Thalassemia

Case

- **Patient:** A 36-year-old male of Burmese descent.
- **Chief Complaint:** Anemia and jaundice.
- **History of Present Illness:** At the time of presentation, He had been chronically jaundiced and anemic since childhood, with multiple episodes of severe anemia requiring transfusion. He reported receiving more than 30 units of blood prior to age 17.

Brit S. Shackley, Thomas A. Drake, Anthony W. Butch. Chronic Microcytic Anemia and Jaundice in a 36-Year-Old Male of Burmese Descent. Lab medicine.2010; 41:78-82

- **Past Medical History:** The patient contracted hepatitis C secondary to blood transfusions he received in Burma. Folic acid was his only medication. He has no history of tobacco or alcohol abuse.

- **Family History:** The patient is married with 1 child and works as an accountant. His mother and 1 sister both have thalassemia, although they are not as severely affected as he is. His father and 3 brothers have no known hematologic disorders.

- **Physical Examination:** Upon presentation, the patient was a well-nourished, well-developed male appearing jaundiced.

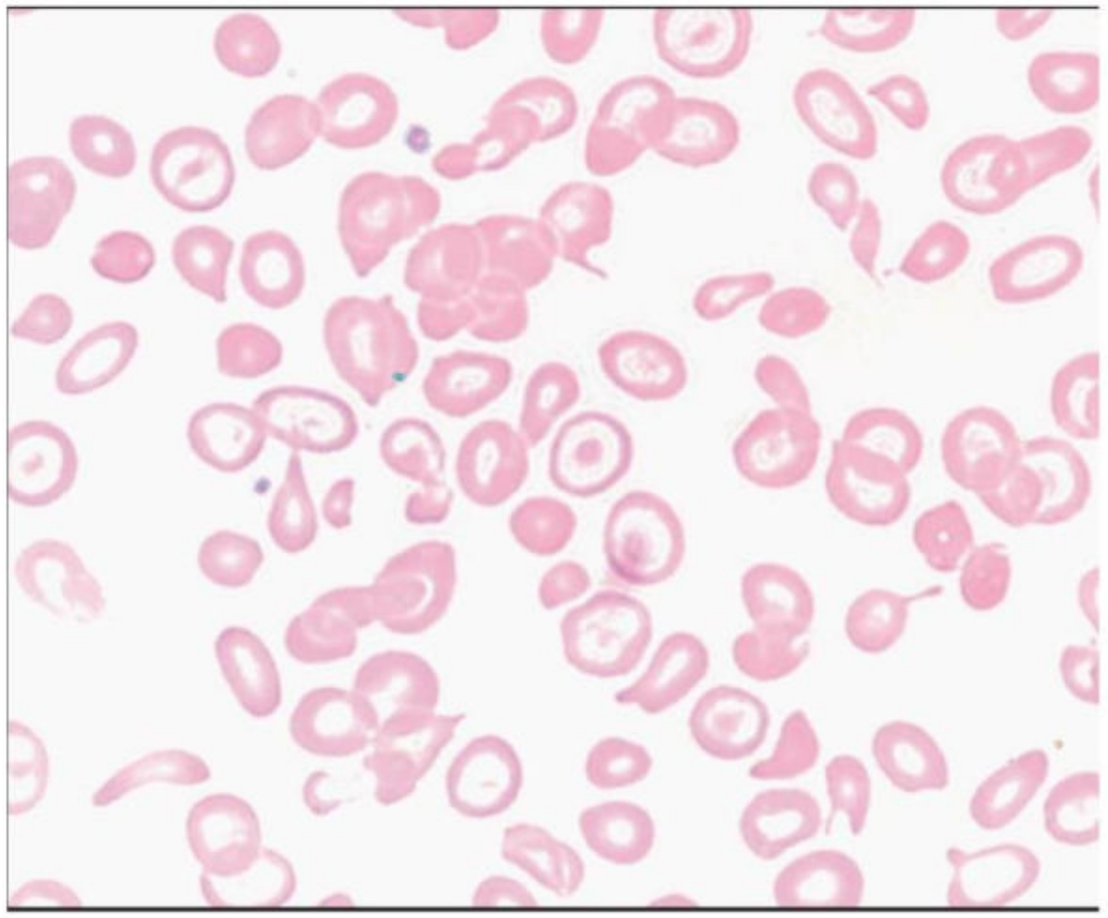
- Non-tender splenomegaly was noted extending to the level of the umbilicus.

- There were no other abnormal findings on physical examination.
- The following vital signs were recorded: blood pressure, 130/75 mm Hg; pulse, 72; and respiration rate, 16.

