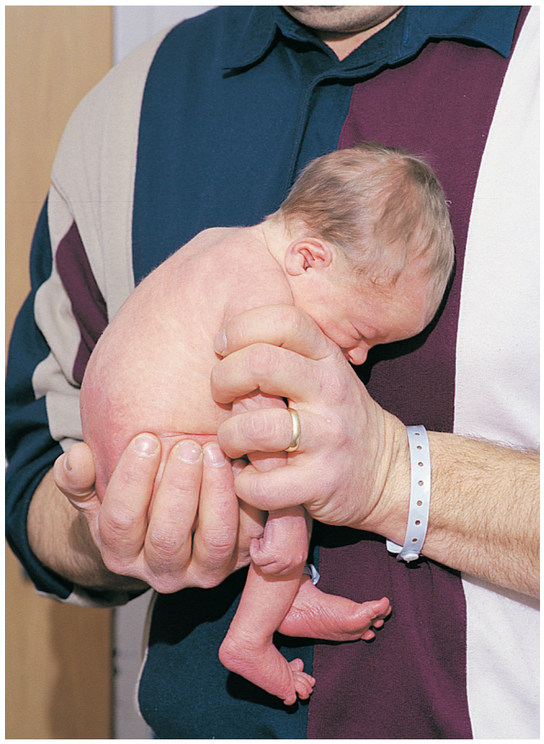
CHAPTER 1

# Overview of Genetics

CHAPTER CONTENTS





The genome tucked into each of this newborn's cells will influence much of the new individual's future—but the environment has a powerful effect too.

Genetics is the study of inherited traits and their variation. Sometimes people confuse genetics with genealogy, which considers relationships but not traits. With the advent of tests that can predict genetic illness, some people have even compared genetics to fortunetelling! But genetics is neither genealogy nor fortunetelling—it is a life science.

**Genes** are the units of heredity. They are biochemical instructions that tell **cells,** the basic units of life, how to manufacture certain proteins. These proteins ultimately underlie specific traits; they provide a great variety of characteristics that create much of our individuality, from our hair and eye color, to the shapes of our body parts, to our talents and personality traits (**figure 1.1**). For example, proteins called keratins comprise our hair and fill our skin cells. One consequence of impaired keratin production is the "scaly skin" disease ichthyosis, shown in figure 6.7.

A gene is composed of the molecule **deoxyribonucleic acid,** more familiarly known as **DNA.** Some traits are determined nearly entirely by genes; most traits, however, also have environmental components. The complete set of genetic information characteristic of an organism, including protein-encoding genes and other DNA sequences, constitutes a **genome.** Researchers at both a multinational public consortium and a private company deciphered the DNA building block sequence of the human genome in 2000 and will be analyzing those results for many years.

Genetics is unlike other life sciences in how directly and intimately it affects our lives, as well as those of our descendants. It obviously impacts our health, because we inherit certain diseases and disease susceptibilities. But principles of genetics also touch history, politics, economics, sociology, art, and psychology, and they force us to wrestle with concepts of benefit and risk, even tapping our deepest feelings about right and wrong. A field of study called **bioethics** was founded in the 1970s to address many of the personal issues that arise in applying medical technology. Bioethicists have more recently addressed concerns that new genetic knowledge raises, such as privacy, confidentiality, and discrimination.

An even newer field is **genomics,** which considers many genes at a time. The genomic approach is broader than the emphasis on single-gene traits that pervaded genetics during the twentieth century. Genomics addresses the more common illnesses influenced by many genes that interact with each other and the environment. Considering genomes also enables us to compare ourselves to other species—the similarities can be astonishing and quite humbling.

a.

b.

**Figure 1.1 Inherited traits.** Genes control many familiar traits, from hair color **(a)** to athletic prowess **(b).**

## 1.1 Genetic Testing

It may take much of the new century to understand our genetic selves. A few individuals have stepped forward to be among the first to probe their genomes. In late 2002, a journalist wrote in *Wired* magazine about undergoing a battery of genetic tests. And J. Craig Venter, who led the private effort to sequence the human genome, acknowledged that his was one of the genomes analyzed. He knows the results, and he has acted on some of them—for example, by taking cholesterol-lowering medication before his cholesterol actually rises to a dangerous level. Venter says that he volunteered his own genetic material to show the world that genome sequencing is not frightening, harmful, or magical and that it can instead be a powerful tool to improve health.

Past editions of this textbook began with a scenario of two college students undergoing genetic testing sometime in the near future. The future is now. Although a laser-based technology that can sequence a genome in minutes is in development, it is more cost-effective, for now, to tailor single, focused tests to detect health-related genetic variants most likely to be present in a particular individual, based on traditional clues such as personal health, family history, and ethnic background. Tests may look for gene variants known to cause illness or DNA sequences statistically associated with increased risk of developing a particular condition in a particular population. Researchers at several biotechnology companies predict that by 2006, genetic screening for many disorders and disease susceptibilities will be routine.

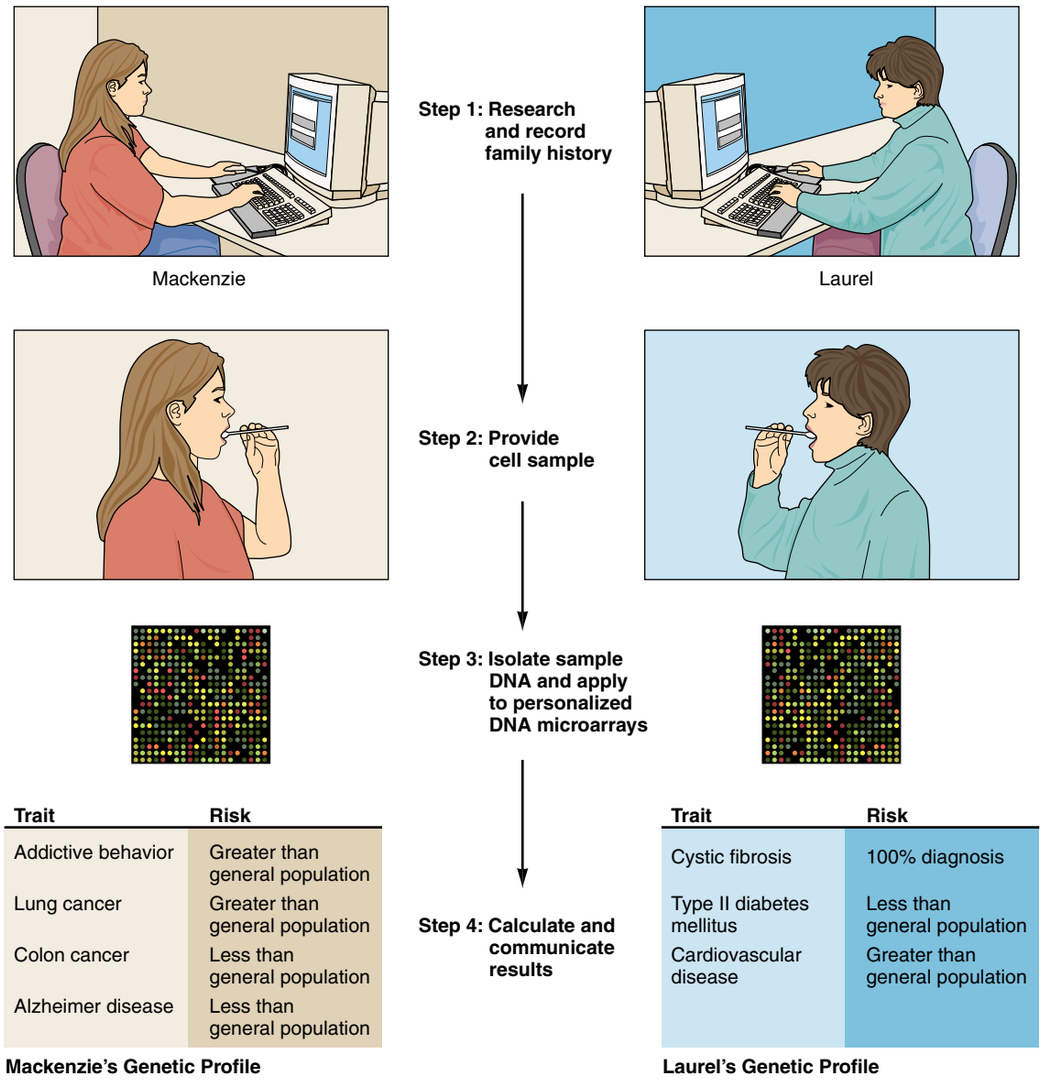
Young people might take genetic tests to prevent, delay, control, or treat symptoms that have a high probability of occurring, or to gain information, perhaps to make decisions about whether to have children or not. Consider two 19-year-old college roommates, Mackenzie and Laurel, who choose to undergo limited and tailored genetic testing. Each has her genome scanned for several hundred genes and DNA sequences. Some of the results illustrate the type of information that lies in our DNA.

Mackenzie requests three panels of tests, based on her family background. An older brother and

her father smoke cigarettes and are prone to alcoholism, and her father's mother, also a smoker, died of lung cancer. Two relatives on her mother's side had colon cancer. Mackenzie also has older relatives on both sides who have Alzheimer disease. She asks for tests to detect genes that predispose her to developing addictions, certain cancers, and inherited forms of Alzheimer disease.

Laurel requests different tests. She frequently has bronchitis and pneumonia, so she has a test for cystic fibrosis (CF), because CF's milder forms increase susceptibility to respiratory infections. These cases often go unrecognized as CF, as Laurel knows from her genetics class. Because her sister and mother also have bronchitis often, she suspects mild CF in the family.

Laurel also requests tests for type II (non-insulin-dependent) diabetes mellitus, because several of her relatives developed this condition as adults. Medication can control the abnormal blood glucose level, but dietary and exercise plans are essential, too. If Laurel knows she is at high risk, she'll adopt these habits now. However, Laurel refuses a test for inherited susceptibility to Alzheimer disease, even though a grandfather died of it. She does not want to know if this currently untreatable condition is likely to lie in her future. Finally, because past blood tests revealed elevated cholesterol, Laurel seeks information about her risk of developing heart and blood vessel (cardiovascular) disease.




| Trait | Risk |
|---|---|
| Addictive behavior | Greater than general population |
| Lung cancer | Greater than general population |
| Colon cancer | Less than general population |
| Alzheimer disease | Less than general population |

**Mackenzie's Genetic Profile**

| Trait | Risk |
|---|---|
| Cystic fibrosis | 100% diagnosis |
| Type II diabetes mellitus | Less than general population |
| Cardiovascular disease | Greater than general population |

**Laurel's Genetic Profile**

**Figure 1.2 Genetic testing.** Genetic tests are slowly becoming part of health care, revealing probabilities of developing certain conditions and refining medical diagnoses.

