

## Analyzing Pedigrees

### INTRODUCTION

You may have heard people say a health condition like asthma or allergies “runs in the family.” That expression means that more than one individual in the family has the condition. That pattern is typically a clue that the condition may be caused, at least in part, by genetics.

So, can you predict who in a family is most likely to inherit a particular health condition? Pedigrees are a tool that can help health professionals do just that. In this activity, you will practice interpreting actual pedigrees and consider their benefits and limitations.

### What Are Pedigrees?

**Pedigrees** are charts that trace the inheritance of a trait or health condition in several biologically related individuals spanning more than one generation.

Most health conditions are determined by the functions of many genes and the environment. However, some are determined largely by a single gene — more precisely, by changes in the DNA (or genetic variants) that affect a single gene. For such conditions, it is possible to infer their pattern of inheritance (for example, autosomal dominant or recessive) by examining pedigrees.

To create a pedigree, health professionals such as **genetic counselors** — who have specialized training in medical genetics and will typically advise individuals about the chances of inheriting or passing on various genetic diseases — combine family history information with, when available, information from medical and genetic tests. They then use the pedigree to identify people who may develop the health condition and/or who may carry genetic variants associated with that condition.

### PROCEDURE

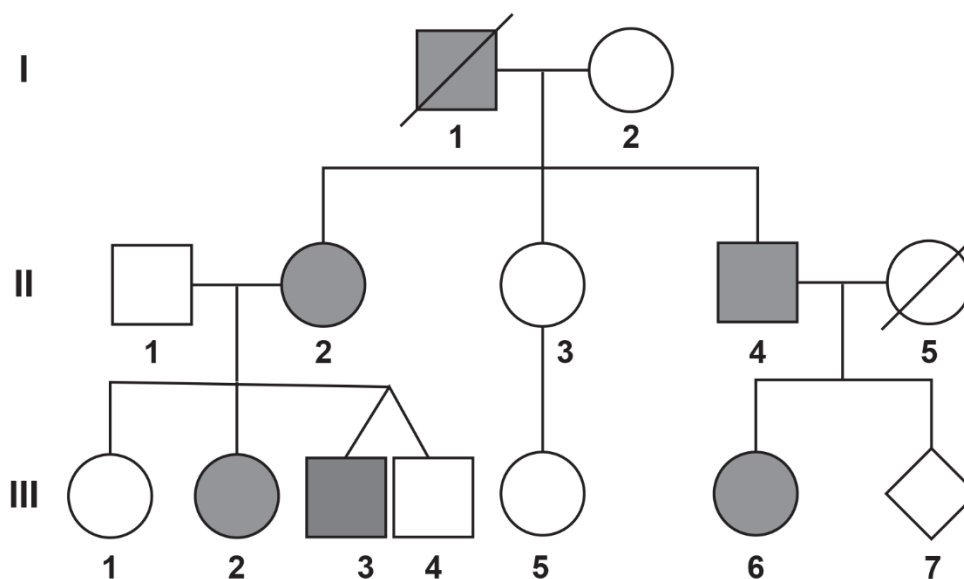
Examine the following pedigrees and answer the questions associated with each. Your instructor may only assign certain pedigrees and questions.

For all the pedigrees in this activity:

- **Shaded symbols** indicate individuals affected with the health condition of interest.
- **Unshaded symbols** indicate unaffected individuals.
- **Squares** indicate men.
- **Circles** indicate women.
- **Diamonds** indicate individuals whose gender is unknown or who do not identify as a particular gender.
- If included, Roman numerals (e.g., I, II, III) on the left-hand side of a pedigree indicate generations. Arabic numerals (e.g., 1, 2, 3) under the pedigree symbols note the number of individuals in that generation.

### PART 1: Practice Interpreting Pedigrees

Examine Pedigree 1, then answer the questions that follow.



**Pedigree 1.** Example of a pedigree.

1. Which of the following can be inferred about Individual 4 in the second generation (Individual II-4)?
  - a. Individual II-4 is a woman.
  - b. Individual II-4 has two known biological children.
  - c. Individual II-4 has one deceased biological sibling who was unaffected.
  - d. Individual II-4 is unaffected.

