Chapter 2

Basic Genetics: The Cell, Mitosis and Meiosis, and Mendelian Laws

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Chapter Outline

2.1 OVERVIEW OF THE CELL: ANATOMY, COMPONENTS, AND FUNCTION

Each cell is a basic building block for any organism living on Earth. These organisms are either unicellular or multicellular. In a unicellular organism, the cell or the organism performs all necessary activities required to sustain life. In a multicellular organism, various cells with specialized functions cooperate and facilitate proper functioning of the whole organism; nevertheless, each single cell in a multicellular organism is seen as the organism's basic unit of structure and function. In other words, life fundamentally occurs at the cellular level.

There are two kinds of living organisms: prokaryotes and eukaryotes. The main difference between the two is that eukaryotes have a well-defined nucleus enclosed in a membranous nuclear envelope; prokaryotes have no nucleus but a region called the nucleoid not separated from the rest of the cell. In eukaryotic cells, the region between the nucleus and the cell membrane, called the cytoplasm, is where the membrane-enclosed organelles are suspended in a semifluid medium called the cytosol. Unlike eukaryotic cells, prokaryotic cells lack most of the organelles in the cytoplasm. Prokaryotic cells are found only in the kingdom Monera (such as bacteria), while protists, fungi, plants, and animals are all eukaryotes. A detailed comparison of eukaryotic and prokaryotic cells is given in Table 2.1. The discussion of cell structure and organelle function in this chapter applies to eukaryotes.

2.1.1 Nucleus and Chromosomes

The nuclear envelope separates the two major cellular compartments: the nucleoplasm and the cytoplasm. The DNA and its associated proteins are referred to as chromatin and reside in the nucleus in eukaryotes. The chromosomes carrying the cell's genes and the machinery to express them reside inside the nucleus. Interactions with histones and other proteins fold each chromosome compactly enough to fit inside the nucleus. In higher organisms, each somatic cell contains

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TABLE 2.1 Comparison of Eukaryotic and Prokaryotic Cells

Feature	Eukaryote	Prokaryote
Cell size	Typically 10–100 μm	Typically 1–10 μm
Nucleus	Present and membrane-bound	Absent but has a nucleoid region without a nuclear membrane
Other organelles	Many membrane-bound organelles	No membrane-bound ribosomes
Genetic material (DNA)	Located in the nucleus and surrounded by a nuclear membrane	Concentrated in the nucleoid
DNA arrangement	Multiple linear chromosomes	Single circular chromosome
RNA synthesis	In the nucleus	In the cytoplasm
Protein synthesis	In the cytoplasm	In the cytoplasm
Cytoplasmic structure	Cytoskeleton and cytoplasmic streaming	No cytoskeleton or cytoplasmic streaming
Organization	Often multicellular	Usually unicellular
Cell division	Mitosis and meiosis	Fission or budding

one set of chromosomes inherited from the maternal parent and a comparable set of chromosomes (homologous, or homologues) from the paternal parent. The number of chromosomes in this dual set is the diploid number. Sex cells, or gametes, which contain half the number of chromosome sets found in somatic cells, are referred to as haploid cells.

2.1.2 Membrane-Bound Organelles in Eukaryotic Cells

The endomembrane system separates the cell into different compartments, or organelles, such as the nucleus, the endoplasmic reticulum (ER), the Golgi apparatus, and lysosomes (see Table 2.2). The endomembrane system is derived from the ER and flows to the Golgi apparatus, from which lysosomes bud. The ER is a continuous system of flattened membrane sacks and tubules that is specialized for protein processing and lipid biosynthesis. The endomembrane system is important for the cell's compartmental organization to function independently and properly. Ribosomes that synthesize proteins destined for insertion into cellular membranes or for export from the cell associate with specialized regions of the ER, called the rough ER owing to the attached ribosomes.

For the most common organelles in eukaryotic cells, the structure and function of each are illustrated, using an animal cell as an example, in Figure 2.1 and Table 2.2.

2.1.3 Nonmembranous Organelles in Eukaryotic Cells

The shape of a cell is maintained by a network of fibers throughout the cytoplasm, called the cytoskeleton. In addition to structural support, the cytoskeleton functions in cell motility, such as the movement of organelles within the cell. The three fiber components of the cytoskeleton are microtubules, microfilaments, and intermediate filaments.

Microtubules are straight, hollow tubes made of tubulins. Two tubulin types, α-tubulin and β-tubulin, are similar molecular units bonded together to form the microtubule wall. Microtubules support the cell and guide the movement of organelles by providing tracks for them equipped with specialized proteins known as motor molecules. Microtubules also help in the separation of chromosomes during cell division, as discussed in later sections.

Microfilaments are solid rods built from actin molecules. Actin molecules are present in chains twisted in a helix form. Microfilaments are especially concentrated and well ordered in muscle cells and are involved in muscle cell contraction. They also play a role in supporting the cell along with the rest of the cytoskeleton.

Intermediate filaments are smaller than microtubules but larger than microfilaments in diameter. These filaments can remain in their original shape, while the microtubules and microfilaments are often disassembled and reconstructed in different parts of the cytoplasm. This suggests that they are especially important in maintaining the shape of a cell and fixing the position of certain organelles.

2.2 CELL REPRODUCTION: CELL CYCLE AND MITOSIS

Cell division may result in cell reproduction in a unicellular organism, cell growth, and development of multicellular organisms, as well as the renewal and repair of tissues in mature organisms. In a prokaryotic cell (e.g., bacterium), the type of cell division is called binary fission. Bacterial DNA is attached to the cell membrane. In preparation for

TABLE 2.2 Most Common Characteristics of Membrane-Bound Organelles in Animal Eukaryotic Cells

