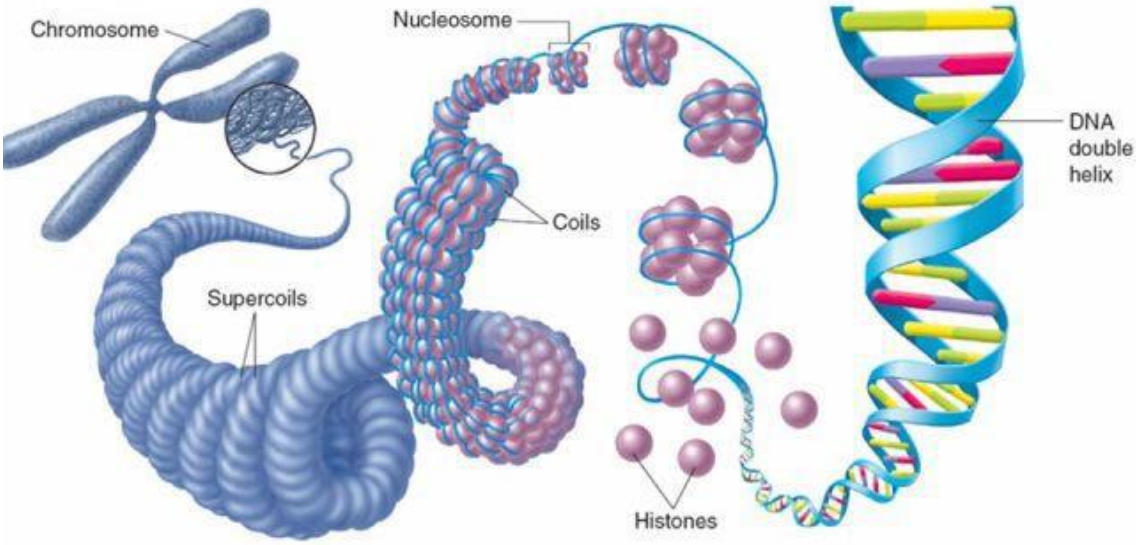
South Valley University Faculty Of Science Zoology Department

GENETICS

For 3rd Entomology and Chemistry Level Students

PROF. DR. HEMELY ABDEL-SHAFY HASSAN
PROFESSOR OF CYTOGENETICS AND MOLECULAR BIOLOGY



2022-2023

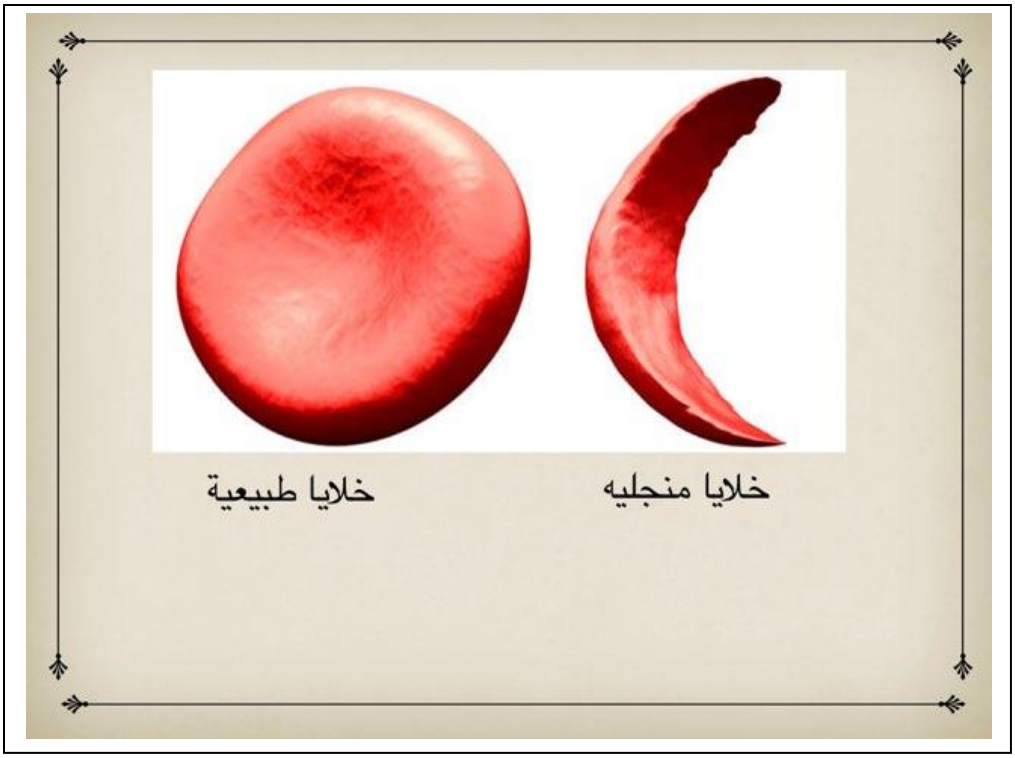
رؤية كلية العلوم

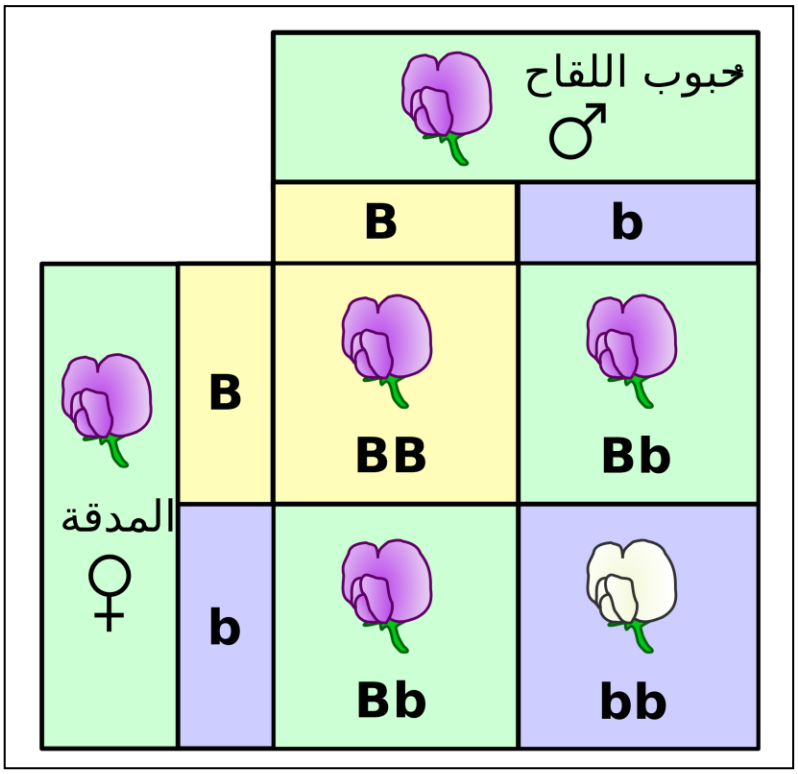
التميز في تعليم العلوم الأساسية والبحث العلمي للمساهمة فى التنمية المستدامة

رسالة كلية العلوم

تقدم كلية العلوم جامعة جنوب الوادى تعليم مميز في مجالات العلوم الأساسية وإنتاج بحوث علمية تطبيقية تدعم اقتصاد الوطن من خلال إعداد خريجين متميزين طبقا للمعايير الأكاديمية القومية، وتطوير مهارات وقدرات الموارد البشرية، وتوفير خدمات مجتمعية وبيئية تلبي طموحات مجتمع جنوب الوادي، وبناء الشراكات المجتمعية الفاعلة.

PATTERNS OF INHERITANCE





PATTERNS OF INHERITANCE

Chapter Outline

8.1: Mendel's Experiments

8.2: Laws of Inheritance

8.3: Extensions of the Laws of Inheritance

Introduction

Genetics is the study of heredity. **Johann Gregor Mendel** set the framework for genetics long before chromosomes or genes had been identified, at a time when meiosis was not well understood. **Mendel** selected a simple biological system and conducted methodical, quantitative analyses using large sample sizes. Because of **Mendel's** work, the fundamental principles of heredity were revealed. We now know that genes, carried on chromosomes, are the basic functional units of heredity with the ability to be replicated, expressed, or mutated. Today, the postulates put forth by **Mendel** form the basis of **classical, or Mendelian genetics**. Not all genes are transmitted from parents to offspring according to **Mendelian genetics**, but **Mendel**'s experiments serve as an excellent starting point for thinking about inheritance.

Mendel's Experiments

By the end of this section, you will be able to:

- Explain the scientific reasons for the success of Mendel's experimental work
- Describe the expected outcomes of monohybrid crosses involving dominant and recessive alleles

Figure 1.1: **Johann Gregor Mendel** set the framework for the study of genetics.

Johann Gregor Mendel (1822–1884) (**Figure 1.1**) was a lifelong learner, teacher, scientist, and man of faith. As a young adult, he joined the Augustinian Abbey of St. Thomas in Brno in what is now the Czech Republic. Supported by the monastery, he taught physics, botany, and natural science courses at the secondary and university levels. In 1856, he began a decade-long research pursuit involving inheritance patterns in honeybees and plants, ultimately settling on pea plants as his primary model system (a system with convenient characteristics that is used to study a specific biological phenomenon to gain understanding to be applied to other systems). In 1865, **Mendel** presented the results of his experiments with nearly 30,000 pea plants to the local natural history society. He demonstrated that traits are transmitted faithfully from parents to offspring in specific patterns. In 1866, he published his work, *Experiments in Plant Hybridization* in the proceedings of the Natural History Society of Brünn.

Mendel's work went virtually unnoticed by the scientific community, which incorrectly believed that the process of inheritance involved a blending of parental traits that produced an intermediate physical appearance in offspring. This hypothetical process appeared to be correct because of what we know now as a continuous variation. **Continuous variation** is the range of small differences we see among individuals in a characteristic like human height. It does appear that offspring is a "blend" of their parents' traits when we look at characteristics that exhibit continuous variation. **Mendel** worked instead with traits that show discontinuous variation. **Discontinuous variation** is the variation seen among individuals when each individual shows one of two or very few easily distinguishable traits, such as violet or white flowers. **Mendel's**

choice of these kinds of traits allowed him to see experimentally that the traits were not blended in the offspring as would have been expected at the time, but that they were inherited as distinct traits. In 1868, **Mendel** became abbot of the monastery and exchanged his scientific pursuits for his pastoral duties. He was not recognized for his extraordinary scientific contributions during his lifetime; in fact, it was not until 1900 that his work was rediscovered, reproduced, and revitalized by scientists on the brink of discovering the chromosomal basis of heredity.

Mendel's Crosses

Mendel's seminal work was accomplished using the garden pea, ***Pisum sativum***, to study inheritance. This species naturally self-fertilizes, meaning that pollen encounters ova within the same flower. The flower petals remain sealed tightly until pollination is completed to prevent the pollination of other plants. The result is highly inbred, or "**true-breeding**," pea plants. These are plants that always produce offspring that look like the parent. By experimenting with true-breeding pea plants, **Mendel** avoided the appearance of unexpected traits in offspring that might occur if the plants were not true breeding. The garden pea also grows to maturity within one season, meaning that several generations could be evaluated over a relatively short time. Finally, large quantities of garden peas could be cultivated simultaneously, allowing **Mendel** to conclude that his results did not come about simply by chance.

Mendel performed **hybridizations**, which involve mating two true-breeding individuals that have different traits. In the pea, which is naturally self-pollinating, this is done by manually transferring pollen from the anther of a mature pea plant of one variety to the stigma of a separate mature pea plant of the second variety.

Plants used in first-generation crosses were called P, or parental generation, plants (**Figure 1.2**). **Mendel** collected the seeds produced by

the P plants that resulted from each cross and grew them the following season. These offspring were called the F1, or the first filial (filial = daughter or son), generation. Once **Mendel** examined the characteristics of the F1 generation of plants, he allowed them to self-fertilize naturally. He then collected and grew the seeds from the F1 plants to produce the F2, or second filial, generation. **Mendel's** experiments extended beyond the F2 generation to the F3 generation, F4 generation, and so on, but it was the ratio of characteristics in the P, F1, and F2 generations that were the most intriguing and became the basis of **Mendel's** postulates.

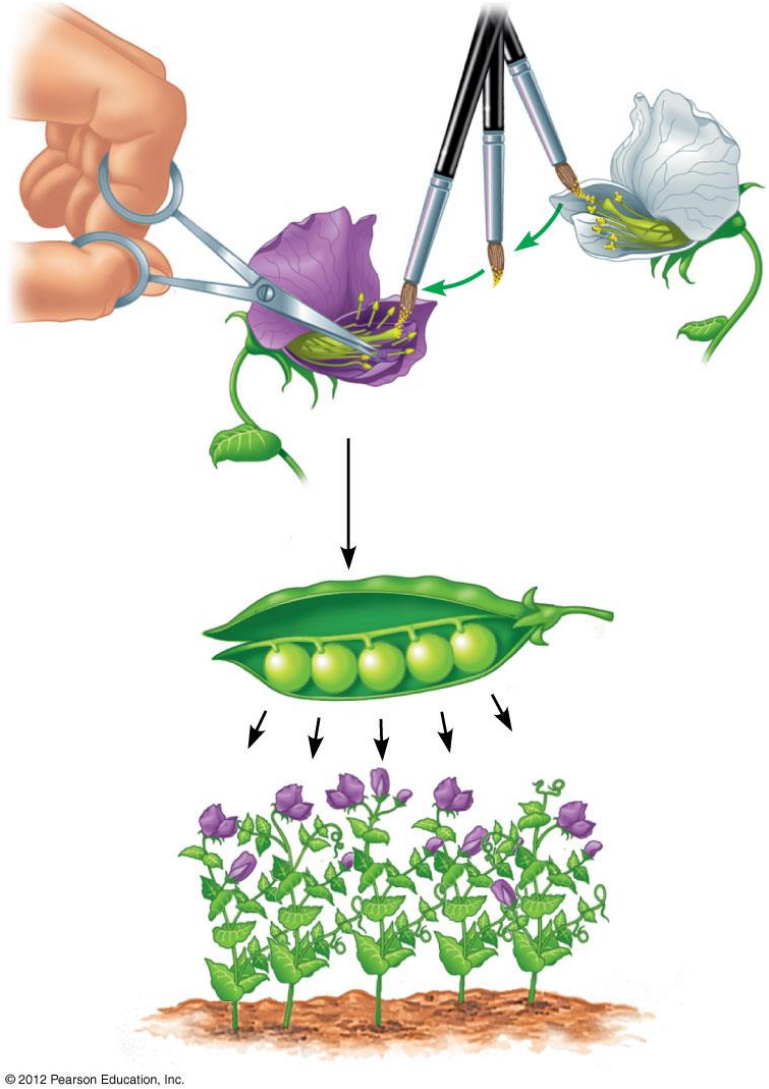


Figure 1.2: Mendel's process for performing crosses included examining flower color.

- **Garden Pea Characteristics Revealed the Basics of Heredity**

In his 1865 publication, **Mendel** reported the results of his crosses involving seven different characteristics, each with two contrasting traits. A trait is defined as a variation in the physical appearance of a heritable characteristic. The characteristics included plant height, seed texture, seed color, flower color, pea-pod size, pea-pod color, and flower position. For the characteristic of flower color, for example, the two contrasting traits were white versus violet. To fully examine each characteristic, **Mendel** generated large numbers of **F1** and **F2** plants and reported results from thousands of **F2** plants.

What results did Mendel find in his crosses for flower color?

First, **Mendel** confirmed that he was using plants that bred true for white or violet flower color. Irrespective of the number of generations that **Mendel** examined, all self-crossed offspring of parents with white flowers had white flowers, and all self-crossed offspring of parents with violet flowers had violet flowers. In addition, **Mendel** confirmed that, other than flower color, the pea plants were physically identical. This was an important check to make sure that the two varieties of pea plants only differed with respect to one trait, flower color.

Once these validations were complete, **Mendel** applied the pollen from a plant with violet flowers to the stigma of a plant with white flowers. After gathering and sowing the seeds that resulted from this cross, **Mendel** found that 100 percent of the **F1** hybrid generation had violet flowers. Conventional wisdom at that time would have predicted the hybrid flowers to be pale violet or for hybrid plants to have equal numbers of white and violet flowers. In other words, the contrasting parental traits were expected to blend in with the offspring. Instead, **Mendel's** results demonstrated that the white flower trait had completely disappeared in the **F1** generation.

Importantly, **Mendel** did not stop his experimentation there. He allowed the **F1** plants to self-fertilize and found that **705** plants in the **F2** generation had violet flowers and **224** had white flowers. This was a ratio of 3.15 violet flowers to one white flower or approximately **3:1**. When **Mendel** transferred pollen from a plant with violet flowers to the stigma of a plant with white flowers and *vice versa*, he obtained approximately the same ratio irrespective of which parent—male or female contributed which trait. This is called a reciprocal cross a paired cross in which the respective traits of the male and female in one cross become the respective traits of the female and male in the other cross. For the other six characteristics that **Mendel** examined, the **F1** and **F2** generations behaved in the same way that they behaved for flower color. One of the two traits would disappear completely from the **F1** generation, only to reappear in the **F2** generation at a ratio of roughly **3:1** (**Figure 1.2**).

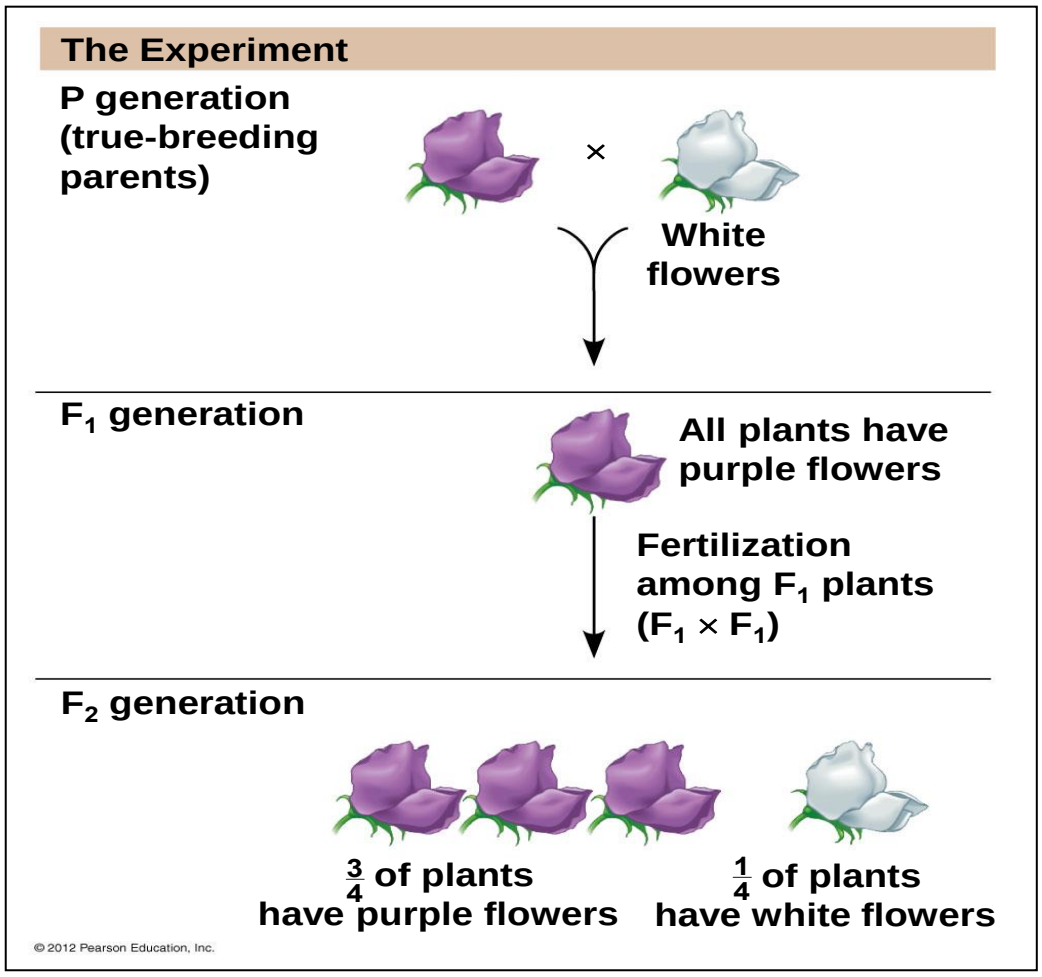


Figure 1.2: **Mendel** performed a monohybrid cross between a plant with purple flowers and a plant with white flowers.

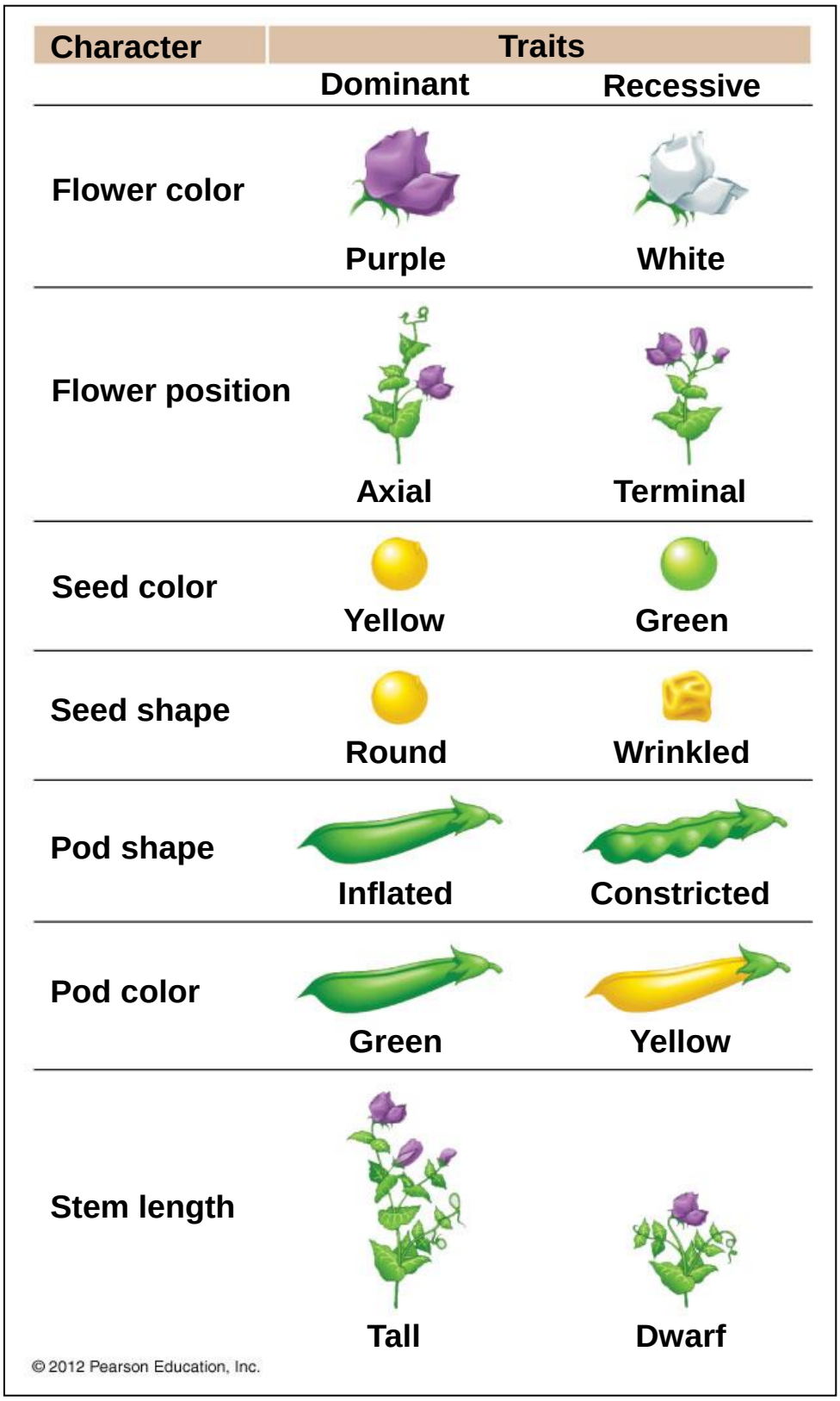


Figure 1.2.2: Mendel identified seven pea plant characteristics.

Upon compiling his results for many thousands of plants, **Mendel** concluded that the characteristics could be divided into expressed and latent traits. He called these dominant and recessive traits, respectively.

Dominant traits are those that are inherited unchanged in a hybridization. **Recessive** traits become latent or disappear in the offspring of a hybridization. The recessive trait does, however, reappear in the progeny of the hybrid offspring. An example of a dominant trait is the violet-colored flower trait. For this same characteristic (flower color), white-colored flowers are a recessive trait. The fact that the recessive trait reappeared in the **F2** generation meant that the traits remained separate (and were not blended) in the plants of the **F1** generation. **Mendel** proposed that this was because the plants possessed two copies of the trait for the flower-color characteristic and that each parent transmitted one of their two copies to their offspring, where they came together. Moreover, the physical observation of a dominant trait could mean that the genetic composition of the organism included two dominant versions of the characteristic, or that it included one dominant and one recessive version. Conversely, the observation of a recessive trait meant that the organism lacked any dominant versions of this characteristic.

For an excellent review of **Mendel's** experiments and to perform your crosses and identify patterns of inheritance, visit **Mendel's** Peas (http://openstaxcollege.org/l/**Mendel**s_peas) web lab.

Laws of Inheritance

By the end of this section, you will be able to:

- Explain the relationship between genotypes and phenotypes in dominant and recessive gene systems
- Use a Punnett square to calculate the expected proportions of genotypes and phenotypes in a monohybrid cross
- Explain Mendel's law of segregation and independent assortment in terms of genetics and the events of meiosis
- Explain the purpose and methods of a test cross

The seven characteristics that **Mendel** evaluated in his pea plants were each expressed as one of two versions or traits. **Mendel** deduced from his results that each individual had two discrete copies of the characters that are passed individually to offspring. We now call those two copies of genes, which are carried on chromosomes. The reason we have two copies of each gene is that we inherit one from each parent. In fact, it is the chromosomes we inherit and the two copies of each gene are located on paired chromosomes. Recall that in meiosis these chromosomes are separated into haploid gametes. This separation, or segregation, of the homologous chromosomes, means also that only one of the copies of the gene gets moved into a gamete. The offspring are formed when that gamete unites with one from another parent and the two copies of each gene (and chromosome) are restored.

For cases in which a single gene controls a single characteristic, a diploid organism has two genetic copies that may or may not encode the same version of that characteristic. For example, one individual may carry a gene that determines white flower color and a gene that determines violet flower color. Gene variants that arise by mutation and exist at the same relative locations on homologous chromosomes are called alleles. **Mendel** examined the inheritance

of genes with just two allele forms, but it is common to encounter more than two alleles for any given gene in a natural population.

- **Phenotypes and Genotypes**

Two alleles for a given gene in a diploid organism are expressed and interact to produce physical characteristics. The observable traits expressed by an organism are referred to as its **phenotype**. An organism's underlying genetic makeup, consisting of both the physically visible and the non-expressed alleles, is called its **genotype**. **Mendel's** hybridization experiments demonstrate the difference between phenotype and genotype. For example, the phenotypes that **Mendel** observed in his crosses between pea plants with different traits are connected to the diploid genotypes of the plants in the **P, F1,** and **F2** generations. We will use a second trait that **Mendel** investigated, seed color, as an example. Seed color is governed by a single gene with two alleles. The yellow-seed allele is dominant and the green-seed allele is recessive. When true-breeding plants were cross-fertilized, in which one parent had yellow seeds and one had green seeds, all of the **F1** hybrid offspring had yellow seeds. That is, the hybrid offspring were **phenotypically** identical to the true-breeding parent with yellow seeds. However, we know that the allele donated by the parent with green seeds was not simply lost because it reappeared in some of the **F2** offspring (**Figure 1.4**). Therefore, the F1 plants must have been **genotypically** different from the parent with yellow seeds.

The **P** plants that **Mendel** used in his experiments were each homozygous for the trait he was studying. Diploid organisms that are homozygous for a gene have two identical alleles, one on each of their homologous chromosomes. The genotype is often written as **YY** or **yy**, for which each letter represents one of the two alleles in the genotype. The dominant allele is capitalized and the recessive allele is lowercase. The letter used for the gene (seed color in this case) is usually related to the dominant

trait (yellow allele, in this case, or "**Y**"). **Mendel's** parental pea plants always bred true because both produced gametes carried the same allele. When **P** plants with contrasting traits were cross-fertilized, all of the offspring were heterozygous for the contrasting trait, meaning their genotype had different alleles for the gene being examined. For example, the **F1** yellow plants that received a **Y** allele from their yellow parent and a **y** allele from their green parent had the genotype **Yy**.

