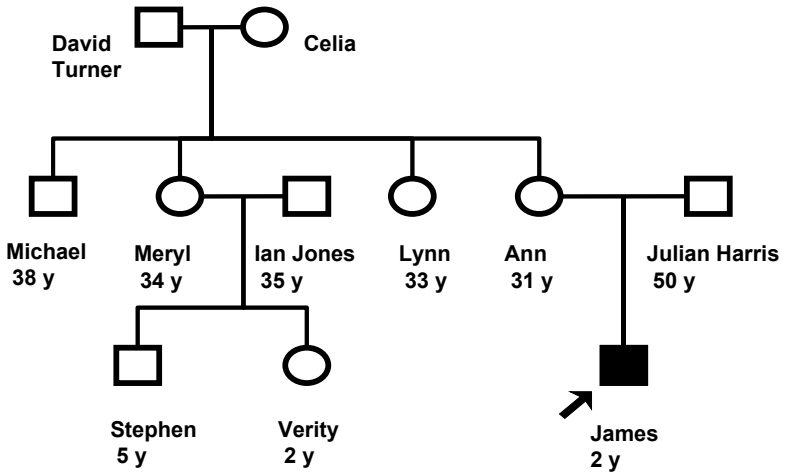
10. What caused my son to be only person in our family with neurofibromatosis?

James (III-3) has neurofibromatosis type 1, diagnosed by his having the typical skin signs (multiple café au lait patches). His development was slower than expected. From the age of 2 his development has regressed rapidly, with recurrent attacks of screaming. His mother is concerned about her risks of having another child affected with neurofibromatosis because of the severity of the condition in James.



Q1 What is the mode of inheritance of NF1?

Neurofibromatosis type 1 is a dominant condition, ie the disease is expressed in heterozygotes. Someone with the disease can pass on either the altered gene or the normal gene to a child. Therefore each child has a 1 in 2 probability of inheriting the condition.

However, neither of James' s parents are shown on the pedigree as having neurofibromatosis type 1.

Q2 What is the most likely cause of James being the only person in the family with neurofibromatosis?

There are several explanations –

a) New mutation

James's neurofibromatosis could be the result of a new mutation - the change in the gene occurring during the production of the egg or sperm which went to make him.

[Note that even though James may be the only person affected in his family (and therefore his disease may be the result of a new mutation), once a person has neurofibromatosis he or she can pass on the altered gene to children]

b) Variation in expression

Some dominant disorders can be very variable in their expression - a person shows some signs of the condition (ie the disease is penetrant) but the number of signs and the degree of severity is variable (ie variation in expression). The previous case history also demonstrates this phenomenon in a family with osteogenesis imperfecta.

c) There is also the possibility of non-paternity, but in the context of seeking genetic advice, this information is usually offered.

To try to decide whether a new mutation or variation in expression is the explanation for James appearing to be an isolated case, it is important to examine other members of the family.

Q3 What evidence from the family tree would support your suggestion?

Note that James's father Julian was 48 when James was born. As the new mutation rate increases for some disorders with increasing paternal age, Julian's age may add support to James's condition being the result of a new paternal mutation.

The increased rate of new mutations with paternal age is a result of the mechanism of sperm production - related to the repeated cell divisions of a stock of primitive sperm producing cells. With the increasing numbers of cell divisions of a stem cell DNA copying errors increase.

Q4 What is the probability that another child which James's parents may have would have neurofibromatosis type 1?

This depends of course on whether James's neurofibromatosis is the result of a new mutation. Careful, detailed physical examination of both his parents should be carried out looking for minor signs of neurofibromatosis.

If the physical examination of James's parents is completely normal, then it is likely that his condition is the result of a new mutation, with a very low recurrence risk (equal to the chance of another new mutation occurring) for a future child. (Note that very occasionally a parent with absolutely no signs can have a second child affected with the same dominant disorder. This can occur if there is mosaicism in the gonads of one of the parents - that is, there are two populations of cells: one with normal genes and one population containing the gene alteration for a dominant disorder. In clinical practice this is extremely unlikely but has been shown to occur rarely).

If either of James's parents is shown to have minor physical signs, this would confirm that he or she has NF1 Each child would then have a 1 in 2 probability of inheriting the altered gene and having NF1. Even though a parent is mildly affected for a dominant disorder, a child can be much more severely affected and vice versa.