Pedigree Analysis: Carrier Probabilities

In these problems you examine family pedigrees displaying a rare disease trait and calculate the probability that various <u>unaffected</u> family members are "carriers," (that is, they carry a single disease allele).

This kind of analysis is important in genetic counseling. For example, if a male and female are both unaffected by a genetic disease trait, but are both are carriers, then for each of their children there is 1 chance in 4 that the child will be affected by the disease.

This figure displays a typical pedigree, in which a single individual is affected by a genetic disease. In each problem,

The first task is to decide if the genetic trait is:
- dominant or recessive
- autosomal or X-linked.

The second task is to decide the probabilities that the founding parents, I-1 and I-2, are carriers, and the probabilities that various unaffected descendents are unaffected, including V-4 and V-5.

The third task is to determine the probability that an individual VI-1, whose phenotype has not been observed, will be affected by the disease trait.

(The diamond means the gender is not specified and the question mark "?" indicates the phenotype with respect to the disease trait is not known.
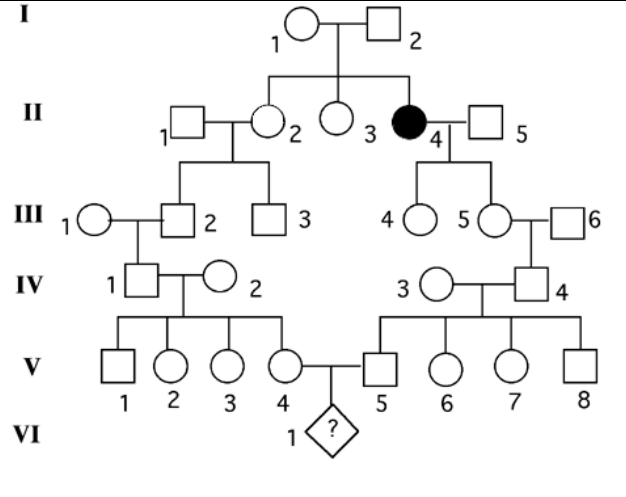
In these Cognitive Tutor problems, we make three simplifying assumptions:

1. **Complete Penetrance**. If an individual represented in the pedigree carries one dominant allele or two recessive alleles for a trait, then that individual will be affected (will express the phenotype associated with the trait).

2. **Rare-in-Population.** In each problem, the trait in question is rare in the general population. **Assume for the purposes of these problems that individuals who marry into the pedigree in the 2nd, 3rd and 4th generations are not carriers**. This does not apply to the founders - the individuals at the top of the pedigree - either or both of whom could be carriers.

3. **Not-Y-Linked**. The causative genes in these problems may be autosomal or X-Linked, but are not Y-linked.

Determining Linkage
The first important step in analyzing carrier probabilities is to determine if the pedigree is autosomal recessive or x-linked recessive, since the two different modes of transmission afford different inferences.

- The disease in the pedigree on the left must be autosomal recessive trait, since the affected daughter has two unaffected parents. (If the trait were dominant, one or the other parent would have to be affected. If the trait were X-linked recessive, her father would have to be affected.)

Autosomal Recessive Traits
A few basic facts about autosomal recessive traits will allow us to calculate the probability that unaffected individuals are carriers:

- An affected individual must be homozygous recessive and must pass one disease allele to each one of its children.
- An affected child must inherit one disease allele from its mother and one from its father.
- A parent with a single disease allele has a probability of ½ of passing the allele to any one of its children.

Calculating Probabilities
- The probability that an individual is a carrier is a number between 0 and 1.
- If we know an unaffected individual must be a carrier, then the probability is 1 that the individual is a carrier.
- If we know an unaffected individual cannot be a carrier, then the probability is 0 that the individual is a carrier.
- If we know that one parent is a carrier (p=1) and the other parent is not (p=0), we know there are two equally likely
   possibilities:
      - If the child inherits the first parent's single disease allele, the child will be a carrier.
      - If the child inherits the first parent's other allele, the child will not be a carrier.
   Since there are a total of two equally likely outcomes, and in one of those two cases the child is a carrier, the probability that the child is a carrier is ½ or 0.5

<u>Calculating the Probability an Unaffected Child is a Carrier When One Parent is Not a Carrier.</u>
If one parent is not a carrier, then a child can only inherit a disease allele from the other parent. In these problems, we can assume that any individual marrying into the family is not a carrier.

As we have just discussed, if the other parent is definitely a carrier, then the probability of passing that allele to a child is ½ and so the probability the child is a carrier is ½.

But suppose that the probability that the other parent is a carrier is only ½ instead of 1. The probability the child will be a carrier is ½ * ½ = ¼. Here's why:

- The probability the parent is a carrier is ½.
- But if the parent is a carrier, the probability of passing the allele to a child is still just ½.
- The probability that the parent is a carrier AND that the parent passes the allele is ½ times ½ = ¼.

In general, if one parent is not a carrier, the probability that a child will be carrier is:
                           ½ times (the probability the other parent is a carrier).
That is, we multiply the probability of passing a disease allele, ½, times the probability that the parent does, in fact, carry the disease allele.

<u>Calculating the Probability an Unaffected Child is a Carrier When Both Parents are Carriers.</u>
Finally, let's consider one more situation. Suppose both parents are carriers. What is the probability that a child who is unaffected is a carrier?

If a carrier mother and a carrier father have a child, there are four possible outcomes which are equally likely. (The probability of each outcome is ¼).

Inherit trait From mother	Inherit trait From father	Phenotype	Carrier?
NO	NO	Unaffected	NO
YES	NO	Unaffected	YES
NO	YES	Unaffected	YES
YES	YES	AFFECTED	NO

But if the child is **unaffected**, we can rule out the fourth outcome, in which the child inherits an allele from both parents.

Given the three equally likely remaining events, what is the proability that if both parents are carriers, an UNAFFECTED child will be a carrier?

X-Linked Traits

Reasoning about carriers of x-linked recessive traits is a little more complicated than reasoning about autosomal recessive traits, but again a few basic facts will allow us to calculate probabilities.

- An affected female must be homozygous recessive and must pass one disease allele to each one of her children.
- Males are hemizygous for an X-Linked trait. An affected male must have a single disease allele.
- An affected male must have inherited the disease allele from his mother.
- An affected male must pass the disease allele to his daughter.
- A male never passes an x-linked trait to a son.
- An unaffected male cannot be a carrier and cannot transmit a disease allele to any child.

Use these facts and the discussion of probabilities above to reason about the X-Linked pedigree problems in this unit