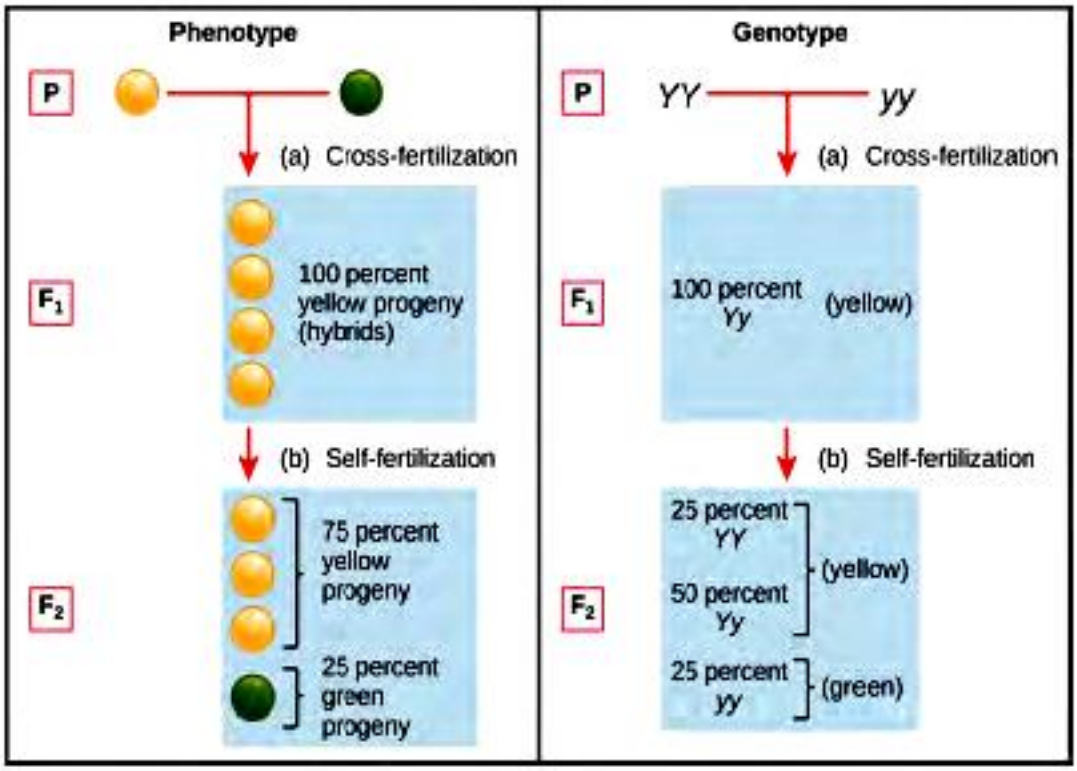


Figure 1.4: Phenotypes are physical expressions of traits that are transmitted by alleles. Capital letters represent dominant alleles and lowercase letters represent recessive alleles. The phenotypic ratios are the ratios of visible characteristics. Genotypic ratios are the ratios of gene combinations in the offspring, and these are not always distinguishable in phenotypes.

- **Law of Dominance**

Our discussion of homozygous and heterozygous organisms brings us to why the **F1** heterozygous offspring were identical to one of the parents, rather than expressing both alleles. In all seven pea plant characteristics, one of the

two contrasting alleles was dominant, and the other was recessive. **Mendel** called the dominant allele the expressed unit factor; the recessive allele was referred to as the latent unit factor. We now know that these so-called **unit factors** are **genes** on homologous chromosomes. For a gene that is expressed in a dominant and recessive pattern, homozygous dominant and heterozygous organisms will look identical (that is, they will have different genotypes but the same phenotype), and the recessive allele will only be observed in homozygous recessive individuals (**Table 1.1**).

Correspondence between Genotype and Phenotype for a Dominant-Recessive Characteristic.

	Homozygous	Heterozygous	Homozygous
Genotype	*YY*	*Yy*	*yy*
Phenotype	yellow	yellow	green

Table 1.1

Mendel's law of dominance states that in a heterozygote, one trait will conceal the presence of another trait for the same characteristic. For example, when crossing true-breeding violet-flowered plants with true-breeding white-flowered plants, all of the offspring were violet-flowered, even though they all had one allele for violet and one allele for white. Rather than both alleles contributing to a phenotype, the dominant allele will be expressed exclusively. The recessive allele will remain latent but will be transmitted to offspring in the same manner as that by which the dominant allele is transmitted. The recessive trait will only be expressed by offspring that have two copies of this allele (**Figure 1.5**), and these offspring will breed true when self-crossed.

- **Monohybrid Cross and the Punnett Square**

When fertilization occurs between two true-breeding parents that differ by only the characteristic being studied, the process is called a monohybrid cross, and the resulting offspring are called monohybrids. **Mendel** performed seven

types of monohybrid crosses, each involving contrasting traits for different characteristics. Out of these crosses, all of the **F1** offspring had the phenotype of one parent, and the **F2** offspring had a **3:1** phenotypic ratio. Based on these results, **Mendel** postulated that each parent in the monohybrid cross contributed one of two paired unit factors to each offspring, and every possible combination of unit factors was equally likely.

- **Mendel's laws reflect the rules of probability**

The results of **Mendel's** research can be explained in terms of probabilities, which are mathematical measures of likelihood. The probability of an event is calculated by the number of times the event occurs divided by the total number of opportunities for the event to occur. A probability of one (100 percent) for some event indicates that it is guaranteed to occur, whereas a probability of zero (0 percent) indicates that it is guaranteed to not occur, and a probability of 0.5 (50 percent) means it has an equal chance of occurring or not occurring.

Figure 1.5: The allele for **albinism**, expressed here in humans, **is recessive**. Both of this child's parents carried the **recessive allele**.

To demonstrate this with a monohybrid cross, consider the case of true-breeding pea plants with yellow versus green seeds. The dominant seed color is yellow; therefore, the parental genotypes were **YY** for the plants with yellow seeds and **yy** for the plants with green seeds. **A Punnett square**, devised by

the British geneticist **Reginald Punnett**, is useful for determining probabilities because it is drawn to predict all possible outcomes of all possible random fertilization events and their expected frequencies. **Figure 1.6** shows a **Punnett square** for a cross between a plant with yellow peas and one with green peas. To prepare a **Punnett square**, all possible combinations of the parental alleles (the genotypes of the gametes) are listed along the top (for one parent) and side (for the other parent) of a grid. The combinations of egg and sperm gametes are then made in the boxes in the table based on which alleles are combined. Each box then represents the diploid genotype of a zygote or fertilized egg. Because each possibility is equally likely, genotypic ratios can be determined from a **Punnett square**. If the pattern of inheritance (dominant and recessive) is known, the phenotypic ratios can be inferred as well. For a monohybrid cross of two true-breeding parents, each parent contributes one type of allele. In this case, only one genotype is possible in the **F** offspring. All offspring are **Yy** and have yellow seeds.

When the **F1** offspring are crossed with each other, each has an equal probability of contributing either a **Y** or a **y** to the **F2** offspring. The result is a 1 in 4 (25 percent) probability of both parents contributing resulting in an offspring with a yellow phenotype; a **25** percent probability of parent **A** contributing a **Y** and parent **B** a **y**, resulting in offspring with a yellow phenotype; a 25 percent probability of parent **A** contributing a y and parent **B** a **Y**, also resulting in a yellow phenotype; and a (25 percent) probability of both parents contributing a y, resulting in a green phenotype. When counting all four possible outcomes, there is a **3** in **4** probability of offspring having the yellow phenotype and a 1 in 4 probability of offspring having the green phenotype. This explains why the results of **Mendel's F2** generation occurred in a 3:1 phenotypic ratio. Using large numbers of crosses, **Mendel** was able to calculate probabilities, found that they fit the model of inheritance, and use these to predict the outcomes of other crosses.

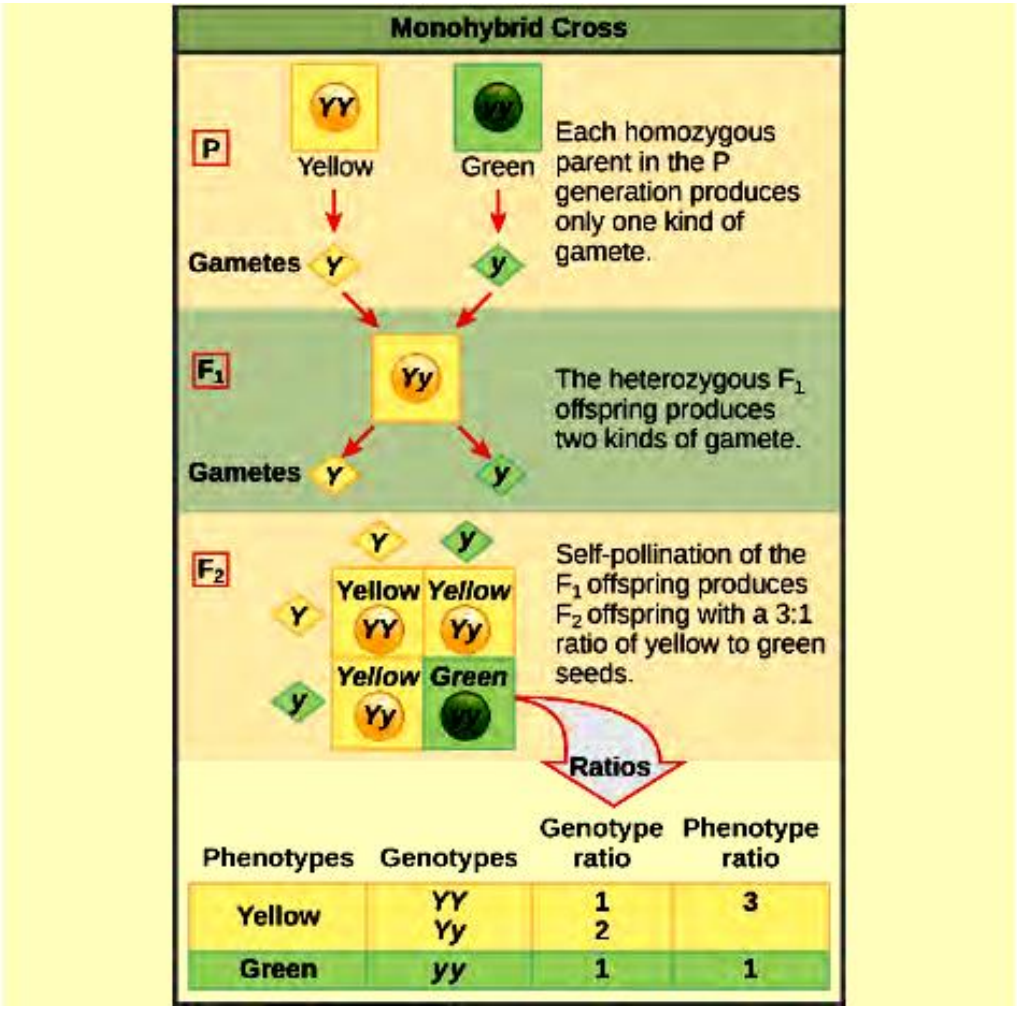


Figure 1.6: This Punnett square shows the cross between plants with yellow seeds and green seeds. The cross between the true-breeding **P** plants produces **F1** heterozygotes that can be self-fertilized. The self-cross of the **F1** generation can be analyzed with a Punnett square to predict the genotypes of the **F2** generation. Given an inheritance pattern of dominant–recessive, the genotypic and phenotypic ratios can then be determined.

In pea plants, round peas (**R**) are dominant to wrinkled peas (**r**). You do a test cross between a pea plant with wrinkled peas (genotype **rr**) and a plant of unknown genotype that has round peas. You end up with three plants, all of which have round peas. **From this data, can you tell if the parent plant is homozygous dominant or heterozygous?**

Mendel's 1st Law of Segregation:

Observing that true-breeding pea plants with contrasting traits gave rise to **F1** generations that all expressed the dominant trait and **F2** generations that expressed the dominant and recessive traits in a **3:1** ratio, **Mendel** proposed the law of segregation. This law states that paired unit factors (genes) must segregate equally into gametes such that offspring have an equal likelihood of inheriting either factor. For the **F2** generation of a monohybrid cross, the following three possible combinations of genotypes result in **homozygous dominant**, **heterozygous**, or **homozygous recessive**. Because heterozygotes could arise from two different pathways (receiving one dominant and one recessive allele from either parent), and because heterozygotes and **homozygous** dominant individuals are phenotypically identical, the law supports **Mendel's** observed **3:1** phenotypic ratio. The equal segregation of alleles is the reason we can apply the **Punnett square** to accurately predict the offspring of parents with known genotypes. The physical basis of **Mendel**'s law of segregation is the first division of meiosis in which the homologous chromosomes with their different versions of each gene are segregated into daughter nuclei. This process was not understood by the scientific community during **Mendel's** lifetime (**Figure 1.7**).

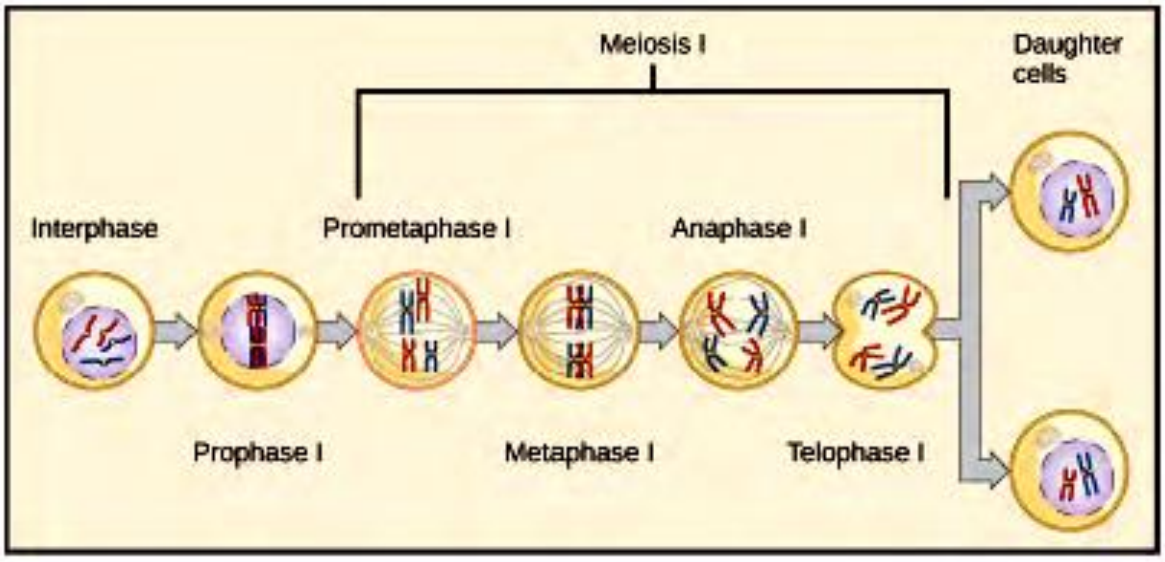


Figure 1.7: The first division in meiosis is shown.

In a simple dominant-recessive inheritance of dominant allele **A** and recessive allele **a**. **a** recessive phenotype always results from a homozygous recessive genotype (***aa***) but a dominant phenotype can result from either the homozygous dominant genotype (***AA***) or a heterozygous genotype (***Aa***). **Wild-type traits**, those prevailing in nature, are not necessarily specified by dominant alleles (**Figure 1.7.1**).

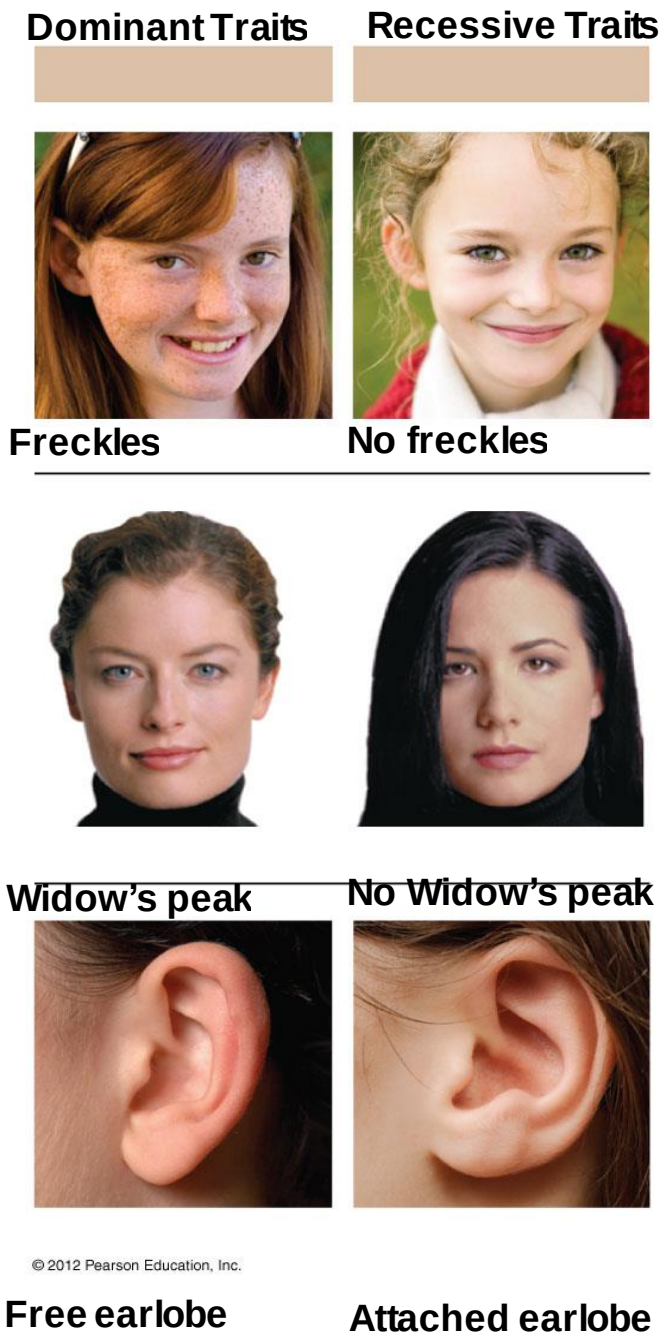


Figure 1.7.1: Genetic traits in humans can be tracked through family pedigrees.

Test Cross

Beyond predicting the offspring of a cross between known homozygous or heterozygous parents, **Mendel** also developed a way to determine whether an organism that expressed a dominant trait was a heterozygote or a homozygote. Called the test cross, this technique is still used by the plant and

animal breeders. In a test cross, the dominant-expressing organism is crossed with an organism that is homozygous recessive for the same characteristic. If the dominant-expressing organism is a homozygote, then all F1 offspring will be heterozygotes expressing the dominant trait (**Figure 1.8**). Alternatively, if the dominant-expressing organism is a heterozygote, the F1 offspring will exhibit a 1:1 ratio of heterozygotes and recessive homozygotes (**Figure 1.8**). The test cross further validates **Mendel's** postulate that pairs of unit factors segregate equally.

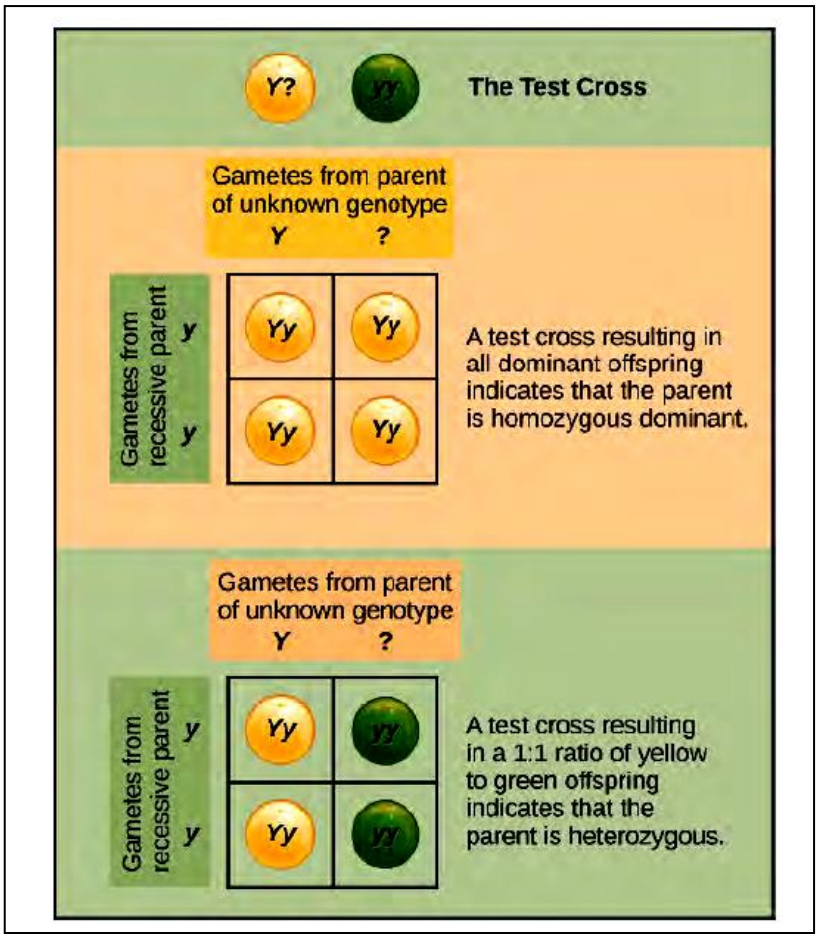


Figure 1.8: A **test cross** can be performed to determine whether an organism expressing a dominant trait is a homozygote or a heterozygote.

▪ Mendel's 2nd Law of Independent Assortment:

Mendel's law of independent assortment states that genes do not influence each other with regard to the sorting of alleles into gametes, and

every possible combination of alleles for every gene is equally likely to occur. An **Independent assortment** of genes can be illustrated by the **dihybrid cross**, a cross between two true-breeding parents that express different traits for two characteristics. Consider the characteristics of seed color and seed texture for two pea plants, one that has wrinkled, green seeds (**rryy**) and another that has round, yellow seeds (**RRYY**). Because each parent is homozygous, the law of segregation indicates that the gametes for the wrinkled green plant all are **ry**, and the gametes for the round yellow plant are all **RY**. Therefore, the **F1** generation of offspring is **RrYy** (**Figure 1.9**).

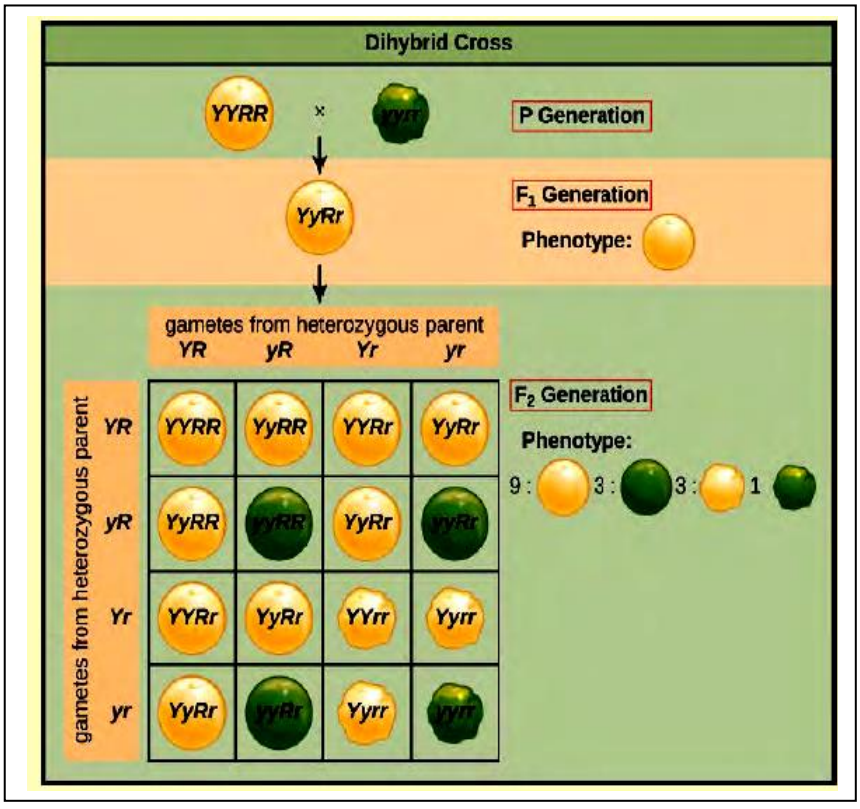


Figure 1.9: A dihybrid cross in pea plants involves the genes for seed color and texture. The **P** cross produces **F1** offspring that are all heterozygous for both characteristics. The resulting **9:3:3:1 F2** phenotypic ratio is obtained using a Punnett square.

In pea plants, purple flowers (**P**) are dominant to white (**p**), and yellow peas (**Y**) are dominant to green (**y**). What are the possible genotypes and phenotypes for a cross between **PpYY** and **ppYy** pea plants? **How many squares would you need to complete a Punnett square analysis of this cross?**

The gametes produced by the **F1** individuals must have one allele from each of the two genes. For example, a gamete could get an **R** allele for the

seed shape gene and either a **Y** or a **y** allele for the seed color gene. It cannot get both an **R** and an **r** allele; each gamete can have only one allele per gene. The law of independent assortment states that a gamete into which an **r** allele is sorted would be equally likely to contain either a **Y** or a **y** allele. Thus, four equally likely gametes can be formed when the **RrYy** heterozygote is self-crossed, as follows: **RY, rY, Ry**, and **ry**. Arranging these gametes along the top and left of a **4 × 4 Punnett square** (**Figure 1.9**) gives us 16 equally likely genotypic combinations. From these genotypes, we find a phenotypic ratio of **9** round–yellow: **3** round–green: **3** wrinkled–yellow: **1** wrinkled–green (**Figure 1.9**). These are the offspring ratios we would expect, assuming we performed the crosses with a large enough sample size.

The physical basis for the law of independent assortment also lies in meiosis I, in which the different homologous pairs line up in random orientations. Each gamete can contain any combination of paternal and maternal chromosomes (and therefore the genes on them) because the orientation of tetrads on the metaphase plane is random (**Figures 1.10**& **1.10.1**).

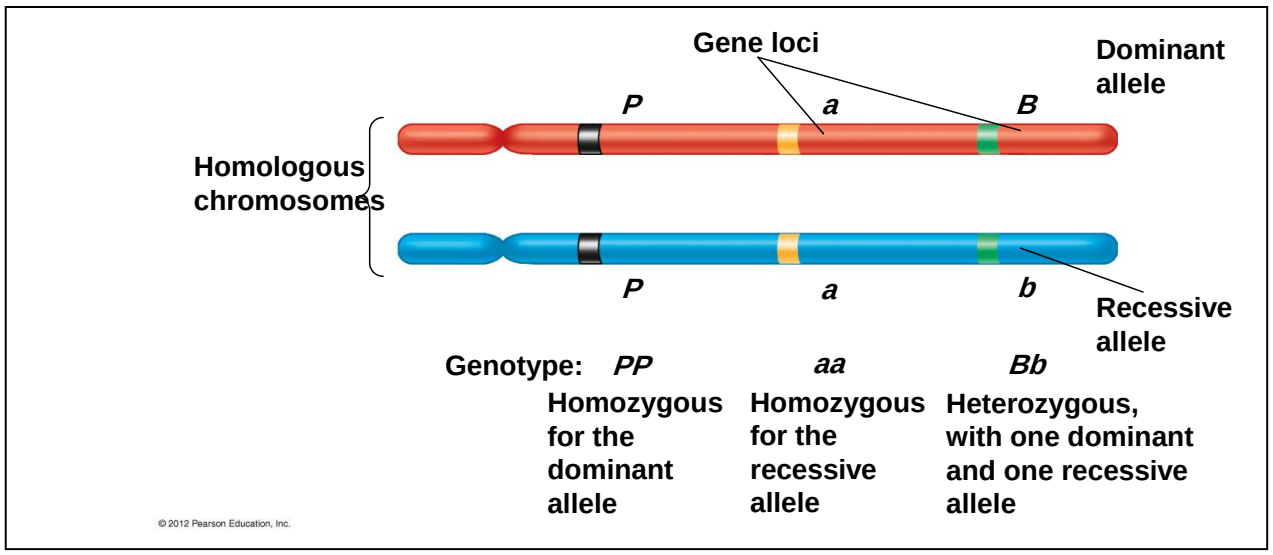


Figure 1.10: Homologous chromosomes bear the alleles for each character.

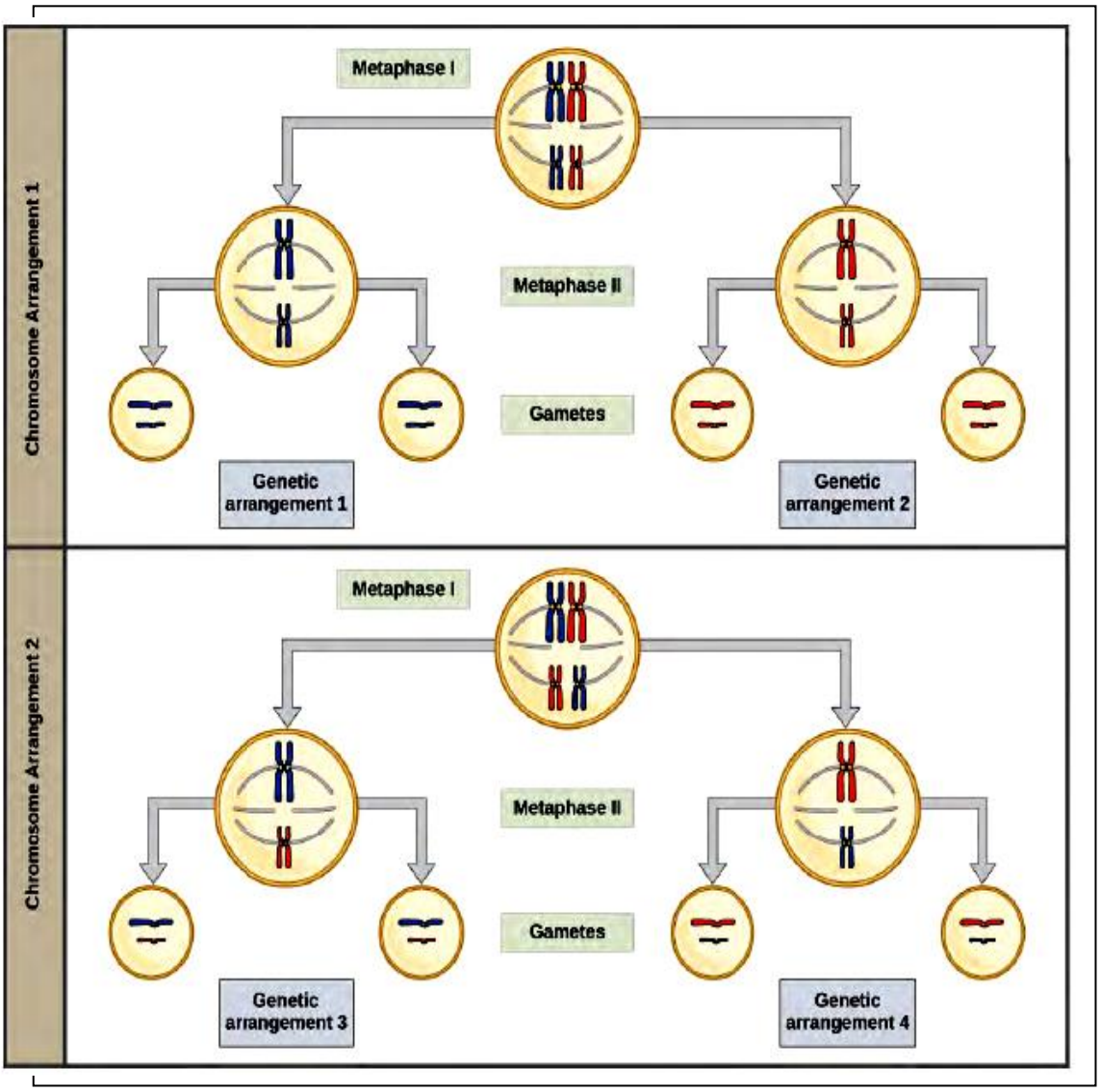


Figure 1.10.1: The random segregation into daughter nuclei that happens during the first division in meiosis can lead to a variety of possible genetic arrangements.

