Genetics of Thalassemia

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- Definition of Thalassemia
- Molecular Genetics
First recognized in 1952 by Dr. Thomas B. Cooley.

The name thalassemia is a Greek term derived from thalassa meaning The sea, plus Emia pertaining to blood.

Thalassemia is called Erythroblastosis, Mediterranean anemia or Cooley's anemia.

Approximately 100,000 babies worldwide are born with severe forms of thalassemia each year. However, the condition occurs more frequently in people of Italian, Greek, Middle Eastern including (Iraq), Southern Asian and African ancestry.
Thalassemia:

Is a group of inherited blood diseases that affect a person's ability to produce hemoglobin in red blood cells. A person with thalassemia does not have enough hemoglobin or red blood cells, which can cause mild to severe anemia.

Hemoglobin: is a protein found in red blood cells. It carries oxygen to all parts of the body.

Normal hemoglobin (also called hemoglobin A) has 4 protein chains, two alpha globin chains and two beta globin chains, and iron containing chemical group called heme.
Molecular Genetics:

The genes that code for the globin chains of hemoglobin are found on chromosome 11 and 16.

Each person has (4 alpha globin genes located on chromosome 16) that code for alpha globin chains of hemoglobin (two from each parent) and each person has (2 beta globin genes located on chromosome 11) controlling the production of beta globin chains of hemoglobin (one from each parent).

This keeps the production of protein chains equal. Thalassemia occurs when a globin genes fails (mutation occurs) and the production of globin protein chains is thrown out of balance.
The genes that code for the globin chains of hemoglobin are found on chromosome 11 and 16.
Sura Zuhair Salih

- Types of Thalassemia
- Alpha Thalassemia
Types of Thalassemia

α –thalassaemia affect α-chain synthesis

β –thalassaemia affect β-chain synthesis
Alpha Thalassemia

• mutation of 1 or more of the 4 alpha globin genes on chromosome 16
• severity of disease depends on number of genes affected
• results in an excess of beta globins
Classification of Alpha Thalassemia:

1- Silent Carriers

- 3 functional alpha globin genes
- No symptoms, but thalassemia could potentially appear in offspring
2- Alpha Thalassemia Trait

• 2 functional globin genes
• results in smaller blood cells that are lighter in colour
• no serious symptoms, except slight anemia
3- Hemoglobin H Disease

- 1 functional globin gene
- results in very lightly coloured red blood cells and possible severe anemia
- hemoglobin H is susceptible to oxidation, therefore oxidant drugs and foods are avoided
- treated with folate to aid blood cell production
4- Alpha Thalassemia Major or (Hydrops Fetalis)

- no functional globin genes
- death before birth (embryonic lethality)
Saad Ghassan Al-Dulaimy

• Beta Thalassemia
Beta Thalassemia

• mutations on chromosome 11
• hundreds of mutations possible in the beta globin gene, therefore beta thalassemia is more diverse
• results in *excess of alpha globins*
Classification of Beta Thalassemia:

1- Beta Thalassemia Trait (Minor)

- slight lack of beta globin
- smaller red blood cells that are lighter in colour due to lack of hemoglobin
- no major symptoms except slight anemia
2- Beta Thalassemia Intermedia

- lack of beta globin is more significant
- bony deformities due to bone marrow trying to make more blood cells to replace defective ones
- causes late development, exercise intolerance, and high levels of iron in blood due to reabsorption in the GI tract
- if unable to maintain hemoglobin levels between 6 gm/dl – 7 gm/dl, transfusion or splenectomy is recommended
3- Beta Thalassemia Major

• complete absence of beta globin
• enlarged spleen, lightly coloured blood cells
• severe anemia
• chronic transfusions required, in conjunction with chelation therapy to reduce iron (desferoxamine)
Pathophysiology of \(\beta\)-Thalassemia Major

- \(\beta\)-Thalassemia genes
  - Excess unbound \(\alpha\)-globin chains
    - Inclusion bodies
    - Increased RBC destruction

- Membrane damage
- Iron excess
- Increased bilirubin production
- Gallstones
- Jaundice

- Anemia
- Massive erythropoiesis
- Extramedullary hematopoiesis

- Defective development
- Iron overload
- Blood transfusion
- Cardiac failure, Cirrhosis, DM

- RE hyperplasia
- Hepatosplenomegaly
- Bone changes

- Increased infection
Saad Farouq Kassir

- Laboratory Diagnosis
Laboratory Diagnosis:

Initial Approach to Suspect

- History
  - Race
  - Family History
  - Age of Onset
  - Development
- Clinical Examination
  - Pallor
  - Jaundice
  - Splenomegaly
  - Skeletal Deformity
  - Pigmentation
- Blood Count and Film
  - Hb MCV MCH Retics
  - RBC Inclusions in Blood or Marrow
  - Hb H Precipitation
- Hemoglobin Electrophoresis
  - Presence of Abnormal Hb
    - To Include Analysis at pH 6-7
      - For Hb H and Hb Barts
  - Hb A2 and Hb F Estimation
    - To Confirm β Thalassemia
- Intracellular Distribution of Hb F
- Globin-Chain Synthesis
- Structural Analysis of Hb Variants, e.g., Hb Lepore
Laboratory Diagnosis:

1- Need to start with patients individual history and family history: Ethnic background important.

