Thalassemia
Its genetics and Therapy

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Thalassemia

- Thalassemia is inherited as an autosomal recessive trait ,hence ,both parents must be carriers to have an affected child.
- Thalassemia may arise as the result of malfunction either of a or b-globin genes ,producing either a- or b-thalassemia.
- The phenotypes are indistinguishable :hemoglobin with an imbalance of either a-or b-chains precipitate, and cause erythrocytes to burst.

Thalassemia

- **The thalassemia is a diverse group of genetic blood diseases characterized by absent or decreased production of normal hemoglobin, resulting in a microcytic anemia of varying degree.**

- **The alpha (a) thalassemias are concentrated in Southeast Asia, Malaysia, and southern China.**

- **The beta (b) thalassemias are seen primarily in the areas surrounding Mediterranean Sea, Africa and Southeast Asia.**

Temporal Globin expression

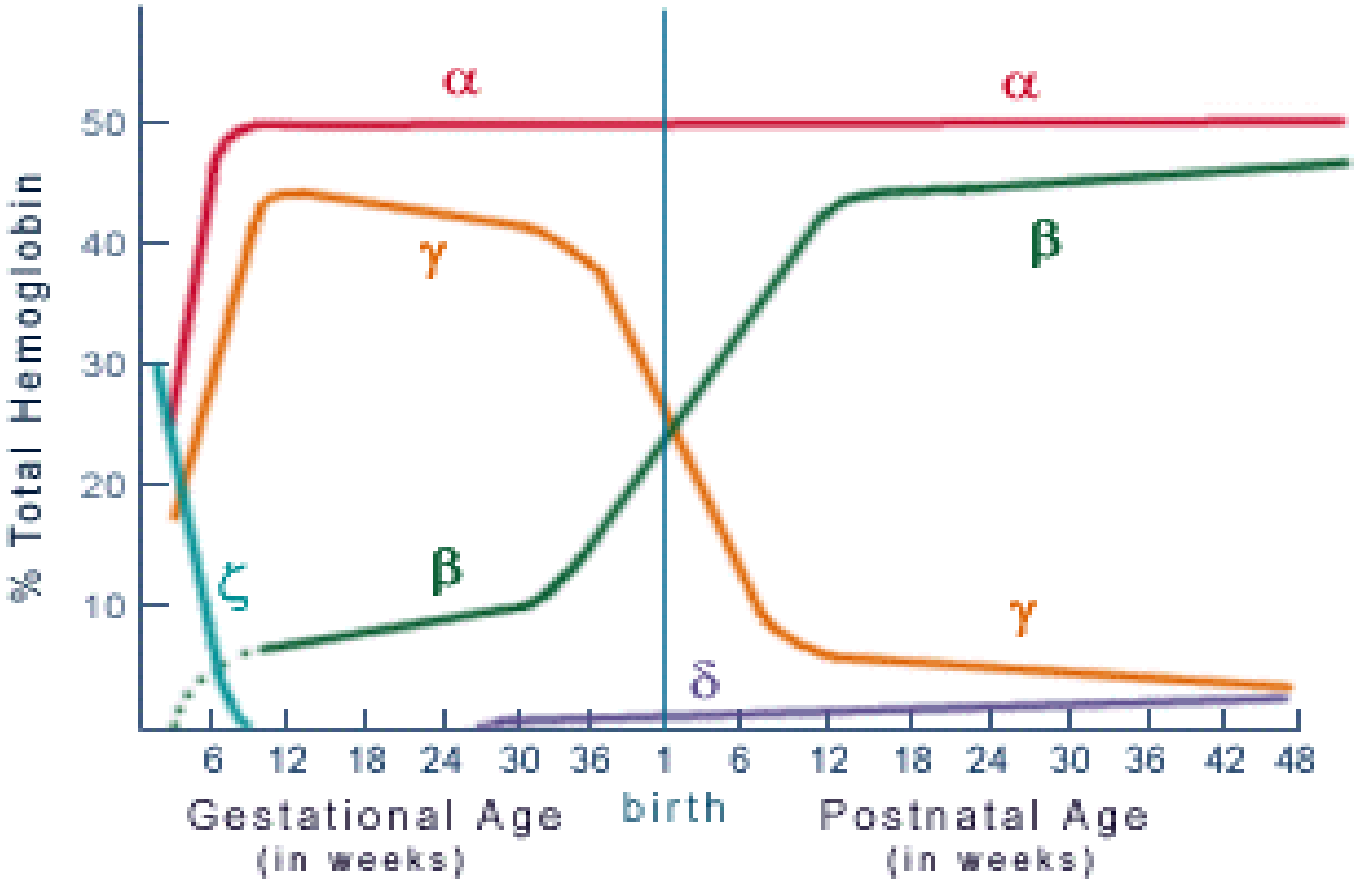
α globin expression is rather stable in fetal and adult life, because it is needed for both fetal and adult hemoglobin production