- **Inherited human disorders show either recessive inheritance in which**
  - two recessive alleles are needed to show disease.
  - heterozygous parents are carriers of the disease-causing allele.
  - the probability of inheritance increases with **inbreeding**, and mating between close relatives.
- **dominant inheritance in which**
  - one dominant allele is needed to show disease.

- dominant lethal alleles are usually **eliminated** from the population.

Table 1.2: Many inherited disorders in humans are controlled by a single gene

TABLE 9.9 SOME AUTOSOMAL DISORDERS IN HUMANS

Disorder	Major Symptoms	Incidence		Comments
Recessive disorders				
Albinism	Lack of pigment in the skin, hair, and eyes	1/22,000		Prone to skin cancer
Cystic fibrosis	Excess mucus in the lungs, digestive tract, liver; increased susceptibility to infections; death in early childhood unless treated	1/2,500	Caucasians	See Module 9.9
Galactosemia	Accumulation of galactose in tissues; mental retardation; eye and liver damage	1/100,000		Treated by eliminating galactose from diet
Phenylketonuria (PKU)	Accumulation of phenylalanine in blood; lack of normal skin pigment; mental retardation	1/10,000	in U.S. and Europe	See Module 9.10
Sickle-cell disease	Sickled red blood cells; damage to many tissues	1/400	African-Americans	See Module 9.13
Tay-Sachs disease	Lipid accumulation in brain cells; mental deficiency; blindness; death in childhood	1/3,500	Jews from central Europe	See Module 4.10
Dominant disorders				
Achondroplasia	Dwarfism	1/25,000		See Module 9.9
Alzheimer's disease (one type)	Mental deterioration; usually strikes late in life	Not known		Familial (inherited) Alzheimer's is a rare form of the disease
Huntington's disease	Mental deterioration and uncontrollable movements; strikes in middle age	1/25,000		See Module 9.9
Hypercholesterolemia	Excess cholesterol in the blood; heart disease	1/500	are heterozygous	See Module 9.11

- **The most common fatal genetic disease in the United States is cystic fibrosis (CF), resulting in excessive thick mucus secretions. The CF allele is**
  - recessive and expressed by mutation of **CFTR** membranous protein.

- results in the accumulation of Cl^- ions inside mucus cells.
- treated by antibiotics and death in early childhood.

- **Dominant human disorders include**
  - achondroplasia, resulting in dwarfism, and
  - Huntington's disease is a degenerative disorder of the nervous system.

- Several technologies can be used for detecting genetic conditions in a fetus.

1. **Amniocentesis** extracts samples of amniotic fluid containing fetal cells and permits
   - After 14-16 weeks of pregnancy.
   - Cell culture for 72 hours.
   - karyotyping and sex determination.
   - biochemical tests on cultured fetal cells to detect other conditions.
2. **Chorionic villus sampling** removes a sample of chorionic villus tissue from the placenta and permits similar karyotyping and biochemical tests after 4 weeks of pregnancy.

■

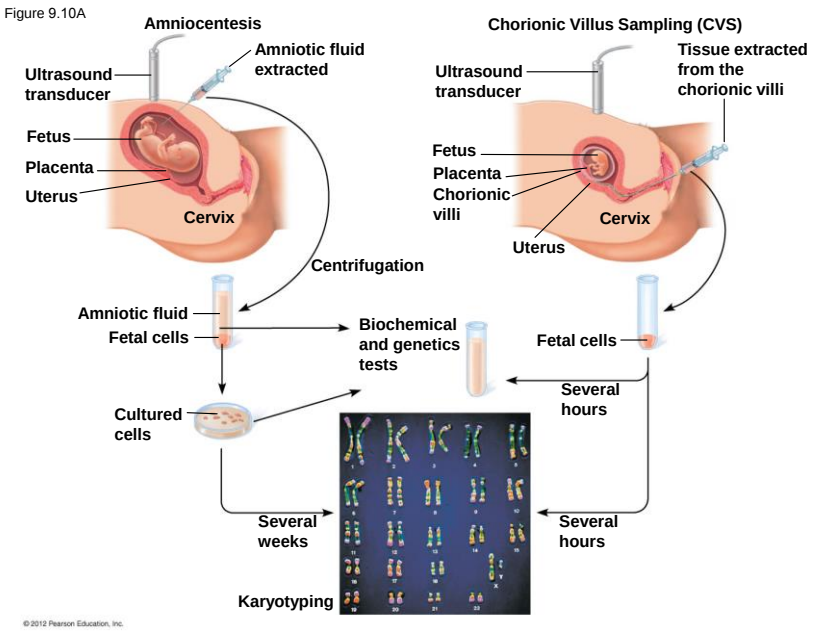


Figure 1.10.2: Several technologies can be used to detect genetic condition such as (1) Chorionic villus sampling after 4 weeks of gestation, and (2) Amniocentesis after 14-16 weeks of gestation.

- **Blood tests on the mother** at 14–20 weeks of pregnancy can help identify fetuses at risk for certain birth defects.
- **Fetal imaging** enables a physician to examine a fetus directly for anatomical deformities. The most common procedure is **ultrasound imaging,** using sound waves to produce a picture of the fetus.
- **Newborn screening** can detect diseases that can be prevented by special care and precautions.

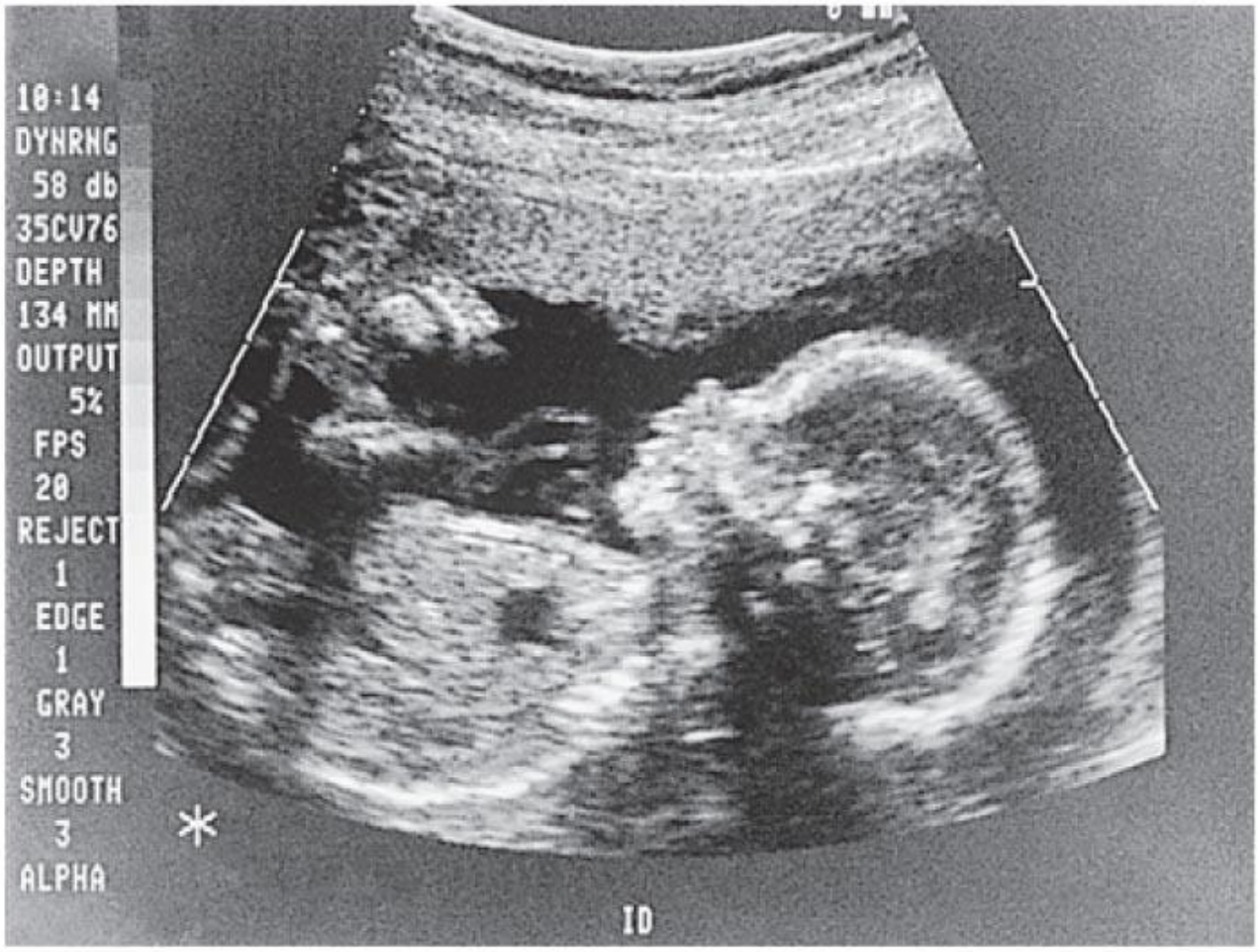


Figure 1.10.3: The most common procedure is **ultrasound imaging,** using sound waves to produce a picture of the fetus.

▪ Extensions of the Laws of Inheritance

By the end of this section, you will be able to:

- Identify non-Mendelian inheritance patterns such as incomplete dominance, codominance, multiple alleles, and sex linkage from the results of crosses
- Explain the effect of linkage and recombination on gamete genotypes
- Explain the phenotypic outcomes of epistatic effects among genes

Mendel studied traits with only one mode of inheritance in pea plants. The inheritance of the traits he studied all followed the relatively simple pattern of dominant and recessive alleles for a single characteristic. There are several important modes of inheritance, discovered after **Mendel's** work, that do not follow the dominant and recessive, single-gene model.

▪ Alternatives to Dominance and Recessiveness

Mendel's experiments with pea plants suggested that:

1) two types of "units" or alleles exist for every gene.

2) alleles maintain **their integrity** in each generation (no blending).

3) in the presence of the dominant allele, the recessive allele is hidden, with no contribution to the phenotype.

Therefore, recessive alleles can be "carried" and not expressed by individuals. Such heterozygous individuals are sometimes referred to as "**carriers**." Since then, genetic studies in other organisms have shown that much more complexity exists, but the fundamental principles of **Mendelian genetics** still hold. In the sections to follow, we consider some of the extensions of **Mendelism**.

- ***Incomplete Dominance:*** in which
  - neither allele is dominant over the other.

- expression of both alleles occurs.

Mendel's results, demonstrating that traits are inherited as dominant and recessive pairs, contradicted the view at that time that offspring exhibited a blend of their parent's traits. However, the heterozygote phenotype occasionally does appear to be intermediate between the two parents. For example, in the **snapdragon**, ***Antirrhinum majus*** (**Figure 1.11**), a cross between a homozygous parent with white flowers ($\mathbf{C^WC^W}$) and a homozygous parent with red flowers ($\mathbf{C^RC^R}$) will produce offspring with pink flowers ($\mathbf{C^RC^W}$). (Note that different genotypic abbreviations are used for **Mendelian** extensions to distinguish these patterns from simple **dominance** and **recessiveness**.) This pattern of inheritance is described as **incomplete dominance**, meaning that one of the alleles appears in the phenotype in the heterozygote, but not to the exclusion of the other, which can also be seen. The allele for red flowers is incompletely dominant over the allele for white flowers. However, the results of a heterozygote self-cross can still be predicted, just as with **Mendelian** dominant and recessive crosses. In this case, the genotypic ratio would be 1 $\mathbf{C^RC^R}$: 2 $\mathbf{C^RC^W}$: 1 $\mathbf{C^WC^W}$, and the phenotypic ratio would be **1:2:1** for red: pink: white. The basis for the **intermediate** color in the heterozygote is simply that the pigment produced by the red allele (**anthocyanin**) is diluted in the heterozygote and therefore appears pink because of the white background of the flower petals.

Figure 1.11: These pink flowers of a heterozygote **snapdragon** result from incomplete dominance.

- **Incomplete dominance results in intermediate phenotypes.**
    - Incomplete dominance does not support the blending hypothesis because the original parental phenotypes reappear in the F_2 generation.
    - One example of incomplete dominance in humans is **hypercholesterolemia**, in which
        - dangerously high levels of cholesterol occur in the blood.
        - heterozygotes have intermediately high cholesterol levels.

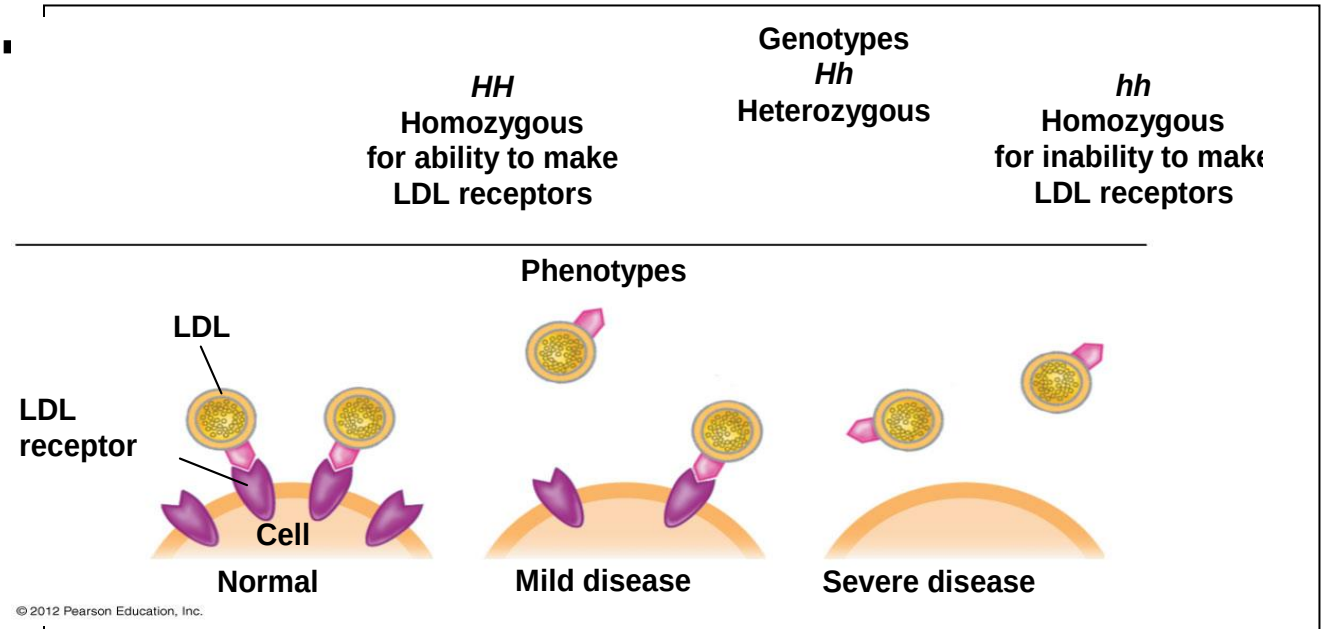


Figure 1.11.1: One example of incomplete dominance in humans is **hypercholesterolemia**, in which dangerously high levels of cholesterol occur in the blood.

Codominance

A variation on incomplete dominance is **codominance**, in which both alleles for the same characteristic are simultaneously expressed in the heterozygote. An example of **codominance** occurs in the **ABO** blood groups of humans. The **A** and **B** alleles are expressed in the form of **A** or **B** molecules present on the surface of red blood cells. Homozygotes (I^AI^A and I^BI^B) express either the **A** or the **B** phenotype, and heterozygotes (I^AI^B) express both phenotypes equally. The I^AI^B individual has blood type **AB**. In a self-cross between heterozygotes expressing a **codominant** trait, the three possible offspring genotypes are phenotypically distinct. However, the **1:2:1** genotypic ratio characteristic of a **Mendelian** monohybrid cross still applies (**Figure 1.12**).

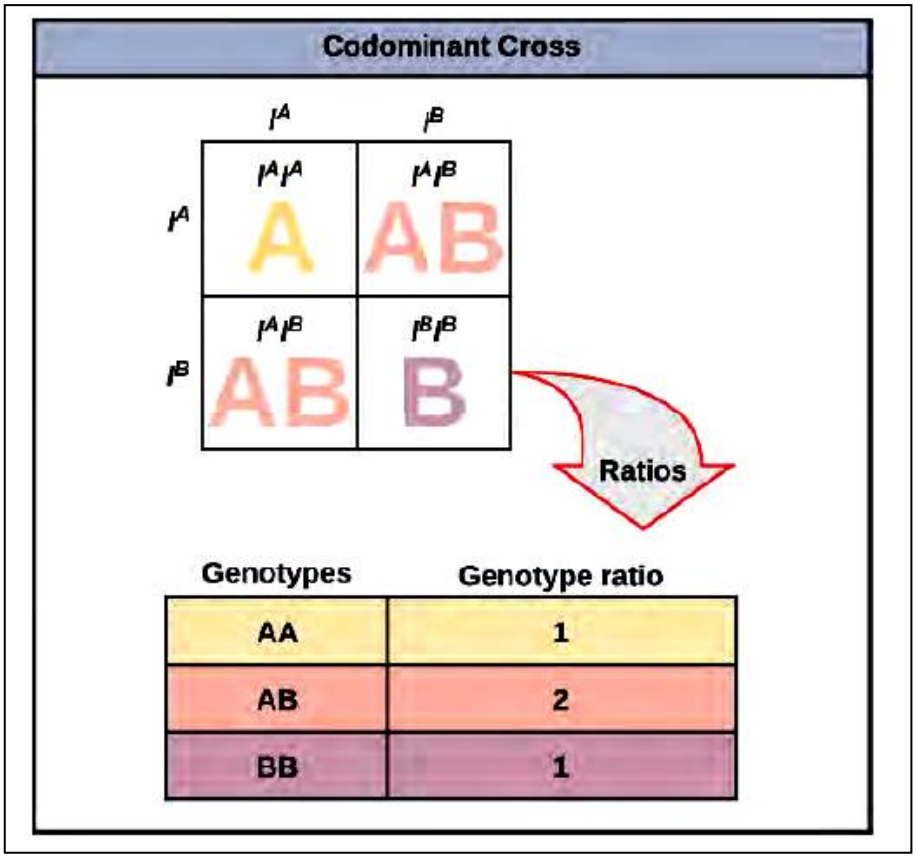
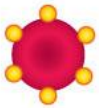
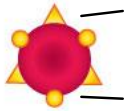


Figure 1.12: This Punnet square shows an **AB/AB** blood type cross.

Blood Group (Phenotype)	Genotypes	Carbohydrates Present on Red Blood Cells	Antibodies Present in Blood	Reaction When Blood from Groups Below Is Mixed with Antibodies from Groups at Left			
				O	A	B	AB
A	I^AI^A or I^Ai	 Carbohydrate A	Anti-B				
B	I^BI^B or I^Bi	 Carbohydrate B	Anti-A				
AB	I^AI^B	 Carbohydrate A and Carbohydrate B	*None*				
O	*ii*	 Neither	Anti-A Anti-B				

 No reaction

 Clumping reaction

Multiple Alleles

Mendel implied that only two alleles, one dominant and one recessive, could exist for a given gene. We now know that this is an oversimplification. Although individual humans (and all diploid organisms) can only have two alleles for a given gene, multiple alleles may exist at the population level, such that many combinations of two alleles are observed. Note that when many alleles exist for the same gene, the convention is to denote the most common phenotype or genotype in the natural population as the **wild type** (often abbreviated "**+**"). All other phenotypes or genotypes are considered variants (mutants) of this typical form, meaning they deviate from the wild type. The variant may be recessive or dominant to the **wild-type allele**.

An example of multiple alleles is the **ABO blood-type** system in humans. In this case, there are three alleles circulating in the population. The $\mathbf{I^A}$ allele codes for **A** molecules on the red blood cells, the $\mathbf{I^B}$ allele codes for **B** molecules on the surface of red blood cells, and the i allele codes for no molecules on the red blood cells. In this case, the $\mathbf{I^A}$ and $\mathbf{I^B}$ alleles are **codominant** with each other and are both dominant over the **i** allele. Although there are three alleles present in a population, each individual only gets two of the alleles from their parents. This produces the genotypes and phenotypes shown in **Figure 1.13**. Notice that instead of three genotypes, there are six different genotypes when there are three alleles. The number of possible phenotypes depends on the dominant relationships between the three alleles.

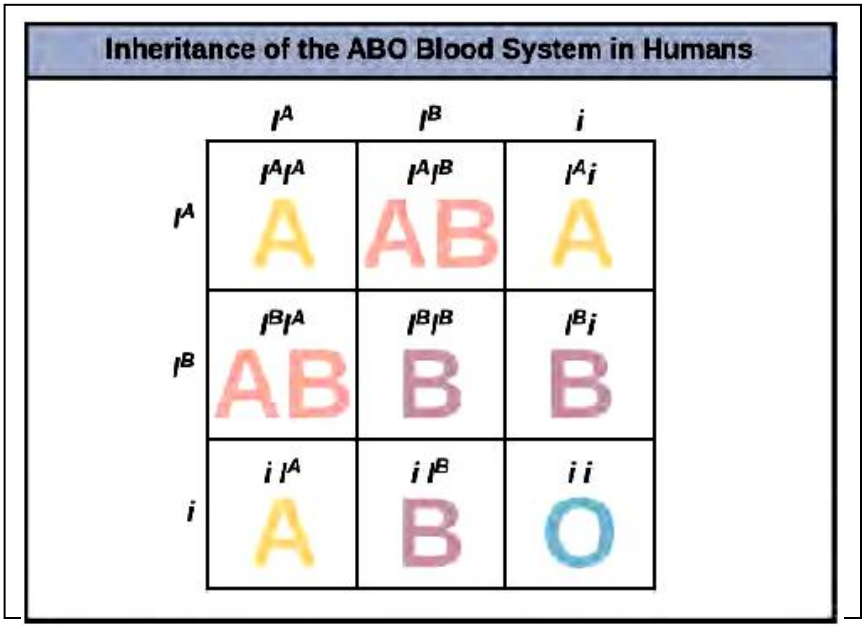
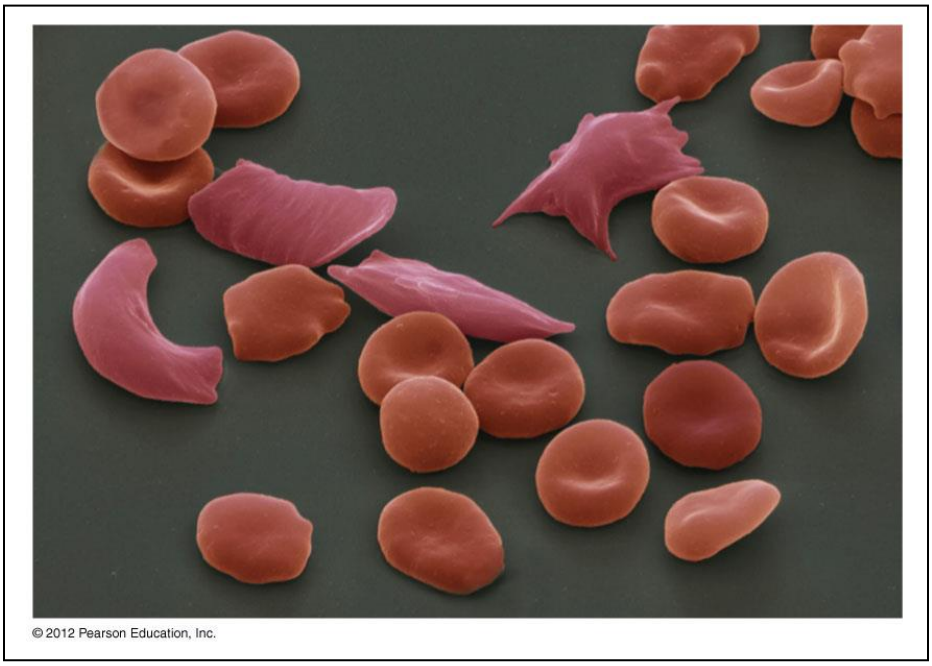


Figure 1.13: Inheritance of the **ABO blood system** in humans is shown.

A single gene may affect many phenotypic characters:

- **Pleiotropy** occurs when one gene influences many characteristics.
- **Sickle-cell disease** is a human example of pleiotropy. This disease:
  - affects the type of hemoglobin produced and the shape of red blood cells.
  - causes anemia and organ damage.
  - Sickle-cell and non sickle alleles are codominant.
  - Carriers of sickle-cell disease are resistant to malaria.



Multiple Alleles Confer Drug Resistance in the Malaria Parasite

Malaria is a parasitic disease in humans that is transmitted by infected female mosquitoes, including ***Anopheles gambiae***, and is characterized by cyclic high fevers, chills, flu-like symptoms, and severe anemia. ***Plasmodium falciparum*** and ***P. vivax*** are the most common causative agents of malaria, and ***P. falciparum*** is the most deadly. When promptly and correctly treated, ***P. falciparum*** malaria has a mortality rate of 0.1 percent. However, in some parts of the world, the parasite has evolved resistance to commonly used malaria treatments, so the most effective malarial treatments can vary by geographic region.

In Southeast Asia, Africa, and South America, ***P. falciparum*** has developed resistance to the anti-malarial drugs chloroquine, mefloquine, and sulfadoxine-pyrimethamine. ***P. falciparum***, which is haploid during the life stage in which it is infective to humans, has evolved multiple drug-resistant mutant alleles of the ***dhps*** gene. Varying degrees of sulfadoxine resistance is associated with each of these alleles. Being haploid, ***P. falciparum*** needs only one drug-resistant allele to express this trait.

In Southeast Asia, different sulfadoxine-resistant alleles of the ***dhps*** gene are localized to different geographic regions. This is a common evolutionary phenomenon that comes about because drug-resistant mutants arise in a population and interbreed with other ***P. falciparum*** isolates in close proximity. **Sulfadoxine-resistant** parasites cause considerable human hardship in regions in which this drug is widely used as an over-the-counter malaria remedy. As is common with pathogens that multiply to large numbers within an infection cycle, ***P. falciparum*** evolves relatively rapidly (over a decade or so) in response to the selective pressure of commonly used anti-malarial drugs. For

this reason, scientists must constantly work to develop new drugs or drug combinations to combat the worldwide malaria burden.

An individual homozygous for the sickle-cell allele

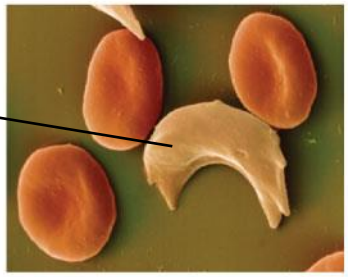
↓

Produces sickle-cell (abnormal) hemoglobin

↓

The abnormal hemoglobin crystallizes, causing red blood cells to become sickle-shaped

Sickled cell



The multiple effects of sickled cells

Damage to organs

- Kidney failure
- Heart failure
- Spleen damage
- Brain damage (impaired mental function, paralysis)

Other effects

- Pain and fever
- Joint problems
- Physical weakness
- Anemia
- Pneumonia and other infections

Sex-Linked Traits

In humans, as well as in many other animals and some plants, the sex of the individual is determined by sex chromosomes one pair of non-homologous chromosomes. Until now, we have only considered inheritance patterns among non-sex chromosomes or autosomes. In addition to 22 homologous pairs of autosomes, human females have a homologous pair of **X** chromosomes, whereas human males have an **XY** chromosome pair. Although the Y chromosome contains a small region of similarity to the **X** chromosome so that they can pair during meiosis, the **Y** chromosome is much shorter and contains fewer genes. When a gene being examined is present on the **X**, but not the **Y**, chromosome, it is **X-linked**.

Eye color in Drosophila, the common fruit fly, was the first **X-linked** trait to be identified. **Thomas Hunt Morgan** mapped this trait to the **X** chromosome in 1910. Like humans, Drosophila males have an **XY** chromosome pair, and females are **XX**. In flies, the wild-type eye color is red ($\mathbf{X^W}$) and is dominant to white eye color ($\mathbf{X^w}$) (**Figure 1.14**). Because of the location of the eye-color gene, reciprocal crosses do not produce the same offspring ratios. Males are said to be hemizygous, in that they have only one allele for any **X-linked characteristic**. Hemizygosity makes descriptions of dominance and recessiveness irrelevant for **XY** males. Drosophila males lack the white gene on the **Y** chromosome; that is, their genotype can only be $\mathbf{X^WY}$ or $\mathbf{X^wY}$. In contrast, females have two allele copies of this gene which can be $\mathbf{X^WX^W}$, $\mathbf{X^WX^w}$, or $\mathbf{X^wX^w}$.