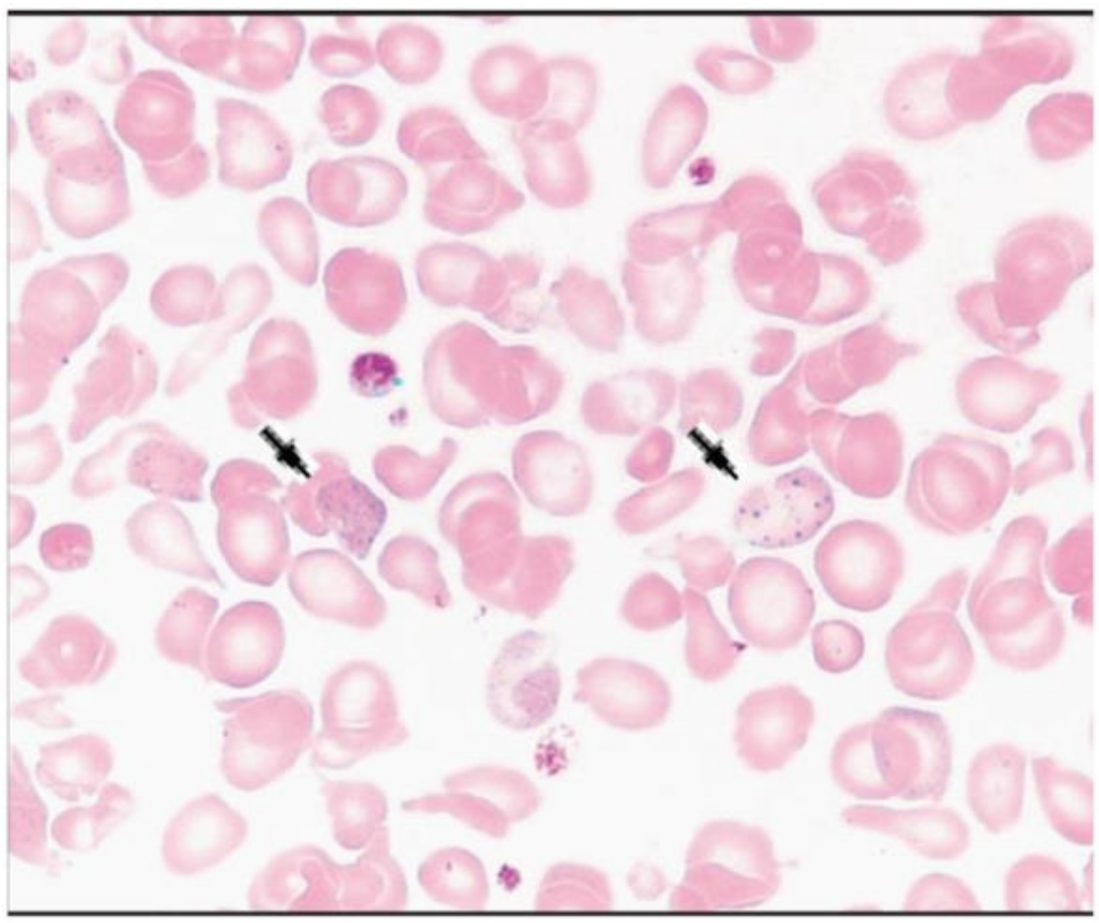
Hematological Report

Hematology		
WBC count	6.9	3.3-9.3 × 10^3/µL
RBC count	5.52	4.21–5.61 × 10^3/µL
Hemoglobin (Hb)	8.3	12.3–16.3 g/dL
Hematocrit	25.9	37.4–47.0%
MCV	48.7	79.0–95.0 fL
MCH	15.0	26.0–32.6 pg
MCHC	32.0	31.7–35.5 g/dL
RDW	22.9	10.7–15.5%
Platelet count	171	143-398 × 10^3/µL
Nucleated RBCs	1.2	0.0%
Reticulocyte count, auto	2.16	0.60–2.06%
Absolute reticulocyte #	0.1218	0.0273-0.1072 × 10^6/µL
Immature reticulocyte fraction	23.7	3.4–14.9%