Organelle	Feature	Function
Nucleus	• Nuclear envelope: lipid double layer • Nuclear pores • Chromatin (mass of DNA)/chromosome (DNA double helix, visible during cell division) • Nucleolus	• Separates the nucleus's contents from the cytoplasm • Regulate nuclear transportation • Holds the cell's genetic material; human somatic cell: 46 chromosomes; sex cells: 23 chromosomes • Synthesizes the ribosome's components to be assembled in the cytoplasm
Ribosomes	• Free ribosomes suspended in cytosol • Ribosomes attached to the endoplasmic reticulum • Two ribosome types are structurally identical and functionally interchangeable	• Synthesize proteins to function within the cytosol • Synthesize proteins to be included in membranes; pack certain organelles (e.g., lysosomes) or export from cell • Interchange occurs when the cell's metabolism changes
Endoplasmic reticulum (ER)	• Rough ER (with studded ribosomes) is confluent with the nuclear outer membrane • Smooth ER (lacking ribosomes) is connected to the rough ER	• Wraps secretory proteins in the transport vesicles (e.g., glycoproteins) and produces membranes for the ER itself or other components of the endomembrane system by adding membrane proteins and phospholipids • Cell type-dependent and may function in lipid synthesis, carbohydrate metabolism, and drug detoxification.
Golgi apparatus	• Stacks of flattened membranous sacs • *cis* face[a] • *trans* face[b]	• Receives, modifies, stores, and dispatches transport vesicles (including their contents, e.g., secretory proteins from the ER) • Receives vesicles • Dispatches vesicles (ER product modification occurs during transit from the *cis* face to the *trans* face)
Lysosomes	• Membrane-bound sacs containing hydrolytic enzymes	• Digest macromolecules through phagocytosis or autophagy
Peroxisomes	• Single membrane-bound organelles containing a collection of enzymes	• Transfer hydrogen from various substrates to oxygen, producing hydrogen peroxide as a by-product. These reactions serve various metabolic functions—e.g., breakdown of fatty acids for mitochondria respiration and detoxification of alcohol in the liver
Mitochondria	• Double-membrane-bound organelles containing ribosomes and DNA • Infoldings of the inner membrane form the cristae • Number of mitochondria varies with the metabolic activity of a cell	• Convert energy for cellular respiration

[a]*One of the two poles of the Golgi apparatus located near ER and receiving the content carried by transport vesicles from ER.* [b]*The other pole of the Golgi apparatus, giving rise to vesicles that travel to other sites.*

fission, it is replicated and attached to the membrane at a site adjacent to the original copy. Continued growth of the cell membrane eventually separates the two copies of DNA, and a cell pinches in two daughter cells, each of which inherits a complete genome.

The genetic material (or genome) in a eukaryotic cell is organized into multiple chromosomes. For example, a human somatic cell has 46 chromosomes, and a reproductive cell (sperm/egg) has 23 (half of the somatic cell chromosomes). Each chromosome is organized in a long, linear

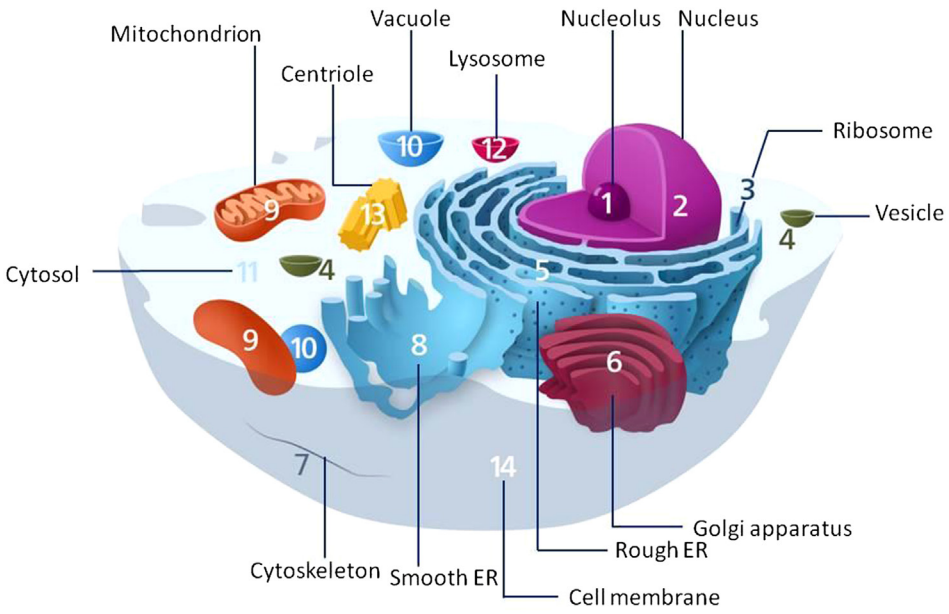

FIGURE 2.1 The most common structures in an animal cell. Genetic material, in the form of DNA, resides in the nucleus. Although vacuoles are included here, they generally exist in protists and plants. *Source: Reproduced from* Wikipedia Commons *(https://en.wikipedia.org/wiki/Organelle).*

DNA molecule representing a number of genes. Various proteins help to maintain the DNA structure. This DNA-protein complex is folded and coiled to produce the chromatid of a chromosome. The chromatid duplicates itself in the interphase of the cell cycle, and the two sister chromatids are held together by a specialized region called the centromere.

In a dividing cell, mitosis alternates with interphase, which takes up most of the time in each cell cycle. Interphase can be further divided into three periods of growth: the G_1 phase ("G" stands for gap, here the first gap), the S phase ("S" stands for synthesis), and the G_2 phase (the second gap). As it goes through interphase, the cell grows by synthesizing proteins and producing cytoplasmic organelles through all three subphases, while the chromosomes are duplicated only during the S phase. Once everything is prepared for cell division, the cell divides in the mitotic (or M) phase. How an animal cell completes its division during the M phase is described later.

Mitosis is conventionally separated into five stages: prophase, prometaphase, metaphase, anaphase, and telophase. During G_2 of interphase (late interphase), the nucleus, which contains one or more nucleoli, is enclosed in the nuclear envelope. Two centrosomes are present just outside of the nucleus. The replicated chromosomes (during the S phase) are still not distinguishable as loosely packed chromatin fibers. During prophase, the nucleoli disappear, and the chromatin fibers are condensed into discrete chromosomes, visible under a light microscope. Each duplicated chromosome consists of two sister chromatids held together by the centromere. As the two centrosomes move away from each other, early mitosis spindle (made of microtubules) begin to appear in the cytoplasm.