Figure 1.14: In Drosophila, the gene for eye color is located on the **X** chromosome. The red eye color is **wild-type** and is dominant to the white eye color.

In an **X-linked** cross, the genotypes of **F1** and **F2** offspring depend on whether the recessive trait was expressed by the male or the female in the **P** generation. Concerning Drosophila eye color, when the **P** male expresses the white-eye phenotype and the female is homozygously red-eyed, all members of the **F1** generation exhibit red eyes (**Figure 1.15**). The **F1** females are heterozygous ($\mathbf{X^WX^w}$), and the males are all $\mathbf{X^WY}$, having received their **X** chromosome from the homozygous dominant **P** female and their **Y** chromosome from the **P** male. A subsequent cross between the $\mathbf{X^WX^w}$ female and the $\mathbf{X^WY}$ male would produce only red-eyed females (with **XWXW** or $\mathbf{X^WX^w}$ genotypes) and both red- and white-eyed males (with $\mathbf{X^WY}$ or $\mathbf{X^wY}$ genotypes). Now, consider a cross between a homozygous white-eyed female and a male with red eyes. The **F1** generation would exhibit only heterozygous red-eyed females ($\mathbf{X^WX^w}$) and only white-eyed males ($\mathbf{X^wY}$). Half of the **F2** females would

be red-eyed ($\mathbf{X^WX^w}$) and half would be white-eyed ($\mathbf{X^wX^w}$). Similarly, half of the **F2** males would be red-eyed ($\mathbf{X^WY}$) and half would be white-eyed ($\mathbf{X^wY}$).

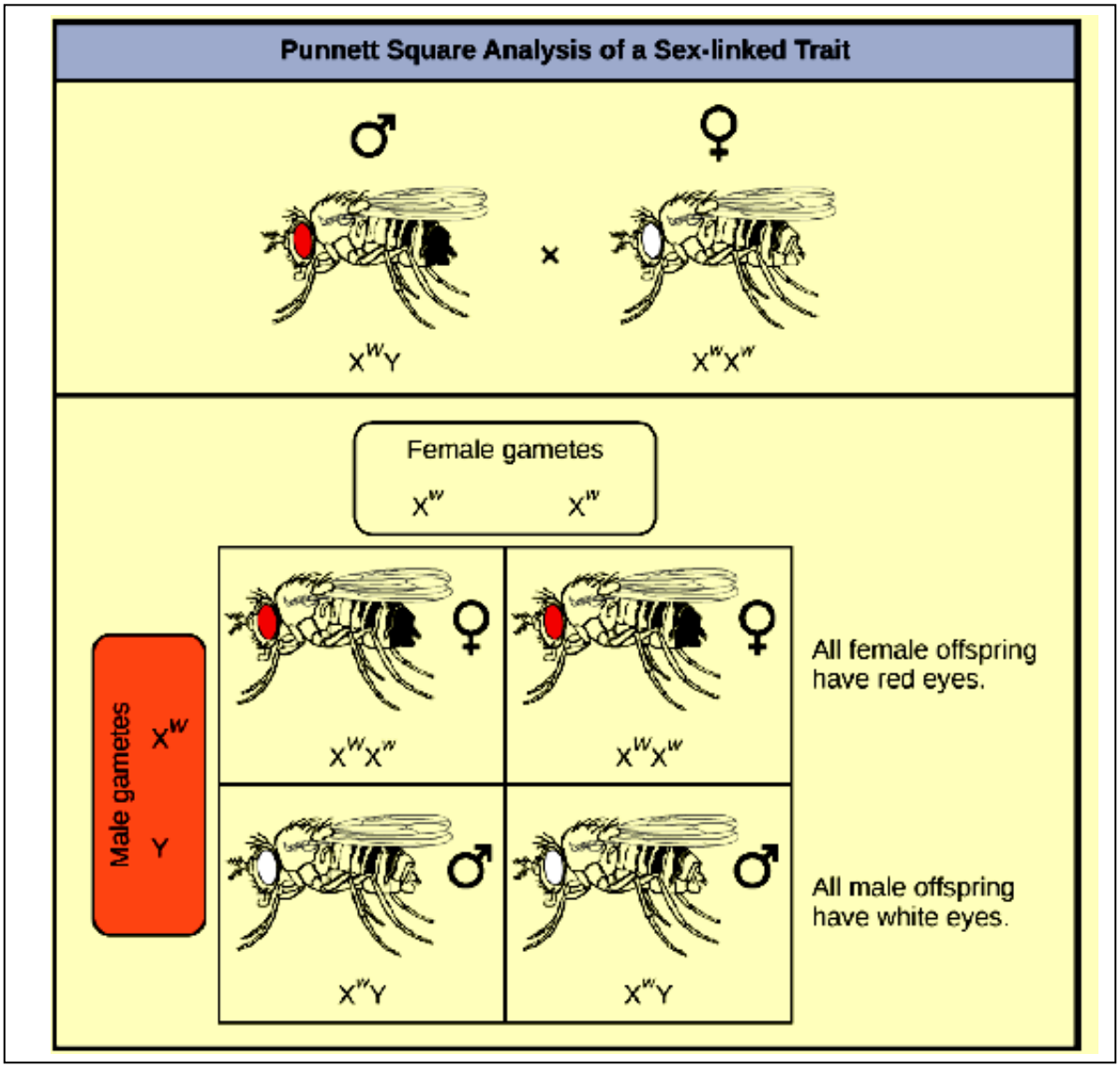
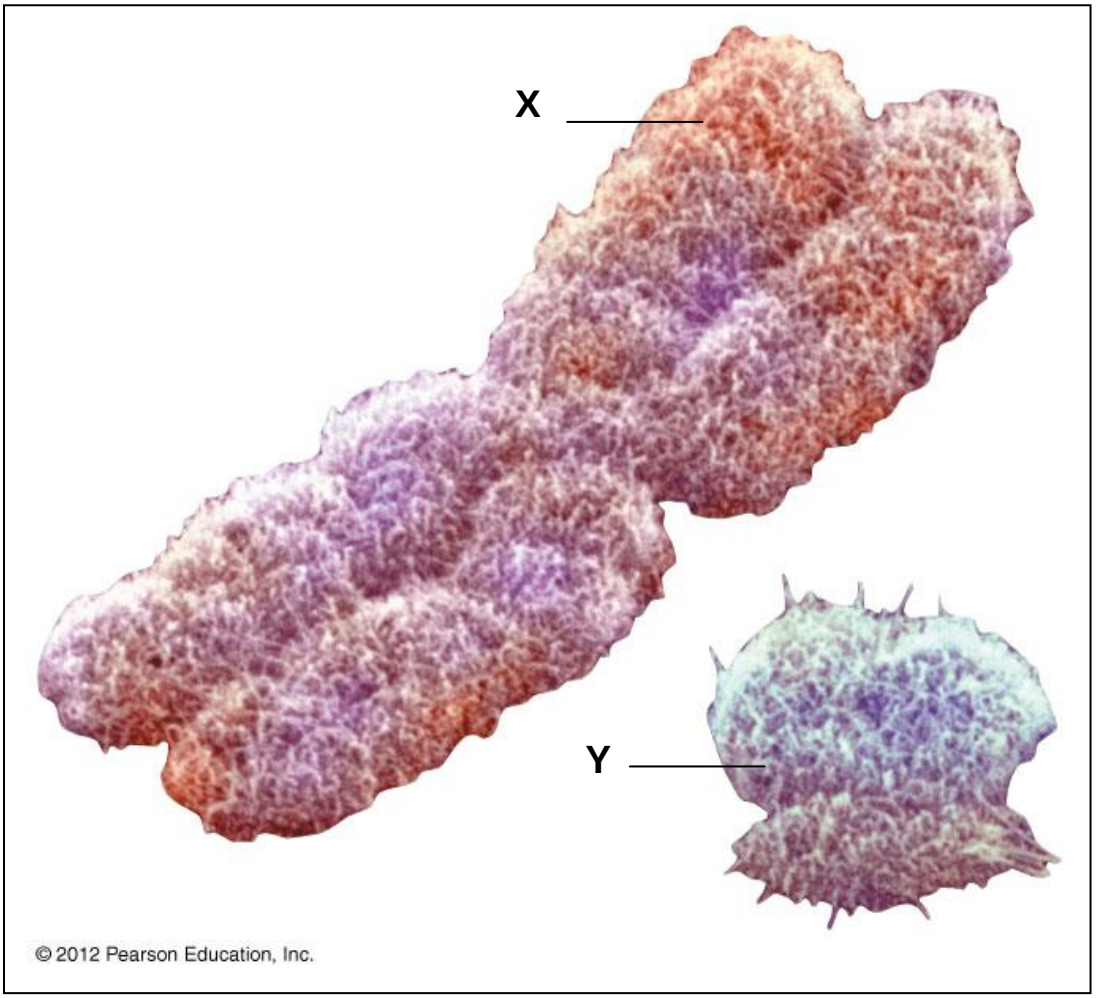


Figure 1.15: Crosses involving **sex-linked** traits often give rise to different phenotypes for the different sexes of offspring, as is the case for this cross involving red and white eye color in *Drosophila*. In the diagram, **w** is the white-eye mutant allele and **W** is the wild-type, red-eye allele.

❖ Chromosomes determine sex in many species

- Many animals have a pair of sex chromosomes,
  - designated X and Y.
  - that determine an individual's sex.
- In mammals,
  - males have XY sex chromosomes.
  - females have XX sex chromosomes.
  - the Y chromosome has genes for the development of testes.
  - an absence of the Y allows ovaries to develop.



What ratio of offspring would result from a cross between a white-eyed male and a female that is heterozygous for red-eye color?

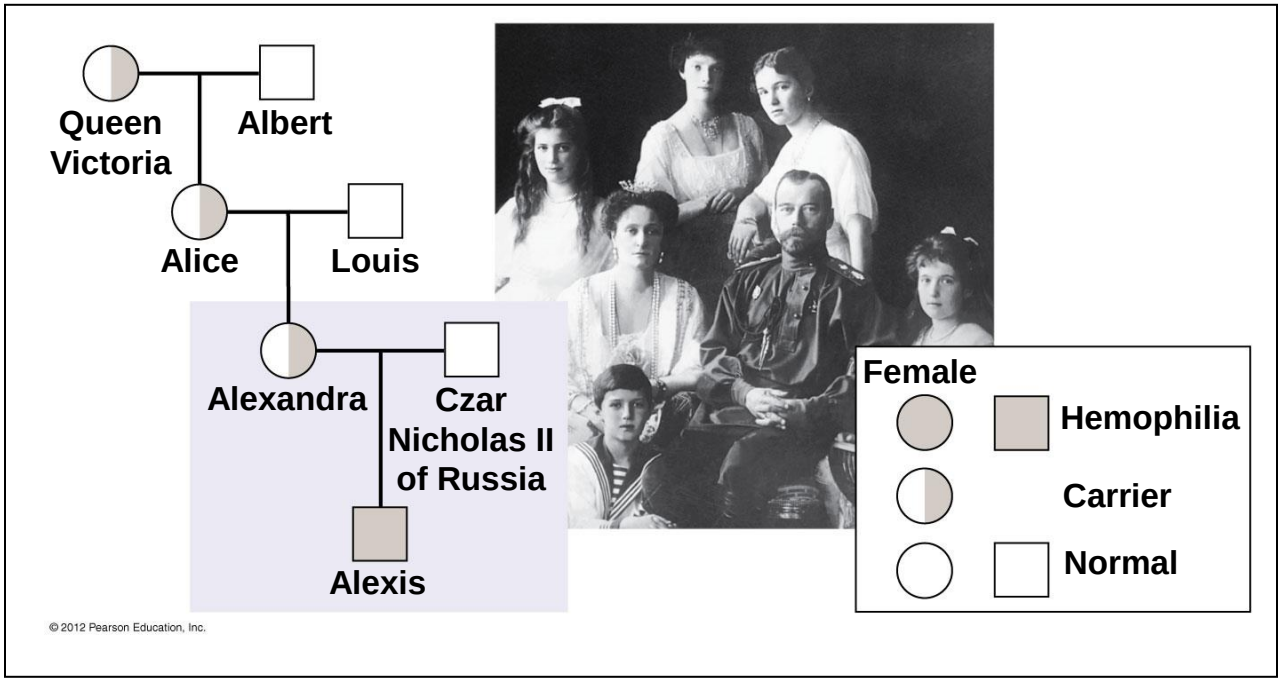
Discoveries in fruit fly genetics can be applied to human genetics. When a female parent is homozygous for a recessive **X-linked** trait, she will pass the trait on to 100 percent of her male offspring, because the males will receive the **Y** chromosome from the male parent. In humans, the alleles for certain conditions (**some color blindness, hemophilia, and muscular dystrophy**) are **X-linked**. Females who are heterozygous for these diseases are said to be carriers and may not exhibit any phenotypic effects. These females will pass the disease to half of their sons and will pass carrier status to half of their daughters; therefore, **X-linked** traits appear more frequently in males than females.

In some groups of organisms with sex chromosomes, the sex with the non-homologous sex chromosomes is female rather than male. This is the case for all birds. In this case, **sex-linked** traits will be more likely to appear in the female, in whom they are **hemizygous**.

❖ Human sex-linked disorders affect mostly males:

- Most sex-linked human disorders are:
  - due to recessive alleles.
  - seen mostly in males.
- A male receiving a single X-linked recessive allele from his mother will have the disorder.
- A female must receive the allele from both parents to be affected.

- **Recessive and sex-linked human disorders include:**
  - **Hemophilia** is characterized by excessive bleeding because hemophiliacs lack one or more of the proteins required for blood clotting.
  - **Red-green color blindness** is a malfunction of light-sensitive cells in the eyes.
  - **Duchenne muscular dystrophy** is a condition characterized by a progressive weakening of the muscles and loss of coordination.



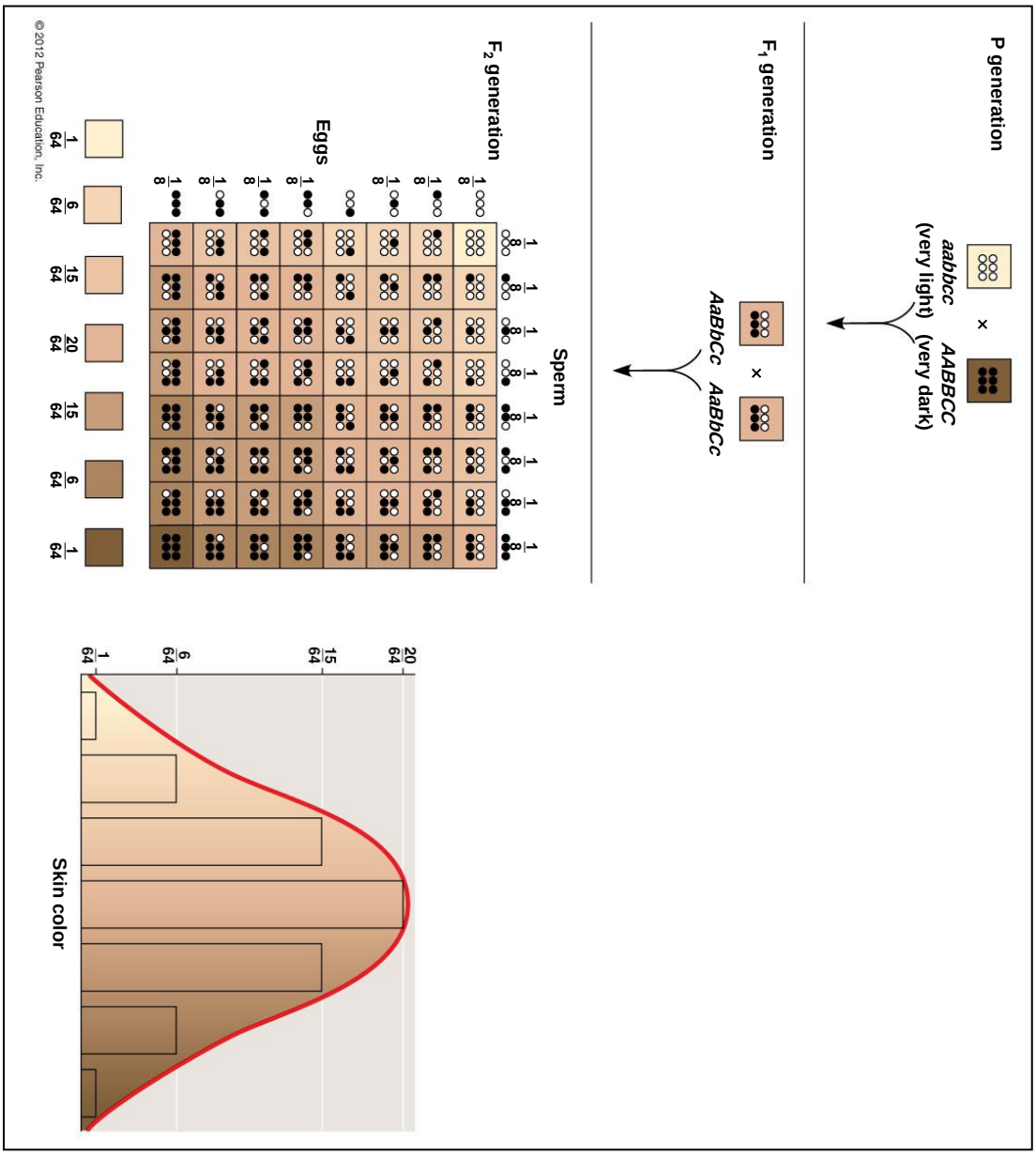
❖ A single character may be influenced by many genes:

- Many characteristics result from a **polygenic inheritance**, in which a single phenotypic character results from the additive effects of two or more genes.

- Human skin color is an example of polygenic inheritance.

❖ The environment affects many characters:

- Many characters result from a combination of heredity and the **environment**. For example,
  - skin color is affected by exposure to sunlight.
  - susceptibility to diseases, such as cancer, has hereditary and environmental components.
  - identical twins show some differences.



❖ Linked Genes Violate the Law of Independent Assortment

Although all of **Mendel's** pea plant characteristics behaved according to the law of independent assortment, we now know that some allele combinations are not inherited independently of each other. Genes that are located on separate, non-homologous chromosomes will always sort independently. However, each chromosome contains hundreds or thousands of genes, organized linearly on chromosomes like beads on a string. The segregation of alleles into gametes can be influenced by **linkage**, in which genes that are located physically close to each other on the same chromosome are more likely to be inherited as a pair. However, because of the process of recombination, or "**crossover**" it is possible for two genes on the same chromosome to behave independently, or as if they are not linked. To understand this, let us consider the biological basis of gene linkage and recombination.

Homologous chromosomes possess the same genes in the same order, though the specific alleles of the gene can be different on each of the two chromosomes. Recall that during interphase and prophase **I** of meiosis, homologous chromosomes first replicate and then synapse, with like genes on the homologs aligning with each other. At this stage, segments of homologous chromosomes exchange linear segments of genetic material (**Figure 1.16**). This process is called recombination, or crossover, and it is a common genetic process. Because the genes are aligned during recombination, the gene order is not altered. Instead, the result of recombination is that maternal and paternal alleles are combined onto the same chromosome. Across a given chromosome, several recombination events may occur, causing extensive shuffling of alleles.

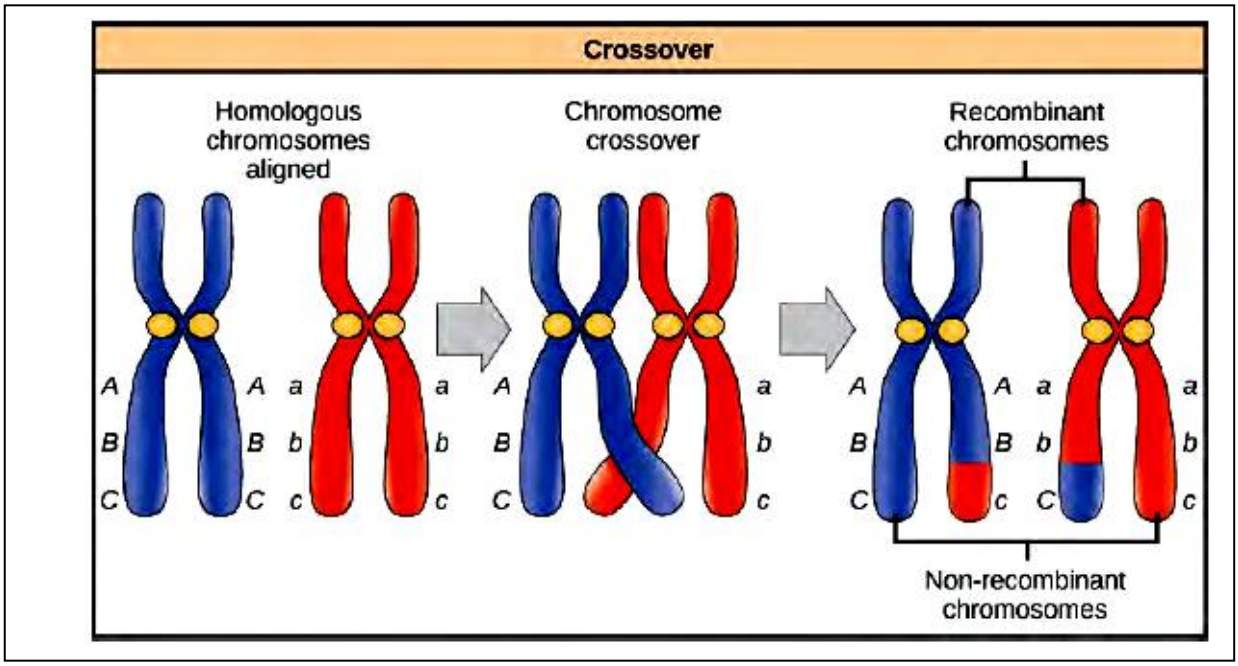


Figure 1.16: The process of **crossover**, or recombination, occurs when two homologous chromosomes align and exchange a segment of genetic material.

When two genes are located on the same chromosome, they are considered linked, and their alleles tend to be transmitted through meiosis together. To exemplify this, imagine a **dihybrid cross** involving flower color and plant height in which the genes are next to each other on the chromosome. If one homologous chromosome has alleles for tall plants and red flowers, and the other chromosome has genes for short plants and yellow flowers, then when the gametes are formed, the tall and red alleles will tend to go together into a gamete and the short and yellow alleles will go into other gametes. These are called the parental genotypes because they have been inherited intact from the parents of the individual-producing gametes. But unlike if the genes were on different chromosomes, there will be no gametes with tall and yellow alleles and no gametes with short and red alleles. If you create a **Punnett square** with these gametes, you will see that the classical **Mendelian** prediction of a **9:3:3:1** outcome of a **dihybrid** cross would not apply. As the

distance between two genes increases, the probability of one or more crossovers between them increases and the genes behave more like they are on separate chromosomes. Geneticists have used the proportion of recombinant gametes (the ones not like the parents) as a measure of how far apart genes are on a chromosome. Using this information, they have constructed linkage maps of genes on chromosomes for well-studied organisms, including humans.

Mendel's seminal publication makes no mention of **linkage**, and many researchers have questioned whether he encountered linkage but chose not to publish those crosses out of concern that they would invalidate his independent assortment postulate. The garden pea has seven chromosomes, and some have suggested that his choice of seven characteristics was not a **coincidence**. However, even if the genes he examined were not located on separate chromosomes, it is possible that he simply did not observe linkage because of the extensive **shuffling effects** of recombination.

❖ Genes on the same chromosome tend to be inherited together:

- **Bateson** and **Punnett** studied plants that did not show a **9:3:3:1 ratio** in the F_2 generation. What they found was an example of linked genes, which
  - are located close together on the same chromosome.
  - tend to be inherited together.

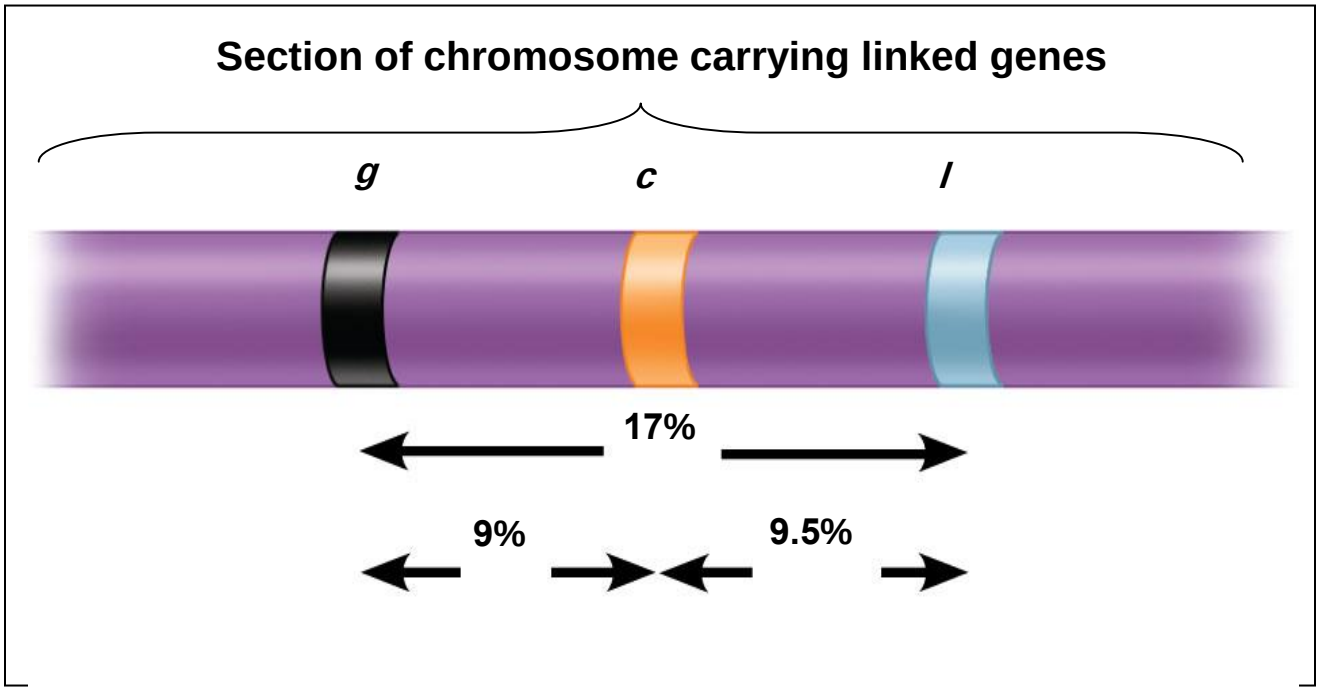
❖ Crossing over produces new combinations of alleles

- **Crossing over** between homologous chromosomes produces new combinations of alleles in gametes.
- Linked alleles can be separated by **crossing over**, forming recombinant gametes.

- The percentage of recombinants is the **recombination frequency**.

❖ Geneticists use crossover data to map genes:

- When examining recombinant frequency, Morgan and his students found that the greater the distance between two genes on a chromosome, the more points there are between them where crossing over can occur.
- **Recombination frequencies** can thus be used to map the relative position of genes on chromosomes.



Epistasis

Mendel's studies in pea plants implied that the sum of an individual's phenotype was controlled by genes (or as he called them, unit factors), such that every characteristic was distinctly and completely controlled by a single gene. Single observable characteristics are almost always under the influence of multiple genes (each with two or more alleles) acting in unison. For example, at least eight genes contribute to eye color in humans.

Eye color in humans is determined by multiple alleles. Use the Eye Color Calculator (**http://openstaxcollege.org/l/eye_color_calc**) to predict the eye color of children from parental eye color.

In some cases, several genes can contribute to aspects of a common phenotype without their gene products ever directly interacting. In the case of organ development, for instance, genes may be expressed sequentially, with each gene adding to the complexity and specificity of the organ. Genes may function in complementary or synergistic fashions, such that two or more genes expressed simultaneously affect a phenotype. An apparent example of this occurs with human skin color, which appears to involve the action of at least three (and probably more) genes. Cases in which inheritance for a characteristic like skin color or human height depends on the combined effects of numerous genes are called polygenic inheritance.

Genes may also oppose each other, with one gene suppressing the expression of another. In **epistasis**, the interaction between genes is antagonistic, such that one gene masks or interferes with the expression of another. "**Epistasis**" is a word composed of Greek roots meaning "standing upon." The alleles that are being masked or silenced are said to be hypostatic to the **epistatic** alleles that are doing the masking. Often the biochemical basis

of epistasis is a gene pathway in which the expression of one gene is dependent on the function of a gene that precedes or follows it in the pathway.

An example of **epistasis** is pigmentation in mice. The wild-type coat color, agouti (**AA**) is dominant to solid-colored fur (**aa**). However, a separate gene **C**, when present as the recessive homozygote (**cc**), negates any expression of pigment from the **A** gene and results in an albino mouse (**Figure 1.17**). Therefore, the genotypes **AAcc, Aacc,** and **aacc** all produce the same albino phenotype. A cross between heterozygotes for both genes (**AaCc** x **AaCc**) would generate offspring with a phenotypic ratio of **9** agouti: **3** black: **4** albino (**Figure 1.17**). In this case, the **C** gene is **epistatic** to the **A** gene.