PBF



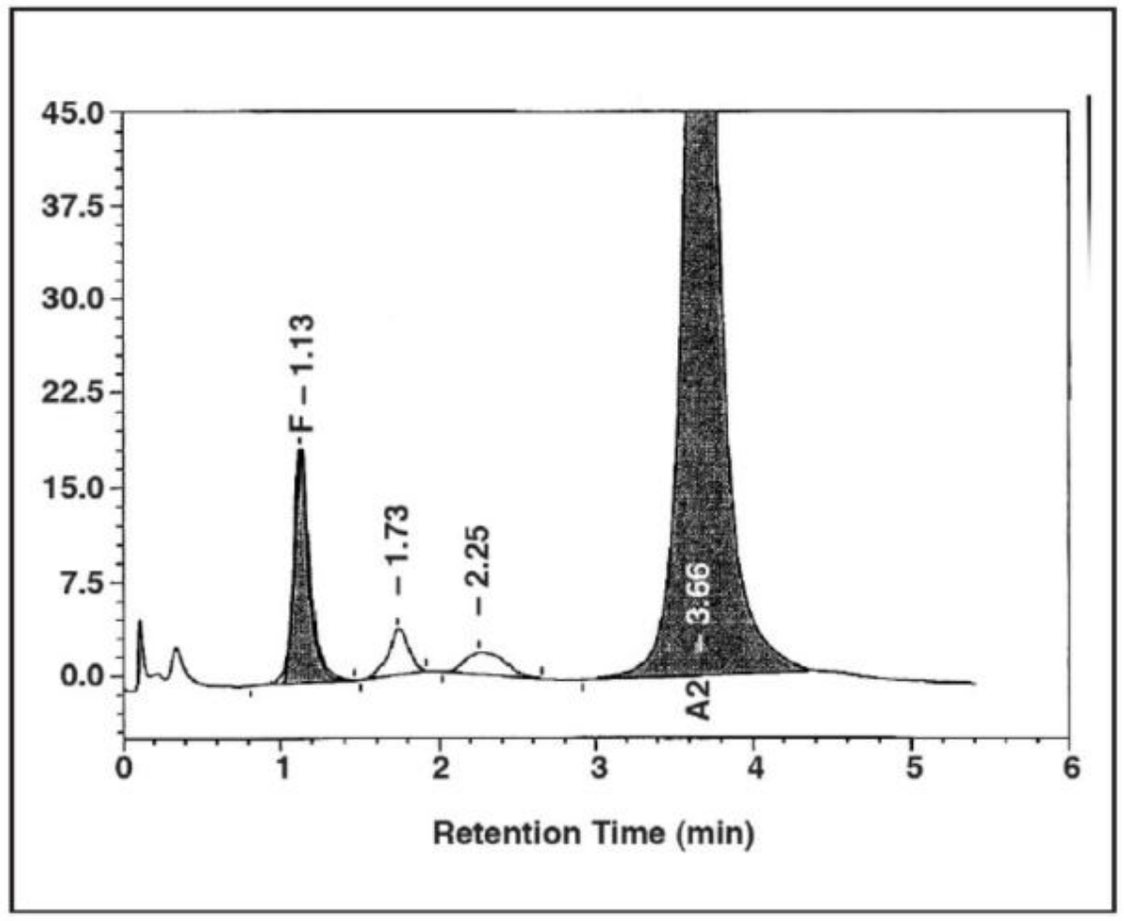
Basophilic stippling



Biochemistry Report

Chemistry		
Sodium	139	136–145 mmol/L
Potassium	3.8	3.6–5.4 mmol/L
Chloride	105	98–108 mmol/L
Total CO_2	26	20–29 mmol/L
Glucose	88	65–110 mg/dL
Urea nitrogen	12	7–23 mg/dL
Total protein	7.5	6.2–8.3 g/dL
Albumin	4.8	3.7–5.1 g/dL
Bilirubin, total	4.7	0.2–1.1 mg/dL
Alkaline phosphatase	45	31–103 U/L
AST	35	7–36 U/L
ALT	37	4–45 U/L
Calcium	9.2	8.7–10.5 mg/dL
Creatinine	0.8	0.5–1.3 mg/dL
Uric acid	6.6	4.0–9.0 mg/dL
Ferritin	1004	10–210 ng/mL

