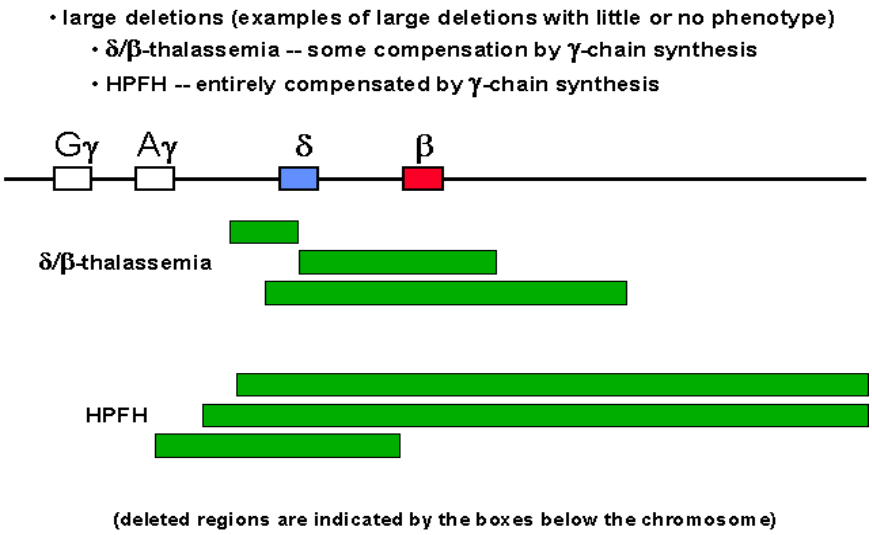
Hb lepore : 10 %

**Clinically :**

Thalassamia intermedia

# 2- δβ Thalassamia

- ↓ or absent synthesis of δ and β globin chains .
- ↑ production of g globin chain, but not enough to compensate for deficient δ and β globin production.
- So excess α chain deposit ⟶ more anaemia than HPFH




## Genetic variants & clinical presentation:

### Homozygous:

(δβ) o/(δβ) o

Hb A : 0

Hb A2: 0

Hb F : 100 %

**Clinically :**

Thalassamia intermedia

**Heterozygous:**

β/(δβ)o

Hb A: < 90 %

Hb A2: N or ↓

Hb F : ↑ 5-20 %

**Clinically :**

Thalassamia minor

## 3- Hereditary Persistence of foetal Hb (HPFH)

- ↓ or absent synthesis of δ and β globin chains .
- The ↑ production of γ globin chain, is sufficient to almost balance α chain synthesis .
- minimal α chain deposit → milder anaemia than δβ thalass.

## Genetic variants & clinical presentation:

**Homozygous:**

HPFH/HPFH

Hb A : 0

Hb A2: 0

Hb F : 100 %

**Clinically :**

no anaemia

↓ MCV, ↓ MCH e' mild polycythemia

**Heterozygous:**

β/ HPFH

Hb A: present

Hb A2: ↓

Hb F : 10-35 %

**Clinically :**

no clinical abnormality

Hb conc is N

MCV & MCH r slightly ↓

# α Thalassaemia

deficient/absent α subunits

**Molecular basis:**

Mainly deletion

**I- Deletion:**

Of short arm of chromosome 16

**II- Non deletion:**

- Mutation of transcription
- ,, ,, processing
- ,, ,, translation

Deletion of both α genes on a chromosome = αo

,, ,, 1 α gene ,, ,, ,, = α+

**Defective fetal & adult Hb production**

Hb A (α2β2)

Hb A2 (α2δ2)

