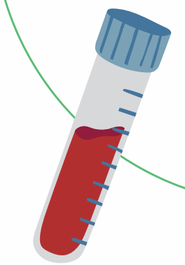
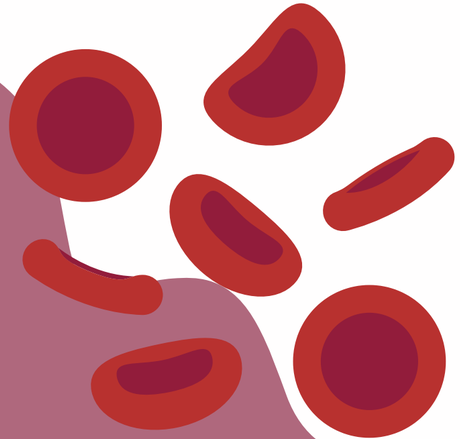
South West
Haemoglobinopathy
Coordinating Centre



HAEMOGLOBINOPATHIES FOR GENERAL PRACTICE

Dr Amy Cooper

Haemoglobinopathy QI Fellow



South West Haemoglobinopathy Coordinating Centre

Today we will cover

What are haemoglobinopathies?

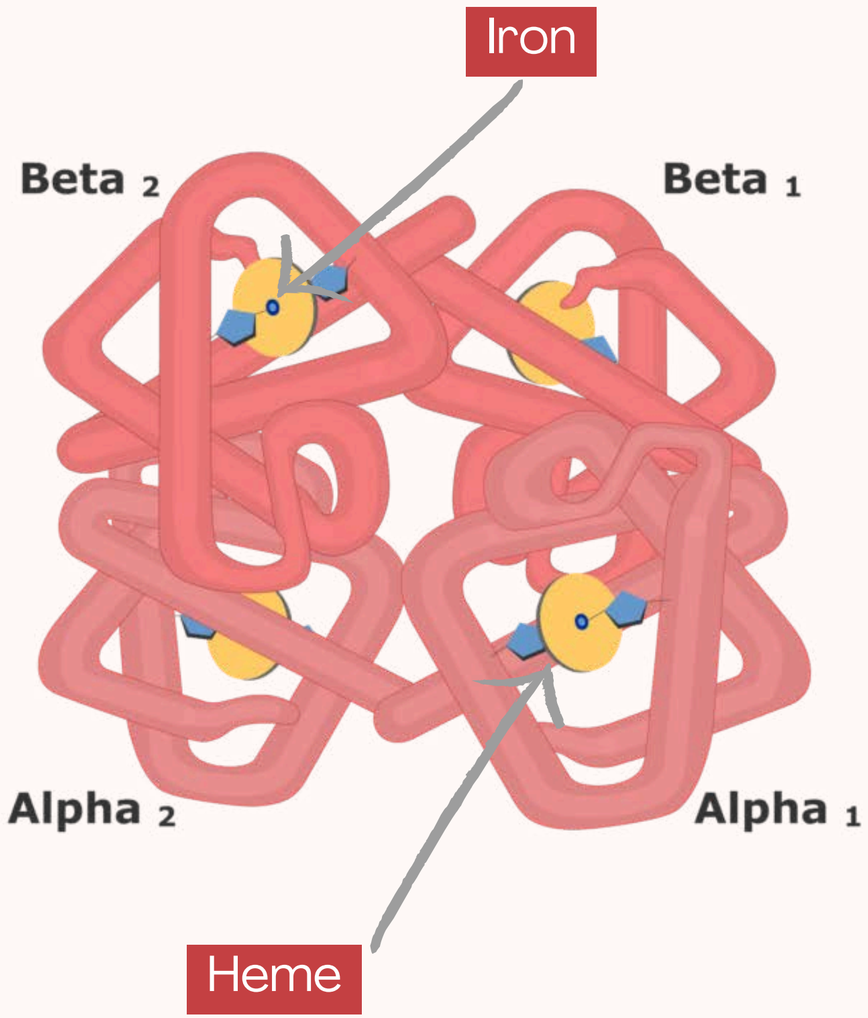
- Basic science underlying conditions
- How to apply this knowledge in understanding the diagnosis and management of the conditions, including trait states
- Haemoglobinopathy screening
- Investigation of microcytosis
- Top things to know about sickle cell disease and thalassaemia

South West
Haemoglobinopathy
Coordinating Centre

HAEMOGLOBIN

- Consists of two alpha and two beta globin chains
- Heme sits inside the globin chain and holds one iron molecule (4 per haemoglobin)
- The iron molecule reversibly binds oxygen (allowing it to carry and give up the O2 molecule)

Reminder - this is what Hb measures!



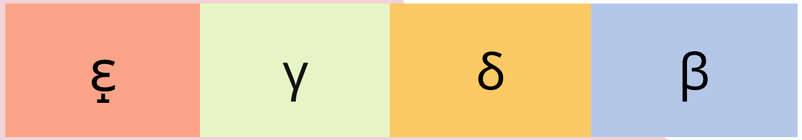
South West
Haemoglobinopathy
Coordinating Centre

NORMAL HAEMOGLOBIN SYNTHESIS

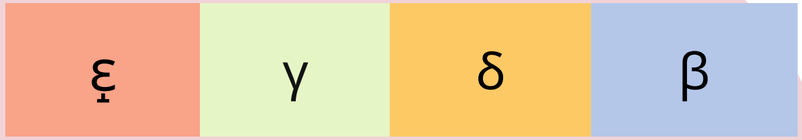
Chromosome 16

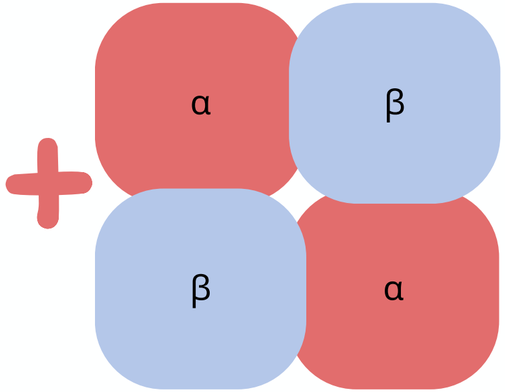
Chromosome 16

Chromosome 11

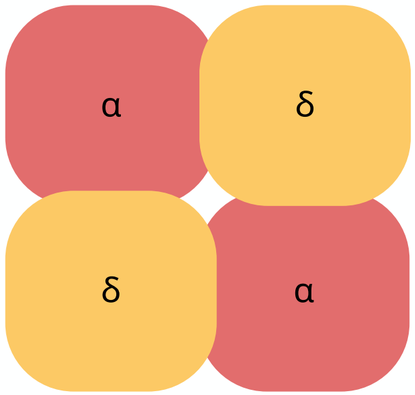


Chromosome 11

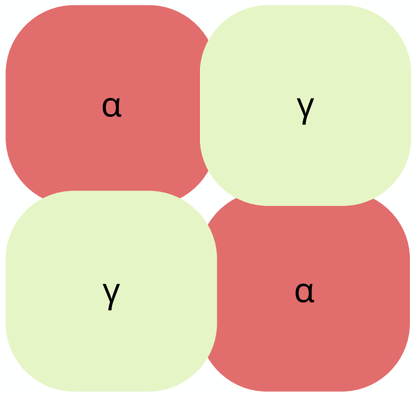




HbA

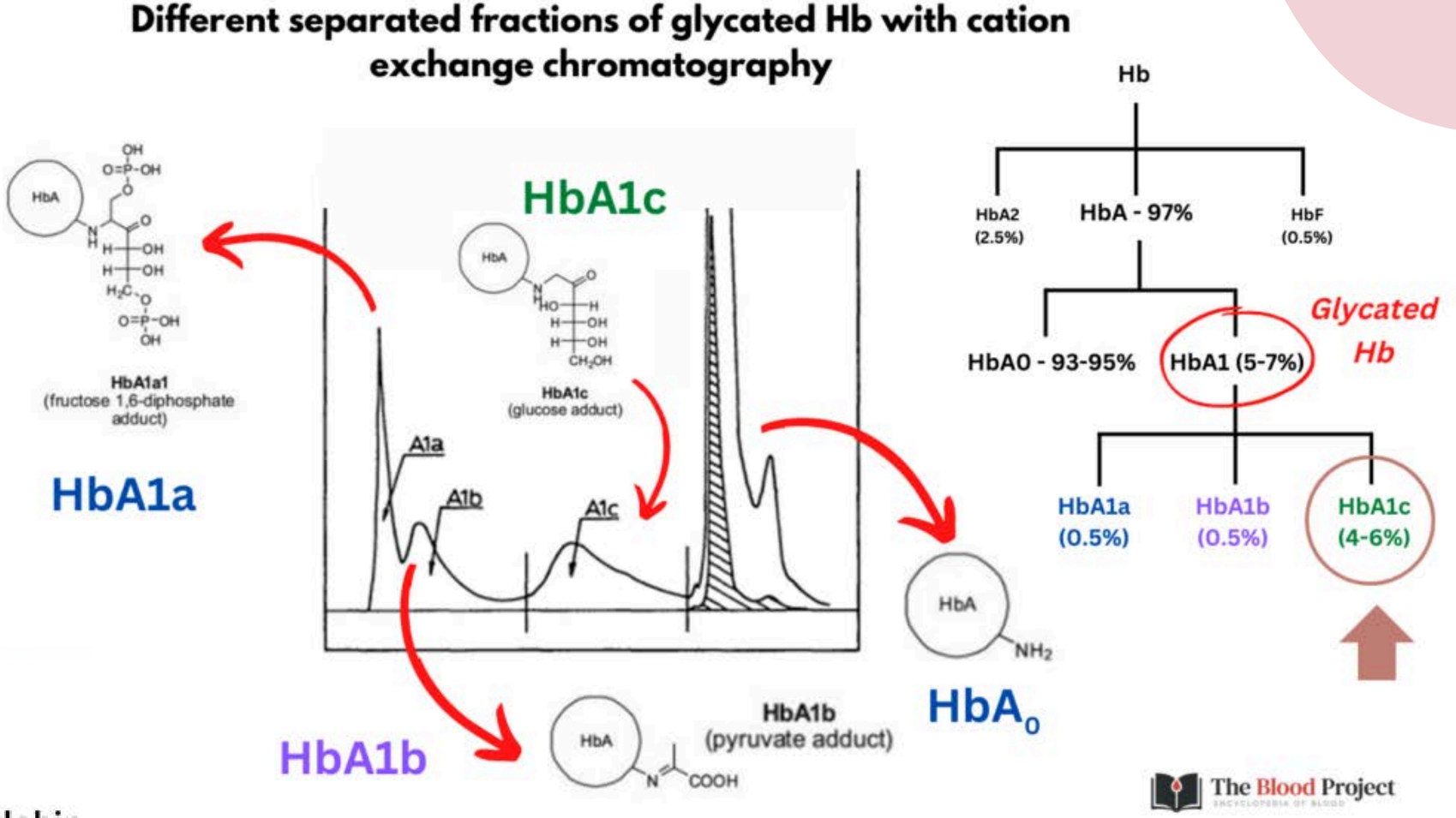


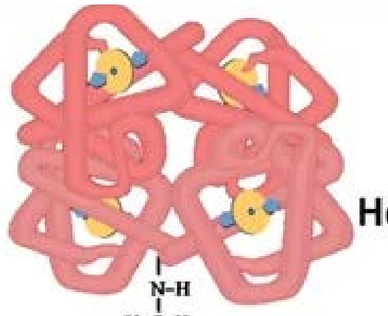
HbA2



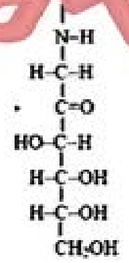
HbF

Normal values:
HbA 97%
HbF 1%
HbA2 2%





Hemoglobin

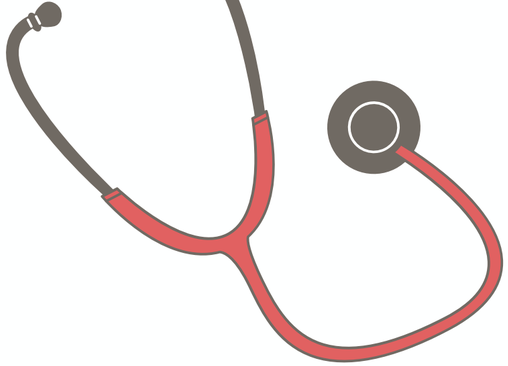


HbA1C

REMINDER: HBA1C

Fructosamine is more appropriate in transfusion-dependent patients

South West
Haemoglobinopathy
Coordinating Centre



HOW CAN HAEMOGLOBIN SYNTHESIS GO WRONG

Structural abnormalities

Haemoglobin is made, but the structure is different to normal haemoglobin due to a genetic mutation (usually affecting the beta gene). Examples include:

- HbS
- HbC

Abnormalities in haemoglobin production

Mutations in alpha or beta genes reduce the production in alpha or beta chains. This reduces the amount of normal haemoglobin. These conditions are called thalassaemias.

South West
Haemoglobinopathy
Coordinating Centre

HOW CAN HAEMOGLOBIN SYNTHESIS GO WRONG

Structural abnormalities

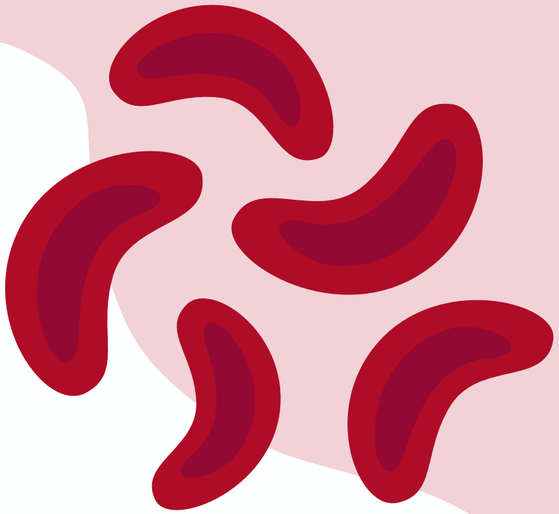
Haemoglobin is made, but the structure is different to normal haemoglobin due to a genetic mutation (usually affecting the beta gene). Examples include:

- HbS
- HbC

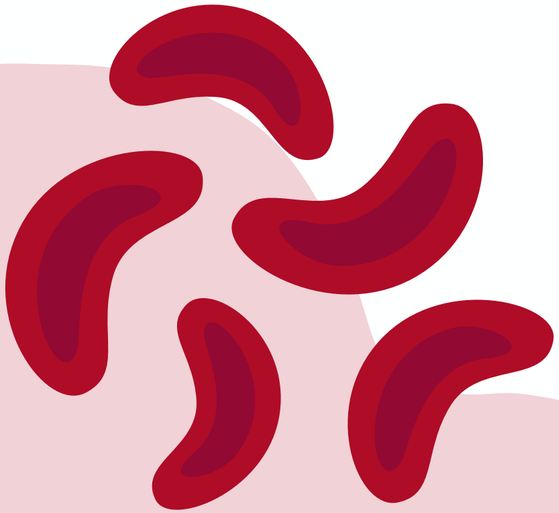
Abnormalities in haemoglobin production

Mutations in alpha or beta genes reduce the production in alpha or beta chains. This reduces the amount of normal haemoglobin. These conditions are called thalassaemias.

