Pedigrees and Modes of Inheritance

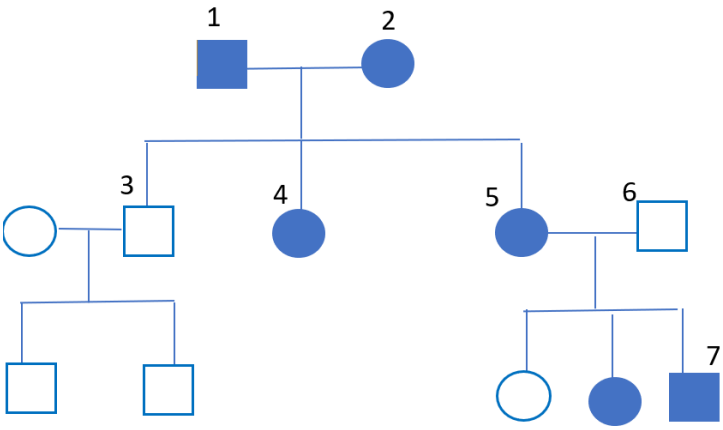
Introduction:

A key aspect of any genetics course is understanding inheritance. Genetic traits can be passed from parent to offspring. Not all traits are as equally likely to be passed down; some traits are more likely to be inherited than others and for some traits. Some offspring are also more likely to inherit a gene than others due to sex.

A pedigree is like a family tree. It shows the relationship between individuals and which individuals are affected by a disease/disorder. A circle on a pedigree represents a female and a square on a pedigree represents a male. Fully shaded shapes represent individuals with an affected phenotype. Unshaded individuals do not show an affected phenotype. There are two ways that carriers (individuals who have an allele of the disorder but do not express it) can be represented. Some pedigrees will indicate that an individual is a carrier with a dot in the center of their shape or by shading in half of their shape. Other pedigrees will not indicate a carrier and will only indicate phenotypes. In these pedigrees, an unshaded shape could be a carrier or a person without the disorder because they both have the same phenotype.

Practice:

Look at the following pedigree and answer the questions.



1. What is the sex of the individual marked as #1?
2. How many children did individual #1 and #2 have together?
3. What is the relationship between individual #5 and individual #6?
4. What is the relationship between individual #5 and individual #7?
5. Which of the numbered individuals are affected by the disorder?

Modes of Inheritance:

A mode of inheritance is a way to describe the pattern that a gene gets passed down to offspring. Knowing the ratio of offspring and/or which individuals are affected can help you figure out the mode of inheritance. By looking at a pedigree you can determine mode of inheritance.

Humans have 23 unique chromosomes. The first 22 are considered autosomal; both sexes have these same chromosomes with the same genes in the same loci. The 23rd set are the sex chromosomes. A chromosomally typical male will have an X chromosome and a Y chromosome while a chromosomally typical female will have two X chromosomes. When looking at pedigrees for this class, the individuals marked as a circle are chromosomally typical females with two X chromosomes and those marked as a square are chromosomally typical males with an X and a Y chromosome.

Because a female only has X chromosomes for sex chromosomes, a father determines the sex of an offspring. A mother will pass down one of her X chromosomes to any offspring while a father will either donate an X chromosome to produce a chromosomally typical female or a Y chromosome to produce a chromosomally typical male.

Sex-linked, autosomal, and mitochondrial inheritance are categories of inheritance that differ greatly based upon what a parent can donate to their offspring. Sex-linked inheritance patterns have a sex-bias because they are on a sex chromosome. There is no sex bias for autosomal inheritance patterns because all sexes have autosomal chromosomes. Mitochondrial DNA comes from a mother to all offspring, regardless of sex. Only mothers can donate mitochondrial DNA to their offspring.

Sex-linked and autosomal are not modes of inheritance but rather categories of inheritance patterns.

What are the two types of autosomal modes of inheritance and what are the three sex-linked modes of inheritance?

Autosomal modes of inheritance:

Sex-linked modes of inheritance:

Which modes of inheritance can have carriers?

Steps for Identifying Mode of Inheritance

While some individuals can identify the mode of inheritance from a pedigree by guessing, a set of instructions can help others. Below, you can find a stepwise pattern to work through pedigrees and an explanation of why this pattern works. This set of instructions uses an elimination method. The goal is to "rule out" modes of inheritance that are unlikely. However, once you arrive at an inheritance pattern, you must check your work.