Each student proceeds through the steps outlined in **figure 1.2.** The first step is to register a complete family history. Next, each young woman swishes a cotton swab on the inside of her cheek to obtain cells, which are then sent to a laboratory for analysis. There, DNA is extracted and cut into pieces, then tagged with molecules that fluoresce under certain types of light. The students' genetic material is then applied to "DNA chips," postage-stamp-sized pieces of glass or nylon with particular sequences of DNA attached. Because the genes on the chip are aligned in fixed positions, this device is technically called a **DNA microarray.**

A typical DNA microarray bears hundreds or even thousands of DNA pieces. (Several companies offer the entire human genome on a chip.) One of Mackenzie's DNA chips bears genes that regulate her circadian (daily) rhythms and encode the receptor proteins on nerve cells that bind neurotransmitters. If Mackenzie indulges in addictive substances or activities, certain variants of these genes may increase her risk of developing addictive behaviors. Another DNA chip screens for gene variants that greatly increase the risk for lung cancer, and a third DNA chip detects genes associated with colon cancer. Her fourth DNA chip is smaller, bearing genes that cause Alzheimer disease and several DNA sequences that are associated with increased risk of developing other types of dementia.

Laurel's chips suit her background and requests. The microarray panel for CF holds 600 DNA sequences from variants of the CF gene associated with milder symptoms. The DNA microarray for diabetes bears gene

variants that reflect how Laurel's circulation transports glucose and how efficiently her cells take it up. The DNA microarray for cardiovascular disease is the largest and most diverse. It includes thousands of genes whose protein products influence blood pressure, blood clotting, and the synthesis, transport, and metabolism of cholesterol and other lipids.

The next day, a **genetic counselor** explains the findings. Mackenzie learns that she is indeed predisposed to develop addictive behaviors and lung cancer—a dangerous combination. But she does not face increased risk for inherited forms of colon cancer or Alzheimer disease.

Laurel does have mild CF, which explains her frequent respiratory infections. The DNA microarray indicates which types of infections she is most susceptible to, and which antibiotics will most effectively treat them—very useful information. She might even be a candidate for gene therapy—periodically inhaling a preparation containing the normal version of the CF-causing gene delivered in a "disabled" virus that would otherwise cause a respiratory infection. The diabetes test panel reveals her risk is lower than that for the general population. Laurel also has several gene variants that raise her blood cholesterol level. The cardiovascular disease DNA microarray panel indicates which cholesterol-lowering drug she will respond to best, should diet and exercise habits be insufficient to counter her inherited tendency to accumulate lipids in the bloodstream.

The DNA tests that Mackenzie and Laurel undergo will become part of their medical records, with tests added as their interests and health status change. For example, shortly before each young woman tries to become pregnant, she and her partner will take tests to detect whether they are carriers for any of several hundred illnesses, because two carriers of the same condition can pass it to offspring even when they are not themselves affected. If Laurel or Mackenzie are in this situation, DNA microarray tests on DNA from a fetus can determine whether it has inherited the illness. Such an alert can ensure that treatment begins soon enough to prevent or minimize symptoms in infants.

Illness may also prompt Laurel or Mackenzie to seek further genetic testing. If either young woman suspects she may have cancer, for example, a type of DNA microarray called an expression panel can determine which genes are turned on or off in affected cells compared to nonaffected cells of the same type. **"Gene expression"** refers to the cell's use of the information in the DNA sequence to synthesize a particular protein. In contrast, the DNA from cheek lining cells that Mackenzie and Laurel have tested reveals specific gene variants and DNA sequences that are present in *all* their cells. An expression panel displays the genes that actively produce specific proteins in the cell types that are affected in an illness.

DNA expression microarrays are very useful in diagnosing and treating cancer. They can identify cancer cells very early, when treatment is more likely to work. These devices also identify a set of 128 key gene variants that indicate cancer, as well as others that reveal if and how quickly the disease will progress. DNA microarrays can also show how tumor cells and the individual's immune system are likely to respond to particular drugs, and which drugs will produce intolerable side effects.

The first DNA microarray to analyze cancer, the "lymphochip," identifies cancer-causing and associated genes in white blood cells (see figure 18.2). A different DNA microarray test, for breast cancer, is used on samples of breast tissue to track the course of the disease and assess treatment. In one study, DNA tests were performed on tumor cells of 20 women with advanced breast cancer before and after a 3-month regimen of chemotherapy. The gene expression pattern returned to normal only in the three women who ultimately responded to the treatment. Therefore, the chip can predict which women are likely to respond to which drugs. A prostate cancer DNA microarray predicts the likelihood that a tumor will spread, information that is important in planning initial treatment.

Though Laurel and Mackenzie will gain much useful information from the genetic tests, their health records will be kept confidential. Laws prevent employers and insurers from discriminating against anyone based on genetic information. This is a practical matter—everyone has some gene variants associated with disease. In general, insurance companies decide whom to insure and at what rates based on symptoms present before or at the time of request for coverage. The results of genetic tests are not clinical diagnoses, but probability statements about how likely certain symptoms are to arise in an individual. The section on health care later in the chapter returns to the issue of insurer or employer discrimination based on genetic test results.

New health care professionals are being trained in genetics and the new field of genomics; older health care workers are also learning how to integrate new genetic knowledge and technology into medical practice. Another change has occurred in the breadth of genetics. In the past, physicians typically encountered genetics only as rare disorders caused by single genes or as chromosome disorders such as trisomy 21 Down syndrome. Today, medical science is beginning to recognize the role that genes play in many common types of conditions.

## Key Concepts

Genetics investigates inherited traits and their variations. Genes, composed of DNA, are the units of inheritance, and they specify particular proteins, though not all DNA encodes protein. A genome is the complete set of genetic instructions for an organism. Human genome information will personalize medicine and predict future illness.

## 1.2 The Breadth of Genetics

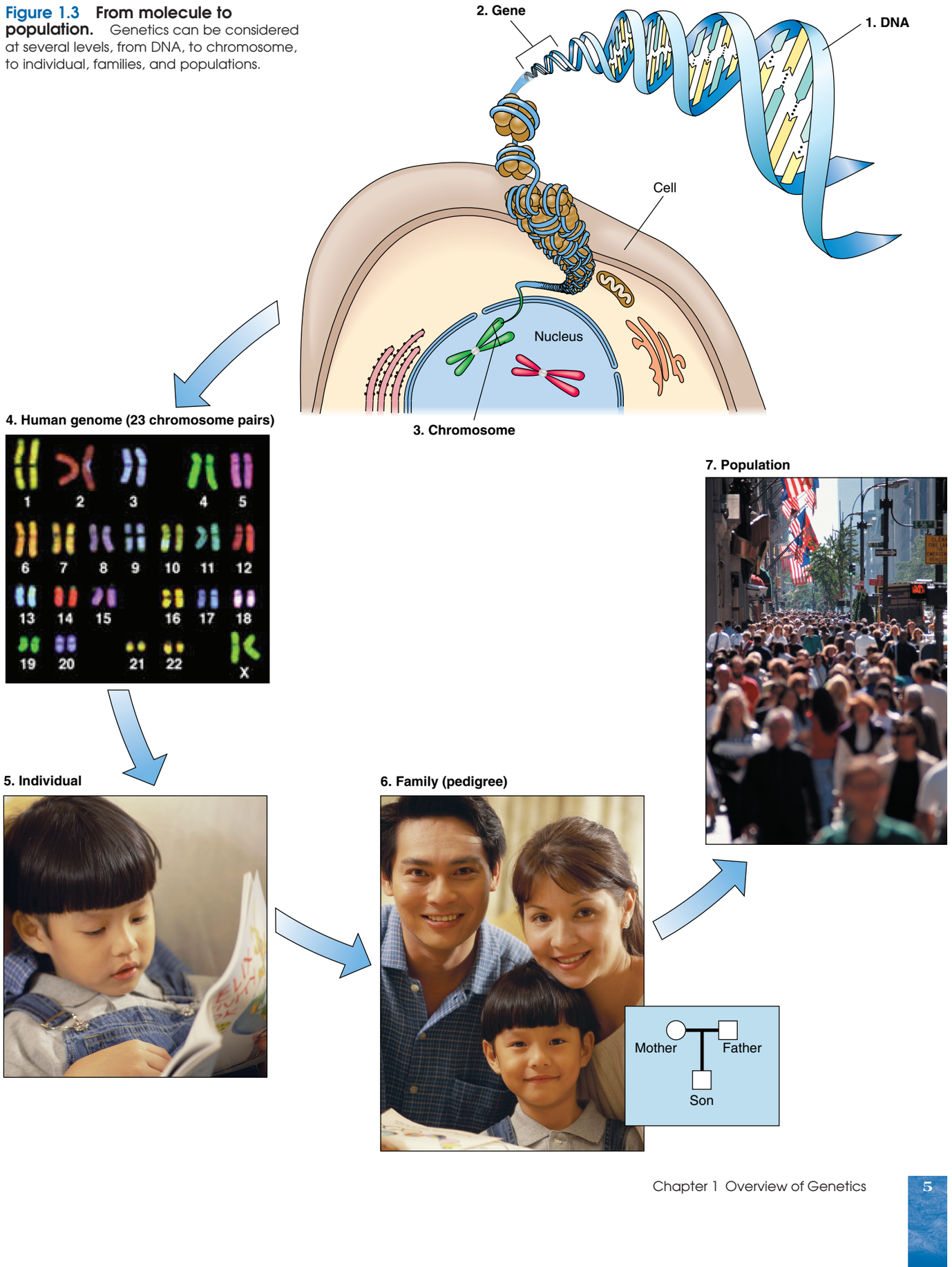
Genetics considers the transmission of information at several levels, from the molecular level to populations and even to the evolution of species (**figure 1.3**).

### DNA

Genes consist of sequences of four types of DNA building blocks—adenine, guanine, cytosine, and thymine, abbreviated A, G, C, and T. Each base bonds to a sugar and a phosphate group to form a unit called a nucleotide. DNA bases are nitrogen-containing, or nitrogenous, bases. In genes, DNA bases provide an alphabet of sorts. Each consecutive three DNA bases specifies the code for a particular amino acid, and amino acids are the building blocks of proteins.

An intermediate language, also encoded in nitrogenous base sequences, is contained in **ribonucleic acid (RNA).** One type of RNA carries a copy of a DNA sequence and presents

**Figure 1.3 From molecule to population.** Genetics can be considered at several levels, from DNA, to chromosome, to individual, families, and populations.



it to other parts of the cell. In this way, the information encoded in DNA can be used to produce RNA molecules, which are then used to manufacture proteins. **Proteomics** is a new field that considers the proteins made in a particular cell type. DNA remains in the nucleus to be passed on when a cell divides.