During prometaphase, the nuclear envelope is broken down, allowing the microtubule spindles to enter the nucleus and interact with the chromosomes. Some of the microtubules attach to a specific site, called the kinetochore, in the centromere region, preparing for chromosome movement. During metaphase, the chromosome's centromeres line up at the equator of the spindle, with each sister chromatid facing the spindle's opposite poles. During anaphase, the sister chromatids are separated from each other, and each one begins to move along the microtubules toward opposite poles. By the end of this phase, the two poles have identical collections of chromosomes.

At telophase, the nucleoli reappear and nuclear envelopes are reformed at the two ends of the cell, where the two sets of chromosomes have gathered. Mitosis, the division of the nucleus, is now complete and is followed immediately by cytokinesis, the division of the cytoplasm. Thereafter, two daughter cells separate shortly after the end of mitosis. In animal cells, cytokinesis starts with a cleavage furrow. Figure 2.2 describes these stages in an animal cell.

The timing and rate of cell division in different parts of an organism are deciding factors in normal growth, development, and maintenance. For example, human skin cells divide frequently, while muscle and nerve cells do not divide at all. Researchers have used cell culture to study the cell cycle and the factors that may influence it, such as nutrients, growth factors, and cell density.

Before cell division, the cell has to pass a checkpoint near the end of the G_1 phase. Cell size—more precisely, the cell's cytoplasmic volume-to-genome ratio—must reach a certain level to pass this checkpoint before DNA synthesis occurs at the S phase. Other environmental and

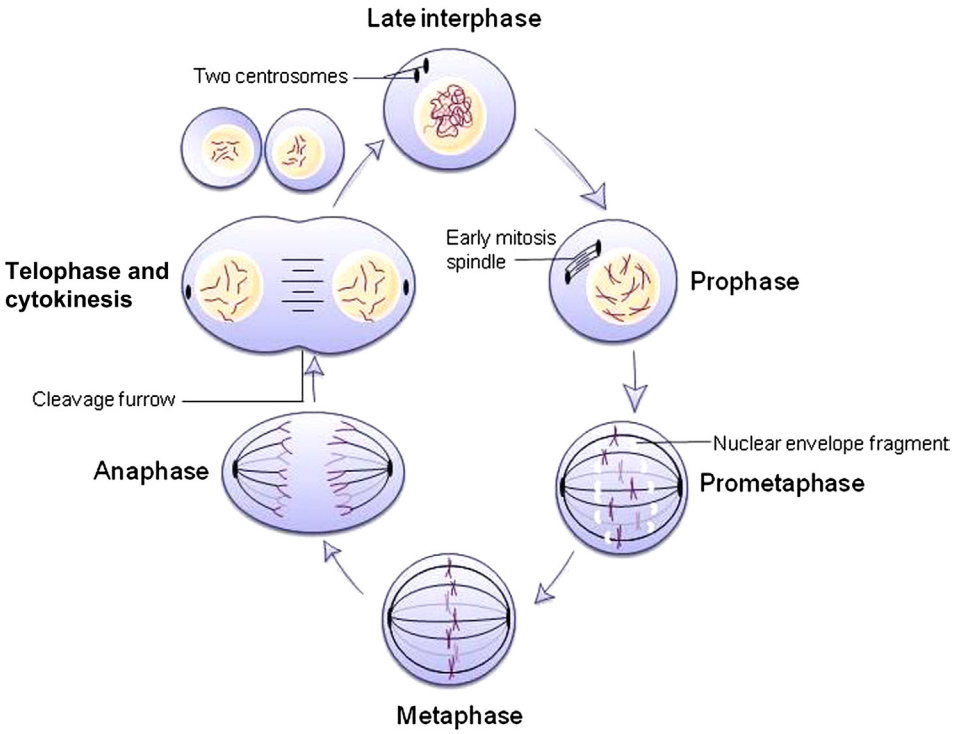

FIGURE 2.2 Cell division—mitosis in an animal cell. In this example, only seven chromosomes are shown.

developmental conditions must also be fulfilled to eventually initiate cell division. Protein kinases, which can be activated by cyclins (a class of regulatory proteins whose concentrations fluctuate cyclically during the cell cycle), regulate other proteins by phosphorylation; they also control the sequential steps of the cell cycle. In short, after the cell passes the checkpoint and is committed to reproduction, cell division is carried out as instructed by regulatory proteins (e.g., kinases, cyclins) in a cyclical manner.

2.3 MEIOSIS

Another form of cell division is meiosis, which occurs only in the ovaries and testes. Meiosis produces the reproductive cells, or gametes (i.e., ova and sperm cells), and reduces the chromosome number by half. Among the 46 human chromosomes, there are two of each type having the same length, centromere position, and band pattern. Such chromosomes are paired up and are referred to as homologous chromosomes, carrying genes controlling the same inherited traits. Each homologous chromosome in each pair is inherited from each parent. The 46 chromosomes can be organized into two sets of 23 chromosomes, with one set from the mother and the other set from the farther.

There are two distinct human sex chromosomes: X and Y. Females have a homologous pair of X chromosomes, while males have one X and one Y. X and Y are called sex chromosomes, and the others (i.e., 22 pairs) are called autosomes. Each gamete with a single set of 23 chromosome is a haploid cell. Fertilization of the gametes (a haploid sperm cell fuses with a haploid ovum, resulting in a fertilized egg known as a zygote) brings the chromosomal number back to 46. Somatic cells are derived from the zygote by mitosis during the development of a sexually mature adult. Diploid cells include the zygote and the somatic cells that have two sets of chromosomes.

Fertilization and meiosis are two features of sexual reproduction and are common to all organisms that reproduce sexually, although the details of sexual life cycles vary across species. The stages of meiotic cell division, using an animal cell as an example, are further illustrated next.

