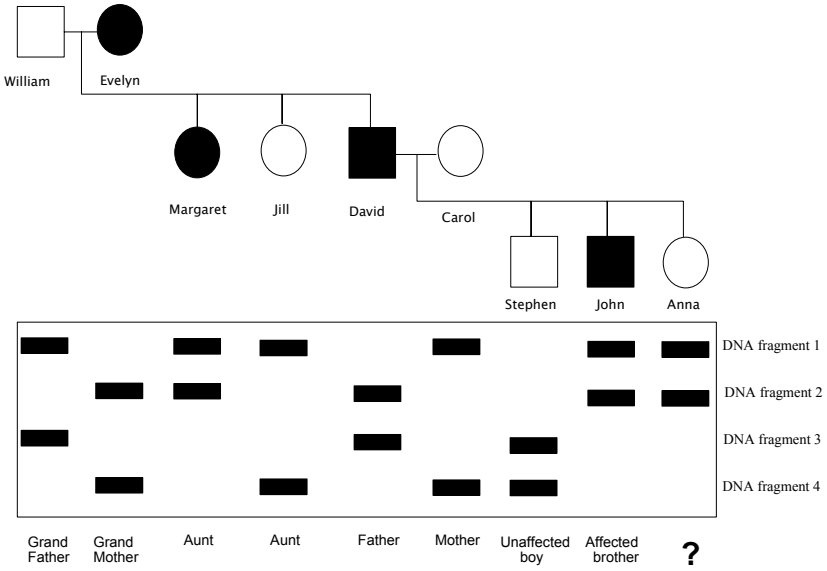
2. Does Anna need medical surveillance for Marfan syndrome?

Members of the Williams family shown below have Marfan syndrome. Marfan syndrome is associated with mutations in the fibrillin gene.

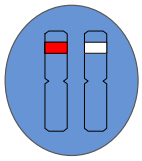
Anna (III-3) has some very minor skeletal features associated with Marfan syndrome. It is well recognised that females may show relatively mild signs, but if Anna has inherited the altered gene cardiac surveillance must be instituted to try to prevent sudden death.

DNA analysis was carried out on samples from all family members and DNA fragments generated by PCR analysis of a CA repeat polymorphism within the fibrillin gene. The results can be used to track the disease gene through the family.



Q1 Which mode of inheritance is suggested by the pattern of affected people in the family?

There are people with Marfan syndrome in three generations; males and females are affected (in equal numbers); affected people have affected and unaffected children; the forms of transmission seen here are female to female; female to male and male to male. All these features are compatible with autosomal dominant inheritance.

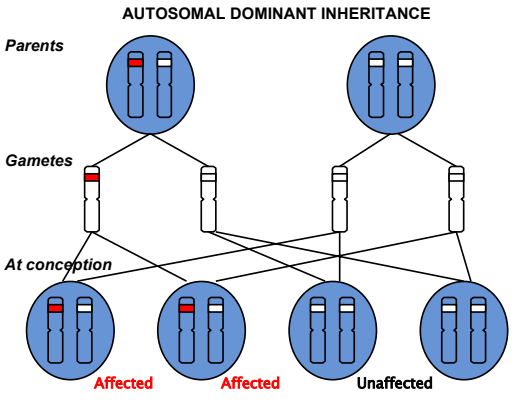


Dominant

Heterozygotes with one copy of the altered gene are affected

Q2 What is the probability that Anna has inherited the condition?

As Marfan syndrome is a dominantly inherited condition a parent passes on either the altered or normal gene. Each child therefore has a 1 in 2; ½; 50% probability of inheriting the condition.



Q3 Is there a DNA marker fragment which is being inherited with the condition? If so, which one?

When using gene tracking to predict disease status, one hopes that the naturally occurring polymorphisms in the gene or marker used will enable the identification of each of the two alleles each person in a family has. One of these alleles would have been inherited from each parent.

Start, then, by looking at the DNA patterns of the grandparents - William and Evelyn. Fortunately, the four alleles at the fibrillin locus can be separately identified.

Next, look at the first child Margaret (who is affected). She has inherited the allele giving DNA fragment 1 from her father and the allele giving DNA fragment 2 from her mother. Next look at her sister Gill, who is unaffected. She too has inherited DNA fragment 1 from her father but has inherited DNA fragment 4 from her affected mother, Evelyn. David her affected brother has inherited DNA fragment 2 from his mother, and DNA fragment 3 from his father. Of the 3 children of Evelyn, the two who have inherited Marfan syndrome both have DNA fragment 2 from her, whilst Gill who is unaffected has DNA fragment number 4.

We now need to identify which allele (DNA fragment 2 or DNA fragment 3) David has passed on to his children. Again, we need to be able to identify the two alleles which his wife Carol has. Fortunately, she has two different alleles from David (she inherited one allele from each of her parents.)

David and Carol have an unaffected son (Stephen) and an affected son (John). Stephen has inherited the allele associated with DNA fragment 3 from his father, who in turn inherited that allele from his own unaffected father, William. John, however, inherited the allele associated with DNA fragment 2 from David his father. David had inherited this allele from his affected mother Evelyn. All four affected people in the family have DNA fragment 2, whilst the two unaffected people (Gill and Stephen) do not have this allele.

Q4 Does Anna need medical surveillance for Marfan syndrome? Give the reason for your decision.

Anna has inherited DNA fragment 2 and therefore has the "at risk" allele, and therefore requires medical surveillance for complications of Marfan syndrome.

Q5 Why is this result likely to be highly accurate in this particular family?

The error associated with gene tracking depends on the physical relationship between the DNA marker used and the gene for the disease.

Crossing over occurs naturally at meiosis between the homologous chromosomes of each pair. When the DNA marker is some distance away along the chromosome from the gene, there is the possibility that crossing over may occur between the disease gene and the DNA marker. When this occurs in a particular meiosis, the DNA marker believed from the family study to be being inherited with the disease gene will now be found next to the normal gene in a daughter gamete, and the DNA marker believed to be next to the normal gene will be next to the disease gene. This would wrongly predict that the person is affected. The error rate is therefore the recombination rate between the disease gene and the marker.

These days the DNA markers used are either within the gene or as physically close to the gene as possible, to reduce the possibility of recombination between marker and disease gene. The diagnostic accuracy of gene tracking is therefore high. If the marker is actually within the gene itself the accuracy is as close to 100% as is possible.