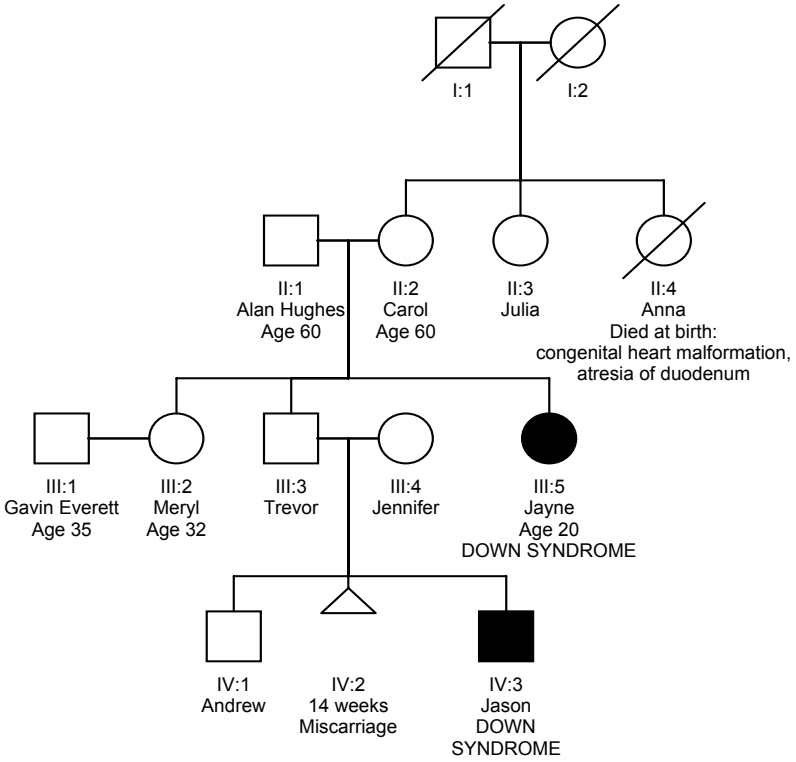
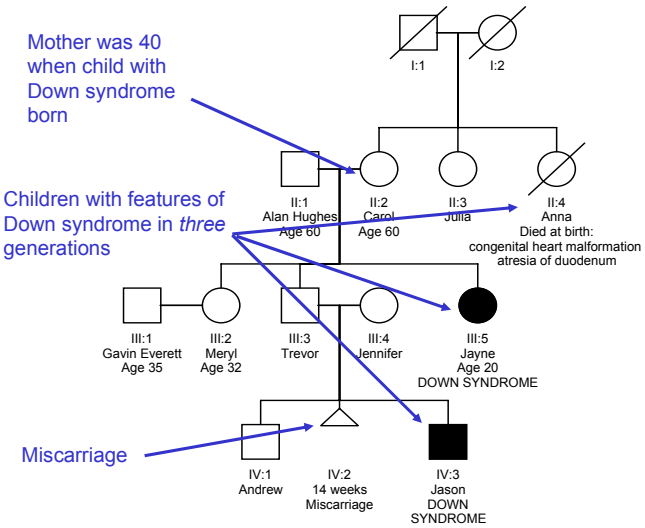
5. Why are there several children with Down syndrome in my family?

Mr and Mrs Everett (III:1 and III:2) are thinking of having children and consult you because they are concerned about Mrs Everett's family history of Down syndrome.



Q1 What features are there of note in the family tree?

Note that the two people with physical features diagnostic of Down syndrome (Jayne and Jason; III:5 and IV:3) are in separate generations, and also that Anna (II:4), who died at birth, had congenital anomalies that are typically associated with Down syndrome. Note also that Mrs Everett's brother's wife Jennifer (III:4) had a miscarriage at 14 weeks. Jayne's mother was aged 40 when Jayne was born.



Q2 What is the most likely mechanism to explain why Down syndrome (a chromosome anomaly) is being inherited in this family?

Having three people in three generations affected with the same condition should raise the suspicion that a single gene condition is being inherited in this family. However, as Down syndrome is known to result from having three copies of the genes on chromosome 21, single gene (autosomal recessive, autosomal dominant and X-linked) inheritance in this family does not need to be considered.

Down syndrome can be caused by the three copies of chromosome 21 all remaining as separate copies (trisomy 21) or can be caused by a Robertsonian translocation where the third copy of chromosome 21 is joined end to end with another chromosome (only chromosomes 13, 14, 15, 21 or 22 are involved in Robertsonian translocations). It is not possible to determine from physical examination if a person has trisomy 21 or a Robertsonian translocation causing Down syndrome because both result in the same clinical features.

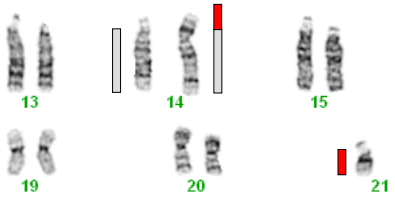
The fact that Jayne's mother was aged 40 when Jayne was born might suggest that Jayne could have trisomy 21 caused by maternal non-disjunction associated with increased maternal age. However the presence of at least two (and possibly three) people with Down syndrome and the miscarriage should raise real concerns that a translocation may be being inherited in this family.

It would therefore be extremely important to check the chromosomes of the two people affected with Down syndrome to confirm their karyotypes. If both had trisomy 21, due to unrelated errors in meiosis in different people, other family members should not be at an increased risk. If Jayne and Jason had a Robertsonian translocation, the concern is that translocation carriers in the family would have a high risk of having a live born baby with Down syndrome.

In fact, both Jayne and Jason were found to have a Robertsonian translocation between chromosome 13 and chromosome 21. Karyotyping was offered to other members of the family. Trevor was found, as expected from the pedigree relationships, to be a carrier of the Robertsonian translocation, but his sister Meryl had normal chromosomes.

This is part of the karyotype of Jason's father.

It shows a **balanced Robertsonian translocation**:
two copies of chromosome 14 and
two copies of **chromosome 21**

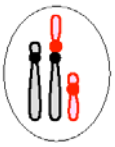


So Jason's father is a carrier of the translocation. He is normal, and has normal health, as he has the correct number of genes, but their location has been altered.

Q3 What is the probability that Andrew (IV:1) is a carrier

Andrew's father Trevor is a carrier of a balanced Robertsonian translocation. As Andrew is normal, he has not inherited the unbalanced form. He has therefore inherited either the normal number 14 and normal number 21 from his father, or the translocation chromosome comprising one chromosome number 14 fused to one chromosome 21. The probability that he is a carrier is therefore **1 in 2**.

Robertsonian translocation: practice points



- Results from breakage of two acrocentric chromosomes (13, 14, 15, 21, 22) at or close to their centromeres, with subsequent fusion of their long arms to form one chromosome.
- Individual clinically normal if no gain or loss of material *(translocation carrier)*
- Unbalanced products may cause chromosomally abnormal baby, miscarriage, stillbirth, infertility

- **Other family members should be offered testing for carrier status**