Interphase, during which each of the chromosomes replicates, is similar to mitosis. After chromosome replication, four daughter cells with only half as many chromosomes as the parent are formed through two meiotic divisions, meiosis I and meiosis II. During meiotic prophase I, two side-by-side homologous chromosomes pair up with each other in a process called synapsis. Chromatids of homologous chromosomes are criss-crossed in a process known as chiasma (see Figure 2.3). From one side this structure helps hold homologous chromosomes together; from the other side, it may result in significant genetic variations in the offspring (discussed in a later section). The two centrosomes move away from each other, and early spindle microtubules are formed between them that are similar to those observed during mitosis.

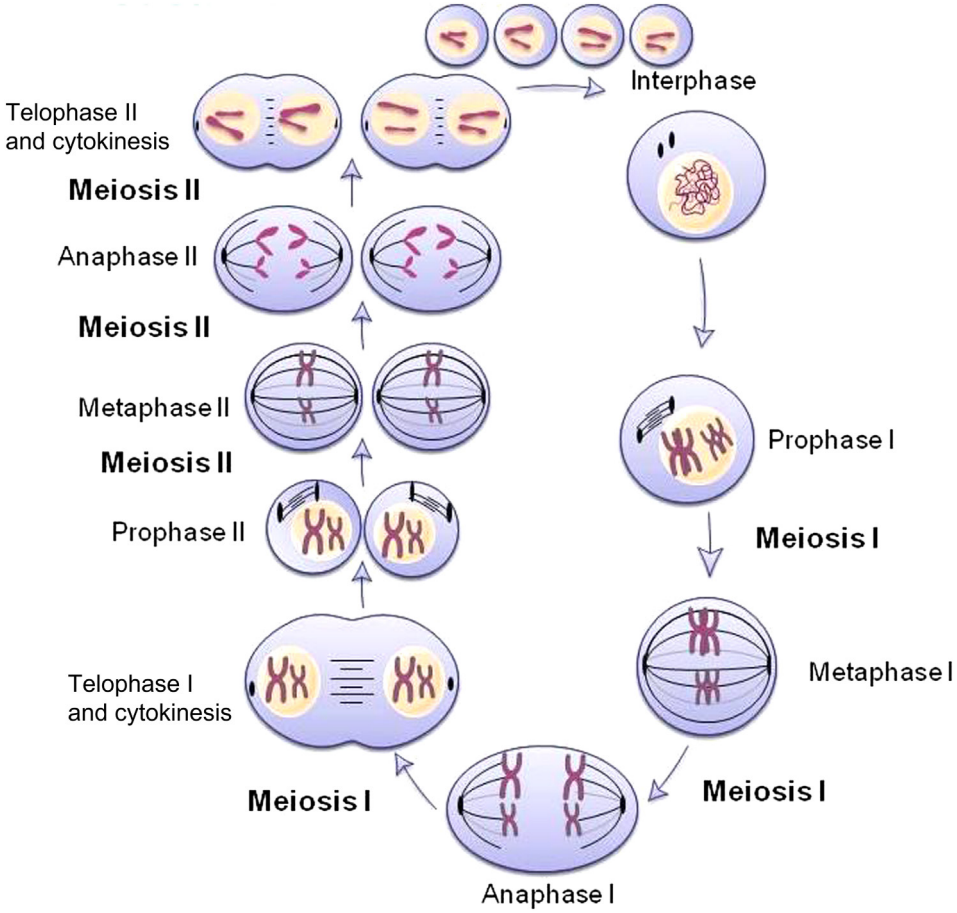

FIGURE 2.3 **Cell division—meiosis in an animal cell with a diploid number of 4 (or two sets of chromosomes).**

During metaphase I, the paired homologous chromosomes are arranged on the spindle equator. Spindle fibers from opposite poles attach to one chromosome of each pair, respectively. During anaphase I, homologous chromosomes move toward the two spindle poles; however, sister chromatids of each chromosome remain attached at the centromere and move together toward the same pole. During telophase I, the homologous chromosome pairs continue to be separated by the spindle. The homologues are finally split, and each pole now has a haploid chromosome set. Cytokinesis occurs at the same time and leads to the formation of two daughter cells at the end of meiosis I.

There is no further chromosomal replication prior to meiosis II, which also includes four subphases like the ones in meiosis I—prophase II, metaphase II, anaphase II, telophase II, and cytokinesis (see Figure 2.3). The differences are that, during metaphase II, chromosomes align in a similar manner to that observed in mitosis, with the spindle fibers attaching to the kinetochores of each chromosome's sister chromatids; during anaphase II, these sister chromatids move toward opposite spindle poles. Four daughter cells are formed following telophase II and cytokinesis, and each daughter cell has a haploid number of chromosomes compared to the zygote or the somatic cells. Table 2.3 compares mitosis and meiosis in an animal cell.

2.3.1 Genetic Variation Introduced by Meiosis: The Mechanisms

At the chromosomal level, a crossing over of two nonsister chromatids of homologous chromosomes during meiosis I (i.e., prophase I) results in individual chromosomes inheriting a portion of DNA from both mother and father. Such an exchange, or crossover, accounts for the recombination of linked genes on the same chromosomes. Independent assortment of chromosomes and random fertilization are also sources of genetic variability.

During meiosis I (i.e., metaphase I), a pair of homologous chromosomes orient independently of any other pair in terms of orientation relative to the two poles of the cell. Starting with two pairs of homologous chromosomes, there are four different combinations possible for a gamete. Based on the haploid number (n), the total number of combinations for the gametes generated by meiosis can be

TABLE 2.3 Comparison of Mitosis and Meiosis in an Animal Cell

	Mitosis	Meiosis
DNA replication	Occurs during interphase	Occurs during interphase
Division number	One division, including prophase, metaphase, anaphase, and telophase	Two divisions (meiosis I and II), each consisting of prophase, metaphase, anaphase, and telophase; homologous chromosomes joining along their length are unique to meiosis
Division outcome	Results in two daughter cells (diploid) genetically identical to the mother cell	Results in four daughter cells (haploid); genetically nonidentical to the parent cell
Significance	Derived from the zygote and has a positive effect on cell growth for repairing tissues	Gamete production; compensates chromosomes' doubling during fertilization by reducing the number of chromosomes to half; produces genetic variability in gametes

calculated as 2^n. In the case of humans, the haploid number is 23; thus, the number of all possible combinations in the gametes is 2^{23}. This independent assortment of homologous chromosomes produces about 8 million chromosomal combinations for human gametes. It produces another form of genetic recombination among unlinked genes that locate on separate nonhomologous chromosomes.

