# Mendelian Genetics

The previous "Cell Division" unit described the general process of Meiosis. In this unit we will examine how Meiosis influences trait inheritance. In other words, we will relate the principles of Meiosis to the passing on of measurable characteristics from parent to offspring. We refer to this as **Mendelian genetics**, because the principles discussed here were originally described by the Czech monk **Gregor Mendel**.

# 1 Central Principle of Genetics

In a stable environment, trait variation is determined by genes. Remember that a gene is a section of DNA that encodes a product. A gene is a discrete unit (individual entity distinct from others). Based on this central principle, the variation we see in organisms is due to variation in genes (in other words, trait variation comes from alleles- which are simply unique versions of a gene). A trait is an observable characteristic, and a unique version of a trait is called a **phenotype**. Based on this central principle, a phenotype is determined by the alleles that an organism possesses, called a **genotype**. While the necessary criterion for this principle is rarely met (because environments are largely variable), it is a foundational principle upon which additional information can be established. The first person to recognize the discrete nature of heredity was Gregor Mendel, the "Father of Genetics".

# 2 Gregor Mendel's Experimental System

In the middle of the 1800s, the monk Gregor Mendel was meticulously measuring traits of his pea plants in the greenhouse of the St. Thomas monastery (in Brno, present-day Czechia). He was particularly interested in seven traits that each showed two distinct phenotypes:

	Trait	Phenotypes
1	Seed (pea) shape	round or wrinkled (angular)
2	Seed (pea) color	<b>yellow</b> or green
3	Flower color	<b>violet</b> or white
4	Pod texture	<b>inflated</b> or constricted
5	Pod color	green or yellow
6	Flower location	<b>axial</b> or terminal
7	Plant height	tall or short

 $\operatorname{\mathbf{Bold}}$  phenotypes represent the dominant form

While breeding plants, Mendel noticed interesting patterns in the inheritance of these traits between generations. To describe one of his experiments, we will consider a single trait: flower color. Mendel bred plants until he obtained plants that would only produce the white flower phenotype when crossed with each other and plants that would only produce the violet flower phenotype when crossed with each other. An organism that consistently produces the same phenotype is called **true-breeding**. Importantly, you can't know if an organism in the parent (**P**) generation is true-breeding after a single generation (called the  $\mathbf{F}_1$  generation); you must cross the resultant organisms with each other to reach the second generation (called the  $\mathbf{F}_2$ generation). If the phenotypes of the organisms in the  $\mathbf{F}_2$  are the same as P, then the **strain** (genetically distinct group of organisms, usually created in a lab) is true-breeding (Figure 1). Mendel then performed two experiments using the traits described in the table above (while he examined all of the traits, we will just focus on a couple of traits for simplicity).



Figure 1: Individuals of a true-breeding strain always produces the same phenotype when crossed with each other.

**NOTE:** Mendel's work was all done using the species *Pisum sativum* (garden pea). This is a diploid organism, therefore the principles of this entire unit are discussed in a diploid context. These principles can be expanded to other ploidy scenarios, but starting with a diploid makes things simple.

## 2.1 1st Experiment: Monohybrid Cross and Segregation of Alleles

Mendel took true-breeding white flower plants and crossed them with true-breeding violet flower plants. The result was an  $F_1$  generation with all violet flower plants. He then took these  $F_1$  plants and crossed them with each other, and ended up with 705 violet flower plants and 224 white flower plants (for a total of 929  $F_2$  plants). By examining the phenotypic proportions (705/929 = 0.76 for violet flowers, 224/929 = 0.24 for white flowers), Mendel calculated a ratio of 3.15 : 1 (violet flower plants : white flower plants) (Figure 2) and noticed an approximate 3 : 1 ratio. From this information, Mendel hypothesized that the flower color trait was determined by discrete, non-blending structures he called "elemente" (which today we know as **genes**), and that two unique versions of the "elemente" determined flower color: a dominant form and a recessive form. Today refer to "unique versions" of a gene as **alleles**.



Figure 2: Outline of Mendel's experimental design and results from his first experiment.