South West
Haemoglobinopathy
Coordinating Centre



Inheritance of variant haemoglobins

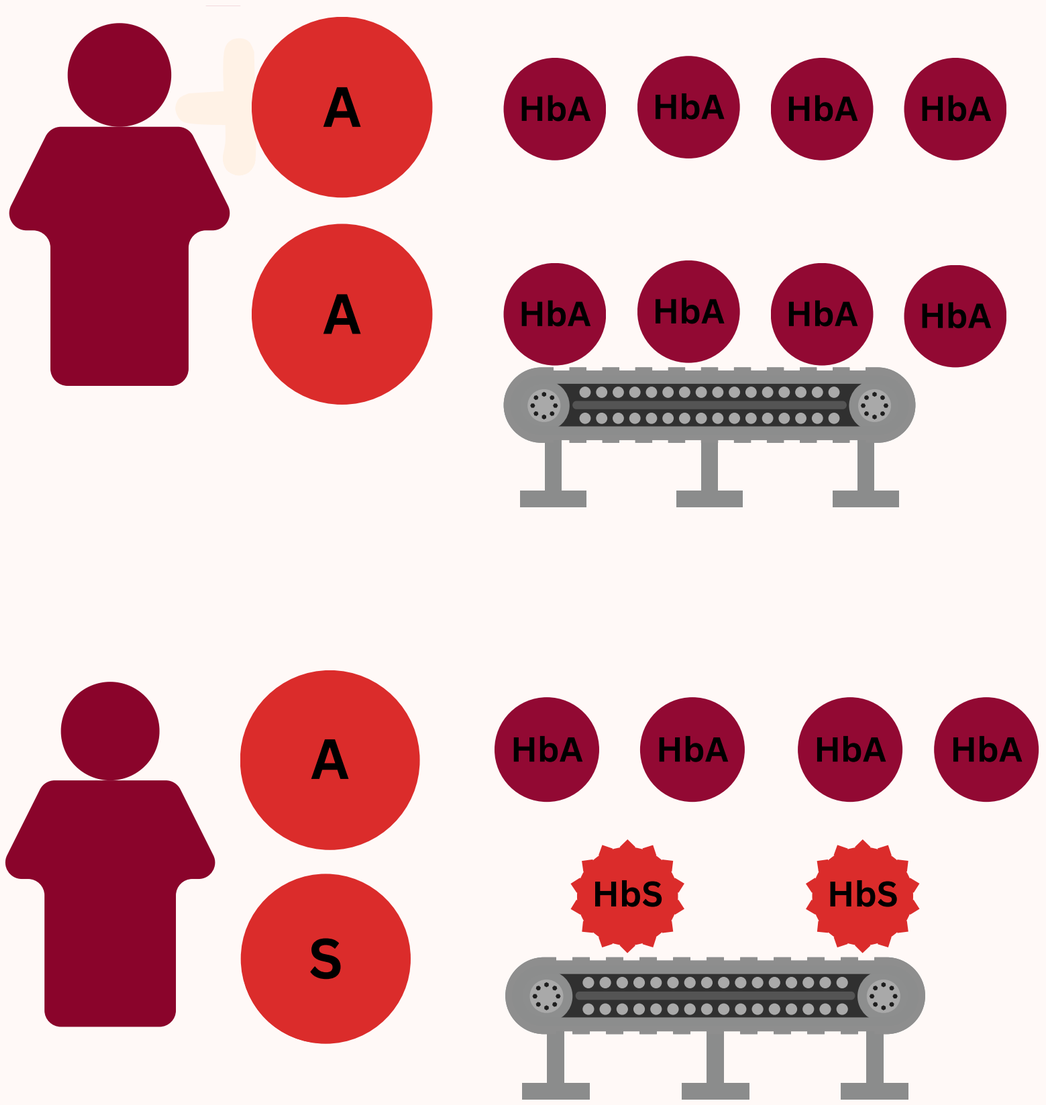


South West
Haemoglobinopathy
Coordinating Centre

IS TRAIT TRULY RECESSIVE?

- Inheritance of sickle cell disease is **autosomal recessive**

- The genes are **codominant**
- Both alleles are expressed independently, which means they both create haemoglobin



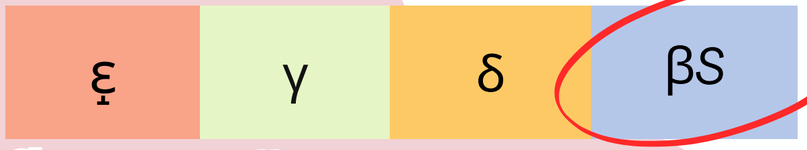
South West
Haemoglobinopathy
Coordinating Centre

SICKLE CELL TRAIT

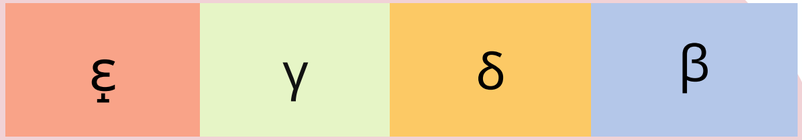
Chromosome 16

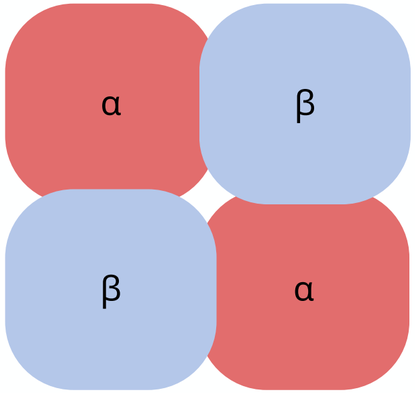
Chromosome 16

Chromosome 11

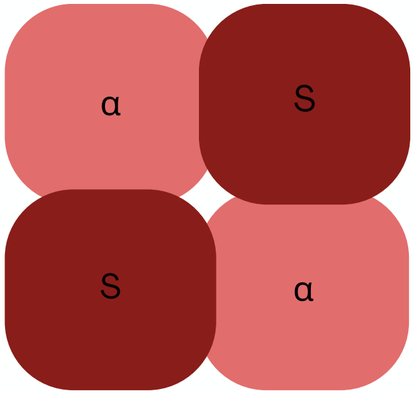


Chromosome 11

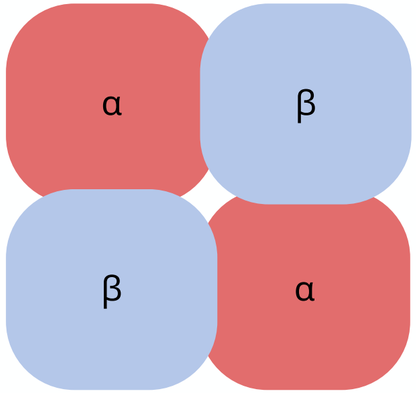




HbA



HbS



HbA

Translates to:
70% HbA
30% HbS
Normal haemoglobin
Normal MCV

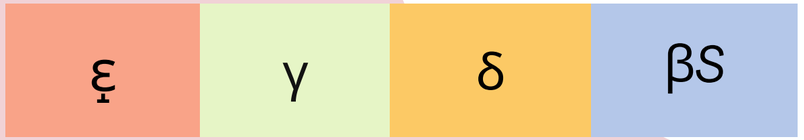
South West
Haemoglobinopathy
Coordinating Centre

HBSS SICKLE CELL DISEASE

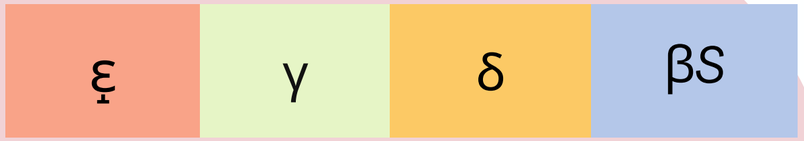
Chromosome 16

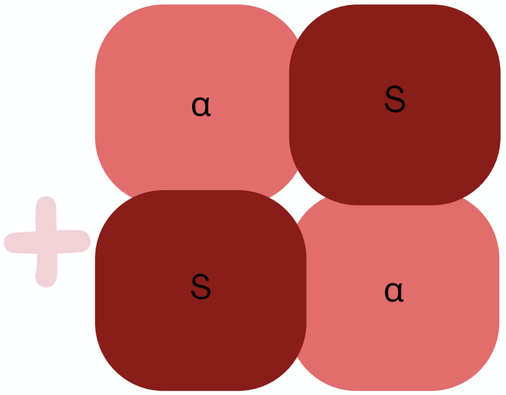
Chromosome 16

Chromosome 11

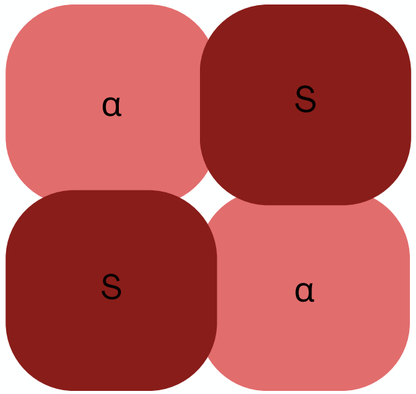


Chromosome 11

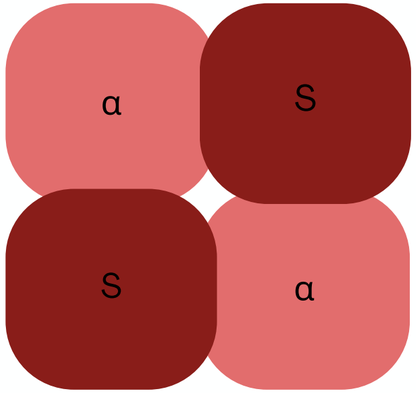




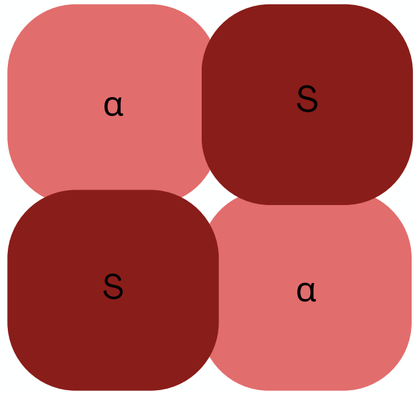
HbS



HbS



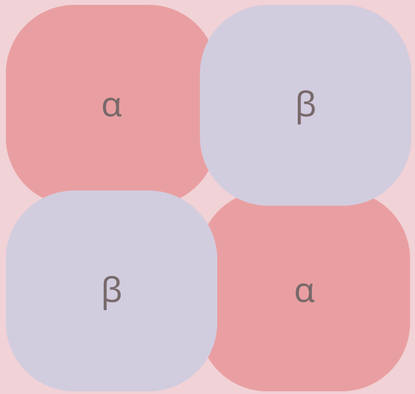
HbS



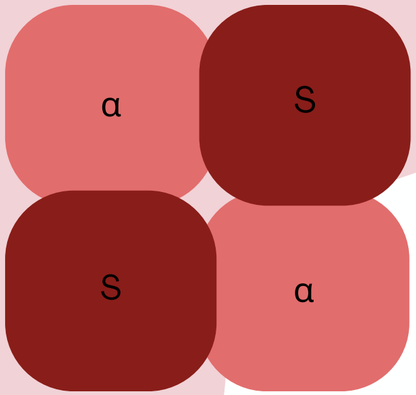
HbS

Results in around
90% HbS
Usual Hb 50-90

SICKLE CELL DISEASE (HBSS)

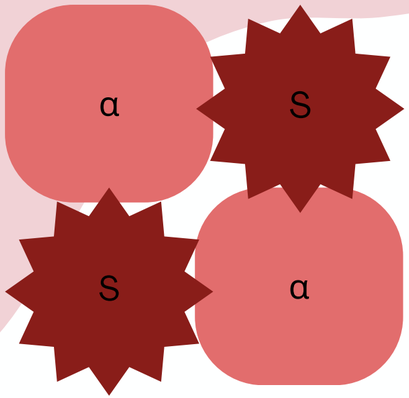


HbA

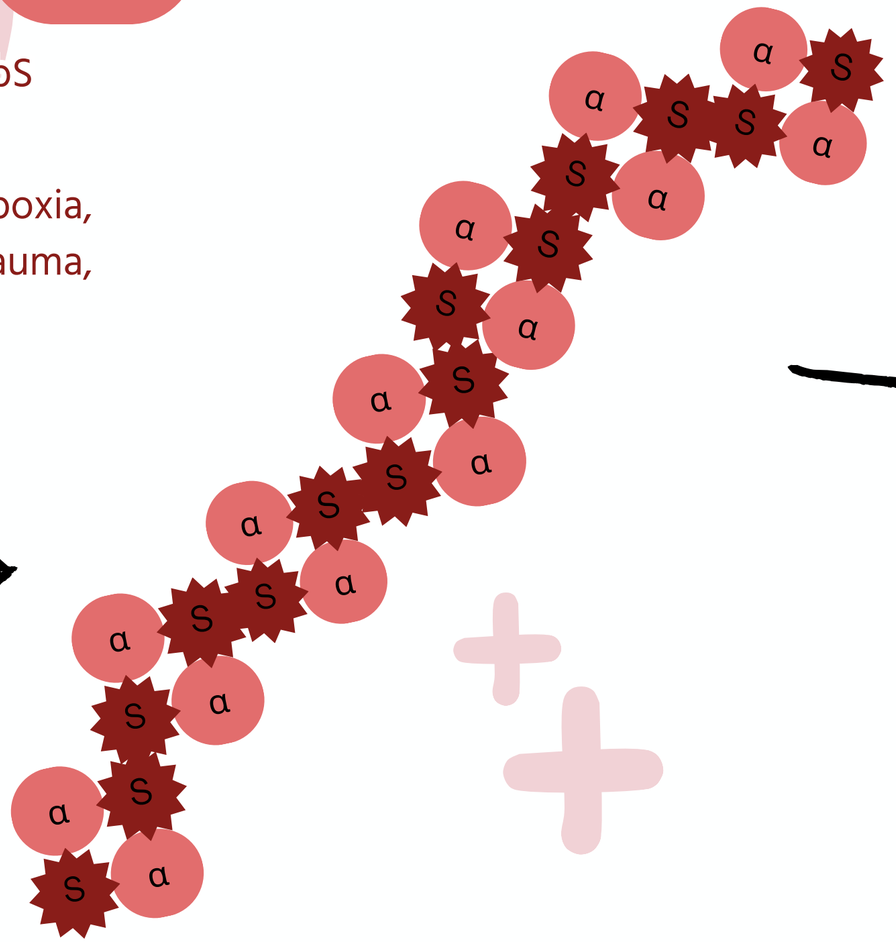


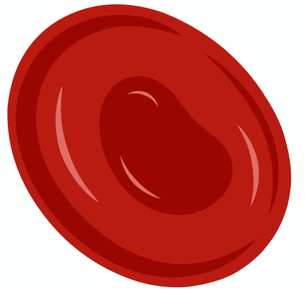
HbS

Stress (e.g. hypoxia, infection, trauma, cold exposure)