HPLC

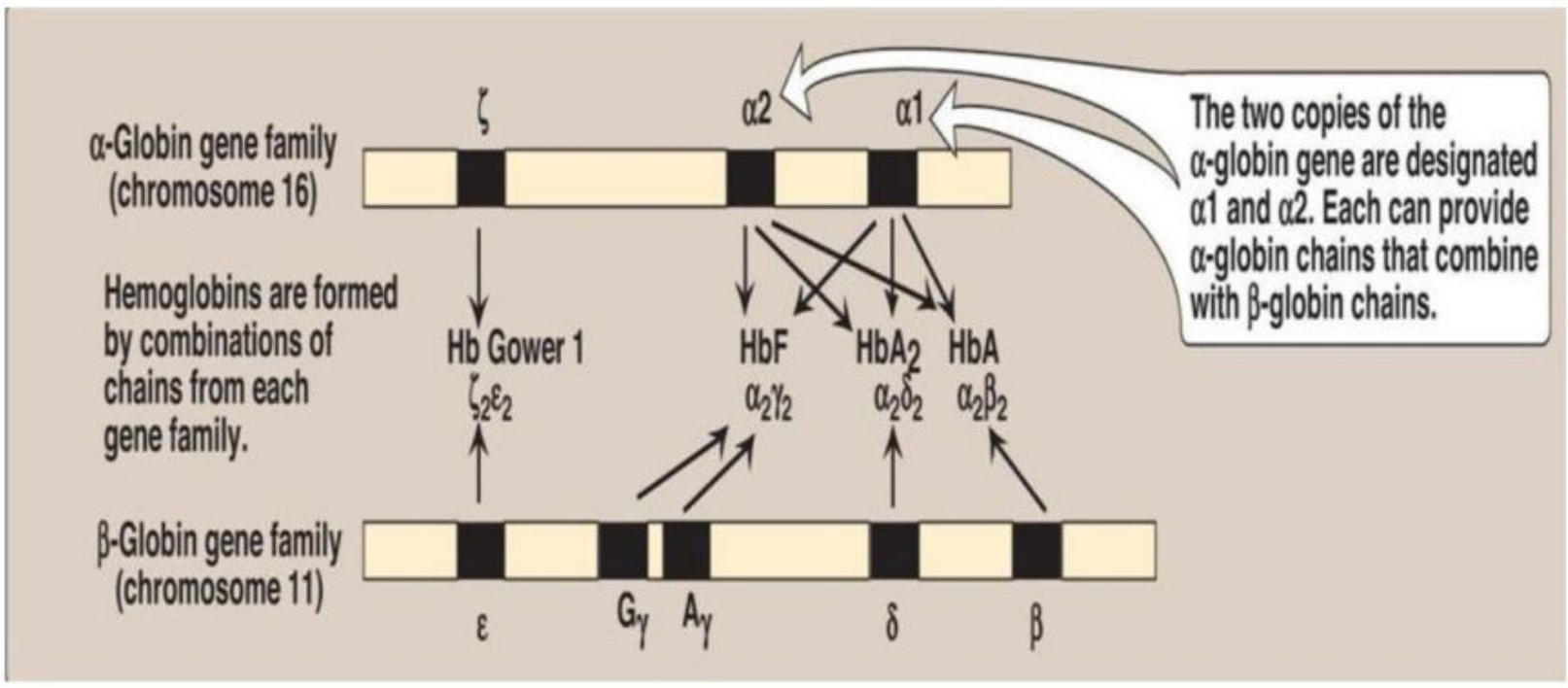


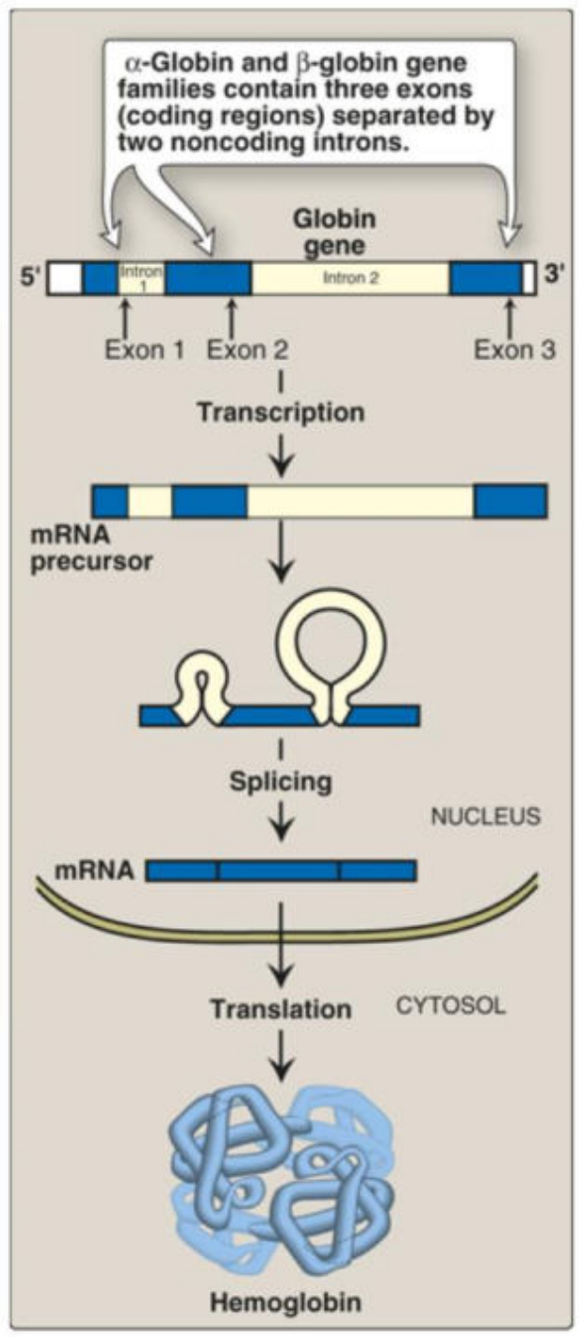
Thalassemia

- Thalassemias are a common cause of hypochromic microcytic anemia which arises from the reduced or absent synthesis of the globin chain of hemoglobin.
- a quantitative defect of hemoglobin synthesis.

