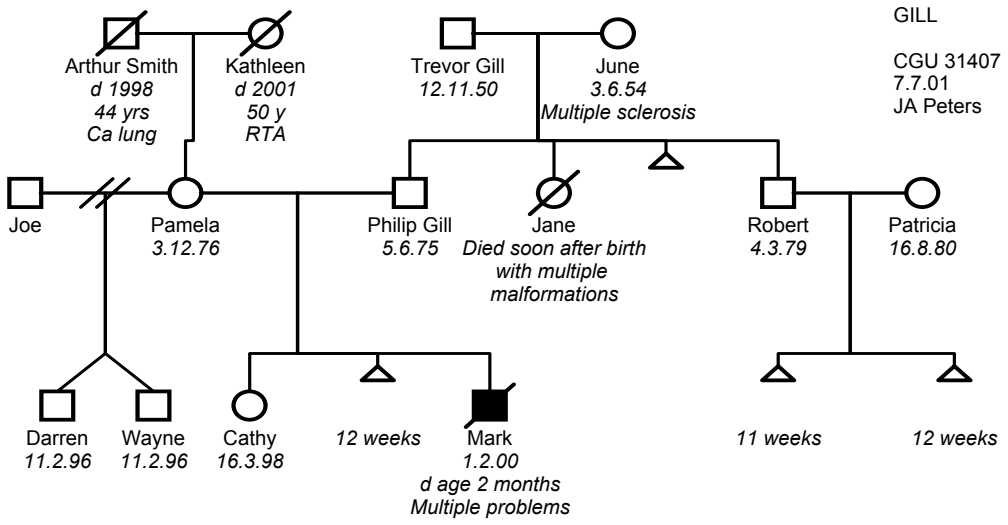
## 6. I would like to know why my son had multiple malformations, and whether it is likely to happen again.




### Q1 What features are there of note in this pedigree?

Note that as well as Mark, Jane also had multiple malformations and died soon after birth, and so it should be considered whether she could have had the same condition as Mark. Note that there are more miscarriages than would be expected, and the affected children are of different sexes, are in different generations, and have multiple malformations.

### Q2 Thinking of the modes of inheritance, Mark's features and the family history, is this likely to be a genetic problem, and if so what is its underlying cause?

Consider whether the single gene modes of inheritance (autosomal dominant, autosomal recessive, and X-linked recessive) or multifactorial inheritance would fit this family pattern.

Dominant inheritance is unlikely as all the parents are unaffected.

Autosomal recessive inheritance is unlikely because Trevor and June Gill, Philip and Pamela Gill and Robert and Patricia Gill would all have to be carriers for the same autosomal recessive disease, which is extremely unlikely. A male and a female were affected with multiple malformations, (as can be found in autosomal recessive conditions) but it would be unusual to find them in successive generations. There is no history of consanguinity in the family: the pedigree confirms that the parents of the affected children are not blood relations.

X-linked recessive inheritance is excluded because a male and a female are affected. Note also that the male (Philip Gill) who links the two affected children is normal (ie does not have an X linked condition), and he has had an affected son (who has inherited his father's Y chromosome, not the X).

Multifactorial inheritance is unlikely as multiple organ systems were involved. (Multifactorial inheritance involves one organ system as the result of a combination of genetic and environmental factors).

In view of the early pregnancy losses, and two children in different generations having multiple malformations, an inherited chromosomal anomaly should be considered. As the parents of the affected children are

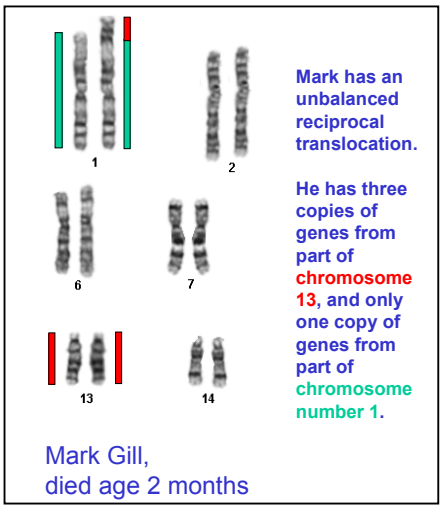
normal, one of them having a balanced reciprocal translocation would be the most likely of the structural rearrangements. (If one of the parents had a deletion, for instance, they would be affected themselves).

Clues that chromosomal imbalance (ie too many or too few copies of particular genes) is causing the pedigree features include more miscarriages than would be expected, and the fact that the affected children have multiple malformations in multiple organ systems timed at different stages of gestation.

