

HEMOGLOBINOPATHIES

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HEMOGLOBINOPATHY

(DISORDERS OF HEMOGLOBIN)

1-REDUCED SYNTHESIS OF NORMAL HEMOGLOBIN

Thalassemias

2-SYNTHESIS OF AN ABNORMAL HEMOGLOBIN

Hb S (Sickle Cell Anemia)

Hb C

Hb D

Hb E

Methemoglobin

THALASEMIAS

A heterogeneous group of disorders

The most frequent of the inherited diseases in the world

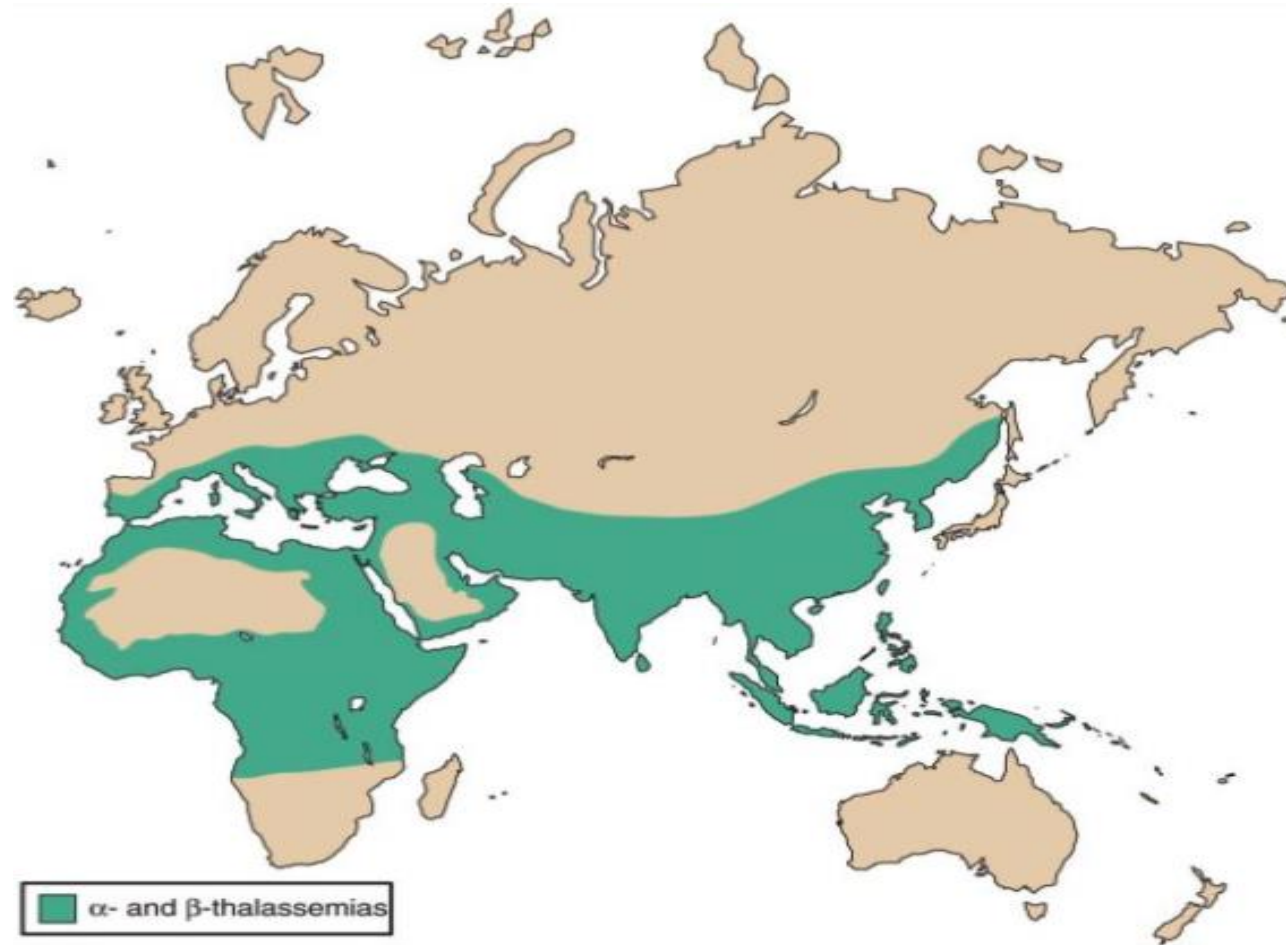
Monogenic disease

There is an inherited defect in rate of synthesis of one or more globin chains

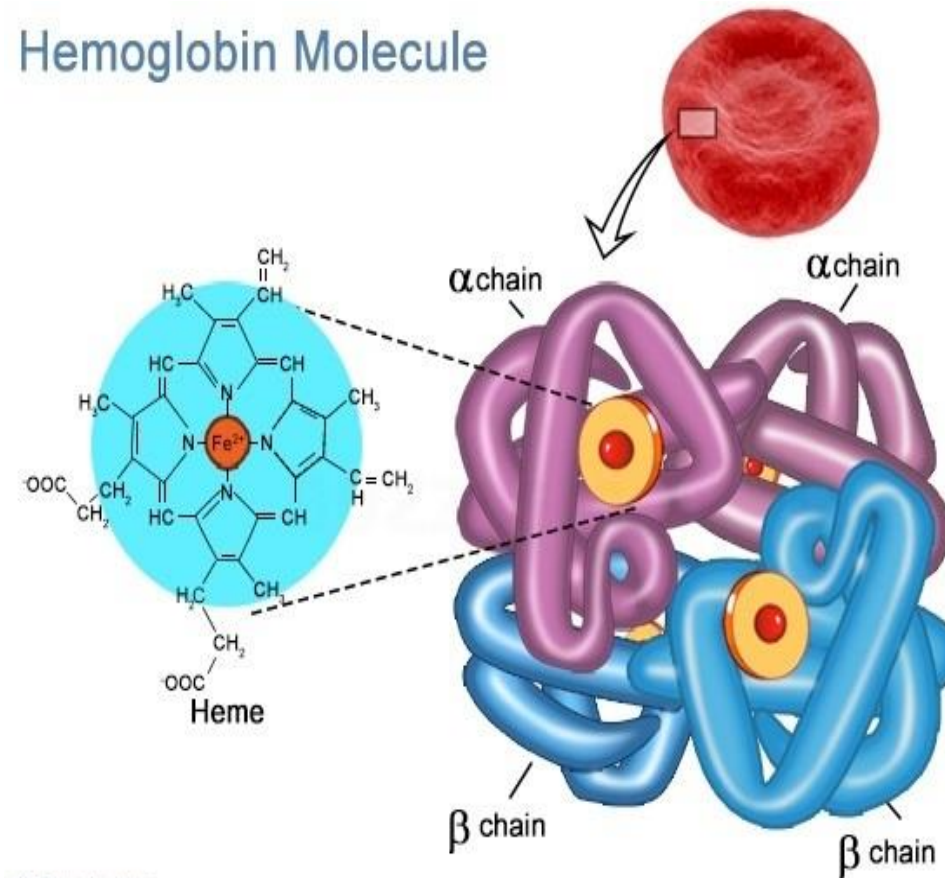
- -Alpha
- -Beta
- -Deltabeta

Common in thalassemia belt countries

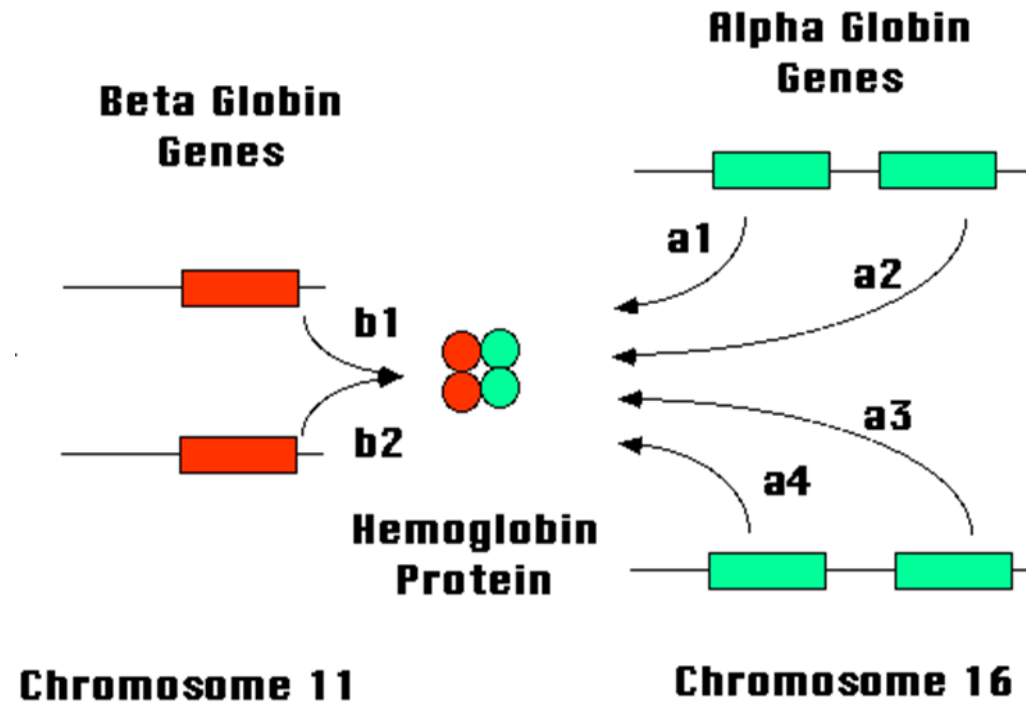
THALASSEMIA BELT



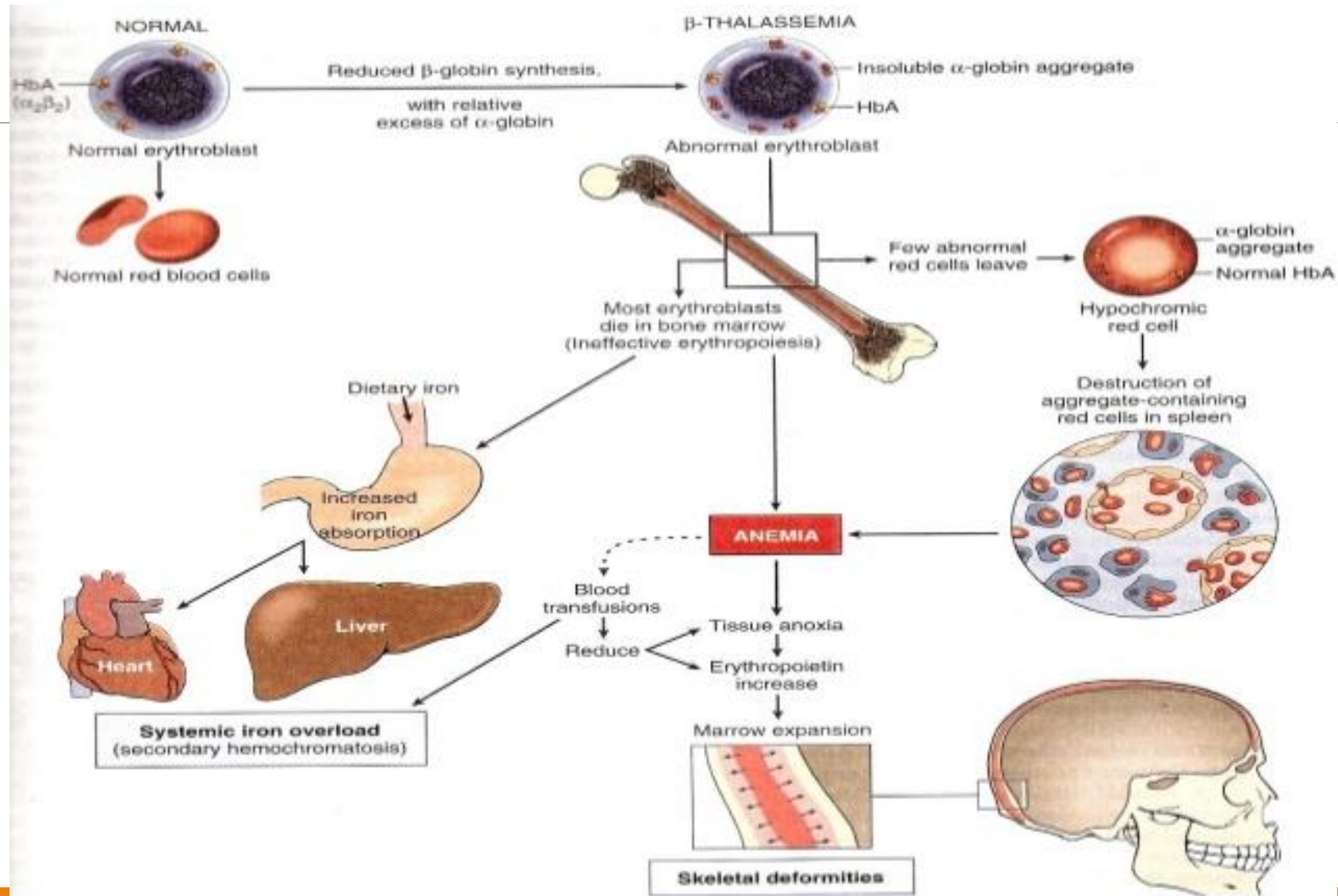
