Lesson 4

July 15, 2020

1 Lesson 4: Inheritance Probability

1.1 Who was Gregor Mendel?

Have you ever wondered why you have your mom's nose? Or your dad's eyes? Or your grandfather's hair? It turns out that, to find an answer, we need to start almost 200 years ago, with a monk in the Czech Republic.

Gregor Mendel was born in what is now the Czech Republic in 1822. His family were farmers, and Mendel grew up gardening and studying beekeeping. As a young man, Mendel became an Augustinian friar, partially to continue his education without having to pay for his studies. While he was at the monastery, Mendel experimented with small plots of the common edible pea, and presented his work to a small group of unenthusiastic scientists in 1862. While he died in 1884 in relative scientific obscurity, his pea experiments gained appreciation over time, so much so that that now Gregor Mendel is considered the father of modern genetics.

If you want to read more about Gregor Mendel's early life and discoveries while at the monetary, please check out FamousScientists.org!

1.2 Why peas?

Although all of Mendel's experiments were carried out with pea plants, he wanted to understand something much more basic and common to all living organisms: the basis of inheritance, or what genetic information is passed between parents and offspring. Peas turned out to be a great model organism for studying inheritance for several reasons:

- Mendel could grow hundreds of plants at a time his small monastery garden
- There are several observable traits that peas can pass from parent to offspring like pea color, pea texture, and flower color
- Pea plants can actually self-breed, meaning that a single plant can act as both the mother and the father to generate its own offspring

1.3 Phenotypes

Mendel began studying peas by observing traits like pea plant height, pea color, and pea shell smoothness. These characteristics are examples of phenotypes, a term used by geneticists to describe an observable trait.

Human traits include phenotypes such as height, eye color, blood pressure, and blood type.

In particular, Mendel was very interested in learning the ratio of plants with specific phenotypes. For example, one ratio he calculated was the number of plants with yellow peas to the number of plants with green peas. In this case, yellow and green are two phenotypes for the trait pea color.

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[3]:
```
greenPeas = 1690.0
yellowPeas = 567.0
print(greenPeas / yellowPeas)
```

```
2.98059964727
```

Mendel counts a few more plants and now there are 3960 green peas and 1318 yellow peas. What is the new ratio?

[6]:
```
greenPeas = 3960.0
yellowPeas = 1318.0
print(greenPeas / yellowPeas)
```

```
3.00455235205
```

1.4 Mendelian Genetic Inheritance

Based on this data, Mendel was the first to hypothesize what we now refer to as Mendelian genetic inheritance. He proposed that parents (mothers and fathers) each contribute half of their offspring's genetic material. We now know (although Mendel did not at the time), that this genetic material is deoxyribonucleic acid, or DNA. DNA makes up genes, which are units of heredity that can determine specific physical characteristics. That is, this genetic material controls the phenotype that we can observe; we refer to the genetic basis of the phenotype as the genotype.

To put it simply, a genotype is the instructions in your DNA, while a phenotype is the trait you have because of those instructions.

In many organisms, including humans, there are two copies of every gene (one inherited from our mother, the other from our father). We refer to each version of a gene as an allele. For example, for a particular gene, let's say that one allele is A and the other allele is a. Then the genotype of that individual, for this particular gene, could be any combination of these alleles - AA, Aa, or aa. If an individual has two copies of the same allele (i.e. AA or aa), then that individual is said to be a homozygote, whereas an individual that has two different alleles (i.e. Aa) is called a heterozygote. These terms can be easily remembered, as "homo" means "same" and "hetero" means "different." Two different alleles can correspond to different phenotypes, e.g. green versus yellow.

1.4.1 Genotype v. Phenotype Quiz

- Phenotype refers to any observable trait.
- Genotype refers to a specific collection of alleles.

1.5 Dominant & Recessive Phenotypes

A natural question that arises is how can we translate genotypes to phenotypes; given a specific genotype, what phenotype will be displayed? This question is simplified in the case of homozygotes because both alleles correspond to the same phenotype.

