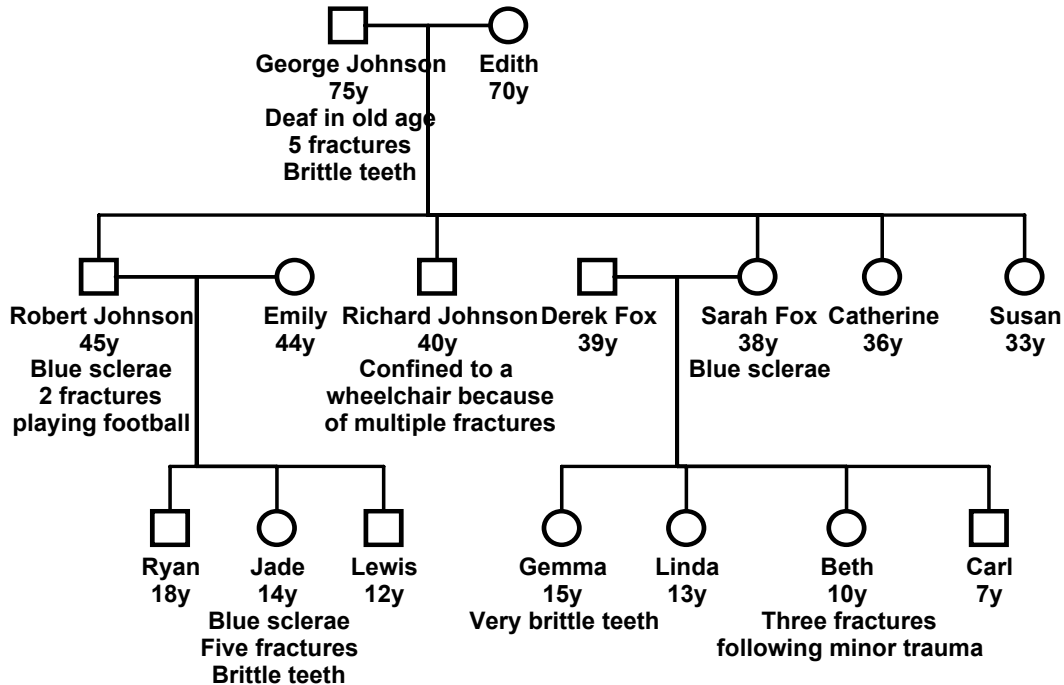


## 8. Why do people in my family fracture their bones so easily?

Ryan Johnson (III-1) was concerned that he, or his children, might be at risk of fractures. Several members of his family have sustained fractures - in varying numbers and degree. Some family members had fractured a bone after very minor trauma.



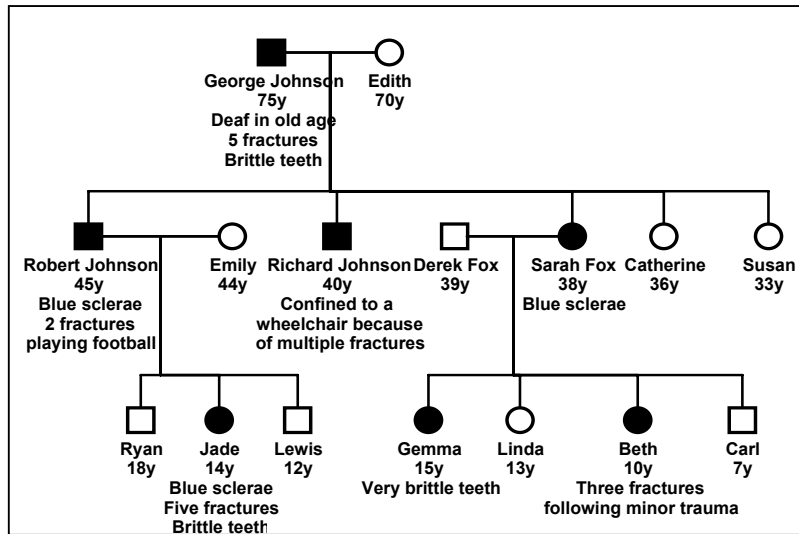
### Q1 Are the other signs which family members show likely to be due to the same condition?

The first question to consider is whether blue sclera and brittle teeth are likely to be part of the same condition which is causing the fractures

Sarah Fox's father, George Johnson, I:1, has fractures and brittle teeth and became deaf in old age. His daughter, Sarah (II:5) has blue sclerae; his granddaughters Gemma and Beth Fox (III:4, III:6) each have one of their grandfather's signs - brittle teeth and fractures respectively. If these people all have the same condition it suggests that its manifestations can be very variable from person to person. Note that Sarah Fox's other two children have no signs.

As Jade Johnson III:2 (age 14y) has three features - blue sclerae, five fractures, brittle teeth – this suggests that these are all components of the condition. Other people have different combinations of these signs.

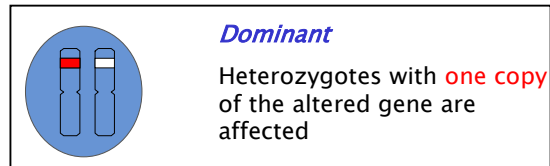
Assuming that any combinations of these signs are indicative that a family member has the condition, the pedigree can be amended as given overleaf to show the affected people.



