Recessive Inheritance

Recessive disorders are often rare, with very few people affected within one family. To show a recessive disease, you need two mutant copies of a gene (alleles). Both parents are carriers — one normal allele and one disease allele. Not all recessive alleles cause disease. Blue eyes are recessive meaning that you need two blue copies if you have one brown copy, your eyes will be brown.

Your family is always telling you that you have your mom’s giggle and Ol’ Uncle Ed’s ears. Lately you’ve begun to be quite proud of your own resemblances to other family members (at least the good-looking ones), and you’re even becoming pretty smart about how genetics works.

As it turns out, you have to be. Unfortunately, cystic fibrosis runs in your family. Right now, you’re young and ‘unattached’, but even though you’re an only child and you don’t have CF, you want to know if one day your kids may have to deal with this serious disease. How can you tell if CF may affect them?

When both alleles of a gene are knocked out, the diseases that can result are classified as recessive. Generally, these mutations cause “loss of function” — the allele isn’t there to produce anything. However, 50% (1 allele out of 2) is still enough to produce the necessary functional gene product. So disease only occurs when both alleles are mutated (and less than 50% of the necessary gene product is made).

In recessive disorders, both parents are carriers. They have one “normal” allele and one mutant allele. To be affected of course, their child has to inherit both mutant alleles — one from each parent. The carrier parents don’t show symptoms because, as we now know, their normal allele (their “50%”) makes the necessary amount of gene product. So, recessive diseases pop up when carriers of the same mutation mate. The chance of this happening increases if the carriers are related by descent.

Doing the Math in Little Squares

To figure out the recurrence risk (the risk of having another affected child), we can do some simple calculations that we can drop into a little table called a Punnet Square.

By convention, dominant alleles are generally written as capital letters and recessive alleles in small letters. Therefore, affected individuals are “aa” and their carrier parents are “Aa”. Now, to figure out the possibility of “aa” occurring again, we just count up the possibilities.

Mom = A a
Dad = A a

Each parent has an equal chance of passing on each allele so the possibilities are:

Mom A + Dad A = AA
Mom A + Dad a = Aa (carrier)
Mom a + Dad A = Aa (carrier)
Mom a + Dad a = aa (affected)

There is one combination that leads to affected child so the probability is ¼ or 25%. There are two possibilities of a carrier, so there is a 50% risk of carrier children (2/4).
Your Situation

In the case of your family and the history of cystic fibrosis, if you had a brother with the disease, but neither of your parents does, each of your parents is an unaffected carrier, as illustrated above. Unhappily, your brother would have inherited both copies of the mutant gene.

You do not have the disease, so you are either an unaffected carrier, or you have no mutant genes for CF. For the sake of your future children (and for your own peace of mind), it would be good if you found out which one you are.

To ensure that your children do not have CF, you will have to make sure that your spouse is not an unaffected carrier. If your spouse is not a carrier, and you are, your children’s odds for CF look like this:

Your children will not have CF, but they will have a 50% chance of being a carrier (Aa).

When you look at families with a recessive disorder, the affected person may be the only affected person in the family. If other family members are affected, they are often siblings because the parents are known carriers, and this, as we have seen, leads to higher risk.

In the case of CF and your family, knowledge is your best ally.
X-Linked Inheritance
Some diseases affect men more than women. Colour blindness is a common example. Females have two X chromosomes, so the normal allele on one X chromosome can compensate for the mutated one on the other. Therefore, women can be unaffected carriers.

The basics first: human females have two X chromosomes, while human males have an X and a Y chromosome. A special type of recessive inheritance, called sex linked, takes advantage of this difference when the mutated allele of a particular gene is found only on the X chromosome.

Colour Blindness

Red-green colour blindness is a case in point. The mutation knocks out the alleles on the X chromosome responsible for the production of proteins in the cells sensitive to red and green light in the retina. Understandably, this disorder affects males much more often than females. Why? Because the XY guys have only one X chromosome, there is no second allele that can compensate for the mutated one. Females, on the other hand, have two X chromosomes, so the normal allele for the gene on one X chromosome can compensate for the mutated one on the other. Therefore, women can be unaffected carriers.

Women: The Stronger X?

The same explanation also works for more serious disorders such as haemophilia and Duchenne’s muscular dystrophy. In haemophilia, the only copy of a clotting factor is lost in affected males so they bleed excessively. Carrier women may bruise more but are essentially unaffected.

In Duchenne’s muscular dystrophy, affected men are missing a muscle protein, dramatically reducing muscle function. Both of these disorders are considered fatal because the affected men do not live to reproduce.

Do the Math in Little Squares

What is the chance of an affected child from a carrier woman?

\[ \text{Mom} = A \ a \]
\[ \text{Dad} = AY \ (\text{Instead of a second allele on the X, Dad has the Y chromosome}) \]

Again, there are 4 possibilities. The chance of an affected boy (aY) is \( \frac{1}{4} \) or 25%. The chance of a carrier girl (Aa) is \( \frac{1}{4} \) or 25%.