For example, let's say that the B allele encodes the brown eye phenotype and the b allele encodes the blue eye phenotype. Then, it follows that a BB homozygote will certainly have brown eyes and a bb homozygous individual will definitely have blue eyes. However, what happens in the case of a heterozygous Bb individual?

In the case of eye color, a heterozygous Bb individual will have brown eyes. This brown eye phenotype (and therefore the B allele) is said to be dominant, whereas the blue eye phenotype (and the b allele) is recessive. In fact, in genotype notation, uppercase letters denote dominant alleles whereas lowercase letters denote recessive alleles.

Let's talk earlobes... Humans can have either attached or detached earlobes. This earlobe phenotype is determined by a genotype. Through many studies, it has been determined that attached earlobes is a dominant phenotype and detached earlobes is a recessive phenotype (actually, this story recently got more complicated - read more here!)

1.5.1 Dominant v. Recessive Quiz

- Since attached earlobes is a dominant phenotype, convention dictates that the uppercase letter E is used.
- Since detatched earlobes is a recessive phenotype, convention dictates that the lowercase letter e is used.
- Since EE is the homozygous dominant genotype, the dominant phenotype (attached earlobes) is expected.

- Since ee is the homozygous recessive genotype, the recessive phenotype (detatched earlobes) is expected.

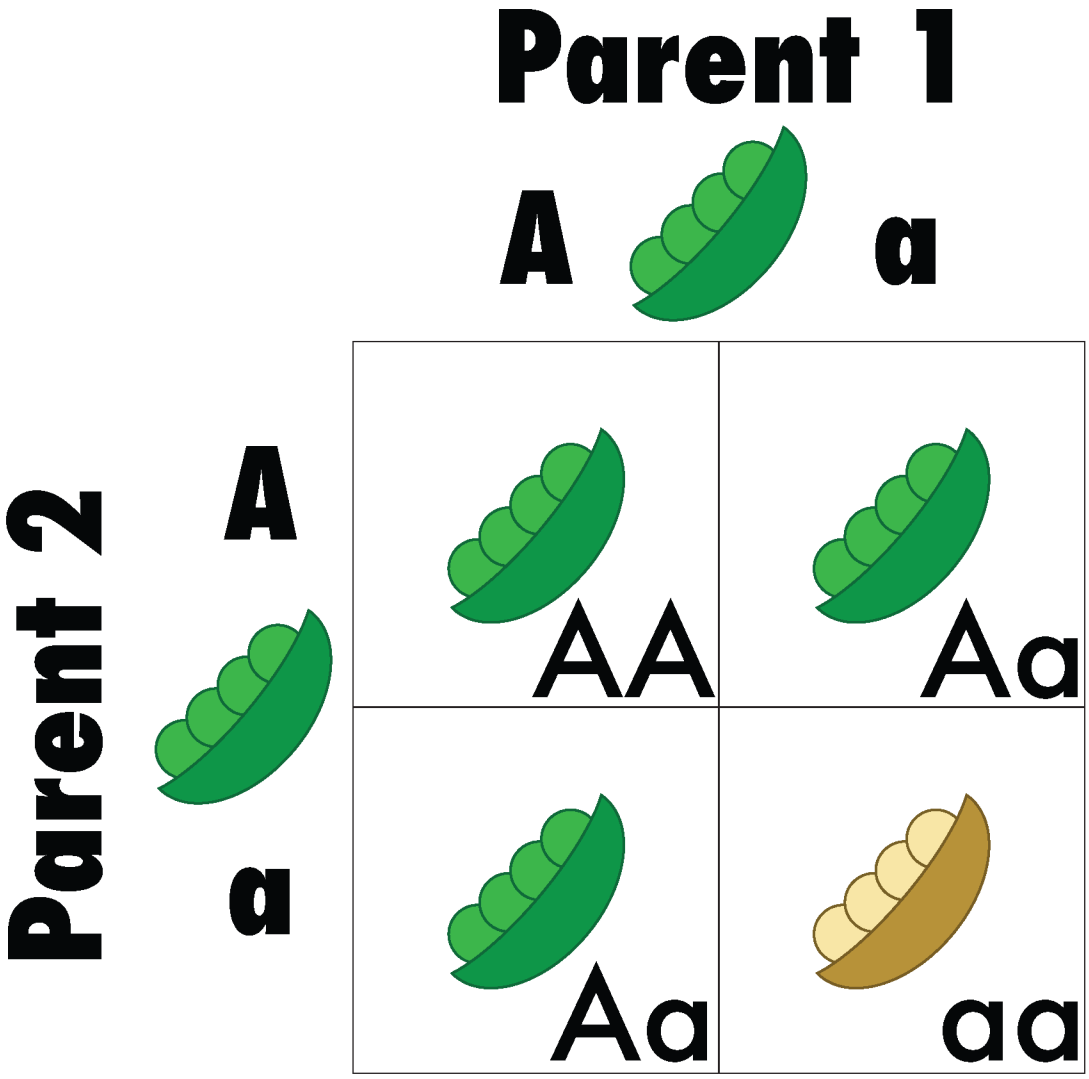
- Since Ee is the heterozygous genotype, the dominant phenotype (attached earlobes) is expected.