β globin appears early in fetal life at low levels and rapidly increases after 30 weeks gestational age, reaching a maximum about 30 weeks postnatally

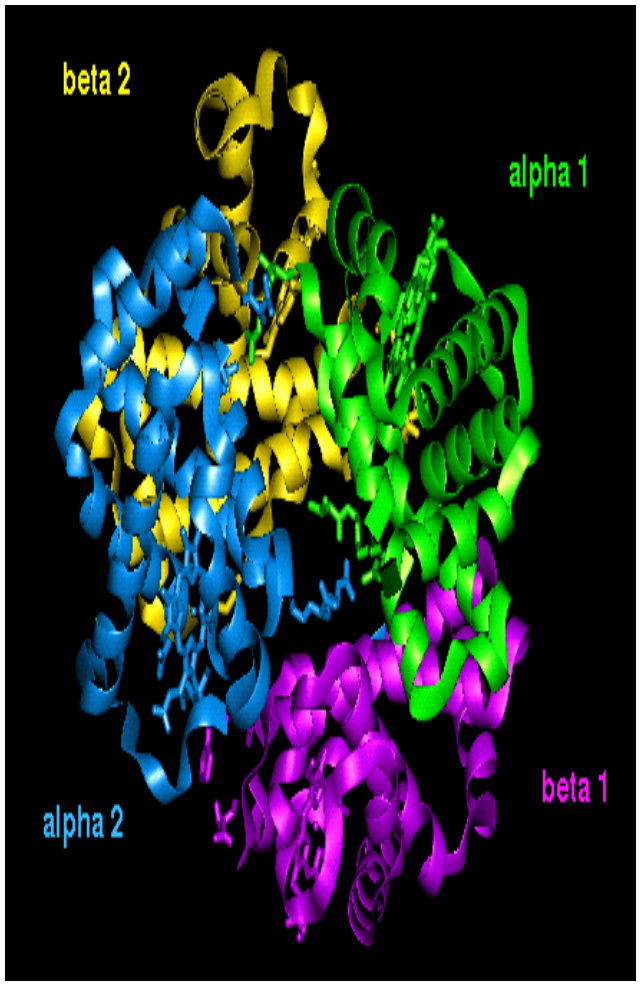
γ globin molecule is expressed at a high level in fetal life (6 weeks) and begins to decline about 30 weeks gestational age, reaching a low level about 48 weeks postgestational age.

δ globin appears at a low level at about 30 weeks gestational age and maintains a low profile throughout life.

Temporal globin expression



- Thalassemia is Genetic Blood disorder.
- Commonest single gene disorder.
- Inherited in an AR manner
- Carriers are clinically normal healthy individuals.
- Moderate to severe anemia.
- Osteoporosis due to bone marrow expansion,Pneumatization of the sinuses is delayed by expanded hematopoiesis.



Thalassemia Pathogenesis

- Hemoglobin concentration reduced in all RBCs
- RBCs are
  - Pale - Hypochromic
  - Small – Microcytic
- Imbalance of Alpha: Beta chain globin synthesis
- Excess globin chain precipitates
- Results in-

1. RBC precursor death in bone marrow
2. Premature removal of circulating RBCs

Clinical Features of Thalassemia

- Severe anemia
- Failure to develop in infants
- Growth retardation
- Hepatomegaly
- Speenomegaly
- Bone marrow expansion
- Pains in bones
- Osteoporosis due to bone marrow expansion,Pneumatization of the sinuses is delayed by expanded hematopoiesis.
- Cardiomyopathy
- Pulmonary hypertension
- Heart failure

Types of Thalassemia

β thal: *excess of a globins*, leading to formation of a globin tetramers (a^4) that accumulate in the erythroblast , leading to ineffective erythropoiesis. Two types of mutations, the β0 in which no β globin chains are produced and β+, in which some β chains are produced but at a reduced rate.

α thal : *excess of b globins*, leading to the formation of β globin tetramers (β^4) called hemoglobin H. Results in hemolysis, generally shortening the life span of the red cell. Hemoglobin H-Constant Spring disease is a more severe form of this hemolytic disorder. Most severe form is a thalassemia major, in which fetus produces no a globins, which is generally incompatible with life.

α-thalassemia

- In most cases of α-thalassemia, α-globin genes are entirely deleted .
- The organization of the α-globin gene cluster ,with two identical α-genes and two closely homologous pseudogenes all close together ,makes unequal crossing over comparatively frequent.
- The severity of α-thalassemia increases as more genes are deleted .
- Symptomless carriers (clinically silent carriers) usually have one deleted gene **(αα/α-),**the absence of two genes **(αα/-- or α-/α-)** produce mild anemia (alpha thalassemia trait),the anemia is severe if three genes **(α-/--)** are missing (hemoglobin H disease) while the disease is fatal if all four genes are deleted.
- Total deletions of the α-globin cluster are therefore more likely to be harmful than deletion of one α-globin gene.