Polymerisation

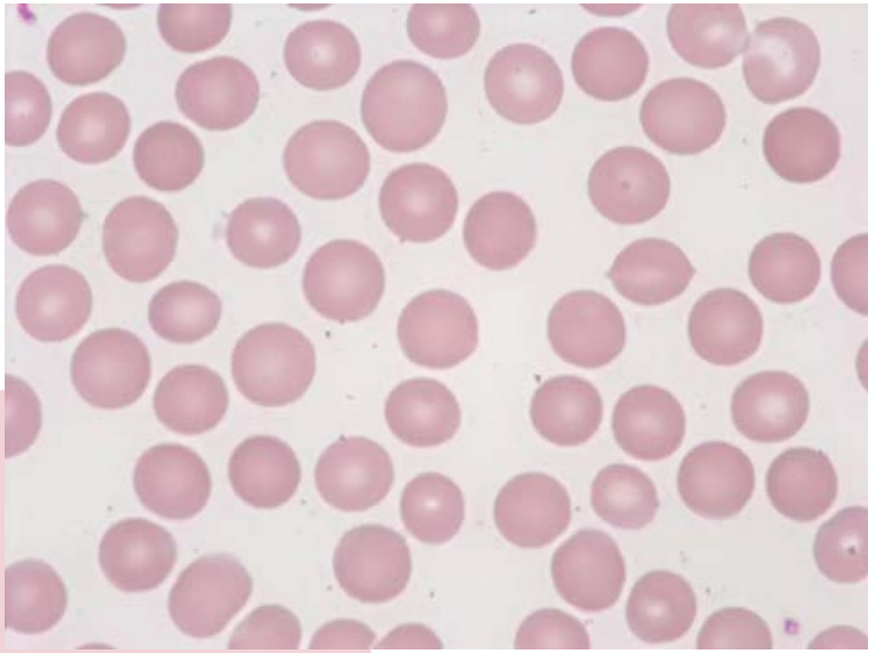




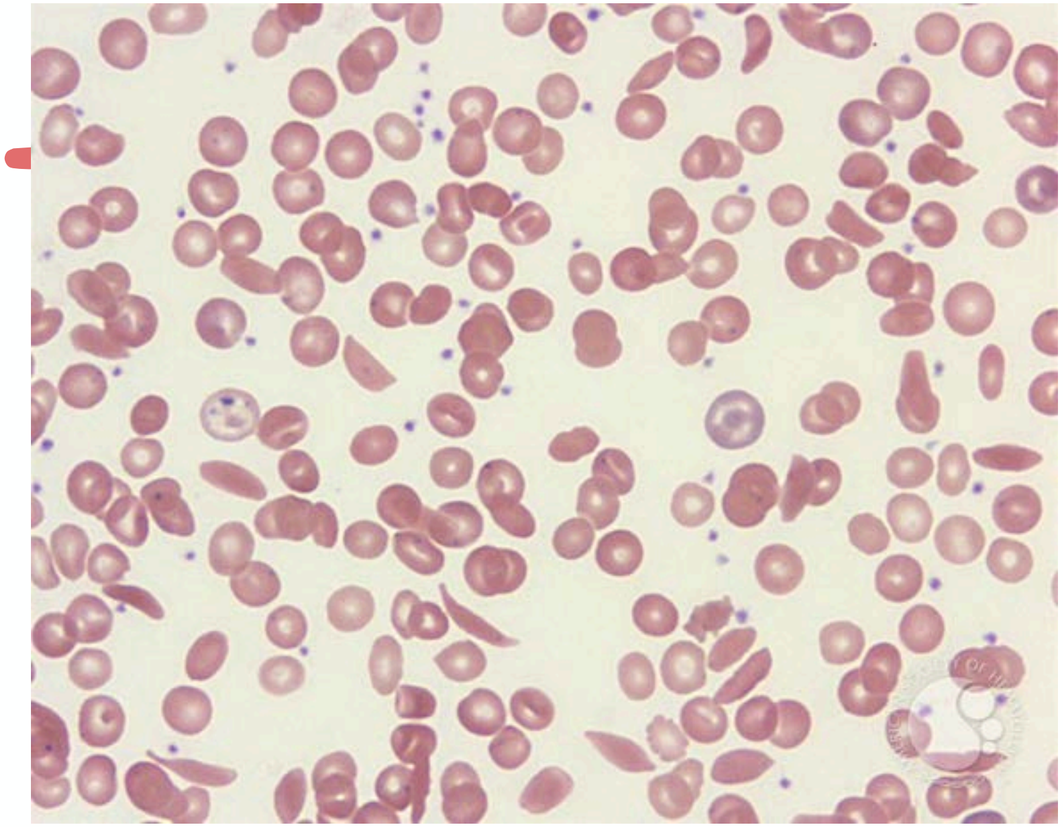
Sickling

South West
Haemoglobinopathy
Coordinating Centre

Low haemoglobin
Low RBC
Often normal MCV (unless co-existing thalassaemia trait - more on this later)



Normal



Sickle cell disease

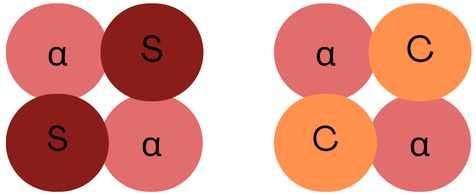
South West
Haemoglobinopathy
Coordinating Centre

OTHER TYPES OF SICKLE CELL DISEASE

Chromosome 11

Chromosome 11

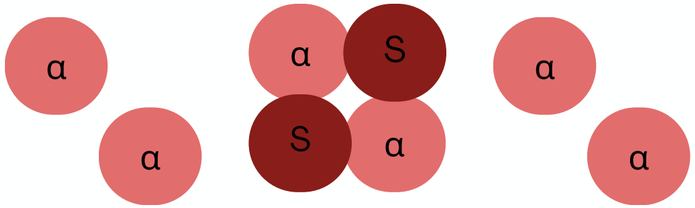
= HbSC disease



Chromosome 11

Chromosome 11

= HbS/beta thalassaemia



South West Haemoglobinopathy Coordinating Centre

When to test for haemoglobin variants

- At birth - heelprick test
- Family planning/antenatal - depending on results of family origin questionnaire (FOQ) (or universal testing in high prevalence areas)
- Pre-operative in at-risk ethnic groups
- At the request of the patient - e.g. premarital testing
- As an investigation of microcytosis, anaemia etc.

From BSH guideline

South West Haemoglobinopathy Coordinating Centre

Family origin questionnaire

Haemoglobin S	African including north African, African-Caribbean, African-American, black British and any other African ethnicity (e.g. central and south American of partly African ethnicity), Greeks, southern Italians including Sicilians, Turks, Arabs, Indians
Haemoglobin C	African including African-Caribbean, African-American, Black British and any other African ethnicity (e.g. Central and South American of partly African ethnicity)
α^0 thalassaemia	Chinese, Taiwanese, Southeast Asian (Thai, Laotian, Cambodian, Vietnamese, Myanmar, Malaysian, Singaporean, Indonesian, Filipino), Cypriot, Greek, Turkish and Sardinian
β thalassaemia	All ethnic groups other than Northern Europeans

From BSH guideline

South West
Haemoglobinopathy
Coordinating Centre

- 28 year old planning a family
- Moved to the UK from Nigeria 3 years ago
- Has been told that her mum is ‘AS’
- Requested a test to see if she is a carrier of sickle cell disease.

What tests do you request?

South West
Haemoglobinopathy
Coordinating Centre

- 28 year old planning a family
- Moved to the UK from Nigeria 3 years ago
- Has been told that her mum is ‘AS’
- Requested a test to see if she is a carrier of sickle cell disease.

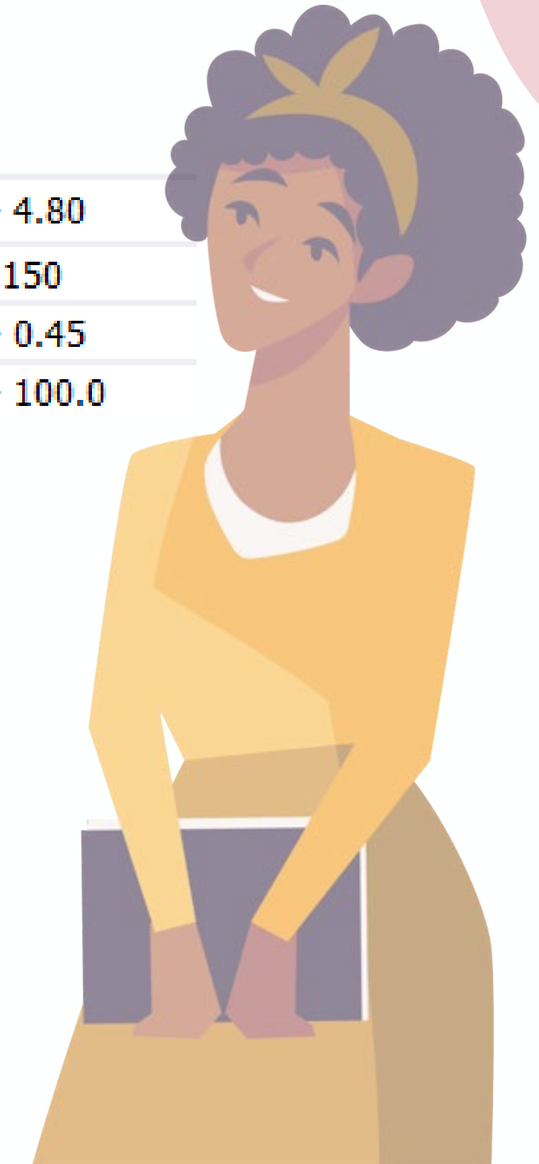
What tests do you request?

FBC

Haemoglobinopathy screen

South West
Haemoglobinopathy
Coordinating Centre

RBC		4.46	10^{12}/L	3.80 - 4.80
Hb		120	g/L	120 - 150
Hct		0.38	L/L	0.37 - 0.45
MCV		84.5	fL	83.0 - 100.0



South West
Haemoglobinopathy
Coordinating Centre

SICKLE SCREEN

Sickle screen	*

Positive

Please note, a negative test does not exclude the presence of a low percentage of haemoglobin S.

Further testing by HPLC to follow.

South West
Haemoglobinopathy
Coordinating Centre

SICKLE SCREEN

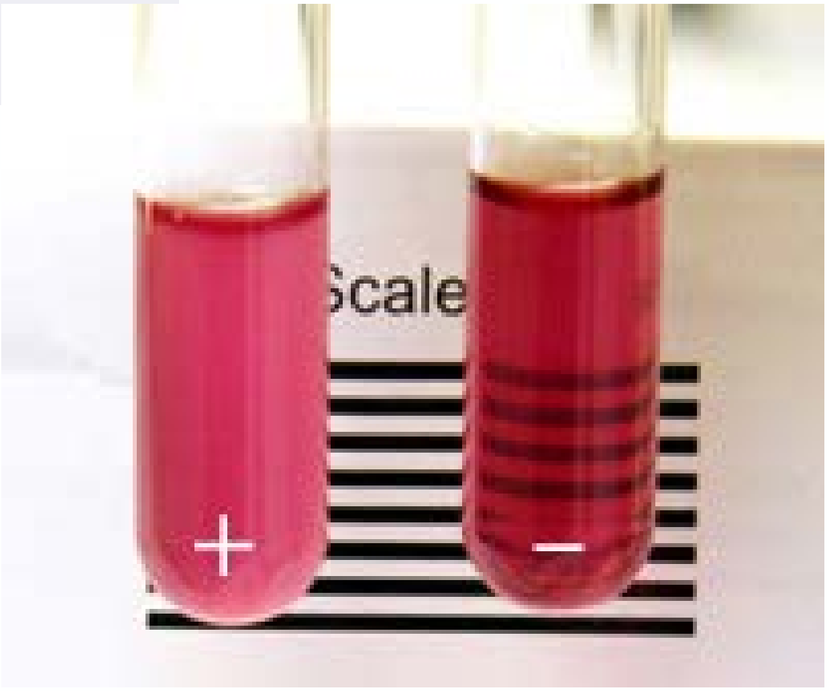
Sickle screen	*	

Positive

Please note, a negative test does not exclude the presence of a low percentage of haemoglobin S.

Further testing by HPLC to follow.

This is positive if there is any HbS present



South West
Haemoglobinopathy
Coordinating Centre

HAEMOGLOBIN ELECTROPHORESIS (HPLC-BIORAD)	
Hb A2 Quantitation	
HbA2 value unavailable due to the presence of an abnormal variant Hb	
Hb F Quantitation	
Haemoglobin	
MCH	
RBC	
MCV	
Haemoglobinopathy Comment	
Results consistent with Sickle Cell carrier (HbA + HbS). No evidence of thalassaemia.	

South West
Haemoglobinopathy
Coordinating Centre

WHAT NEXT?

1. Genetic testing to confirm sickle cell trait?
2. Partner testing?
3. Take transfusion history?
4. Inform patient?
5. Refer to haematology?

South West
Haemoglobinopathy
Coordinating Centre

WHAT NEXT?

Let’s organise partner testing....

South West
Haemoglobinopathy
Coordinating Centre

HbAA

HbAS

South West
Haemoglobinopathy
Coordinating Centre

0% chance of having a child with sickle cell disease

(50% chance of being a carrier)

HbAA

HbAS

South West
Haemoglobinopathy
Coordinating Centre

HbAS

HbAS

South West
Haemoglobinopathy
Coordinating Centre

25% chance of having a child with sickle cell disease

(50% chance of being a carrier, 25% chance unaffected)

HbAS

HbAS

South West
Haemoglobinopathy
Coordinating Centre

HbSS

HbAS

South West
Haemoglobinopathy
Coordinating Centre

50% chance of having a child with sickle cell disease

(50% chance of being a carrier)

HbSS

HbAS

South West
Haemoglobinopathy
Coordinating Centre

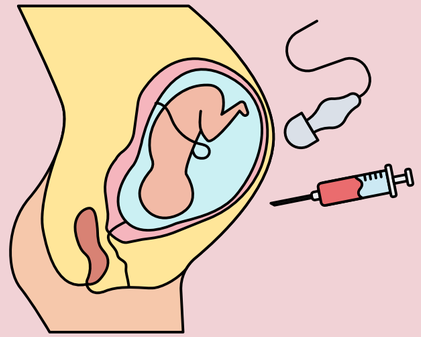
50% chance of having a child with sickle cell disease

(50% chance of being a carrier)

HbSS

HbAS

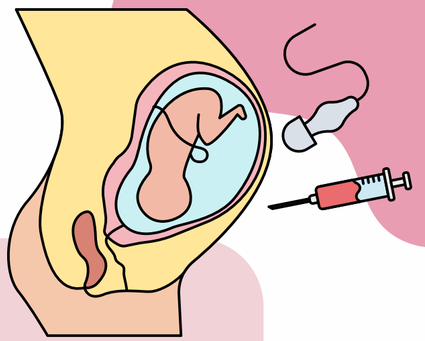
South West
Haemoglobinopathy
Coordinating Centre



Question: what can we do about the risk of having a child with HbSS?