Random fertilization adds another layer to the creation of genetic variations. For a zygote to form, a human ovum representing one out of 8 million possible chromosome combinations is fertilized by a sperm cell, whose chromosome composition presents 8 million different possibilities as well. Therefore, without taking crossover into account, 64 (8×8) million diploid combinations for a zygote are possible.

The three mechanisms just described reorder the genes carried by individuals in a population; nevertheless, the fundamental factor that explains genetic diversity in a population is mutation.

2.4 MENDELIAN LAWS

Around 1857, Gregor Mendel began breeding garden peas in an abbey garden to study the mechanism of inheritance. In this section, we examine in detail the heredity principles developed by Mendel and the application of his model to the inheritance of human variations.

Mendel's choice of the pea as his experimental organism may be explained as follows. First, there are many varieties of peas. For example, flower color, seed color, and shape vary among different pea varieties, and such characteristics can all be used to observe inheritance patterns. Second, working with peas allowed Mendel to strictly control hybridization. Since carpels and stamens are almost completely enclosed by the petals of pea flowers, instead of allowing self-fertilization from the same plant, Mendel could cross-pollinate between different varieties (e.g., pea plants with different flower color) by removing the immature stamens and transferring pollen from another plant onto the emasculated flowers. In this way he controlled the parentage of the hybridized seeds.

In his breeding experiments, Mendel cross-pollinated purple-flower and white-flower pea plants and ensured that both plant types (either purple flowers or white flowers) were self-pollinated in the first place and that their offspring were of the same variety. This is known as true breeding (e.g., a purple-flower plant always produces offspring having purple flowers through self-pollination). Hybridization is defined as the mating of two true-breeding varieties. The true-breeding parents are referred to as the P generation, and the first generation of offspring is referred to as the F_1 generation. Self-pollination of the F_1 generation produces the F_2 generation. Mendel followed these generations in his experiments. It was after the quantitative analysis of the F_2 generation that two main principles of heredity were revealed: the law of segregation and the law of independent assortment.

2.4.1 The Law of Segregation

In his flower color breeding experiments, Mendel used the true-breeding peas, with purple and white flowers respectively, as the parental (or P) generation. Like their parents, the F_1 offspring all had purple flowers. Mendel allowed them to self-pollinate, and the white-flower peas reappeared in the F_2 generation. More specifically, Mendel observed 705 plants with purple flowers and 224 with white flowers. An approximate ratio for this observation is 3 (purple) to 1 (white). Along with flower color, Mendel examined the pattern of inheritance for flower position, seed color, seed

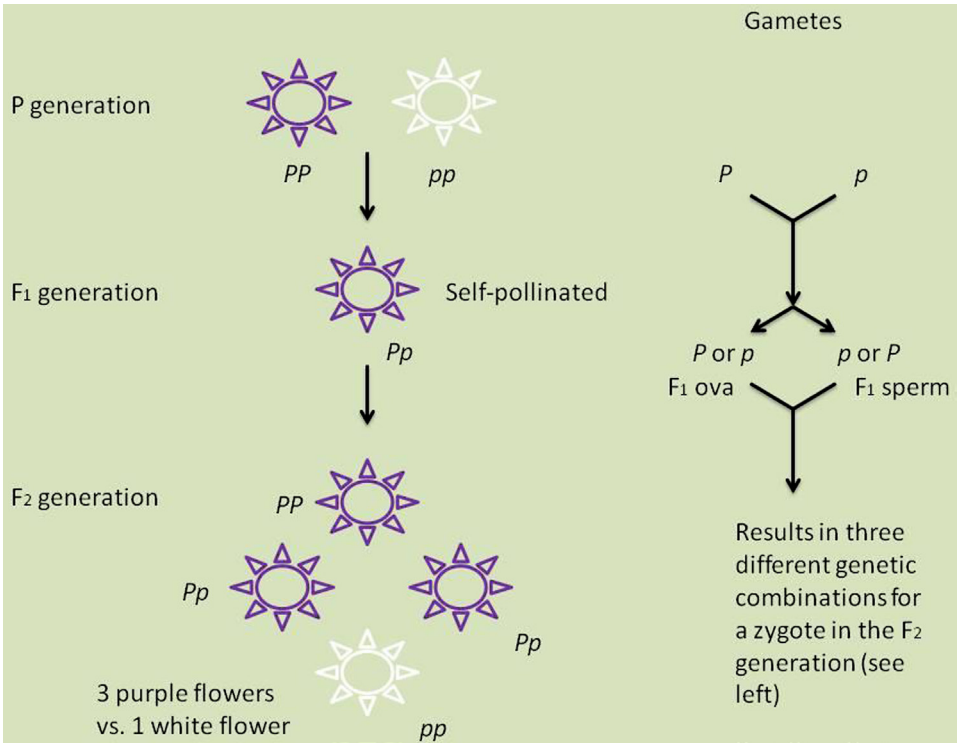

FIGURE 2.4 **Mendel's law of segregation.** Shown is Mendel's crossing experiment for a single character (e.g., flower color).

shape, pod shape, pod color, and stem length; he observed that all of the pea plants followed the same pattern of inheritance as that seen in flower color, with a typical ratio of 3:1 in the F_2 generation.