PATHOPHYSIOLOGY - Hemoglobin



PATHOPHYSIOLOGY



PATHOGENESIS



BETA THALASSEMIA

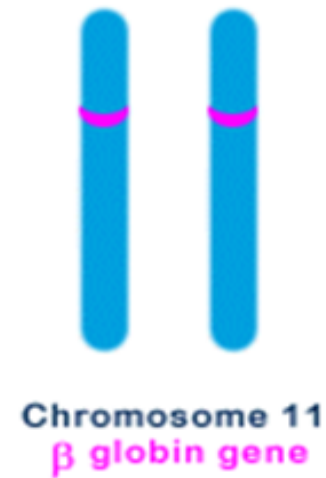
Beta-globin gene affected

2 genes

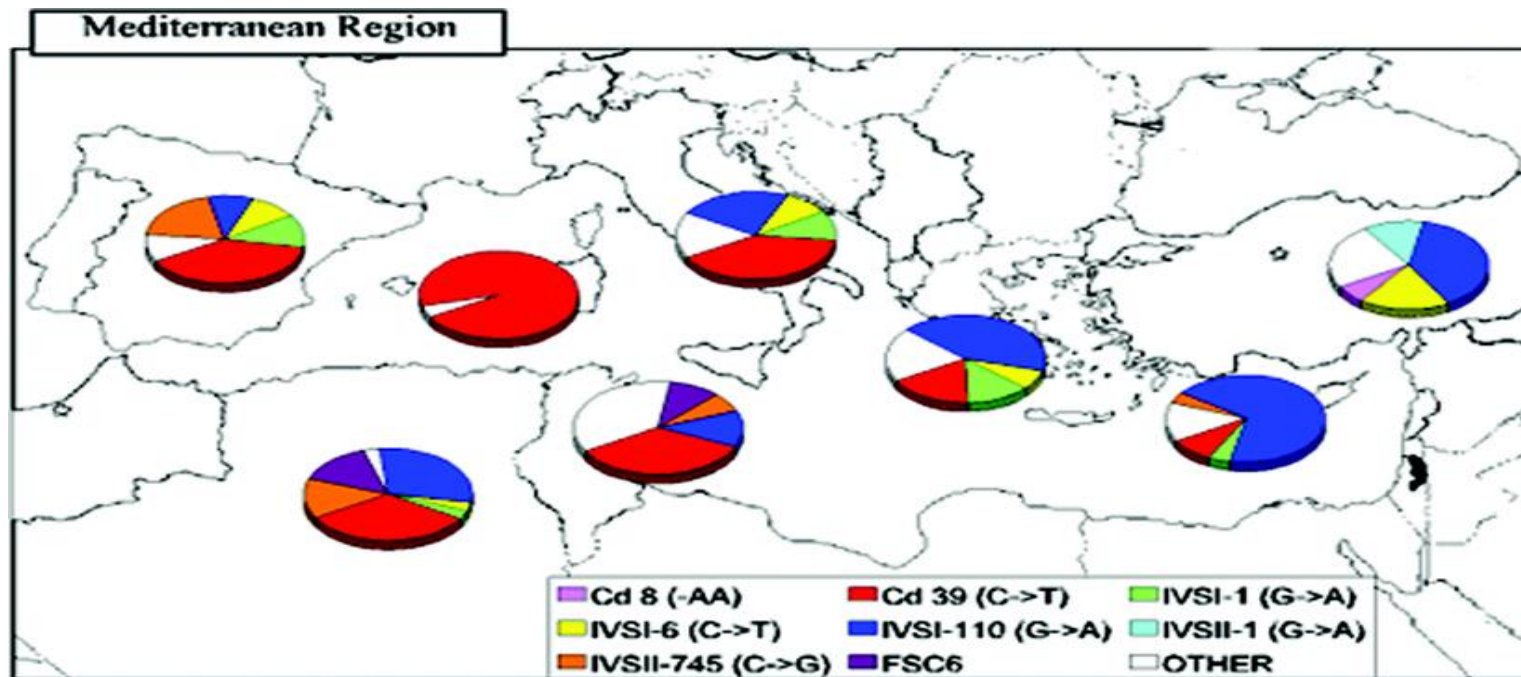
Located on chromosome 11

Point mutations

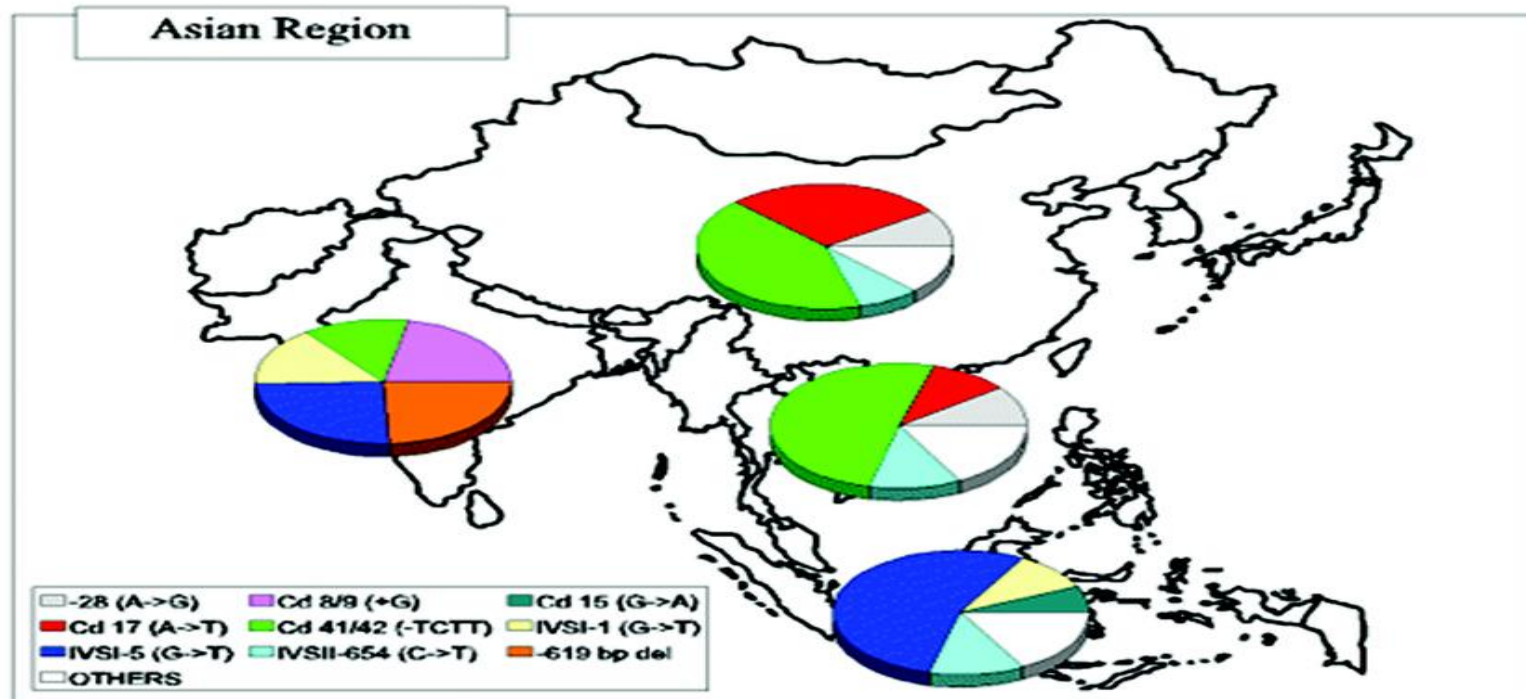
Population specific mutations



Beta Thalassemia Mutations



Beta Thalassaemia Mutations