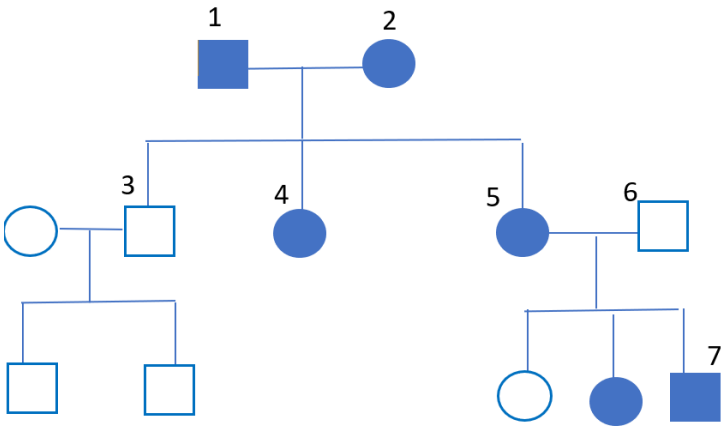
Steps:

1. Check if this is mitochondrial inheritance.
    - Mitochondrial inheritance is not sex-linked or autosomal because this DNA is passed down in the mitochondria from a mother to all of her offspring. This mode of inheritance can be proven to not be the inheritance pattern if any biological fathers pass on the disorder and/or if any children from an affected mother are not affected.
    - There is only one copy of mitochondrial DNA so the genes in this DNA are always expressed. This means there can never be any carriers or skipping of generations.
2. Check to see if there is a sex-bias in affected (or carrier) individuals. Sex-biases indicate that the mutation is on a sex chromosome (X or Y).
    - If there is a sex bias, proceed to step 3 to decide which sex-linked inheritance pattern the disorder is.
    - If there is not a sex bias (meaning there are an approximately equal number of female and male individuals affected), proceed to step 4 for autosomal inheritance patterns.
3. If you see a sex bias, you should proceed with the following steps to determine which sex-linked inheritance pattern this could be. *Warning: You cannot simply call something "sex linked" for an inheritance pattern. This is not a full answer*
    a. Determine if this mutation is on the Y chromosome.
        - Only chromosomal male individuals (indicated with a square) will have a Y chromosome. These individuals have only one Y chromosome, so if they inherited the mutation, they will always express it and thus there will never be carriers for chromosomal typical males. If there are no carriers, there cannot be any skipping of generations.
        - A father will always pass a Y-linked mutation to all of his sons but cannot pass this mutation to any daughters. This means there will always be an affected Dad and affected sons in every generation and the mutation cannot suddenly appear after unaffected generations.
        - If there are any females affected, carriers, skipping of generations, or fathers who do not pass the mutation to their sons, the mode of inheritance for your mutation is not Y-linked.
    b. If your mutation is sex linked and it is not on the Y chromosome, it is on the X chromosome. Use the following notes to narrow your mode of inheritance down to X-linked dominant inheritance or X-linked recessive inheritance. *Note, stating only X-linked inheritance is not a full answer. You must state X-linked dominant or X-linked recessive for the mode of inheritance*

- X-linked recessive mutations can be inherited by either sex, but more males than females will be affected. This is because females can be carriers for this mutation because they have two X chromosomes while males only have one. Mothers can pass a mutated X chromosome to either sons or daughters. For a female to show the affected (mutant) phenotype she must have inherited a mutated X chromosome from both her mother and father while for a male to show the affected phenotype, he only needs one mutated X chromosome (that he inherited from his mother). Fathers can pass down a mutated X chromosome only to daughters and never to sons.
    - If you see fathers passing this mutation to sons or an affected mom with an unaffected son, you know that the inheritance pattern is not X-linked recessive.
- X-linked dominant mutations can also affect either sex, however more females than males will be affected. To understand why this is, lets discuss probability. A female has two X chromosomes and either X chromosome has a probability of being mutant. She has twice as many locations she can get this mutation when compared to a male sibling. Only one mutated X chromosome is required to show the mutant (affected) phenotype because the mutant allele is dominant to the wildtype allele. X-linked dominant mutations are on an X chromosome, so a mother can pass down a mutated X chromosome to either sons or daughters and a father can only donate a mutated X chromosome to his daughters.
    - If you see fathers passing this mutation to sons or an affected son with an unaffected mother, you know that the inheritance pattern is not X-linked dominant.
    - **Question**: Is it possible to have an unaffected son from an affected mother? If so, how?