Mendel developed a theory to explain the observed inheritance pattern in flower color that can be separated into four hypotheses:

- Different versions of genes account for variations appearing in the F_2 generation. For example, an alternative gene version is present in white flowers relative to the version in purple flowers. Different gene versions are now known as alleles.
- Two alleles from each parent are inherited to represent a trait. This is not difficult to understand given what we encountered during the discussion of meiosis: in a diploid cell, one homologous chromosome of a pair is inherited from each parent; a genetic locus is thus represented twice along the paired homologous chromosomes. The alleles may be matched at a homologous locus—for example, the true-breeding P generation in flower color—and the alleles may be different at the same locus—for example, the F_1 generation (see Figure 2.4).
- Two different alleles can be either dominant (fully expressed to control for an organism's appearance) or recessive (no noticeable effect on appearance). Thus Mendel's F_1 plants inherited a purple-flower allele from one parent and a white-flower allele from the other parent. That the F_1 plants are purple is possibly because the purple-flower allele (the *P* allele, as shown in Figure 2.4) has a dominant effect on flower color, while the white-flower allele (the *p* allele, as also shown in Figure 2.4) is a recessive allele and its effect on flower color is masked by the dominant *P* allele.
- The two alleles segregate during the formation of a gamete, which means that the reproductive cell (sperm or ovum) has only one of them. As in the F_1 plants, half of the gametes receive the dominant allele and half receive the recessive allele (Figure 2.4). The separation of alleles into gametes is actually the central idea of Mendel's law of segregation.

Figure 2.4 shows how the model of segregation explains the 3:1 ratio observed in the F_2 generation. Two classes of F_1 gametes are formed. When alleles segregate, half of the gametes receive a *P* allele (purple flower) and the rest receive a *p* allele (white flower). During self-pollination, the two classes of an ovum's gametes unite randomly with the two classes of a sperm's gametes, resulting in a total of four possible combinations in a fertilized egg. In the F_2 generation, one-fourth of the plants apparently have two *P* alleles, leading to the expression of purple flowers. Half of the plants have one *P* and one *p* allele and have purple flowers according to the third hypothesis. One-fourth of the F_2 offspring have white flowers with the two *p* alleles, expressing the recessive white flower feature. This accounts for the exact ratio of 3:1 observed in the F_2 generation.

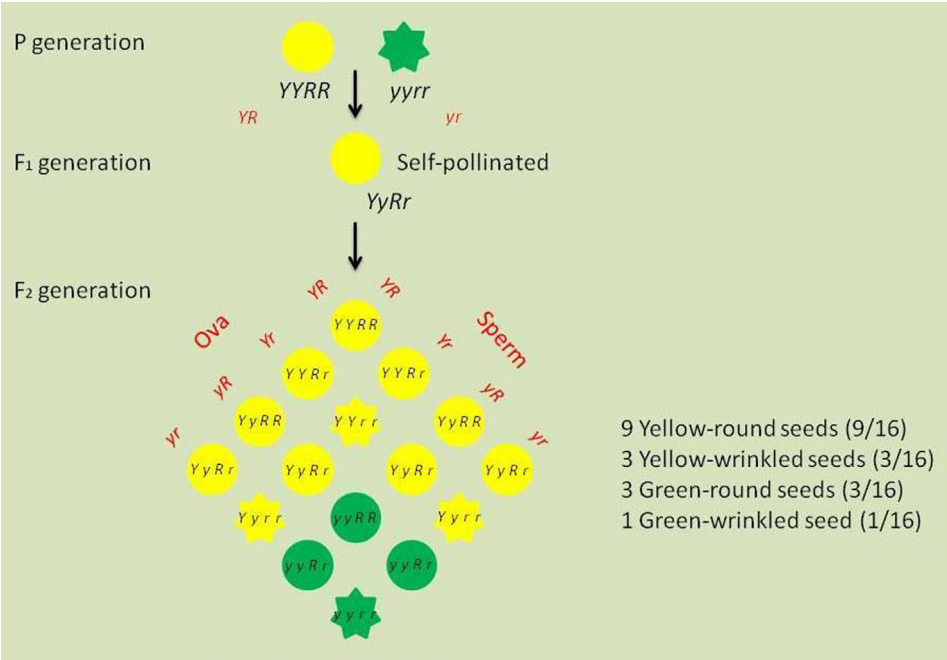

FIGURE 2.5 Mendel's law of independent assortment. Shown is Mendel's crossing experiment between true-breeding parents differing in two characters, seed color and seed shape.

A pair of identical alleles of a gene accounting for an inherited trait is said to be homozygous for that gene. Two different alleles at the same genetic locus representing a trait are said to be heterozygous at that locus. In the example of flower color in peas, *PP* and *pp* are homozygous for purple and white flowers, respectively, with *Pp* as the heterozygous type. Another concept that describes the observed physical appearance is the phenotype, whose genetic make-up is called its genotype. In the same case of flower color, both *PP* and *Pp* express the dominate phenotype of purple flowers, but they are different genotypes.

2.4.2 The Law of Independent Assortment

Mendel discovered the model of allele segregation into gametes using parental varieties that differ in a single character (e.g., flower color). He also conducted mating experiments on parental varieties differing in two characters (e.g., seed color and shape). From previous crossing experiments in single characters, including seed color and shape, Mendel already knew that yellow is a dominant trait (for the *Y* allele) relative to green (for the *y* allele), and that round is a dominant trait (for the *R* allele) relative to wrinkled (for the *r* allele). Breeding a plant with yellow-round seeds (*YYRR*) to a plant with green-wrinkled seeds (*yyrr*), produces F_1 offspring with yellow-round seeds (*YyRr*). Following self-fertilization of the F_1 plants, will the *Y* and *R* alleles still be transmitted together to the F_2 generation, or will the two allele pairs segregate independently of each other? To answer this question, we now take a look at the overall design and theoretical outcome of Mendel's experiment on crossing peas differing in both seed color and shape (Figure 2.5).

The experiment produces a ratio of 9:3:3:1 in the F_2 generation: nine yellow-round seeds, three yellow-wrinkled seeds, three green-round seeds, and one green-wrinkled seed (Figure 2.5). In this example, four gametes are formed given self-pollination of the F_1 generation: *YR*, *Yr*, *yR*, and *yr*. When these four ovum classes are fused with four sperm classes, 16 different combinations of gametes' alleles are generated in the F_2 offspring (Figure 2.5). The results of this experiment support the independent segregation of each pair of alleles into gametes. Indeed, Mendel obtained 315 yellow-round, 108 green-round, 101 yellow-wrinkled, and 32 green-wrinkled seeds from his experiment—a ratio of roughly 9:3:3:1. This pattern of inheritance is now defined as Mendel's law of independent assortment.