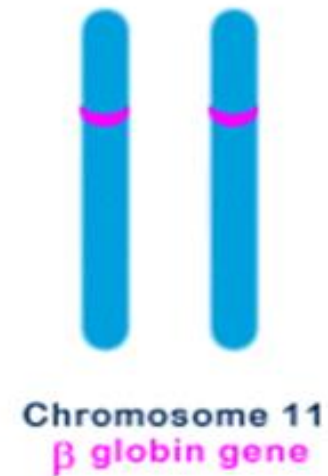
BETA THALASSEMIA

2 GENES - **Thalassemia Major**

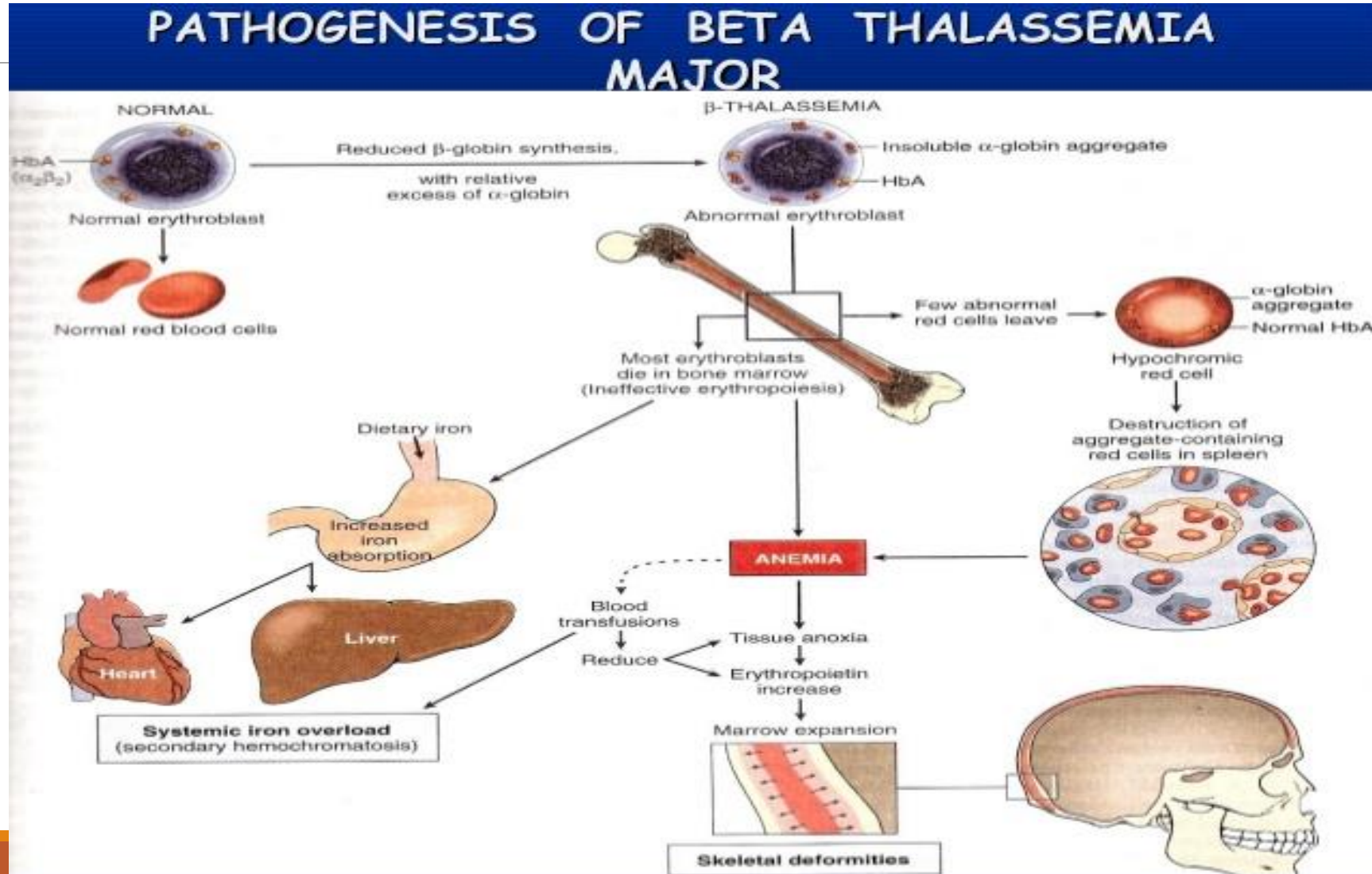
- Homozygous
- Compound heterozygous (thalassemia intermedia)

1 GENE - **Thalassemia Minor**

- Heterozygous



PATHOGENESIS



Facial appearance



© Elsevier, Nussbaum et al: Thompson and Thompson's Genetics in Medicine 7e - www.studentconsult.com