South West Haemoglobinopathy Coordinating Centre

Options - genetic counselling



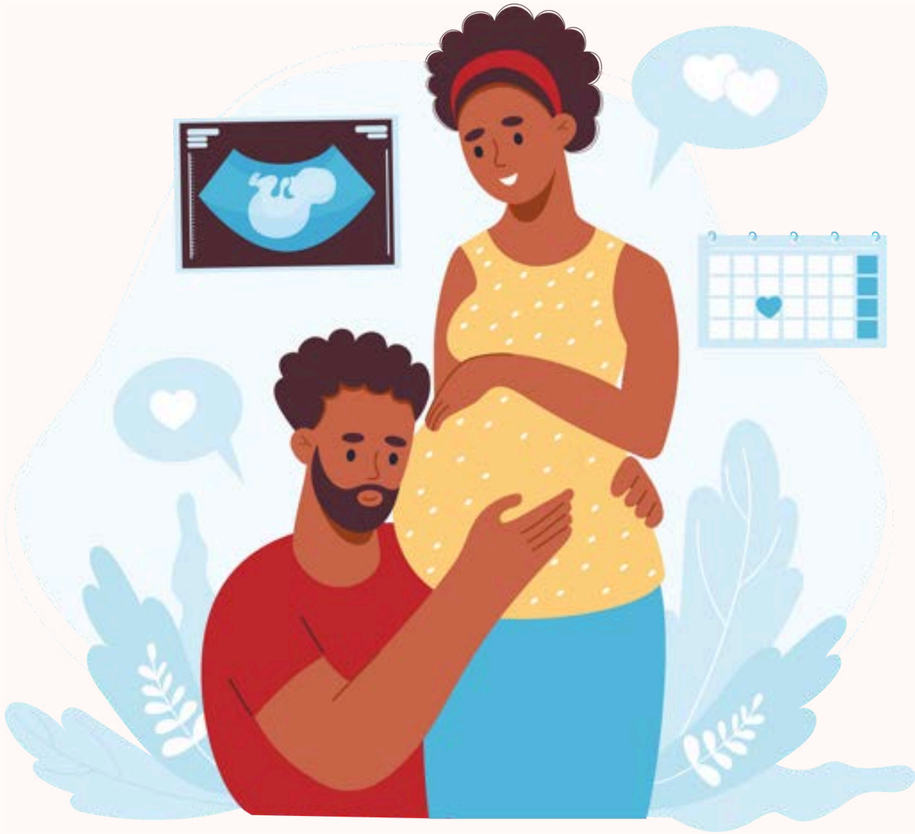
- Remain childless
- Consider adoption
- Gamete donation (one or both parents would not be the biological parent, uses assisted conception techniques)
- Conceive naturally, accepting the risk of the child being born with HbSS
- Conceive naturally with pre-natal diagnosis and have TOP as an option if the fetus is affected
  - Amniocentesis between 15-20 weeks
  - Chorionic villus sampling after 10 weeks
- Pre-implantation genetic diagnosis (PGD)

Reference: https://www.england.nhs.uk/wp-content/uploads/2013/04/e01-p-a.pdf

South West Haemoglobinopathy Coordinating Centre

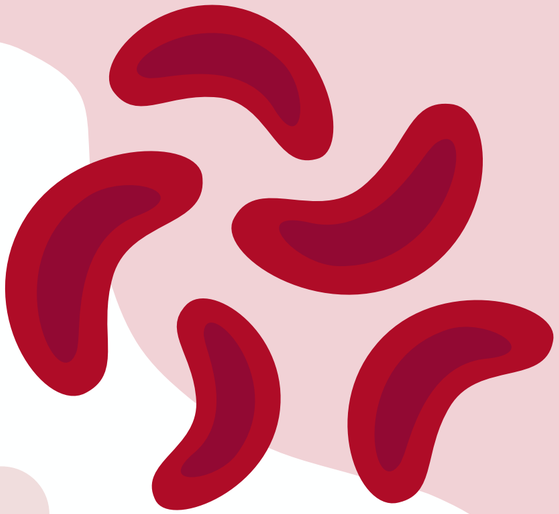
PRE-IMPLANTATION GENETIC DIAGNOSIS (PGD)

- Utilises IVF to select an unaffected embryo
- Available for any genetic condition which is at a 10% or higher risk of being inherited (HbSS at least 25%)
- Inclusion criteria extensive, including:
  - Female partner under age of 40
  - Female BMI between 20-30
  - Both partners must be non-smokers
  - No living unaffected children
- Eligible couples will be offered 3 cycles

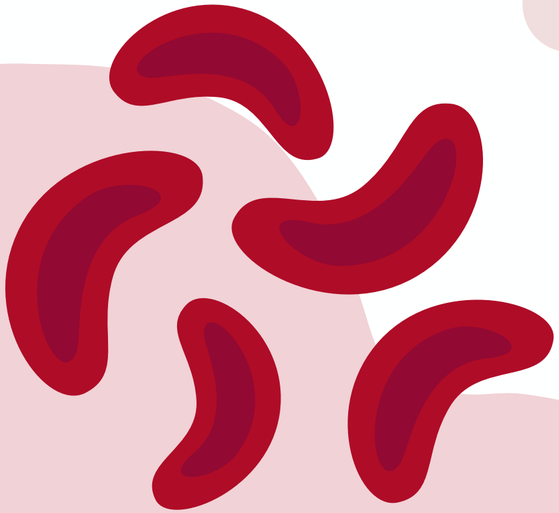


Refer to clinical genetics to access

South West
Haemoglobinopathy
Coordinating Centre



Quick facts about sickle cell disease



South West
Haemoglobinopathy
Coordinating Centre

WHAT DO SICKLED CELLS DO IN THE BODY?

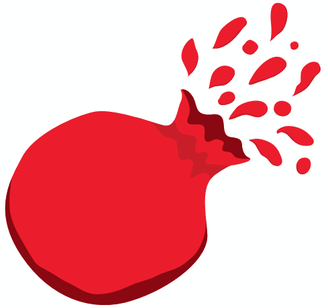
Vaso-occlusion

Sickled cells are rigid and non-deformable. They can get stuck in small vessels leading to ischaemia, organ damage and pain

Haemolysis

The abnormal sickled cells are destroyed through intravascular haemolysis. The lifespan of a sickle cell is around 10 days.

Haemolysis causes local vascular damage and promotes systemic inflammation



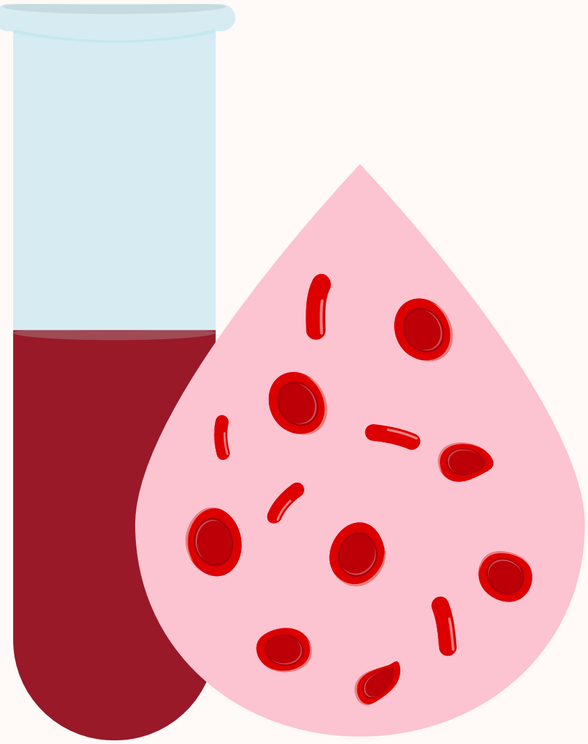
Regular folic acid supplementation supports red cell development in the setting of ongoing haemolysis

South West Haemoglobinopathy Coordinating Centre

A NOTE ON ANAEMIA

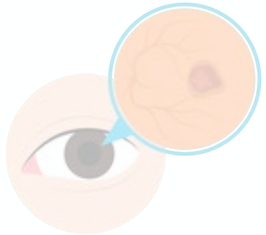
- Patients with sickle cell disease have been anaemic since birth
- Able to tolerate anaemia with minimal side effects
- Usual Hb can range from 50-90 with HbSS, and 90-130 with HbSC

Anaemia without symptoms does not usually require blood transfusion



South West
Haemoglobinopathy
Coordinating Centre

(SOME) CONSEQUENCES OF SICKLE CELL DISEASE



Sickle retinopathy

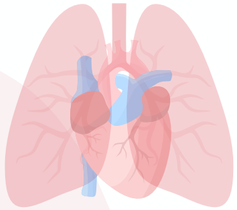
- More common in HbSC
- Patients have annual screening in ophthalmology clinic

Sickle nephropathy

- Starts in infant years
- Initially presents as proteinuria - manage with ACEis
- May progress to dialysis dependence

Priapism

- Can be acute (fulminant) or subacute/chronic (stuttering).
- Often require emergency management in ED.
- May be on etilefrine or pseudoephedrine



Pulmonary hypertension

- Chronic haemolysis/sickling with acute insults increases risk
- Patients have 5 yearly echo screening and pulmonary function tests through clinic

Painful crisis

- As a result of vaso-occlusion
- Patients will usually try to self-manage at home first. Will attend ED if pain not settling.

Asplenia

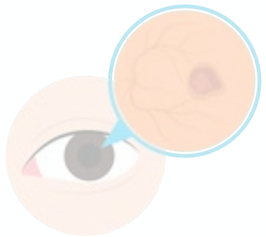
- Functional +/- radiological asplenia
- All patients should be offered lifelong penicillin V prophylaxis
- Pneumovax 5 yearly, men B + ACWY, yearly influenza vaccine

Stroke

- Most common in paediatrics but can happen at any age
- Suspect in any new neurological symptoms
- May be managed with long term red cell exchange

South West
Haemoglobinopathy
Coordinating Centre

(SOME) CONSEQUENCES OF SICKLE CELL DISEASE



Sickle retinopathy

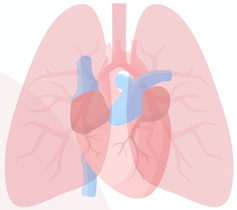
- More common in HbSC
- Patients have annual screening in ophthalmology clinic

Sickle nephropathy

- Starts in infant years
- Initially presents as proteinuria - manage with ACEis
- May progress to dialysis dependence

Priapism

- Can be acute (fulminant) or subacute/chronic (stuttering).
- Often require emergency management in ED.
- May be on etilefrine or pseudoephedrine



Pulmonary hypertension

- Chronic haemolysis/sickling with acute insults increases risk
- Patients have 5 yearly echo screening and pulmonary function tests through clinic

Painful crisis

- As a result of vaso-occlusion
- Patients will usually try to self-manage at home first. Will attend ED if pain not settling.

Asplenia

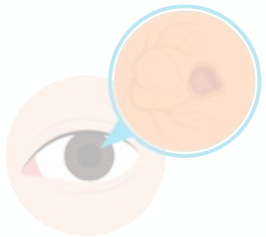
- Functional +/- radiological asplenia
- All patients should be offered lifelong penicillin V prophylaxis
- Pneumovax 5 yearly, men B + ACWY, yearly influenza vaccine

Stroke

- Most common in paediatrics but can happen at any age
- Suspect in any new neurological symptoms
- May be managed with long term red cell exchange

South West
Haemoglobinopathy
Coordinating Centre

(SOME) CONSEQUENCES OF SICKLE CELL DISEASE



Sickle retinopathy

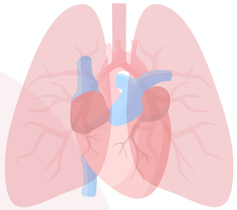
- More common in HbSC
- Patients have annual screening in ophthalmology clinic

Sickle nephropathy

- Starts in infant years
- Initially presents as proteinuria - manage with ACEis
- May progress to dialysis dependence

Priapism

- Can be acute (fulminant) or subacute/chronic (stuttering).
- Often require emergency management in ED.
- May be on etilefrine or pseudoephedrine



Pulmonary hypertension

- Chronic haemolysis/sickling with acute insults increases risk
- Patients have 5 yearly echo screening and pulmonary function tests through clinic

Painful crisis

- As a result of vaso-occlusion
- Patients will usually try to self-manage at home first. Will attend ED if pain not settling.

Asplenia

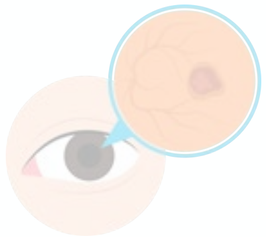
- Functional +/- radiological asplenia
- All patients should be offered lifelong penicillin V prophylaxis
- Pneumovax 5 yearly, men B + ACWY, yearly influenza vaccine

Stroke

- Most common in paediatrics but can happen at any age
- Suspect in any new neurological symptoms
- May be managed with long term red cell exchange

South West
Haemoglobinopathy
Coordinating Centre

(SOME) CONSEQUENCES OF SICKLE CELL DISEASE



Sickle retinopathy

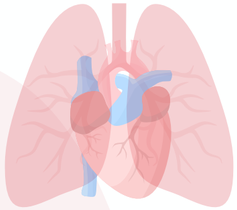
- More common in HbSC
- Patients have annual screening in ophthalmology clinic

Sickle nephropathy

- Starts in infant years
- Initially presents as proteinuria - manage with ACEis
- May progress to dialysis dependence

Priapism

- Can be acute (fulminant) or subacute/chronic (stuttering).
- Often require emergency management in ED.
- May be on etilefrine or pseudoephedrine

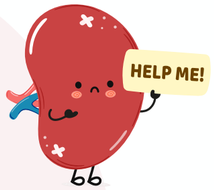


Pulmonary hypertension

- Chronic haemolysis/sickling with acute insults increases risk
- Patients have 5 yearly echo screening and pulmonary function tests through clinic

Painful crisis

- As a result of vaso-occlusion
- Patients will usually try to self-manage at home first. Will attend ED if pain not settling.



