Non-Mendelian Genetics

The previous "Mendelian Genetics" unit described the two major principles discovered by Gregor Mendel for traits he studied in garden peas. In this unit we will examine traits that don't follow the same inheritance patterns as the traits that Mendel studied. For that reason, this unit is called **non-Mendelian genetics**.

1 Characteristics of a Mendelian Trait

Mendelian traits are:

1. **Discrete** (i.e., there are two distinct phenotypes)
2. **Bi-allelic** (i.e., there are only two alleles)
3. **Dominant/recessive** (i.e., heterozygote shows dominant phenotype)
4. **Not linked** (i.e., they independently assort)
5. **Determined by equal probability of alleles** (i.e., segregation)
6. **Encoded by a single gene** (i.e., one gene = one trait)

2 Discrete

If a trait has more than two discrete (a.k.a. distinct) phenotypes, then it is not Mendelian. Examples of this include incomplete dominance, co-dominance, and lethal alleles. Each of these scenarios also violate the "Dominant/recessive" assumption that is described below (since in all scenarios the heterozygous genotype does not exhibit the full phenotype of the homozygous dominant genotype).

2.1 Incomplete Dominance

Incomplete dominance is the inheritance pattern when a single dominant allele isn't enough to produce the phenotype of the homozygous dominant genotype; the heterozygote exhibits an intermediate (which is a third phenotype) between the homozygous recessive and homozygous dominant phenotypes. If a single gene encodes a trait with three phenotypes (where one is an intermediate between the other two), this trait is incompletely dominant. "Intermediate" is an important word here: the heterozygous phenotype is not simply a blending of the two phenotypes, it is a "partial" expression of the dominant phenotype. An example of incomplete dominance is if the recessive allele encodes no pigment protein and the dominant allele encodes a pigment protein, this could result in white coloration from lack of a pigment protein in homozygous recessive individuals [ww], red coloration from many proteins encoded by both alleles of a homozygous dominant individual [WW], and an intermediate pink coloration from some proteins encoded by a single allele of a heterozygous individual [Ww]).

NOTE: You may have previously learned incomplete dominance as a "blending" of two phenotypes. This is not the case. Incomplete dominance is specifically the scenario where a partial expression of the dominant phenotype is manifest in the heterozygote. If a phenotype is the result of a "blend" of two phenotypes due to the expression of both alleles, this is co-dominance.

2.2 Co-Dominance

Co-Dominance is the inheritance pattern when neither allele is dominant over the other; the heterozygote exhibits both traits. If a single gene encodes a trait with two distinct phenotypes and an additional phenotype that exhibits both of the other traits, this trait is co-dominant. This is different from incomplete dominance, because there is no recessive allele- both alleles encode a product. An example of incomplete dominance is if one allele ('B') encodes a blue pigment protein and the other allele ('Y') encodes a yellow pigment protein, this would result in blue phenotype in homozygous 'B' individuals [BB], yellow phenotype in homozygous 'Y' individuals [YY], and a phenotype with both blue and yellow in the heterozygote [BY]). At a close scale, you would be able to see both the blue and the yellow pigments. However, if you "zoomed out" the colors may start to blend and the phenotype could look green! This is not incomplete dominance, because the heterozygote is not an intermediate. Instead, the heterozygote expresses both of the allele products equally.

2.2.1 MN Blood Type

Most people are familiar with the 'ABO' and 'Rh+/Rh-' blood antigens, however there are several other blood antigens that are unknown by the general public. For example, many have never heard of the 'MN' blood antigens. A glycophorin gene on Chromosome 4 in humans encodes the 'MN' trait, and there are two alleles. The 'L^M' allele (sometimes just called 'M') produces the 'M' antigen, and the 'L^N' allele (sometimes just called 'N') produces the 'N' antigen. Individuals homozygous for either allele have 'M'- (for the 'L^ML^M' genotype) or 'N'-type (for the 'L^NL^N' genotype) blood. However, individuals with both alleles ('L^ML^N' genotype) express both products, and have 'MN'-type blood. Because neither allele is dominant and both are co-expressed, the 'MN' blood trait is co-dominant. While these blood antigens are less clinically significant with respect to mismatches (e.g., in blood donation or pregnancy), pre-transfusion and pre-natal antibody testing can help establish whether steps need to be taken to protect a patient.