Only about 1.5 percent of the DNA in the human genome encodes protein. The rest of the DNA includes many highly repeated sequences with unknown functions; sequences that activate or suppress protein-encoding genes; viral nucleic acid sequences that have inserted into the human genome; and other sequences whose origin and function are yet to be discovered. Only recently, for example, have researchers discovered that RNA actually controls itself. Small, double-stranded RNA molecules can bind to the single-stranded, protein-encoding messenger type of RNA, squelching a gene's activity. This process is called **RNA interference,** or RNAi, discussed in chapter 11. Its discovery not only helps to explain how genes are controlled, but illustrates how we are constantly learning about new aspects of gene function.

## Genes, Chromosomes, and Genomes

Individual protein-encoding genes may differ from each other by small changes in the DNA base sequence. The variants of a gene are called **alleles,** and these changes in DNA sequence arise by a process called **mutation.** Some mutations cause disease; others provide variation, such as freckled skin; and some mutations may help. For example, one mutation makes a person's cells unable to manufacture a surface protein that binds HIV. These people are resistant to HIV infection. This genetic variant might have remained unknown had AIDS not arisen. Many mutations have no visible effect at all because they do not change the encoded protein in a way that affects its function, just as a minor spelling error does not obscure the meaning of a sentence.

Parts of the DNA sequence can vary among individuals, yet not change external appearance or health. A variant in sequence that is present in at least 1 percent of a population is called a **polymorphism.** A polymorphism can occur in a part of the DNA that encodes protein, or in a part that does not.

*Polymorphism* is also a general term that means "many forms." A polymorphism can be helpful, harmful, or, in most instances, have no obvious effect.

Researchers have identified millions of **single nucleotide polymorphisms** (SNPs, pronounced "snips"), which are single base sites that differ among individuals. The human genome may include up to 20 million SNPs, or 1 in every 1,250 or so DNA nucleotides, although they are not evenly distributed. DNA microarrays can include both disease-causing mutations and SNPs that merely mark places where people differ. Researchers conduct an association study to identify combinations of SNPs that are found almost exclusively among people with a particular disorder. In this way, SNP patterns detected with DNA microarrays are associated with disease risks.

Genes are part of larger structures called **chromosomes,** which also include proteins that the DNA wraps around. A human cell has 23 pairs of chromosomes. Twenty-two pairs are **autosomes,** or chromosomes that do not differ between the sexes. The autosomes are numbered from 1 to 22, with 1 the largest. The other two chromosomes, the X and the Y, are **sex chromosomes.** The Y chromosome bears genes that determine maleness. In humans, a female has two X chromosomes and a male has one X and one Y.

Charts called **karyotypes** order the chromosome pairs from largest to smallest. The chromosomes are stained with dyes or fluorescent chemicals bound to specific DNA sequences to create different patterns, which can reveal abnormalities.

The 23 chromosome pairs in a human cell hold two complete sets of genetic information. The human genome contains 24,000 or more protein-encoding genes, scattered among 3 billion DNA bases among each set of 23 chromosomes. Two entire genomes are tucked into each of a person's many cells. Geneticist Hermann J. Muller wrote in 1947, "In a sense we contain ourselves, wrapped up within ourselves, trillions of times repeated."

## Cells, Tissues, and Organs

A human body consists of trillions of cells. All cells except red blood cells (which are actually fragments) contain all of the genetic instructions, but cells differ in appearance and function because they use only some of their genes, a process called **differentiation.** Specialized cells aggregate and interact to form tissues, which in turn form the organs and organ systems.

Organs include rare, less specialized cells, called **stem cells,** that can divide to yield another stem cell and a cell that goes on to differentiate. Thanks to stem cells, organs can grow and repair damage. When researchers better understand how stem cells function, these cells may be used to heal injuries or replace cells destroyed in degenerative disorders such as Parkinson disease and Alzheimer disease.

## Individual

Two terms distinguish the alleles that are *present* in an individual from the alleles that are *expressed.* The **genotype** refers to the underlying instructions (alleles present), while the **phenotype** is the visible trait, biochemical change, or effect on health (alleles expressed). Alleles are further distinguished by how many copies it takes to affect the phenotype. A **dominant** allele produces an effect when present in just one copy (on one chromosome), whereas a **recessive** allele must be present on both chromosomes to be expressed. (Alleles on the Y chromosome are an exception; recessive alleles on the X chromosome in males are expressed because there is no second X chromosome to block expression.)

## Family

Individuals are genetically connected into families. A person has half his or her genes in common with each parent and each sibling, and one-quarter with each grandparent. First cousins share one-eighth of their genes.

Traditionally, the study of traits in families has been called transmission genetics or Mendelian genetics, for Gregor Mendel, who pioneered the study of single genes using pea plants. Molecular genetics, which considers DNA, RNA, and proteins, often begins with transmission genetics, when an interesting trait or illness in a family comes to a researcher's attention. Charts called pedigrees represent the members of a family and indicate which individuals have particular inherited traits. Figure 1.3 includes a pedigree for a mother, father, and son.

## Population

Above the family level of genetic organization is the population. In a strict biological sense, a population is a group of interbreeding individuals. In a genetic sense, a population is a large collection of alleles, distinguished by their frequencies. People from a Swedish population, for example, would have a greater frequency of alleles that specify light hair and skin than people from a population in Ethiopia who tend to have dark hair and skin. The fact that groups of people look different and may suffer from different health problems reflects the frequencies of their distinctive sets of alleles. All the alleles in a population constitute the **gene pool.** (An individual does not have a gene pool.)

Population genetics is very important in applications such as health care and forensics. It is also the very basis of evolution. In fact, evolution is technically defined as changing allele frequencies in populations. These small-scale genetic changes foster the more obvious species distinctions we most often associate with evolution.

## Evolution

Comparing DNA sequences for individual genes, or the amino acid sequences of the proteins that the genes encode, can reveal how closely related different types of organisms are (**figure 1.4**). The underlying assumption is that the more similar the sequences are, the more recently two species diverged from a shared ancestor.

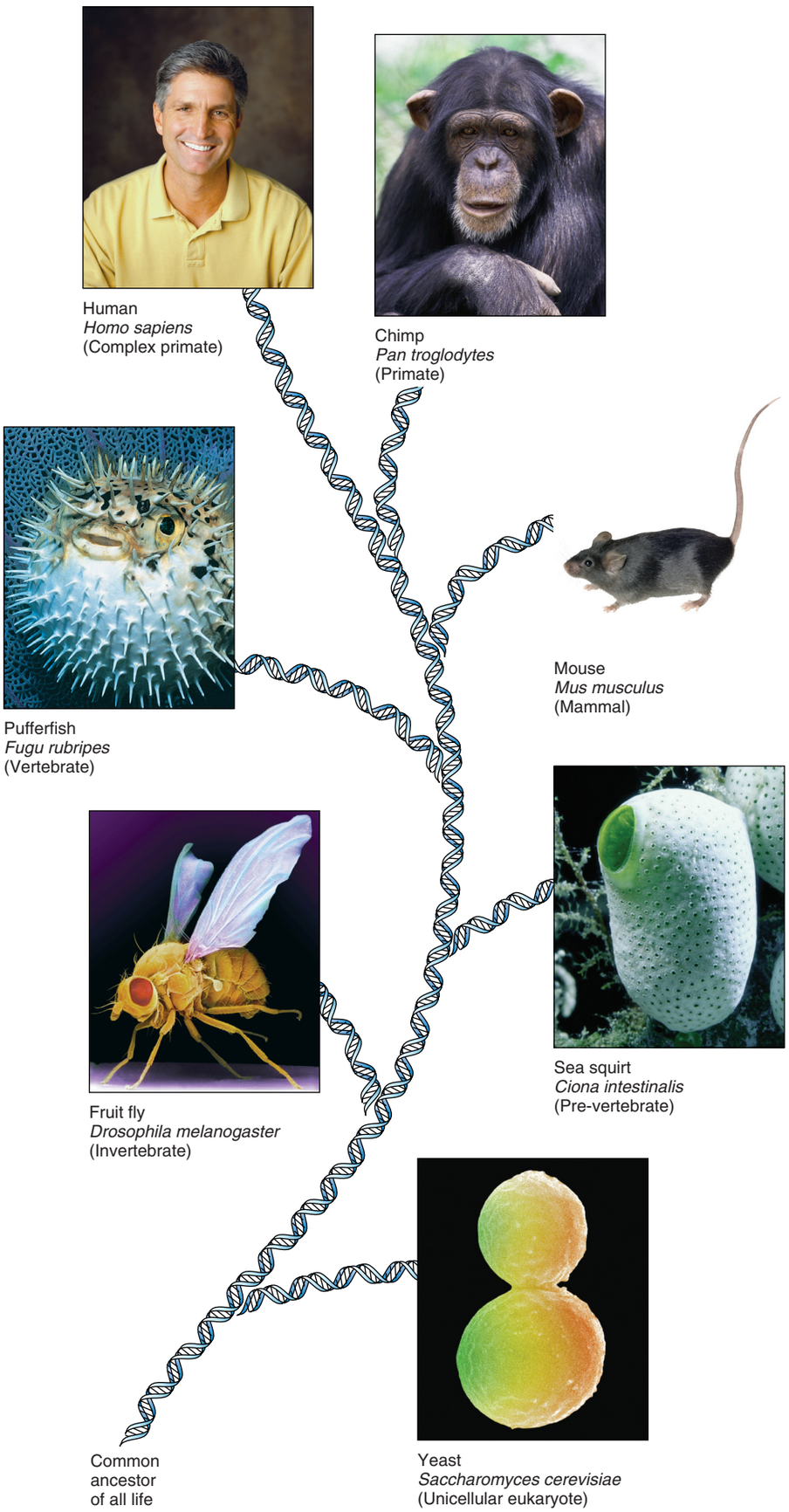



**Figure 1.4 Genes and genomes reveal our place in the world.** All life is related, and different species share a basic set of genes that makes life possible. The more closely related we are to another species, the more genes we have in common. This illustration depicts how humans are related to certain contemporaries who are also having their genomes sequenced—a process that will reveal just how closely related we are.

During evolution, species diverged from shared ancestors. For example, humans diverged more recently from chimps, our closest relative, than from mice, pufferfish, sea squirts, flies, or yeast. Said one researcher who works with the sea squirt, "These little sardinelike guys illuminate where we came from. They are our relatives, as icky as they might look." We even share genes with yeast, a single-celled fungus that nonetheless uses the same biochemical pathways that we do to acquire energy and carry out metabolism.

