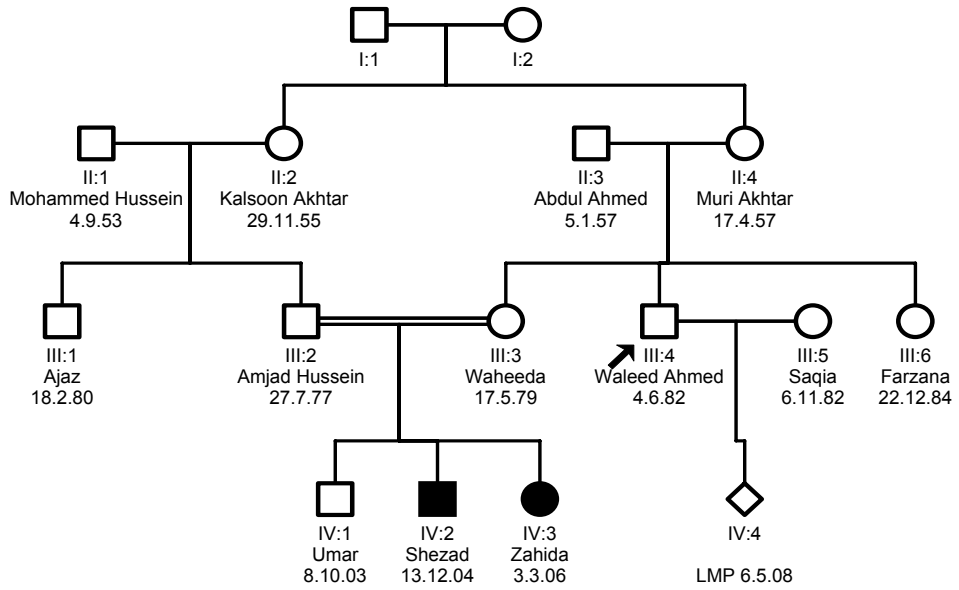
8. Is my baby at risk of the blood disorder which my nephew and niece have?

Whaleed Ahmed is referred when his wife is 15 weeks pregnant. His sister has two children with a blood disorder.



Q1 If this is an inherited condition what is the most likely mode of inheritance and why?

Note that the diagnosis of the blood disorder in Waleed's nephew and niece is not known yet!

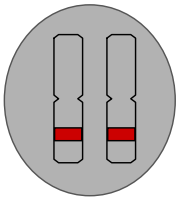
However, the most likely mode of inheritance would be autosomal recessive because

1 Male and female affected in same sibship in one generation
2 Neither parent affected
3 The parents are blood relatives **(Consanguineous** - Where two people are related by blood (i.e. share at least one common ancestor))

Q2 The condition is confirmed as beta-thalassaemia. Does this change the information about the genetics of the condition?

The inheritance of beta-thalassaemia is known to be an autosomal recessive condition. The diagnosis therefore confirms the mode of inheritance of the condition in this family.
Recessive - A trait expressed only in homozygotes

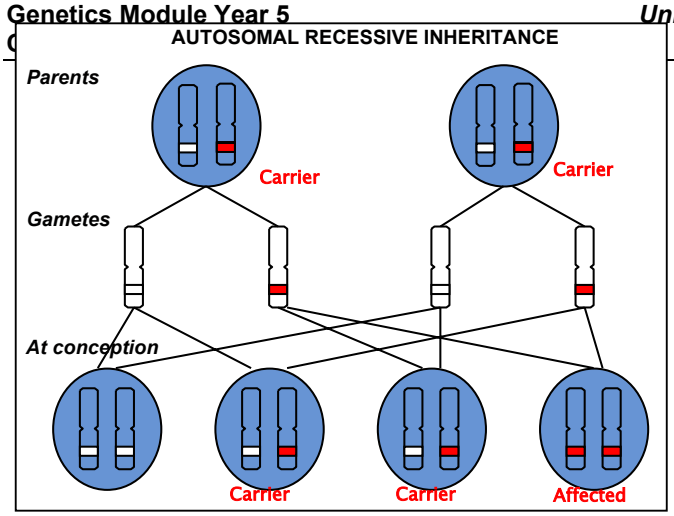
It would now be possible to determine who are carriers in the family by haematological tests. One may need to determine the probability of a person being a carrier for a recessive condition where carrier detection tests are not available by using Mendelian genetic principles.