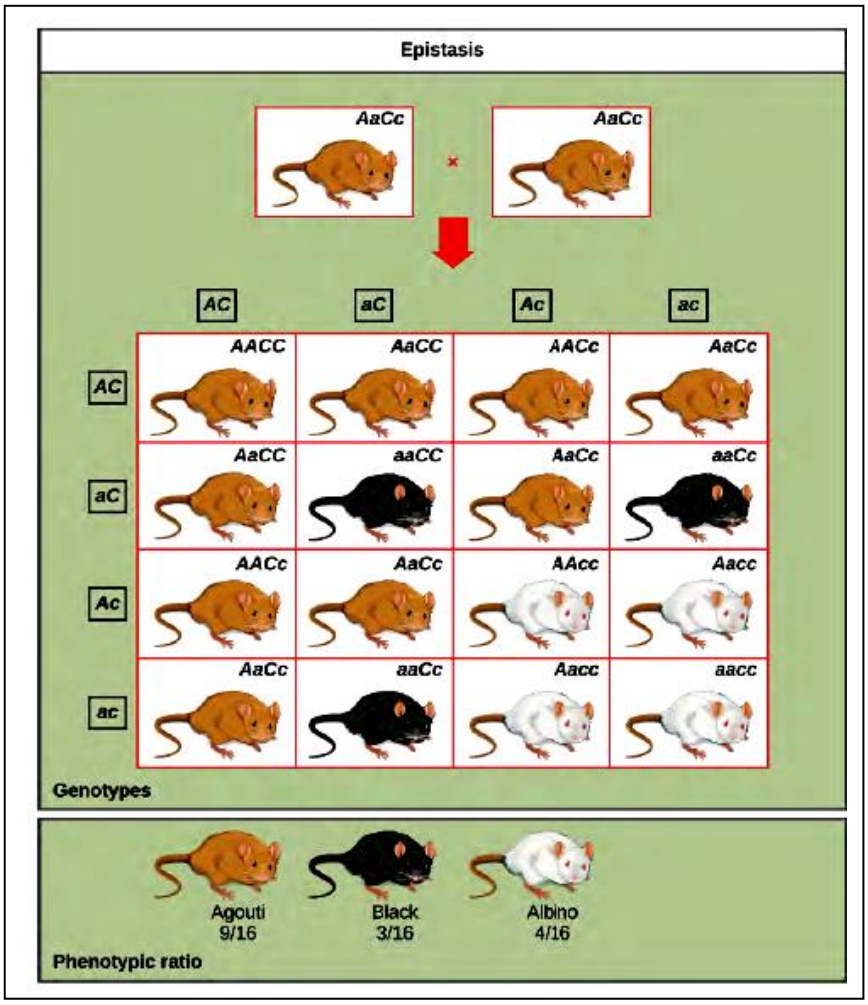


Figure 1.17: In this example of **epistasis**, one gene (**C**) masks the expression of another (**A**) for coat color. When the **C** allele is present, coat color is

expressed; when it is absent (**cc**), no coat color is expressed. Coat color depends on the **A** gene, which shows dominance, with the recessive homozygote showing a different phenotype than the heterozygote or dominant homozygote.

KEY TERMS

Allele: one of two or more variants of a gene that determines a particular trait for a characteristic.

Codominance: in a heterozygote, complete and simultaneous expression of both alleles for the same characteristic.

Continuous variation: a variation in a characteristic in which individuals show a range of traits with small differences between them.

Dihybrid: the result of a cross between two true-breeding parents that express different traits for two characteristics.

Discontinuous variation: a variation in a characteristic in which individuals show two, or a few, traits with large differences between them.

Dominant: describes a trait that masks the expression of another trait when both versions of the gene are present in an individual.

Epistasis: an interaction between genes such that one gene masks or interferes with the expression of another.

F1: the first filial generation in a cross; the offspring of the parental generation.

F2: the second filial generation produced when F1 individuals are self-crossed or fertilized with each other.

Genotype: the underlying genetic makeup, consisting of both physically visible and non-expressed alleles, of an organism.

Hemizygous: the presence of only one allele for a characteristic, as in X-linkage; hemizygosity makes descriptions of dominance and recessiveness irrelevant.

Heterozygous: having two different alleles for a given gene on the homologous chromosomes.

Homozygous: having two identical alleles for a given gene on the homologous chromosomes.

Hybridization: the process of mating two individuals that differ, to achieve a certain characteristic in their offspring.

Incomplete dominance: in a heterozygote, expression of two contrasting alleles such that the individual displays an intermediate phenotype.

Law of dominance: in a heterozygote, one trait will conceal the presence of another trait for the same characteristic.

Law of independent assortment: genes do not influence each other concerning the sorting of alleles into gametes; every possible combination of alleles is equally likely to occur.

Law of segregation: paired unit factors (i.e., genes) segregate equally into gametes such that offspring have an equal likelihood of inheriting any combination of factors.

Linkage: a phenomenon in which alleles that are located close to each other on the same chromosome are more likely to be inherited together.

Model system: a species or biological system used to study a specific biological phenomenon to gain the understanding that will be applied to other species.

Monohybrid: the result of a cross between two true-breeding parents that express different traits for only one characteristic.

P: the parental generation in a cross.

Punnett square: a visual representation of a cross between two individuals in which the gametes of each individual are denoted along the top and side of a grid, respectively, and the possible zygotic genotypes are recombined at each box in the grid.

Phenotype: the observable traits expressed by an organism.

Recessive: describes a trait whose expression is masked by another trait when the alleles for both traits are present in an individual.

Reciprocal cross: a paired cross in which the respective traits of the male and female in one cross become the respective traits of the female and male in the other cross.

Recombination: the process during meiosis in which homologous chromosomes exchange linear segments of genetic material, thereby dramatically increasing genetic variation in the offspring and separating linked genes.

Test cross: a cross between a dominant expressing individual with an unknown genotype and a homozygous recessive individual; the offspring phenotypes indicate whether the unknown parent is heterozygous or homozygous for the dominant trait.

Trait: a variation in an inherited characteristic.

Wild type: the most commonly occurring genotype or phenotype for a given characteristic found in a population.

X-linked: a gene present on the X chromosome, but not the Y chromosome.

REVIEW QUESTIONS

1. Imagine that you are performing a cross involving seed color in garden pea plants. What traits would you expect to observe in the F1 offspring if you cross true-breeding parents with green seeds and yellow seeds? Yellow seed color is dominant over the green.
    a. only yellow-green seeds.
    b. only yellow seeds.
    c. 1:1 yellow seeds: green seeds.
    d. 1:3 green seeds: yellow seeds.

2. Imagine that you are performing a cross involving seed texture in garden pea plants. You cross true-breeding round and wrinkled parents to obtain **F1** offspring. Which of the following experimental results in terms of the numbers of plants are closest to what you expect in the **F2** progeny?
    a. 810 round seeds.
    b. 810 wrinkled seeds.
    c. 405:395 round seeds: wrinkled seeds.
    d. 610:190 round seeds: wrinkled seeds.

3. The observable traits expressed by an organism are described as its …….
    a. phenotype.
    b. genotype.
    c. alleles.
    d. zygote.

4. A recessive trait will be observed in individuals that are …… for that trait.
    a. heterozygous.
    b. homozygous or heterozygous.
    c. homozygous.
    d. diploid.

5. What are the types of gametes that can be produced by an individual with the genotype **AaBb**?
    a. **Aa, Bb.**
    b. **AA, aa, BB, bb.**
    c. **AB, Ab, aB, ab.**
    d. **AB, ab**.

6. What is the reason for doing a test cross?
    a. to identify heterozygous individuals with the dominant phenotype.
    b. to determine which allele is dominant and which is recessive.
    c. to identify homozygous recessive individuals in the F2.
    d. to determine if two genes assort independently.

7. If black and white true-breeding mice are mated and the result is all gray offspring, what inheritance pattern would this be indicative of?
    a. dominance.

b. codominance.
c. multiple alleles.
d. incomplete dominance.

8. The **ABO** blood groups in humans are expressed as the **IA, IB**, and **i** alleles. The I^A allele encodes the **A** blood group antigen, **IB** encodes **B**, and **i** encodes **O**. Both **A** and **B** are dominant to **O**. If a heterozygous blood type **A** parent (I^Ai) and a heterozygous blood type **B** parent (I^Bi) mate, one-quarter of their offspring are expected to have the AB blood type (I^AI^B) in which both antigens are expressed equally. Therefore, ABO blood groups are an example of:
a. multiple alleles and incomplete dominance.
b. codominance and incomplete dominance.
c. incomplete dominance only.
d. multiple alleles and codominance.

9. In a cross between a homozygous red-eyed female fruit fly and a white-eyed male fruit fly, what is the expected outcome?
a. all white-eyed male offspring.
b. all white-eyed female offspring.
c. all red-eyed offspring.
d. half white-eyed make offspring.

10. When a population has a gene with four alleles circulating, how many possible genotypes are there?
a. 3.
b. 6.
c. 10.
d. 16.

CRITICAL THINKING QUESTIONS:

11. Describe one of the reasons that made the garden pea an excellent choice of a model system for studying inheritance.

12. Use a **Punnett square** to predict the offspring in a cross between a dwarf pea plant (homozygous recessive) and a tall pea plant (heterozygous). What is the phenotypic ratio of the offspring?

13. Use a **Punnett square** to predict the offspring in a cross between a tall pea plant (heterozygous) and a tall pea plant (heterozygous). What is the genotypic ratio of the offspring?

14. Can a male be a carrier of red-green color blindness?

15. Could an individual with blood type **O** (genotype **ii**) be a legitimate child of parents in which one parent had blood type **A** and the other parent had blood type **B**?

MOLECULAR BIOLOGY

MOLECULAR BIOLOGY

Chapter Outline

9.1: The Structure of DNA

9.2: DNA Replication

9.3: Transcription

9.4: Translation

9.5: How Genes Are Regulated

Introduction

The three letters "**DNA**" have now become associated with **crime solving, paternity testing, human identification,** and **genetic testing**. **DNA** can be retrieved from hair, blood, or saliva. Except for identical twins, each person's **DNA** is unique and it is possible to detect differences between human beings based on their unique **DNA sequence**.

DNA analysis has many practical applications beyond forensics and paternity testing. **DNA** testing is used for tracing genealogy and identifying pathogens. In the medical field, **DNA** is used in diagnostics, new vaccine development, and cancer therapy. It is now possible to determine **predisposition** to many diseases by analyzing genes.

DNA is the genetic material passed from parent to offspring for all life on Earth. The technology of molecular genetics developed in the last half-century has enabled us to see deep into the history of life to deduce the relationships between living things in ways never thought possible. It also allows us to understand the workings of evolution in populations of organisms. Over a thousand species have had their entire genome sequenced, and there have been thousands of individual human genome sequences completed. These sequences will allow us to understand human disease and the relationship of humans to the rest of the tree of life. Finally, molecular genetics techniques have revolutionized plant and animal breeding for human agricultural needs. All of these advances in biotechnology depended on basic research leading to the discovery of the structure of **DNA** in 1953, and the research since then has uncovered the details of **DNA** replication and the complex process leading to the expression of **DNA** in the form of proteins in the cell.

▪ The Structure of DNA

By the end of this section, you will be able to:

- Describe the structure of DNA
- Describe how eukaryotic and prokaryotic DNA is arranged in the cell

In the 1950s, **Francis Crick** and **James Watson** worked together at the University of **Cambridge**, **England**, to determine the structure of **DNA**. Other scientists, such as **Linus Pauling** and **Maurice Wilkins**, were also actively exploring this field. **Pauling** discovered the secondary structure of proteins using X-ray crystallography. **X-ray crystallography** is a method for investigating molecular structure by observing the patterns formed by X-rays shot through a crystal of the substance. The patterns give important information about the structure of the molecule of interest. In **Wilkins'** lab, researcher **Rosalind Franklin** was using X-ray crystallography to understand the structure of DNA. **Watson** and **Crick** were able to piece together the puzzle of the **DNA** molecule using **Franklin's** data (**Figure 2.1**). **Watson** and **Crick** also had key pieces of information available from other researchers such as **Chargaff's** rules. **Chargaff** had shown that of the four kinds of monomers (nucleotides) present in a **DNA** molecule, two types were always present in equal amounts and the remaining two types were also always present in equal amounts. This meant they were always paired in some way. In 1962, **James Watson, Francis Crick**, and **Maurice Wilkins** were awarded the **Nobel Prize** in Medicine for their work in determining the structure of **DNA**.

Now let's consider the structure of the two types of nucleic acids, **deoxyribonucleic acid** (**DNA**) and **ribonucleic acid** (**RNA**). The building blocks of DNA are nucleotides, which are made up of three parts: deoxyribose (5-carbon sugar), a phosphate group, and a nitrogenous base (**Figure 2.2**). There are four types of nitrogenous bases in DNA. **Adenine** (**A**) and **guanine**

(**G**) are double-ringed **purines**, and **cytosine** (**C**) and **thymine** (**T**) are smaller, single-ringed **pyrimidines**. The nucleotide is named according to the nitrogenous base it contains.

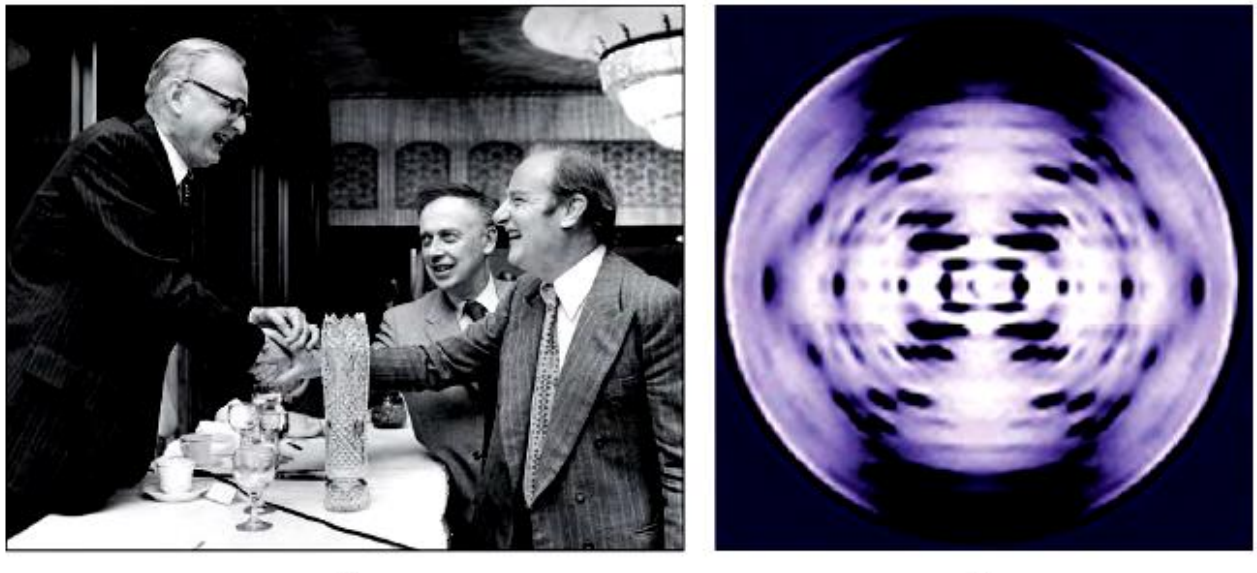
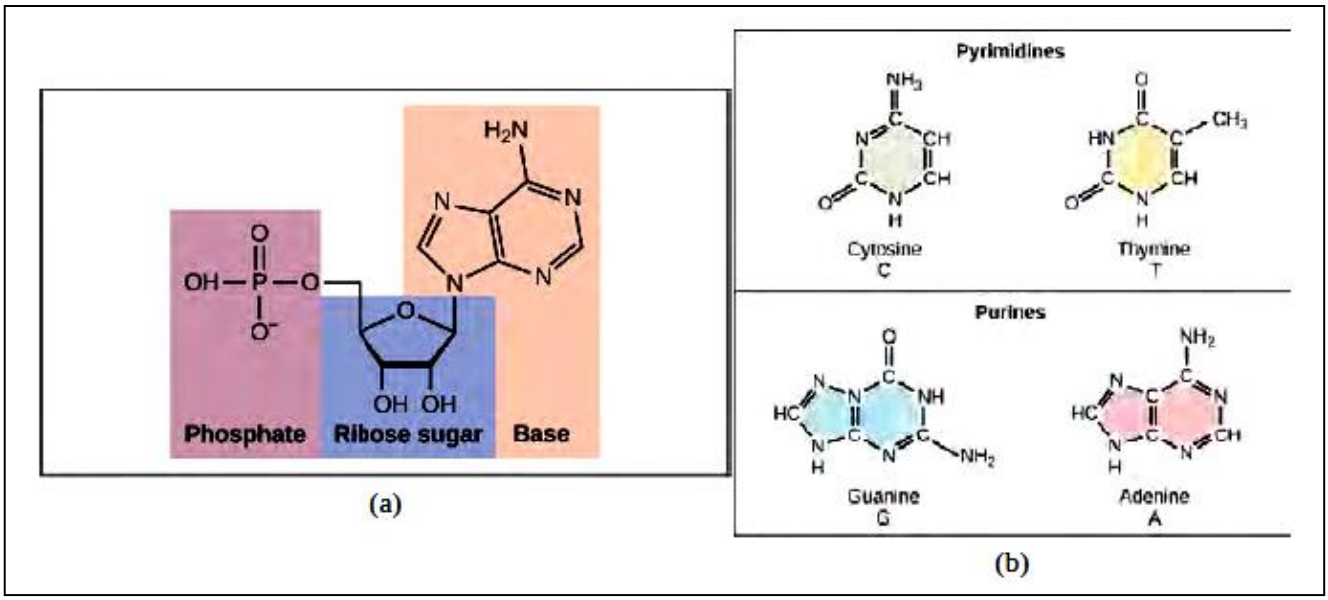


Figure 2.1: Pioneering scientists (a) **James Watson** and **Francis Crick** are pictured here with American geneticist **Maclyn McCarty**. Scientist **Rosalind Franklin** discovered (b) the X-ray diffraction pattern of **DNA**, which helped to elucidate its double helix structure.

The phosphate group of one nucleotide bonds covalently with the sugar molecule of the next nucleotide, and so on, forming a long polymer of nucleotide monomers. The **sugar-phosphate** groups line up in a "**backbone**" for every single strand of **DNA**, and the nucleotide bases stick out from this backbone. The carbon atoms of the five-carbon sugar are numbered clockwise from the oxygen as 1', 2', 3', 4', and 5' (1' is read as "one prime"). The phosphate group is attached to the 5' carbon of one nucleotide and the 3' carbon of the next nucleotide. In its natural state, each **DNA** molecule is composed of two single strands held together along their length with hydrogen bonds between the bases.

Watson and **Crick** proposed that the **DNA** is made up of two strands that are twisted around each other to form a right-handed helix, called a double helix. Base pairing takes place between a purine and pyrimidine: namely, **A** pairs with **T**, and **G** pairs with **C**. In other words, adenine and thymine are

complementary base pairs, and cytosine and guanine are also complementary base pairs. This is the basis for **Chargaff's rule**; because of their complementarity, there is as much **adenine** as **thymine** in a **DNA** molecule and as much **guanine** as **cytosine**. **Adenine** and **thymine** are connected by two hydrogen bonds, and **cytosine** and **guanine** are connected by three hydrogen bonds. The two strands are anti-parallel in nature; that is, one strand will have the 3' carbon of the sugar in the "upward" position, whereas the other strand will have the 5' carbon in the upward position. The diameter of the **DNA**



double helix is uniform throughout because a **purine** (two rings) always pairs with a **pyrimidine** (one ring) and their combined lengths are equal. (**Figure 2.3**).

Figure 2.2: (a) Each **DNA** nucleotide is made up of sugar, a phosphate group, and a base. (b) **Cytosine** and **thymine** are pyrimidines. **Guanine** and **adenine** are purines.

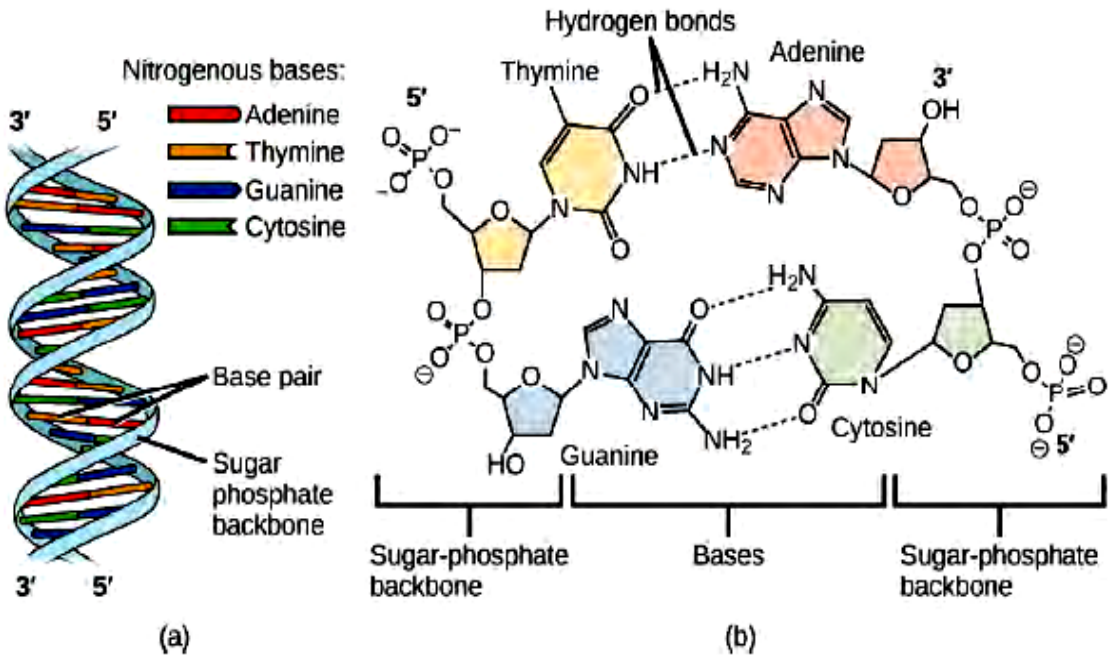


Figure 2.3: DNA (a) forms a double-stranded helix and (b) **adenine** pairs with **thymine** and **cytosine** pairs with **guanine**.

▪ The Structure of RNA

There is a second nucleic acid in all cells called ribonucleic acid, or **RNA**. Like **DNA**, **RNA** is a polymer of nucleotides. Each of the nucleotides in **RNA** is made up of a nitrogenous base, a five-carbon sugar, and a phosphate group. In the case of **RNA**, the five-carbon sugar is ribose, not deoxyribose. Ribose has a hydroxyl group at the 2' carbon, unlike deoxyribose, which has only a hydrogen atom (**Figure 2.4**).

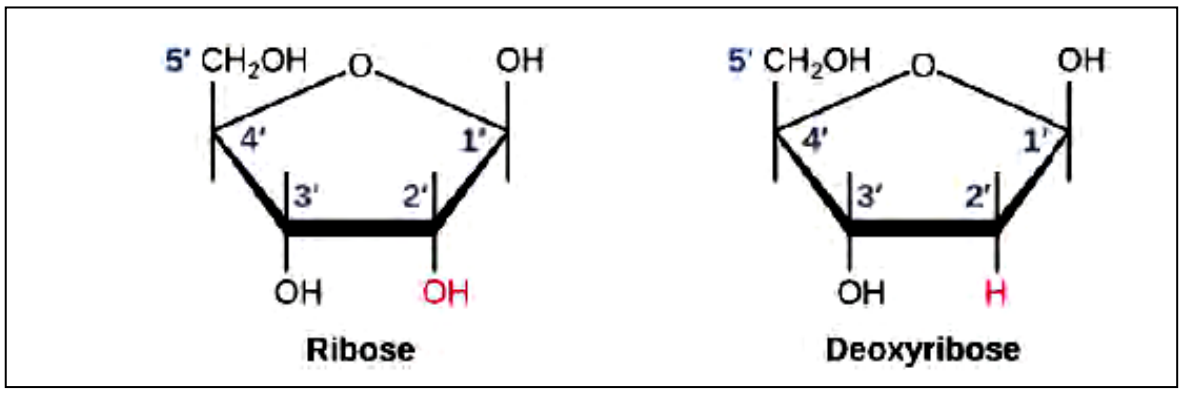


Figure 2.4: The difference between the ribose found in **RNA** and the deoxyribose found in **DNA** is that ribose has a hydroxyl group (**OH**) at the 2' carbon.

RNA nucleotides contain the nitrogenous bases **adenine, cytosine,** and **guanine**. However, they do not contain **thymine**, which is instead replaced by **uracil**, symbolized by a "**U**." **RNA** exists as a single-stranded molecule rather than a double-stranded helix. Molecular biologists have named several kinds of **RNA** based on their functions. These include messenger **RNA** (**mRNA**), transfer **RNA** (**tRNA**), and ribosomal **RNA** (**rRNA**) molecules that are involved in the production of proteins from the **DNA** code.

- **How DNA is arranged in the cell?**

DNA is a working molecule; it must be replicated when a cell is ready to divide, and it must be "read" to produce the molecules, such as proteins, to carry out the functions of the cell. For this reason, the **DNA** is protected and packaged in very specific ways. In addition, **DNA** molecules can be very long. Stretched end-to-end, the **DNA** molecules in a single human cell would come to a length of about **2 meters**. Thus, the **DNA** for a cell must be packaged in a very ordered way to fit and function within a structure (the cell) that is not visible to the naked eye. The chromosomes of prokaryotes are much simpler than those of eukaryotes in many of their features (**Figure 2.5**). Most **prokaryotes** contain a single, **circular** chromosome that is found in an area in the cytoplasm called the **nucleoid**.

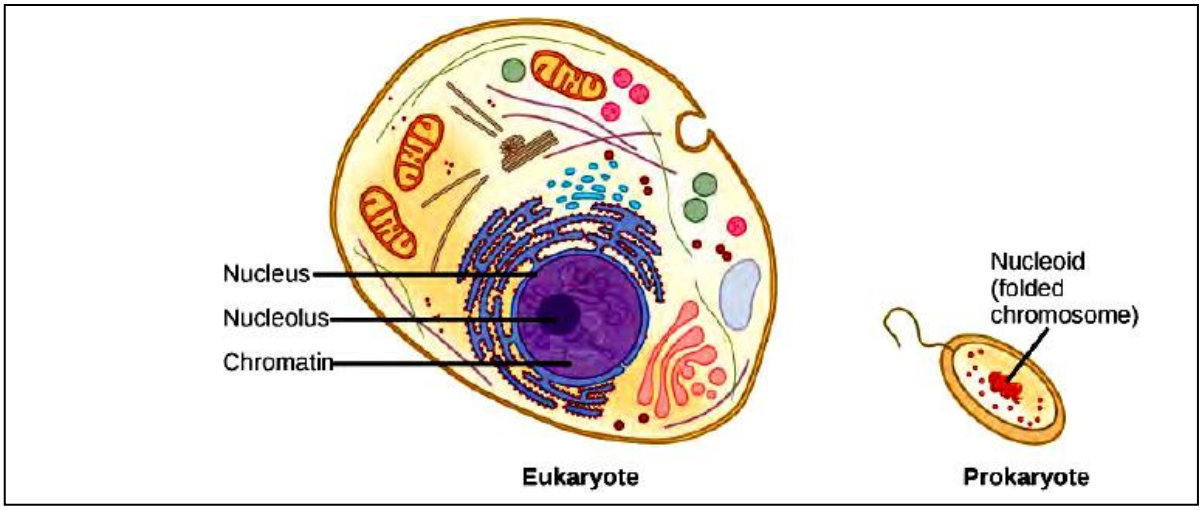


Figure 2.5: A eukaryote contains a well-defined nucleus, whereas, in prokaryotes, the chromosome lies in the cytoplasm in an area called the **nucleoid**.

The size of the genome in one of the most well-studied prokaryotes, ***Escherichia coli***, is 4.6 million base pairs, which would extend a distance of about 1.6 mm if stretched out. So **how does this fit inside a small bacterial cell?** The **DNA** is twisted beyond the double helix in what is known as supercoiling. Some proteins are known to be involved in the **supercoiling**; other proteins and enzymes help in maintaining the supercoiled structure.

Eukaryotes, whose chromosomes each consist of a linear **DNA** molecule, employ a different type of packing strategy to fit their **DNA** inside the nucleus (Figure 9.7). At the most basic level, **DNA** is wrapped around proteins known as histones to form structures called nucleosomes. The **DNA** is wrapped tightly around the histone core. This nucleosome is linked to the next one by a short strand of **DNA** that is free of histones. This is also known as the "**beads on a string**" structure; the **nucleosomes** are the "**beads**" and the short lengths of **DNA** between them are the "string." The nucleosomes, with their **DNA** coiled around them, stack compactly onto each other to
form a **30-nm** wide fiber. This fiber is further coiled into a thicker and more compact structure. At the **metaphase stage** of mitosis, when the chromosomes are lined up in the center of the cell, the chromosomes are at their most compacted. They are approximately **700 nm** in width and are found in association with scaffold proteins.

In interphase, the phase of the cell cycle between mitoses at which the chromosomes are decondensed, eukaryotic chromosomes have two distinct regions that can be distinguished by staining. There is a tightly packaged region that stains darkly and a less dense region. The darkly staining regions usually contain genes that are not active and are found in the regions of the centromere and telomeres. The lightly staining regions usually contain genes that are active, with DNA packaged around nucleosomes but not further compacted.