1. α Thalessemia
2. β Thalessemia

Organization of Globin genes

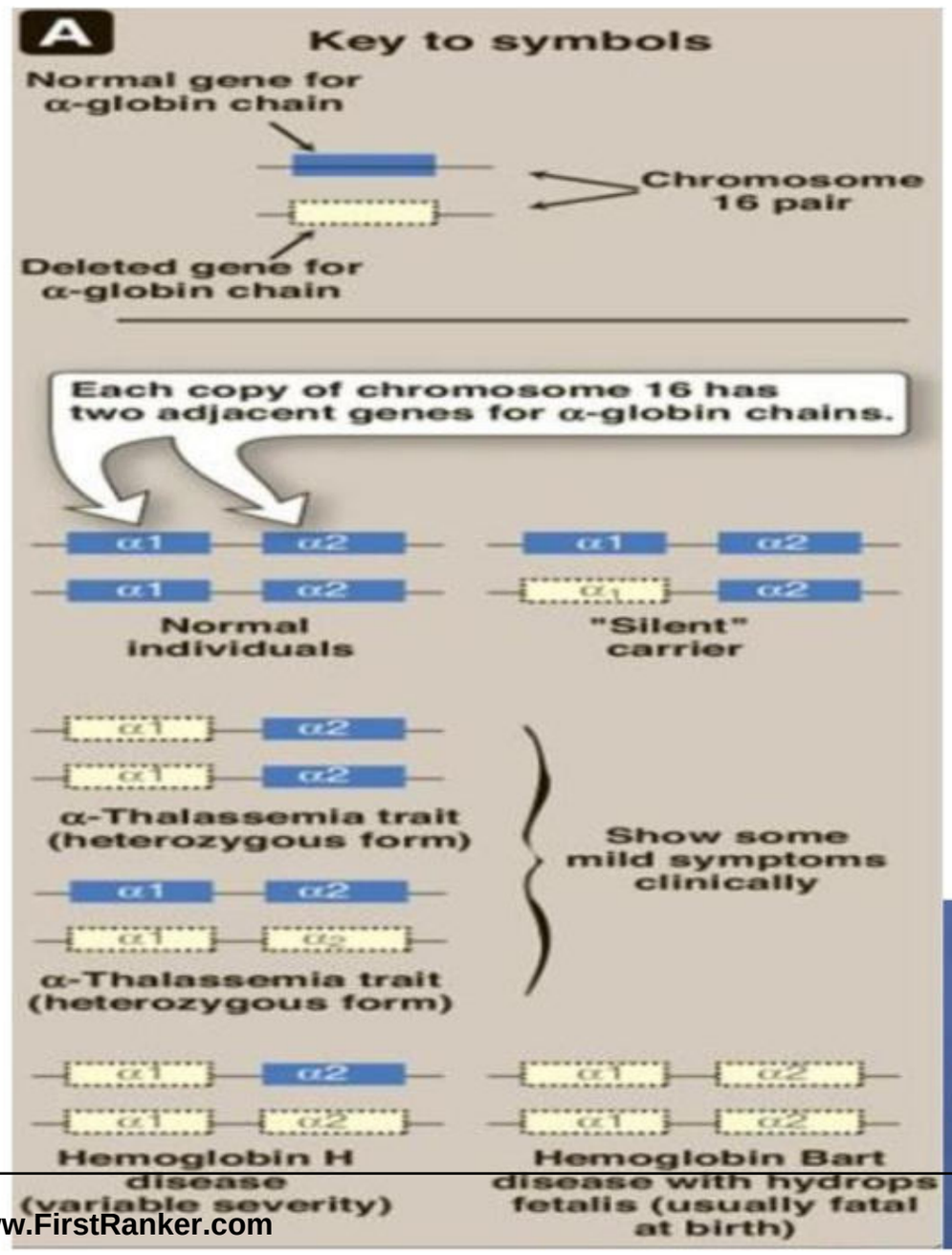


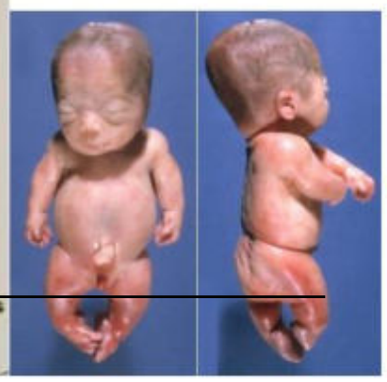


α Thalassemia

- Deletions in the α-globin gene cluster account for most of the mutations.

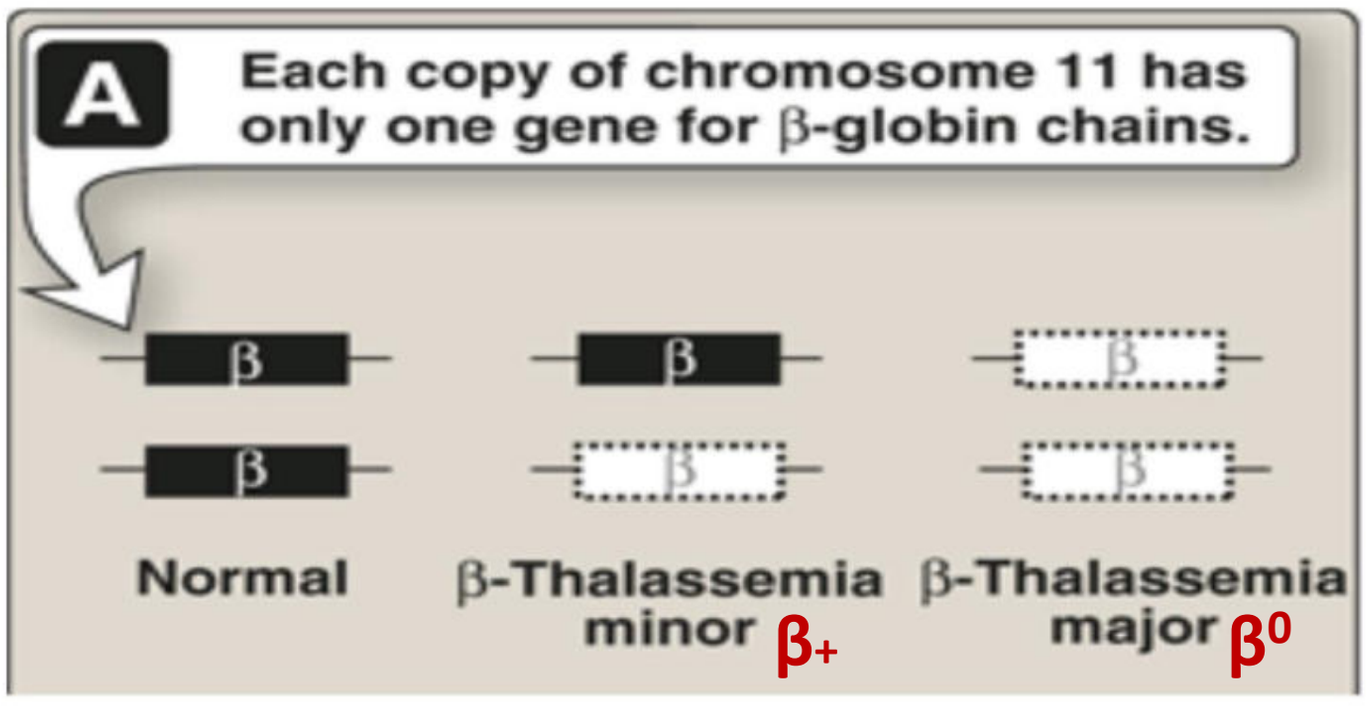
- 1 or 2 alleles deleted: αThal Trait
- 3 alleles deleted: HbH Disease
- All 4 deleted: Hb Bart/Hydrops Fetalis (Fatal at Birth)





β Thalassemia

- Inherited mutation of the beta-globin gene,
- Reduced synthesis of the beta globin chain of hemoglobin.
- The highest prevalence is in people of Mediterranean, Middle Eastern, and Asian descent



- Beta-thalassemia minor, also called carrier or trait, heterozygous state that is usually asymptomatic with mild anemia