Genome sequence comparisons reveal more about evolutionary relationships than comparing single genes. Humans, for example, share more than 98 percent of the DNA sequence with chimpanzees. Our genomes differ from theirs more in gene organization and in the number of copies of genes than in the overall sequence. Still, learning the functions of the human-specific genes may explain the differences between us and them. Genome comparisons can clarify our kinship with other species, too. Consider the aardvark, a mammal with a distinctive long snout, also known as the "earth pig." A study that compared specific genes on the chromosomes of various placental mammals found that humans differ the most from the aardvark. This suggests that the aardvark is the most primitive placental mammal (a mammal that nurtures its unborn young through a maternal organ called a placenta).

Humans also share many DNA sequences with mice, pufferfish, and fruit flies. At the level of genetic instructions for building a body, we are not very different from other organisms. We even share some genes necessary for life with single-celled organisms such as yeast.

Comparisons of person to person at the genome level reveal that we are incredibly like one another. Studies of polymorphisms among different modern ethnic groups reveal that modern humans arose in Africa and haven't changed very much since. The gene pools of all groups are subsets of the modern African gene pool. One study compared 377 highly variable genome regions among people in 52 populations from Africa, Eurasia, East Asia, Oceania, and the Americas. The study found 99.9 percent of the DNA examined identical in sequence.

Genome analyses also confirm that race, as defined by skin color, is a social concept, not a biological one. "Race" is actually defined by fewer than 0.01 percent of our genes. Put another way, two members of different races may have more alleles in common than two members of the same race. Very few, if any, gene variants are unique to any one racial or ethnic group. Imagine if we defined race by a different small set of genes, such as the ability to taste bitter substances!

**Table 1.1** defines some of the terms used in this section, and is a summary of most of this book.

## Key Concepts

Genetics can be considered at different levels: DNA, genes, chromosomes, genomes, individuals, families, and populations. • A gene can exist in more than one form, or allele. • Comparing genomes among species reveals evolutionary relatedness.

**Table 1.1**

### A Mini-Glossary of Genetic Terms

| Term | Definition |
|---|---|
| Allele | An alternate form of a gene; a gene variant. |
| Autosome | A chromosome not involved in determining sex. |
| Chromosome | A structure, consisting of DNA and protein, that carries the genes. |
| DNA | Deoxyribonucleic acid; the molecule whose building block sequence encodes the information that a cell uses to construct a particular protein. |
| Dominant | An allele that exerts a noticeable effect when present in just one copy. |
| Gene | A sequence of DNA that has a known function, such as encoding protein or controlling gene expression. |
| Gene expression | A cell's use of DNA information to manufacture specific proteins. |
| Gene pool | All of the genes in a population. |
| Genome | A complete set of genetic instructions in a cell, including DNA that encodes protein as well as other DNA. |
| Genomics | The new field of investigating how genes interact and comparing genomes. |
| Genotype | The allele combination in an individual. |
| Karyotype | A size-order display of chromosomes. |
| Mendelian trait | A trait that is completely determined by a single gene. |
| Multifactorial trait | A trait that is determined by one or more genes and by the environment. Also called a complex trait. |
| Mutation | A change in a gene that affects the individual's health, appearance, or biochemistry. |
| Pedigree | A diagram used to follow inheritance of a trait in a family. |
| Phenotype | The observable expression of an allele combination. |
| Polymorphism | A site in a genome that varies in 1 percent or more of a population. |
| Recessive | An allele that exerts a noticeable effect only when present in two copies. |
| RNA | Ribonucleic acid; the molecule that enables a cell to synthesize proteins using the information in DNA sequences. |
| Sex chromosome | A chromosome that carries genes whose presence or absence determines sex. |

## 1.3 Genes Do Not Usually Function Alone

For much of its short history, the field of genetics dealt almost exclusively with the few thousand traits and illnesses that are clearly determined by single genes, also called **Mendelian traits.** A database called "Online Mendelian Inheritance in Man (OMIM)" lists and describes all known single-gene traits and disorders in humans. OMIM numbers are noted in the appendix for disorders that are mentioned in the text.

Genetics is much more complicated, however, than a one-gene-one-disease paradigm. Most genes do not function alone, but are influenced by the actions of other genes, and sometimes by factors in the environment as well. Traits that are determined by one or more genes and the environment are called **multifactorial,** or complex, traits (**figure 1.5**). (The term *complex traits* has different meanings in a scientific and a popular sense, so this book uses the more precise term *multifactorial.*)

Confusing matters further is the fact that some illnesses occur in different forms—some inherited, some not, some Mendelian, some multifactorial. Usually the inherited forms are rarer, as is the case for Alzheimer disease, breast cancer, and Parkinson disease.

Researchers can develop treatments based on the easier-to-study inherited form of an illness that physicians can then use to treat more common, multifactorial forms. For example, the drugs called statins that millions of people take to lower cholesterol were developed from work on the one-in-a-million children with familial hypercholesterolemia (see figure 5.2).

Knowing whether a trait or illness is Mendelian or multifactorial is important for predicting the risk of recurrence. The probability that a Mendelian trait will occur in another family member is simple to calculate using the laws that Mendel derived, discussed in chapter 4. In contrast, predicting the recurrence of a multifactorial trait is difficult because several contributing factors are in play. Inherited breast cancer illustrates how the fact that genes rarely act alone can complicate calculation of risk.

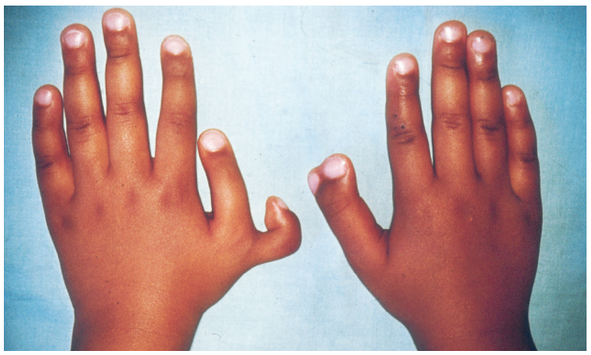
Mutations in a gene called *BRCA1* cause fewer than 5 percent of all cases of breast cancer. But studies of the disease incidence in different populations have yielded confusing results. In Jewish families of eastern European descent (Ashkenazim) with many members affected at a young age, inheriting the most common *BRCA1* mutation confers an 86 percent chance of developing the disease over a lifetime. But women from other ethnic groups who inherit this allele may have only a 45 percent chance of developing breast cancer. A possible explanation is that the second group has different alleles of other genes that interact with *BRCA1* than do the eastern European Jewish families.

Environmental factors may also affect the gene's expression. For example, exposure to pesticides that mimic the effects of estrogen may be an environmental contributor to breast cancer. It can be difficult to tease apart genetic and environmental contributions to disease. BRCA1 breast cancer, for example, is especially prevalent in Long Island, New York. This population includes both many Ashkenazim and many people exposed to pesticides.

Increasingly, predictions of inherited disease are considered in terms of "modified genetic risk," which takes into account single genes as well as environmental and family background information. A modified genetic risk is necessary to predict BRCA1 breast cancer occurrence in a family.

The fact that the environment modifies gene actions counters the concept of **genetic determinism,** or the idea that an inherited trait is unchangeable and its appearance inevitable. The idea that "we are our genes" can be very dangerous. In predictive testing for inherited disease, the potential for environmental effects requires that results be presented as risks rather than foregone conclusions. That is, a person might be told that she has a 45 percent chance of developing BRCA1 breast cancer, not, "You will get breast cancer." Conversely, a person can inherit the normal form of the *BRCA1* gene and still develop breast cancer from a different cause. One danger of do-it-yourself at-home testing for genetic disease is that a person may conclude that the detection of a mutation means unavoidable disease. Such test results only predict risk, and they must be considered with other factors.

Genetic determinism as part of social policy can be particularly harmful. In the past, for example, the assumption that one ethnic group is genetically less intelligent than another led to lowered expectations and fewer educational opportunities for those perceived as biologically inferior. Environment, in fact, has a huge impact on intellectual development. The bioethics essay in chapter 8 considers genetic determinism further.



a.

b.

**Figure 1.5 Mendelian versus multifactorial traits.**
**(a)** Polydactyly—extra fingers and/or toes—is a Mendelian trait, determined by a single gene. **(b)** Hair color is multifactorial, controlled by at least three genes plus environmental factors such as the bleaching effects of sun exposure.

## Key Concepts

Inherited traits are determined by one gene (Mendelian) or by one or more genes and the environment (multifactorial). Even the expression of single genes is affected to some extent by the actions of other genes. Genetic determinism is the idea that an inherited trait cannot be modified.

## 1.4 Geneticists Use Statistics to Represent Risks

Predicting the inheritance of traits in individuals is not a precise science, largely because of the many influences on gene function and the uncertainties of analyzing multiple factors. Genetic counselors calculate risks for clients who want to know the chance that a new family member will inherit a particular disease—or has inherited it, but does not yet exhibit the symptoms.

In general, risk assessment estimates the degree to which a particular event or situation represents a danger to a population. In genetics, that event is the likelihood of inheriting a particular gene or gene combination. The genetic counselor can infer that information from a detailed family history, or from the results of tests that identify a gene variant or an absent or abnormal protein.

Risks can be expressed as absolute or relative figures. **Absolute risk** is the probability that an individual will develop a particular condition. **Relative risk** is the likelihood that an individual from a particular population will develop a condition in comparison to individuals from another group, usually the general population. Relative risk is expressed as a ratio of the probability in one group compared to another. In genetics, relative risks might be calculated by evaluating any situation that might elevate the risk of developing a particular condition, such as one's ethnic group, age, or exposure to a certain danger. The threatening situation is called a **risk factor.** For example, chromosome abnormalities are more common in the offspring of older mothers. Pregnant women who undergo testing for Down syndrome caused by an extra chromosome 21 are compared by age to the general population of pregnant women to derive the relative risk that they are carrying a fetus that has the syndrome. The risk factor is age.

Determining a relative risk may seem unnecessary, because an absolute risk applies to an individual. However, relative risks help health care providers identify patients most likely to have the conditions for which absolute risks can be calculated, and patients most likely to benefit from particular medical tests. A problem that genetic counselors face in assessing risk, however, is that statistics tend to lose their meaning in a one-on-one situation. To a couple learning that their fetus has Down syndrome, it is immaterial that the relative risk was low based on population statistics pertaining to their age group.