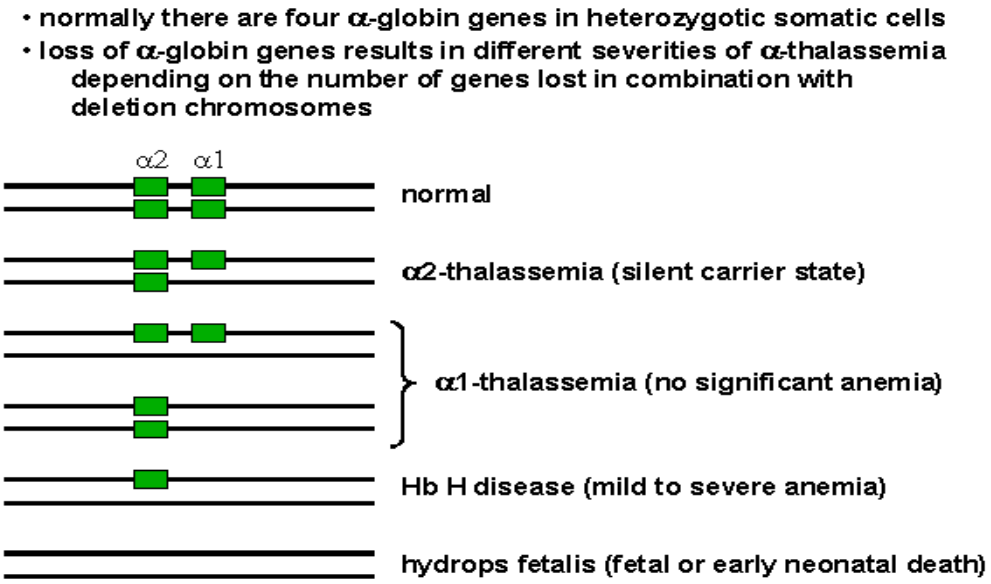
Hb F (α2γ2)

In fetus: ↑ γ Hb Barts (γ4)

In adults : ↑ β Hb H (β4)

**Types:**

- Silent Carrier
- Trait (Minor)
- Hemoglobin H Disease
- Major (Hemoglobin Bart's)




## Classification & Terminology of α Thalassemia

- Normal αα/αα
- Silent carrier - α/αα
- Minor -α/-α

  --/αα

- Hb H disease --/-α
- Barts hydrops fetalis --/--

# α Thalassemia

- Result from gene deletions
- One deletion—Silent carrier; no clinical significance
- Two deletions—a Thal trait; mild hypochromic microcytic anemia
- Three deletions—Hgb H; variable severity, but less severe than Beta Thal Major
- Four deletions—Bart's Hgb; Hydrops Fetalis; In Utero or early neonatal death

# Clinical Outcomes of Alpha Thalassemia

- **Silent carriers**
  - asymptomatic
  - "normal"
- **Alpha Thalassemia minor (trait)**
  - no anemia
  - microcytosis

    -unusually small red blood cells due to fewer Hb in RBC
  - "normal"
- **Alpha Thalassemia intermedia ("Hemoglobin H")**
  - microcytosis & hemolysis (breakdown of RBC)

    - results in severe anemia
  - bone deformities
  - splenomegaly (enlargement of spleen)
  - "severe and life threatening"
- **Alpha Thalassemia major**
  - Hb Bart's
  - fatal hydrops fetalis
  - occurs in utero

## Hydrops Foetalis

- No α chain at all (loss of 4 genes)
- Most severe form due to intra-uterine hypoxia, pallor, oedema, HSM
- Intra-uterine death (incompatible e' life)

**Hb E/P:**

Hb barts: (γ4) (γ2 γ2)

Hb H : (β4) (β2β2)

Hb Portland: (ζ 2 γ2)

**N.B:** Hb H & Hb barts have high O2 affinity.

**D.D:**

Rh incompatibility

| | **Rh incompatibility** | **Hydrops Foetalis** |
|---|---|---|
| **Rh of baby** | + ve | -ve<br>or<br>+ve |
| **Direct Coomb's** | Strong + ve | -ve |
| **Hb electrophoresis** | Normal | Abnormal<br>Hb H or barts |

# Hb H disease

Deletion of 3 α genes  αo/α+  --/-α

Hb H :  (β4)  (β2β2)

**C/P:**

- Chronic H.A
- Hb : 7-10 g/dl
- Hypochromia, target cs
- ↑Retics: 5-10 %
- Splenomegaly, hypersplenism
- Bony changes

**Lab diagnosis:**

**Evidences**

**CBC:**

- MHA
- Anisocytosis, poikilocytosis
- Retics 5-10%
- Hb H : brilliant cresyl blue → inclusion bodies in all cells → golf ball appearance
- **Hb E/P:**

On acid ph 6-7

- **At birth :**

Hb barts (γ4) : 20-40 %

Hb F, A (the rest)