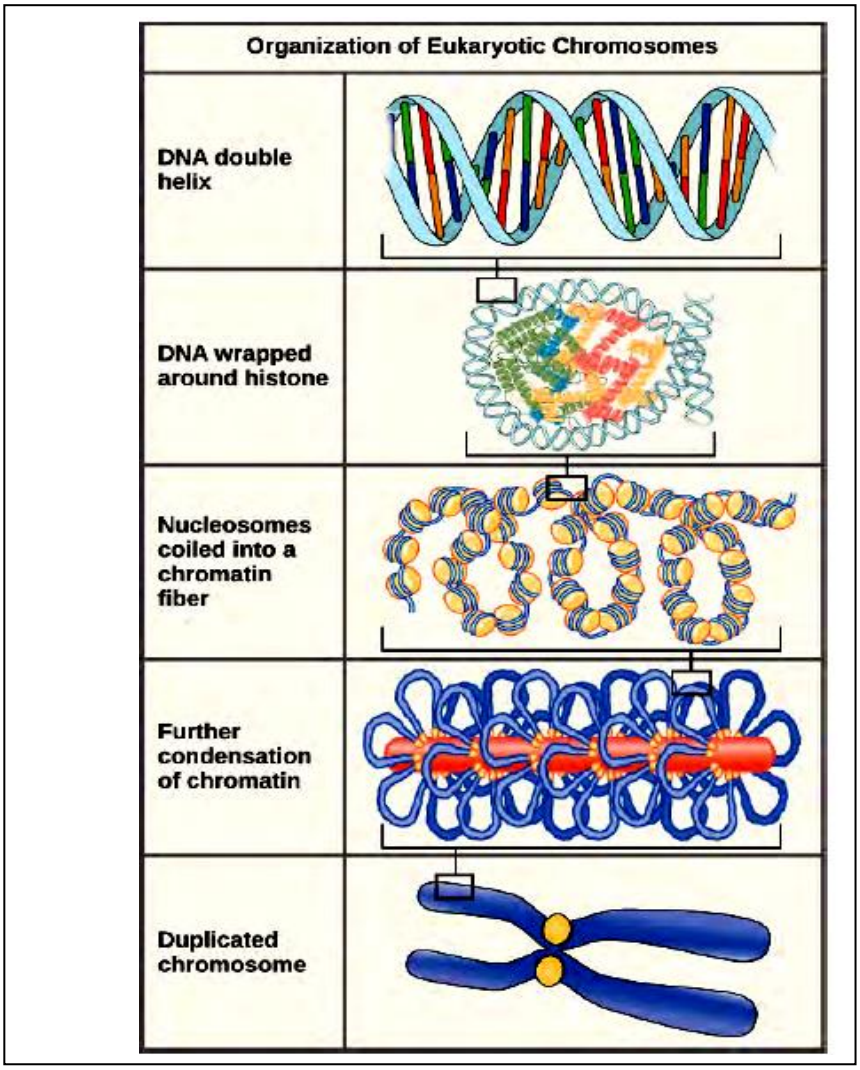


Figure 2.6: These figures illustrate the compaction of the eukaryotic chromosome.

- **DNA Replication**:

By the end of this section, you will be able to:

- Explain the process of DNA replication
- Explain the importance of telomerase to DNA replication
- Describe mechanisms of DNA repair

When a cell divides, each daughter cell must receive an identical copy of the **DNA**. This is accomplished by the process of **DNA** replication. The replication of **DNA** occurs during the **synthesis** phase, or **S phase**, of the cell cycle, before the cell enters mitosis or meiosis.

The elucidation of the structure of the double helix provided a hint as to how **DNA** is copied. Recall that **adenine** nucleotides pair with **thymine** nucleotides and **cytosine** with **guanine**. This means that the two strands are complementary to each other. For example, a strand of **DNA** with a nucleotide sequence of **AGTCATGA** will have a complementary strand with the sequence **TCAGTACT** (**Figure 2.7**).

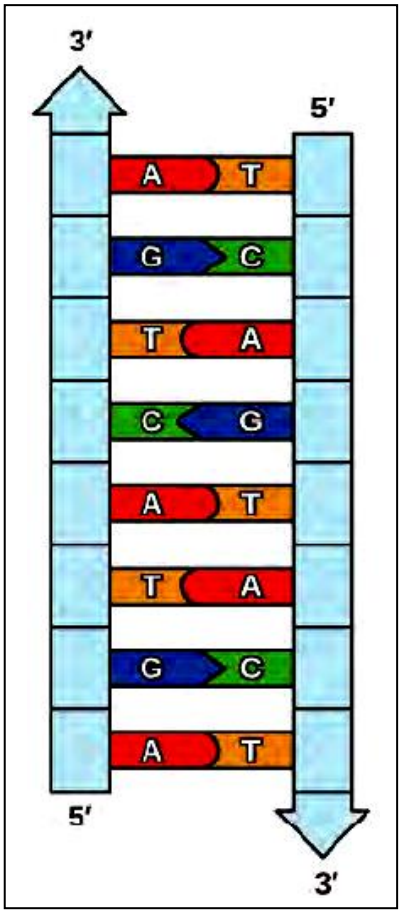


Figure 2.7: The two strands of **DNA** are complementary, meaning the sequence of bases in one strand can be used to create the correct sequence of bases in the other strand.

Because of the complementarity of the two strands, having one strand means that it is possible to recreate the other strand. This model for replication suggests that the two strands of the double helix separate during replication, and each strand serves as a template from which the **new complementary** strand is copied and called **semi-conservative replication** (**Figure 2.8**).

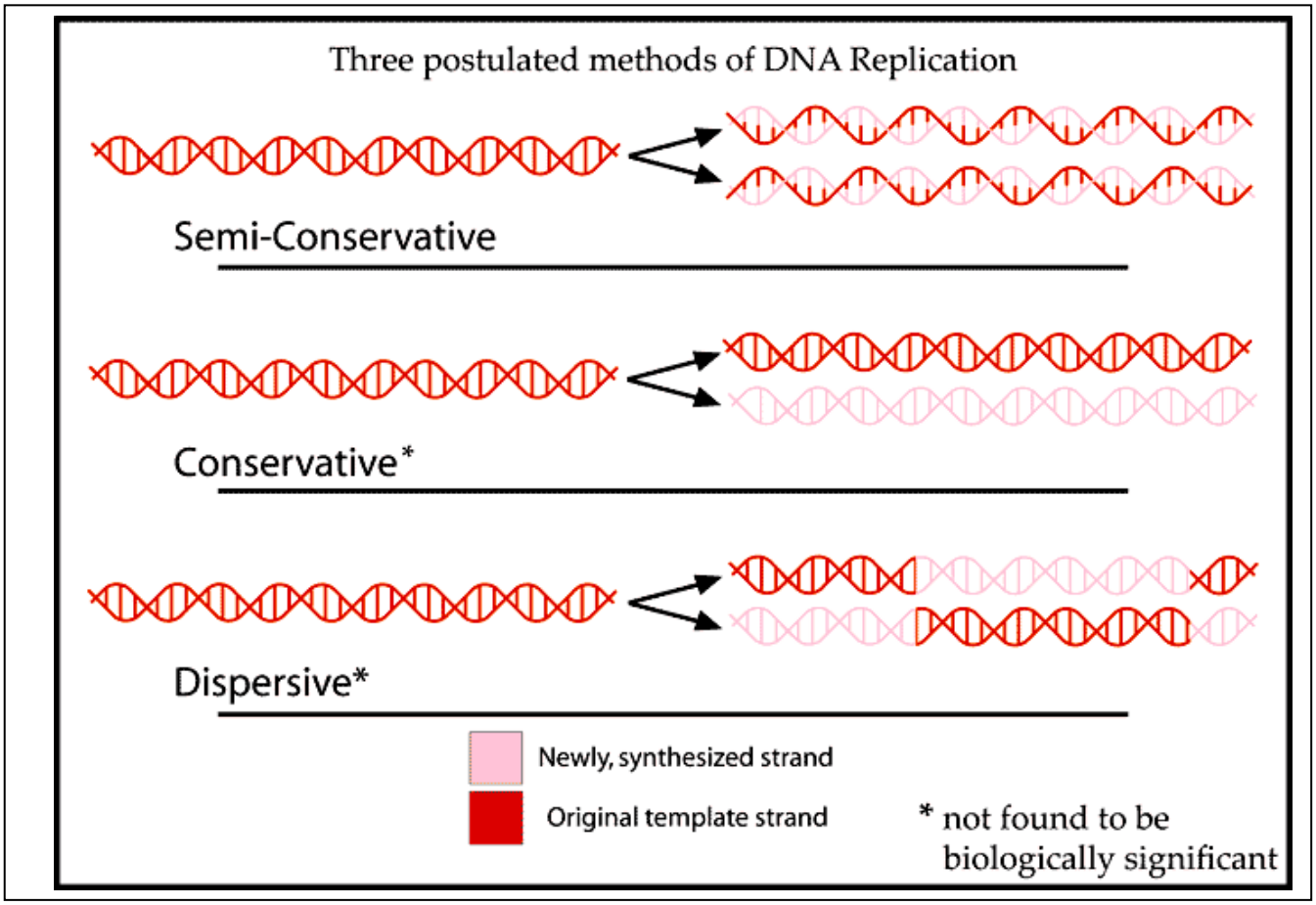


Figure 2.8: Three postulated models for **DNA** replications.

During **DNA replication**, each of the two strands that make up the double helix serves as a template from which new strands are copied. The new strand will be complementary to the parental or "old" strand. Each new double strand consists of one parental strand and one new daughter strand. This is known as **semiconservative replication**. When two **DNA** copies are formed, they have an identical sequence of nucleotide bases and are divided equally into two daughter cells.

DNA Replication in Eukaryotes

Because eukaryotic genomes are very complex, **DNA** replication is a very complicated process that involves several enzymes and other proteins. It occurs in three main stages: initiation, elongation, and termination.

Recall that eukaryotic **DNA** is bound to proteins known as histones to form structures called **nucleosomes**. During initiation, the **DNA** is made accessible to the proteins and enzymes involved in the replication process. **How does the replication machinery know where on the DNA double helix to begin?**

It turns out that there are specific nucleotide sequences called **origins of replication** at which replication begins. Certain proteins bind to the origin of replication while an enzyme called **helicase** unwinds and opens up the **DNA** helix. As the **DNA** opens up, **Y-shaped** structures called **replication forks** are formed (**Figure 2.9**). Two replication forks are formed at the origin of replication, and these get extended in both directions as replication proceeds. There are multiple origins of replication on the eukaryotic chromosome, such that replication can occur simultaneously from several places in the genome.

During elongation, an enzyme called **DNA polymerase** adds **DNA** nucleotides to the 3' end of the template. Because DNA polymerase can only add new nucleotides at the end of a backbone, a **primer** sequence, which provides this starting point, is added with complementary RNA nucleotides. This primer is removed later, and the nucleotides are replaced with DNA nucleotides. One strand, which is complementary to the parental DNA strand, is synthesized continuously toward the replication fork so the polymerase can add nucleotides in this direction. This continuously synthesized strand is known as the **leading strand**. Because DNA polymerase can only synthesize DNA in a 5' to 3' direction, the other new strand is put together in short pieces called **Okazaki fragments**. The Okazaki fragments each require a primer made of RNA to start

the synthesis. The strand with the Okazaki fragments is known as the **lagging strand**. As synthesis proceeds, an enzyme removes the RNA primer, which is then replaced with DNA nucleotides, and the gaps between fragments are sealed by an enzyme called **DNA ligase**.

The process of DNA replication can be summarized as follows:

1. **DNA** unwinds at the origin of replication.
2. New bases are added to the complementary parental strands. One new strand is made continuously, while the other strand is made in pieces.
3. Primers are removed, new **DNA** nucleotides are put in place of the primers and the backbone is sealed by **DNA ligase**.

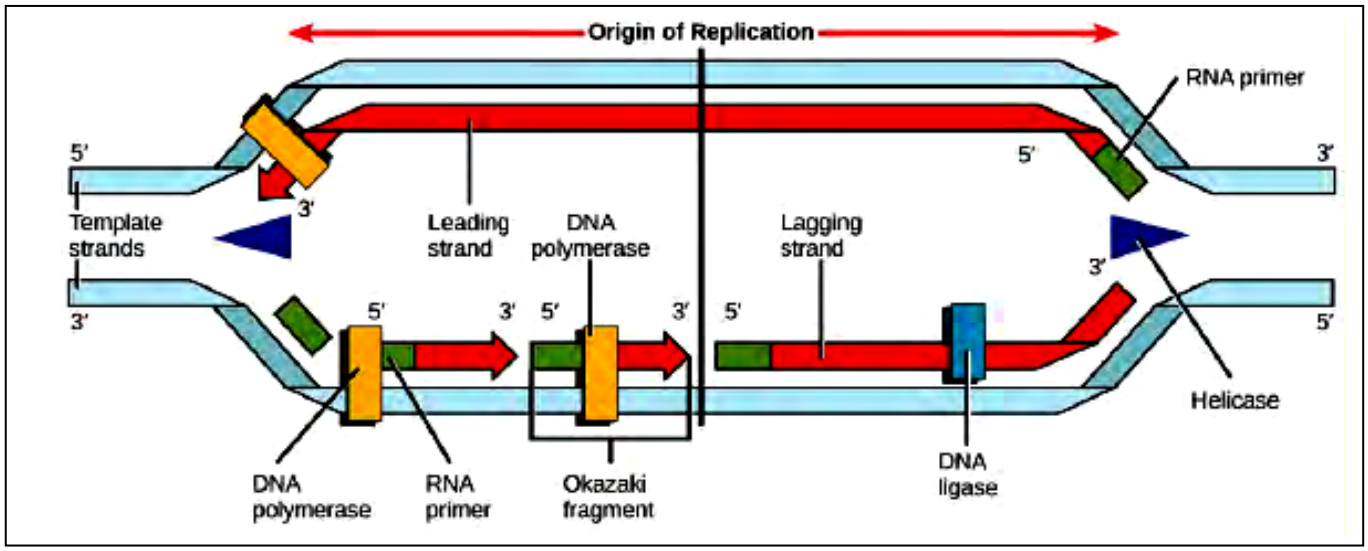


Figure 2.9: A replication fork is formed by the opening of the origin of replication, and helicase separates the **DNA** strands. An **RNA** primer is synthesized and elongated by the **DNA** polymerase. On the **leading strand**, **DNA** is synthesized continuously, whereas, on the **lagging strand**, **DNA** is synthesized in short stretches. The **DNA** fragments are joined by **DNA ligase** as shown.

You isolate a cell strain in which the joining together of **Okazaki** fragments is impaired and suspect that a mutation has occurred in an enzyme found at the replication fork. **Which enzyme is most likely to be mutated?**

- ***Telomere Replication***

Because eukaryotic chromosomes are linear, **DNA** replication comes to the end of a line in eukaryotic chromosomes. As you have learned, the **DNA** polymerase enzyme can add nucleotides in only one direction. In the **leading strand**, synthesis continues until the end of the chromosome is reached; however, on the lagging strand, there is no place for a primer to be made for the **DNA** fragment to be copied at the end of the chromosome. This presents a problem for the cell because the ends remain unpaired, and over time these ends get progressively shorter as cells continue to divide. The ends of the linear chromosomes are known as **telomeres,** which have repetitive sequences that do not code for a particular gene. As a consequence, it is **telomeres** that are shortened with each round of **DNA** replication instead of genes. For example, in humans, a six base-pair sequence, **5'-TTAGGG-3'**, is repeated 100 to 1000 times.

The discovery of the enzyme telomerase (**Figure 2.10**) helped in the understanding of how chromosome ends are maintained. The telomerase attaches to the end of the chromosome, and complementary bases to the **RNA** template are added to the end of the **DNA** strand. Once the lagging strand template is sufficiently elongated, **DNA** polymerase can now add nucleotides that are complementary to the ends of the chromosomes. Thus, the ends of the chromosomes are replicated.

In human cells, the last **RNA primer** of the lagging strand may be positioned as much as **70 to 100 nucleotides** away from the chromosome end. Thus, the single-stranded overhangs produced by incomplete end replication in humans are fairly long, and the chromosome shortens significantly with each round of cell division.

Telomerase is typically found to be active in germ cells, adult stem cells, and some cancer cells. For her discovery of telomerase and its action, **Elizabeth Blackburn** (**Figure 2.11**) received the **Nobel Prize** for Medicine and Physiology in **2009**.

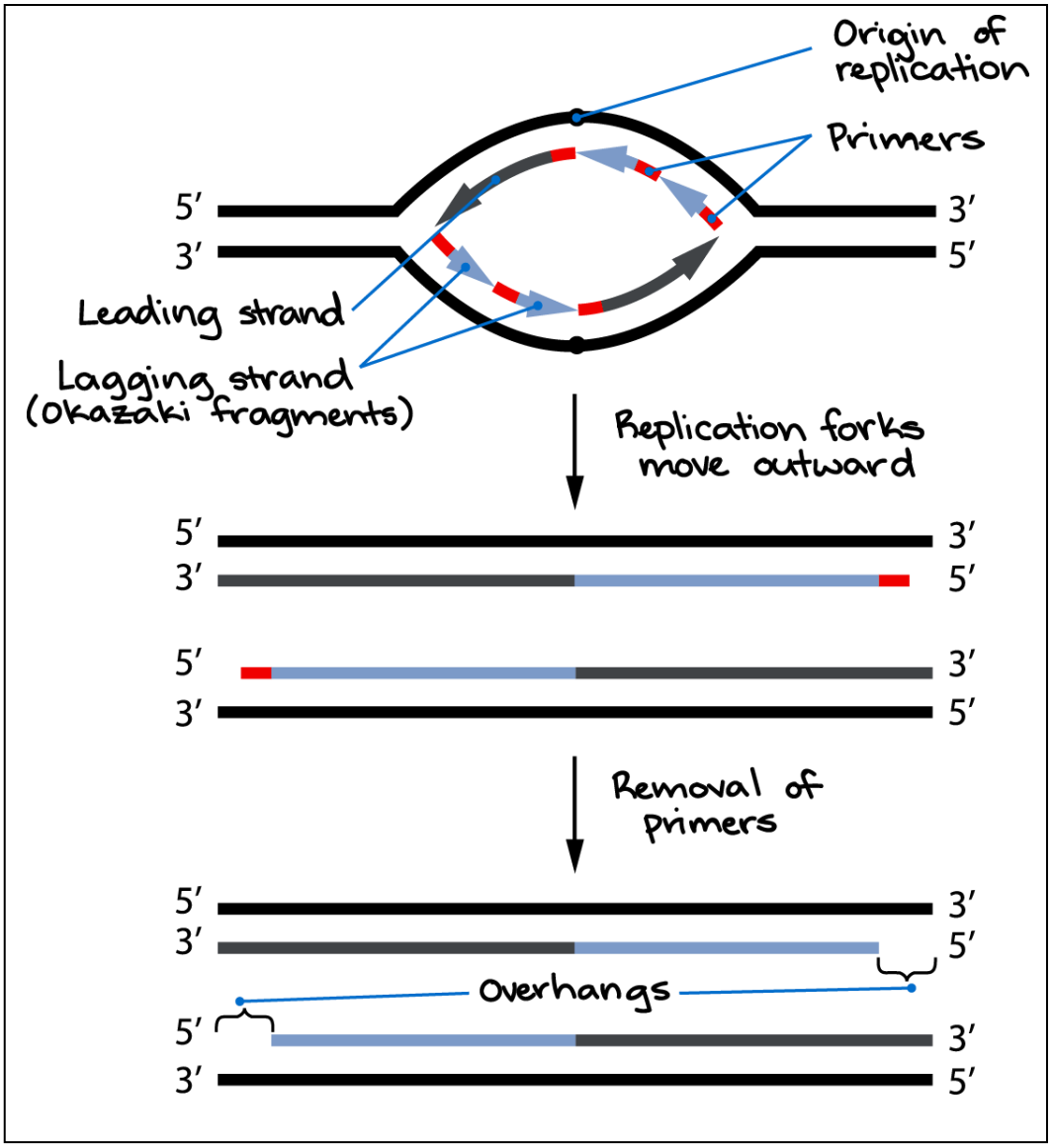


Figure 2.10: A real eukaryotic chromosome would have multiple origins of replication and multiple replication bubbles, but the end-replication problem would be the same as shown above "**Telomere shortening**".

Figure 2.11: Elizabeth Blackburn, 2009 **Nobel Laureate**, was the scientist who discovered how telomerase works.

Telomerase is not active in adult somatic cells. Adult somatic cells that undergo cell division continue to have their telomeres shortened. This essentially means that telomere shortening is associated with aging. In 2010, scientists found that telomerase can reverse some age-related conditions in mice, and this may have potential in regenerative medicine. **Telomerase**-deficient mice were used in these studies; these mice have tissue atrophy, stem-cell depletion, organ system failure, and impaired tissue injury responses. **Telomerase** reactivation in these mice caused the extension of telomeres, reduced **DNA** damage, reversed neurodegeneration, and improved the functioning of the testes, spleen, and intestines. Thus, **telomere reactivation** may have the potential for treating age-related diseases in humans.

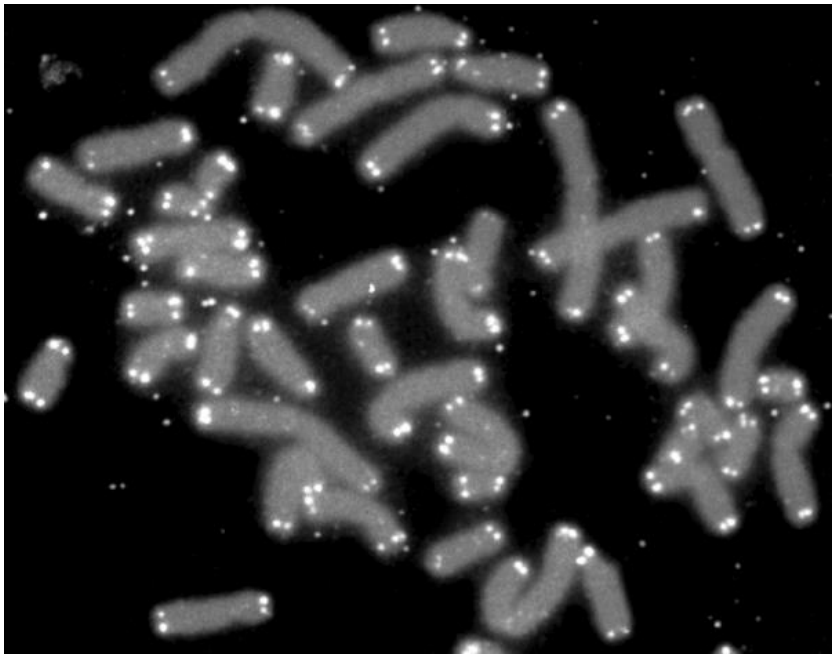


Figure 2.12: Telomeres appear as the bright spots at the ends of each chromosome in the picture shown above as "**Telomere caps**".

- ***DNA Replication in Prokaryotes***

Recall that the prokaryotic chromosome is a circular molecule with a less extensive coiling structure than eukaryotic chromosomes. The eukaryotic chromosome is linear and highly coiled around proteins. While there are many similarities in the **DNA** replication process, these structural differences necessitate some differences in the **DNA** replication process in these two life forms.

DNA replication has been extremely well-studied in prokaryotes, primarily because of the small size of the genome and a large number of variants available. ***Escherichia coli*** has 4.6 million base pairs in a single circular chromosome, and all of it gets replicated in approximately 42 minutes, starting from a single origin of replication and proceeding around the chromosome in both directions. This means that approximately 1000 nucleotides are added per second. The process is much more rapid than in eukaryotes. **Table 2.1** summarizes the differences between prokaryotic and eukaryotic replications.

Differences between Prokaryotic and Eukaryotic Replications

Property	Prokaryotes	Eukaryotes
Origin of replication	Single	Multiple
Rate of replication	1000 nucleotides/s	50 to 100 nucleotides/s
Chromosome structure	circular	linear
Telomerase	Not present	Present

Table 2.1

❖ DNA Repair

DNA polymerase can make mistakes while adding nucleotides. It edits the **DNA** by proofreading every newly added base. Incorrect bases are removed and replaced by the correct base, and then polymerization continues (**Figure 2.13a**). Most mistakes are corrected during replication, although when this does not happen, the **mismatch repair** mechanism is employed. **Mismatch repair** enzymes recognize the wrongly incorporated base and excise it from the **DNA**, replacing it with the correct base (**Figure 2.13b**). In yet another type of repair, **nucleotide excision repair**, the **DNA** double-strand is unwound and separated, the incorrect bases are removed along with a few bases on the **5'** and **3'** end, and these are replaced by copying the template with the help of **DNA polymerase** (**Figure 2.13c**). Nucleotide excision repair is particularly important in correcting **thymine dimers**, which are primarily caused by **UV** (ultraviolet) light. In a thymine dimer, two thymine nucleotides adjacent to each other on one strand are covalently bonded to each other rather than their complementary bases. If the **dimer** is not removed and repaired it will lead to a **mutation**. Individuals with flaws in their **nucleotide excision repair genes** show extreme sensitivity to sunlight and develop skin cancers early in life.

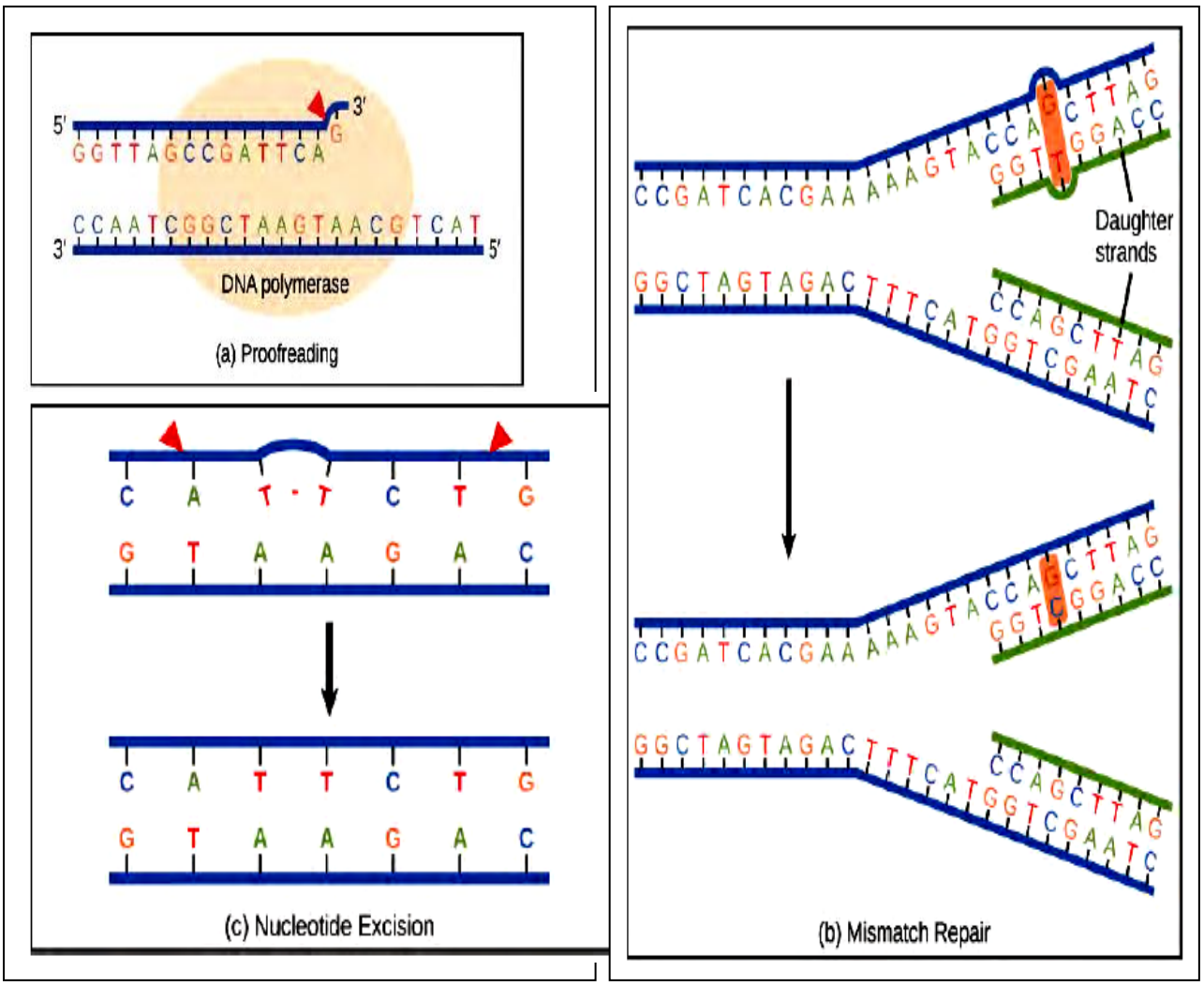


Figure 2.13: **Proofreading** by **DNA polymerase (a)** corrects errors during replication. In **mismatch repair (b),** the incorrectly added base is detected after replication. The mismatch repair proteins detect this base and remove it from the newly synthesized strand by nuclease action. The gap is now filled with the correctly paired base. **Nucleotide excision (c)** repairs **thymine dimers**. When exposed to **UV**, **thymines** lying adjacent to each other can form thymine dimers. In normal cells, they are excised and replaced.

Most mistakes are corrected; if they are not, they may result in a mutation defined as a permanent change in the **DNA** sequence. Mutations in **repair genes** may lead to serious consequences like **cancer**.

- **Transcription**:

By the end of this section, you will be able to:

- Explain the central dogma
- Explain the main steps of transcription
- Describe how eukaryotic mRNA is processed

In both prokaryotes and eukaryotes, the second function of **DNA** (the first was replication) is to provide the information needed to construct the proteins necessary so that the cell can perform all of its functions.

To do this, the **DNA** is "read" or transcribed into an **mRNA** molecule. The **mRNA** then provides the code to form a protein by a process called translation. Through the processes of **transcription** and **translation**, a **protein** is built with a specific sequence of amino acids that was originally encoded in the **DNA**. This module discusses the details of **transcription**.

❖ The Central Dogma: DNA Encodes RNA; RNA Encodes Protein

The flow of genetic information in cells from **DNA** to **mRNA** to **protein** is described by the **central dogma** (**Figure 2.14**), which states that genes specify the sequences of **mRNAs**, which in turn specify the sequences of proteins.