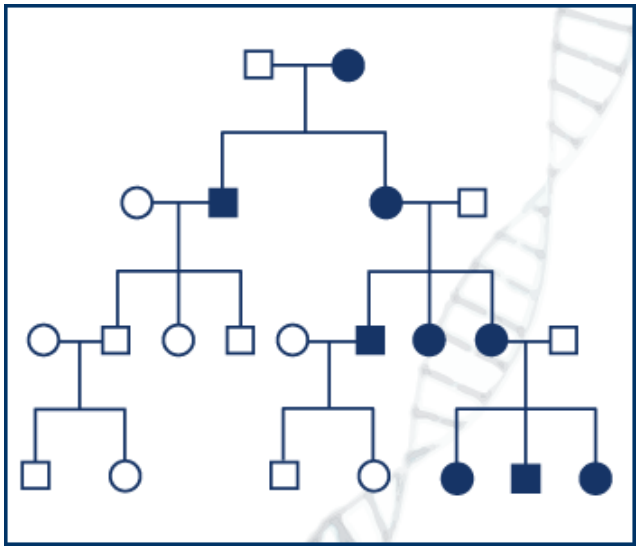
4. If you do not see a sex bias, you should proceed with the following steps to determine which autosomal inheritance pattern this could be. *Warning: You cannot simply call something autosomal inheritance for an inheritance pattern. This is not a full answer. You must state also if it is dominant or recessive.*
    a. Autosomal recessive inheritance patterns can be passed down and inherited by either sex equally. Two mutant alleles are required for an individual to show the mutant phenotype. This means that carriers and skipping of generations can exist. An affected individual must have inherited one mutant allele from both parents.
    b. Autosomal dominant inheritance patterns can be passed down and inherited by either sex equally. Only one mutant allele is required for an individual to show the mutant phenotype.

Practice:



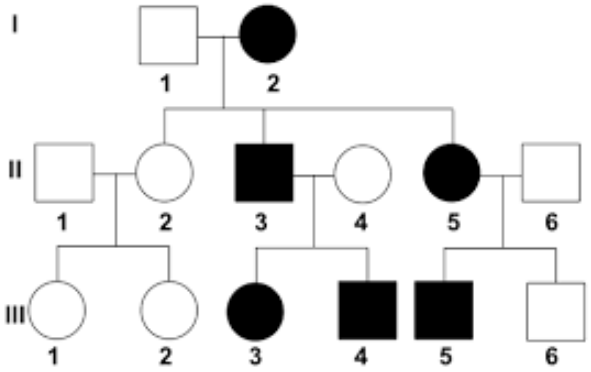
1.

a. Mode of inheritance:



2.

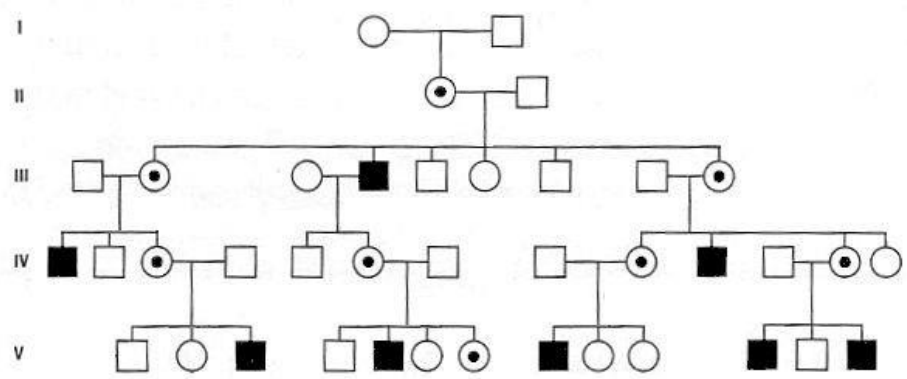
a. Mode of inheritance:

3. 

a. Mode of inheritance:

b. What is the genotype of individual 2 in the P1 generation?

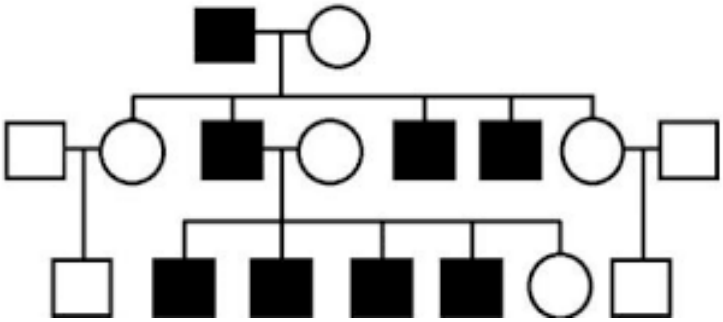
c. What is the phenotype of the individual in the P1 generation labeled 1?

4. 

a. What do the circles with dots represent in this pedigree?

b. Mode of inheritance:

c. What genotype would an individual represented by a shaded square have?

5. 
    a. Mode of inheritance:

Challenge problem:

If you see a disorder pedigree where all of the males in a family are affected, is the inheritance pattern necessarily Y-linked?