General view



Skull X-Ray



LABORATORY

COMPLETE BLOOD COUNT

- Severe anemia (Hb 2-3 gr/dl)
- Peripheral smear-anisopoikilocytosis

BONE MARROW

- Erythroid hyperplasia

HEMOGLOBIN ELECTROPHORESIS

- Hb F ↑ (10-90%)
- Hb A absent
- Hb A2 N, ↓, ↑

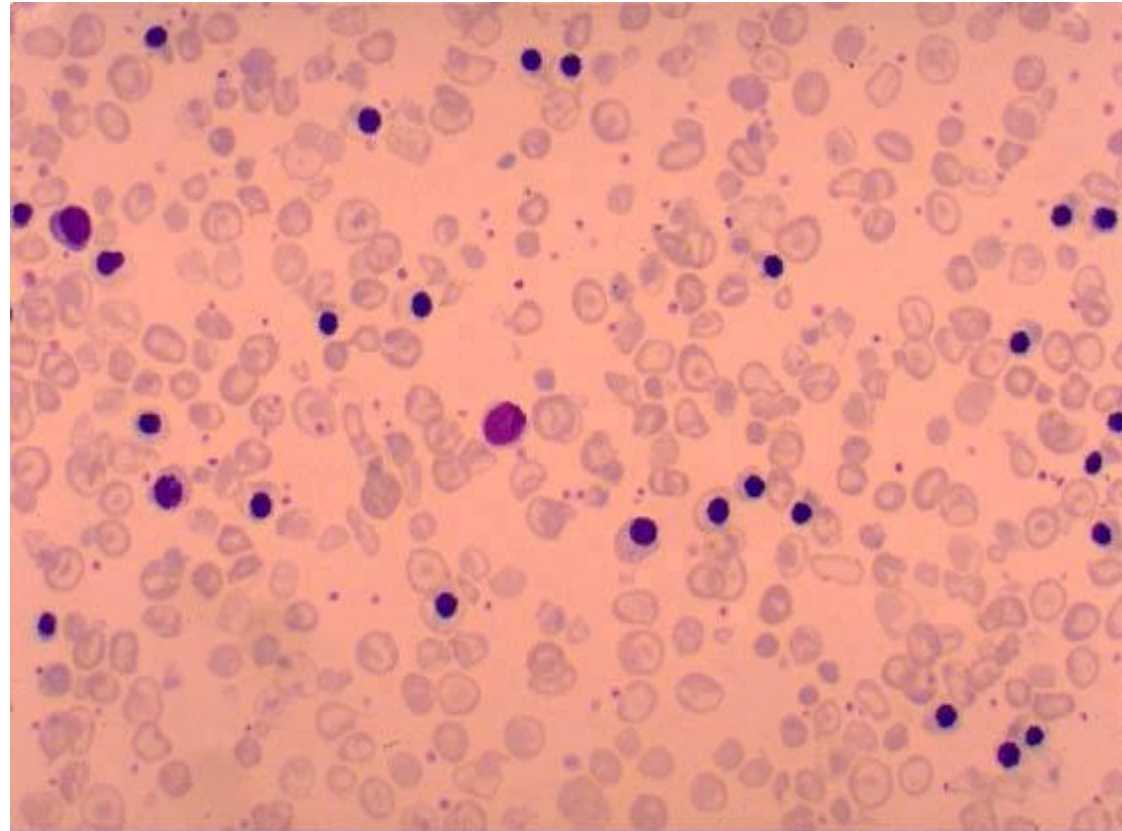
GLOBIN CHAIN ANALYSIS

- Alfa/beta ratio abnormal (↑)

MUTATION ANALYSIS

- Point mutations

Peripheral Smear



MANAGEMENT

1- Blood Transfusion

2- Iron Chelation

3- Splenectomy

4- Stem Cell Transplantation

Endocrine replacement

Immunisation

TRANSFUSION

Once a month

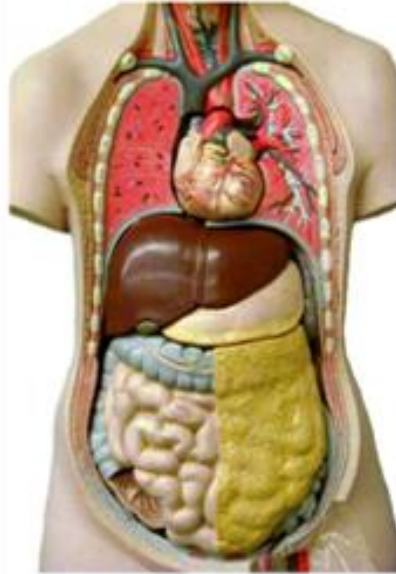
Red cell suspension
10 ml/kg

Hb before – after transfusion
(9 – 12 gr/dl)



Iron Overload (Hemochromatosis)

Demir yüklenmesine baęlı organ hasarı



Klinik

- Pituiter → Büyüme bozukluğu
- Kalp → Kardiyomyopati, kalp yetmezlięi
- Karacięer → Siroz
- Pankreas → Diabetes Mellitus
- Gonadlar → hipogonadizm, infertilite

Courtesy of Dr. M. D. Cappellini.

Evaluation of Iron Overload

1-Serum ferritin level*

2-Marrow iron assesement (marrow aspiration)

3-Hepatic iron assesement (liver biopsy)

4-Liver / Marrow CT/MRI (T2*)

IRON CHELATION

Desferal (DFO)

- Subcutaneous (SC) infusion
- 20-40 mg/kg
- Every day of a week
- Nightly infusion for 8-12 hours
- With Vitamin C (ascorbic acid)

Weak compliance!

Expensive!

Desferal Pump



Other Chelation Agents

Ferriprox (deferiprone)

Exjade (deferasirox)

Fuarte

Defroni

Side effects (Agranulocytosis, neutropenia, GI symptoms)

EXJADE

Per oral (PO)
After 2 years of age
20 mg/kg/day



Exjade-Tabletten

125 mg



250 mg



500 mg



Tabletten nicht in tatsächlicher Grösse abgebildet

SPLENECTOMY

When blood requirement is increased

- 200 ml/kg/year ↑

After the age of 5

Immunisation



BTM child, X15 spleen

STEM CELL TRANSPLANTATION

Curative

80 % success rate

- HLA-matched donor
 - Only 10% of patients!
- Before 16-year of age
- Hepatomegaly absent