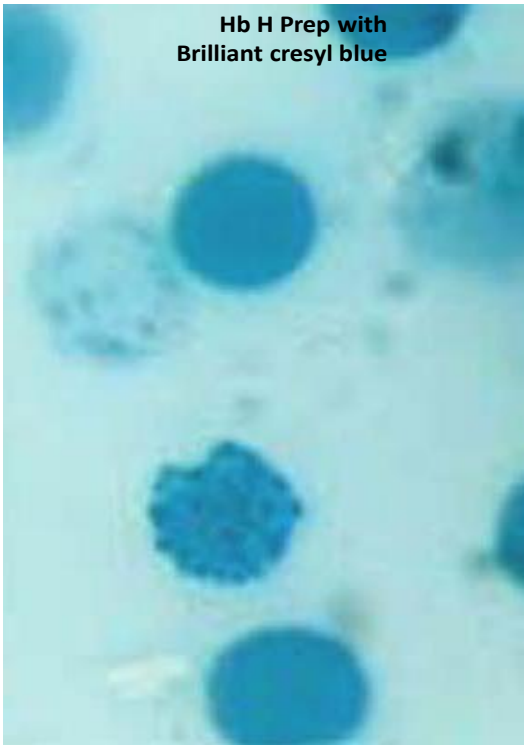
- **After 1 year:**

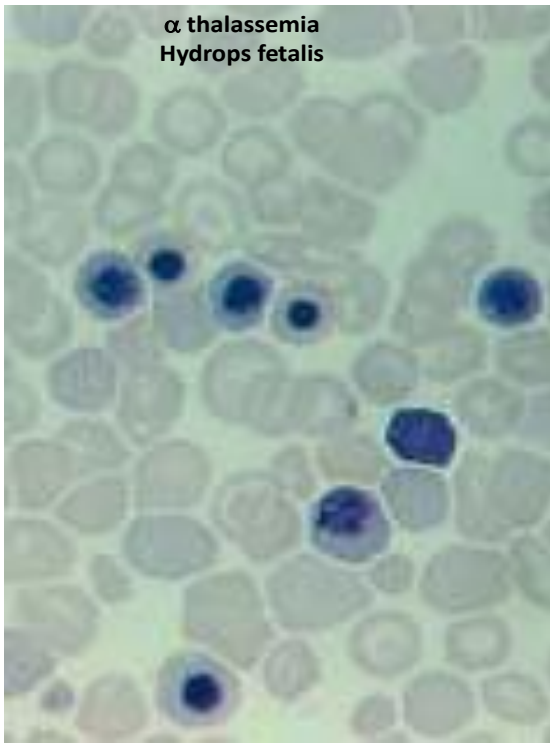
Hb H : 5-40 %

± Hb barts

Hb A : 25 %

Hb A2 : ↓




**Acquired Hb H disease**

- Observed in association e' pre-leukemic syndromes as MDS
- Occurs in elderly men

**Lab:**

RBCs r dimorphic : normal & hypochromic cells

**Diagnosis:**

Incubation on brilliant cresyl blue stain for 1 hour ⟶ Golf-ball appearance

**Hb E/P:**

Hb H 5-70 %

**Clinical & Haematological features of α thalassamia syndromes**

| Phenotype | Genotype | C/P | Newborn | After 1 year |
|---|---|---|---|---|
| **Hydrops Foetalis** | (- -/- -) | Neonatal death e' severe anaemia | Hb barts (γ4) 80-90 % | Doesn't live |
| **Hb H disease** | (- -/- α) | Ch. H.A as thalas. intermedia | Hb barts 20-40 % Hb A,F | Hb H 5-30 % ± Hb barts Hb A, A2 |
| **Thalass. minor** | (- α/- α) (- -/α α) | Little or no anaemia e' ⬇MCV, MCH | Hb barts 2-10 % | Normal |
| **Silent carrier** | (- α/α α) | No clinical or haematological abnormalities | Hb barts 0-2% | Normal |

## Alpha Thalassemias

- Usually no treatment indicated
- 4 deletions incompatible with life
- 3 or fewer deletions have only mild anemia

## Treatments for Alpha Thalassemia

- Silent Carrier – no treatment required
- Trait (Minor) – no treatment required
- Hemoglobin H Disease – Folate
  - avoid iron supplements
- Major (Hemoglobin Bart's) –RBC transfusion while still in doubt, else fetus is stillborn or dies shortly

# Program for preventation of thalassaemia

**I- Genetic counseling:**

Screening all population at school age & warning carrier about the risk of marriage to another carrier

**II- Pre-natal diagnosis & carrier detection:**

**A- Sampling:**

1- Amniocentesis (15-17 weeks)

2- Chorionic villous sampling ( 9-10 wks)

**B- DNA analysis:**

i- Southern blot

ii- Restriction enzymes

iii- PCR- RFLP

iv- PCR amplification of DNA