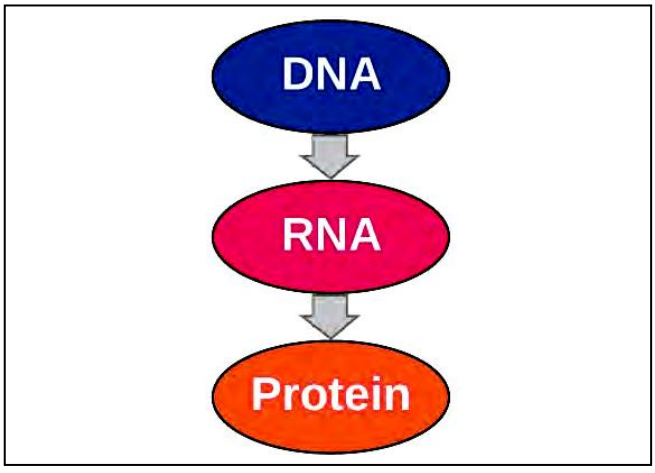


Figure 2.14: The central dogma states that **DNA** encodes **RNA**, which in turn encodes **protein**.

The copying of **DNA** to **mRNA** is relatively straightforward, with one nucleotide being added to the **mRNA** strand for every complementary nucleotide read in the **DNA** strand. The protein translation is more complex because groups of three **mRNA** nucleotides correspond to one amino acid of the protein sequence. However, as we shall see in the next module, the protein translation is still systematic, such that nucleotides 1 to 3 correspond to amino acid 1, nucleotides 4 to 6 correspond to amino acid 2, and so on.

❖ Transcription: from DNA to mRNA

Both prokaryotes and eukaryotes perform fundamentally the same process of **transcription**, with the important difference of the membrane-bound nucleus in eukaryotes. With the genes bound in the nucleus, transcription occurs in the nucleus of the cell and the **mRNA** transcript must be transported to the cytoplasm. The prokaryotes, which include **bacteria** and **archaea**, lack membrane-bound nuclei and other organelles, and **transcription** occurs in the cytoplasm of the cell. In both prokaryotes and eukaryotes, transcription occurs in three main stages: **initiation, elongation,** and **termination.**

1. Initiation:

Transcription requires the **DNA** double helix to partially unwind in the region of **mRNA** synthesis. The region of unwinding is called a **transcription bubble**. The **DNA** sequence onto which the proteins and enzymes involved in **transcription** bind to initiate the process is called a **promoter**. In most cases, **promoters** exist upstream of the genes they regulate. The specific sequence of a **promoter** is very important because it determines whether the corresponding gene is transcribed all of the time, some of the time, or hardly at all (**Figure 2.15**).

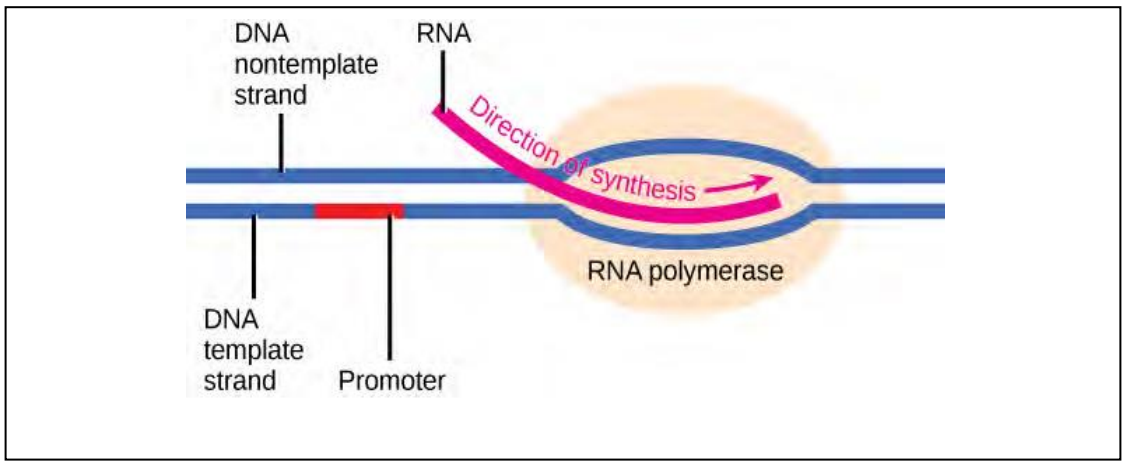


Figure 2.15: The initiation of **transcription** begins when **DNA** is unwound, forming a **transcription bubble**. Enzymes and other proteins involved in **transcription** bind at the **promoter**.

2. Elongation

Transcription always proceeds from one of the two **DNA** strands, which is called the **template strand**. The **mRNA** product is complementary to the template strand and is almost identical to the other **DNA** strand, called the **nontemplate strand**, with the exception that **RNA** contains a uracil (**U**) in place of the thymine (**T**) found in **DNA**. During **elongation**, an enzyme called **RNA polymerase** proceeds along the **DNA** template adding nucleotides by base pairing with the **DNA** template in a manner similar to **DNA** replication, with the difference that an **RNA** strand is being synthesized that does not remain bound to the **DNA** template. As elongation proceeds, the **DNA** is continuously unwound ahead of the core enzyme and rewound behindit(**Figure2.16**).

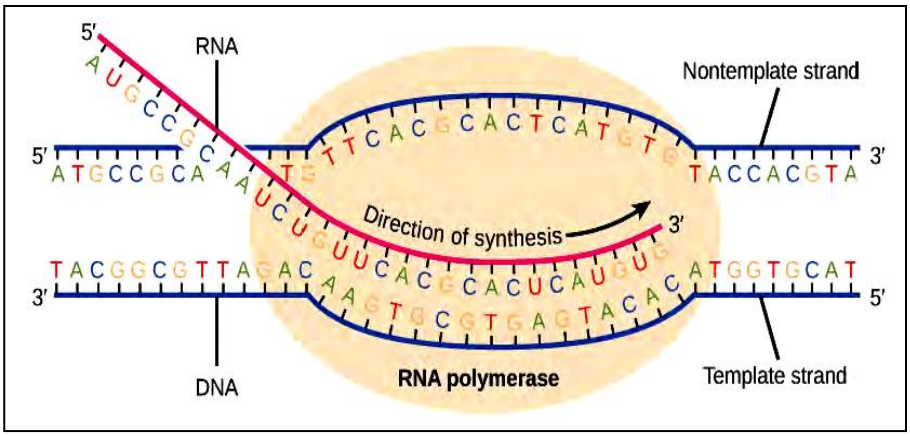


Figure 2.16: During **elongation**, **RNA** polymerase tracks along the **DNA** template, synthesizes **mRNA** in the **5' → 3'** direction, and unwinds then rewinds the **DNA** as it is read.

3. Termination

Once a gene is transcribed, the prokaryotic polymerase needs to be instructed to dissociate from the **DNA** template and liberate the newly made **mRNA**. Depending on the gene being transcribed, there are two kinds of termination signals, but both involve repeated nucleotide sequences in the **DNA** template that result in **RNA** polymerase stalling, leaving the **DNA** template, and freeing the **mRNA** transcript.

On **termination**, the process of **transcription** is complete. In a prokaryotic cell, by the time **termination** occurs, the transcript would already have been used to partially synthesize numerous copies of the encoded protein because these processes can occur concurrently using multiple ribosomes (polyribosomes) (**Figure 2.17**). In contrast, the presence of a nucleus in eukaryotic cells precludes simultaneous **transcription** and **translation**.

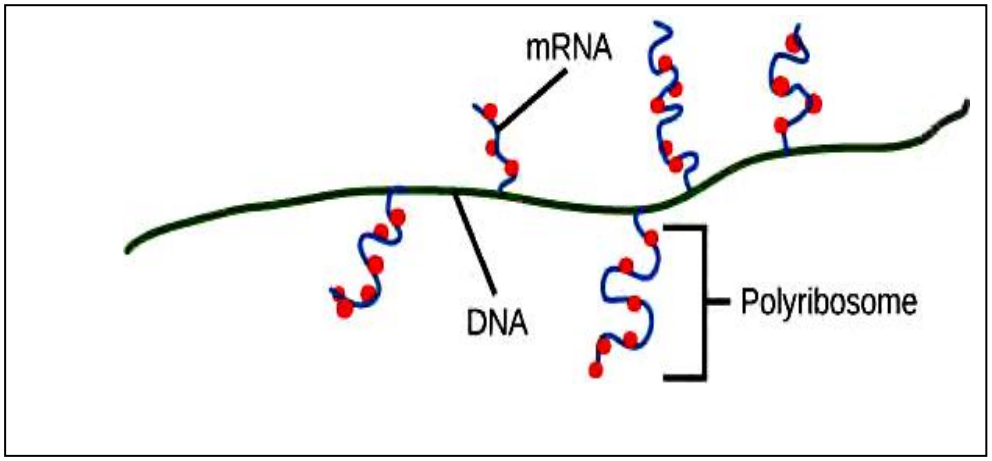


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Figure 2.17: Multiple polymerases can transcribe a single bacterial gene while numerous ribosomes concurrently translate the **mRNA** transcripts into polypeptides. In this way, a specific protein can rapidly reach a high concentration in the bacterial cell

Eukaryotic RNA Processing

The newly transcribed eukaryotic **mRNAs** must undergo several processing steps before they can be transferred from the nucleus to the cytoplasm and translated into a protein. The additional steps involved in **eukaryotic mRNA** maturation create a molecule that is much more stable than a **prokaryotic mRNA**. For example, **eukaryotic mRNAs** last for several hours, whereas the typical **prokaryotic mRNA** lasts no more than five seconds. The **mRNA** transcript is first coated in **RNA-stabilizing proteins** to prevent it from degrading while it is processed and exported out of the nucleus. This occurs while the **pre-mRNA** still is being synthesized by adding a special nucleotide "**cap**" to the **5' end** of the growing transcript. In addition to preventing degradation, factors involved in protein synthesis recognize the cap to help initiate **translation** by ribosomes.

Once elongation is complete, an enzyme then adds a string of approximately **200 adenine** (**A**) residues to the **3' end**, called the **poly-A tail**.

This modification further protects the **pre-mRNA** from degradation and signals to cellular factors that the transcript needs to be exported to the cytoplasm.

Eukaryotic genes are composed of protein-coding sequences called **exons** (*ex*-on signifies that they are *ex*pressed) and *int*ervening sequences called **introns** (*int*-ron denotes their *int*ervening role). **Introns** are removed from the **pre-mRNA** during processing. **Intron** sequences in **mRNA** do not encode functional proteins. All of a pre-mRNA's introns must be completely and precisely removed before protein synthesis so that the **exons** join together to code for the correct amino acids. If the process errs by even a single nucleotide, the sequence of the rejoined **exons** would be shifted, and the resulting protein would be **nonfunctional**. The process of removing **introns** and reconnecting **exons** is called **splicing** (**Figure 2.18**). **Introns** are removed and degraded while the **pre-mRNA** is still in the nucleus.

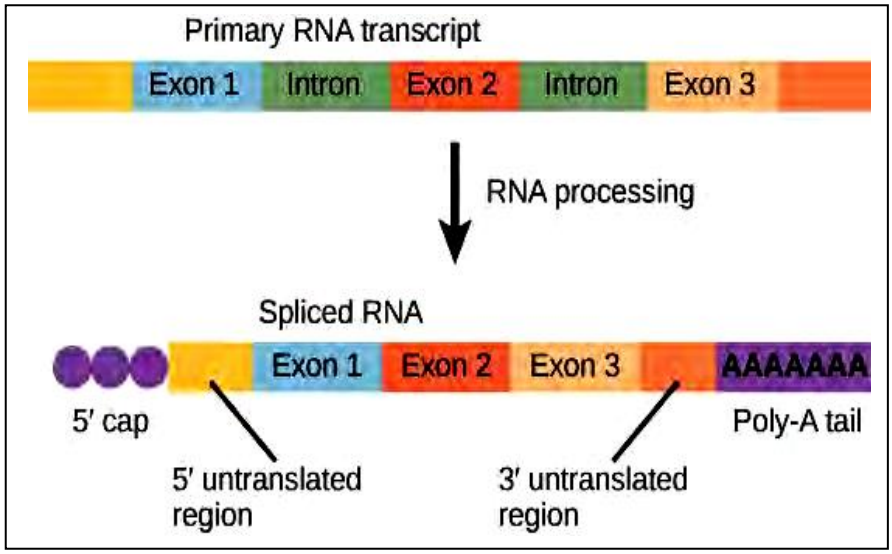


Figure 2.18: Eukaryotic **mRNA** contains **introns** that must be spliced out. A **5' cap** and **3' tail** are also added.

Translation:

By the end of this section, you will be able to:

- Describe the different steps in protein synthesis
- Discuss the role of ribosomes in protein synthesis
- Describe the genetic code and how the nucleotide sequence determines the amino acid and the protein sequence

The synthesis of proteins is one of a cell's most energy-consuming metabolic processes. In turn, proteins account for more mass than any other component of living organisms (except for water), and proteins perform a wide variety of functions of a cell. The process of **translation**, or protein synthesis, involves decoding an **mRNA** message into a polypeptide product. Amino acids are covalently strung together in lengths ranging from approximately **50** amino acids to more than **1,000**.

The Protein Synthesis Machinery

In addition to the **mRNA** template, many other molecules contribute to the process of translation. The composition of each component may vary across species; for instance, ribosomes may consist of different numbers of ribosomal **RNAs** (**rRNA**) and polypeptides depending on the organism. However, the general structures and functions of the protein synthesis machinery are comparable from bacteria to human cells. **Translation** requires the input of an **mRNA** template, ribosomes, **tRNAs**, and various enzymatic factors (**Figure 2.19**).

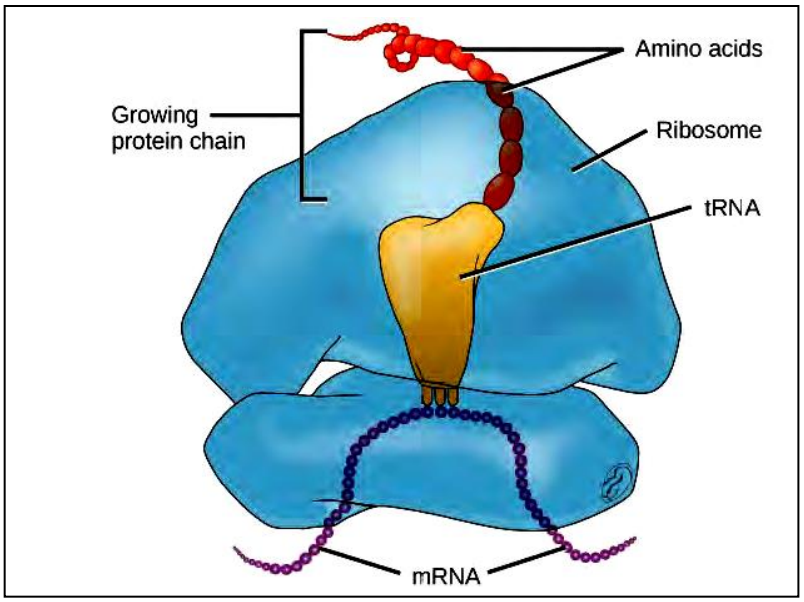


Figure 2.19: The protein synthesis machinery includes the large and small subunits of the ribosome, **mRNA**, and **tRNA**.

In ***E. coli***, there are **200,000** ribosomes present in every cell at any given time. A ribosome is a complex macromolecule composed of structural and catalytic **rRNAs** and many distinct polypeptides. In eukaryotes, the nucleolus is completely specialized for the synthesis and assembly of **rRNAs**.

Ribosomes are located in the cytoplasm of prokaryotes and the cytoplasm and endoplasmic reticulum of eukaryotes. Ribosomes are made up of a large and a small subunit that come together for translation. The small subunit is responsible for binding the **mRNA** template, whereas the large subunit sequentially binds **tRNAs**, a type of **RNA** molecule that brings amino acids to the growing chain of the polypeptide. Each **mRNA** molecule is simultaneously translated by many ribosomes, all synthesizing protein in the same direction.

Depending on the species, **40 to 60 types** of **tRNA** exist in the cytoplasm. Serving as adaptors, specific **tRNAs** bind to sequences on the

mRNA template and add the corresponding amino acid to the polypeptide chain. Therefore, **tRNAs** are the molecules that actually "**translate**" the language of **RNA** into the language of proteins. For each **tRNA** to function, it must have its specific amino acid bonded to it. In the process of **tRNA** "**charging**," each **tRNA** molecule is bonded to its correct amino acid.

The Genetic Code

To summarize what we know to this point, the cellular process of transcription generates messenger **RNA (mRNA)**, a mobile molecular copy of one or more genes with an alphabet of **A, C, G,** and **uracil** (**U**). Translation of the **mRNA** template converts nucleotide-based genetic information into a protein product. Protein sequences consist of **20** commonly occurring amino acids; therefore, it can be said that the protein alphabet consists of **20 letters**. Each amino acid is defined by a three-nucleotide sequence called the triplet codon. The relationship between a nucleotide codon and its corresponding amino acid is called the genetic code.

Given the different numbers of "letters" in the **mRNA** and protein "alphabets," combinations of nucleotides corresponded to single amino acids. Using a three-nucleotide code means that there are a total of **64** (**4 × 4 × 4**) possible combinations; therefore, a given amino acid is encoded by more than one nucleotide triplet (**Figure 2.20**).

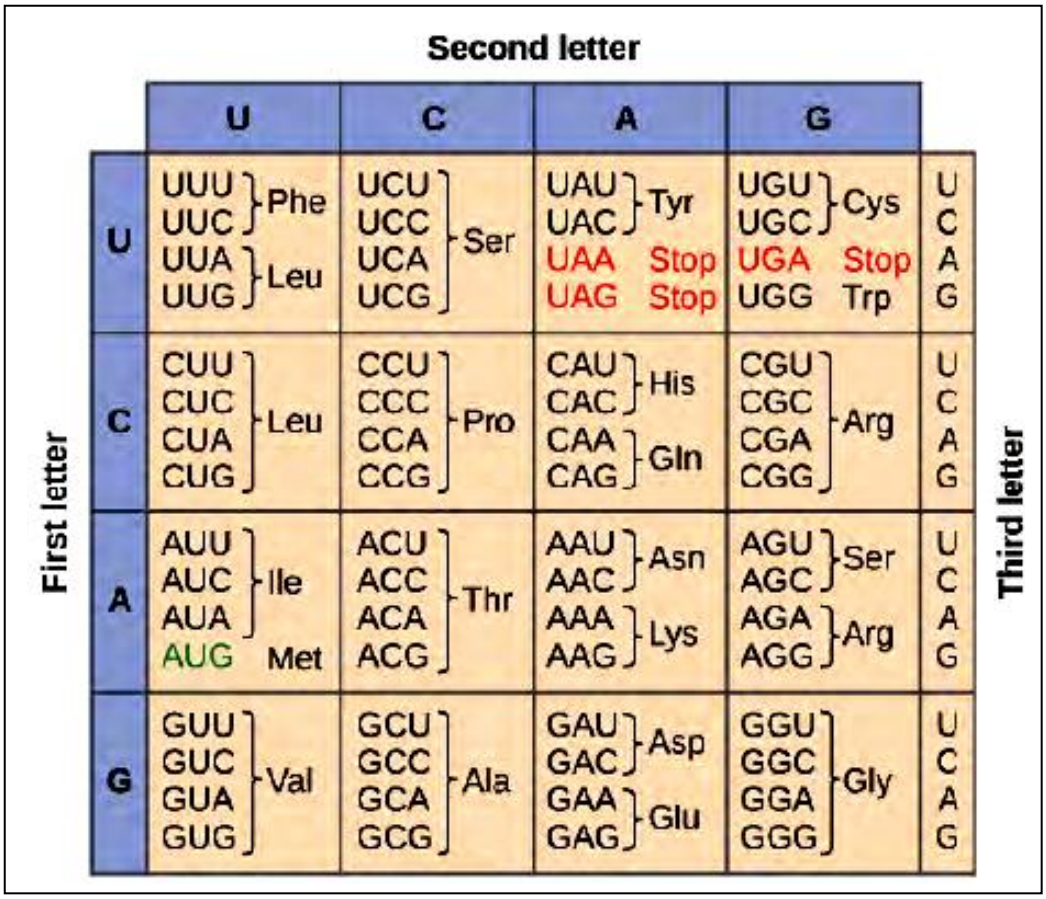


Figure 2.20: This figure shows the **genetic code** for translating each nucleotide triplet, or **codon**, in **mRNA** into an amino acid or a termination signal in a nascent protein.

Three of the **64** codons terminate protein synthesis and release the polypeptide from the translation machinery. These triplets are called **stop codons**. Another codon, **AUG**, also has a special function. In addition to specifying the amino acid **methionine (Met)**, it also serves as the **start codon** to initiate **translation**. The reading frame for translation is set by the **AUG start codon** near the **5'** end of the **mRNA**. The genetic code is **universal**. With a few exceptions, virtually all species use the same genetic code for protein synthesis, which is powerful evidence that all life on Earth shares a common origin.

❖ The Mechanism of Protein Synthesis

Just as with mRNA synthesis, protein synthesis can be divided into three phases: **initiation, elongation,** and **termination**. The process of translation is similar in prokaryotes and eukaryotes. Here we will explore how translation occurs in ***E. coli***, a representative prokaryote, and specify any differences between prokaryotic and eukaryotic translation.

Protein synthesis begins with the formation of an initiation complex. In ***E. coli***, this complex involves the small ribosome subunit, the **mRNA** template, three initiation factors, and a special initiator **tRNA**. The **initiator tRNA** interacts with the AUG start codon, and links to a special form of the amino acid methionine that is typically removed from the polypeptide after translation are complete.

In **prokaryotes** and **eukaryotes**, the basics of polypeptide elongation are the same, so we will review elongation from the perspective of ***E. coli***. The large ribosomal subunit of ***E. coli*** consists of three compartments: the **A site** binds incoming charged **tRNAs** (**tRNAs** with their attached specific amino acids). The **P site** binds charged **tRNAs** carrying amino acids that have formed bonds with the growing polypeptide chain but have not yet dissociated from their corresponding **tRNA**. The **E site** releases dissociated **tRNAs** so they can be recharged with free amino acids. The ribosome shifts one codon at a time, catalyzing each process that occurs in the three sites. With each step, a charged **tRNA** enters the complex, the polypeptide becomes one amino acid longer, and an uncharged **tRNA** departs. The energy for each bond between amino acids is derived from **GTP**, a molecule similar to **ATP** (**Figure 2.21**). Amazingly, the ***E. coli*** translation apparatus takes only 0.05 seconds to add each amino acid, meaning that a **200-amino acid polypeptide** could be translated in just **10** seconds.

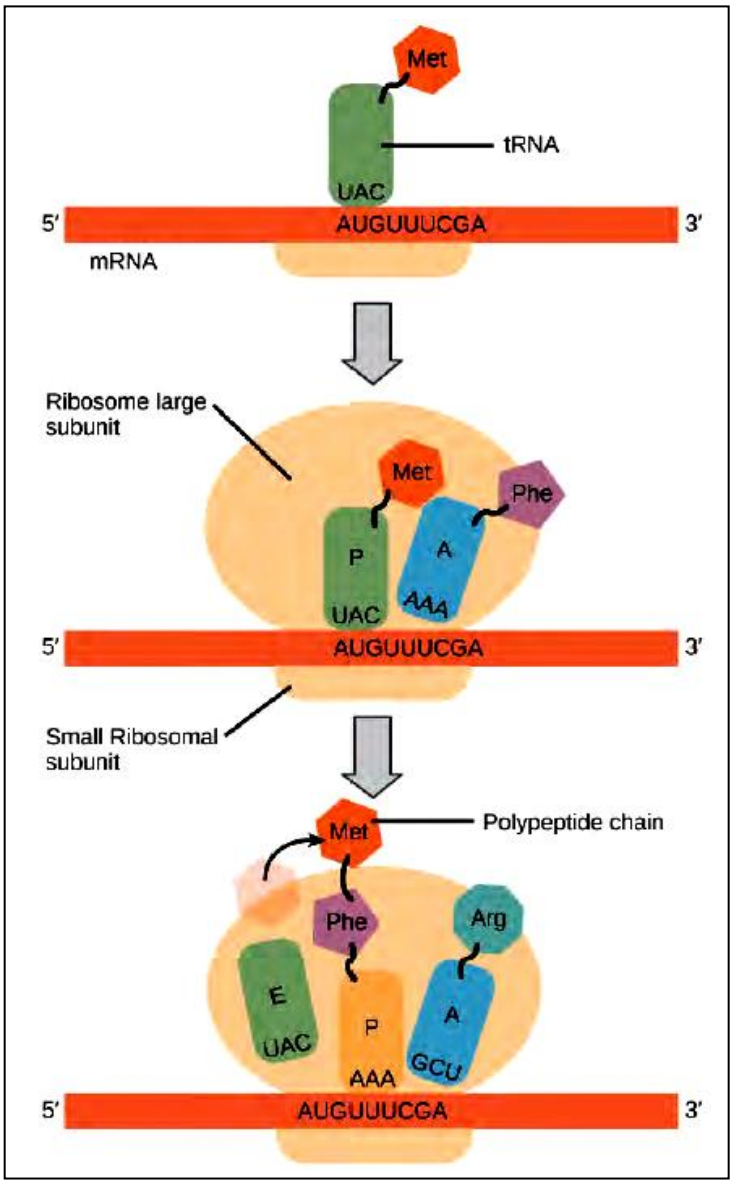


Figure 2.21: **Translation** begins when a **tRNA anticodon** recognizes a codon on the **mRNA**. The large ribosomal subunit joins the small subunit, and a second **tRNA** is recruited. As the **mRNA** moves relative to the ribosome, the polypeptide chain is formed. Entry of a release factor into the **A site** terminates translation and the components dissociate.

Termination of **translation** occurs when a **stop codon** (**UAA, UAG,** or **UGA**) is encountered. When the ribosome encounters the stop codon, the growing polypeptide is released and the ribosome subunits dissociate and leave the **mRNA**. After many ribosomes have completed translation, the **mRNA** is degraded so the nucleotides can be reused in another **transcription reaction**.

Transcribe a gene and translate it to protein using complementary pairing and the genetic code at this site

By the end of this section, you will be able to:

- Discuss why every cell does not express all of its genes
- Describe how prokaryotic gene expression occurs at the transcriptional level
- Understand that eukaryotic gene expression occurs at the epigenetic, transcriptional, post-transcriptional, translational, and post-translational levels

For a cell to function properly, necessary proteins must be synthesized at the proper time. All organisms and cells control or regulate the transcription and translation of their **DNA** into **protein**. The process of turning on a gene to produce **RNA** and **protein** is called **gene expression**. Whether in a simple unicellular organism or a complex multicellular organism, each cell controls when and how its genes are expressed. For this to occur, there must be a mechanism to control when a gene is expressed to make **RNA** and **protein**, how much of the protein is made, and when it is time to stop making that protein because it is no longer needed.

Cells in multicellular organisms are specialized; cells in different tissues look very different and perform different functions. For example, a muscle cell

is very different from a liver cell, which is very different from a skin cell. These differences are a consequence of the expression of different sets of genes in each of these cells. All cells have certain basic functions they must perform for themselves, such as converting the energy in sugar molecules into energy in **ATP**. Each cell also has many genes that are not expressed and expresses many that are not expressed by other cells, such that it can carry out its specialized functions. In addition, cells will turn on or off certain genes at different times in response to changes in the environment or at different times during the development of the organism. Unicellular organisms, both eukaryotic and prokaryotic, also **turn on** and **off genes** in response to the demands of their **environment** so that they can respond to special conditions.

The control of **gene expression** is extremely complex. Malfunctions in this process are detrimental to the cell and can lead to the development of many diseases, including cancer.

Prokaryotic versus Eukaryotic Gene Expression

To understand how gene expression is regulated, we must first understand how a gene becomes a functional protein in a cell. The process occurs in both prokaryotic and eukaryotic cells, just in slightly different fashions.

Because prokaryotic organisms lack a cell nucleus, the processes of transcription and translation occur almost simultaneously. When the protein is no longer needed, transcription stops. As a result, the primary method to control what type and how much protein is expressed in a prokaryotic cell is through the regulation of **DNA** transcription into **RNA**. All the subsequent steps happen automatically. When more protein is required, more transcription occurs. Therefore, in prokaryotic cells, the control of gene expression is almost entirely at the transcriptional level.

The first example of such control was discovered using ***E. coli*** in the 1950s and 1960s by French researchers and is called the lac operon. The lac operon is a stretch of **DNA** with three adjacent genes that code for proteins that participate in the absorption and metabolism of lactose, a food source for ***E. coli***. When lactose is not present in the bacterium's environment, the lac genes are transcribed in small amounts. When lactose is present, the genes are transcribed and the bacterium is able to use the lactose as a food source. The operon also contains a promoter sequence to which the **RNA polymerase** binds to begin transcription; between the promoter and the three genes is a region called the operator. When there is no lactose present, a protein known as a repressor binds to the operator and prevents **RNA polymerase** from binding to the **promoter**, except in rare cases. Thus very little of the protein products of the three genes are made. When lactose is present, an end product of lactose metabolism binds to the repressor protein and prevents it from binding to the operator. This allows **RNA** polymerase to bind to the promoter and freely transcribe the three genes, allowing the organism to metabolize the lactose.

Eukaryotic cells, in contrast, have intracellular organelles and are much more complex. Recall that in eukaryotic cells, the **DNA** is contained inside the cell's nucleus and it is transcribed into **mRNA** there. The newly synthesized **mRNA** is then transported out of the nucleus into the cytoplasm, where ribosomes translate the **mRNA** into **protein**. The processes of transcription and translation are physically separated by the nuclear membrane; transcription occurs only within the nucleus, and translation only occurs outside the nucleus in the cytoplasm. The regulation of gene expression can occur at all stages of the process (**Figure 2.22**). Regulation may occur when the **DNA** is uncoiled and loosened from nucleosomes to bind transcription factors (**epigenetic level**) when the **RNA** is transcribed (**transcriptional level**) when **RNA** is processed and exported to the cytoplasm after it is

transcribed (**post-transcriptional level**) when the **RNA** is translated into protein (**translational level**), or after the protein has been made (**post-translational level**).