Classification & Terminology

Alpha- Thalassemia

- Silent carrier - $\alpha/\alpha\alpha$
- Normal $\alpha\alpha/\alpha\alpha$
- Minor $-\alpha/-\alpha$

  $--/\alpha\alpha$
- Hb H disease $--/-\alpha$
- Barts hydrops fetalis $--/--$

Classification & Terminology
Beta Thalassemia

• Normal	β/β
• Minor	β/β^0
	β/β^+
• Intermedia	β^0/β^+
• Major	β^0/β^0
	β^+/β^+

Thalassemia trait

- A symptomatic
- Healthy individual
- Carrier of the disease

β^{T}/β^{N}

Thalassemia Intermedia

- **Late onset > 2 Year**
- **Hb 7-9g%**
- **Transfusion may or may not**

β^T/β^T **or** β^T/β^N

Beta thalassemia major

- No beta chain produced (no HbA)
- Severe microcytic anemia occurs gradually in the first year of life
- Marrow expansion
- Iron overload
- Growth failure and death

Beta thalassemia major

- Transfusion
- Iron chelation
- Bone Marrow Transplantation

Untreated β thalassemia

- Major: Death in first or second decade of life
- Intermedia: Usually normal life span
- Minor/Minima: Normal life span

β-thalassemia

- The pathology of β-thalassemia is far more complex than that of the α-thalassemias. Major deletions are only minor cause .
- The genetic alteration which lead to β-thalassemia fall into three classes:

  β^+-thalassemia

  β^0-thalassemia

  δβ-thalassemia

In β^{+-}thalassemia the synthesis of β-globin chain is reduced but perceptible.

In β^0-thalassemia ,there is a complete absence of β–chain synthesis.

In δβ-thalassemia there is a total lack of both δ-and β-chain synthesis.

β-thalassemia mutations

- Five types of non-deletioanal mutations lead to the β–thalassemia syndrome:
  - nonsense mutation
  - missense mutation
  - frame shift mutation
  - RNA processing mutation
  - transcriptional mutation

β^0-thalassemia mutations

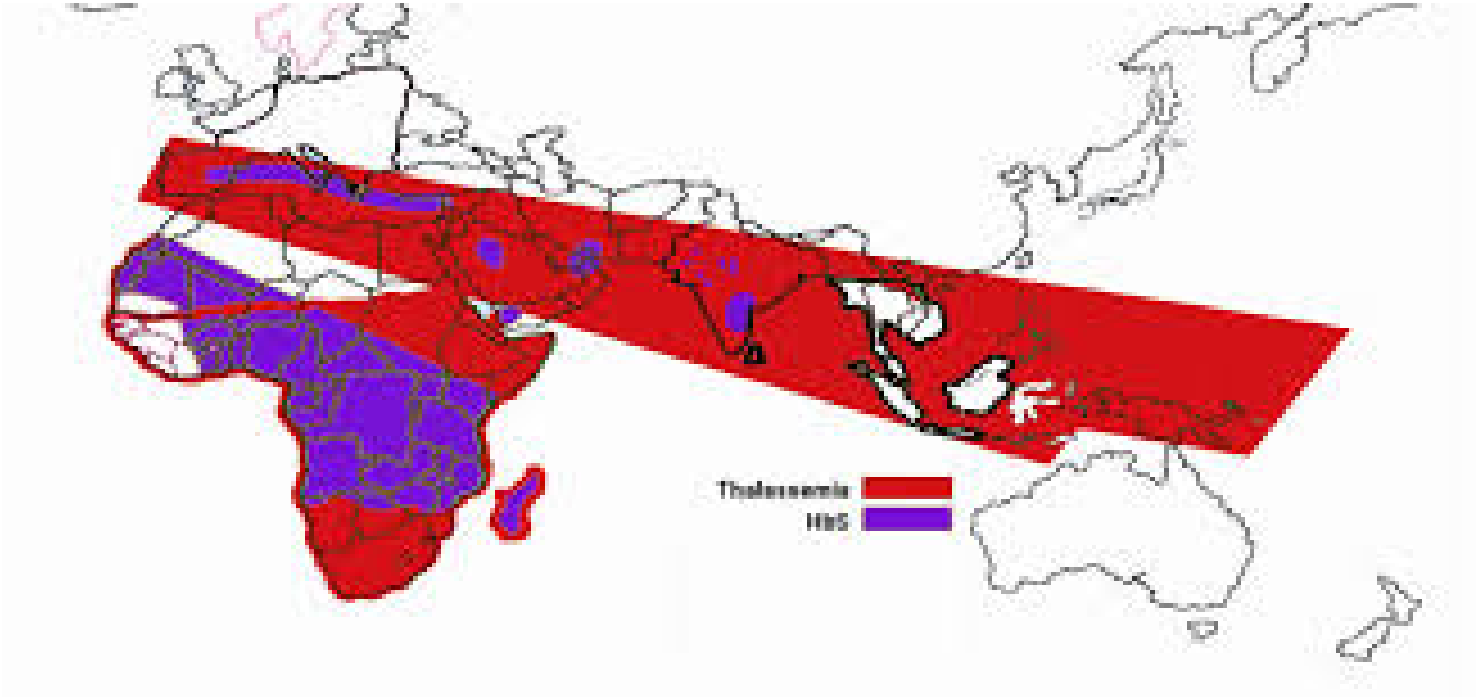
(1) Nonsense mutations,resulting from nucleotide substitution,lead to premature termination of b-globin mRNA translation ,phenotypically causes b^0-thalassemia ,with complete absence of effective synthesis . Codon 39 is changed from CAG ,encoding glutamine ,to UAG, a stop codon.