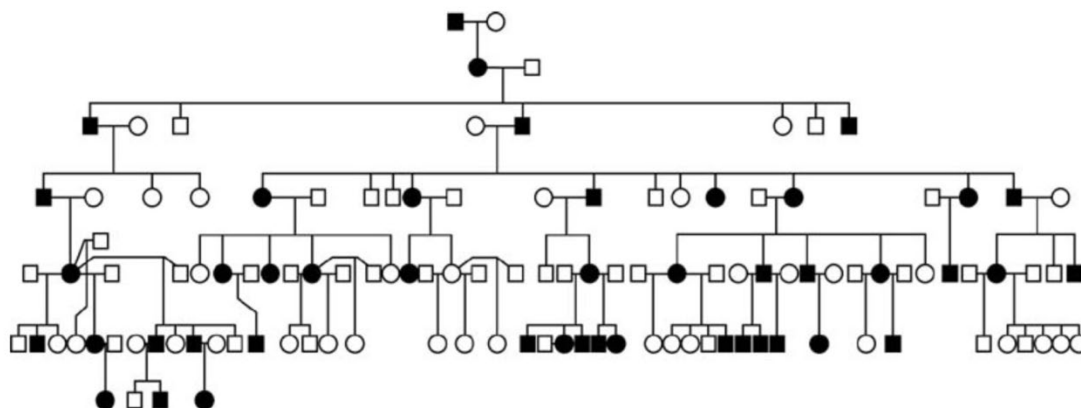
Explain your reasoning for the answer you selected:

2. Individual II-3 had a child (Individual III-5) using a sperm donor. Which of the following can be inferred about Individual III-5?
  - a. She is not genetically related to other individuals in Generation III.
  - b. She has inherited 50% of her DNA from Individual II-3.
  - c. She has not inherited any DNA from Individual II-3.
  - d. She is affected with the health condition of interest.

Explain your reasoning for the answer you selected:

## PART 2: Examining Patterns of Autosomal Inheritance

Now examine Pedigree 2, a larger pedigree published in a scientific journal.

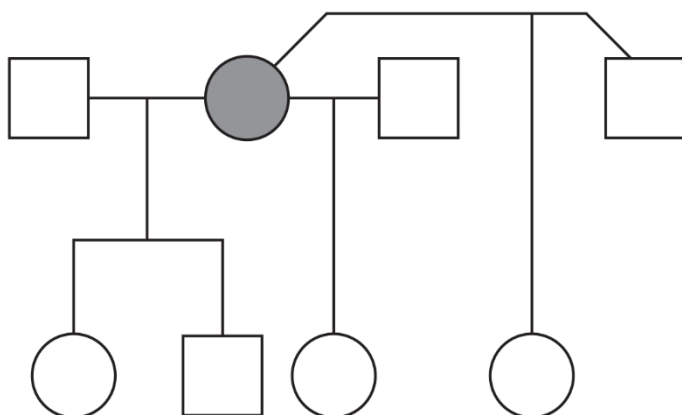


**Pedigree 2.** A large pedigree spanning seven generations. (Adapted from Zoghbi et al. 1988.)

3. Pedigree 2 most likely shows the inheritance of an autosomal dominant condition because:
- Most affected individuals are men.
  - The family is very large.
  - The condition occurs in every generation.
  - Filled symbols always show an autosomal dominant trait.

Explain your reasoning for the answer you selected:

4. The following figure represents a small section of Pedigree 2.



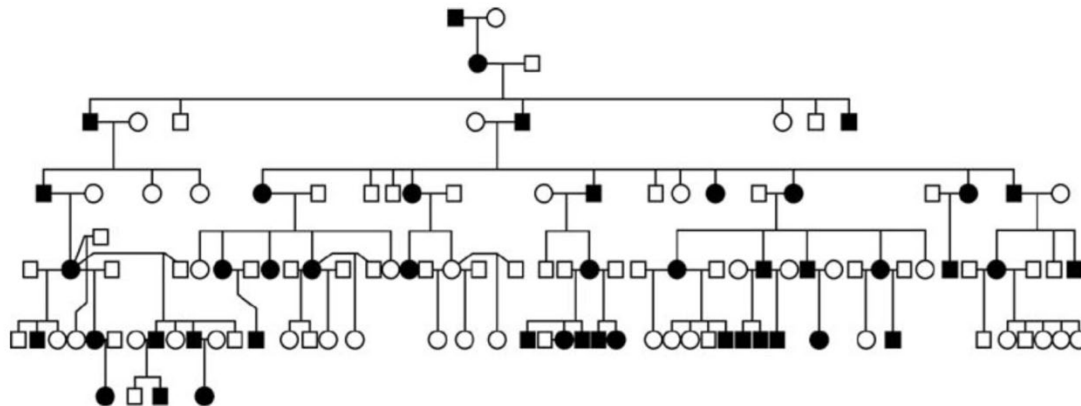
Which of the following does this figure show about the affected individual?

- She has several affected biological children.
- She had four biological children with three different partners.
- She had three biological children with two different partners.
- She has three biological siblings who are all unaffected.