1.6 Phenotype Ratios

We can visualize the inheritance of genotypes from parents to offspring using Punnett squares. Punnett squares show the genotype of each parent along two sides of a square and all of the potential genotypes of the offspring inside the square. Recall that Mendel often observed a 3 : 1 ratio of dominant to recessive phenotypes (phenotypes included pea color, plant height, flower color, etc.) when he crossed two heterozygous peas. Using a Punnett square, we can understand why a Aa x Aa cross (heterozygous cross) yields this ratio: essentially, this cross had four possible offspring with equal probability:

- 1 AA genotype, dominant phenotype
- 2 Aa genotype, dominant phenotype
- 1 aa genotype, recessive phenotype

This is an example Punnett square between two heterozygous (Aa) pea plants, which yields a 3 green : 1 yellow phenotypic ratio of potential offspring.



1.6.1 Punnett Square Quiz

- An AA x aa cross can only result in Aa offspring, which would all display the dominant phenotype.
- An AA x Aa cross can result in two possible offspring genotypes (AA and Aa), both of which would display the dominant phenotype.
- An aa x Aa cross can result in two possible offspring genotypes (Aa and aa), one of which would have a green phenotype (Aa) and the other would have a yellow phenotype (aa)

1.7 Calculating Ratios

Let's say we want to write a piece of code to determine if a given sample shows a 3:1 phenotype ratio. We can store each of the observed numbers of pea phenotypes in a variable, and then divide

these values to calculate the phenotype ratio. Then, to determine if this ratio is equal to 3, we can deploy an if statement.

[9]:
```
# Imagine Mendel observed 9 green and 3 yellow peas
greenPeas = 9.0
yellowPeas = 3.0
ratio = greenPeas/yellowPeas
if ratio == 3.0:
    print("There is an exact 3 : 1 phenotype ratio!")
```

```
There is an exact 3 : 1 phenotype ratio!
```

If you flipped a coin 100 times and observed 57 heads and 43 tails, would you assume that the coin was rigged? Probably not. In the same way, phenotypic ratios can vary slightly around the 'true' or expected value due to random chance.

In a real scientific experiment, we do not expect to observe an exact 3 : 1 phenotype ratio due to random noise in the system. For example, if you flip a fair coin twice, you will most often observe one head and one tail, but that is not necessarily true. If you continue to flip your coin hundreds of times, you are increasingly likely to observe approximately 50% heads and 50% tails. In real life, we would need to modify the above code to accommodate an approximate 3 : 1 ratio, rather than an exact 3 : 1 ratio. Let's say that we will allow ratios as low as 2.7 and as high as 3.3 (plus or minus 10% of 3) to be called a 3 : 1 ratio. Then, our if statement would look look like the following:

[10]:
```
# Imagine Mendel observed 340 green and 125 yellow peas
greenPeas = 340.0
yellowPeas = 125.0
ratio = greenPeas/yellowPeas
if ratio > 2.7 and ratio < 3.3:
    print("There is about a 3 : 1 phenotype ratio!")
else:
    print("There is not a 3 : 1 phenotype ratio!")
```

```
There is about a 3 : 1 phenotype ratio!
```

[12]:
```
if ratio > 2.7 and ratio < 3.3:
    print("There is about a 3 : 1 phenotype ratio (" + str(ratio) + ")!")
else:
    print("There is not a 3 : 1 phenotype ratio!")
```

```
There is about a 3 : 1 phenotype ratio (2.72)!
```

1.8 Checkpoint

Write code to determine if Mendel observed a 3 : 1 phenotype ratio in his pea texture data (he observed 1005 smooth peas and 350 wrinkled peas) and his pea plant heights.

[16]:
```
smoothPeas = 1005.0
wrinkledPeas = 350.0
ratio = smoothPeas/wrinkledPeas
```

```
if ratio > 2.7 and ratio < 3.3:
    print("There is about a 3 : 1 phenotype ratio (" + str(ratio) + ")!")
else:
    print("There is not a 3 : 1 phenotype ratio!")
```

```
There is about a 3 : 1 phenotype ratio (2.87142857143)!
```

Do the same calculation on Mendel's observation of pea plant height (he saw 6 tall plants and 1 short plant)

[17]:
```
tallPeas = 6.0
shortPeas = 1.0
ratio = tallPeas/shortPeas
if ratio > 2.7 and ratio < 3.3:
    print("There is about a 3 : 1 phenotype ratio (" + str(ratio) + ")!")
else:
    print("There is not a 3 : 1 phenotype ratio!")
```

```
There is not a 3 : 1 phenotype ratio!
```

1.9 What do peas have to do with human health?

So far, we've talked about Mendelian inheritance in terms of traits like pea color and eye color. However, Mendelian inheritance also governs the transmission of many less desirable qualities, such as diseases. We refer to these diseases, appropriately, as "Mendelian diseases." Mendelian diseases can be recessive (examples include Tay-Sachs disease and cystic fibrosis) or dominant (examples include Huntington's disease and Marfan syndrome).

Although there are many Mendelian traits, most traits are not actually controlled by a single gene. Instead, many different genes contribute to the final phenotype. We refer to these traits as "polygenic" (i.e. "multiple genes"). For example, skin tone and susceptibility to heart disease are polygenic. In the next section, we will discuss principles applicable to the study of these kinds of traits, which necessitate more advanced computational skills and tools.

In the next lesson, we'll talk about height and weight, two such polygenic traits. Continue on to learn more!

1.10 Lesson 4 Summary

In this lesson, we've learned about the difference between genotype and phenotype. We've also learned about the difference homozygous and heterozygous genotypes as well as dominant and recessive phenotypes. We also visualized Mendelian inheritance using Punnett squares.

Let's put together everything we've learned into one final exercise:

1. Brachydactyly is a medical term which literally means "shortness of the fingers and toes." This trait is inherited in a Mendelian fashion. Imaging you are in Medical school and interested in studying this recessive trait. You assemble a cohort of patients and sequence their genomes and find the following genotypes: AA - 10, Aa - 25, aa - 11. Calculate the following:

   a. The number of patients with average-length fingers and toes?

b. The ratio of patients with average-length digits to those with brachydactyly?

Hint: You know now that in a Mendelian trait, homozygous dominant (AA) and heterozygous (Aa) genotype carriers will display the dominant phenotype, while homozygous recessive genotype carriers will display the recessive phenotype.

[25]:
```
AA = 10.0
Aa = 25.0
aa = 11.0
print(AA + Aa) # number of patients with average-length fingers and toes
print((AA + Aa) / aa) # ratio of patients with average-length digits to those␣
 ↪with brachydactyly
```

```
35.0
3.18181818182
```