Asplenia

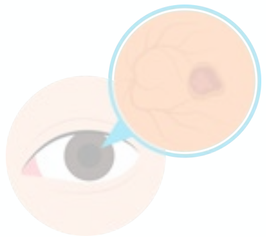
- Functional +/- radiological asplenia
- All patients should be offered lifelong penicillin V prophylaxis
- Pneumovax 5 yearly, men B + ACWY, yearly influenza vaccine

Stroke

- Most common in paediatrics but can happen at any age
- Suspect in any new neurological symptoms
- May be managed with long term red cell exchange

South West
Haemoglobinopathy
Coordinating Centre

(SOME) CONSEQUENCES OF SICKLE CELL DISEASE



Sickle retinopathy

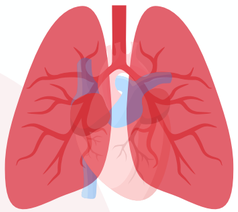
- More common in HbSC
- Patients have annual screening in ophthalmology clinic

Sickle nephropathy

- Starts in infant years
- Initially presents as proteinuria - manage with ACEis
- May progress to dialysis dependence

Priapism

- Can be acute (fulminant) or subacute/chronic (stuttering).
- Often require emergency management in ED.
- May be on etilefrine or pseudoephedrine



Pulmonary hypertension

- Chronic haemolysis/sickling with acute insults increases risk
- Patients have 5 yearly echo screening and pulmonary function tests through clinic

Painful crisis

- As a result of vaso-occlusion
- Patients will usually try to self-manage at home first. Will attend ED if pain not settling.

Asplenia

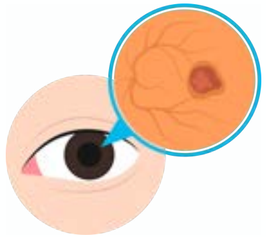
- Functional +/- radiological asplenia
- All patients should be offered lifelong penicillin V prophylaxis
- Pneumovax 5 yearly, men B + ACWY, yearly influenza vaccine

Stroke

- Most common in paediatrics but can happen at any age
- Suspect in any new neurological symptoms
- May be managed with long term red cell exchange

South West
Haemoglobinopathy
Coordinating Centre

(SOME) CONSEQUENCES OF SICKLE CELL DISEASE



Sickle retinopathy

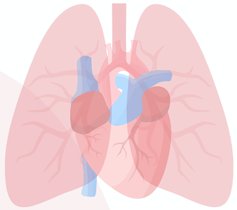
- More common in HbSC
- Patients have annual screening in ophthalmology clinic

Sickle nephropathy

- Starts in infant years
- Initially presents as proteinuria - manage with ACEis
- May progress to dialysis dependence

Priapism

- Can be acute (fulminant) or subacute/chronic (stuttering).
- Often require emergency management in ED.
- May be on etilefrine or pseudoephedrine



Pulmonary hypertension

- Chronic haemolysis/sickling with acute insults increases risk
- Patients have 5 yearly echo screening and pulmonary function tests through clinic

Painful crisis

- As a result of vaso-occlusion
- Patients will usually try to self-manage at home first. Will attend ED if pain not settling.

Asplenia

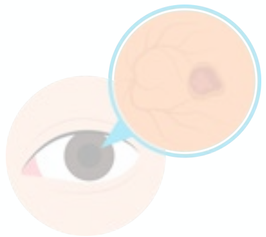
- Functional +/- radiological asplenia
- All patients should be offered lifelong penicillin V prophylaxis
- Pneumovax 5 yearly, men B + ACWY, yearly influenza vaccine

Stroke

- Most common in paediatrics but can happen at any age
- Suspect in any new neurological symptoms
- May be managed with long term red cell exchange

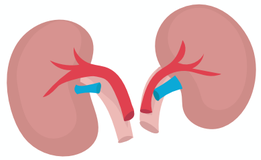
South West
Haemoglobinopathy
Coordinating Centre

(SOME) CONSEQUENCES OF SICKLE CELL DISEASE



Sickle retinopathy

- More common in HbSC
- Patients have annual screening in ophthalmology clinic

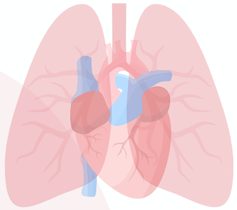


Sickle nephropathy

- Starts in infant years
- Initially presents as proteinuria - manage with ACEis
- May progress to dialysis dependence

Priapism

- Can be acute (fulminant) or subacute/chronic (stuttering).
- Often require emergency management in ED.
- May be on etilefrine or pseudoephedrine



Pulmonary hypertension

- Chronic haemolysis/sickling with acute insults increases risk
- Patients have 5 yearly echo screening and pulmonary function tests through clinic

Painful crisis

- As a result of vaso-occlusion
- Patients will usually try to self-manage at home first. Will attend ED if pain not settling.

Asplenia

- Functional +/- radiological asplenia
- All patients should be offered lifelong penicillin V prophylaxis
- Pneumovax 5 yearly, men B + ACWY, yearly influenza vaccine

Stroke

- Most common in paediatrics but can happen at any age
- Suspect in any new neurological symptoms
- May be managed with long term red cell exchange

South West Haemoglobinopathy Coordinating Centre

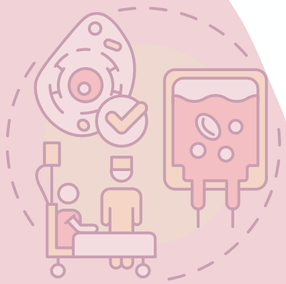
Treatments for sickle cell disease

Gene therapy

- New emerging treatment option
- Gene editing technology causes more HbF to be made
- Will be available to those with severe disease

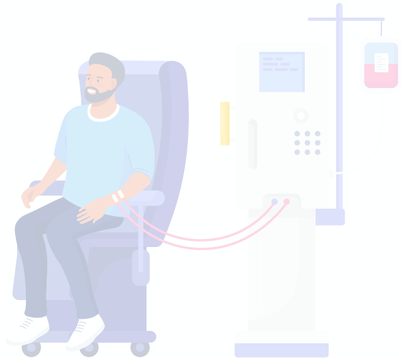
Hydroxycarbamide

- Only oral treatment available at the time of writing
- Increases HbF, which protects against polymerisation and sickling of red cells
- Generally well tolerated
- Can occasionally cause cytopenias
- Causes a raised MCV when taken correctly



Stem cell transplant

- Available to those with a matched sibling donor
- The only available curative option at present



Red cell exchange

- Usually offered to people who have had severe complications (like stroke, acute chest syndrome)
- Transfuse ~8 units of red cells while removing the patient's sickle cells every ~4-6 weeks
- Long term treatment

South West Haemoglobinopathy Coordinating Centre

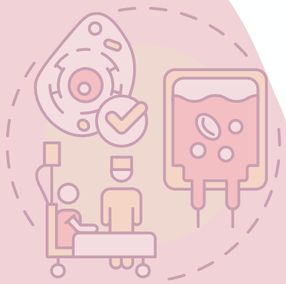
Treatments for sickle cell disease

Gene therapy

- New emerging treatment option
- Gene editing technology causes more HbF to be made
- Will be available to those with severe disease

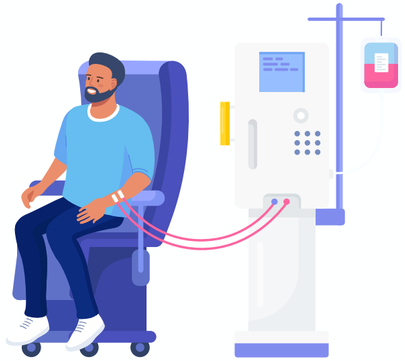
Hydroxycarbamide

- Only oral treatment available at the time of writing
- Increases HbF, which protects against polymerisation and sickling of red cells
- Generally well tolerated
- Can occasionally cause cytopenias
- Causes a raised MCV when taken correctly



Stem cell transplant

- Available to those with a matched sibling donor
- The only available curative option at present



Red cell exchange

- Usually offered to people who have had severe complications (like stroke, acute chest syndrome)
- Transfuse ~8 units of red cells while removing the patient's sickle cells every ~4-6 weeks
- Long term treatment

South West Haemoglobinopathy Coordinating Centre

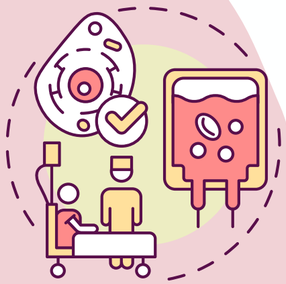
Treatments for sickle cell disease

Gene therapy

- New emerging treatment option
- Gene editing technology causes more HbF to be made
- Will be available to those with severe disease

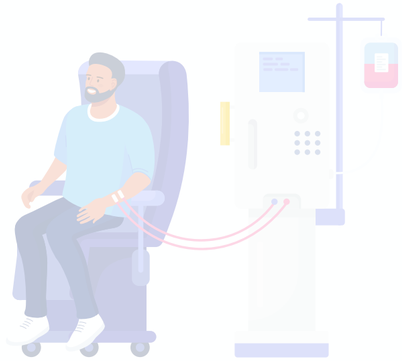
Hydroxycarbamide

- Only oral treatment available at the time of writing
- Increases HbF, which protects against polymerisation and sickling of red cells
- Generally well tolerated
- Can occasionally cause cytopenias
- Causes a raised MCV when taken correctly



Stem cell transplant

- Available to those with a matched sibling donor
- The only available curative option at present



Red cell exchange

- Usually offered to people who have had severe complications (like stroke, acute chest syndrome)
- Transfuse ~8 units of red cells while removing the patient's sickle cells every ~4-6 weeks
- Long term treatment

South West Haemoglobinopathy Coordinating Centre

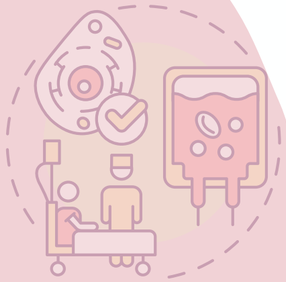
Treatments for sickle cell disease

Gene therapy

- New emerging treatment option
- Gene editing technology causes more HbF to be made
- Will be available to those with severe disease

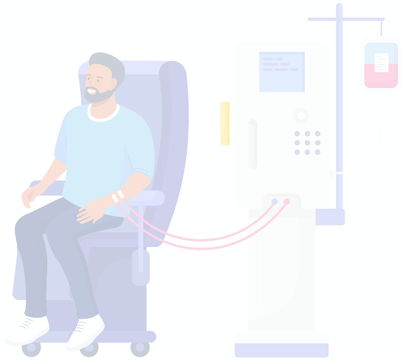
Hydroxycarbamide

- Only oral treatment available at the time of writing
- Increases HbF, which protects against polymerisation and sickling of red cells
- Generally well tolerated
- Can occasionally cause cytopenias
- Causes a raised MCV when taken correctly



Stem cell transplant

- Available to those with a matched sibling donor
- The only available curative option at present



Red cell exchange

- Usually offered to people who have had severe complications (like stroke, acute chest syndrome)
- Transfuse ~8 units of red cells while removing the patient's sickle cells every ~4-6 weeks
- Long term treatment

South West Haemoglobinopathy Coordinating Centre

WHAT ABOUT SICKLE CELL TRAIT?

- This is not a disease state and individuals do not get acute or chronic complications (in general)
- To be aware:
  - Good to know for peri-operative management
  - Precautions if extreme exercise or altitudes
  - Risk of renal medullary cell carcinoma - bear in mind if presenting with haematuria

Sickle cell trait is not seen in haematology clinic

South West
Haemoglobinopathy
Coordinating Centre

what to do next?

If you want to know your sickle cell status you can ask your GP for a blood test. In some parts of the country there are also local sickle cell centres that can arrange a blood test for you.

You may have been screened for sickle cell disease. Screening is offered .

- To all newborn babies as part of the newborn bloodspot (heelprick test) when your baby is five days old. The key reason for offering newborn screening for sickle cell disease is because babies with sickle cell disease are vulnerable to serious infections. By identifying babies early in life , they can be prescribed penicillin and be referred for specialist care, so that they stay healthy.

Newborn screening also detects babies who have the trait (also known as a carrier) for sickle cell disease.

- To all pregnant women early in pregnancy (ideally by ten weeks) . Antenatal screening identifies parents to be who have the trait (also known as a carrier). If the mother is identified with the trait, the baby's father is offered a screening test.

SICKLE CELL SOCIETY

If you would like to know more about sickle cell disorder or the work of the Sickle Cell Society please contact.

Sickle Cell Society
54 Station Road
London
NW10 4UA

T: 0208 961 7795
F: 0208 961 8346

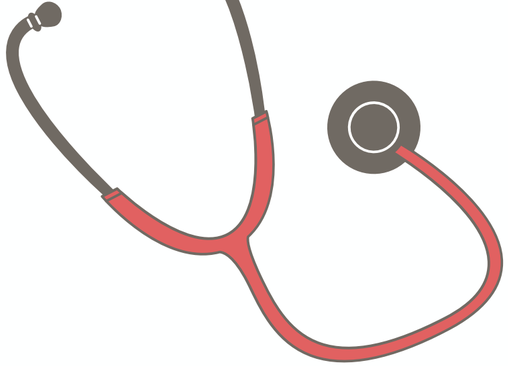
E: info@sicklecellsociety.org
www.sicklecellsociety.org

The evidence base for this leaflet is available on request and on our website.

SICKLE CELL SOCIETY

Sickle Cell Disorder & Sickle Cell Trait

South West
Haemoglobinopathy
Coordinating Centre



HOW CAN HAEMOGLOBIN SYNTHESIS GO WRONG

Structural abnormalities

Haemoglobin is made, but the structure is different to normal haemoglobin due to a genetic mutation (usually affecting the beta gene). Examples include:

- HbS
- HbC

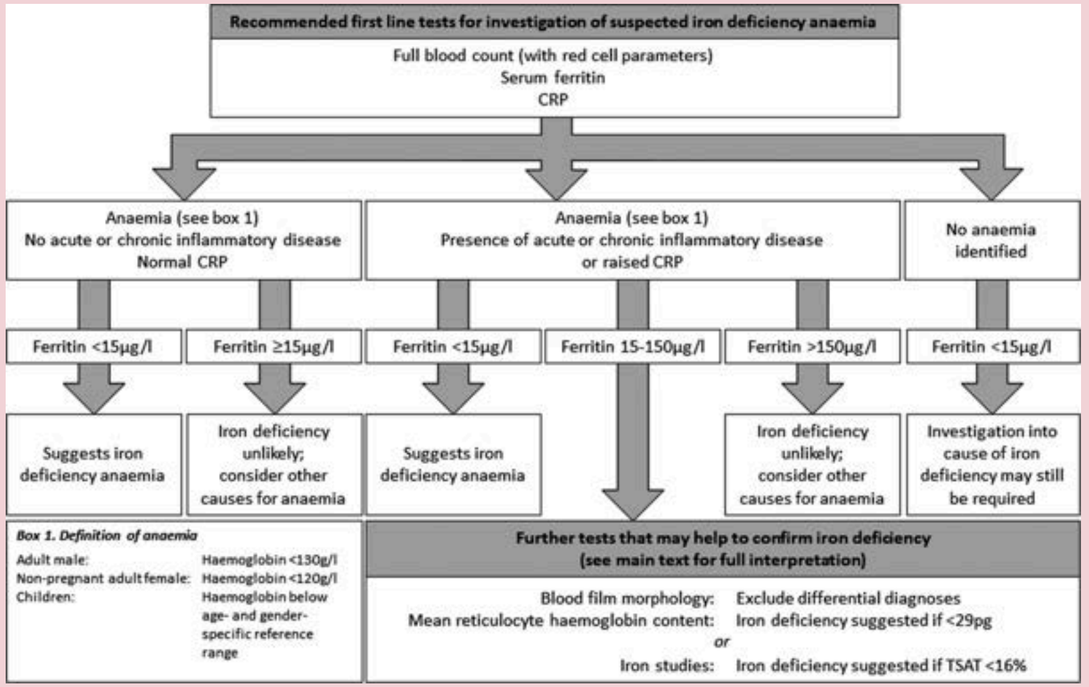
Abnormalities in haemoglobin production

Mutations in alpha or beta genes reduce the production in alpha or beta chains. This reduces the amount of normal haemoglobin. These conditions are called thalassaemias.