ENDOCRINE THERAPY

Replacement of deficient hormone

Diabetes therapy

IMMUNISATION

Hepatit B



BETA THALASSEMIA INTERMEDIA

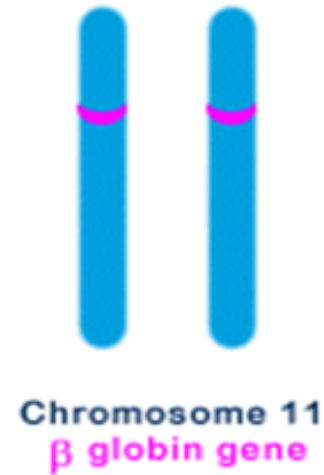
Compound heterozygosity

Clinical phenotype moderate

No need for regular transfusion

Iron overload may develop

- Increased intestinal absorption



BETA THALASSEMIA MINOR

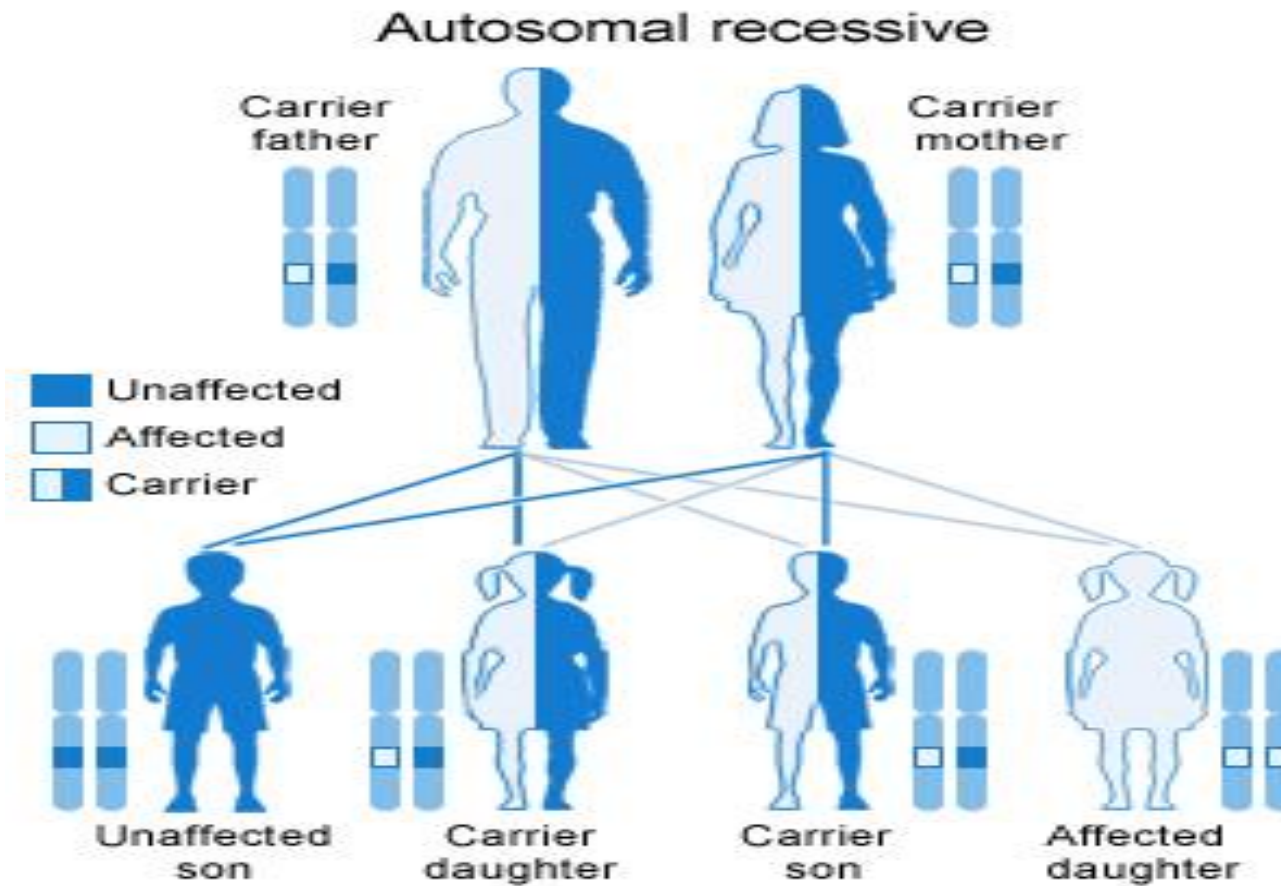
No symptoms

Microcytosis on CBC (MCV 80 fl ↓)

Hemoglobin electrophoresis Hb A2 ↑ (%3.5 and above)



Genetic Counseling



U.S. National Library of Medicine

BETA THALASEMIA PRENATAL DIAGNOSIS

1-CHORDOSYNTHESIS

Cord blood (globin chain synthesis)

Delayed diagnosis

2-CHORIONIC VILLUS SAMPLING (CVS)

Amniosynthesis (DNA analysis)

Early diagnosis

Pre-Implantation Genetic Diagnosis (PGD)

Looking for the genetic alterations that affect a particular gene, one can avoid the transmission of diseases such as cystic fibrosis, thalassemia or muscular dystrophy, among others.

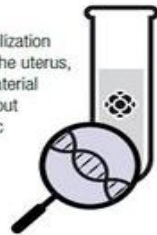


Chromosomal alterations affect either the number or the structure of chromosomes. This technique allows their detection as well as the detection of other alterations, such as, Turner and Down syndromes.



A Genetic study

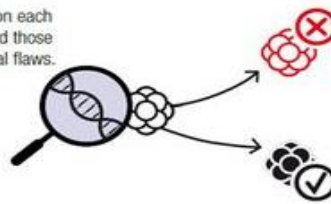
Following the in vitro fertilization and before transfer into the uterus, a study of the genetic material of the embryo is carried out to detect possible genetic defects.



It is performed when the embryos are between 6 and 8 cells, usually on day 3 of development.

B Embryo Biopsy

A biopsy is performed on each of the embryo to discard those with concrete congenital flaws.



C Embryo transfer

From 1 to 3 healthy embryos are transferred.



The embryos that are not transferred can be frozen.

GENE THERAPY

Experimental level...

ALPHA THALASEMIA

Alpha globin chain synthesis disturbed

Alpha globin gene **deletion**

4 genes

Chromosome 16

Clinical phenotype variability



GENOTYPE-CLINICAL PHENOTYPE

α -thalassemia(genetic)

NO. OF GENES PRESENT	GENOTYPE	CLINICAL CLASSIFICATION
4 genes	$\alpha\alpha/\alpha\alpha$	Normal
3 genes	$\alpha\alpha/-\alpha$	Silent carrier
2 genes	$-\alpha/-\alpha$ or $\alpha\alpha/-$ $-$	α thalassemia trait
1 gene	$-\alpha/-$ $-$	Hb H Ds
0 genes	$- -/-$ $-$	Hb Barts / Hydrops fetalis

HYDROPS FETALIS 4 alpha globin genes deleted



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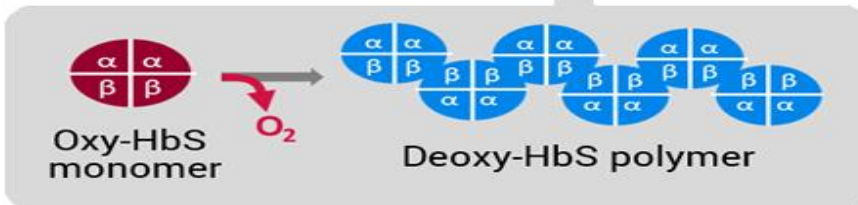
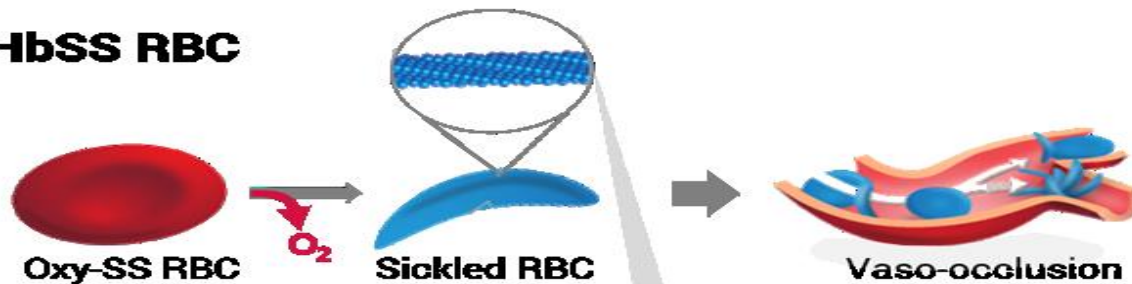
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SICKLE CELL ANEMIA (SCA)