**Q2 If so, how does it appear to be being inherited?**

The signs and symptoms are diagnostic of osteogenesis imperfecta type 1 (which is known to be inherited as an autosomal dominant).

**Dominant** - A trait/disease expressed in a heterozygote



**Q3 What are the pedigree features to confirm this?**

The pedigree features are compatible with and confirm autosomal dominant inheritance:

- In three generations
- Males and female affected
- Male to male transmission (so the gene is not on the X chromosome)
- Affected people have affected and unaffected children

**Q4 What is the probability that a child of Ryan Johnson (III:1) will inherit the condition?**

The pedigree pattern shows autosomal dominant inheritance - an affected member will have one copy of the "normal" gene and one copy of the altered gene. There is a 1 in 2 chance that a child will inherit the altered gene from an affected parent.

However, if we assume that Ryan is unaffected after clinical examination (normal teeth and sclerae) at age 18 y and therefore he has not inherited the gene, the probability is very small (or nil)

**Q5 What is the probability that a child of Gemma Fox will inherit the condition?**

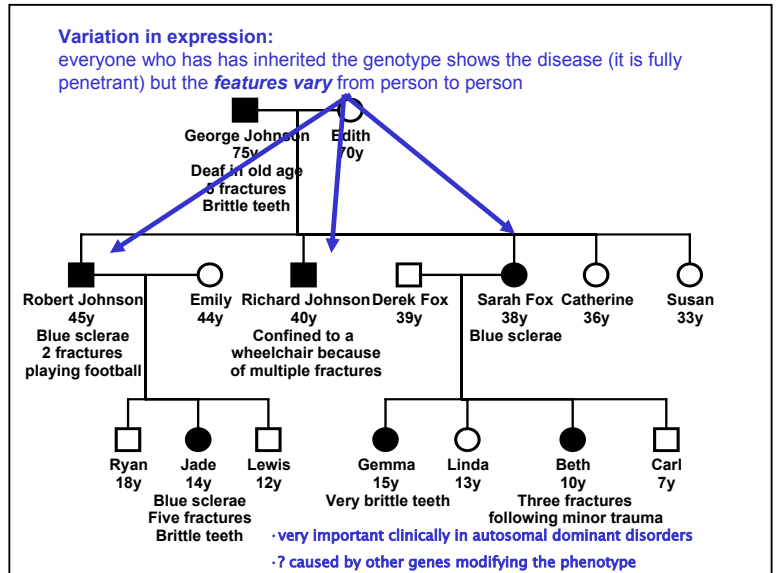
As Gemma has very brittle teeth with an appearance compatible with dentinogenesis imperfecta, this is a sign that although she is mildly affected she does have the altered gene for osteogenesis imperfecta. Therefore each of her children has a 1 in 2 probability of inheriting the gene for the condition. Unfortunately, they could be more severely affected.

**Q6 People seem to have different manifestations of the condition. What genetic phenomenon is being shown in this family? Why is it clinically important?**

The severity and presence of the individual signs of osteogenesis imperfecta vary from person to person. This is called variation in expression, which is a characteristic of many dominant disorders. It is therefore extremely important to examine everyone in this family carefully for minor signs (eg blue sclerae).

Note that even though the condition may give only minor signs, it appears to be fully penetrant - that is, everyone who has inherited the altered gene shows physical signs.

(There is an animated tutorial on autosomal dominant inheritance on the homepage of the genetics website)



*Some background information about osteogenesis imperfecta*

The term osteogenesis imperfecta (OI) is used to describe a heterogeneous group of disorders characterized by brittle bones. A useful clinical classification recognises four main subtypes, but although useful clinically, the classification is being shown to be a major oversimplification in the light of molecular genetic information. Type 1 OI, as seen in the family above, is the most common form, and has frequent fractures, blue sclerae, osteosclerosis causing deafness in 50%, dentinogenesis imperfecta and is inherited as an autosomal dominant condition. Type II is the perinatal lethal form, with multiple fractures at birth and poor mineralisation of bone; it is usually caused by a new dominant mutation. Type III is usually severe, causing progressive deformities and short stature. Type IV is like type I but with white sclerae and may be milder. Germline mosaicism for a new dominant mutation has been shown to account for rare instances of affected siblings being born to unaffected parents. Type 1 collagen is found in bone, tendon and skin and is comprised of two  $\alpha 1(I)$  and one  $\alpha 2$  collagen chains. Mutations in several families with type I OI have been determined in the  $\alpha 1(I)$  gene. A frequently observed defect is the inactivation of one allele at the  $\alpha 1(I)$  locus, resulting in half the amount of the  $\alpha 1(I)$  protein being produced. As type 1 collagen requires a ratio of 2:1 of  $\alpha 1(I)$  to  $\alpha 2$  chains for triple helix formation, there is an excess of  $\alpha 2$  chains which are degraded. Only half the normal amount of type 1 collagen is produced, presumably related to the fragility of the bones. Unlike the situation in which the protein product is an enzyme, a reduction of 50% in this structural protein has significant phenotypic consequences.