2- Perform clinical examination:
   - Pallor indicating anemia.
   - Jaundice indicating anemia.
   - Splenomegaly due to pooling of abnormal cells.
   - Skeletal deformity especially in Beta Thalassemia major.
Laboratory Diagnosis of Thalassaemia
3- Thalassemia is diagnosed using **blood tests**, including a **Complete blood count (CBC)** and special hemoglobin studies.

A **CBC** provides information about the amount of hemoglobin and the different kinds of blood cells, such as red blood cells in a sample of blood. People with Thalassemia have fewer red blood cells than normal and less hemoglobin than normal in their blood.
Laboratory Findings

- Hb concentration – Decreased
- ESR – Mild increased
- WBC – Neutrophilic leucocytosis or normal
- RBC count – Markedly decreased
- PCV – Markedly decreased
- MCV, MCH, MCHC – reduced
- Reticulocyte count – Increased
- Platelet count – May be increased
Blood film in normal person and in β- Thalassemia major patient showing Hypochromia and Microcytosis:

**Normal**

**Thalassaemia**
Blood film in β-Thalassemia major

Peripheral blood smear of Beta Thalassemia major shows:
Hypochromic Microcytic anemia poikilocytic RBCs, Target cells, Basophilic Stippling, Tear Drop cells, Nucleated RBCs.

Poikilocytic red cells (elliptocytes¹, schistocytes², target cells³, tear drop⁴, spherocytes⁵ & hypochromic⁶) usually present in Thalassemia Major.
Beta Thalassemia Major

Peripheral Blood Smear

- Anisopoikilocytosis
- Microcytic Hypochromic
- Tear Drop Cell

- Basophilic Stippling
- Target Cell
4- Hemoglobin Electrophoresis:
- Hemoglobin studies measure the types of hemoglobin in a blood sample.
- Can differentiate among Hb A, Hb A2, and Hb F, as well as detect presence of abnormal hemoglobins.

5- Hemoglobin Quantitation:

Elevation of Hb A2 excellent way to detect heterozygote carrier of beta thalassemia. Variations in gene expression in Thalassemia results in different amounts of Hb A2 being produced. Can also quantitate levels of Hb F.
6- Routine Chemistry Tests:
Indirect bilirubin elevated in Thalassemia major and intermediate.
Assessment of iron status, total iron binding capacity, and ferritin level important in differentiating Thalassemia from iron deficiency anemia.

7- Globin Chain Testing:
Determines ratio of globin chains being produced.

8- DNA Analysis:
Determine specific defect at molecular DNA level.

9- Family genetic studies are also helpful in diagnosing Thalassemia.
This involves taking a family history and doing blood tests on family members.

10- Prenatal testing:
can determine if an unborn baby has Thalassemia and how severe it is likely to be.
Sama Naal Salouha

- Inheritance of Thalassemia
Inheritance of Thalassemia:

The two main types of thalassemia are alpha and beta. Both types of Thalassemia are inherited in the same manner. **Autosomal Recessive Inheritance:** Parents who carry the mutated thalassemia gene can pass it on to their child. A child who inherits one mutated gene is considered to be a carrier, which sometimes called thalassemia trait.
Inheritance of Thalassemia:

1- If both parents have normal hemoglobin:
   all their children will be normal 100%.
Inheritance of Thalassemia:

2- If only one parent has Thalassemia trait (also called carriers):

- 50% chance of having a child with thalassemia trait and
- 50% chance of having a normal child

None of the couples' children will get thalassemia major.
Inheritance of Thalassemia:

3- If both parents have Thalassemia trait (carriers):

25% chance of having a child with Thalassemia major, because the baby could receive two thalassemic genes (one from each parent) and have moderate to severe form of disease.

50% chance of having a child with Thalassemia trait (carriers), because the baby could receive one normal gene from one parent and one variant gene from the other parent and have thalassemia trait.

25% chance of having a normal child, because the baby could receive two normal genes (one from each parent) and have normal blood.
Zahraa Jasim Al- Aarajy

- Inheritance of Thalassemia
- Treatment
Inheritance of Thalassemia:

4- If a Thalassemic major marries a Thalassemic carrier:
   in each pregnancy there is a:
   50% chance that the child will be Thalassemic major and a
   50% chance that it will be a carrier.
Inheritance of Thalassemia:

5- If a Thalassemic major married a normal: all the children will be carriers 100%. Because they must inherit a thalassemia gene from their thalassemic parent, but they must also inherit a normal gene from the normal parent, so none of them can possibly have thalassemia major.
Inheritance of Thalassemia:
6- If one Thalassemic major marries another thalassemic major:
   all their children will be Thalassemics major 100%.
   because the baby could receive two thalassemia genes (one from each parent) and have a moderate to severe form of disease.

![Diagram showing inheritance of Thalassemia](image)
TREATMENT OF THALASSEMIA

1. CONVENTIONAL TREATMENT
   - BLOOD TRANSFUSION
   - IRON CHELATION
2. HEMOGLOBIN F STIMULATION
3. TREATMENT OF COMPLICATION
   - INFECTIONS
   - HEART FAILURE ETC.
4. CURE
   - BONE MARROW AND STEM CELLS TRANSPLANTATION
   - GENE THERAPY