Normal RBC



HbSS RBC



Hb S synthesis

Result of the substitution of valine for glutamic acid at position 6 in the beta chain

Sensitive to hypoxia

Strong tendency to aggregate in a highly ordered fashion, resulting in multiple microtubules arranged in helical form

Deforms red cell into a variety of rigid shapes, including the classical sickle shape

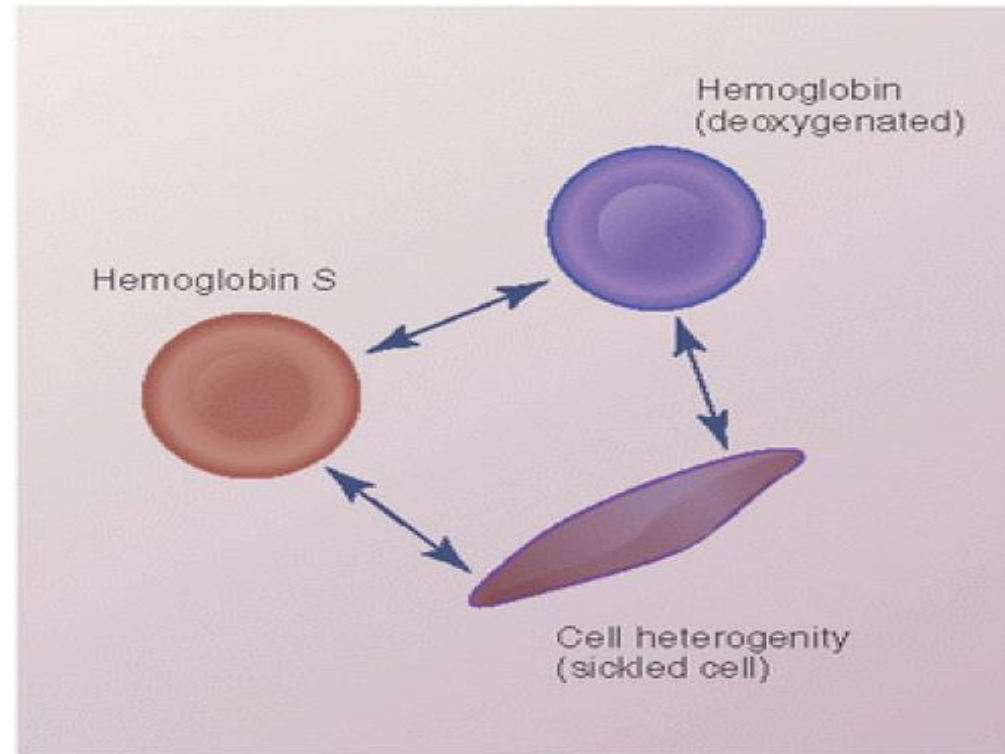
Blood viscosity $\uparrow$, vascular stasis, tissue damage:

Pain

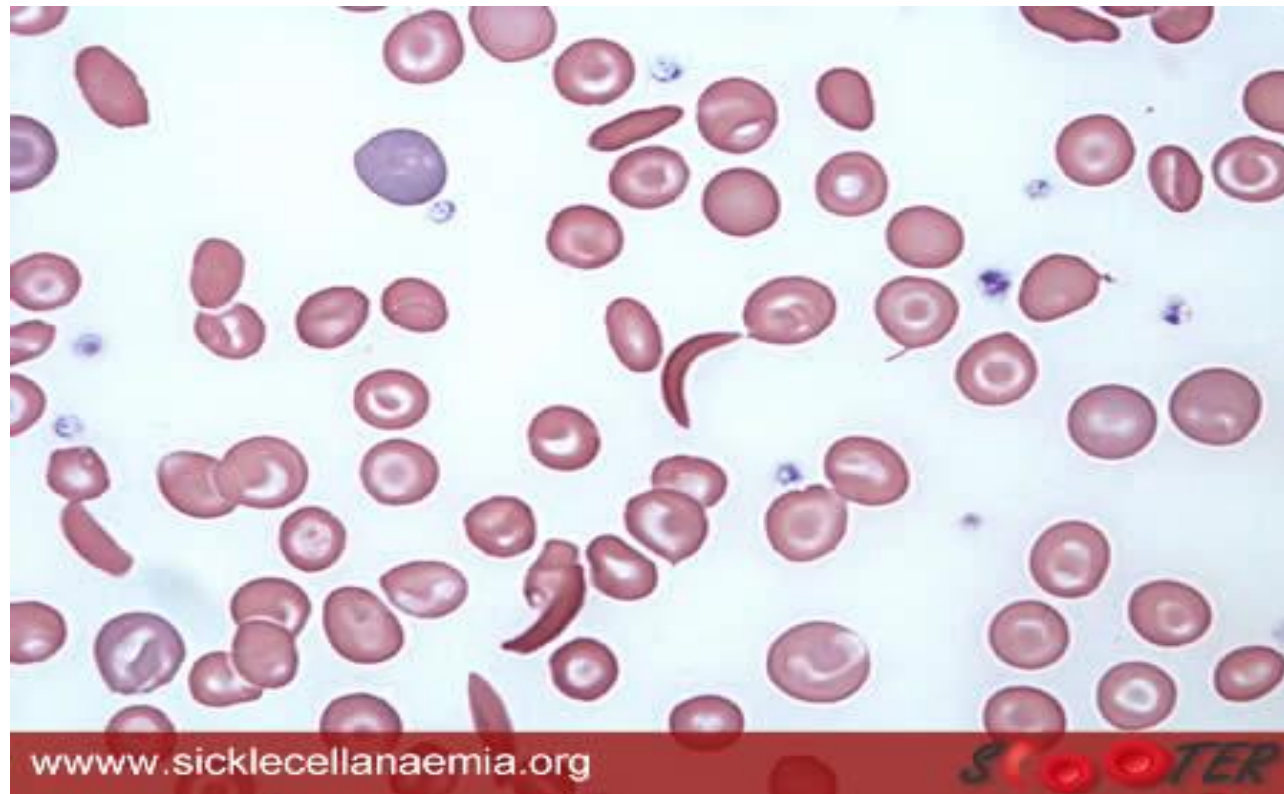
When a cell sickles and unsickles repeatedly, irreversible membrane damage occurs, cell is destroyed:

Anemia

Sickling process



SCA (peripheral smear) - sickle shape



SCA - Complications

Acute chest syndrome

Organ failures

- Kidneys (medullar hypoxia, papillary necrosis, hypostenuria)

Cholelithiasis

Hand-Foot syndrome

Pulmonary hypertension

Stroke and eye complications

Priapism

Autosplenectomy

SCA - Symptoms



SCA - Hand-Foot Syndrome



SCA - CRISES

Vaso-occlusive or painful crises

Sequestration crises

Aplastic crises

Hemolytic crises (?)