The differences in the regulation of **gene expression** between **prokaryotes** and **eukaryotes** are summarized in **Table 2.2.**

Differences in the Regulation of Gene Expression of Prokaryotic and Eukaryotic Organisms

Prokaryotic organisms	Eukaryotic organisms
Lack nucleus	Contain nucleus
RNA transcription and protein translation occur almost simultaneously	RNA transcription occurs prior to protein translation, and it takes place in the nucleus. RNA translation to protein occurs in the cytoplasm. RNA post-processing includes addition of a 5' cap, poly-A tail, and excision of introns and splicing of exons.
Gene expression is regulated primarily at the transcriptional level	Gene expression is regulated at many levels (epigenetic, transcriptional, post-transcriptional, translational, and post-translational)

Table 2.2.

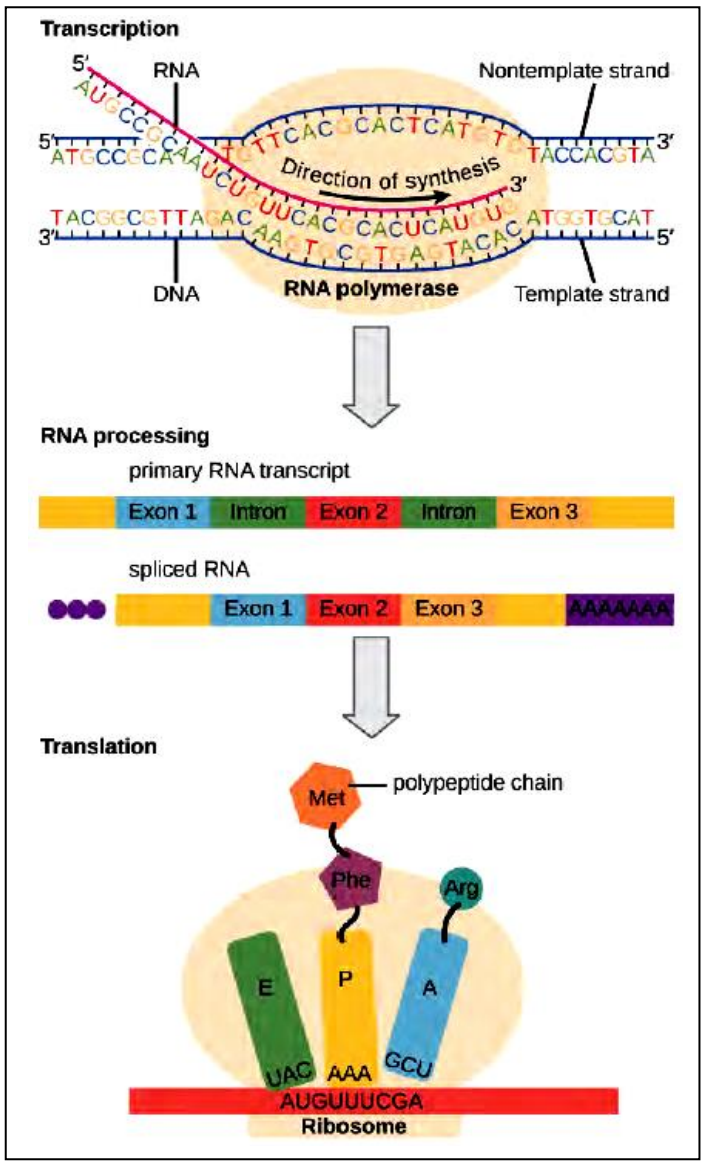


Figure 2.22: Eukaryotic gene expression is regulated during transcription and **RNA** processing, which takes place in the nucleus, as well as during protein translation, which takes place in the cytoplasm. Further regulation may occur through **post-translational modifications** of proteins.

❖ Alternative RNA Splicing

In the 1970s, genes were first observed that exhibited **alternative RNA splicing**. Alternative **RNA splicing** is a mechanism that allows different protein products to be produced from one gene when different combinations of **introns** (and sometimes **exons**) are removed from the transcript (**Figures 2.23**& **2.24**). This alternative splicing can be haphazard, but more often it is

controlled and acts as a mechanism of gene regulation, with the frequency of different splicing alternatives controlled by the cell as a way to control the production of different protein products in different cells, or at different stages of development. Alternative splicing is now understood to be a common mechanism of gene regulation in eukaryotes; according to one estimate, **70% of genes** in humans are expressed as **multiple proteins** through **alternative splicing**.

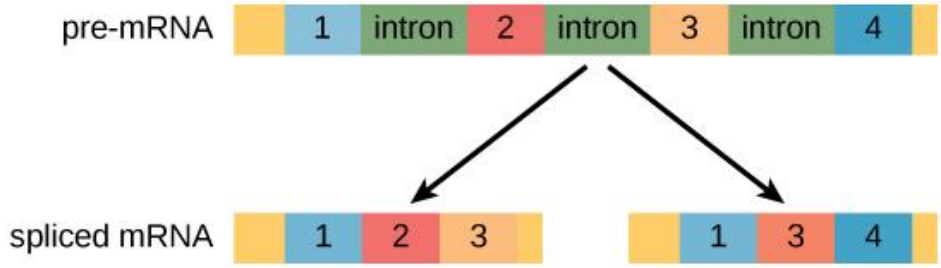


Figure 2.23: Pre-mRNA can be **alternatively spliced** to create different proteins.

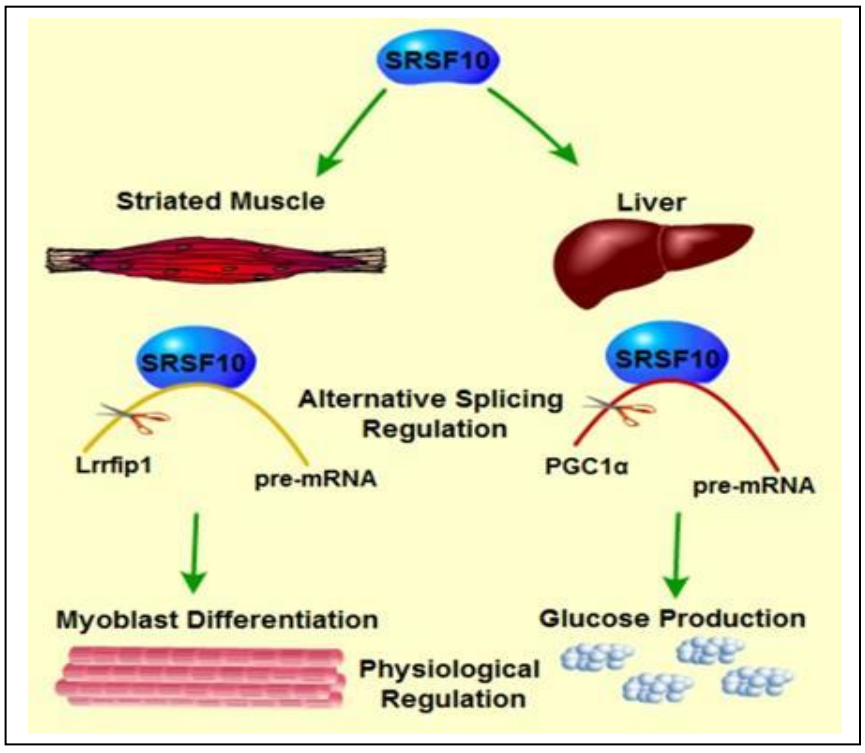


Figure 2.24: RNA splicing allows for the production of multiple protein isoforms from a single gene by removing introns and combining different exons.

How could alternative splicing evolve? Introns have a beginning and ending recognition sequence, and it is easy to imagine the failure of the splicing mechanism to identify the end of an **intron** and find the end of the next **intron**, thus removing two **introns** and the intervening **exon**. There are mechanisms in place to prevent such **exon** skipping, but mutations are likely to lead to their failure. Such “mistakes” would more than likely produce a **nonfunctional protein**. Indeed, the cause of many genetic diseases is **alternative splicing** rather than mutations in a sequence. However, **alternative splicing** would create a protein variant without the loss of the original protein, opening up possibilities for the adaptation of the new variant to new functions. **Gene duplication** has played an important role in the evolution of new functions in a similar way by providing genes that may evolve without eliminating the original functional protein.

Hardy-Weinberg Equilibrium

Allele frequencies (or percentages, if you prefer) in a population will remain in Hardy-Weinberg Equilibrium (HWE) from generation to generation if the following assumptions are met:

1. Natural selection is not occurring
2. Migration (Gene Flow) is not occurring
3. Mutation is not occurring
4. Genetic Drift is not occurring (drift is less likely in populations of large size)
5. Mating occurs at random

Although these assumptions are rarely true in the natural world, they allow us to calculate an expected allele frequency. Significant differences between the **observed** and **expected** frequencies indicate that "something" (i.e. one or more of the above) is going on, and therefore tell us that "microevolution" is occurring.

Calculating *Expected* Allele and Genotype frequencies:

In the simplest possible situation we have a single gene with only two alleles. These alleles might be A and a, or A_1 and A_2. Let's say that A or A_1= tall, and a or A_2= short. Don't worry for now whether the alleles are dominant and recessive or co-dominant. They will have frequencies p and q in a population. (Because there are only two possibilities and they have to add up to 100%, p + q = 1.)

If we know the allele frequencies, we can predict the genotype frequencies. The ***expected*** genotype frequencies of the two alleles are calculated as shown. This ought to look familiar: it's our old friend the Punnet's Square. Allele A or A_1 has a frequency of p, and allele a or A_2 has a frequency of q. Multiply the allele frequencies to the get the probability of each genotype.

Allele		A	a
	Frequency	p	q
A	p	p^2	pq
a	q	pq	q^2

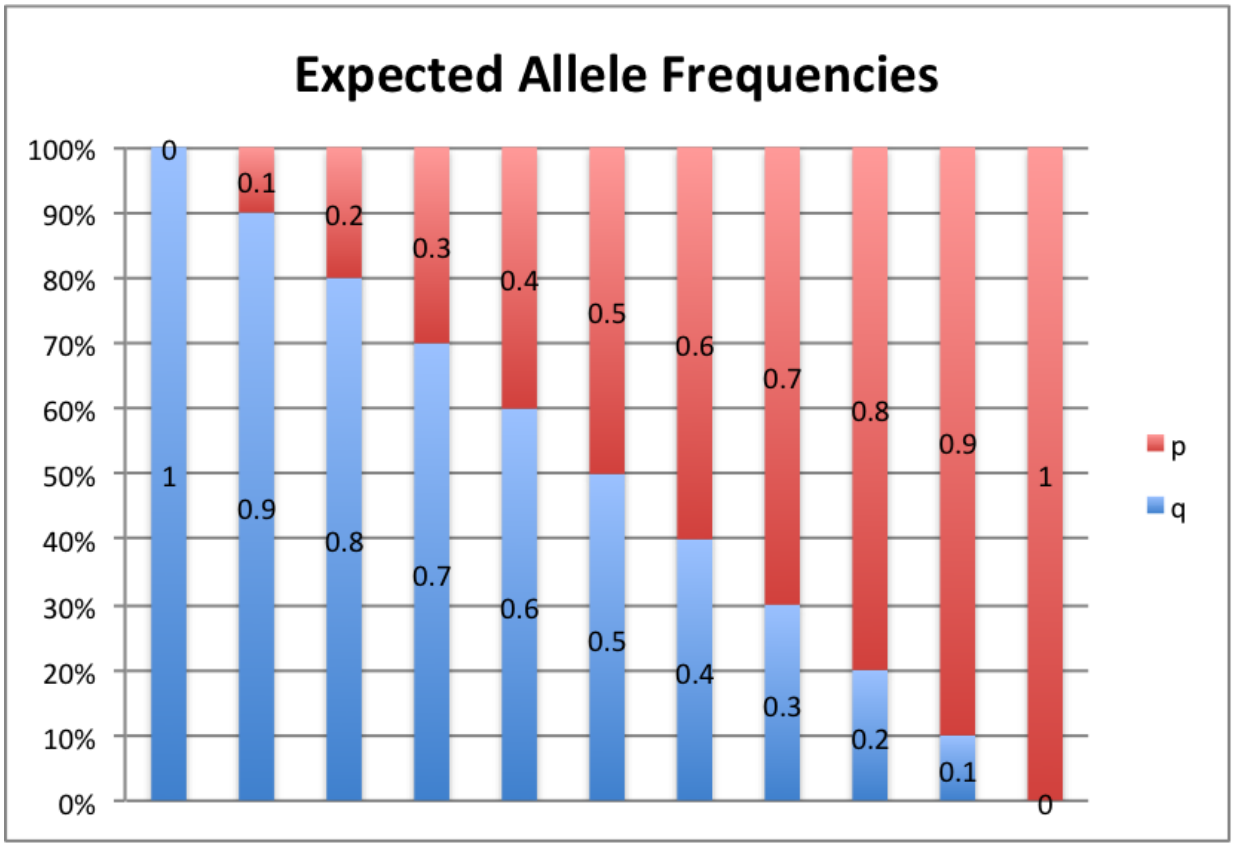
or

Allele		A_1	A_2
	Frequency	p	q
A_1	p	p^2	pq
A_2	q	pq	q^2

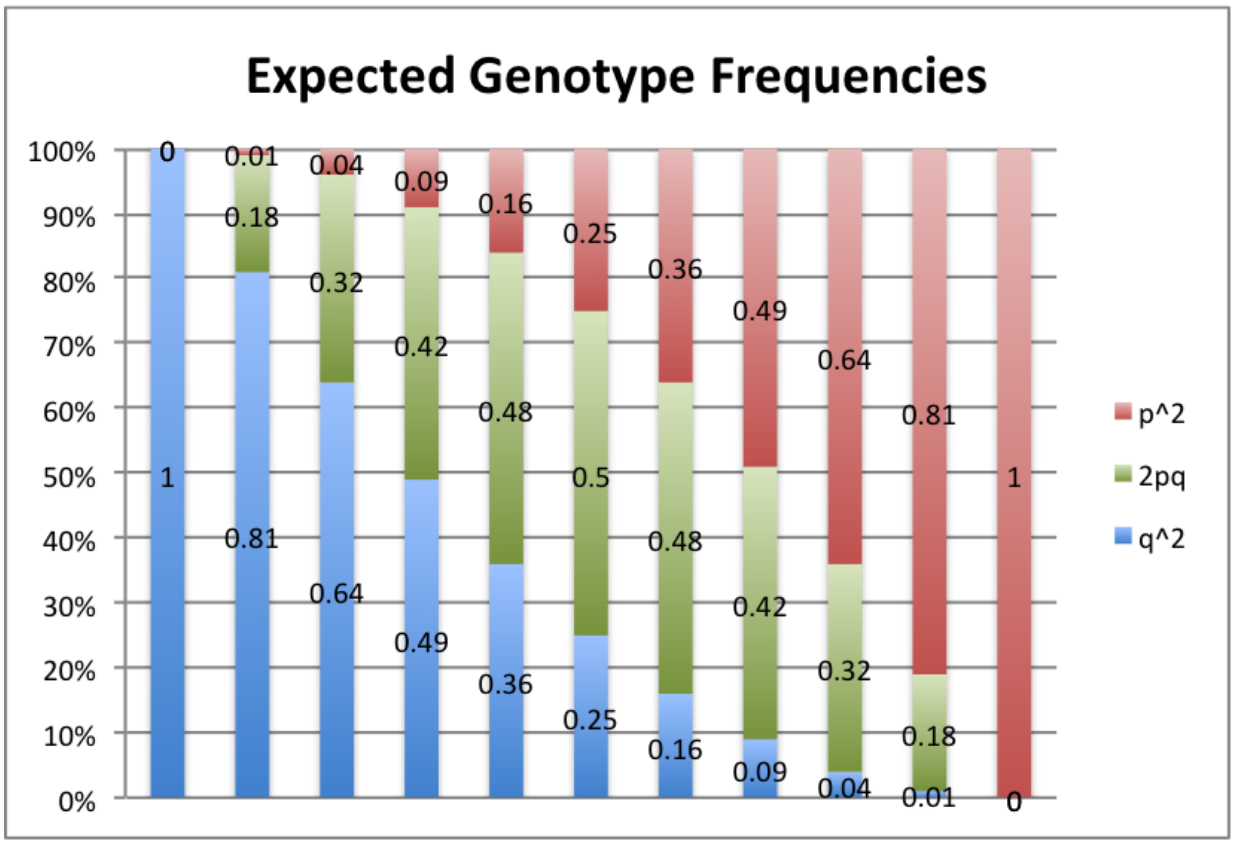
In other words, $p^2 + pq + pq + q^2 = 1$, or 100%. The expected frequencies of the genotypes are therefore:

Genotype	Expected Frequency
AA or A_1A_1	$p * p = p^2$
Aa or A_1A_2	pq + pq (or 2pq)
aa or A_2A_2	$q * q = q^2$

Let's take a look at some graphs of this to make it a little easier to see. For values of p from 0 to 1, in intervals of 0.1, here's what we get:



p+q=1, so p=1-q and q=1-p



Red represents the frequency of the AA or A_1A_1 genotype, green is the Aa or A_1A_2 genotype, and blue is the aa or A_2A_2 genotype.

All of the above has to do with the allele and genotype frequencies we would expect to see. Next, let's look at the real world situation so we can compare.

Calculating *Observed* Allele and Genotype Frequencies:

In a real world population, we can only see phenotypes, not genotypes or alleles. However, in a population of genotypes AA, Aa and aa, the **observed** frequency of allele A equals the sum of all of the AA genotype plus half of Aa genotype (the A half). The observed frequency of allele a is therefore half of the Aa individuals (the a half) plus all of aa individuals. If you know one value, you can of course just subtract it from 1 (100%) to get the value of the other. In other words, the observed frequency of A = 100%(AA) + 50%(Aa) and a = 50%(Aa) and 100%(aa)

Phenotype	Genotype	Makeup	Frequency
Tall	AA	100% A	p^2
Tall	Aa	50% A and 50% a	2pq
Short	aa	100% a	q^2

or

Phenotype	Genotype	Makeup	Frequency
Tall	A_1A_1	100% A_1	p^2
Medium	A_1A_2	50% A_1 and 50% A_2	2pq
Short	A_2A_2	100% A_2	q^2

Tip: If the alleles are codominant, each phenotype is distinct (you can distinguish between tall, medium and short) and your job is easier. If the alleles are ***dominant and recessive***, we can't visually tell the homozygous AA from the heterozygous Aa genotypes (both are tall), so it's best to start with the homozygous recessive (short) aa individuals. Count up the aa types and you have the observed q^2. Then, take the square root of q^2 to get q, and then subtract q from 1 to get p. Square p to get p^2 and multiply 2*p*q to get the observed heterozygous Aa genotype frequency.

Conclusion:

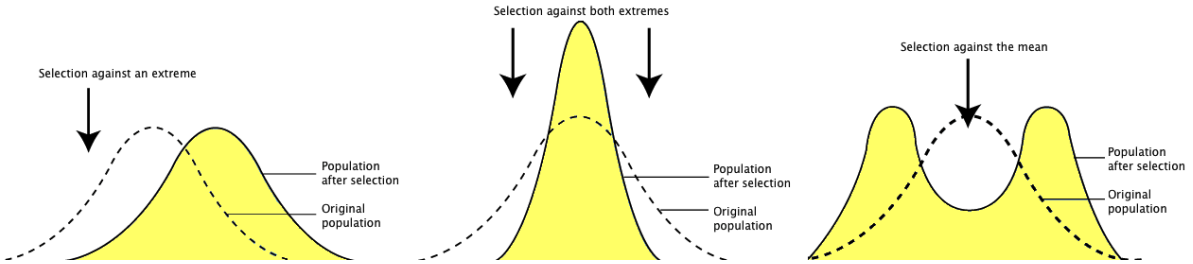
If observed and expected **genotype frequencies** are **significantly different**, the population is out of HWE.

	Genotype Frequencies		
	AA	Aa	aa
Observed			
Expected			
Difference			

or

	Genotype Frequencies		
	A_1A_1	A_1A_2	A_2A_2
Observed			
Expected			
Difference			

Question: Why might observed and expected phenotype frequencies differ? Imagine the following scenarios where natural selection is at work. Situation one favors only one tail of the distribution. Perhaps the tallest, perhaps the shortest, but not both. This is directional selection. Now imagine that both tails of the distribution are selected against, and only the middle is favored. This is called stabilizing selection. Next imagine that the extremes on both ends are favored. This is called disruptive selection. In each of these scenarios, what would happen over time?



Before (dotted line) and after (yellow shaded area) directional selection, stabilizing selection, and disruptive selection.

Examples:

One common misconception is that dominant alleles will rise in frequency and recessive alleles will decline in frequency over time. In reality, allele frequencies will not change from one generation to the next if the assumptions listed above are not violated. A good example of this is human ABO blood type. Type O blood is recessive but it remains the most common.

In the hwe.xlsx Excel Spreadsheet, there are three examples to help make this more concrete.

Example 1: Allele A is dominant and allele a is recessive. Set the original frequencies of p (allele A) and q (allele a) at 0.6 and 0.4 in Generation 1. These are highlighted in blue. All other numbers are calculated from these two original data points. The frequency of genotype AA is determined by squaring the allele frequency A. The frequency of genotype Aa is determined by multiplying 2 times the frequency of A times the frequency of a. The frequency of aa is determined by squaring a. Try changing p and q to other values, ensuring only that p and q always equal 1. Does it make any difference in the results?

Example 2: Alleles A_1 and A_2 are co-dominant. In this case, A_1 is at a frequency of 0.25 and A_2 is at a frequency of 0.75.

Example 3: Alleles A and a are dominant and recessive. Note that allele A is at very low frequency despite being dominant. Does it increase in frequency?

Problem:

The second sometimes confusing thing about HWE is that after all of the examples above, you may wonder if it is possible for the observed and expected frequencies to differ. Here's an example where they do:

In a population of snails, shell color is coded for by a single gene. The alleles A_1 and A_2 are co-dominant. The genotype A_1A_1 makes an orange shell. The genotype A_1A_2 makes a yellow shell. The genotype $A_2\ A_2$ makes a black shell. 1% of the snails are orange, 98% are yellow, and 1% of the snails are black.

Observed frequency of A_1 allele = 0.01 + 0.5(.98) = 0.50 = 50%

p^2 = Expected frequency of A_1A_1 = 0.25

2pq = Expected frequency of A_1A_2 = 0.50

q^2 = Expected frequency of $A_2\ A_2$ = 0.25

Phenotype	Orange	Yellow	Black
Genotype	A_1A_1	$A_1\ A_2$	A_2A_2
Observed	1%	98%	1%
Expected	25%	50%	25%
Difference	-24%	+48%	-24%

There are significantly fewer orange and black snails than expected, and significantly more yellow snails than expected. It appears that this is a case of stabilizing selection, since both tails appear to be strongly selected agains

KEY TERMS

Alternative RNA splicing: a **post-transcriptional** gene regulation mechanism in eukaryotes in which multiple protein products are produced by a single gene through alternative splicing combinations of the **RNA** transcript.

Codon: three consecutive nucleotides in **mRNA** that specify the addition of a specific amino acid or the release of a polypeptide chain during translation.

DNA ligase: the enzyme that catalyzes the joining of **DNA** fragments together.

DNA polymerase: an enzyme that synthesizes a new strand of **DNA** complementary to a template strand.

Deoxyribose: a five-carbon sugar molecule with a **hydrogen atom** (**H**) rather than a **hydroxyl group (OH)** in the 2' position; the sugar component of **DNA** nucleotides.

Double helix: the molecular shape of **DNA** in which two strands of nucleotides wind around each other in a spiral shape.

Epigenetic: describing **non-genetic regulatory factors**, such as changes in modifications to **histone proteins** and **DNA** that control access to genes in chromosomes.

Exon: a sequence present in protein-coding **mRNA** after completion of **pre-mRNA splicing**

Gene expression: processes that control whether a gene is expressed.

Genetic code: the amino acids that correspond to three-nucleotide codons of **mRNA**.

Helicase: an enzyme that helps to open up the **DNA** helix during **DNA** replication by breaking the hydrogen bonds.

Intron: non–protein-coding intervening sequences that are spliced from **mRNA** during processing.

Lagging strand: during replication of the **3' to 5'** strand, the strand is replicated in short fragments and away from the **replication fork**.

Leading strand: the strand that is synthesized continuously in the **5' to 3'** direction that is synthesized in the direction of the **replication fork**.

mRNA: messenger **RNA**; a form of **RNA** that carries the nucleotide sequence code for a protein sequence that is translated into a polypeptide sequence.

Mismatch repair: a form of **DNA repair** in which non-complementary nucleotides are recognized, excised, and replaced with correct nucleotides.

Mutation: a permanent variation in the nucleotide sequence of a genome.

Nitrogenous base: a nitrogen-containing molecule that acts as a base; often referring to one of the **purine** or **pyrimidine** components of nucleic acids.

Nontemplate strand: the strand of **DNA** that is not used to transcribe **mRNA**; this strand is identical to the **mRNA** except that **T** nucleotides in the **DNA** are replaced by **U** nucleotides in the **mRNA.**

Nucleotide excision repair: a form of **DNA repair** in which the **DNA** molecule is unwound and separated in the region of the nucleotide damage, the damaged nucleotides are removed and replaced with new nucleotides using the complementary strand, and the **DNA** strand is resealed and allowed to rejoin its complement.

Okazaki fragments: the **DNA** fragments that are synthesized in short stretches on the **lagging strand**.

Phosphate group: a molecular group consisting of a central phosphorus atom bound to four oxygen atoms.

Post-transcriptional: control of gene expression after the **RNA** molecule has been created but before it is translated into protein.

Post-translational: control of gene expression after a protein has been created.

Primer: a short stretch of **RNA** nucleotides that is required to initiate replication and allow **DNA polymerase** to bind and begin replication.

Promoter: a sequence on **DNA** to which **RNA polymerase** and associated factors bind and initiate transcription.

RNA polymerase: an enzyme that synthesizes an **RNA** strand from a **DNA** template strand.

rRNA: ribosomal **RNA**; molecules of **RNA** that combine to form part of the ribosome.

Replication fork: the Y-shaped structure formed during the initiation of replication.

Semiconservative replication: the method used to replicate **DNA** in which the double-stranded molecule is separated and each strand acts as a template for a new strand to be synthesized, so the resulting **DNA**

molecules are composed of one new strand of nucleotides and one old strand of nucleotides.

Splicing: the process of removing introns and reconnecting exons in a **pre-mRNA**.

Start codon: the **AUG** (or, rarely **GUG**) on an **mRNA** from which translation begins; always specifies **methionine** (**Met**).

Stop codon: one of the three **mRNA** codons that specify termination of translation.

tRNA: transfer **RNA**; an **RNA** molecule that contains a specific three-nucleotide anticodon sequence to pair with the mRNA codon and also binds to a specific amino acid.

Telomerase: an enzyme that contains a catalytic part and an inbuilt **RNA** template; it functions to maintain telomeres at chromosome ends.

Telomere: the **DNA** at the end of linear chromosomes.

Template strand: the strand of **DNA** that specifies the complementary **mRNA** molecule.

Transcription bubble: the region of locally unwound **DNA** that allows for transcription of **mRNA**.

REVIEW QUESTIONS

1. Prokaryotes contain a …….chromosome, and eukaryotes contain ……. chromosomes.
   a. single-stranded circular; single-stranded linear.
   b. single-stranded linear; single-stranded circular.
   c. double-stranded circular; double-stranded linear.
   d. double-stranded linear; double-stranded circular.

2. DNA replicates by which of the following models?
   a. conservative.
   b. semiconservative.
   c. dispersive.
   d. none of the above.

3. The initial mechanism for repairing nucleotide errors in DNA is ……..
   a. mismatch repair.
   b. DNA polymerase proofreading.
   c. nucleotide excision repair.
   d. thymine dimers.

4. A promoter is …….
   a. a specific sequence of **DNA** nucleotides.
   b. a specific sequence of **RNA** nucleotides.
   c. a protein that binds to **DNA**.
   d. an enzyme that synthesizes **RNA**.

5. Portions of eukaryotic **mRNA** sequence that are removed during **RNA** processing are ……
   a. exons.
   b. caps.
   c. poly-A tails.
   d. introns.

6. The **RNA** components of ribosomes are synthesized in the …….
   a. cytoplasm.
   b. nucleus.
   c. nucleolus.
   d. endoplasmic reticulum.

7. How long would the peptide that is translated from this mRNA sequence:
   5'-AUGGGCUACCGA-3'?
   a. 0.
   b. 2.
   c. 3.
   d. 4.

8. Control of gene expression in eukaryotic cells occurs at which level(s)?
   a. only the transcriptional level

b. epigenetic and transcriptional levels
c. epigenetic, transcriptional, and translational levels
d. epigenetic, transcriptional, posttranscriptional, translational, and posttranslational levels.

9. Post-translational control refers to:
a. regulation of gene expression after transcription.
b. regulation of gene expression after translation.
c. control of epigenetic activation.
d. period between transcription and translation.

- **CRITICAL THINKING QUESTIONS**

10. Describe the organization of the eukaryotic chromosome.

11. Describe the structure and complementary base pairing of **DNA**.

12. How do the linear chromosomes in eukaryotes ensure that its ends are replicated completely?

13. Transcribe and translate the following **DNA** sequence (nontemplate strand): **5'-ATGGCCGGTTATTAAGCA-3'**?

14. Describe how controlling gene expression will alter the overall protein levels in the cell.