Mathematically, absolute and relative risk are represented in different ways. Odds and percentages are used to depict absolute risk. For example, Mackenzie's absolute risk of developing inherited Alzheimer disease over her lifetime is 4 in 100 (the odds), or 4 percent. Determining her relative risk requires knowing the risk to the general population. If that risk is 10 in 100, then Mackenzie's relative risk is 4 percent divided by 10 percent, or 0.4. A relative risk of less than 1 indicates the chance of developing a particular illness is less than that for the general population; a value greater than 1 indicates risk greater than that for the general population. Mackenzie's 0.4 relative risk means she has 40 percent as much risk of inheriting Alzheimer disease as the average person in the general population; a relative risk of 8.4, by contrast, would indicate a greater-than-8-fold risk compared to an individual in the general population.

Determining the risks for Alzheimer disease is actually more complicated than depicted in this hypothetical case. Several genes are involved, the percentage of inherited cases isn't known, and prevalence is highly associated with age. Elevated risk is linked to having more than one affected relative and to an early age of onset. But Alzheimer disease is a very common illness—about 40 percent of people over age 85 have the condition.

Risk estimates can change depending upon how groups being compared are defined. For a couple who has a child with an extra chromosome, such as a child with Down syndrome, the risk of recurrence is 1 in 100, a figure derived from looking at many families who have at least one such child. Therefore, the next time the couple has a child, two risk estimates are possible for Down syndrome—1 in 100, based on the fact that they already have an affected child, and the risk associated with the woman's age. The genetic counselor presents the highest risk, to describe a worst-case scenario. Consider a 23-year-old and a 42-year-old woman who have each had one child with the extra chromosome of Down syndrome. Each faces a recurrence risk of 1 in 100 based on medical history, but the two women have different age-associated risks—the 23-year-old's is 1 in 500, but the 42-year-old's is 1 in 63. The counselor provides the 1 in 100 figure to the younger woman, but the age-associated 1 in 63 figure to the older woman.

Geneticists derive risk figures in several ways. **Empiric risk** comes from population-level observations, such as the 1 in 100 risk of having a second child with an extra chromosome. Another type of risk estimate derives from Mendel's laws. A child whose parents are both carriers of sickle cell disease, for example, faces a 1 in 4, or 25 percent, chance of inheriting the disease. This child also has a 1 in 2, or 50 percent, chance of being a carrier, like the parents. The risk is the same for each offspring. It is a common error to conclude that if two carrier parents have a child with an inherited disorder, the next three children are guaranteed to be healthy. This isn't so, because each conception is an independent event.

## Key Concepts

Risk is an estimate of the likelihood that a particular individual will develop a particular condition. Absolute risk is the probability that an individual will develop a certain condition. Relative risk is based on the person's population group compared to another population group.

## 1.5 Applications of Genetics

Barely a day goes by without some mention of genetics in the news. Genetics is impacting many areas of our lives, from health care choices, to what we eat and wear, to unraveling our pasts and controlling our futures.

Thinking about genetics evokes fear, hope, anger, and wonder, depending on context and circumstance. **Figure 1.6** shows an artistic view of genetics. Following are glimpses of applications of genetics that we will explore more fully in subsequent chapters.

## Establishing Identity and Origins

Comparing DNA sequences to establish or rule out identity, relationships, or ancestry is becoming routine. This approach, called **DNA profiling,** has many applications.

### Forensics

Before September 11, 2001, the media reported on DNA profiling only sporadically, usually in the wake of plane crashes where victims needed to be identified or in spectacular criminal cases. The terrorist attacks on the World Trade Center and the Pentagon made DNA profiling a daily task for many months, as investigators meticulously compared DNA sequences in bone and teeth collected from the scenes to hair and skin samples from hairbrushes, toothbrushes, and clothing of missing people, as well as to DNA samples from relatives.

A more conventional forensic application matches a rare DNA sequence in tissue left at a crime scene to that of a sample from a suspect. This is statistically strong evidence that the accused person was at the crime scene, or that someone cleverly planted evidence of his or her presence. Although DNA evidence is usually considered along with eyewitness testimony and other evidence, states that maintain DNA databases of convicted felons often get "cold hits"—when DNA at a crime scene matches a criminal's DNA in the database.

The United Kingdom, where DNA profiling was pioneered in the middle 1980s, has for years collected DNA from all convicts. In the United States, Virginia was the first state to establish such a database. Since 1989, law enforcement officials in Virginia have scored cold hits in hundreds of robberies, rapes, homicides, carjackings, woundings, and various other crimes. The database currently includes the DNA of more than 187,000 felons.

DNA profiling has been equally successful in overturning convictions. Illinois has led the way; there, in 1996, DNA tests exonerated the Ford Heights Four, men convicted of a gang rape and double murder who had spent eighteen years in prison, two of them on death row. In 1999, the men received compensation of $36 million for their wrongful conviction. A journalism class at Northwestern University initiated the investigation that gained the men their freedom. The case led to new state laws granting death row inmates new DNA tests if their convictions could have arisen from mistaken identity, or if DNA tests were performed when they were far less accurate. In 2003, Governor George Ryan was so disturbed by the number of overturned convictions based on DNA evidence that shortly before he left office, he commuted the sentences of everyone on death row to life imprisonment, much to the dismay of the families of murder victims.

Maintaining DNA databases on convicted felons is generally accepted because criminals give up certain civil rights. Establishing such databases on the general public is another story. Bioethics: Choices for the Future discusses some of the first general population databases.

### Rewriting History

DNA can help to flesh out details of history, and sometimes springs surprises. Consider the offspring of Thomas Jefferson's slave, Sally Hemings (**figure 1.7**). Rumor at the

**Figure 1.6 Genetic science inspires art.** This sleek, symmetrical depiction of the double helix of DNA adorns the four-story spiral staircase in the Life Sciences building at the University of California in Davis.

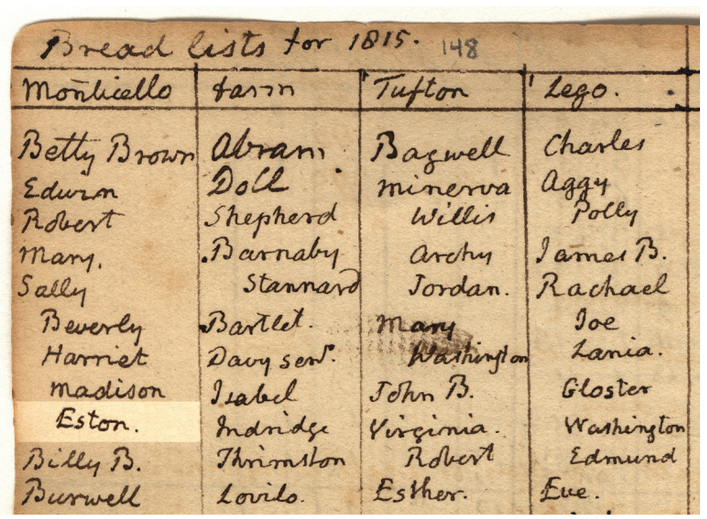



**Figure 1.7 DNA clarifies history.** Analysis of DNA sequences on the Y chromosomes of some of Thomas Jefferson's descendants indicate that either the president, his brother, or one of his nephews fathered Eston Hemings, a son of slave Sally Hemings.

## Bioethics: Choices for the Future

# Population Genetic Databases—Beyond Iceland

More than a dozen nations are recording genetic, genealogical, lifestyle, and health information on citizens to discover the inherited and environmental influences on common disorders. The plans vary in how people participate, but they raise similar concerns: Who will have access to the information? How can people benefit from providing it? How might it be abused?

The first country to make headlines for collecting genetic information on a population level was Iceland. In 1998, a company called deCODE Genetics received government permission to collect existing health and genealogy records and to add DNA sequence data. Many Icelandic families can trace their families back more than a thousand years and have family tree diagrams etched in blood on old leather. Participation in the database is presumed—citizens must file a special form to opt out of the project. DeCODE has used the information to identify genes that contribute to several common disorders (**table 1**). Their strategy groups people by clinical condition and identifies parts of the genome that they uniquely share, then finds genes in these regions whose functions could explain the symptoms.

The Estonian Genome Project uses registries for patients with cancers, Parkinson disease, diabetes mellitus, and osteoporosis. When patients show up for appointments, they learn about the project and are asked for details of their health histories and to donate DNA. Researchers then match variations in the DNA sequence to particular medical conditions.

Researchers in the United Kingdom are recruiting half a million individuals between the ages of 45 and 69, the age range when many common illnesses begin, to donate DNA to a "biobank." Investigators will search for connections among DNA sequence variants, health, and lifestyle characteristics as the population ages over the next three decades. Another effort, called GenomeEUtwin, has amassed data on more than 600,000 pairs of twins from eight European nations for decades. The Estonian, UK Biobank, GenomeEUtwin, and a Canadian project, called Cartagene, have joined to form the Public Population Project in Genomics. All are public. Like deCODE, the other population genetic databases share the goal of using genetic information to develop diagnostic tests and treatments. Bioethicists have suggested strategies to ensure that individuals benefit from such projects, such as:

- Preserving choice in seeking genetic tests.
- Protecting privacy by legally restricting access to genome information.
- Tailoring genetic tests to genes that are most relevant to an individual.
- Refusing to screen for trivial traits in embryos or fetuses.

**Table 1**

**Disease-Related Genes Identified in Iceland**

| |
|---|
| Alzheimer disease |
| Anxiety disorder |
| Hypertension |
| Myocardial infarction |
| Osteoarthritis |
| Osteoporosis |
| Schizophrenia |
| Stroke |
| Type II diabetes mellitus |

time placed Jefferson near Hemings nine months before each of her seven children was born, and the children themselves claimed to be presidential offspring. A Y chromosome analysis revealed that Thomas Jefferson could have fathered Heming's youngest son, Eston—but so could any of several other Jefferson family members. The Y chromosome, because it is present only in males, is faithfully passed from father to son. Researchers identified very unusual DNA sequences on the Y chromosomes of descendants of Thomas Jefferson's paternal uncle, Field Jefferson. These men were checked because the president's only son with wife Martha had died in infancy, making it impossible to check his direct descendants. The Jefferson family's unusual Y chromosome matched that of descendants of Eston Hemings, supporting the talk of the time.

## Tracing Origins

DNA profiling can provide details of times past. For example, bone cells from a child buried in a Roman cemetery in the year 450 A.D. had DNA sequences from the parasite that causes malaria. This genetic evidence is consistent with other signs of malaria, such as very porous bones and historical accounts of an epidemic contributing to the fall of the Roman Empire.

Reaching farther back, DNA profiling can clarify relationships from Biblical times. Consider a small group of Jewish people, the cohanim, who share distinctive Y chromosome DNA sequences. The cohanim have a special status as priests in the religion. By considering the number of DNA differences between cohanim and other Jewish people, how long it takes DNA to mutate, and the average human generation time of 25 years, researchers extrapolated that the cohanim Y chromosome pattern originated 2,100 to 3,250 years ago—which includes the time when Moses lived. According to religious documents, Moses' brother Aaron was the first priest.

The Jewish priest DNA signature also appears today among the Lemba, a population of South Africans with black skin. Researchers thought to look at them for the telltale gene variants because their customs suggest a Jewish origin—they do not eat pork (or hippopotamus), they circumcise their newborn sons, and they celebrate a

weekly day of rest. Today, the Lemba clearly practice Judaism (**figure 1.8**).

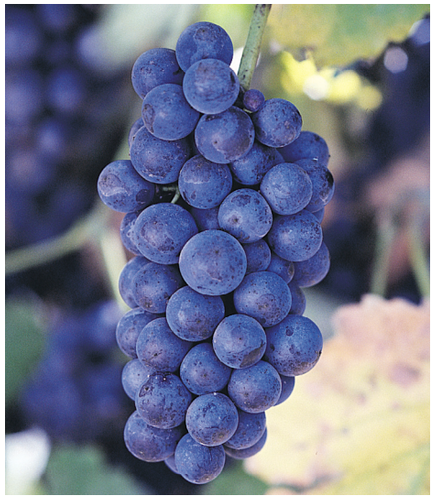
DNA profiling can also trace origins for organisms other than humans. For example, researchers analyzed DNA from the leaves of 300 varieties of wine grapes, in search of the two parental strains that gave rise to the sixteen major types of wine grapes existing today (**figure 1.9**). One parent was already known—the bluish-purple Pinot grape. But the second parent, revealed in the DNA, was a surprise—a variety of white grape called Gouais blanc that was so unpopular it hadn't been cultivated for years and was actually banned during the Middle Ages. Thanks to DNA analysis, vintners now know to maintain both parental stocks, to preserve the gene pool from which all wines descend.

## Peeks at Evolution—Dog Origins

DNA evidence has refined our ideas of where and how domestic dogs originated. Instead of evolving from the gray wolf in North America some 15,000 years ago, as had been thought, dogs more likely descended from wolves in China 25,000 or more years ago. Comparisons of DNA sequences among dogs from all over the globe and among their nearest relatives—wolves, jackals, and coyotes—point to one origin, followed by several separations into populations that led to the very diverse hundreds of modern breeds. The dogs of Eurasia have the most variable genomes—that is, the genomes of other dogs are subsets of the Eurasian canines—suggesting that the ancestral dogs were Eurasian, most likely from China. Archaeological evidence indicates that five basic types of dogs accompanied humans across the Bering Strait 15,000 to 10,000 years ago (see figure 15.14), and later, Europeans brought others—yet all ultimately came from China. Such breed names as the Mexican hairless, Alaskan husky, Chesapeake Bay retriever, and Newfoundland are not true to their genetic heritage (**figure 1.10**)!

**Figure 1.8 Y chromosome DNA sequences reveal origins.** The Lemba, a modern people with dark skin, have the same Y chromosome DNA sequences as the cohanim, a group of Jewish priests. The Lemba practiced Judaism long before DNA analysis became available.

a.



b.

**Figure 1.9 Surprising wine origins.** **(a)** Gouais blanc and **(b)** Pinot (noir) grapes gave rise to nineteen modern popular wines, including Chardonnay.

Determining how dogs became our best friends requires some speculation and imagination, but genetics is involved here, too. A widely accepted scenario is that dogs gradually descended from wolves as they learned to live with people. One view envisions people befriending the more docile wolves, perhaps keeping them as pets or hunters. When these wolf-dogs bred, they passed on the genes that impart their gentleness, and over time, a new breed was selected. An alternate view is that the founding wolves separated themselves from their herds by being bold enough to forage around human settlements to find food. Experiments on dogs today indicate that they may possess certain skills that enable them to uncannily interpret human communication cues. For example, monkeys are unable to identify under which of two objects a person has hidden food; dogs do it with ease, presumably watching the person for clues. The fact that dogs raised with people as well as those raised only with other dogs are equally good at following and remembering where the person put the food suggests that this skill is inborn—that is, inherited.

However and whenever the modern dog separated itself from its wolf brethren, humans then controlled their breeding to create such divergent-looking animals as the chihuahua and the St. Bernard. The dog genome sequence, published in draft form in 2003, will provide guidelines to identify the gene variant combinations that distinguish a poodle from a pug, a beagle from a boxer. Reading 14.2 explores the genetics of dogs and cats further.

## Health Care

Inherited illness caused by a variant in a single gene differs from other types of illnesses in several ways (**table 1.2**). First, the recurrence risk of single-gene disorders can be predicted using the laws of inheritance chapter 4 describes. In contrast, an infectious disease requires that a pathogen be passed from one person to another—a much less predictable circumstance.

A second key distinction of inherited illness is that the risk of developing symptoms can be predicted. This is because all genes are present in all cells, even if they are not

a.

b.

c.

**Figure 1.10 Dog origins.** It's easy to see that dogs descended from gray wolves **(a)** when we look at a Siberian husky **(b),** but the relationship isn't as clear for many of the other 576 breeds, such as the Mexican hairless **(c).** Despite their names, the Alaskan husky and the Mexican hairless trace their roots to Asia, not North America.

**Table 1.2**

**How Genetic Diseases Differ from Other Diseases**

1. One can predict recurrence risk in other family members.
2. Predictive testing is possible.
3. Different populations may have different characteristic frequencies.
4. Correction of the underlying genetic abnormality may be possible.

expressed in every cell. The use of genetic testing to foretell disease is termed predictive medicine. For example, some women who have lost several relatives at young ages to BRCA1 breast cancer and who know they have inherited the gene variant that causes the illness call themselves "previvors," in contrast to survivors. Some BRCA1 "previvors" have their breasts removed to prevent the cancer. A medical diagnosis, however, is still made based on existing symptoms. This is because some people who inherit gene variants associated with particular symptoms never develop them, because of interactions with other genes or environmental factors.

A third feature of genetic disease is that an inherited disorder may be much more common in some populations than others. Certain genes do not "like" or "dislike" certain types of people, but we tend to pick partners in nonrandom ways that can cause particular gene variants to cluster in certain groups. This phenomenon has economic consequences. While it might not be "politically correct" to offer a "Jewish genetic disease screen," as several companies do, it makes biological sense—a dozen disorders are much more common among Ashkenazim.

So far, tests are available to identify about 1,000 single-gene disorders, but each year, only about 250,000 people in the United States take these tests. Many people fear that employers or insurers will discriminate based on the results of genetic tests—or even on the simple action of taking the tests. Yet millions regularly have their cholesterol checked! However, studies from Canada on more than a decade of offering predictive genetic testing for Huntington disease indicate that fear of health insurance discrimination might not be a major factor in not taking a test—Canada has national health care. More older people took the test, to guide financial decisions and future plans, than did younger people to help make decisions about having children. Investigations in London showed that testing for cystic fibrosis did not significantly affect reproductive decisions either.

Despite the slow start to predictive genetic testing in some nations, in the U.S. legislation to prevent the misuse of genetic information in the insurance industry has been in development since 1993. The 1996 Health Insurance Portability and Accountability Act passed by the U.S. Congress stated that genetic information, without symptoms, does not constitute a preexisting condition, and individuals could not be excluded from group coverage on the basis of a detected genetic predisposition. But the law did not cover individual insurance polices, nor did it stop insurers from asking people to have genetic tests. In February 2000, U.S. President Bill Clinton issued an executive order prohibiting the federal government from obtaining genetic information for employees or job applicants and from using such information in promotion decisions. Since then, more than a dozen bills have been introduced in Congress to prevent genetic discrimination, and most states have enacted antidiscrimination legislation. Yet because the legislation is still in flux, and because the media reports anecdotal cases of health insurance denial or higher premiums following a genetic test, many people continue to fear the misuse of genetic information. For example, in Germany a young healthy woman was refused employment as a teacher because a relative has Huntington disease.

Balancing the perceived risks to privacy that genetic tests present are the possibilities that such tests can lower health care costs. If people know their inherited risks, they can take measures to forestall or ease symptoms that environmental factors might trigger—for example, by eating

healthy foods, not smoking, exercising regularly, avoiding risky behaviors, having frequent medical exams, and beginning treatments earlier. Genetic tests can also enable people to make more informed reproductive decisions. People who know that they can transmit an inherited illness may elect not to have children, or to use one of the assisted reproductive technologies chapter 21 discusses.

A few genetic diseases can be treated. Supplying a missing protein can prevent some symptoms, such as providing a clotting factor to a person who has the bleeding disorder hemophilia. **Gene therapy,** in contrast, theoretically provides a more lasting cure by replacing the instructions for producing the protein. In Their Own Words on page 17 describes gene therapy to treat hemophilia. Unfortunately, the word *theoretically* in the last sentence is important, because gene therapy has been less successful than researchers hoped when the first experiments went well in 1990. In recent years, an 18-year-old died in a gene therapy experiment, and young children developed leukemia when the healing gene healed, but also inserted into a cancer-causing gene, as discussed in chapter 20. These and other gene therapies currently being developed alter cells that are affected in the particular illness. The changes cannot be passed to offspring, unless the healing gene enters sperm or eggs (which has happened). Gene therapy that intentionally alters sperm or eggs is more controversial and unlikely to be pursued.

## Agriculture

The field of genetics arose from agriculture. Traditional agriculture is the controlled breeding of plants and animals to select individuals with certain combinations of useful inherited traits, such as seedless fruits or lean meat. **Biotechnology** is the use of organisms to produce goods (including foods and drugs) or services, and it is an ancient art as well as a modern science. One ancient example of biotechnology is using microorganisms to ferment fruits to manufacture alcoholic beverages, a technique the Babylonians used by 6000 B.C.

Traditional agriculture is imprecise, because it shuffles many genes—and, therefore, many traits—at a time. The application of DNA-based techniques, part of modern biotechnology, enables researchers to manipulate one gene at a time, adding control and precision to agriculture. Biotechnology that creates organisms that harbor new genes or that over- or underexpress their own genes is often popularly called "genetic engineering," but the resulting organisms are technically termed genetically modified (GM). More specifically, an organism with genes from another species is termed transgenic. Golden rice, for example, manufactures beta carotene (a vitamin A precursor) using "transgenes" from petunia and bacteria. It also stores twice as much iron as unaltered rice because one of its own genes is overexpressed (**figure 1.11**). These nutritional boosts bred into edible rice strains may help prevent vitamin A and iron deficiencies in people who eat them. Another genetically modified crop is *bt* corn, which contains a gene from the bacterium *Bacillus thuringiensis* that enables the plant to produce a protein that kills certain leaf-devouring insect larvae pests. Organic farmers have used the protein as a pesticide for decades, but *bt* corn can make its own. Growing the GM crop has greater yield using less synthetic pesticide than growing non-GM corn.

GM animals secrete into their milk "foreign" proteins, such as clotting factors, that serve as human pharmaceuticals. This provides a much purer and safer preparation than the pooled blood extracts that once transmitted infections. Plants can also be genetically modified to produce proteins that serve as drugs, called "pharm crops." An organism's own gene expression can be boosted too. GM cows given extra copies of their genes that encode the milk protein casein produce protein-rich milk that eases cheese manufacture.

People in the United States have been safely eating GM foods for a decade. But in Europe, many people object to GM foods, seemingly on ethical grounds or based on fear. Officials in France and Austria have called such crops "not natural," "corrupt," and "heretical." **Figure 1.12** shows an artist's rendition of some of these fears. Food labels in Europe indicate whether a product is "GM-free." Europe has a moratorium on approving GM foods, and if it is ever lifted, stricter labeling requirements will be imposed. Some objections to GM foods arise from lack of knowledge. A public opinion poll in the United Kingdom discovered, for example, that a major reason citizens avoid eating GM foods is that they do not want to eat DNA! One British geneticist wryly observed that the average meal provides about 150,000 kilometers (about 93,000 miles) of DNA. Ironically, British people ate GM foods for years before concern arose. For example, tomatoes with a gene added to delay ripening vastly outsold regular tomatoes in England, because they were cheaper.

Other concerns about GM organisms may be better founded. For example, labeling can prevent a person from having an allergic reaction to an ingredient in a food that wouldn't naturally be there, such as a peanut protein in corn. An ecological concern is that field tests may not adequately predict the effects of GM plants on ecosystems. GM crops have been found to grow in places beyond where they were planted, thanks to wind pollination. Corn genetically modified to produce a pig vaccine, for example, was found growing in a soybean field near the test plot in Nebraska. Some GM organisms, such as fish that grow to twice normal size or become able to survive at temperature extremes, may be so unusual that they disrupt ecosystems.

**Figure 1.11 Nutrient-boosted crops, courtesy of biotechnology.** Golden rice, a transgenic plant, will be made available to farmers everywhere. Its extra nutrients can help combat vitamin A and iron deficiencies.

The success of genetically modified crops also depends upon where they are cultivated. Consider *bt* cotton, which, like *bt* corn, produces its own insecticide. In field tests on small farms in India, where pests are common and chemical pesticides are usually not used, GM cotton yields were nearly double those of unaltered cotton. The same GM cotton was less successful in China, the United States, and Europe, where most pests are killed with chemical pesticides. The GM cotton did not fare better in these regions because pests were already well-controlled. The experiment therefore suggests that this GM cotton might be valuable in southeast Asian and sub-Saharan Africa, where insect pests are prevalent. In other nations, using the GM cotton may lessen reliance on chemical pesticides.

## Genetics from a Global Perspective

Because genetics so intimately affects us, it cannot be considered solely as a branch of life science. Equal access to testing, misuse of information, and abuse of genetics to intentionally cause harm are compelling issues that parallel scientific progress.

Genetics and genomics are rapidly spawning technologies that promise to vastly improve quality of life. But at least for the next few years, tests and treatments will be costly and not widely available to most people. While those in economically and politically stable nations may look forward to genome-based individualized health care, what some have called "Cadillac medicine," those in other nations just try to survive, often lacking basic vaccines and medicines. In an African nation where two out of five children suffer from AIDS and many die from other infectious diseases, newborn screening for rare single-gene defects hardly seems important. However, genetic disorders weaken people so that they become more susceptible to infectious diseases, which they can pass to others.

Human genome information can ultimately benefit everyone. Consider drug development. Today, there are fewer than 500 types of drugs. Genome information from humans and our pathogens and parasites is revealing new drug targets. **Table 1.3**

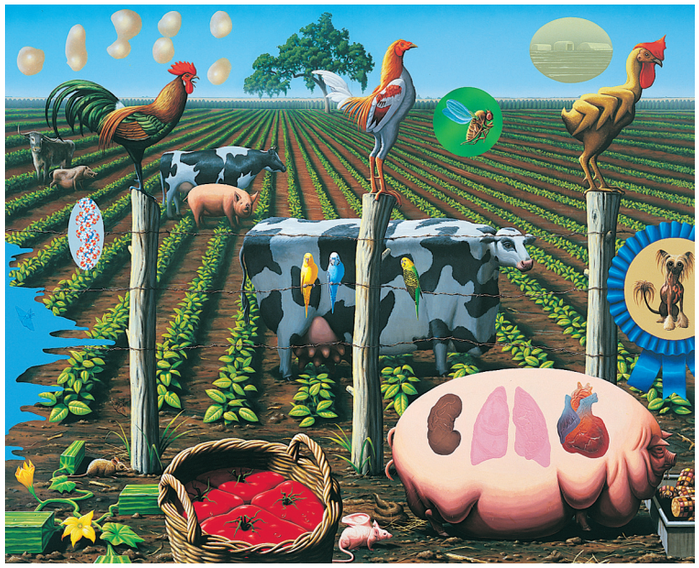


**Figure 1.12 Biotechnology and art.** Artist Alexis Rockman vividly captures some fears of biotechnology, including a pig used to incubate spare parts for sick humans, a muscle-boosted, boxy cow, a featherless chicken with extra wings, a mini-warthog, and a mouse with a human ear growing out of its back.

**Table 1.3**

### Pathogens with Sequenced Genomes

| Pathogen | Human Disease |
|---|---|
| **Bacterial** | |
| *Borrelia burgdorferi* | Lyme disease |
| *Brucella suis* | Fever (infertility in other animals) |
| *Campylobacter jejuni* | Food poisoning |
| *Clostridium perfringens* | Food poisoning |
| *Enterococcus faecalis* | Urinary tract, wound, intestinal, and heart infections |
| *Listeria monocytogenes* | Lethal infection in newborns |
| *Mycobacterium tuberculosis* | Tuberculosis |
| *Neisseria meningitides* | Meningitis and septicemia (brain membrane inflammation and blood poisoning) |
| *Streptococcus pyogenes* | Puerperal fever, scarlet fever, pharyngitis, impetigo, cellulitis, "flesh-eating bacteria" |
| *Treponema pallidum* | Syphilis |
| *Vibrio cholerae* | Cholera |
| *Yersinia pestis* | Plague |
| **Nonbacterial** | |
| *Brugia malayi* (a worm) | Elephantiasis (grossly enlarged lymph nodes) |
| *Entamoeba histolytica* | Intestinal infection |
| *Plasmodium falciparum* | Malaria |
| *Schistosoma mansoni* | Schistosomiasis |
| *Toxoplasma gondii* | Birth defects, opportunistic infection in AIDS |
| *Trypanosoma brucei* | African sleeping sickness |
| *Trypanosoma cruzi* | Chagas disease |

## In Their Own Words

# Living with Hemophilia

Don Miller was born in 1949 and is semi-retired from running the math library at the University of Pittsburgh. Today he has a sheep farm. On June 1, 1999, he was the first hemophilia patient to receive a disabled virus that delivered a functional gene for clotting factor VIII to his bloodstream. Within weeks he began to experience results. Miller is one of the first of a new breed of patient—people helped by gene therapy. Here he describes his life with hemophilia and his treatment. It worked—today his disease is under control.

The hemophilia was discovered when I was circumcised, and I almost bled to death, but the doctors weren't really sure until I was about 18 months old. No one where I was born was familiar with it.

When I was three, I fell out of my crib and I was black and blue from my waist to the top of my head. The only treatment then was whole blood replacement. So I learned not to play sports. A minor sprain would take a week or two to heal. One time I fell at my grandmother's house and had a 1-inch-long cut on the back of my leg. It took five weeks to stop bleeding, just leaking real slowly. I didn't need whole blood replacement, but if I moved a little the wrong way, it would open and bleed again.

I had transfusions as seldom as I could. The doctors always tried not to infuse me until it was necessary. Of course there was no AIDS then, but there were problems with transmitting hepatitis through blood transfusions, and other blood-borne diseases. All that whole blood can kill you from kidney failure. When I was nine or ten I went to the hospital for intestinal polyps. I was operated on and they told me I'd have a 10 percent chance of pulling through. I met other kids there with hemophilia who died from kidney failure due to the amount of fluid from all the transfusions. Once a year I went to the hospital for blood tests. Some years I went more often than that. Most of the time I would just lay there and bleed. My joints don't work from all the bleeding.

By the time I got married at age 20, treatment had progressed to gamma globulin from plasma. By then I was receiving gamma globulin from donated plasma and small volumes of cryoprecipitate, which is the factor VIII clotting protein that my body cannot produce pooled from many donors. We decided not to have children because that would end the hemophilia in the family.

I'm one of the oldest patients at the Pittsburgh Hemophilia Center. I was HIV negative, and over age 25, which is what they want. By that age a lot of people with hemophilia are HIV positive, because they lived through the time period when we had no choice but to use pooled cryoprecipitate. I took so little cryoprecipitate that I wasn't exposed to very much. And, I had the time. The gene therapy protocol involves showing up three times a week.

The treatment is three infusions, one a day for three days, on an outpatient basis. So far there have been no side effects. Once the gene therapy is perfected, it will be a three-day treatment. A dosage study will follow this one, which is just for safety. Animal studies showed it's best given over three days. I go in once a week to be sure there is no adverse reaction. They hope it will be a one-time treatment. The virus will lodge in the liver and keep replicating.

In the eight weeks before the infusion, I used eight doses of factor. In the fourteen weeks since then, I've used three. Incidents that used to require treatment no longer do. As long as I don't let myself feel stressed, I don't have spontaneous bleeding. I've had two nosebleeds that stopped within minutes without treatment, with only a trace of blood on the handkerchief, as opposed to hours of dripping.

I'm somewhat more active, but fifty years of wear and tear won't be healed by this gene therapy. Two of the treatments I required started from overdoing activity, so now I'm trying to find the middle ground.

Don Miller

lists some of the pathogens whose genomes have been sequenced and the illnesses they cause. Global organizations, including the United Nations, World Health Organization, and the World Bank, are discussing how nations can share new diagnostic tests and therapeutics that arise from genome information.

## Key Concepts

Genetics has applications in diverse areas. Matching DNA sequences can clarify relationships, which is useful in forensics, establishing identity, and understanding certain historical events. • Inherited disease differs from other disorders in its predictability; the possibility of predictive testing; characteristic frequencies in different populations; and the potential of gene therapy to correct underlying abnormalities.

- Agriculture, both traditional and biotechnological, applies genetic principles.
- Human genome information has tremendous potential but must be carefully managed.

# Summary

## 1.1 Genetic Testing

1. Genes are the instructions to manufacture proteins, which determine inherited traits.
2. A **genome** is a complete set of genetic information. A cell contains two genomes of DNA.
3. People can choose specific gene tests, based on family and health history, to detect or even predict risk of developing certain conditions. **DNA microarrays** detect many genes at once. Expression arrays indicate which proteins a cell makes.

## 1.2 The Breadth of Genetics

4. **Genes** are sequences of **DNA** that encode both the amino acid sequences of proteins and the RNA molecules that carry out protein synthesis. **RNA** carries the gene sequence information so that it can be utilized, while the DNA is transmitted when the cell divides. Much of the genome does not encode protein.
5. Variants of a gene arise by **mutation.** Variants of the same gene are **alleles.** They may differ slightly from one another, but they encode the same product. A **polymorphism** is a general term for a particular site or sequence of DNA that varies in one percent or more of a population. The **phenotype** is the gene's expression. An allele combination constitutes the **genotype.** Alleles may be **dominant** (exerting an effect in a single copy) or **recessive** (requiring two copies for expression).
6. **Chromosomes** consist of DNA and protein. The 22 types of **autosomes** do not include genes that specify sex. The X and Y **sex chromosomes** bear genes that determine sex.
7. The human genome contains about 3 billion DNA bases. Cells **differentiate** by expressing subsets of genes. **Stem cells** divide to yield other stem cells and cells that differentiate.
8. Pedigrees are diagrams used to study traits in families.
9. Genetic populations are defined by their collections of alleles, termed the **gene pool.**
10. Genome comparisons among species reveal evolutionary relationships.

## 1.3 Genes Do Not Usually Function Alone

11. Single genes determine **Mendelian traits.**
12. **Multifactorial traits** reflect the influence of one or more genes and the environment. Recurrence of a Mendelian trait is predicted based on Mendel's laws; predicting recurrence of a multifactorial trait is more difficult.
13. **Genetic determinism** is the idea that expression of an inherited trait cannot be changed.

## 1.4 Geneticists Use Statistics to Represent Risks

14. Risk assessment estimates the probability of inheriting a particular gene. **Absolute risk,** expressed as odds or a percentage, is the probability that an individual will develop a particular trait or illness over his or her lifetime.
15. **Relative risk** is a ratio that estimates how likely a person is to develop a particular phenotype compared to another group, usually the general population.
16. Risk estimates are **empiric,** based on Mendel's laws, or modified to account for environmental influences.

## 1.5 Applications of Genetics

17. **DNA profiling** can establish identity, relationships, and origins.
18. In inherited diseases, recurrence risks are predictable and a causative mutation may be detected before symptoms arise. Some inherited disorders are more common among certain population groups. **Gene therapy** attempts to correct certain genetic disorders.
19. Genetic information can be misused, especially by employers and insurers.
20. Agriculture is selective breeding. **Biotechnology** is the use of organisms or their parts for human purposes. A **transgenic** organism harbors a gene or genes from a different species.

# Review Questions

1. Place the following terms in size order, from largest to smallest, based on the structures or concepts they represent:
   a. chromosome
   b. gene pool
   c. gene
   d. DNA
   e. genome
2. Distinguish between:
   a. an autosome and a sex chromosome
   b. genotype and phenotype
   c. DNA and RNA
   d. recessive and dominant traits
   e. absolute and relative risks
   f. pedigrees and karyotypes
   g. gene and genome
3. List four ways that inherited disease differs from other types of illnesses.
4. Cystic fibrosis is a Mendelian trait; height is a multifactorial trait. How do the causes of these characteristics differ?
5. Mutants are often depicted in the media as being abnormal, ugly, or evil. Why is this not necessarily true?
6. Health insurance forms typically ask for applicants to list existing or preexisting symptoms. How do the results of a genetic test differ from this?

# Applied Questions

1. Breast cancer caused by the *BRCA1* gene affects 1 in 800 women in the general U.S. population. Among Jewish people of eastern European descent, it affects 2 in 100. What is the relative risk for this form of breast cancer among eastern European Jewish women in the United States?
2. In a search for a bone marrow transplant donor, why would a patient's siblings be considered before first cousins?
3. Keeping DNA databases of convicted felons has led to the solution of many crimes, and the exonerations of many innocent people. What might be the benefits and dangers of establishing databases on everyone? How should such a program be instituted?
4. How is *genetic engineering* a vague term, while *transgenic organism* is more precise?
5. Researchers have always published genome sequences, including those of organisms and viruses that cause disease (pathogens). Such freely available data are essential to scientific research, as they provide researchers with information that could be used to develop treatments. Since the terrorist attacks of September 11, 2001, however, some editors of scientific journals have considered restricting the publication of the genome sequences of pathogens for fear that terrorists would use the information to create "weaponized" versions—bacteria or viruses that spread more easily or cause more severe symptoms, for example. Do you think publication of genome sequences should be restricted? Cite a reason for your answer.

## Web Activities

6. Many artists have been inspired by aspects of genetics, from the elegance of nucleic acid molecules to common fears of genetic technologies. Look at the following websites, select a work of art, and describe what it represents.

   http://www.dna50.org/main.htm

   http://gnn.tigr.org/articles/art_gallery.shtml
7. Genetics inspires cartoonists, too. Look at http://cartoonbank.com, and search under "DNA." Select a cartoon that misrepresents genetics, and explain how it is inaccurate, misleading, or sensationalized.
8. The website from GeneLink Inc. (http://www.bankdna.com/dnabanking.asp) announces "the world's first family-centered DNA bank and hereditary genetic information services." A client sends a sample of his or her DNA, obtained with a cheekbrush, to the company, which then examines certain genes. Explore the website, and discuss the pros and cons of using this type of service to learn about your DNA.

## Case Studies

9. Morris has a DNA microarray test for several genes that predispose to developing prostate cancer. He learns that his overall relative risk is 1.5, compared to the risk in the general population. Overjoyed, he tells his wife that his risk of developing prostate cancer is only 1.5 percent. She says no, his risk is 50 percent greater than that of the average individual in the general population. Who is correct?
10. Benjamin undergoes a genetic screening test and receives the following relative risks:

    | | | |
    |---|---|---|
    | – | addictive behaviors | 0.6 |
    | – | coronary artery disease | 2.3 |
    | – | kidney cancer | 1.4 |
    | – | lung cancer | 5.8 |
    | – | diabetes | 0.3 |
    | – | depression | 1.2 |

    Which conditions is he more likely to develop than someone in the general population, and which conditions is he less likely to develop?
11. The Larsons have a child who has inherited cystic fibrosis. Their physician tells them that if they have other children, each faces a 1 in 4 chance of also inheriting the illness. The Larsons tell their friends, the Espositos, of their visit with the doctor. Mr. and Mrs. Esposito are expecting a child, so they ask their physician to predict whether he or she will one day develop multiple sclerosis—Mr. Esposito is just beginning to show symptoms. They are surprised to learn that, unlike the situation for cystic fibrosis, recurrence risk for multiple sclerosis cannot be easily predicted. Why not?
12. Burlington Northern Santa Fe Railroad asked its workers for a blood sample, and then supposedly tested for a gene variant that predisposes a person for carpal tunnel syndrome, a disorder of the wrists caused by repetitive motions. The company threatened to fire a worker who refused to be tested; the worker sued the company. The Equal Employment Opportunity Commission ruled in the worker's favor, agreeing that the company's action violated the Americans with Disabilities Act.
    a. Do you agree with the company or the worker? What additional information would be helpful in taking sides?
    b. How is the company's genetic testing not based on sound science?
    c. How can tests such as those described for the two students at the beginning of this chapter be instituted in a way that does not violate a person's right to privacy, as the worker in the railroad case contended?

Learn to apply the skills of a genetic counselor with additional cases found in the *Case Workbook in Human Genetics.*

Genetics in the news

# Suggested Readings

Burgermeister, Jane. October 11, 2003. Teacher was refused job because relatives have Huntington's disease. *The British Medical Journal* 327:827. Genetic discrimination is more likely in some nations than others.

Duncan, David Ewing. November 2002. 100% genetically analyzed. *Wired.* A journalist learns his possible genetic future—a bit melodramatic, but a fairly accurate look at where health care is headed.

Gavaghans, Helen. November 11, 2002. UK Biobank to go on the political agenda. *The Scientist* 16(22):24–25. As the British population ages, disease-causing genes will be identified.

Kirkness, Ewen, et al. September 26, 2003. The dog genome: Survey sequencing and comparative analysis. *Science* 301:1898–1903. Dogs have counterparts to 360 human diseases.

Kristof, Nicholas D. February 11, 2003. Staying alive, staying human. *The New York Times,* p. F1. Another reporter has his genome scanned.

Lee, Henry C. and Frank Tirnady. 2003. *Blood Evidence.* Cambridge, Mass.: Perseus Publishing. How DNA is revolutionizing forensics.

Lewis, Ricki. October 20, 2003. A genetic check-up: Lessons from Huntington disease and cystic fibrosis. *The Scientist* 17(20):24–26. Testing for common disorders is more complex than testing for single gene disorders.

Lewis, Ricki. February 12, 2002. Race and the clinic: Good science or political correctness? *The Scientist* 16(4):14. Race may not be a biological concept, but differences in gene frequencies among people of different skin colors may be clinically significant.

Lewis, Ricki. September 3, 2001. Where the bugs are: Forensic entomology. *The Scientist* 15(17):10. DNA profiling of insects provides helpful clues to solving crimes.

Lewis, Ricki. July 24, 2000. Keeping up: Genetics to genomics in four editions. *The Scientist* 14:46. A look at the evolution of this textbook.

Paabo, Svante. February 16, 2001. The human genome and our view of ourselves. *Science* 291:1219. Knowing the sequence of the human genome provides new ways of looking at ourselves.

Savolainen, Peter et al. November 22, 2002. Genetic evidence for an East Asian origin of domestic dogs. *Science* 298:1610–13. All dogs may descend from Chinese wolves.

Singer, Peter A. and Abdallah S. Daar. October 5, 2001. Harnessing genomics and biotechnology to improve global health equity. *Science* 294:87–89. The New African Initiative is an effort to ensure that all cultures have access to biotechnology.

Vastag, Brian. January 8, 2003. Gene chips inch toward the clinic. *The Journal of the American Medical Association* 289(2):155–56. Applications of DNA microarray technology are now regular reading in medical journals.

Ye, Xudong, et al. January 14, 2000. Engineering the provitamin A (beta carotene) biosynthetic pathway into (carotenoid-free) rice endosperm. *Science* 287:303–5. "Golden rice" may prevent human malnutrition.

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