Explain your reasoning for the answer you selected:

Pedigree 2 is of a large family with several members affected by **spinocerebellar ataxia 1 (SCA1)**, a condition that involves the nervous system. Most individuals with SCA1 don't have any symptoms as children. However, over time, people with SCA1 start to lose control over their balance and movement. The symptoms gradually worsen, and people typically die 10 to 30 years after symptoms first appear. There is currently no cure for SCA1.

SCA1 is caused by genetic variants in a single gene. Individuals with one copy of a SCA1-associated variant are almost certain to develop SCA1. Almost all individuals with SCA1 are heterozygous, since individuals with two copies of the variant have very severe symptoms and are unlikely to survive into adulthood.



**Pedigree 2.** This large pedigree shows the inheritance of SCA1. (Adapted from Zoghbi et al. 1988.)

5. If an individual affected with SCA1 has a biological child with an individual without the condition, what are the chances that their child has SCA1?
  - a. 0%
  - b. 25%
  - c. 50%
  - d. 100%

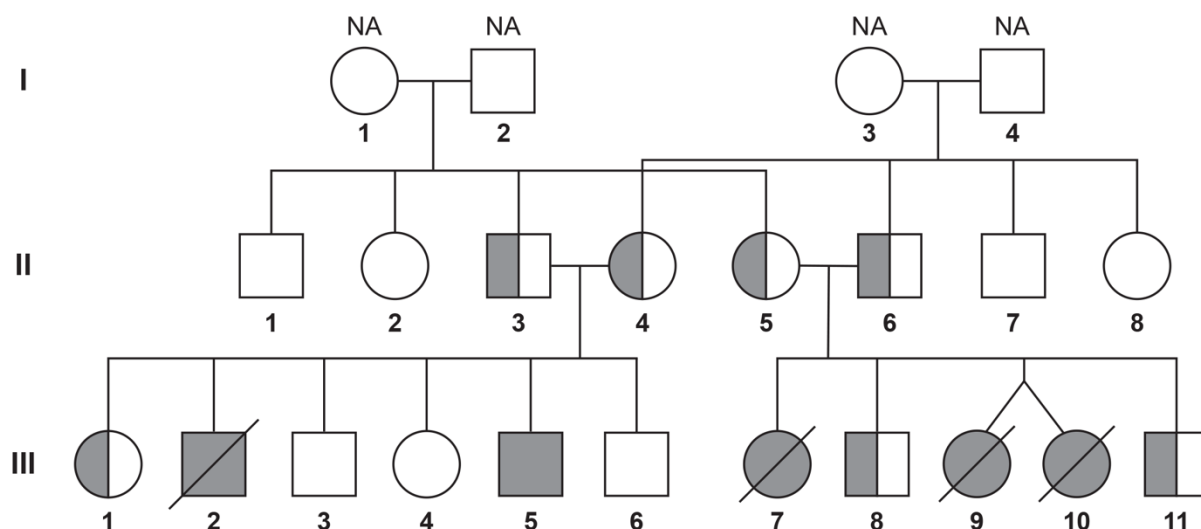
Explain your reasoning for the answer you selected:

6. If one of your genetic relatives had SCA1, do you think you would want to get tested for a genetic variant associated with the condition? (There are no right or wrong answers.)
  - a) Yes
  - b) No

Explain your reasoning for the answer you selected:

**Beta thalassemia major** is an inherited condition in which the body produces low levels of functioning hemoglobin. **Hemoglobin** is the protein in your red blood cells that binds oxygen. People with beta thalassemia major do not get enough oxygen delivered to the cells of their body, which may cause them to feel tired, weak, or short of breath. Doctors can usually diagnose beta thalassemia major in children during their first two years of life. With proper medical care, most individuals with beta thalassemia major can have minimal symptoms.

Pedigree 3 shows a large extended family with several individuals with beta thalassemia major.



**Pedigree 3.** A pedigree that shows the inheritance of beta thalassemia major. The half-shaded symbols represent individuals who are heterozygous carriers, which means that they “carry” one copy of the variant associated with beta thalassemia major, but they don’t typically have disease symptoms. NA means no available data regarding the condition. (Adapted from Baig et al. 2008.)

7. Pedigree 3 is typical of autosomal recessive inheritance because:
- Most affected individuals are women.
  - Many people have died, as shown by the crossed-out symbols.
  - Affected individuals inherited DNA from individuals who are also affected.
  - Affected individuals inherited DNA from individuals who are carriers.