(2) Frameshift mutations always appear in regions with direct sequence repeats –the mRNAs transcribed from these regions are highly unstable and mutations lead to altered amino-acid sequences ,premature termination of protein synthesis and causes b^0 thalassemia. A rare mutation is found in 2% of the individuals ,frameshift at codon 6, resulted in a truncated protein.

Demographics: Thalassemia

Found most frequently in the Mediterranean, Africa, Western and Southeast Asia, India and Burma.

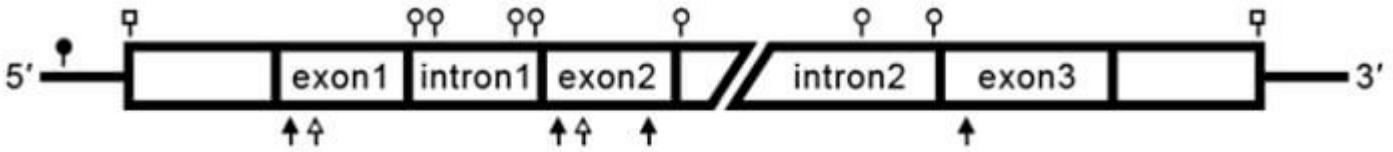
Distribution parallels that of *Plasmodium falciparum*



http://www.shodhsangam.rkdf.ac.in/papers/HEMATOLOGICAL.pdf

Genetics of Thalassemia

- **Autosomal Recessive Traits**
- **Mutational heterogeneity**
- There are more than 200 different thalssemia mutations reported from all over the world



β-Globin Gene

- Transcription (promotor)
- RNA modification (5' capping, 3' polyadenylation)
- RNA splicing
- Frame-shift
- Non-sense codon

https://www.middleeastmedicalportal.com/disorder-of-thalassemias-and-hemoglobinopathies-a-genetic-overview/

Special Cases of Thalassemia

Hb Lepore: $\delta\beta$ fusion seen in some types of $\delta\beta$ thalassemia

Hb Constant Spring

- α chain with 31 additional amino acids
- --/$\alpha^{cs}\alpha$

Hereditary persistence of fetal hemoglobin (HPFH)

Thalassemia/HbS

Thalassemia/HbE

Thalassemia/HbD

Special Cases of Thalassemia

Hb Barts & hydrops fetalis

- Barts is a γ^4 tetramer
- Associated with --/--
- Lethal
- High concentrations are capable of sickling

Hb H

- β^4 tetramer
- Associated with --/-α thalassemia

Course and Treatment
Thalassemia

- Time of presentation
  - Related to degree of severity
  - Usually in first few years of life
  - Untreated severe α thalassemia
    - --/--: Prenatal or perinatal death
    - --/-α & --/$\alpha^{cs}\alpha$: Normal life span with chronic hemolytic anemia

Therapy

- **Blood Transfusion**
- **Bone marrow transplant**
- **Gene therapy (by Gene augmentation therapy approach)**

Other therapies for Thalassemia

Other therapies for Thalassemia

- Erythropoetin
- Fetal Hb augmentation
- Antioxidant
- Vitamin D

Support therapies

- Cheation therapy
- Osteocast repacement therapy

Thalassemia Prevention

- Preventive programs in (i) public education, (ii) population screening, genetic counseling and prenatal diagnosis have been very effective in reducing the birth rate of β-thalassemia major.

- Combination of hematological and molecular techniques offers the most reliable and accurate strategy for β-thalassemia prenatal diagnosis

- Development of molecular techniques not only made it possible to offer prenatal diagnosis at an early stage of the pregnancy but they can help to resolve diagnostic problems.