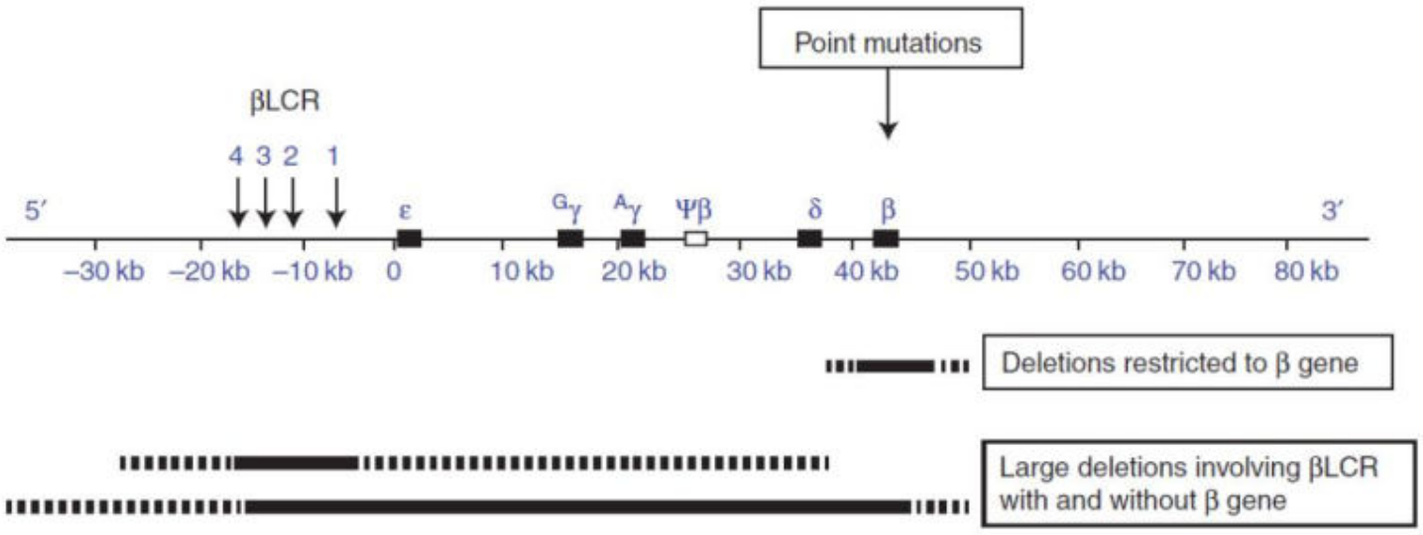
- Homozygosity or compound heterozygosity for beta-thalassemia mutations cause a more severe spectrum of anemias called beta thalassemia intermedia and beta-thalassemia major.

- These two are distinguished clinically by transfusion dependence.
- Beta-thalassemia major requires routine transfusions, and intermedia does not

Beta Thalassemia - StatPearls - NCBI Bookshelf

Molecular Mechanisms

- **α-thalassemia**: deletions in the α-globin gene cluster account for most of the mutations,
- **β-thalassemia** : mutations involving one (or a limited number of nucleotides) within the β gene or its immediate flanking regions



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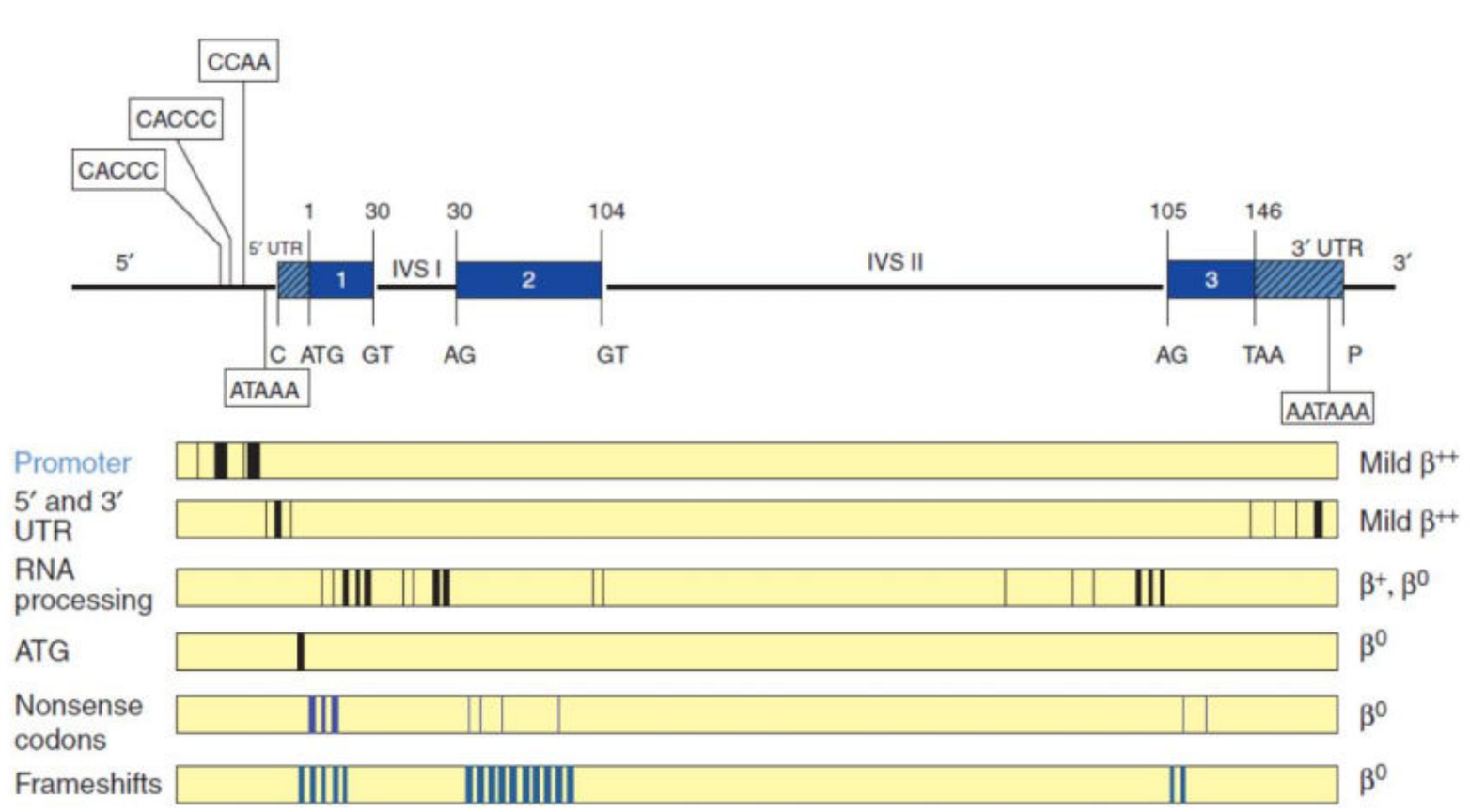
Point Mutations in β Thalassemia