If you know that the child is going to be a boy, the risk increases because now there are only two possibilities:

\[ \text{Mom A + Dad Y} = AY \]
\[ \text{Mom A + Dad Y} = aY \ (\text{affected boy}) \]
So, the risk of an affected boy is \( \frac{1}{2} \) or 50%.

Understanding modes of inheritance helps you identify you and your family’s risk for developing an inherited disease. If you have a family history of disease, you can work with a genetic counselor or your medical professionals to help ensure that your children’s futures are long, healthy ones.
Dominant Inheritance

Families with dominant inheritance show the disease in every generation, often with several affected family members in each generation. Diseases are considered dominant when only one mutant copy is needed for disease. In terms of eye colour, brown is dominant so only one copy of brown is needed to have brown eyes.

Diseases are classified as dominant when only one allele has to be mutated to see disease — in this case, the mutant allele is dominant over the normal one.

Often, dominant mutations are ‘gain of function’ — that is, the gene product is produced at the wrong place or time. Because 50% gene product (one allele) is enough to perform functions, cells can learn a ‘new trick’ from the mutant allele’s product(s) and often mess up normal processes.

Having extra fingers or toes is an example of this. Polydactyly can appear in families as a dominant inherited trait. But in most cases, it’s just delightfully, weirdly benign and isn’t linked to genetic disease.

Families with dominant inheritance for a disease show the disease in every generation and there are often several affected family members in each one. Unless the disease involves a sex-limited structure like the uterus or penis, males and females are affected equally. Every affected child has had an affected parent.

Calculating Possibilities

When you do calculations with dominant disorders, the mutant allele is written in CAPITAL LETTERS to distinguish it from ‘normal’ (opposite to the recessive calculations). To keep things really straight, use the letter d when dealing with dominant disorders.

If dad is affected, what is the chance that his child will be affected?

Note: We assume that affected individuals with a dominant condition are heterozygous = one mutant and one normal allele. There is a small theoretical possibility that someone could be homozygous for 2 dominant mutations but it would be incredibly rare. (Geneticists like to stick with the obvious).

Mom = dd
Dad = Dd

Each parent has an equal chance of passing on each allele, so the possibilities are:

1. Mom d + Dad D = Dd (affected)
2. Mom d + Dad d = dd
3. Mom d + Dad D = Dd (affected)
4. Mom d + Dad d = dd

Any child who receives ‘D’ from dad will be affected = 50% (2/4 possibilities).
Dominant Negative

There is another class of dominant disorders that doesn’t lead to a gain of function in the gene product. On the contrary, these kinds of mutations not only disable the gene product from the mutated allele, but they ALSO take the ‘normal’ product down too. Therefore, instead of missing 50% of the gene product as a result of one mutated allele, there is almost no normal product left and disease results.

*Osteogenesis Imperfecta* is one such disease. In the severe form, the mutated fibre interferes with normal bone growth so disease results, even though one allele is expressed properly. It is kind of like the annoying kid in the back of the class – not only is he not paying attention but he often distracts all the kids around him.
Multifactorial Inheritance
Many of the common diseases in developed countries are multifactorial, meaning there are many factors involved in disease progression. This activity should help you understand how genes and environment can interact to cause disease.

Genes, Environment & Disease

We used to divide diseases into ‘genetic’ and ‘environmental’ but many disorders are a combination of the two categories. There are disorders arising from mutations in one gene (ex. Huntington’s or colour blindness) – but the manifestation of these diseases can be influenced by a patient’s environment. In contrast, diseases caused primarily by environment can be affected by someone’s genetic background. For example, AIDS requires infection by the HIV virus – but some people have a mutation that prevents the virus from entering their cells and therefore can’t be infected. In other patients, their genetic make-up can affect the disease progression.

Multifactorial Inheritance

Many of the common diseases in developed countries like Canada fall into the multifactorial inheritance category, examples being diabetes, MS, and heart disease. Basically, multifactorial means there are many factors involved in disease progression, and a combination of genetics and environment.

We will use the example of heart disease to illustrate the many factors that can cause multifactorial diseases. In Canada, heart disease and stroke account for up to 1/3 of deaths. It does run in families but not in a nice, neat pattern like a single gene disease. The risk of developing heart disease increases if you are related to someone with heart disease and/or you are exposed to certain environmental factors.

Additional Facts about Heart Disease

- Heart disease is an umbrella term for multiple conditions including: coronary artery disease, heart attacks and congestive heart failure.
- The risk for developing heart disease is increased in relatives of people with heart disease (genetic factors).
- Heart disease increases in the presence of certain environmental events. These include smoking, lack of exercise and poor nutrition.

REMEMBER: This activity does not predict your actual risk of developing heart disease. It is a model to show how genetic and environmental events can interact to produce disorders.

If you would like more information about heart disease or stroke, please contact your family doctor.

Instructions

1. Roll the die as instructed. Record the points awarded in the spreadsheet.
2. Add up your score to find out if this fictional person will develop heart disease.

