All of us are familiar with inheritance – the characteristics of organisms that are passed from generation to generation. We readily compare facial features of children to their parents remarking at similarities (or differences) and often select our pets based on pedigree (their genetic heritage). We know that our genetic information is stored in DNA that is passed from cell to cell and from generation to generation as inheritable characteristics. We know, too, that for most inheritable characteristics there are at least two different variants, or traits, possible – that's why we have differences in inheritance.

The region of a DNA molecule that stores a specific genetic instruction is called a gene. The precise location where a gene is found on a chromosome is known as the locus for the gene. Since chromosomes of diploid organisms come in homologous pairs, each cell of a diploid organism typically has two "genes" or a "gene pair" for each inheritable trait, one on each of the homologues.

The alternative forms (variants) of genes are located on the homologous chromosomes and are called alleles. Alleles are the specific traits for the gene. For example, we may grow a plant in our garden for a particular flower color, for which there are two variants (or alternative forms) – white or purple. The gene is a description of the flower color. The alleles for that gene are white or purple. To be precise, we inherit alleles of the homologous chromosomes or "gene pair".

A haploid gamete has one allele of each "gene pair" (or one of each homologous chromosome) but not both. The diploid number of chromosomes is restored at fertilization along with the homologous chromosomes and gene pairs when two gametes fuse.

In this section of biology we will look at how genes (alleles) are expressed in individuals, and how genes (alleles) are transmitted from generation to generation within species.
We did not always know that genes were located on chromosomes. We did not even know that inheritable traits, or genes, came in pairs. Gregor Mendel, in the mid-1800s, was the first to publish that inheritable traits (genes) were discrete units that came in pairs with scientific evidence to validate his conclusions. His work went unappreciated for several decades because no one seemed to understand what it meant. In the early 1900's, three plant geneticists, Hugo DeVries, Carl Correns and Erich von Tschermark, independently made the same conclusions about inheritance, and Mendel's papers were "rediscovered". Soon after, Walter Sutton showed that Mendel's principles of inheritance applied to chromosomes and that chromosomes are the units of heredity, which resulted in the chromosome theory of inheritance.

Prior to Mendel, the subject of inheritance was mostly guesswork even though the practice of selective animal and plant breeding was well established. Plants have been crossbred for at least 5000 years throughout the world. Kolreuter demonstrated hybridization in tobacco in the 1700's in which the hybrids were different from either parent, but had some of each parent's characteristics. This was important because it dispelled earlier thoughts on how inheritance "worked". Kolreuter had also shown that second generation hybrids had even more variation; some were more similar to the "grandparents" than the parents. Kolreuter's hybrids showed that some traits were masked in some individuals only to reappear in subsequent generations. This was largely overlooked at the time, being attributed to "full restoration of the original powers" (whatever that meant).

Several other researchers did studies similar to Kolreuter's in the 1700's, while developing new variants for horticulture and agriculture. T. A. Knight even used Mendel's garden pea, and obtained results similar to Mendel's. But none of these early researchers on hybridization provided objective explanations for the results they saw, nor did they quantify their data.

Moreover, virtually nothing was known of the mechanisms of inheritance beyond the presence of an egg and a sperm in animals, and pollen and carpel in plants in the 1800's. Lots of ideas about inheritance had been postulated over the "eons". Ancient Greeks, for example, put forth that individual body parts (in particulate form) were transmitted from parent to offspring. An earlier term used was "pangens". One peculiar explanation for inheritance was the homunculus, a miniature person intact in the sperm that was nurtured within the womb.

Most popular in the 1800's was the idea that characteristics of parents were "blended" in offspring that generally, but not always, had features of both parents. No one went so far as to question why, after several generations, variations still were present, since differences over time should have been thoroughly blended. Moreover, the offspring could have just the trait of one parent. Did the other trait just disappear? How did a trait that disappeared in one generation "mysteriously" reappear in later generations? No one had an answer.
The subject of variation among individuals and how different variants were passed on (or apparently not passed on) from generation to generation was important to science in the 1800's. It was Gregor Mendel's work in the mid-1800's that gave us the answer to how inheritable characteristics were passed from generation to generation. Mendel's work coincided with the publications of Darwin and Wallace, who addressed variation among the individuals of populations as the foundation for which selective agents could act through time, in the process of evolution.

**Gregor Mendel's Contribution to the Subject of Inheritance**

Mendel observed how a set of specific traits of the garden pea was transmitted from generation to generation. Mendel kept precise records of the thousands of numbers of offspring (and their characteristics) produced in his crosses. He then established mathematical probabilities and explanations to validate his observations. Although others had studied inheritance, Mendel's educational experiences in math and observing plant variation helped him design and analyze his experiments carefully.

- Mendel chose an organism that had a number of "true breeding" traits easy to observe, and one that he could readily cross-pollinate artificially.
- Mendel carefully selected seven characteristics that had "either-or" traits. That is, the alternatives did not have intermediate forms; they were either "A" or "B", not something that was almost "A" or mostly "B".
- Mendel designed the experiments carefully. Mendel took plants from true breeding parents (P generation) to get his first generation (F₁ hybrids), and then self-crossed the first generation offspring to form a second generation (F₂).
- Mendel obtained large sample sizes for good data analysis, and kept excellent records of what he did.

Gregor Mendel carefully tabulated his results for his crosses using the seven different pea characteristics. For each he observed the following:

- 100% of the first generation hybrids expressed the trait of just one parent. For example, when a parent with purple flowers was crossed with a parent producing white flowers, 100% of their offspring had purple flowers.
- When first generation peas were crossed among themselves, 75% of the second generation offspring had the expressed the trait of the first generation offspring (purple flowers) but 25% expressed the trait of the second parent (white flowers). If, as some thought, the trait of the second parent was lost, the second generation would also have been the same as the first generation (purple flowers). He called the parental trait that appeared in the first generation offspring dominant, and the one that did not appear in the first generation offspring, but was expressed in 25% of the second generation recessive. All seven pea traits that Mendel observed had clear dominant and recessive forms.
Mendel's Pea Traits and Experimental Results

Mendel concluded from his research that the units of heredity were discrete particulate factors that occur in pairs. Each pea plant had two factors or discrete units for each trait, one from each parent. Mendel also concluded that the paired units of heredity segregate from one another in the formation of gametes, and that fertilization restores the pairs for the next generation. He further concluded when he studied the inheritance of two traits that one set of paired factors segregated independently of other paired factors in the formation of gametes. Mendel's work also demonstrated that these discrete factors retain their integrity from generation to generation. Mendel's conclusions were formulated into two laws: Law of Segregation and Law of Independent Assortment.

Mendel's hypothesis for inheritance, using vocabulary in use today, can be summarized as follows:

A gene has alternative forms, which accounts for the variations observed in inheritable characteristics. The alternative forms of a gene are called alleles. To relate this to what we know about homologous chromosomes, the alleles for a gene are located at the same locus on the homologous chromosomes.

A diploid individual inherits two alleles for each gene, one from each parent. The two alleles for a gene may be the same or they may be different. If the two alleles are the same, the individual is said to be homozygous for that trait. If the two alleles are different, the individual will be heterozygous for the trait.
Gametes have just one allele for each gene and are **haploid**. The two alleles for a gene are separated during Meiosis I when homologous chromosomes pair and then separate. 50% of the gametes receive one allele and 50% of the gametes receive the second allele. If the parent is homozygous for a characteristic (pure breeding), all of the gametes will have the same allele. If the parent is heterozygous, 50% will have one allele, and 50% will have the alternative allele.

When the two alleles for a gene pair are different from each other (heterozygous), in the **traditional Mendelian inheritance** patterns, only one of the alleles will be expressed, and the second will not affect the organism's appearance. The allele always expressed is said to be **dominant**, and the one that is not expressed is **recessive**.

Since a dominant allele is always expressed, individuals that are heterozygous will have a recessive allele as well as the expressed dominant allele. The **genotype** is the specific genetic makeup of an individual, or total combination of alleles present, both those expressed and those not expressed. The **phenotype** is the "visible" expression of one's genes.

Fertilization restores the pairs of alleles for the next generation. This statement is critical to the particulate theory of inheritance and dispels the blending theory, commonly held through the 19th century.

**Note:** These statements are true for the traits tested in Mendel's peas and for many genes, but are not universally true, as we shall discuss in more detail later. Many genes have alleles that are equally expressed, or, as is often the case, one allele may be sufficient to produce the gene product, but heterozygous individuals may produce less of the product than homozygous individuals. There are also genes that have more than 2 alleles within the population. Many genetic characteristics are the result of two or more genes interacting with each other, and with the environment.
Mendel's **Law of Segregation** addresses the segregation of alleles: Pairs of genes segregate during the formation of gametes during meiosis, so that each gamete has one of each gene pair (one allele) but not both. Fertilization restores the gene pairs on the homologous chromosomes.

Mendel demonstrated his **Principle of Segregation** with his multitude of **monohybrid crosses**, a cross in which the F₁ generation, which appeared dominant, was crossed with the recessive parent. If the F₁s were heterozygous, their offspring would exhibit equal proportions of both dominant and recessive forms. If the F₁s were pure breeding, like their dominant parent, the offspring would express only the dominant phenotype. In the test cross, the offspring had equal proportions of both the dominant and the recessive phenotype.

Mendel further validated his Principle of Segregation with the **heterozygous test cross**, a cross in which the F₁ generation, which appeared dominant, was crossed with the recessive parent. If the F₁s were heterozygous, their offspring would exhibit equal proportions of both dominant and recessive forms. If the F₁s were pure breeding, like their dominant parent, the offspring would express only the dominant phenotype. In the test cross, the offspring had equal proportions of both the dominant and the recessive phenotype.
Mendel's Law of Independent Assortment was derived from crossing two traits at one time, a dihybrid cross. We observed during meiosis that homologous pairs of chromosomes independently align along the equator at metaphase I. Maternal chromosomes of some pairs align towards one pole some of the time, and the other pole some of the time. Each meiosis event has a different alignment pattern. Alleles located on different chromosomes are assorted independently into the gametes formed.

Mendel's Law of Independent Assortment applies to genes that are located on different chromosomes. We shall discuss later how genes located on the same chromosome (gene linkage) are inherited.

As expected, equal numbers of each of the four possible phenotypes result with a dihybrid heterozygous test cross, which crosses an individual heterozygous for both traits with one that is homozygous recessive for both traits.
Mendel's specific crosses and predicted phenotypic ratios are thoroughly discussed in your text. **You will be responsible for knowing these inheritance patterns and the predicted inheritance ratios for each outside of lecture.** You will also be responsible for other types of inheritance patterns that are in your text or discussed in class.

Prior to doing Mendelian inheritance problems you should review your knowledge of homologous chromosomes and the process of meiosis, since the homologous chromosomes "carry" the alleles, or alternative forms for each gene. Determining gamete possibilities is doing meiosis.

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**Mendel's Use of Mathematical Probability**

Note that Mendelian inheritance predictions follow the mathematical laws of probability. Although it is fairly "easy" to diagram a monohybrid test and a dihybrid test using Punnett squares (see above), making predictions and looking at results for increasing numbers of genes or other inheritance observations becomes tedious and time consuming. Applying probability laws is much faster and easier.

For example, if there are two alleles (R and r) for a monohybrid cross, and the individuals being crossed have one of each, the probability of making gametes with the R allele is 1/2 and the probability of making gametes with the r allele is 1/2 for each individual. Predicting offspring possibilities uses probability and rules of multiplication and addition as discussed in your text. In this example, the probability for AA is 1/2R X 1/2R or 1/4. The same is true for rr, Rr and rR.
Using probability rules allows us to make predictions for the inheritance of several alleles at a time.

### Probability for Two Alleles

<table>
<thead>
<tr>
<th>Allele Combination</th>
<th>Probability Calculation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ppyyRr</td>
<td>( \frac{1}{4} \text{ (probability of } pp) \times \frac{1}{2} \text{ (yy)} \times \frac{1}{2} \text{ (Rr)} )</td>
<td>( \frac{1}{16} )</td>
</tr>
<tr>
<td>ppYyrr</td>
<td>( \frac{1}{4} \times \frac{1}{2} \times \frac{1}{2} )</td>
<td>( \frac{1}{16} )</td>
</tr>
<tr>
<td>Ppyyrr</td>
<td>( \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} )</td>
<td>( \frac{1}{8} )</td>
</tr>
<tr>
<td>PPyyrr</td>
<td>( \frac{1}{4} \times \frac{1}{2} \times \frac{1}{2} )</td>
<td>( \frac{1}{16} )</td>
</tr>
<tr>
<td>ppyyrr</td>
<td>( \frac{1}{4} \times \frac{1}{2} \times \frac{1}{2} )</td>
<td>( \frac{1}{16} )</td>
</tr>
</tbody>
</table>

**Chance of at least two recessive traits** = \( \frac{9}{16} \) or \( \frac{3}{8} \)

A probability calculation with three alleles that at least two will be recessive
**Humans and Mendelian Inheritance**
Historically, most of our information about human genetics, which, like all organisms, follows basic rules of inheritance, has come from careful analysis of family histories, or pedigrees, sometimes over many generations.

Much of our interest and study of inheritance in humans comes from the study of inherited diseases or "disorders", rather than the study of traits that confer more advantage to the individual, or as often done in biology labs, study traits that are easily observed. We study genetic diseases hoping to find ways to improve the condition. Pedigree analysis not only reveals our genetic history, it can also predict future patterns in offspring, which is of much use in genetic counseling.

It is only within the last generation that advances in molecular genetics have led to much better analyses of the inheritance of specific genetic traits. Molecular biology and genetic technology research provide us with better methods of identifying and treating genetic disorders. In this section we will look at how pedigrees are used to predict human Mendelian inheritance patterns. *We will look more closely at methods of analysis and treatments of gene disorders in our section on mutations and genetic diseases, and in our genetic technology unit.*

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### Characteristics of Dominant Allele Inheritance
- All children who express the trait have a parent who also expresses the trait.
- About half the children of a parent who expresses the trait express the trait.

### Characteristics of Recessive Allele Inheritance
- It is common for both parents of a child who expresses the trait to **not** express the trait. Both parents are typically "carriers" (heterozygous) for the trait.
- About 1/4 of the children of two "carriers" will express the trait. If one parent expresses the trait and the other parent is a "carrier", about 1/2 of the children will express the trait.
- Both sexes will express the trait equally.
Beyond Mendel: Genes, Alleles and Gene Interactions:
Given the lack of knowledge about chromosomes, molecular genetics, mitosis or meiosis at that time, Mendel’s work was outstanding, as far as it went. Each of the genes that Mendel chose had clear dominant and recessive alleles, and each inheritable trait was found on different chromosomes.

Mendel set the direction for inheritance research. Throughout the 20th century, geneticists continued to examine how genetic information is transmitted. Not all inheritance results match Mendel’s predictions. Many, if not most phenotypic expressions are the result of gene or allele interactions. Each gene involved may fit a Mendelian prediction, but how alleles interact alters the predicted ratios.

We shall now turn our attention to some inheritance patterns that go beyond the basic Mendelian predictions, both for the alleles of single genes and for interactions involving more than one gene.

Allele Interactions
Most organisms have a diploid phase in their life cycle, with homologous chromosomes in their cells. The "typical" gene has two alleles, one on each of the homologous chromosomes, one inherited from its "father" and one from its "mother". The two alternative alleles are found in all members of the population. This was true for the genes that Mendel observed and tracked. However, genes, or their alleles, are subject to mutation. (Mutation is defined as a change in the DNA – See Mutation and Molecular Medicine section later.) New alleles may result from mutations and be passed on to subsequent generations. Moreover, some alleles do not exhibit dominance patterns. And some alleles may have more than one phenotypic effect. At this time we shall look at some inheritance patterns that involve allele interactions not predicted by Mendelian inheritance.

Allele Interactions – Genes with Multiple Alleles
There are many genes in which we find more than two alternative alleles at the single gene locus among members of the species. When this is the case, the allele variation in the population is known as the inheritance of multiple alleles. Multiple alleles must be observed and measured in a population, not in an individual.
• A diploid individual can inherit just two of the possible alleles found within the population (one on each of the homologous chromosomes).
• Multiple alleles increase the amount of variation possible within the population.

Some Examples of Multiple Alleles
Coat color in rabbits has 4 alleles:
• C codes for dark gray fur
• c codes for albino (no pigmentation)
• c^{ch} codes for Chinchilla (a mottled fur pattern)
• c^{h} codes for light gray fur
Each rabbit gets two of the four, resulting in 5 common phenotypes. The alleles have a dominance hierarchy: C, c<sup>ch</sup>, ch, c

- Any rabbit that inherits a C (CC, Cc<sup>ch</sup>, Cch or Cc) will be dark gray
- A rabbit that is homozygous c<sup>ch</sup>c<sup>ch</sup> is chinchilla
- A rabbit that inherits c<sup>h</sup>c<sup>h</sup> or chc) will be light gray
- A rabbit that is homozygous c<sup>h</sup>c<sup>h</sup> or heterozygous chc is Himalayan
- A rabbit that is homozygous cc is albino

The human A,B,O alleles of the "I" gene that code for glycoproteins on red blood cells are perhaps the best known example of multiple alleles. The I<sup>A</sup> (A) and I<sup>B</sup> (B) alleles are co-dominant. The i (O) allele is recessive

<table>
<thead>
<tr>
<th>Blood Type</th>
<th>Genotype</th>
<th>Red Blood Cell Coating</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>AA or AO</td>
<td>N-acetyl-galactosamine</td>
</tr>
<tr>
<td></td>
<td>I&lt;sup&gt;A&lt;/sup&gt; I&lt;sup&gt;A&lt;/sup&gt; or I&lt;sup&gt;A&lt;/sup&gt; i</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>BB or BO</td>
<td>Galactose</td>
</tr>
<tr>
<td></td>
<td>I&lt;sup&gt;B&lt;/sup&gt; I&lt;sup&gt;B&lt;/sup&gt; or I&lt;sup&gt;B&lt;/sup&gt; i</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
<td>Antigen A Antigen B</td>
</tr>
<tr>
<td></td>
<td>I&lt;sup&gt;A&lt;/sup&gt; I&lt;sup&gt;B&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>OO</td>
<td>Antigen O</td>
</tr>
<tr>
<td></td>
<td>ii</td>
<td></td>
</tr>
</tbody>
</table>

A second, unrelated gene that produces a coating on the red blood cells is the Rh gene. It is a Mendelian dominant. Rh<sup>+</sup> individuals produce the coating; Rh<sup>-</sup> (recessive) individuals do not. For blood typing, one can be A<sup>+</sup>, A<sup>-</sup>, B<sup>+</sup>, B<sup>-</sup>, AB<sup>+</sup>, AB<sup>-</sup>, O<sup>+</sup> or O<sup>-</sup>. There are also variant alleles for each of the blood types beyond those discussed in introductory biology classes.

The A and B coatings and the Rh factor are antigens that trigger antibody reactions of the immune system when an individual receives donor blood that is not genetically compatible. The antibody-antigen reaction causes the antigen-coated donor cells to "agglutinate" and form blood clots. This is important for blood transfusions. Recently, it was discovered that some bacteria have enzymes that degrade the A and B antigens. It may be possible to treat donor blood with these enzymes "converting" any blood type donated blood into "O" with no antigens present. (The immune system is discussed in Biology 212.)
Allele Interactions – The Dominance Continuum

Mendel's F₁ offspring always resembled a dominant parent, because each of the genes Mendel chose to study showed complete dominance by one allele, (Note: We can say the gene has dominance (but it is not correct to say "dominant gene or recessive gene – alleles can be dominant or recessive). However, genes do not always have dominant and recessive alleles. Some alleles are co-dominant, in which each allele is equally and separately expressed. In other cases, called incomplete dominance, the heterozygous form will have some intermediate expression between the two homozygous forms, again with both alleles being expressed to some degree.

The concept of dominance depends on how the allele is coded for and expressed in the phenotype. When a gene "lacks" dominance, whether it is co-dominance or incomplete dominance, there are three different phenotypes, two homozygous phenotypes (AA and A'A') and a third distinct heterozygous phenotype (AA'). Moreover, many genes may be metabolically without dominance, but undetected in the phenotype since the gene product of the heterozygous individual is adequately expressed for the function that needs to be done.

A. Incomplete Dominance

Incomplete dominance was once assumed to be the "failure" of the presumed "dominant" allele to completely mask the "recessive" allele. However, with incomplete dominance, both alleles are coded, and both get expressed to some degree.

- The heterozygote first generation has some intermediate phenotype between the two homozygous forms, often expressed as an apparent blending of the two alleles.
- Snapdragons, 4 O'clock and carnation flowers all exhibit incomplete dominance in the expression of flower color. When homozygous red flowers are crossed with homozygous white flowers, the offspring, all heterozygous, have pink flowers. The texture of human hair similarly can be straight, wavy or curly.

\[ F₁ \text{ generation} \quad \text{Eggs} \rightarrow \text{Sperm} \rightarrow \text{F₂ generation} \]

\[ 1:2:1 \quad \text{C}^{0} \text{C}^{0}, \text{C}^{0} \text{C} \text{W}, \text{C} \text{W} \text{C} \text{W} \]

\[ \text{mother} \quad \text{father} \quad \text{eggs} \]

\[ \text{Sperm} \quad \text{c} \text{c}_1, \text{c}_1, \text{c}_1, \text{c}_1 \quad \text{c}_1, \text{c}_1, \text{c}_1, \text{c}_1 \]

\[ \text{c}_1 \text{c}_1, \text{c}_1 \text{c}_2, \text{c}_2 \text{c}_2 \]

\[ \text{c}_1 \text{c}_2, \text{c}_2 \text{c}_2, \text{c}_2 \text{c}_2 \]
B. **Co-Dominance**

In co-dominance, both alleles are equally expressed, or coded for, in the heterozygote. Both alternative expressions appear in the heterozygous individuals. The Roan cattle pattern and the A-type and B-type red blood cell glycoproteins previously discussed are examples of co-dominant alleles. (The "O" allele is recessive.)

C. **Variable Expressivity and Penetrance**

The meaning of dominant and recessive blurs further when the impact of the gene is metabolic as mentioned briefly above, and when gene expression is influenced by environmental conditions.

- **Penetrance** is the proportion of individuals who have a particular genotype that express the phenotype.
- **Expressivity** is the degree to which a genotype, and particularly a dominant allele, is expressed from individual to individual and within an individual. The expression of a gene, in particular, can be affected by the environment *(See later)*.

For example, those who are homozygous recessive for Tay-Sachs disease die. Tay-Sachs is a disease in which a crucial enzyme needed to degrade specific brain lipids called gangliosides is not synthesized. Heterozygotes produce about half as much of the enzyme as those who are homozygous "normal" but do not have symptoms of Tay-Sachs disease, because the amount of enzyme produced is sufficient. Genetically, the gene is one that lacks dominance – one allele is coding for enzyme production and the second allele is not coding for enzyme production. Functionally, Tay-Sachs is classified as a recessive genetic disorder.

![Enzyme Function with Tay-Sachs Alleles](image)

The same situation is true for the gene that causes hemophilia, and for many genes for which the alternative alleles are produce "X" or do not produce "X". If the amount of "X" coded for by one allele is sufficient for the needed function, then the individual's phenotype will not be affected.
Dominant and Recessive Revisited

As you can tell from the discussion on penetrance and expressivity that even though we use the term "gene or allele interactions", alleles don’t really interact – they are either coded or not coded in the cells. The expression of a gene in the cell is a consequence of the pathway taken.

- The DNA of the recessive allele might be defective so that it cannot be read and coded in the cell.
- The DNA of a recessive allele might code for a defective enzyme molecule, so the chemical reaction for which that enzyme is "needed" does not take place.

In some cases, when one is heterozygous, the allele that does not have defective code can produce sufficient enzyme to prevent symptoms of the disease, such as in Tay-Sachs mentioned above. Many alleles that appear to be dominant may be so only because the phenotypic effect of the gene is the same in both homozygous and heterozygous individuals.

It should also be noted that dominance is not related to frequency or abundance of an allele in the population. Dominance refers solely to the expression of the allele when it is present in the individual. An allele that is dominant may be very common in the population or exceedingly rare. All dominant means is that the allele, if present in the genotype of the individual, will be expressed in the individual's phenotype.

To summarize the issue of dominance and recessiveness:
- The range of dominance goes from complete to co-dominant to variations of "incomplete".
- Dominance or lack thereof reflects the mechanisms by which alleles are expressed in the individuals. A dominant allele does not "subdue" a recessive allele.
- There is no relationship between dominance and the frequency of an allele in a population.
Genes with More Than One Effect - Pleiotropy (Pleio means "more")
The phenotype conferred by a gene can (and often does) result in many additional alterations in the individual, some of which seem unrelated to each other. Most genes are probably pleiotropic, but some are dramatically so, and the term is used for those whose impacts are multiple.

Examples of pleiotropy include
- The albino condition (no pigment produced) affects eye and skin sensitivity to light in many animals
- Chickens and some other birds with "frizzle" feathers can't insulate properly so the birds can't thermoregulate, which impacts many metabolic functions.
- Cystic Fibrosis in Humans affects an ion channel protein. Because excess mucus accumulates, cilia do not function and there are multiple respiratory, digestive tract problems, as well as blockage of pancreatic ducts.

- Abnormal hemoglobin affects the shape of red blood cells at low oxygen levels, which leads to a number of metabolic problems. However, heterozygotes have malarial resistance. The normal and abnormal alleles are co-dominant.
Gene Interactions Involving Two or More Genes
A Mendelian dihybrid cross involves two genes. In Mendelian inheritance, both genes are independent genes and code for two different phenotypic expressions. The predicted F₂ ratio is based on the outcomes of the four different possible gamete types.

We find, however, that two (or more) genes often interact, equally or unequally, to produce just one phenotypic expression. This is true for many of our human characteristics. Sometimes they are different genes, and sometimes multiple copies of one gene located on different chromosomes.

When we have two genes interacting, we still have a "dihybrid" cross and 4 gamete types, but the phenotypic ratio may differ from Mendel's 9:3:3:1. There are a number of different gene interactions, each of which has subtle differences that can be determined through close inspection of the inheritance pattern and phenotypes produced. With more than two genes, we get expanded ratios and ultimately a continuum of variation. We will discuss some of the more common gene interactions.

Two Equal Genes – One Phenotype
Two independent genes can equally affect one characteristic. When this happens, the F₂ ratio is an exact Mendelian dihybrid cross, except that one characteristic is affected by the four alleles of the two genes rather than two independent characteristics, such as flower color and seed shape. This is often called collaboration. Some examples of collaboration include comb shape in poultry, feather color in parakeets and kernel color in wheat.

Inheritance of Feather Color in Parakeets
Epistasis: Unequal Genes – One Phenotype

In epistasis, which means "standing upon", one gene controls or alters the expression of a second gene, so that expected phenotypes do not appear. For example, the gene to distribute (or deposit) pigment can be overridden by a second gene that blocks (inhibits) or alters pigment production. The epistatic gene can be either a dominant allele or a recessive (which requires that both of the homologous chromosomes have the recessive allele). Epistasis may involve genes that code for enzymes catalyzing steps in a metabolic pathway. If one enzyme is non-functional, even when a second works, the pathway is blocked and the phenotypic expression is altered. Epistasis is readily seen in pigment production and distribution genes.

In Labrador dogs, the gene "B" produces dark pigment. Dogs that are homozygous "BB" or heterozygous "Bb" have black fur and those that are homozygous "bb" have brown fur. The gene "E" controls the distribution of the pigment in fur. "ee" inhibits pigment distribution; "EE" and "Ee" genotypes do not inhibit pigment distribution. A dog with the "eebb" genotype will have yellow fur and a brown nose and lips because it produces some pigment but can't distribute it. A dog with "eeB_" will have a yellow coat color with a black nose and lips; it can produce the dark pigment but can't distribute it in fur. A chocolate lab will be "E_bb". It produces some pigment and can distribute the pigment (no "ee" inhibition). A black lab will be "E_B_", and can both produce dark pigment and distribute the dark pigment in its fur.
Mice have a similar epistasis with fur pigmentation. Mice have black or brownish-gray fur depending on the inheritance of a gene for pigmentation. (BB or Bb results in Black fur. bb results in brownish-gray fur.) A second epistatic gene (CC, Cc or cc) can prevent the distribution of any pigment in the fur. "cc" results in white mice. CC or Cc does not inhibit pigment.

An epistatic gene also controls expression of anthocyanin pigment in corn.

AA or Aa = Produce anthocyanin pigment
aa = Do not produce anthocyanin pigment
BB or Bb = Pigment distribution allowed
bb = No pigment distributed
Inheritance of Eye Color in Humans – Two Copies of the Same Gene

The gene, OCA2, determines the amount of melanin pigment produced in the iris of the eye. We have two copies of the OCA2 gene. The four alleles either code to produce pigment or "no pigment". We have variation within the population because each allele is expressed. It's "simply" a matter of how many total alleles of "produce pigment" you inherit*. However, the expression of OCA2 is influenced by adjacent single nucleotide polymorphisms (SNPs), discussed in our genetic technology section. Those who have a "TGT" SNP at three locations on both gene copies are more likely to be blue-eyed, while those who have have no TGT rarely have blue eyes.

First Iris Layer Pigment
- AA = Produce lots of pigment
- Aa = Produce some pigment
- aa = Do not produce pigment

Second Iris Layer Pigment
- BB = Produce lots of pigment
- Bb = Produce some pigment
- bb = Do not produce pigment

*There is also a gene that may be related to the red-hair gene that alters light brown to hazel and light blue to green.

Polygenic Inheritance – Multiple Copies of the Same Gene

The traits that we have so far discussed all have phenotypes resulting from the interaction of one or two genes. With eye color, we saw that the phenotype was the collective result of two copies of one gene and four alleles. Although there are four alleles, there are only two allele alternatives (make pigment or do not make pigment). a difference from previous examples of two different gene interactions.

When a number of genes, or copies of genes are coded, the number of possible different phenotypes increases so that we observe continuous or quantitative variation in the population with respect to that genetic characteristic, in other words, a continuum. Continuous variation involves several gene pairs on independent chromosomes, all of which specify additive information for the same trait. We call this type of inheritance polygenic or quantitative inheritance. The individual phenotype is the result of the combined interaction of all the alleles at all of the gene loci involved.
Continuous variation can most easily be demonstrated when population data shows a **bell-shaped distribution** pattern when graphed. Skin and hair pigmentation and height are examples of polygenic inheritance in humans. It is believed that there are at least three independent genes, each of which lacks dominance, responsible for producing the melanin pigment in human skin (and in hair). In addition, the synthesis of melanin in skin is activated by light exposure, increasing the phenotypic variation possible.

Note: It can be easy to confuse the inheritance of multiple alleles in a single individual within a population with the inheritance of genes that have many copies on different chromosomes in a single individual. It’s important to understand the difference.
The Influence of the Environment on Gene Expression

Many inheritance patterns are affected by environmental factors that influence gene expression. For example, the genetic potential for height, addressed above as an example of polygenic inheritance, can only be realized if children have adequate nutrition during their growth years. Melanin production is influenced by light exposure (which explains the "tanning" business). Physical activity is critical for muscle development. Studying appropriately helps improve exam performances. The interaction of the environment with gene expression results in greater variation among individuals in the population.

Although one's genotype is "fixed", the expression of the phenotype is not rigid, but subject to a range of possibilities related to environmental influences.

The classic study on environmental control of gene expression was done with the pigmentation gene found in Siamese and Himalayan cats and in Himalayan rabbits. Typically, the animal's extremities are pigmented while the body core remains unpigmented or cream colored. The pigmentation gene is activated when the temperature falls below a certain point, which is about 35° C. To demonstrate that the pattern was temperature controlled, the backs of rabbits were shaved and ice packs placed on the shaved portion for several weeks. When new fur grew, it was pigmented.

The winter/summer pigmentation in ptarmigan, arctic fox and ermine are also temperature controlled.

Conditions of the environment regulate a number of genes that affect morphology and color patterns. Even types of foods consumed affect gene expression.
The degree to which environment and genes "interact" can be addressed with the same terms used for dominance: **Expressivity** and **Penetrance**. Expressivity addresses the degree to which the genotype is expressed in an individual and the environmental factors addressed above play important roles in the expressivity of many genes, and particularly in quantitative inheritance.

Ultimately each individual is a combination of his/her genetic potential and response to the multitude of environmental factors to which he/she is exposed -- the so-called **norm of reaction** for the genotype. This norm of reaction appears broadest for polygenic inheritance, also called by geneticists **multifactorial inheritance**, to reflect both the variation in genotypes possible with the many genes and the range of environmental influences. The genes that determine the complex characteristic interactions are known as **quantitative trait loci**. Finding these loci is important for agriculture to maximize productivity.
Hybrid Vigor
Before we turn to the discussion of chromosomes and genes, we should address one more "feature" of gene interactions: "hybrid vigor". Charles Darwin first noted that hybrids are often more vigorous than either parent. Recall that the offspring in a Mendelian cross between two homozygous parents are called hybrids. Darwin noted that when two individuals, which are homozygous for a number of traits are crossed, their offspring are often more "vigorous" in some of the traits than either parent. In 1908 George Shull made the same observation with hybrid corn, noting that both height and weight improved. In fact, virtually all corn grown today and many of our other agricultural crops are hybrids, and often polyploids (see later). This hybrid vigor is known as heterosis. The mechanism for heterosis is not understood.

The reverse is often true as well. The more closely related two individuals are the more likely it is that deleterious recessive genes can be expressed. When this occurs, it is referred to as inbreeding depression. Most human cultures have prohibitions on close intermarriage for this reason.
<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendelian</td>
<td>Inheritance patterns in which a single gene affects a single trait, and the alleles segregate and assort independently. These patterns include simple dominant/recessive traits, X-linked traits controlled by a single gene, incomplete dominance, codominance, and sex-influenced traits (refer back to Table 16.1).</td>
</tr>
<tr>
<td>Epistasis</td>
<td>A type of gene interaction in which the alleles of one gene mask the effects of a dominant allele of another gene.</td>
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<tr>
<td>Continuous variation</td>
<td>Inheritance pattern in which the offspring display a continuous range of phenotypes. This pattern is produced by the additive interactions of several genes, together with environmental influences.</td>
</tr>
<tr>
<td>Linkage</td>
<td>Inheritance patterns involving two or more genes that are close together on the same chromosome. These genes do not assort independently.</td>
</tr>
<tr>
<td>Extranuclear inheritance</td>
<td>Transmission pattern of genes found in the DNA of mitochondria or chloroplasts, which are inherited independently of genes in the nucleus and do not segregate during meiosis. Usually these genes are inherited from the mother.</td>
</tr>
<tr>
<td>X inactivation</td>
<td>Phenomenon of female mammals in which one X chromosome is inactivated in every somatic cell, producing a mosaic phenotype. Most genes on the inactivated X chromosome are not expressed.</td>
</tr>
<tr>
<td>Genomic imprinting</td>
<td>Inheritance pattern in which an allele from one parent is inactivated in the somatic cells of the offspring, while the allele from the other parent is expressed.</td>
</tr>
<tr>
<td>Maternal effect</td>
<td>Inheritance pattern in which the genotype of the mother determines the phenotype of the offspring. This occurs because maternal effect genes of the mother provide gene products to developing egg cells.</td>
</tr>
<tr>
<td>Simple Mendelian inheritance</td>
<td><strong>Inheritance pattern:</strong> Pattern of traits determined by a pair of alleles that display a dominant/recessive relationship and are located on an autosome. The presence of the dominant allele masks the presence of the recessive allele.</td>
</tr>
<tr>
<td>X-linked inheritance</td>
<td><strong>Inheritance pattern:</strong> Pattern of traits determined by genes that display a dominant/recessive relationship and are located on the X chromosome. In mammals and fruit flies, males are hemizygous for X-linked genes. In these species, X-linked recessive traits occur more frequently in males than in females.</td>
</tr>
<tr>
<td>Incomplete dominance</td>
<td><strong>Inheritance pattern:</strong> Pattern that occurs when the heterozygote has a phenotype intermediate to the phenotypes of the dominant and recessive homozygotes, as when a cross between red-flowered and white-flowered plants produces pink-flowered offspring.</td>
</tr>
<tr>
<td>Codominance</td>
<td><strong>Inheritance pattern:</strong> Pattern that occurs when the heterozygote expresses both alleles simultaneously. For example, a human carrying the A and B alleles for the ABO antigens of red blood cells produces both the A and the B antigens (has an AB blood type).</td>
</tr>
<tr>
<td>Sex-influenced inheritance</td>
<td><strong>Inheritance pattern:</strong> Pattern that occurs when an allele is recessive in one sex and dominant in the other. An example is pattern baldness in humans.</td>
</tr>
<tr>
<td>Molecular basis of inheritance patterns</td>
<td><strong>Molecular basis:</strong> In many cases, the amount of protein produced by a heterozygote, which may be 50% of that produced by a dominant homozygote, is sufficient to produce the dominant trait.</td>
</tr>
<tr>
<td>Molecular basis</td>
<td><strong>Molecular basis:</strong> In a female with one recessive X-linked allele (a hemizygote), the protein encoded by the dominant allele is sufficient to produce the dominant trait. A male with a recessive X-linked allele (a hemizygote) does not have a dominant allele and does not make any of the functional protein.</td>
</tr>
<tr>
<td>Molecular basis</td>
<td><strong>Molecular basis:</strong> 50% of the protein encoded by the normal (wild-type) allele is not sufficient to produce the normal trait.</td>
</tr>
<tr>
<td>Molecular basis</td>
<td><strong>Molecular basis:</strong> The codominant alleles encode proteins that function slightly differently from each other. In a heterozygote, the function of each protein affects the phenotype uniquely.</td>
</tr>
<tr>
<td>Molecular basis</td>
<td><strong>Molecular basis:</strong> Sex hormones affect the molecular expression of genes, which can have an impact on the phenotype.</td>
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