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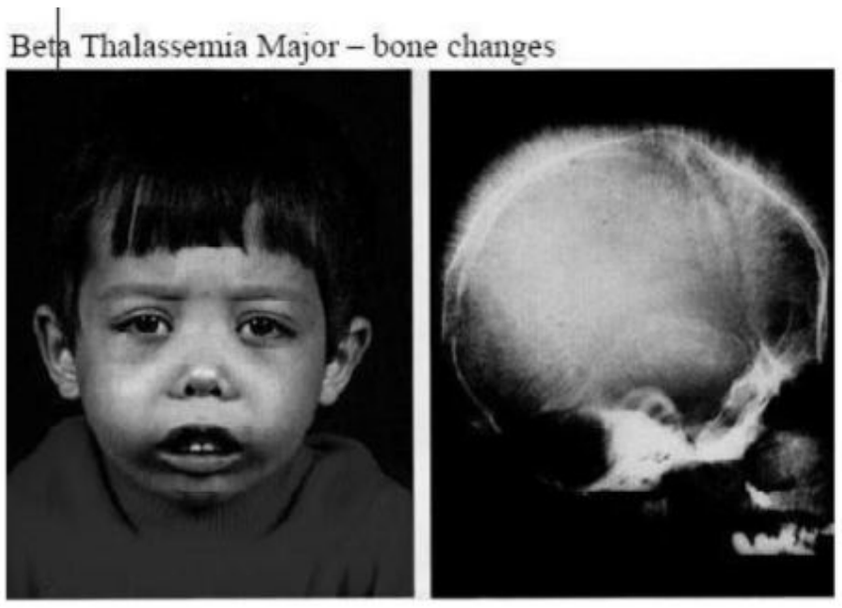
Clinical Features

- **Beta-thalassemia minor** is typically discovered incidentally on routine CBC. Patients may have mild symptoms of anemia without significant physical exam findings.
- Beta-thalassemia intermedia encompasses a wide range of clinical presentations but no transfusion required
- can present in children as young as two years of age with growth and developmental delay
- Milder forms of beta thalassemia intermedia may first present in adults as fatigue and pallor



- **Beta-thalassemia major** present between 6 and 24 months of age when hemoglobin production transitions from fetal (HbF) to adult (HbA).
- Severe anemia ensues and presents as feeding problems, irritability, failure to thrive, pallor, and abdominal enlargement from hepatosplenomegaly
- Frontal bossing, maxillary hypertrophy, and long bone deformities are common skeletal findings.

Pathophysiological Mechanisms of βThal Major

1. Decreased hemoglobin synthesis causing anemia and an increase in HbF and HbA2 as there are decreased beta chains for HbA formation

2. the relative excess alpha chains form insoluble alpha chain inclusions that cause marked intramedullary hemolysis

- This ineffective erythropoiesis leads to severe anemia and erythroid hyperplasia with bone marrow expansion and extramedullary hematopoiesis

- The bone marrow expansion leads to bony deformities, characteristically of the facial bones which cause frontal bossing and maxillary protrusion

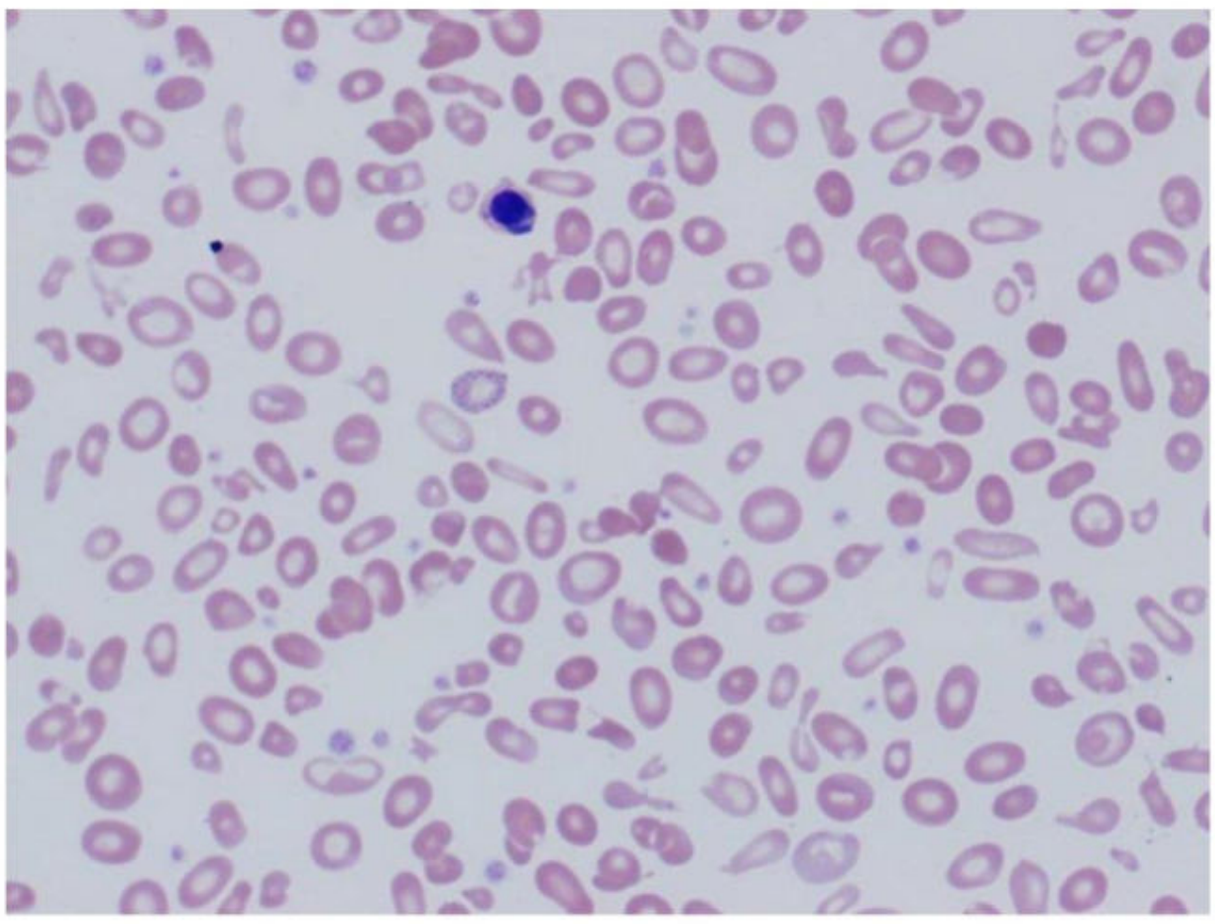
- Hepatosplenomegaly from extramedullary hematopoiesis and ongoing hemolysis also causes thrombocytopenia and hepatic dysfunction.