2.4.3 Mendelian Patterns of Inheritance in Humans

In modern genetics, Mendelian principles have been extended to more complex inherited traits than Mendel described. His peas have a relatively simple genetic basis—each character is determined by only one gene with two versions (or alleles), of which one is completely dominant. In fact, the relationship between genotype and phenotype for the majority of heritable traits is very complicated, but the laws of segregation and independent assortment can still be applied.

Recall from previous sections that pea characters, such as flower color, seed color, and seed shape, are completely controlled by their respective dominant alleles: *P*, *Y*, and *R*. In the case of flower color, Mendel's heterozygous F_1 offspring (*Pp*) all had purple flowers because the *P* allele shows a completely dominant effect over the recessive *p* allele. However, some heterozygous genotypes may cause incomplete dominance, meaning that the appearance of those heterozygous individuals has an intermediate phenotype between the phenotypes of the parent generation. Along with complete and incomplete dominance patterns of inheritance, there is co-dominance, in which a heterozygous individual expresses both phenotypes of the two alleles. Furthermore, the dominant effect of one allele on a phenotype is reflected by the mechanisms/pathways from genotype to phenotype, which does not imply the ability of one allele to mute another at the DNA level or the abundance of that allele in a population.

The relationship between genotype and phenotype may also be explained by multiple gene alleles (instead of only the two reported by Mendel); pleiotropy (i.e., one gene affects several phenotypic traits); epistasis (i.e., a gene at one locus interferes with the expression of a second gene at a different locus); and environment (e.g., nutrition affects human height and sun exposure affects skin color). Some characters, such as human height and skin color, result from an additive effect of two or more genes in a continuous fashion. These characters are said to be polygenic. Environment influences these polygenic traits, which are thus known as multifactorial.

Mendel's discovery of the patterns of individual gene transmission from parents to offspring led to Mendelian models, which were developed and broadly used to explain the inheritance patterns of epistasis and polygenic characters. In the case of human inheritance, family pedigree analysis shows evidence that supports Mendelian patterns, with some following those patterns recessively (i.e., inherited from the heterozygous genotype) or dominantly (i.e., inherited from the dominant allele). Besides these simple Mendelian disorders, humans are more prone to diseases that have a multifactorial basis. For example, heart disease, diabetes, cancer, and many others diseases are the result of multiple genes, interactions between genes, and interactions between genes and the environment. Using technologies developed in recent years, studies have been conducted on the genetic and environmental components of multifactorial human traits. These will be discussed in later chapters.

2.5 PUBLIC DATABASES FOR BIOMEDICAL RESEARCH IN HUMANS

Groups of researchers have formed large-scale, international collaborations with the goal of creating accessible public databases of human genetic or epigenomic data. These databases will aid basic biomedical research that promotes understanding of the biology of human health and disease. Such projects include the International HapMap Project, the 1000 Genomes Project, the Encyclopedia of DNA Elements (ENCODE), and the Roadmap Epigenomics Project.

The International HapMap Project (http://hapmap.ncbi.nlm.nih.gov/) focuses on the identification of the common patterns (haplotypes) of genetic variations and the determination of tag single-nucleotide polymorphisms (SNPs) that represent them. Analysis of 1.6 million SNPs in 11 populations of African, European, and Asian ancestries has been carried out, with a total sample size of 1184 (HapMap Phase I, II, and III, called "HapMap 3") [1]. This integrated dataset effectively captures common variants with minor allele frequency (MAF) of $\geq 5\%$ in the related populations, and it has improved imputation accuracy for variants with lower frequencies (MAF $\leq 5\%$). The project provides a robust reference panel for studying human genetic variation across various diseases and other common complex traits [1].

In October 2012, the 1000 Genomes Project (www.1000genomes.org/) Consortium announced the sequencing data from 1092 human genomes for 14 populations drawn from Europe, East Asia, Sub-Saharan Africa, and the Americas. This includes low-coverage whole-genome sequence data (2–6 times), targeted deep-exome sequence data (50 times), and dense SNP genotype data. Ultimately, ~2500 individuals from 26 populations will be sequenced. The aim of the 1000 Genomes Project is to generate a more comprehensive catalog of genetic variations by capturing SNPs at a frequency of 1% in the human genome [2].

ENCODE (http://genome.ucsc.edu/ENCODE/), funded by the National Human Genome Research Institute (NHGRI), began in September 2003 with the aim of identifying all functional elements in the human genome. These include protein-coding regions, RNA-transcribed regions, transcription factor binding sites, chromatin structure and histone modification sites, and DNA methylation sites. So far, the overall results reflect only a small portion of the potential functional elements encoded in the genome [3]. Other factors, modifications, and cell types can be studied and added to create a larger and more comprehensive database for understanding the functions of the human genome. Also, integration with other, related projects (for example, the Roadmap Epigenomics Project) will allow a deeper analysis of genes and regulatory factors and an understanding of the mechanisms of regulation [3].

The Roadmap Epigenomics Project (www.roadmapepigenomics.org/) was developed for documenting human epigenomic data to map DNA methylation, histone modification, chromatin accessibility, and small RNA transcripts using next-generation sequencing technologies in stem cells and *ex vivo* normal tissues. These are representative of the tissues involved in human disease. Normal epigenomes are provided and serve as a reference for possible combined investigation

with other projects. The raw sequence data, epigenomic signatures, and integrated maps are released rapidly into the public domain. Standardized protocols and analytical tools are also provided as guidelines to the scientific community.

2.6 CONCLUSION

In this chapter, we first looked at the cell structure and function of organelles using an animal cell. We then moved to the topics of cell division, including mitosis, which produces two daughter cells identical to the parent cell, and meiosis, which generates four daughter cells different from the parent cell as well as from each other. Last, we reviewed Mendel's crossing experiments on garden peas and the fundamental concepts of inheritance revealed by his experiments. The impact of these principles on human genetics was also reviewed, followed by information on several publicly available databases for human biomedical research.