South West
Haemoglobinopathy
Coordinating Centre

Approaching microcytosis

- Iron deficiency - most common



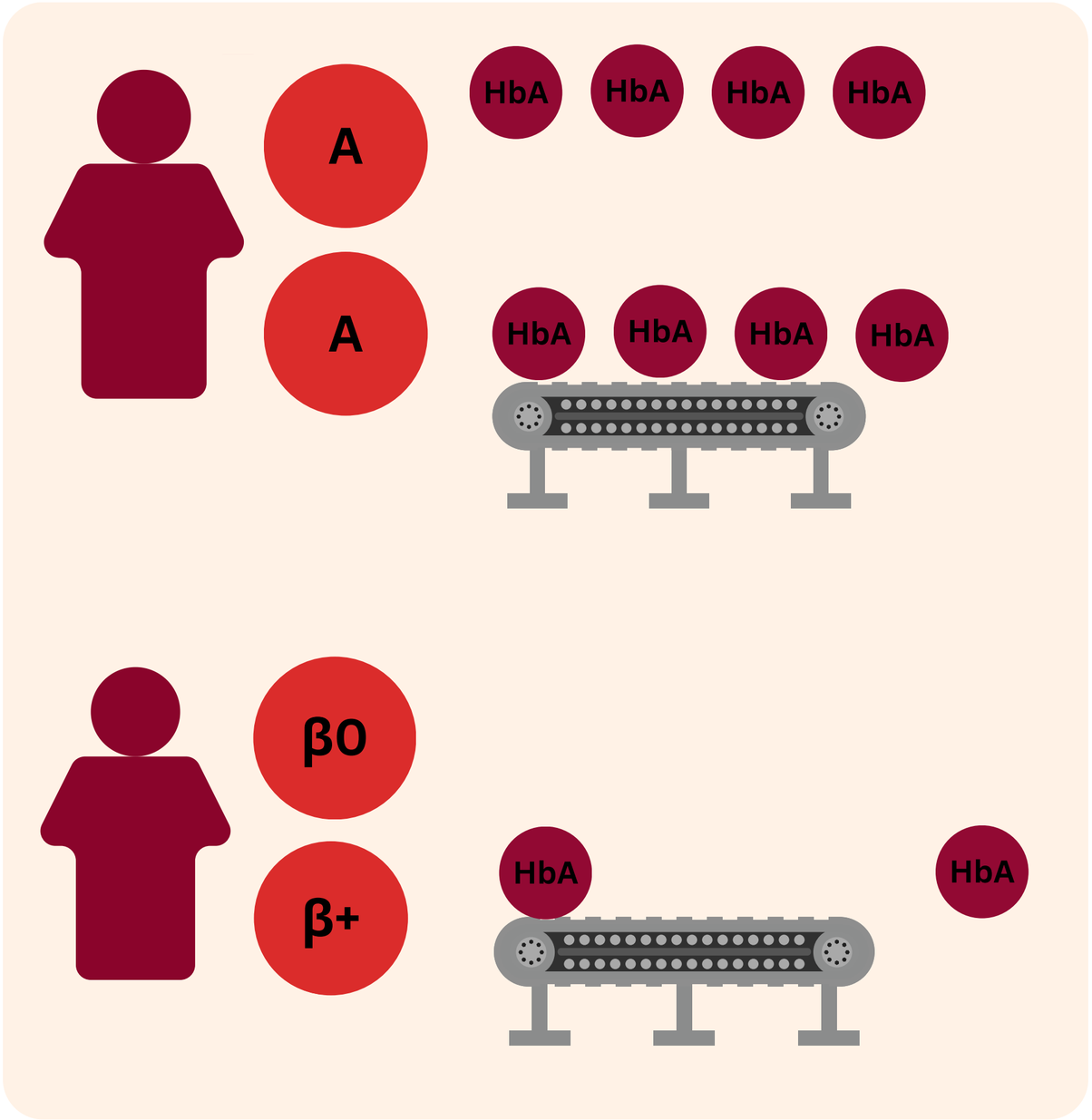
South West
Haemoglobinopathy
Coordinating Centre

Approaching microcytosis

- Iron deficiency - most common
- If not iron deficient - think thalassaemia trait
  - Step 1 - history and examination
  - step 2 - haemoglobinopathy screen
  - Step 3 - genetic testing if diagnostic conundrum/alpha thalassaemia while planning a family - to be discussed!

South West Haemoglobinopathy Coordinating Centre

Haemoglobin production in thalassaemia



Chromosome 11

ε	γ	δ	βO

+

Chromosome 11

ε	γ	δ	β+

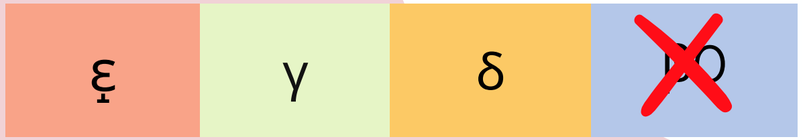
South West
Haemoglobinopathy
Coordinating Centre

BETA THALASSAEMIA MAJOR

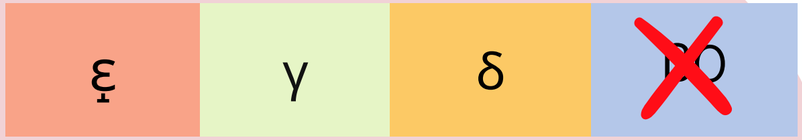
Chromosome 16

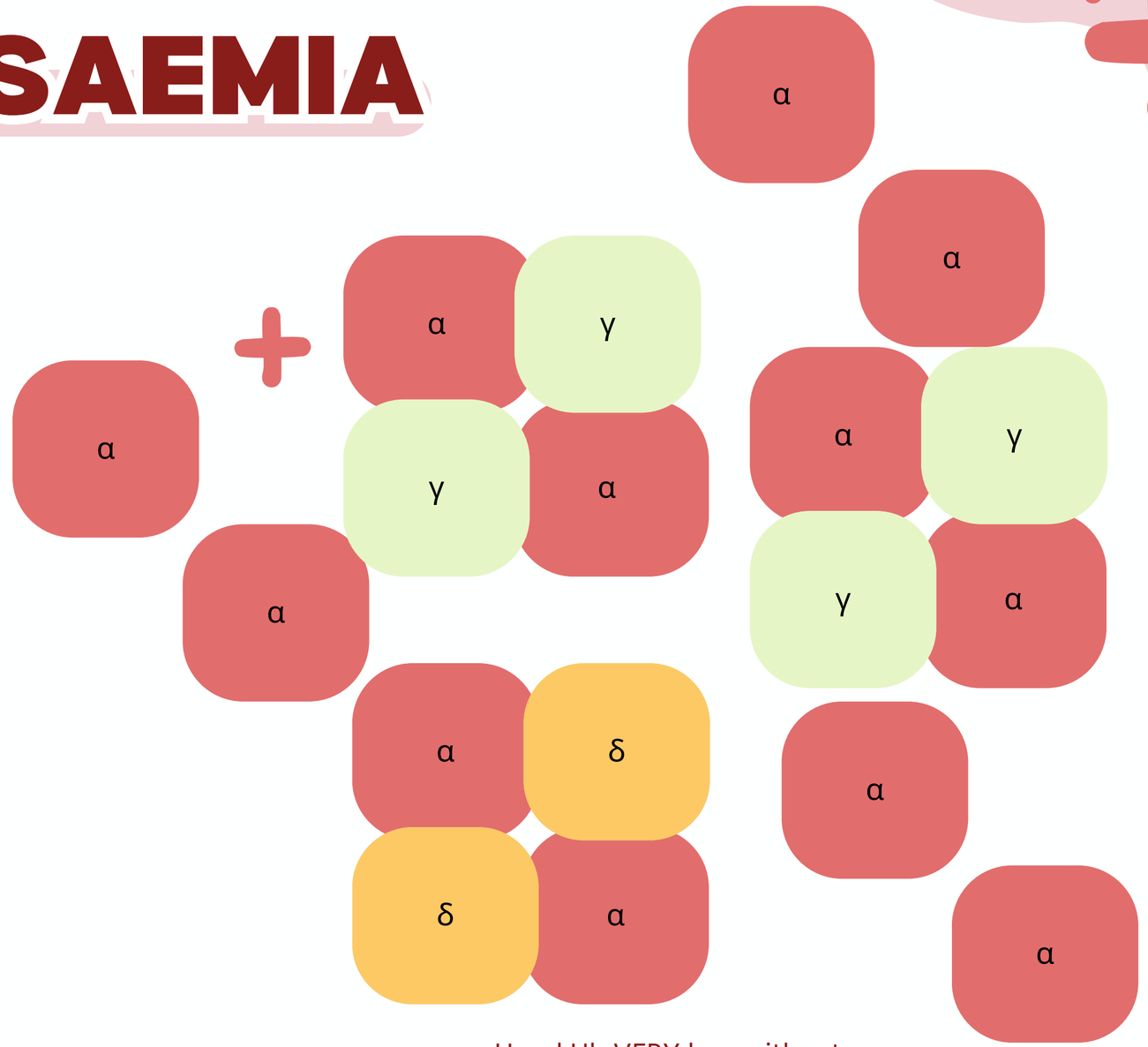
Chromosome 16

Chromosome 11



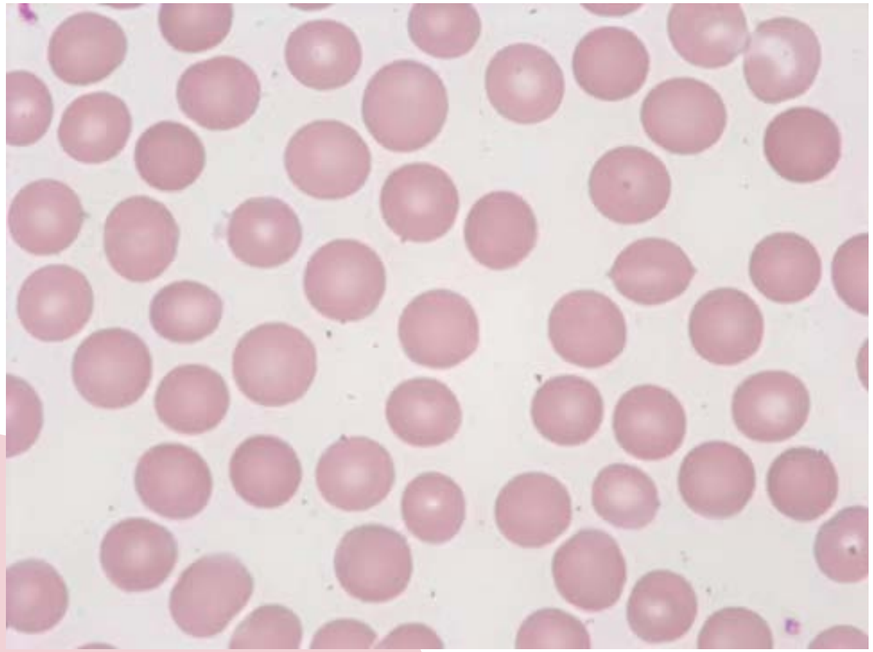
Chromosome 11



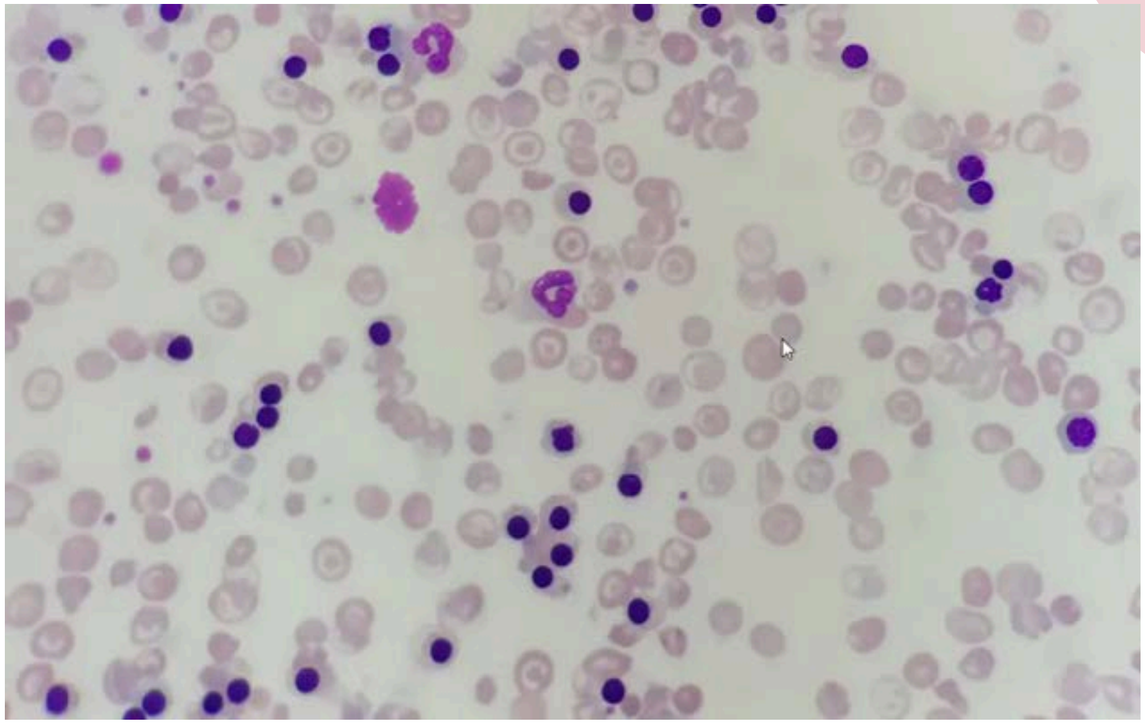


Usual Hb VERY low without transfusion
Significant microcytosis

South West
Haemoglobinopathy
Coordinating Centre

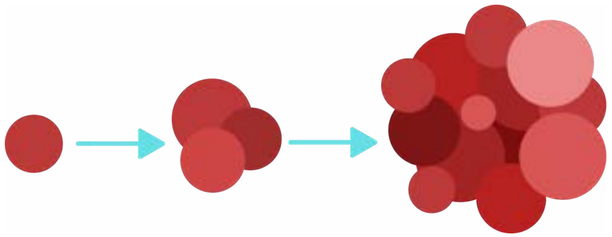


Normal

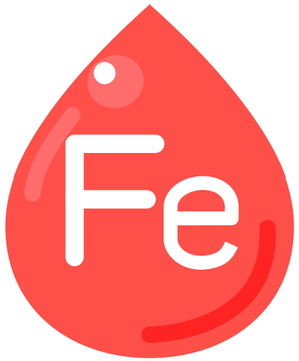


Thalassaemia major

PROBLEMS WITH THALASSAEMIA



Extramedullary haematopoesis ensues to try to improve anaemia



The body desperately tries to compensate for the anaemia by absorbing more iron, leading to **iron overload.**