## Q3 What test might be helpful in confirming this?

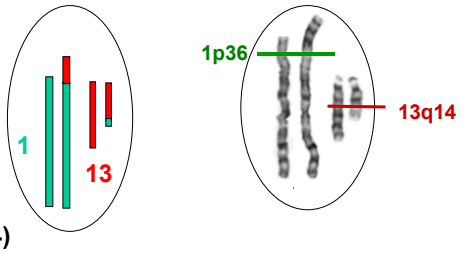
### Chromosomal analysis in Mark Gill

The most useful investigation would be chromosomal analysis in Mark Gill, which because of his pattern of anomalies, was undertaken soon after birth. This confirmed that he had an unbalanced reciprocal translocation. If it is not possible to undertake a karyotype in the affected person, then both parents should have their chromosomes examined. We always test both parents, even though the family history in this case suggests that a genetic cause on Philip's side of the family may be the more likely. In fact, Philip was found to be carrier of a balanced reciprocal translocation.




**Philip Gill:**
***carrier of a balanced reciprocal translocation between the short arm of one chromosome number 1 and the long arm of one chromosome number 13***

**46,XY,t(1;13)(p36;q14)**



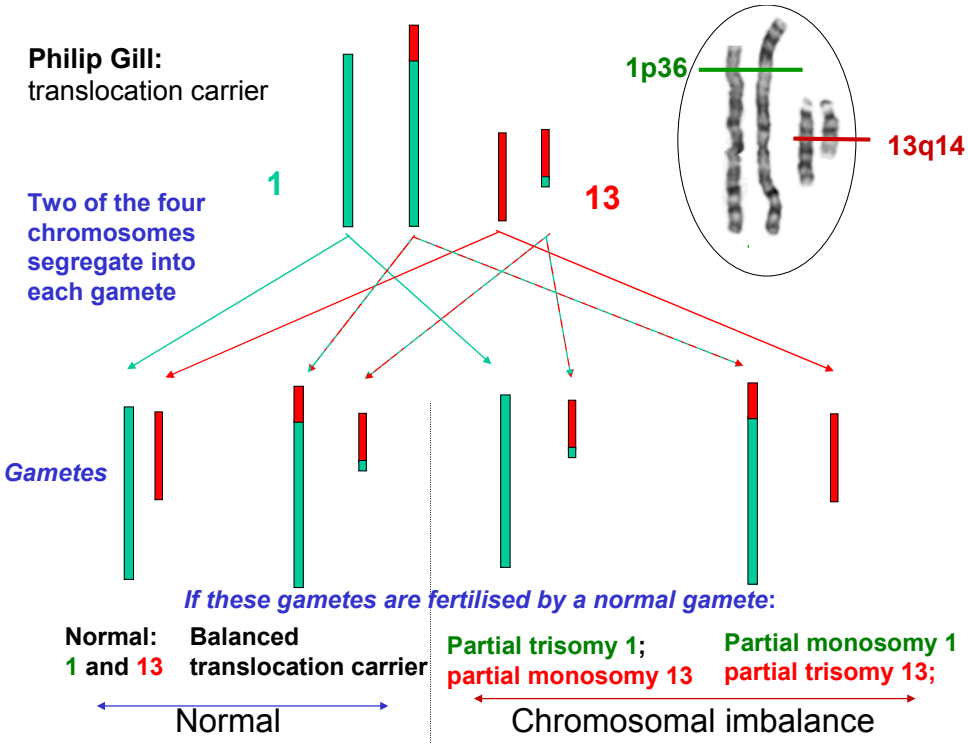

## Q4 What is the probability that Cathy (III:1) is a carrier?

**1 in 2; ½; 50%; 50:50.**

Philip was shown to have a balanced reciprocal translocation. As Kathy is unaffected she must have inherited either a normal chromosome pattern or the balanced reciprocal translocation from Philip. The probability of her being a carrier is therefore 1 in 2. It is important to offer carrier testing to other members of a family where someone is shown to have a balanced reciprocal translocation.

Indeed other members of Philip's family were offered testing.

On the next page is a diagram showing the translocation, and the different gametes which result from meiosis.




**Q5 Why is it important to offer other members of the family the appropriate genetic test?**

To give them information as to whether they are carriers of the translocation. If they are carriers of a balanced translocation this will have no effect on their health but may result in problems (miscarriage, stillbirth, multiple congenital abnormalities, developmental delay, mental retardation) in children.

More information about reciprocal translocations can be found on the genetics website.