

Video Tutorial 5.1: Analysing a pedigree

Pedigree analysis can be used to understand the pattern of inheritance of a genetic trait when the number of offspring is low but information about multiple generations is available. As a result, pedigrees – or family trees – are particularly useful in studying inheritance in humans and domesticated animals for which good records are available.

A pedigree diagrams parents and their offspring over several generations. Remember that males are depicted as squares and females as circles. A filled symbol is an affected individual, someone who shows the phenotype of interest, and open symbols are individuals who are not affected.

A horizontal line connecting two individuals is a mating or a couple, and a vertical line indicates a generation and the resulting offspring or children of the couple. The generations are numbered along the left of the pedigree using Roman numerals. Individuals within each generation are assigned Arabic numerals, shown under each symbol.

The first thing to look for when analyzing a pedigree is whether there are unaffected parents who have an affected offspring, as in this example. Here, in Pedigree A, the son II-1 is affected, but neither of his parents show the trait. We can deduce that trait is recessive.

In Pedigree B, we see that the daughter II-2 is affected, as is her father, individual I-1. If we see that all affected individuals have an affected parent, then we can deduce that the trait is dominant.

In many genetics questions, you are asked to determine the probability that an unknown individual will be affected by a particular genetic trait. Let's work through a pedigree shown in Chapter 5 of the text.

In this example, a woman, Individual III-2, is pregnant. Since a number of her relatives have the same particular genetic disorder, she wants to know the likelihood or probability that her unborn child, represented by the question mark, will be affected. We can do a careful step-wise analysis of the phenotypes and likely genotypes in the family tree to determine the probability of the child having the trait.

Let's start with what we know from the pedigree. Neither the woman nor her husband (Individual III-1) is affected by the genetic trait of interest. The trait is rare, but the woman's brother (Individual III-3), her aunt (Individual II-6), her grandmother (Individual I-4), and her husband's uncle (Individual II-1) are all affected.

First, we have to determine how this trait is inherited, whether it is dominant or recessive. Individual II-6 and her mother I-4 are affected, but we notice that both Individuals II-1 and III-3 have the trait but do not have an affected parent. As mentioned earlier, seeing an affected child with unaffected parents tells us that the trait is recessive. Let's label all the affected individuals as **aa** since they must be homozygous recessive.

Since neither the expectant mother nor the father shows this recessive trait, their child can only be affected if both of them are heterozygotes. So our next step is to figure out the probability that each of them is heterozygous.

Let's begin with the mother, Individual III-2. Her parents must both be heterozygotes and have the genotype **Aa** (*big A, little a*), because her brother is affected by the trait. We can write these genotypes on the pedigree. Since her parents are both **Aa**, what is the probability that she herself is also **Aa**?

You may have immediately thought that the answer is one-half, since half of the offspring in a cross of two heterozygotes have the **Aa** genotype. But we need to think a little more carefully and include an important piece of information in our analysis. Since the woman herself is not affected, she cannot be **aa** and must be either **AA** or **Aa**. We note this as **A₋**. Among those who are **A₋**, two-thirds are **Aa**, and one-third are **AA**, as we can see in a Punnett square involving two heterozygous parents. So the mother's probability of being **Aa**, knowing that she is not affected by the trait, is two-thirds.

Now we turn to her husband, Individual III-1. We have to go back further in the pedigree this time. He is not affected, so he is **A₋**. His father, Individual II-3, is unaffected and assumed to have the genotype **AA**, as the trait is rare and he is marrying into the family. He is unlikely to be a carrier, unless there is evidence to the contrary.

His mother, Individual II-2, is not affected either. Her parents must both be heterozygous, as they had an affected son. We can note on our pedigree that the paternal grandparents I-1 and I-2 must both have been **Aa** and their daughter (II-2) must be **A₋**. As before, the probability that this individual is a carrier is two-thirds. If she has a two-thirds probability of being **Aa**, then III-1, who is her son, has a one-third probability of being **Aa**. This is because there is a 50% chance he will have received the **a** allele from his mother. We have used the product rule here – we multiplied the probability that his mother is **Aa**, which is $2/3$, times the probability that he inherited the **a** allele from her, which is $1/2$. One half of $2/3$ is $1/3$.

We are not quite done yet. The probability that the husband is **Aa** is one-third. The probability that the pregnant woman is **Aa** is two-thirds. In order for them to have an affected child, both of them must be carriers.

If both parents are carriers, the probability that their child is affected, that is, has the genotype **aa**, is one-fourth. We can use the product rule again, multiplying these probabilities to calculate the overall probability that both of them are **Aa** and that they have an affected child. Thus, the total probability that the child will be affected is $1/3 * 2/3 * 1/4$ or $2/36$, which is equal to $1/18$. This is the probability that the husband is a carrier times the probability that the expectant mother is a carrier times the probability that their child will be affected if both parents are heterozygotes.

Let's ask one more question. What is the probability that the child will not be affected? You could calculate this by carefully determining all of the possible ways that the child would inherit one **A** (*big A*) allele, which is all that is needed to be unaffected. But it is generally simpler to work out the probability that the child will be affected, as we did, and subtract this from 1. In this scenario, the probability that the child is not affected must be $1 - 1/18$, or $17/18$.

This is a relatively complicated pedigree question, but by methodically working through the possibilities and recognizing the probabilities from Mendelian ratios, we arrived at a solution. This problem illustrates two important points to consider in solving pedigrees. First, the probability that the expectant mother is **Aa** is two-thirds, not one-half, since we know that she is not affected by the disorder. Second, even if both parents are heterozygotes, the probability of having an affected child is only one-fourth.

Following the basic steps outlined in the approach illustrated here, you can analyze the majority of pedigrees you may encounter.