Treatment is with regular blood transfusion and iron chelation

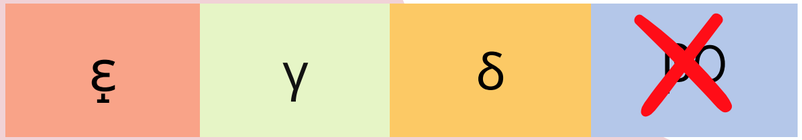
South West
Haemoglobinopathy
Coordinating Centre

BETA THALASSAEMIA INTERMEDIA

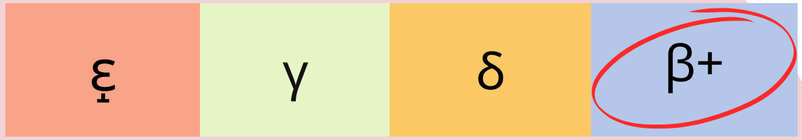
Chromosome 16

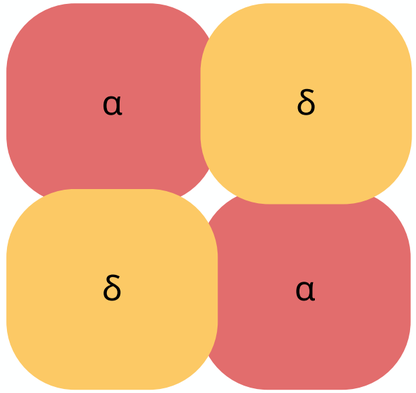
Chromosome 16

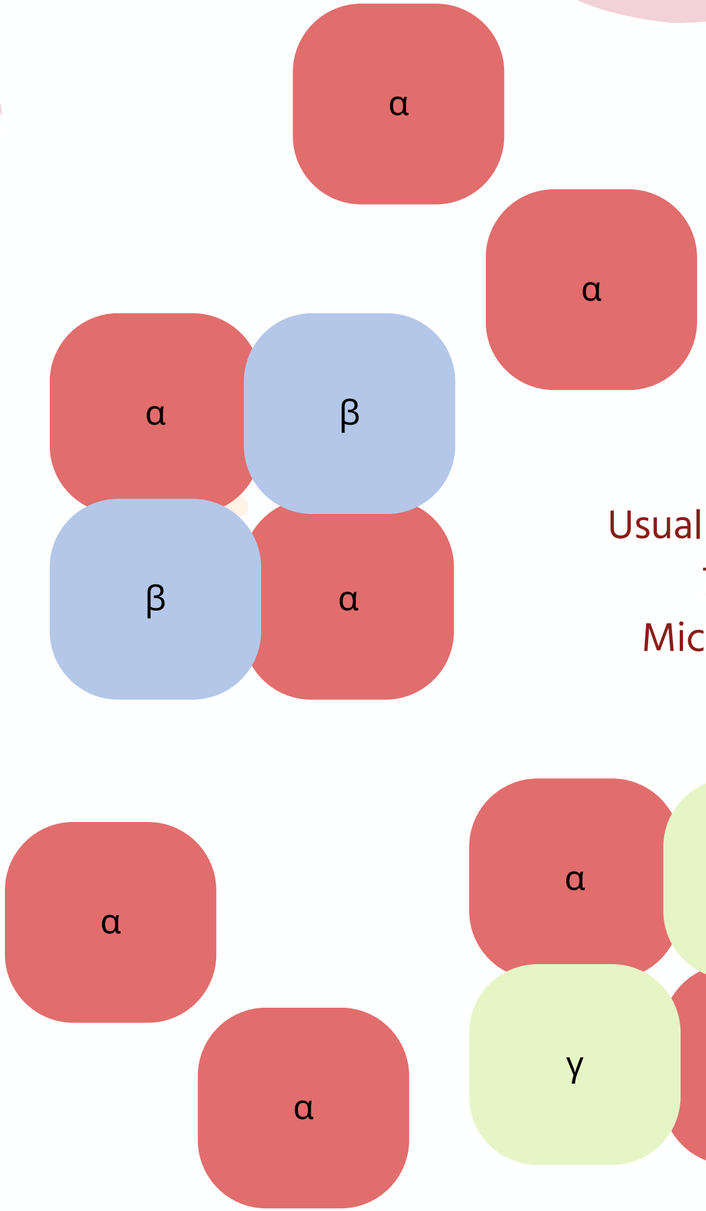
Chromosome 11



Chromosome 11







Usual Hb around
70-80
Microcytosis

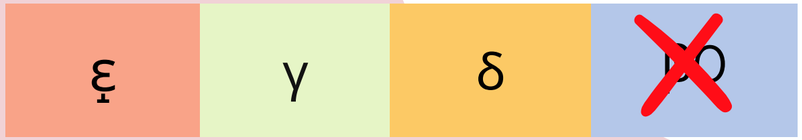
South West
Haemoglobinopathy
Coordinating Centre

BETA THALASSAEMIA TRAIT

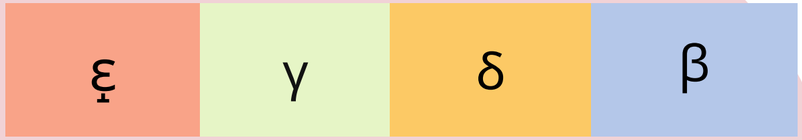
Chromosome 16

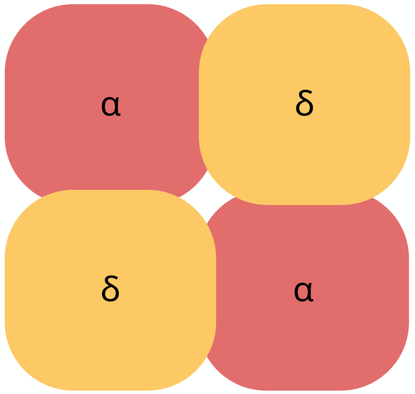
Chromosome 16

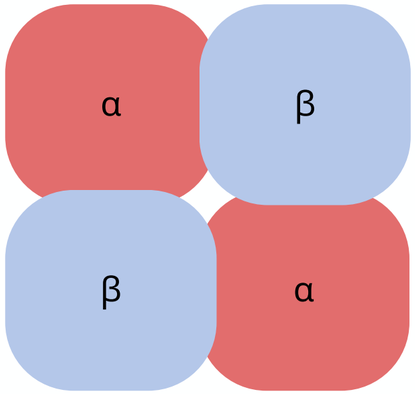
Chromosome 11

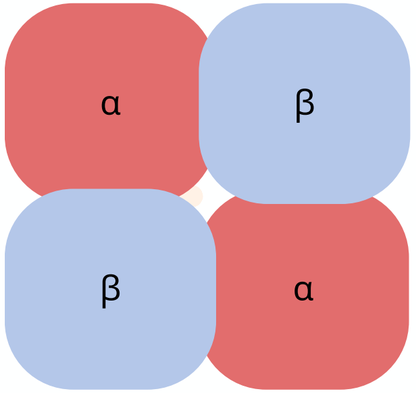


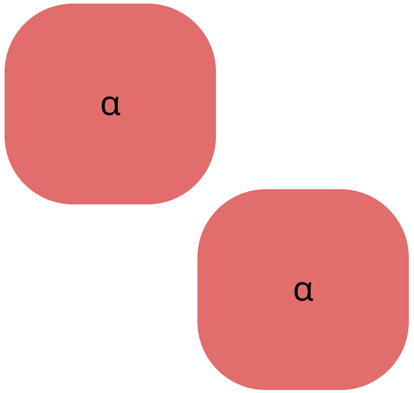
Chromosome 11

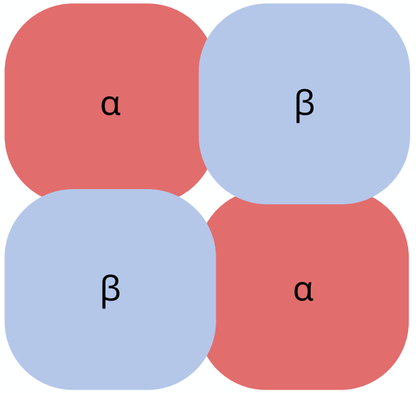












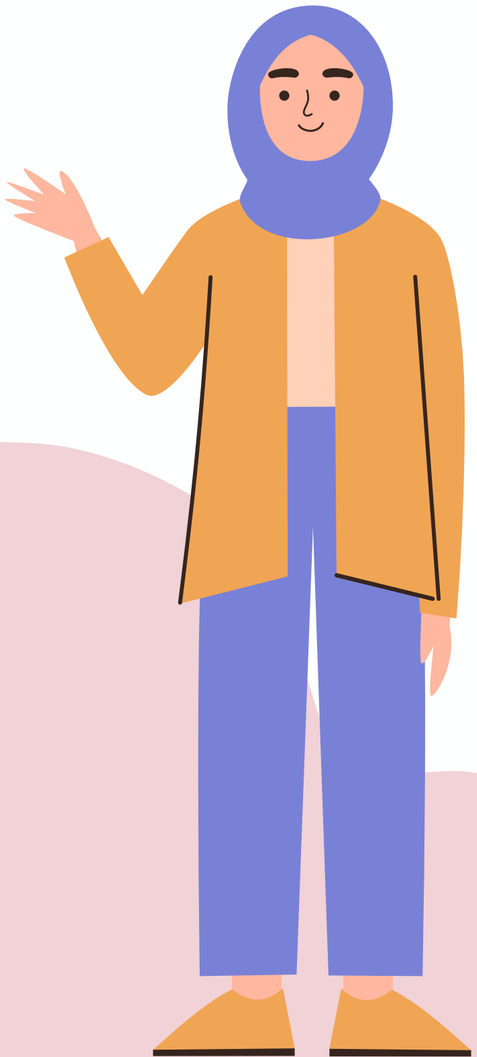
Usual Hb around
100-130
Microcytosis

South West
Haemoglobinopathy
Coordinating Centre

BETA THALASSAEMIA TRAIT

FULL BLOOD COUNT					
White Cell Count		6.05	10^9/L	4.0 - 11.0
RBC	*	5.55	10^{12}/L	3.80 - 5.30
Haemoglobin	*	110	g/L	120 - 150
Haematocrit	*	0.361	L/L	0.37 - 0.45
MCV	*	65.0	fL	83 - 100
MCH	*	19.8	pg	27.0 - 32.0
MCHC	*	305	g/L	310 - 350

South West
Haemoglobinopathy
Coordinating Centre



Antenatal screening

- If known beta thalassaemia trait or beta thalassaemia major/intermedia - partner testing +/- refer to genetic counselling

- All others - FBC and haemoglobinopathy screen

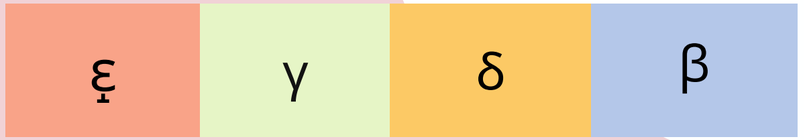
South West
Haemoglobinopathy
Coordinating Centre

ALPHA THALASSAEMIA MAJOR

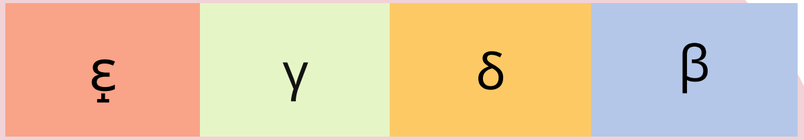
Chromosome 16

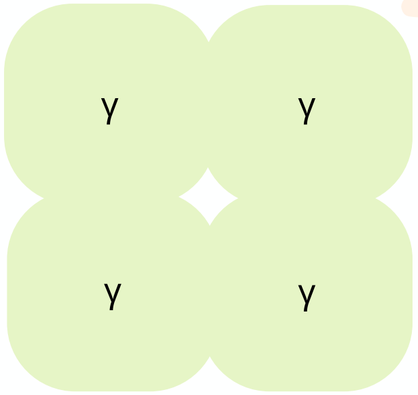
Chromosome 16

Chromosome 11

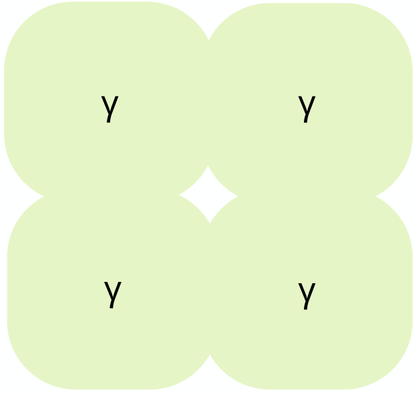


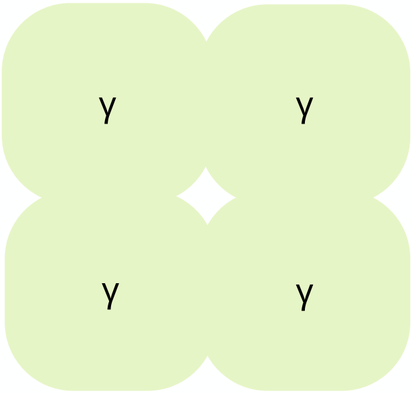
Chromosome 11





Hb Barts





- Very high O2 affinity - will not give up O2 into tissues of fetus
- Accumulates in red cells

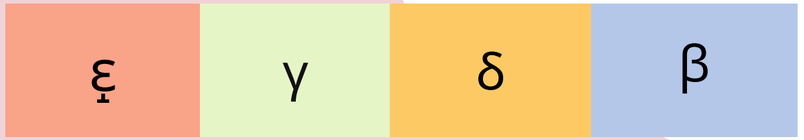
South West
Haemoglobinopathy
Coordinating Centre

ALPHA THALASSAEMIA MAJOR

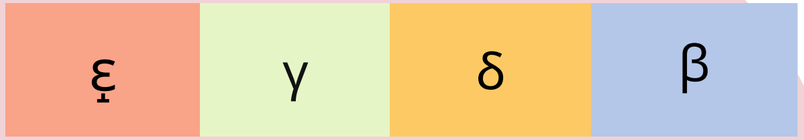
Chromosome 16

Chromosome 16

Chromosome 11



Chromosome 11



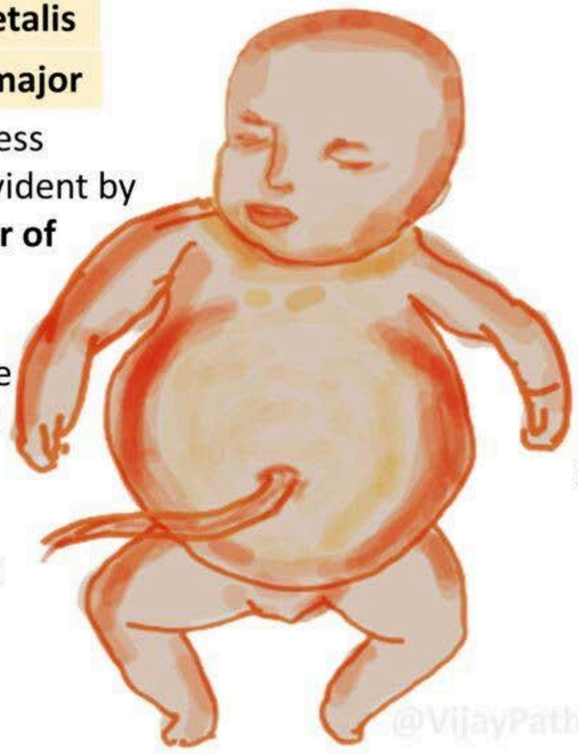
Hb Bart's hydrops fetalis

alpha thalassemia major

Signs of fetal distress usually become evident by the **third trimester of pregnancy**

fetus shows severe pallor, generalized edema, and massive hepatosplenomegaly

similar to that seen in hemolytic disease of the newborn



Why NOT before 3rd month?

due to the expression of ζ chains, an embryonic globin that pairs with γ chains to form a functional ζ2γ2 Hb tetramer.