Autosomal recessive – reminder

To be affected with an autosomal recessive disorder, a person must have inherited two copies of the altered gene – one from each parent

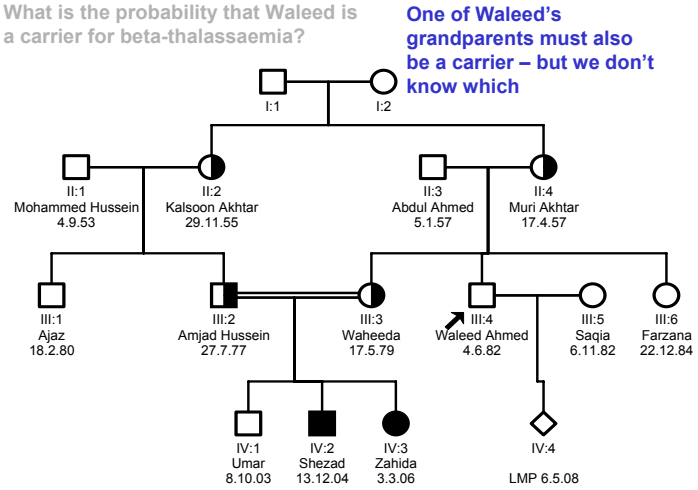
Background information on beta thalassaemia
Due to underproduction of β-globin chain of haemoglobin. Different types of mutation result in either reduced or absent production of β-globin chains (β^+ and β^0 respectively). People homozygous for β^0 have a severe transfusion dependent anaemia. Blood film in homozygotes shows severe hypochromia, microcytosis with target cells. HbF is increased.



Carrier frequency in people of Indo-Pakistani ancestry is high (1 in 15). Over 100 mutations characterised with particular mutations more common in certain geographical areas.

Q3 What is the probability of Whaleed being a carrier for beta-thalassaemia?

Waleed's sister Waheeda must be a carrier (as must her husband Amjad). Therefore Waheeda inherited the altered gene from one of her parents (Abdul and Muri), who can pass on either this altered allele or the normal β-globin allele to Waleed.
Therefore, Waleed has a one in two probability of being a carrier.
For most recessive diseases the carrier frequency is low, so we usually assume that only one of each pair of grandparents is a carrier (especially if they are unrelated to each other).



Q4 What is the probability of Whaleed's wife being a carrier for beta-thalassaemia?

This depends on whether there is a family history of the recessive disease in her family, and/or the probability of a member of the population being a heterozygote in the population from which his wife comes.

If this is known, a simple calculation can give the probability of their unborn baby having inherited thalassaemia. We need to be able to work out carrier frequencies for situations when carrier testing is not available, but in this case the situation can be resolved by a simple haematological test on both Whalid and his wife. This would say with certainty whether or not either or both or neither were carriers.

Waleed's wife's probability of being a carrier (assuming there are no affected people in her family) is that of a member of the general population, and will vary according to the incidence of the disease in that population.

Q5 What is the probability that Umar (3:1) is a carrier for beta-thalassaemia?

Umar, the unaffected son of Waleed's sister, has a 2/3 chance of being a carrier.

Before he was born, there were four combinations of parental alleles he could inherit: 1/4 two normal genes, 2/4 one normal and one altered gene, 1/4 two altered genes. As he is unaffected, the last possibility is excluded, leaving a 2/3 probability that he is a carrier.

(An animated tutorial explaining autosomal recessive segregation is on the homepage of the genetics website)

Q6 If Whaleed and his wife are found to be carriers, what prenatal diagnostic test might be available?

Prenatal diagnosis may be possible by DNA analysis in the first trimester using either gene tracking or by direct analysis of the familial mutations if they are known. Over 100 mutations have been characterised by the National Haemoglobinopathy Molecular Genetics laboratory in Oxford. As particular mutations are more common in certain geographical areas, it is important to inform the laboratory of the areas of origin of the families, so that tests most likely to find the mutations as quickly as possible can be performed. For families where DNA analysis is not possible, second trimester diagnosis may be possible on fetal blood.