Roll 1: Genetic Contribution
Roll the die
Start a total with your current roll number:
1. No family history through to 6. Strong family history

Roll 2: Blood Pressure
High blood pressure can increase risk for developing heart disease because blood vessels can become weak and/or prone to blockage.

Roll the die and add points.
1, 2 or 3: No points (normal blood pressure)

4, 5 or 6: Add 2 (high blood pressure)

Roll 3: Smoking
People who smoke or are exposed to smoke tend to develop more blood clots in their arteries, reduced blood oxygen levels and elevated blood pressure.

Roll the die and add points.
1 or 2: No points (non-smoker)

3 or 4: Add 1 (some smoke exposure)

5 or 6: Add 3 (heavy smoker)

Roll 4: Nutrition
A diet high in fat can cause the arteries to become narrow, which makes it harder for the blood to circulate.

Roll the die and add points.
1, 2 or 3: No points (low fat diet)

4, 5 or 6: Add 3 (high fat diet)

Add your points. If the score is 10 or more, the fictional person will develop heart disease.

This shows how genetic and environmental loads work together.

If you have a genetic load of 6, you need only 4 points to cross the threshold that gives you an affected person. But if your genetic load is 3, you need 7 points to cross. In the first case (genetic load of 6), less environment is needed for the disease. But if the genetic load is less (3), you need more environmental exposure to cross the threshold.
Cancer Mutations
Cancer is usually inherited in a dominant fashion because there are many affected individuals in several generations. However, both copies of a gene need to be mutated before cancer appears. This article explores this paradox.

When we look at ‘cancer families’, there is a dominant mode of inheritance because there are many affected individuals in several generations. So, these people must have inherited a mutation that causes their cells to become cancerous, right?

But the cancers often appear late in life – if a mutation was going to cause cancer, shouldn’t it show up right away?

The majority of known mutations in familial cancers are in tumour suppressors. These gene products normally prevent the cell from growing out of control. They’re kind of like ‘Cell Parents’ setting curfew, ensuring their little cells stop their activity at the appropriate time. And if the little cells don’t obey their parents, there are consequences – for cells, it is called programmed cell death (and you thought your parents were strict!).

However, if the parents aren’t there, no curfew is enforced and the cells activities continue unchecked. In the case of a cell, this may mean that it will grow too much or stop listening to their environmental cues. And since the parents aren’t there, there no consequences for these misbehaving little cells...they’ll continue to grow more than the surrounding cells, and a tumour results.

Recessive Dominance?
Again, 50% of normal tumour suppressor is enough to keep cells in check. Both alleles have to be lost before a cell goes crazy. But wait a minute – doesn’t that mean it’s a recessive disorder? And this is the confusing part: molecularly, the cancers are recessive molecularly, but when we look at families, the inheritance is dominant.

To explain: As we age, we accumulate all kinds of mutations in our cells – from the environment, from the aging process, from exposure to harmful chemicals and radiation. In people with an inherited mutation in one tumour suppressor, it only takes one more mutation to knock out the second ‘good’ allele in one cell to allow a tumour to develop. But in someone who has two good copies of the tumour suppressor in every cell, the acquired mutations have to work much harder to knock out both these copies.

This is why people with inherited mutations get cancer earlier, and often in more than one site – because it only takes one little mutation to start things happening. As acquired mutations are so common, it is almost guaranteed that they will be affected sometime in their life. At first, this may seem very scary, but when you think about it, if people know they have inherited mutations, they can undergo careful routine screening to catch any developing tumours before they spread. Knowledge is power and in this case, longer life!
FUN FACT

Mendel's rules have shaped our modern-day genetics. However, some people think that he may have 'fudged' the results of his plant experiments.

Gregor Mendel was a 19th Century monk who discovered the laws of inheritance (dominant and recessive genes etc.). More recent analysis of his results suggest that they are "too good to be true". Mendelian inheritance involves the random selection of possible traits from parents, with particular probabilities of particular traits. It seems from Mendel's raw data that chance played a smaller part in his experiments than it should. This does not imply fraud on the part of Mendel.

First, the experiments were not "blind" (see the questions about double blind experiments and the experimenter effect). Deciding whether a particular pea is wrinkled or not needs judgment, and this could bias Mendel's results towards the expected. This is an example of the "experimenter effect".

Second, Mendel's Laws are only approximations. In fact it does turn out that in some cases inheritance is less random than his Laws state.

Third, Mendel might have neglected to publish the results of 'failed' experiments. It is interesting to note that all 7 of the characteristics measured in his published work are controlled by single genes. He did not report any experiments with more complicated characteristics. Mendel later started experiments with a more complex plant, hawkweed, could not interpret the results, got discouraged and abandoned plant science.


Here are some articles etc. that you might want to check. Mendel got the black eye from a runs test that Fisher conducted but others disagree.


_________. 1985. Mendel, the empiricist. J. Hered. 76:49-54.