Hb Portland I

Survival in early development

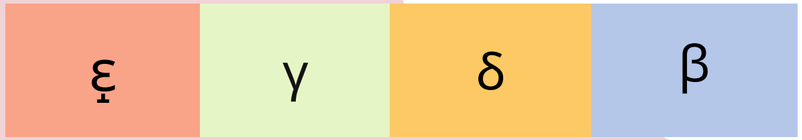
South West
Haemoglobinopathy
Coordinating Centre

HBH DISEASE (ALPHA THALASSAEMIA DISEASE)

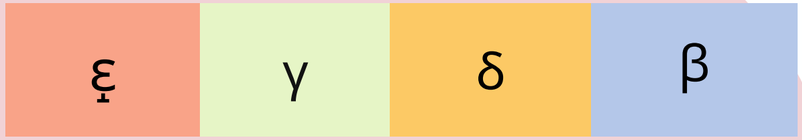
Chromosome 16

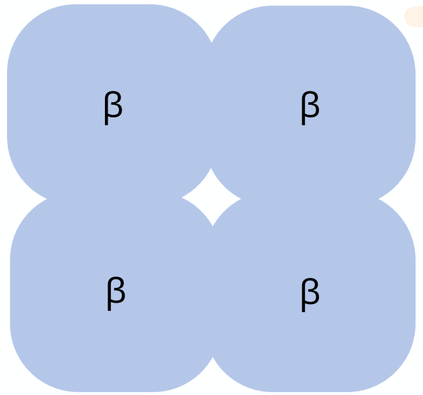
Chromosome 16

Chromosome 11



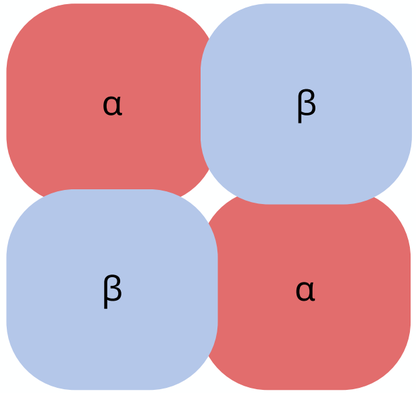
Chromosome 11

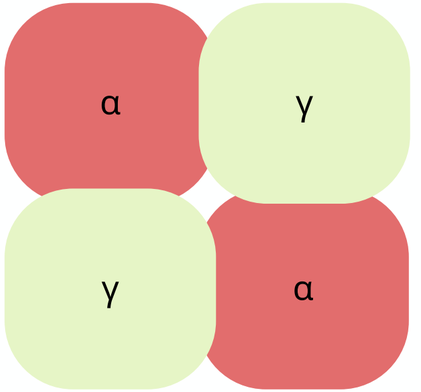


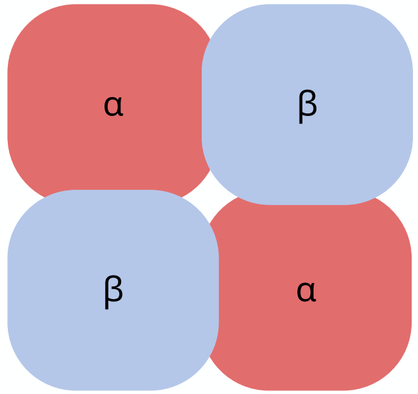


HbH

Usual Hb around 80
Microcytosis
HbH% up to 40%
Haemolysis, splenomegaly





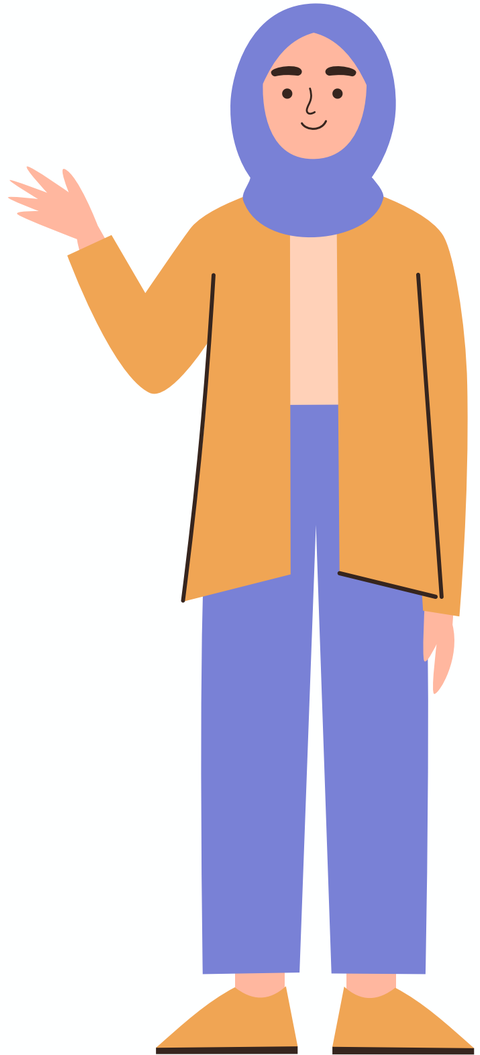


South West
Haemoglobinopathy
Coordinating Centre

- 28 year old planning a family
- Moved to the UK from Pakistan 3 years ago
- She has heard about a family history of alpha thalassaemia but she is well

Requested a test to see if she is a carrier of alpha thalassaemia.

Here are the results...



South West
Haemoglobinopathy
Coordinating Centre

HAEMOGLOBIN ELECTROPHORESIS (CE-SEBIA)				
Copy Bristol Haemoglobinopathy Service		Yes		
Hb A2 Quantitation		2.5	%	1.5 - 3.5
Hb F Quantitation		<0.3	%	>up to 0.90
Haemoglobin		128.0	g/L	
MCH		25.6	pg	
RBC		5.01	10^{12}/L	
MCV		76.1	fL	
Haemoglobinopathy Comment				

Results consistent with possible alpha

thalassaemia carrier.

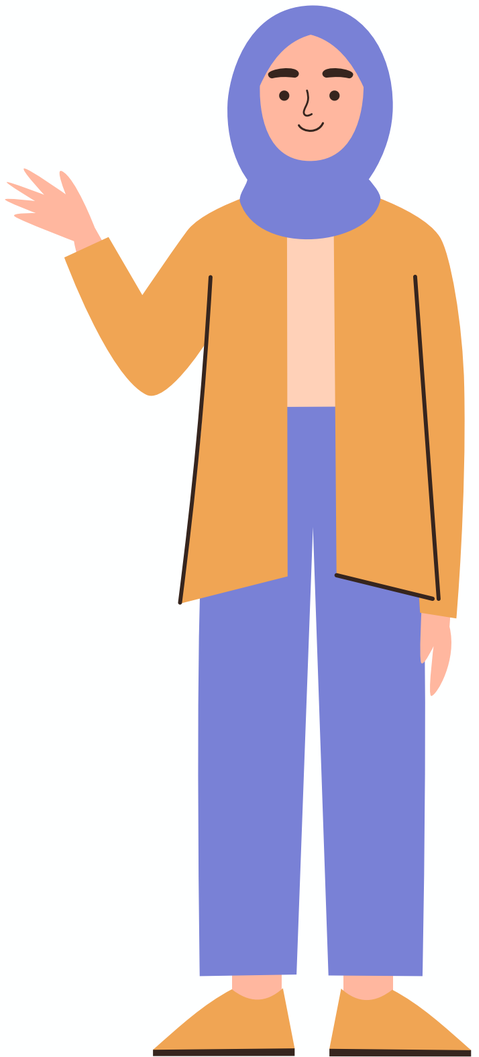
Reduced MCH can also be caused by iron deficiency

so clinical correlation is required.

No evidence of haemoglobin variant or beta

thalassaemia.

Is this important?



South West
Haemoglobinopathy
Coordinating Centre

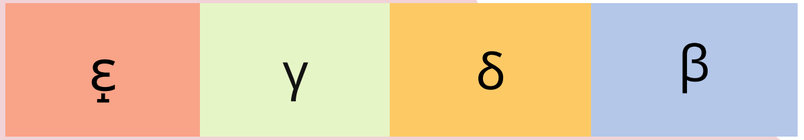
ALPHA THALASSAEMIA TRAIT - ARE ALL TRAITS EQUAL?

Chromosome 16

Chromosome 16

Chromosome 11

Chromosome 11



Chromosome 16

Chromosome 16

Chromosome 11

Chromosome 11

South West Haemoglobinopathy Coordinating Centre

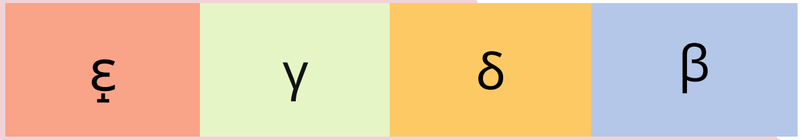
ALPHA THALASSAEMIA TRAIT - ARE ALL TRAITS EQUAL?

Chromosome 16

Chromosome 16

Chromosome 11

Chromosome 11



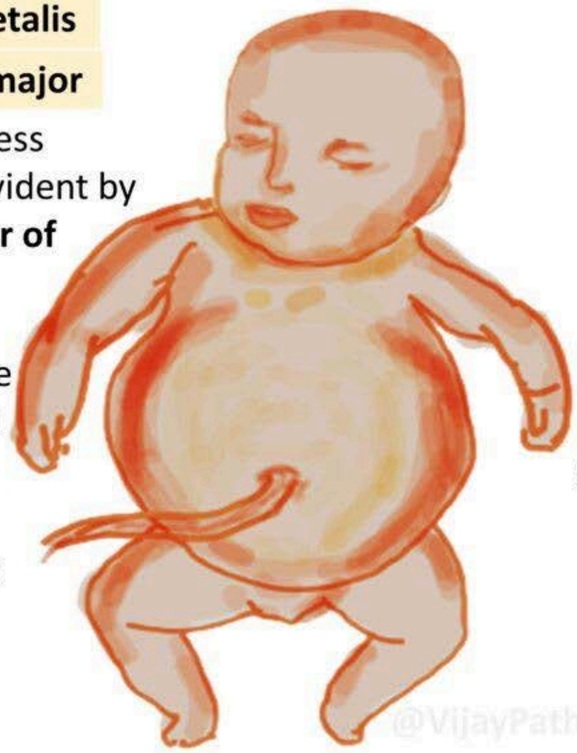
Hb Bart's hydrops fetalis

alpha thalassemia major

Signs of fetal distress usually become evident by the **third trimester of pregnancy**

fetus shows severe pallor, generalized edema, and massive hepatosplenomegaly

similar to that seen in hemolytic disease of the newborn



Why NOT before 3rd month?

due to the expression of ζ chains, an embryonic globin that pairs with γ chains to form a functional ζ2γ2 Hb tetramer.

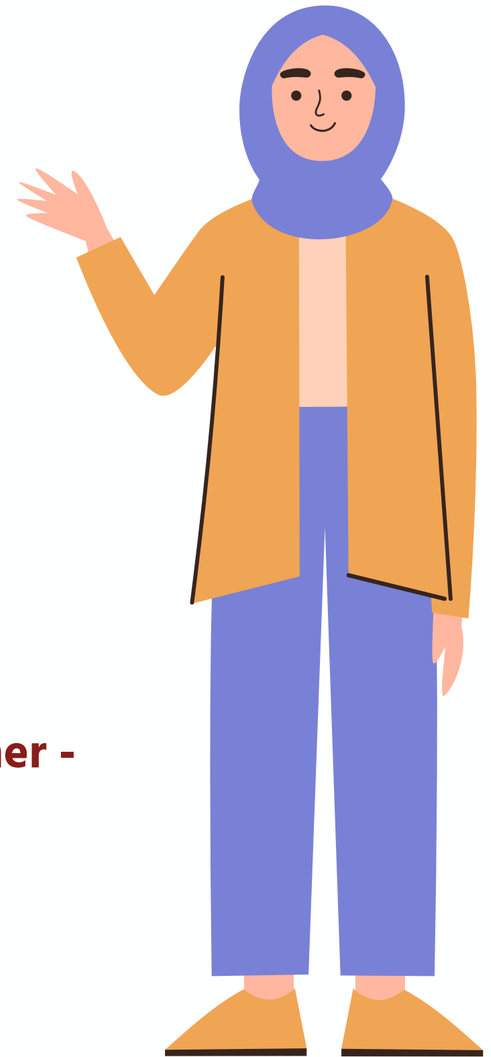
Hb Portland I

Survival in early development

South West
Haemoglobinopathy
Coordinating Centre

- 28 year old planning a family
- Moved to the UK from Pakistan 3 years ago
- She has heard about a family history of alpha thalassaemia but she is well

Requested a test to see if she is a carrier of alpha thalassaemia.



Genetic testing required of mother +/- father - dramatically changes management
Refer for genetic counselling

South West
Haemoglobinopathy
Coordinating Centre

In summary

- HbS carrier - refer for genetic counselling if partner also a carrier of HbS or beta thalassaemia.
  - Genetic testing not required

- Beta thalassaemia trait or disease - partner testing +/- genetic counselling
  - Genetic testing not usually required

- Alpha thalassaemia trait - partner testing required. Early genotyping to uncover type of thalassaemia
  - Refer to genetic counselling if either parent is alpha-zero