GLOSSARY

Allele one version of a gene at a given locus along a chromosome

Band During cell division, the specific staining pattern (light and dark stripes) is observed for chromosomes. Such patterns can help in identifying chromosomes and evaluating their structure

Binary fission a type of cell division that applies to prokaryotes, such as bacteria. One cell is divided in two, with two complete and identical genomes present in the two daughter cells

Centromere a constricted chromosomal region that holds sister chromatids together during cell division. The centromere also separates a chromosome into a short arm and a long arm

Character a heritable feature that varies among individuals

Chromatid during the S phase of the cell cycle, each chromosome is duplicated. Following replication, each chromosome consists of two identical sister chromatids, which contain matched copies of the DNA sequence at every locus

Chromatin fiber the 30 nm coil of DNA and proteins that forms the basic structure of chromatin

Cytokinesis the division of the cytoplasm. Cytokinesis immediately follows the division of the nucleus

Cytoskeleton protein filaments within cells that maintain cell shape and cell movement

DNA the molecule that encodes the genes responsible for the structure and function of an organism. Genetic information carried by DNA molecules is transmitted from one generation to the next

DNA methylation methyl groups, consisting of one carbon atom and three hydrogen atoms, attach to DNA molecules at cytosine bases, resulting in reduced transcription of the gene

Endomembrane system all membranes, which are suspended in the cytoplasm within a cell, can divide the cell into structural and functional compartments/organelles. In a eukaryotic cell, endomembrane organelles include the nuclear envelope, the endoplasmic reticulum, the Golgi apparatus, lysosomes, vacuoles, vesicles, and the cell membrane. The endomembrane system does not contain mitochondrial membranes

Epigenomics the study of global gene expression changes caused by epigenetic processes that do not involve any change in the underlying DNA sequence

Epistasis the expression of one gene depends on the expression of one or more independently inherited genes

Eukaryote an organism whose cells contain a nucleus and other membrane-bound components. Many unicellular organisms, such as protozoa, are eukaryotes. All multicellular organisms—animals, plants, and fungi—are eukaryotes

Exome the part of the genome that corresponds to exons, which are the coding sequences of DNA present in mature messenger RNA. The exome constitutes about 1% of the total human genome

Gamete a cell/gamete that carries half the genetic information of an individual fuses with another cell/gamete in organisms that reproduce sexually. There are two types of gametes: a sperm is produced by a male and an ovum is produced by a female

Gene the basic physical unit of heredity. For example, a segment of DNA that is arranged in a linear manner along a chromosome is a gene. A gene codes for a specific protein that has a particular characteristic or function

Genome the entire genetic material found in a cell. In the case of humans, the genome includes 23 pairs of chromosomes in the nucleus and the chromosomes contained in a cell's mitochondria

Genotype the genetic make-up of a cell or organism. Also, a set of alleles inherited at a locus

Haplotype a set of alleles or single-nucleotide polymorphisms found on the same chromosome, tending to be inherited together

Imputation in statistics, imputation is a process of replacing missing data with other estimated probable values. In genetics, imputation is a method used to fill in missing genotypes in a study dataset

Kinetochore a protein structure on chromatids, allowing the spindle fibers to attach and pull the sister chromatids apart during cell division

Linked genes genes on the same chromosome tend to be segregated and inherited together

Locus the location or the physical site of an individual gene or DNA sequence on a chromosome

Minor allele frequency the frequency of the least common allele in a given population

Mutation an alteration in a DNA sequence from its natural state. The effect of any mutation might be deleterious or benign

Next-generation sequencing a high-throughput sequencing technology relative to capillary electrophoresis–based Sanger sequencing, producing thousands or millions of sequences simultaneously. This technology can be applied to DNA analysis, RNA analysis, and gene regulation analysis

Organelle a subcellular structure within a cell. An organelle is usually enclosed by its own membrane for executing its specific function independently of other organelles in a cell, particularly a eukaryotic cell

Organism any living system that has the ability to grow, reproduce, maintain homeostasis within itself, and function independently. An organism may be either unicellular or multicellular. All organisms on Earth can be further divided into eukaryotes and prokaryotes

Phenotype a gene's expression of observable physical and/or biochemical characteristics. Some phenotypes are heavily influenced not only by genes but also by the environment

Pleiotropy multiple physical effects caused by a single gene. The underlying mechanism of pleiotropy may be a gene involved in different metabolic pathways that contribute to different phenotypes

Prokaryote an organism lacking a membrane-enclosed nucleus. Most prokaryotes are unicellular. No membrane-bound organelles are present in the prokaryotic cells. The intracellular components

of a prokaryotic cell are gathered together and enclosed only by the cell membrane

Recombination the new combinations of the traits in offspring that are inherited from its parents, now more commonly known as the exchange of a DNA segment between two homologous chromosomes during meiosis, which causes new combinations of hereditary material in a gamete

RNA a molecule synthesized from the DNA template, with the alternating sugar ribose to replace the deoxyribose present in a DNA molecule. Different types of RNA exist in a cell: messenger RNA, ribosomal RNA, transfer RNA, and some small RNAs

Sequencing the technique for determining the exact DNA sequence or nucleotides (A, C, G, and T). DNA-sequencing technology is developing fast and becoming less expensive. For example, whole-genome and whole-exome sequencing is now available for studying the association between a DNA sequence and a disease

Single nucleotide polymorphism a change in a single nucleotide at a genetic locus with a minor allele frequency of 1% or higher in a population

Somatic cell the cell forms the body of an organism. For example, in humans, somatic cells form all internal organs, skin, bones, and connective tissues. Somatic cells are diploid

Synapsis the pairing of two homologous chromosomes at the early stage of meiosis. This allows the matching of homologous chromosomal pairs and prepares for possible crossover between them

Trait a variant of a character, which may be determined by genes, the environment, and the interactions between the two

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REFERENCES

[1] Altshuler DM, Gibbs RA, Peltonen L, Altshuler DM, Gibbs RA, Peltonen L, et al. Integrating common and rare genetic variation in diverse human populations. Nature 2010;467(7311):52–8.

[2] Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, et al. An integrated map of genetic variation from 1,092 human genomes. Nature 2012;491(7422):56–65.

[3] Dunham I, Kundaje A, Aldred SF, Collins PJ, Davis CA, Doyle F, et al. An integrated encyclopedia of DNA elements in the human genome. Nature 2012;489(7414):57–74.