- Complications of beta-thalassemia include iron overload and bone-deforming marrow expansion with extramedullary hematopoiesis.

Laboratory Findings

- Microcytic anemia
- Reference range or increased red blood cell count
- Reference range red cell distribution width.
- Peripheral smear, red blood cells are hypochromic with increased target cells.
- There may be significant anisopoikilocytosis (variation of size and shape) in cases of beta-thalassemia major.
- Confirmation: Hemoglobin electrophoresis/ HPLC

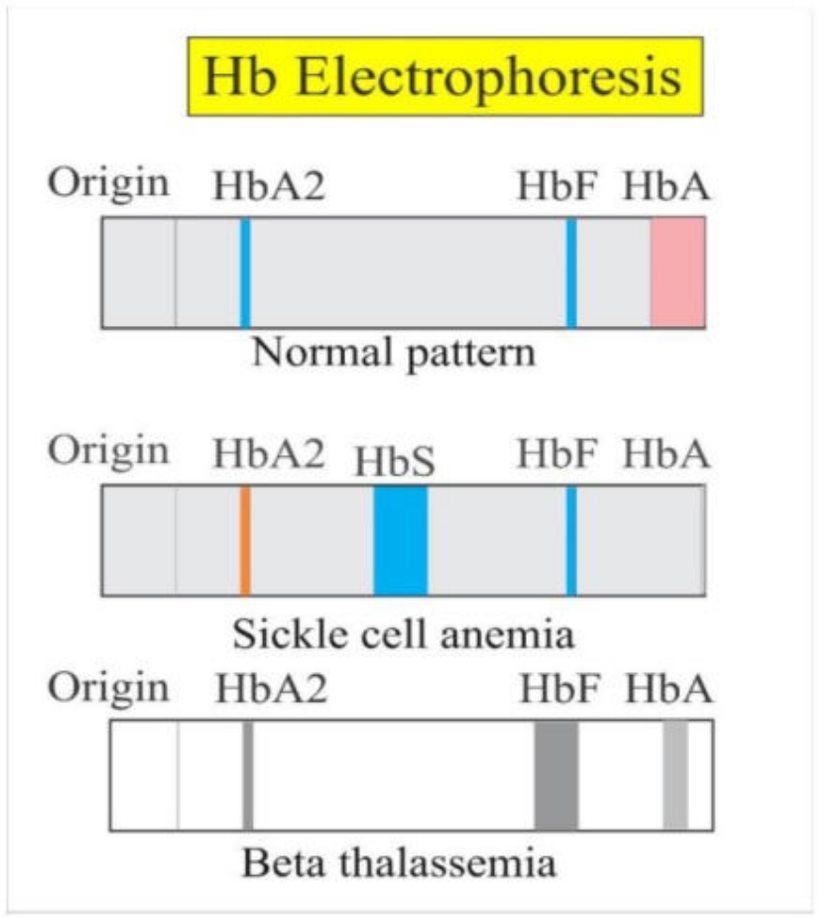
PBF



Peripheral blood, beta-thalassemia (clinically intermedia) showing anisopoikilocytosis, a nucleated red cell, and basophilic stippling.
David T. Lynch, MD and Todd R. Needs, DO

Hb Electrophoresis

- **Abnormal percentages of HbA, HbA2, and sometimes HbF.**
- Decreased HbA percentage
- Mildly increased HbA2; less than 10%
- Variably increased HbF.



- Patients with beta(+) alleles will have variably decreased HbA levels, and those that are homozygous beta(0) will produce no HbA.

- Beta thalassemia minor characteristically has increased HbA2 (4-8%) with variably normal-to-low elevations of HbF.

- Beta-thalassemia major typically shows markedly elevated HbF (30-to-greater than 95%) with normal to mildly elevated HbA2.

Treatment

- Thalassemia minor is a carrier state, it is typically asymptomatic. Genetic counseling and prenatal diagnosis might be indicated when carriers are detected.

- Thalassemia major is treated with red blood cell transfusion. The aim of transfusion is mainly to suppress erythroid expansion. It also serves to mitigate symptoms of anemia and to inhibit gastrointestinal iron absorption.

- The iron status of routinely transfused patients must be monitored. Clinical signs of iron overload and serial serum ferritin remain the most reliable method to evaluate iron overload

- Iron chelation therapy is generally started after patients have received 10 to 20 transfusions or have serum ferritin levels > 1000 ng/mL.

Thank You!