SCA – Precipitating Factors

Hypoxia

Dehydration

Infection

Cold

Altitude

Exercise

SCA - WHEN SUSPECTED?

Unexplained pain and swelling (esp. in hands and feet)

Pneumonia

Menengitidis

Sepsis

Neurological findings

Splenomegaly

Anemia

SCA - DIAGNOSIS

Sickling test (screening test)

Peripheral smear

Hemoglobin electrophoresis

Mutation analysis

SCA - MANAGEMENT

Prophylaxis

Pain management

Reducing abnormal hemoglobin (Hb S)

Stem cell transplantation

PROPHYLAXIS

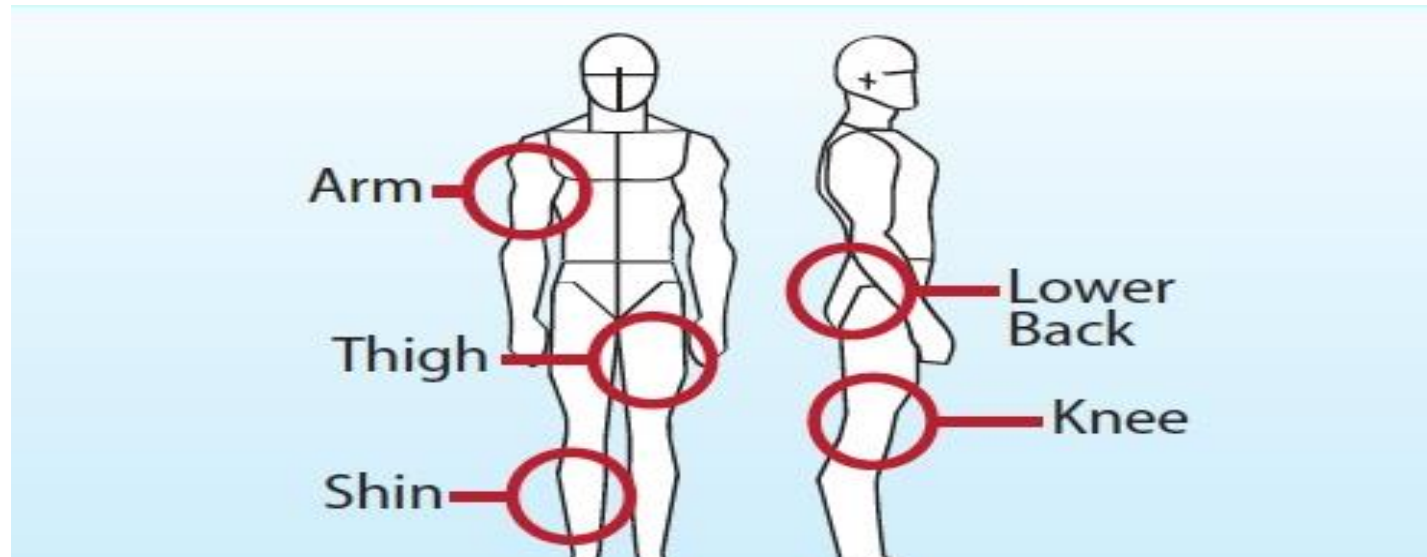
- To avoid the precipitating factors
 - Dehydration
 - Hypoxia
 - Infection
 - Cold
 - Altitude
 - Exercise

ANALGESIA Drug Addiction!

Mild - Acetaminofen, NSAID+Opioid

Moderate - Sedative, anxiolytics

Severe - Morphin, Meperidine



REDUCING ABNORMAL HB S (30% ↓)

Blood transfusion

Exchange transfusion

Plasmapheresis (red cell exchange apheresis)

Hidroxyurea

Plasmapheresis



Hidroxyurea

Hb F↑

HbS ↓

Tissue oxygenisation↑

Inflammation ↓

- Crises ↓



STEM CELL TRANSPLANTATION

Severe cases

HLA matched donor 20%

Success rate ~100%

Family cord blood banking for sickle cell disease: a twenty-year experience in two dedicated public cord blood banks.

[Rafii H¹](#), [Bernaudin F²](#), [Rouard H³](#), [Vanneaux V⁴](#), [Ruggeri A⁵](#), [Cavazzana M⁶](#), [Gauthereau V⁷](#), [Stanislas A⁸](#), [Benkerrou M⁹](#), [De Montalembert M¹⁰](#), [Ferry C¹¹](#), [Giot R¹²](#), [Arnaud C¹³](#), [Kamdem A¹⁴](#), [Gour J¹⁵](#), [Touboul C¹⁶](#), [Cras A¹⁷](#), [Kuentz M¹⁸](#), [Rieux C¹⁹](#), [Vot F²⁰](#), [Cappelli B²¹](#), [Maio KT²²](#), [Paviglianiti A²⁰](#), [Kenzey C²⁰](#), [Larghero J²³](#), [Gluckman E²⁴](#).

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Bone Marrow as a Hematopoietic Stem Cell Source for Gene Therapy in Sickle Cell Disease: Evidence from Rhesus and SCD Patients.

[Uchida N¹](#), [Fujita A¹](#), [Hsieh MM¹](#), [Bonifacino AC²](#), [Krouse AE²](#), [Metzger ME²](#), [Donahue RE²](#), [Tisdale JF¹](#).

 **Author information**

SICKLE CELL TRAIT

Hb S 30%

No crisis in normal conditions

- Only severe hypoxia/infection can precipitate crisis

Normally shaped red cells on smear

No anemia

OTHER ABNORMAL HEMOGLOBINS Hb variants

Hb C *Beta 6 Glu>Lys*

Hb D *Beta 121 Glu<Gln*

Hb E *Beta 26 Glu>Lys*

S-C

S-D

S-E

SUPPORT GROUPS



Northern California
Comprehensive Thalassemia Center



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