2.3 Overdominance

Sometimes there are scenarios where the heterozygote exhibits a phenotype that isn't an intermediate or a joint expression between both alleles. Instead, the phenotype of the heterozygote is a characteristic outside the range of the other genotypes. Sometimes this confers a fitness advantage in heterozygotes, which is known as **heterosis**. Little is known about why this occurs in specific scenarios, but it is hypothesized that the joint expression of two alleles sometimes results in reaping the independent benefits that the two alleles confer.

2.3.1 Sickle Cell Disease

The human gene *HBB* encodes a critical component for hemoglobin, the protein that carries oxygen from the lungs to cells. A common variant (allele) of this gene results in the hemoglobin molecules "sticking" together more often, which causes red blood cells to be shaped like a "sickle". Individuals who are homozygous for this variant ('ss') have reduced blood-oxygen levels that results in increased risk of respiratory problems, bacterial infections, stroke, kidney failure, and other health concerns. Individuals who are homozygous for not having the variant ('SS') do not have the sickle cell phenotype. Individuals who are heterozygous ('Ss') do not experience the increased health risks, AND they have increased immunity against malaria. The single 'S' allele is sufficient to produce the amount of normal red blood cells for oxygen transfer, and the single 's' allele creates enough sickle-shaped red blood cells to make it difficult for the malaria pathogen to reproduce within the blood.

3 Bi-Allelic

If a gene has more (or less) than two alleles, then the trait it encodes is not Mendelian.

3.1 More than 2 alleles

A gene that has more than two alleles will not follow follow a Mendelian inheritance pattern. A trait encoded by a gene with multiple alleles can also exhibit multiple inheritance patterns, such as complete dominance between one group of alleles and co-dominance between another group of alleles.

3.1.1 ABO Blood Type

The 'ABO' blood antigen group exhibits two characteristics that make this group of antigens non-mendelian: (1) The 'A' and 'B' antigens are co-dominant (e.g., someone with type 'AB' blood has both 'I^A' and 'I^B' alleles whose products are both expressed), and (2) there are three alleles ('I^A', 'I^B', and 'i').

3.2 Less than 2 alleles

This should be intuitive- a gene with less than two alleles means that there is no variation at that gene- therefore, there is no way to examine the effect of gene variation on trait variation!

4 Dominant/Recessive

If a trait is encoded by a bi-allelic gene but the phenotypes of the alleles do not follow a dominant/recessive pattern where the heterozygote exhibits the phenotype of the dominant allele, then the trait is not Mendelian. Traits that violate this rule are bound to violate the "Discrete" rule above (resulting in more/less than two discrete phenotypes).

4.1 Two alleles, one phenotype

If a gene has two alleles (e.g., there are two distinct versions of a gene) but each encodes the same phenotype, then neither allele is dominant over the other. It should be intuitive that you can't study the inheritance pattern of a trait that doesn't have phenotypic variation (despite the fact that there may be genetic variation). This also violates the "Discrete" rule above, since there are not two discrete phenotypes.

5 Not Linked

This requirement is only relevant when considering multiple traits. In order for multiple traits to follow the rules of Mendelian genetics (e.g., a dihybrid cross resulting in the 9:3:3:1 ratio because of independent assortment), then the genes encoding these traits must be unlinked. In other words, they must be able to independently assort during Meiosis. Genes that are on separate chromosomes follow this pattern (e.g., Mendel's traits for 'seed shape' and 'seed color' were on different chromosomes).

5.1 Gene Linkage

Genes that are close together on the same chromosome will be inherited together. Even though crossing over occurs, recombination between genes that are close together is less frequent. When two genes are inherited together more likely than you would expect given the assumption of Independent Assortment, these genes are said to be "**linked**". Genes that are **completely linked** are always inherited together. Genes that are **incompletely** (or **partially**) **linked** are inherited together more frequently than you would expect given the assumption of Independent Assortment, but they do separate sometimes. We will cover gene linkage extensively in a later unit.

5.1.1 Hair and Eye Color

Hair and eye color are inherited together more often than would be expected under independent assortment. For example, It is more common for an individual to have blue eyes and blonde hair or brown eyes and brown hair than to have an individual with blue eyes and brown hair or brown eyes and blonde hair. This is because the gene encoding hair color and the gene encoding eye color are partially linked.

6 Determined by equal probability of alleles

It assumed that for a Mendelian trait p x 0.5 numbers of each gene will be present in the gametes (where p = ploidy). In other words, for a diploid (p = 2), there should be a copy of each gene in every gamete. Traits encoded by genes that violate this rule are not Mendelian.

6.1 Sex-linked Traits

Do not confuse sex-linked traits with gene linkage- they are totally different concepts! A sex-linked trait is simply a trait that is encoded by a gene on a **sex chromosome**. Many organisms have **sexual dimorphism** (differences between sexes) within their genomes due to heteromorphic sex chromosomes. In these organisms, one sex is **homogametic** (contains homologous sex chromosomes) and the other is **heterogametic** (contains non-homologous sex chromosomes). For example, in humans (and mammals in general) females are generally homogametic (have two 'X' chromosomes) whereas males are generally heterogametic (have an 'X' and a 'Y' chromosome). Systems such as this, where the male is the heterogametic sex, are known as '**XY**' systems. Alternatively, there are organisms where females are generally the heterogametic sex and males are the homogametic sex. These are known as '**ZW**' systems (the male genotype is 'ZZ' and the female genotype is 'ZW'). If a gene is on one of these chromosomes in a heteromorphic system (either 'XY' or 'ZW'), then the trait encoded by that gene is known as a **sex-linked trait**, and it will not follow a Mendelian inheritance pattern.

6.1.1 Red-Green Color Blindness

Red-green color blindness in humans is a recessive condition that results from a variant on the opsin genes that are on the 'X' chromosome (allele 'X^c'). Individuals that contain a single functional opsin gene (allele 'X') do not experience red-green color blindness (e.g., females with genotype 'XX' or 'XX^c' and males with genotype 'XY'). Individuals that contain no functional opsin gene experience red green color blindness (e.g., females with genotype 'X^cX^c' and males with genotype 'X^cY'). Males are more likely to experience color blindness (and any sex-linked recessive condition) because they only have one copy of a gene that is on the X chromosome.

7 Encoded by a Single Gene

If variation in a trait is not the result of variation in a single gene, then the trait is not Mendelian.

7.1 Epistasis

The term for when traits result from the interaction between multiple genes is known as **Epistasis**. We will talk about epistasis extensively in a later unit. The opposite of epistasis, when multiple traits are the result of a single gene, is known as **pleiotropy**. A gene with pleiotropic effects can encode traits that are Mendelian, since any given trait of interest is encoded by a single gene.

7.2 Phenotypic Plasticity

If a trait is variable between individuals with the same genotype, then the observed differences in the trait are a result of something other than genetics. When this occurs, it is because differences in the environment of the organisms create the variance in the trait. The term 'environment' is more than it may seem. Environment, in this context, is anything outside of the genetic sequence within the DNA. This includes the conditions outside of the organism (e.g., temperature, humidity), the presence of pathogens within the organisms (e.g., bacteria, virus), the nutrient status within the organism, and even the **epigenetic** modifications of the DNA itself (we will learn about these in a later unit). Differences in the environment of organisms with the same exact genetic composition can result in different phenotypes, and this is known as **phenotypic plasticity**.