Mendel hypothesized that for a trait, each individual possesses two copies of a gene (e.g., each plant had two copies of the 'Flower Color' gene). He thought that one allele ('F') created the violet coloration, and that the other allele ('f') created the white coloration. He also suggested that one allele was **dominant** over the other allele (called the **recessive** allele); the dominant is represented with an uppercase letter (e.g., 'F') and the recessive allele is represented with a lowercase letter (e.g., 'f'). Under this hypothesis, individuals with two recessive alleles ('ff') had white flowers, whereas individuals with just one dominant allele (i.e., individuals with 'FF' or 'Ff) had violet flowers (Figure **??**). The combination of alleles in an individual is known as its **genotype** (e.g., 'FF', and 'ff' are the genotypes that encode violet flowers, and 'ff' is the genotype that encodes white flowers). A genotype with two of the same alleles (e.g., 'FF' or 'ff') is called **homozygous**. Homozygous genotypes can either be **homozygous dominant** (having both of the dominant alleles; e.g., 'FF') or **homozygous recessive** (having both of the recessive alleles; e.g., 'Ff').



Figure 3: Phenotypes and genotypes of individuals for a trait that exhibits complete dominance.

While each parent can potentially pass on either of its alleles to offspring, only one allele *at* random is passed on to an individual offspring. For example, a parent plant with genotype 'Ff' can pass on either the 'F' allele or the 'f' allele to an offspring, and the probability of either is 50% (just like a coin flip). This ground-breaking idea suggested by Mendel, that the alleles for a gene randomly segregated into their own gamete, is called the **Law of Segregation of Alleles**. Not only did Mendel suggest this as the mechanism of inheritance for a trait, he proved it with his experiment.

### 2.1.1 The Monohybrid Cross

Remember above, when Mendel crossed the violet  $F_1$  plants and obtained the ratio of 3 : 1 (violet : white)? This is called a **monohybrid cross**, because it is a cross focused on one gene between heterozygous individuals. 'Mono' is Greek for 'one', and in this example Mendel was only focused on the gene controlling flower color. 'Hybrid' is Latin for 'mixed', and the two individuals being crossed have mixed alleles from their true-breeding parents ('F' and 'f'). If the Law of Segregation of Alleles is true, you would expect that each individual in a monohybrid cross (remember, each individual is 'Ff') has 50% probability of passing on the 'F' allele and 50% probability of passing on the 'f' allele. This means that the offspring of the  $F_2$  generation can have the genotypes 'FF', 'Ff', or 'ff'. To understand the predicted frequency for each of these genotypes in the  $F_2$  generation, it is important to understand two important rules of probability: **The 'AND' Rule** and **The 'OR' Rule**. Read these rules below and do the practice problem before checking if Mendel's results fit with the Law of Segregation of Alleles.



Figure 4: Three ways of depicting the outcomes of the monohybrid cross: schematic of how  $F_1$  alleles contribute to the  $F_2$  genotypes where each arrow represents a gamete (left), using the probability rules to calculate the frequency (a.k.a., probability) of phenotypes in the  $F_2$  (middle), and using a Punnet square to calculate the frequency (a.k.a., probability) of phenotypes in the  $F_2$  (right).

### 2.1.2 Probability

**Probability** is the frequency at which something occurs, and it can be used to understand how likely it is that something will occur. This frequency can be expressed as a value between 0-1 (0

= never happens, 1 = always happens) or a percentage (which is simply the decimal value x 100). To calculate the frequency you take the number of times an event happened and divide it by the total number of times it *could* have happened. For example, if you flip a coin 1,000,000,000 times and got 'heads' 499,972,631 times, you would calculate the probability of getting heads by dividing 499,972,631 by 1,000,000,000 and get 0.499972631 (you could round this up to 0.5).

### 2.1.3 The 'AND' Rule: Multiplication

This is the rule to follow if you are trying to calculate probability of an event and you hear yourself say 'and'. This rule is used when you want to know the probability of multiple events happening together or subsequently. For example, let's say you plan to flip a coin two times, and you want to know the probability of getting 'heads' the first time AND the probability of getting 'heads' the second time. To do this, you multiply the probability of the events together  $(0.5 \times 0.5)$ . Therefore, the probability of getting 'heads' on the first flip and the second flip is  $0.5 \times 0.5 = 0.25$ . This rule is also known as the 'product' rule.