Explain your reasoning for the answer you selected:

8. If a carrier has a biological child with an individual with beta thalassemia major, what are the chances the child has beta thalassemia major?
- 0%
  - 25%
  - 50%
  - 100%

Explain your reasoning for the answer you selected:

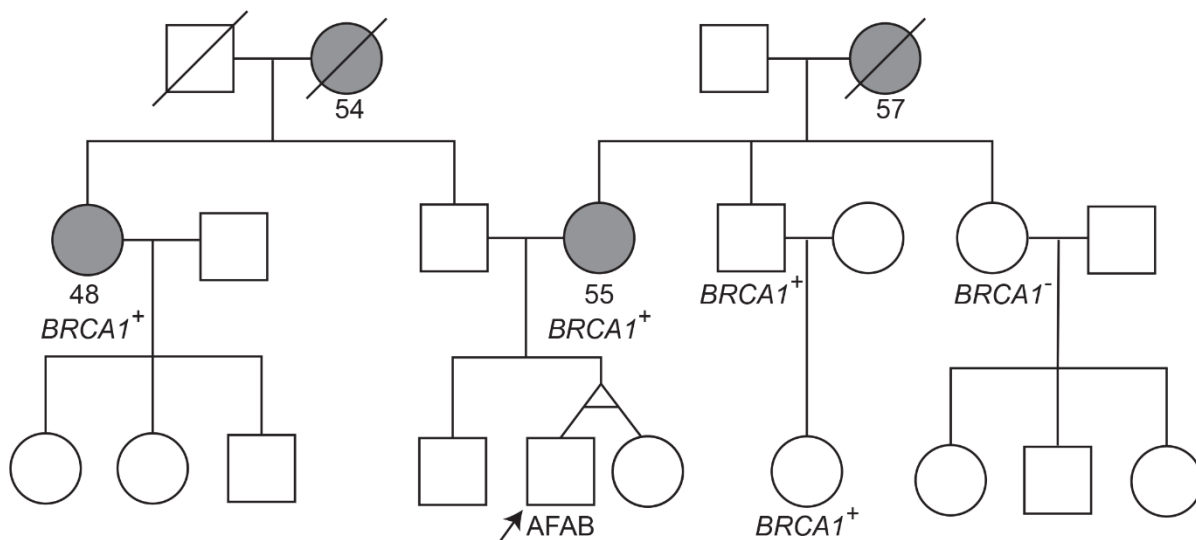
9. If one of your relatives had beta thalassemia major, do you think you would want to get tested for the disease-associated variant? (There are no right or wrong answers.)
- Yes
  - No

Explain your reasoning for the answer you selected:

### PART 3: Determining Inherited Breast Cancer Risk

One rare type of inherited breast cancer is associated with variants that affect a gene called *BRCA1*. About 13% of cisgender women will develop breast cancer sometime during their lives; 55%–72% of women with the disease-associated *BRCA1* variant will develop breast cancer. In contrast, about 0.1% of cisgender men in the general population will develop breast cancer, and the probability increases to about 1% if they have the harmful *BRCA1* variant (Ibrahim et al. 2018). Individuals with harmful *BRCA1* variants are also more likely to develop additional types of cancers, including ovarian, pancreatic, and prostate cancers and melanoma.

Pedigree 4 shows several individuals with breast cancer and the harmful *BRCA1* variant.



**Pedigree 4.** A pedigree that shows the inheritance of breast cancer associated with *BRCA1* variants. The numbers below the symbols indicate the age at which the cancer was diagnosed. Individuals tested for the genetic variant associated with breast cancer have *BRCA1+* (variant present) or *BRCA1-* (variant absent) under their symbol. AFAB means assigned female sex at birth. The arrow indicates the individual who sought genetic counseling. (Adapted from Sacca et al. 2019.)

10. A 19-year-old transgender man visited a genetic counselor to find out whether he is more likely to develop breast cancer. This individual is indicated with an arrow in Pedigree 4. Is it possible he would have inherited the *BRCA1* variant associated with breast cancer?
  - a. No, because he is a man.
  - b. Yes, because his monozygotic twin has breast cancer.
  - c. No, because his biological parents do not have breast cancer.
  - d. Yes, because one of his biological parents has the harmful *BRCA1* variant.

Explain your reasoning for the answer you selected:

11. To reduce the chance of developing breast cancer, some individuals with the harmful *BRCA1* variant may decide, in consultation with their doctors, to have their breasts and/or ovaries removed before any signs of cancer develop. If you were the individual seeking genetic counseling, would you want to get tested for the *BRCA1* variant? (There are no right or wrong answers.)
  - a. Yes
  - b. No

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Explain your reasoning for the answer you selected:

12. Reflect on how your thinking has changed by doing this activity. Write your answer by completing the following prompts.

I used to think:

And now I think: