Mendelian inheritance describes inheritance patterns that obey two laws:

- Law of segregation
- Law of independent assortment

Simple Mendelian inheritance involves:

- A single gene with two different alleles. Alleles display a simple dominant/recessive relationship.

When gene expression does not adhere to a simple dominant/recessive mode, or when more than one pair of genes influence the expression of a single character, the classic 3:1 and 9:3:3:1 F₂ ratios are usually modified.

Traits can deviate from the simple dominant/recessive relationship. In spite of the greater complexity of these situations, the fundamental principles set down by Mendel still hold.

### INHERITANCE PATTERN OF SINGLE GENES

There are many ways in which two alleles of a single gene may govern the outcome of a trait. Table 4.1 describes several different patterns of Mendelian inheritance. These patterns are examined with two goals in mind:

1. Understanding the relationship between the molecular expression of a gene and the trait itself
2. The outcome of crosses. In a simple dominant/recessive relationship, the recessive allele does not affect the phenotype of the heterozygote. So how can the wild-type phenotype of the heterozygote be explained?

There are two possible explanations:

1. 50% of the normal protein is enough to accomplish the protein’s cellular function.
2. The heterozygote may actually produce more than 50% of the functional protein. The normal gene is “up-regulated” to compensate for the lack of function of the defective allele.

In **incomplete dominance** the heterozygote exhibits a phenotype that is intermediate between the corresponding homozygotes. 50% of the protein encoded by one copy of the allele is not sufficient to produce the normal trait.

Example: Flower color in the four o’clock plant.

Whether a trait is dominant or incompletely dominant may depend on how closely the trait is examined.

Take, for example, the characteristic of pea shape. Mendel visually concluded that RR and Rr genotypes produced round peas; rr genotypes produced wrinkled peas. However, a microscopic examination of round peas reveals that not all round peas are “created equal.”
**Incomplete penetrance:** In some instances, a dominant allele is not expressed in a heterozygote individual. Example = Polydactyly which is an autosomal dominant trait. Affected individuals have additional fingers and/or toes. A single copy of the polydactyly allele is usually sufficient to cause this condition. In some cases, however, individuals carry the dominant allele but do not exhibit the trait. The term indicates that a dominant allele does not always “penetrate” into the phenotype of the individual. *(Incomplete penetrance)*

The measure of penetrance is described at the population level. If 60% of heterozygotes carrying a dominant allele exhibit the trait allele, the trait is 60% penetrant. **Note:** In any particular individual, the trait is either penetrant or not

**Expressivity** is the degree to which a trait is expressed. In the case of polydactyly, the number of digits can vary. A person with several extra digits has high expressivity of this trait. A person with a single extra digit has low expressivity.

The molecular explanation of expressivity and incomplete penetrance may not always be understood. In most cases, the range of phenotypes is thought to be due to influences of the environment and/or other genes.

**Environmental conditions may have a great impact on the phenotype of the individual**

Example: Phenylketonuria: Autosomal recessive disorder in humans caused by a defect in the gene that encodes the enzyme phenylalanine hydroxylase, which converts phenylalanine to tyrosine. Affected individuals cannot metabolize phenylalanine. Phenylalanine will thus accumulate and will ultimately causes a number of detrimental effects like Mental retardation.

Newborns are now routinely screened for PKU. Individuals with the disease are put on a strict dietary regimen. Their diet is essentially phenylalanine-free. These individuals tend to develop normally.

**Overdominance** is the phenomenon in which a heterozygote is more vigorous than both of the corresponding homozygotes. It is also called heterozygote advantage. Example = Sickle-cell anemia which is an autosomal recessive disorder.

Affected individuals produce abnormal form of hemoglobin. Two alleles:

- \( Hb^A \) Encodes the normal hemoglobin, hemoglobin A
- \( Hb^S \) Encodes the abnormal hemoglobin, hemoglobin S

\( Hb^S \) individuals have red blood cells that deform into a sickle shape under conditions of low oxygen tension

This has two major ramifications

1. Sickling phenomenon greatly shortens the life span of the red blood cells and anemia results
2. Odd-shaped cells clump and there is partial or complete blocks in capillary circulation. Thus, affected individuals tend to have a shorter life span than unaffected ones. The sickle cell allele has been found at a fairly high frequency in parts of Africa where malaria is found. How come?

- Malaria is caused by a protozoan, *Plasmodium*. This parasite undergoes its life cycle in two main parts:
- One inside the *Anopheles* mosquito
- The other inside red blood cells

Red blood cells of heterozygotes, are likely to rupture when infected by *Plasmodium sp.* This prevents the propagation of the parasite. Therefore, *Hb^A^Hb^S^* individuals are “better” than *Hb^S^Hb^S^*, because they do not suffer from sickle cell anemia and from *Hb^A^Hb^A^*, because they are more resistant to malaria.

At the molecular level, overdominance is due to two alleles that produce slightly different proteins. But how can these two protein variants produce a favorable phenotype in the heterozygote? Well, there are three possible explanations for overdominance at the molecular/cellular level:

1. Disease resistance
2. Homodimer formation
3. Variation in functional activity

A microorganism will infect a cell if certain cellular proteins function optimally. Heterozygotes have one altered copy of the gene. Therefore, they have slightly reduced protein function. This reduced function is not enough to cause serious side effects but it is enough to prevent infections.

Examples include:
- Sickle-cell anemia and malaria
- Tay-Sachs disease. Heterozygotes are resistant to tuberculosis.

Some proteins function as homodimers. Composed of two different subunits encoded by two alleles of the same gene.

*\( A1A1 \) homozygotes, make only A1A1 homodimers
*\( A2A2 \) homozygotes, make only A2A2 homodimers
*\( A1A2 \) heterozygotes, make A1A1 and A2A2 homodimers and A1A2 homodimers

For some proteins, the A1A2 homodimer may have better functional activity, giving the heterozygote superior characteristics.

A gene, *E*, encodes a metabolic enzyme. Allele *E1* encodes an enzyme that functions better at lower temperatures while allele *E2* encodes an enzyme that functions better at higher temperatures.

*\( E1E2 \) heterozygotes produce both enzymes. Therefore they have an advantage under a wider temperature range than both *\( E1E1 \) and *\( E2E2 \) homozygotes.

**Overdominance** is related to a common mating strategy used by animal and plant breeders:

Two different highly inbred strains are crossed. The hybrids may display traits superior to both parents. This phenomenon is termed **hybrid vigor or heterosis**.

**Heterosis** is used to improve quantitative traits such as size, weight and growth rate. Heterosis is different from overdominance, because it typically involves many genes. Nevertheless, its beneficial effects may be attributed to overdominance in one or more heterozygous genes.

Many genes have **multiple alleles**. Three or more different alleles.

An interesting example is coat color in rabbits. Four different alleles

\[
\text{C (full coat color)} \\
\text{c^{ch} (chinchilla pattern of coat color) Partial defect in pigmentation}
\]
The himalayan pattern of coat color is an example of a temperature-sensitive conditional allele. The enzyme encoded by this gene is functional only at low temperatures. Therefore, dark fur will only occur in cooler areas of the body. This is also the case in the Siamese pattern of coat color in cats. In a breed of dairy cattle called Brown Swiss, the opposite phenotype occurs. The coat in the cooler parts of the body is light-colored. The allele in this case is likely to be cold-sensitive. Its enzymatic product does not work well at lower temperatures.

**Codominance:** A heterozygote expresses both alleles simultaneously.

The ABO blood group provides another example of multiple alleles and also codominance. It is determined by the type of antigen present on the surface of red blood cells. Antigens are substances that are recognized by antibodies produced by the immune system. There are three different types of antigens found on red blood:

- Antigen A, which is controlled by allele $I^A$
- Antigen B, which is controlled by allele $I^B$
- Antigen O, which is controlled by allele $i$

The carbohydrate tree on the surface of RBCs is composed of three sugars. A fourth can be added by the enzyme glycosyl transferase.

- The $i$ allele encodes a defective enzyme. The carbohydrate tree is unchanged.
- $I^A$ encodes a form of the enzyme that can add the sugar N-acetylgalactosamine to the carbohydrate tree.
- $I^B$ encodes a form of the enzyme that can add the sugar galactose to the carbohydrate tree.

Thus, the A and B antigens are different enough to be recognized by different antibodies. For safe blood transfusions to occur, the donor’s blood must be an appropriate match with the recipient’s blood. For example, if a type O individual received blood from a type A, type B or type AB blood, antibodies in the recipient blood will react with antigens in the donated blood cells. This causes the donated blood to agglutinate. A life-threatening situation may result because of clogging of blood vessels.

The Inheritance Pattern of X-linked Genes Can Be Revealed by Reciprocal Crosses

1. Mammalian females have two X chromosomes, mammalian males have only one.
   a. Any gene on the X, known as an “X-linked gene”, will therefore only be present at one copy in male cells.
   b. Duchenne muscular dystrophy (DMD) is a disease caused by an X-linked recessive allele.
   c. Males are therefore more likely to get DMD due to having only one possible copy of the gene associated with DMD.
   d. In a pedigree (Figure 4.10), multiple males will likely be affected, while very few females will be affected.
   e. A reciprocal cross reverses the sexes and phenotypes to identify if the gene under
study is X-linked, since X-linked genes will not behave the same in reciprocal crosses.

Genes Located on Mammalian Sex Chromosomes Can Be Transmitted in an X-linked, a Y-linked, or a Pseudoautosomal Pattern
1. A sex-linked gene is found on one, but not both, of the sex chromosomes (X and Y).
   a. Because there are many more X-linked genes than Y-linked genes, the terms “sex-linked” and “X-linked” have become synonymous.
2. The term hemizygous describes the single copy of X-linked genes in males.
3. Holandric genes are those located on the Y chromosome.
4. A small group of genes, including Mic2, are located on both the X and Y chromosomes and are classified as showing pseudoautosomal inheritance.

Some Traits Are Influenced by the Sex of the Individual
1. Sex-influenced inheritance indicates that an allele is dominant in one sex, but recessive in the other.
   a. An example in humans is male-pattern baldness. The trait is dominant in males but recessive in females.
   b. Sex-influenced traits do not need to be on the sex chromosomes.
2. A sex-limited trait is expressed in only one of the sexes.
   a. Examples are breast development in human females, beard growth in human males, and hen-feathering in chickens.
   b. The expression of these traits is determined by sex hormones and causes sexual dimorphism.
   c. DHT, a molecular relative of testosterone, is produced in males in much higher amounts than seen in females, and causes baldness.

Lethal Alleles
- Essential genes are those that are absolutely required for survival
- The absence of their protein product leads to a lethal phenotype
- It is estimated that about 1/3 of all genes are essential for survival
- Nonessential genes are those not absolutely required for survival
- A lethal allele is one that has the potential to cause the death of an organism
- These alleles are typically the result of mutations in essential genes
- They are usually inherited in a recessive manner
- Many lethal alleles prevent cell division. These will kill an organism at an early age.
- Some lethal allele exert their effect later in life, e.g., Huntington disease which is characterized by progressive degeneration of the nervous system, dementia and early death. The age of onset of the disease is usually between 30 to 50.

Conditional lethal alleles may kill an organism only when certain environmental conditions prevail
- Temperature-sensitive (ts) lethals. A developing Drosophila larva may be killed at 30 C, but it will survive if grown at 22 C.

Semilethal alleles kill some individuals in a population, not all of them.
Environmental factors and other genes may help prevent the detrimental effects of semilethal genes. 
- A lethal allele may produce ratios that seemingly deviate from Mendelian ratios
  An example is the “creeper” allele in chicken. Creepers have shortened legs and must creep along. Such birds also have shortened wings. Creeper chicken are heterozygous. Creeper allele is lethal in homozygous condition giving 2:1 phenotypic ratio.

Single Genes Have **Pleiotrophic Effects**
1. The multiple effects of a single gene on the phenotype of an organism is called pleiotropy, and occurs due to: 
   a. The expression of a single gene can affect cell function in more than one way.
   b. A gene may be expressed in different cell types.
   c. A gene may be expressed at different stages of development.

**GENE INTERACTIONS:** 
occur when two or more different genes influence the outcome of a single trait. Indeed, morphological traits such as height, weight and pigmentation are affected by many different genes in combination with environmental factors.

We will next examine three different cases, all involving two genes that exist in two alleles. The three crosses we will perform can be illustrated in this general pattern

\[
AaBb \times AaBb
\]

Where \(A\) is dominant to \(a\) and \(B\) is dominant to \(b\)
If these two genes govern two different traits, a 9:3:3:1 ratio is predicted among the offspring. However, the two genes in this section do affect the same trait the 9:3:3:1 ratio may be affected.

**Inheritance of comb morphology in chicken.** First example of gene interaction
Discovered by William Bateson and Reginald Punnett in 1906
Comb types come in four different morphologies
Refer to **Figure 4.16**
Thus, the \(F_2\) generation consisted of chickens with four types of combs
9 walnut : 3 rose : 3 pea : 1 single
Bateson and Punnett reasoned that comb morphology is determined by two different genes

\[
R (\text{rose comb}) \text{ is dominant to } r \\
P (\text{pea comb}) \text{ is dominant to } p \\
R \text{ and } P \text{ are codominant (walnut comb)} \\
rp {\text{and}} p \text{ produces single comb}
\]

Note: Mendel’s laws of segregation and independent assortment still hold!

**Inheritance of flower color in the sweet pea.** Also discovered by Bateson and Punnett
*Lathyrus odoratus* normally has purple flowers.
Bateson and Punnett obtained several true-breeding varieties with white flowers
They carried out the following cross

\[
P: \text{True-breeding purple} \times \text{true-breeding white} \\
F_1: \text{Purple flowered plants}
\]
F₂: Purple- and white-flowered in a 3:1 ratio
These results were not surprising
Thus, the F₂ generation contained purple and white flowers in a ratio of 9 purple : 7 white

Bateson and Punnett reasoned that flower color is determined by two different genes
C (one purple-color-producing) allele is dominant to c (white)
P (another purple-color-producing) allele is dominant to p (white)
cc or pp masks P or C alleles, producing white color
Thus, a plant that is homozygous for either recessive white allele, would develop a white flower. Regardless whether or not the other gene contains a purple-producing allele

The term epistasis describes the situation in which a gene can mask the phenotypic effects of another gene.

Epistatic interactions often arise because two (or more) different proteins participate in a common cellular function

For example, an enzymatic pathway
If an individual is homozygous for either recessive allele
It will not make any functional enzyme C or enzyme P
Therefore, the flowers remain white

A Cross Involving a Two-Gene Interaction Can Produce Three Distinct Phenotypes Due to Epistasis
1. The coat color for rats is controlled by two genes, agouti and colored.
   a. One function allele of each gene leads to agouti color.
   b. Homozygous mutant for the agouti gene causes rat to be black
   c. Homozygous mutant for the colored gene means rat will be albinos.
   d. This is an example of a gene modifier effect, with the alleles of one genes modifying the phenotypic effects of another gene (but not masking the other gene).
   This produces a 9:3:4 ratio.

Due to Gene Redundancy, Loss-of-Function Alienes May Have No Effect on Phenotype
1. To study genes, investigators will often make mutations in a gene and study the phenotypic effects.
2. An organism that has had both copies of a gene mutated is said to have undergone a gene knockout.
3. Not all gene knockouts produce a phenotype, because a second gene can sometimes compensate for the loss of function of the knocked out gene. This is called gene redundancy.
4. Gene duplication can lead to redundancy.
   a. Paralogs are previously identical genes created by gene duplication that are now different due to accumulated mutations.
5. Gene redundancy can lead to offspring ratio that differ from the 9:3:3:1 patterns seen in simple Mendelian genetics.