### 2.1.4 The 'OR' Rule: Addition

This is the rule to follow if you are trying to calculate probability of an event and you hear yourself say 'or'. This rule is used when you want to know the probability of an event happening from several options. For example, let's say you plan to flip a coin one time, and you want to know the probability of getting 'heads' OR 'tails'. To do this, you add the probability of the events together (0.5 + 0.5). Therefore, the probability of getting 'heads' or 'tails' when you flip a coin is 0.5 + 0.5 = 1 (it would be impossible to get something else!). This rule is also known as the 'sum' rule.

**Practice Question:** For a monohybrid cross between flowers heterozygous for flower color (genotype 'Ff') that resulted in 929 offspring, how many of those would you expect to be of genotype 'FF'? How many would you expect to be of genotype 'Ff'? How many would you expect to be of genotype 'ff'? What is the expected genotypic ratio?

**Solution:** There are two parents: P1 (gentoype 'Ff') and P2 (genotype 'Ff'). An offspring of genotype 'FF' would require that P1 gives an 'F' allele (probability = 0.5) AND P2 also gives an 'F' allele (probability = 0.5). Therefore, the probability of having an 'FF' offspring is  $0.5 \ge 0.25$ . This means you would expect that 929  $\ge 0.25 = 232.25$  offspring have the 'FF' genotype.

An offspring of genotype 'ff' would require that P1 gives an 'f' allele (probability = 0.5) AND P2 also gives an 'f' allele (probability = 0.5). Therefore, the probability of having an 'ff' offspring is  $0.5 \ge 0.25$ . This means you would expect that 929  $\ge 0.25 = 232.25$  offspring have the 'FF' genotype.

This is where it gets tricky. An offspring of genotype 'Ff' would require that P1 gives an 'F' allele (probability = 0.5) AND P2 also gives an 'f' allele (probability = 0.5). OR P1 gives an 'F' allele (probability = 0.5) AND P2 also gives an 'f' allele (probability = 0.5). Therefore, the probability of having an 'Ff' offspring is  $(0.5 \times 0.5) + (0.5 \times 0.5) = 0.5$ . This means you would expect that 929 x 0.5 = 464.5 offspring have the 'FF' genotype.

You can verify that these are all of the possibilities (and check your work) by adding together the probabilities: 0.25 + 0.5 + 0.25 = 1 ('FF' + 'Ff' + 'ff'). To get the genotypic ratio, simply take the smallest probability (0.25 in this case) and multiply it by a number so that it equals 1 (0.25 x 4 = 1). Then multiply all of the probabilities by that number (0.25 x 4 = 1, 0.5 x 4 = 2). Your ratio is 1 : 2 : 1 ('FF' : 'ff') : 'ff')

**Practice Question:** For a monohybrid cross between flowers heterozygous for flower color (genotype 'Ff') that resulted in 929 offspring, how many would you expect to have violet flowers? How many would you expect to have white flowers? What is the expected phenotypic ratio? (Before solving this problem, you need to first complete the previous practice problem)

Solution: Now you need to think about the phenotypes of these genotypes. Violet flowers can have genotype 'FF' or 'Ff', so you can simply add up the expected number of of these genotypes: 232.25 + 464.5 = 696.75 expected violet flowers. White flowers can only have genotype 'ff', so we just use the genotype number: 232.25 expected white flowers.

You get the ratios the same way as described above. Because the probability of violet is 0.75 (0.25 + 0.5 ['FF' + 'Ff']) and the probability of white is 0.25 ['ff'], we have a ratio of 3 : 1.

Mendel's results from his experiment (which we referenced above) were 705 violet flowers and 224 white flowers. Based on our estimations from the practice problems above (696.75 violet and 232.25 white), do his results fit the Law of Segregation of Alleles? They are pretty close! Why do you think they aren't exactly what we predicted? If you flip a coin 1,000 times, do you think you would get exactly 500 'heads'? Because of sampling, you probably won't. In later sections of this book we will introduce statistical tests you can use to see if your data match expectations under a given hypothesis.

### 2.1.5 Meiotic Context for the Segregation of Alleles

While Mendel had no understanding of chromosomes or Meiosis, his Law of Segregation of Alleles makes perfect sense in the context of Meiosis. Let's think about how this would look for the gametes produced by the  $F_1$  plants. An individual  $F_1$  plant inherited a genome from  $P_1$  and a genome from  $P_2$ . Because we are focused on one genes in Mendel's monohybrid cross experiment, we will just imagine this using a pair of homologous chromosomes. When the homologous pairs separate from each other in Anaphase I, each daughter cell ends up with just one chromosome. When the sister chromatids separate from each other in Anaphase II, the resulting gametes each contain only one allele. The Law of Segregation of Alleles is a result of chromosomal separation in Anaphase I and Anaphase II (Figure 5).

### 2.1.6 The Punnet Square

A more visual approach to understanding probability with genetic crosses is using a **Punnet square**, which is simply a matrix (or grid) that depicts cross outcomes. In a Punnett square, the side and top show the possible gametes for parents. Figure 4 (right panel) depicts a monohybrid cross. The top of the matrix has the possible gametes from P1 (which is male in this case), and the side of the matrix shows the possible gametes from P2 (female). Because the Law of Independent Assortment states that each gamete can only have one allele for a gene, you'll notice that the gametes only contain one allele. A Punnet square also accounts for the random nature of allele segregation- the top only has two options (columns), so each allele has a 1/2 (0.5) probability. This is the same for the side, there are only two options (rows), so each allele has a 1/2 (0.5) probability. Each cell within the matrix represents a fertilization event between the gametes of the parents. It easy to see the 1: 2: 1 genotypic ratio and 3: 1 phenotypic ratio with a Punnet square.





## 2.2 2nd Experiment: Dihybrid Cross and Independent Assortment

Mendel was also interested in the inheritance patterns of two traits (seed [pea] shape and seed [pea] color) together, under the assumption that these two traits were controlled by two different genes. In his second experiment, he crossed plants that were true breeding for round/yellow seeds (parent  $P_1$ ) with plants that were true breeding for wrinkled/yellow seeds (parent  $P_2$ ) and ended up with  $F_1$  plants that were all round/yellow. Just as he did in his first experiment (the monohybrid cross), Mendel then took the  $F_1$  plants and crossed them with each other. Of the 556 total seeds in the  $F_2$  generation, 315 (or 57%) were round/yellow seeds, 101 (or 18%) were wrinkled/yellow seeds, 108 (or 19%) were round/green seeds, and were 32 (6%) or wrinkled/green seeds. Mendel noticed an approximate phenotypic ratio of 9 : 3 : 3 : 1 for these phenotypes (round/yellow : wrinkled/yellow : round/green : wrinkled green) (Figure 6).

**NOTE**: The seed phenotype belongs to the plant it will become, not the plant who's pod the seed is in. It is a common pitfall to attribute seed shape / color to the parent plant. For example, a round seed of genotype 'Rr' might be within the pod of a plant with the 'rr' genotype (which originally came from an wrinkled seed).



Figure 6: Outline of Mendel's experimental design and results from his second experiment.

**Practice problem**: What were the genotypes for the parent plants  $(P_1 \text{ and } P_2)$  from Mendel's second experiment?

**Solution**: Because there are two traits here (one gene for seed shape, another gene for seed color), each plant genotype should include four alleles (two alleles for the seed shape gene, and two alleles for the seed color gene). By looking at the  $F_1$ , we know which traits are dominant: round is dominant over wrinkled, and yellow is dominant over green. So we can use this information to give upper- or lower-case letters to each allele: 'R' for round, 'r' for wrinkled; 'Y' for yellow, 'y' for green (you could have used any letters, these are just the commonly used letters for these traits). Since  $P_1$  (round/yellow) and  $P_2$  (wrinkled/green) were true-breeding for their traits, we know that there genotypes must be 'RRYY' for  $P_1$  and 'rryy' for  $_2$ 

**Practice problem**: What were the genotypes for the  $F_1$  plants from Mendel's second experiment?

Solution: Think about the alleles that each parent can give. The round/yellow parent can only give an 'R' and a 'Y' allele. The wrinkled/green parent can only give an 'r' and a 'y' allele. While the Law of Segregation states that only one allele per gene can be given to offspring, keep in mind that we are now looking at two separate genes. Therefore, one allele for each gene is given to offspring, and the genotype for all of the  $F_1$  individuals is 'RrYy'.

Mendel hypothesized that alleles of different traits were inherited independent of each other.

For example, even though the 'R' allele and the 'Y' allele present in an  $F_1$  plant were inherited from the same parent ( $P_1$ ), they did not both have to be passed on in the same gamete by that  $F_1$  plant. In other words, the gamete genotypes of the  $F_1$  plants don't have to be either 'RY' or 'ry'- they could be 'RY', 'Ry', 'rY', or 'ry'. The Law of Segregation of Alleles still applies here- so only one allele of each gene is present in a gamete (e.g., you can't have a gamete with genotype 'RR', 'rr', or 'Rr', because each gamete contains only one allele for each gene- the 'R' and 'r' alleles are both alleles for the seed shape gene).

In this hypothesis for Mendel's second experiment, he suggested that the alleles of different genes are unlinked to each other. In other words, the gene for seed shape and the gene for seed color are inherited independent of each other. This ground-breaking idea suggested by Mendel is called the **Law of Independent Assortment**. Not only did Mendel suggest this as the mechanism of inheritance for multiple traits, he proved it with his experiment.

#### 2.2.1 The Dihybrid Cross

This second experiment is similar to the first (starting by crossing two true-breeding individuals and then crossing their offspring with each other), but this time he was examining two genes together (the gene controlling seed shape and the gene controlling seed color). For this reason, this is called a **dihybrid cross** (two genes, both heterozygous). The explanation for the outcome of this cross is more complex than that of the monohybrid cross, and it is easiest to understand when visualized in a Punnet square (Figure ??). In this figure, you can see the possible gamete genotypes with their respective proportions (shown in the row/column headers: each has a 1/4 probability) and the genotypes of the fertilized offspring (shown in the cells of the matrix). To obtain the phenotypic ratio, simply categorize the phenotype for each genotype and then count them up (9 round/yellow, 3 round/green, 3 wrinkled/yellow, 1 wrinkled/green).

#### 2.2.2 Probability Rules and the Dihybrid Cross

It is also useful to consider how the probability rules contribute to the observed ratios in Mendel's dihybrid cross. Because we are crossing individuals from the  $F_1$  generation, let's call the parents of this cross  $F_{1A}$  and  $F_{1B}$ . Keep in mind that the genotype of both  $F_{1A}$  and  $F_{1B}$  is 'RrYy'. Each parent can create four possible gametes ('RY', 'Ry', 'rY', or 'ry'), all of which have the same probability (since there are four possibilities, each gamete has 1/4 [or 0.25] probability). Therefore, the possible genotypes in the  $F_2$  generation are 'RRYY', 'RrYY', 'RRYy', 'RrYy', 'RRYy', 'RrYy', 'RrYy', or 'ry'), and 'rryy'. You can use the rules of probability to calculate the frequency (i.e., probability) of these genotypes in the  $F_2$  generation.



Figure 7: Punnet square showing the results of Mendel's dihybrid cross.



allele, and the Law of Segregation means that either can be passed on with equal probability). We can use the AND rule to calculate the probability as  $0.5 \ge 0.5 \ge 0.0625$ .

**Practice Question:** What is the expected frequency of 'rrYy' in the  $F_2$  assuming the Law of Independent Assortment?

There are a couple of ways you could solve this problem:

**Solution A:** There are a two gametic genotype combinations that could combine for this  $F_2$  genotype: ( $F_{1A}$  'rY' AND  $F_{1B}$  'rY') OR ( $F_{1A}$  'rY' AND  $F_{1B}$  'rY'). We can simply plug in the probability for each of these gametic genotypes: (0.25 AND 0.25) OR (0.25 AND 0.25). Using the 'AND' and the 'OR' rules of probability, this becomes: (0.25 x 0.25) + (0.25 x 0.25) = 0.125.

**Solution B:** This would require  $F_{1A}$  AND  $F_{1B}$  to both give an 'r' allele. AND this would require either of the following: ( $F_{1A}$  gives a 'Y' allele AND  $F_{1B}$  gives a 'y' allele) OR ( $F_{1A}$  gives a 'y' allele AND  $F_{1B}$  gives a 'Y' allele). So we have  $F_{1A}$  'r' AND  $F_{1B}$  'r' AND ( ( $F_{1A}$  'Y' AND  $F_{1A}$  'y') OR ( $F_{1A}$  'y' AND  $F_{1A}$  'Y')). We can simply plug in the probability of each parent giving these alleles: 0.5 AND 0.5 AND ( (0.5 AND 0.5) OR (0.5 AND 0.5)). Using the 'AND' and the 'OR' rules of probability, this becomes: 0.5 x 0.5 x ( (0.5 x 0.5) + (0.5 x 0.5)) = 0.125.

#### 2.2.3 Meiotic Context for Independent Assortment

While Mendel had no understanding of chromosomes or Meiosis, his Law of Independent Assortment makes perfect sense in the context of Meiosis if we assume that the genes he examined were on different chromosomes (which, luckily, they were!). Let's think about how this would look for the gametes produced by the  $F_1$  plants. An individual  $F_1$  plant inherited a genome from  $P_1$  and a genome from  $P_2$ . Because we are focused on two genes in Mendel's dihybrid cross experiment, we will just visualize this using two pairs of homologous chromosomes: A pair for chromosome 1 and a pair for chromosome 2 (Figure 8). When the homologous pair for chromosome 1 aligns on the metaphase plate during Metaphase I, the arrangement (i.e., whether the chromosome from  $P_1$  or  $_2$  is on the left side) is random. This is the same case for the homologous pair for chromosome 2, and the arrangement for chromosome 2 is independent of the arrangement for chromosome 1. Because chromosome 1 "assorts" independently of chromosome 2, you can mix-and-match the alleles from the parents for the gametes that will be created. **The Law of Independent Assortment is a result of chromosomes arranging independent of one another during Metaphase I.** 

When just looking at two homologous pairs, the number of possible gametes is simply 4 (while there are 8 gametes resulting from Meiosis, you'll notice that there are only 4 unique gametes). However, this number increases exponentially as you include other chromosomes. For example, if we considered 3 homologous pairs, the number of possible gametes from independent assortment is 8. For 4 homologous pairs, the number of possible gametes is 16. For 23 homologous pairs (which is the case in humans), the number of possible gametes is 8,388,608. It is unfeasible to calculate the number of possible gametes by drawing out Meiosis! Luckily there is a simple math trick: the number of possible gametes =  $p^n$ , where p = ploidy and n = the number of chromosomes in a single set. For instance, in humans p = 2 (diploid) and n = 23.  $2^{23} = 8,388,608$ .



Figure 8: Depiction of how Meiosis results in the Law of Independent Assortment.

Uniquely You: Based on the math shown in the above paragraph, there was a 1/8,388,608 probability for the genetics of the sperm cell that created you, AND a 1/8,388,608 probability for the genetics of the egg cell that created you. Because both of these made you, we can use the 'AND' rule to figure out their probability together! The probability of getting 'you' from your parents is 1/8,388,608 x 1/8,388,608 = 1/70,368,744,177,664 (0.000000000014%). And this is without accounting for recombination in chromosomes! If we include recombination and epigenetics (which we'll discuss later in this semester) this probability becomes very close to zero. Dr. Seuss was right when he said "There is no one alive who is Youer than You"!

# Exercises

- 1. If you cross a garden pea true-breeding for green seeds with one true-breeding for yellow seeds, what proportion of the offspring do you expect to have green seeds?
  - (a) 0
  - (b) 1/2
  - (c) 1/4
  - (d) 3/4
  - (e) all of them
- 2. You perform a monohybrid cross to examine garden pea plant height. If you performed this cross and obtained 900 tall plants in the  $F_2$  generation, approximately how many short plants would you expect to have in the  $F_2$  generation?
  - (a) 100
  - (b) 200
  - (c) 300
  - (d) Not enough information to know

- 3. Tay-Sachs is a recessive disease. What is the probability that two parents who are heterozygous have a child with Tay-Sachs disease?
  - (a) 1/4
  - (b) 2/4
  - (c) 3/4
  - (d) 0/4
- 4. Tay-Sachs is a recessive disease. What is the probability that the first two children of a heterozygous couple both have Tay-Sachs disease?
  - (a) 1/4
  - (b) 1/2
  - (c) 1/16
  - (d) 1/8
- 5. Tay-Sachs is a recessive disease. What is the probability that one of the first two children of a heterozygous couple has Tay-Sachs disease?
  - (a) 1/4
  - (b) 1/2
  - (c) 1/16
  - (d) 1/8

## Answers

- 1. A
- 2. C
- 3. A
- 4. C
- 5. B