12 CHROMOSOMES AND HUMAN INHERITANCE

Strange Genes, Richly Tortured Minds

"This man is brilliant." That was the extent of a letter of recommendation from Richard Duffin, a mathematics professor at Carnegie Mellon University. Duffin wrote the line in 1948 on behalf of John Forbes Nash, Jr. (Figure 12.1). Nash was twenty years old at the time and applying for admission to Princeton University's graduate school.

Over the next decade, Nash made his reputation as one of America's foremost mathematicians. He was socially awkward, but so are many highly gifted people. Nash showed no symptoms of paranoid schizophrenia, a mental disorder that eventually debilitated him.

Full-blown symptoms emerged in his thirtieth year. Nash had to abandon his position at the Massachusetts Institute of Technology. Two decades passed before he was able to return to his pioneering work in mathematics.

Of every hundred people worldwide, one is affected by *schizophrenia*. This neurobiological disorder (NBD) is characterized by delusions, hallucinations, disorganized speech, and abnormal social behavior. As researchers know, exceptional creativity often accompanies schizophrenia. It also accompanies other NBDs, including autism, chronic depression, and bipolar disorder, which manifests itself as jarring swings in mood and social behavior.

Compared to the general population, highly intelligent individuals are *less* likely to develop NBDs—unless they also happen to be outside-the-box creative thinkers. Disturbingly creative writers alone are eighteen times more suicidal, ten times more likely to be depressed, and twenty times more likely to have bipolar disorder. Virginia Woolf's suicide after a prolonged mental breakdown is a tragic example.

We now have evidence that even emotionally healthy people who show creative brilliance have more personality traits in common with the mentally impaired than they do with individuals closer to the norm. For instance, they, too, are hypersensitive to environmental stimuli. Some may be on a razor's edge between mental stability and instability. Those who do go on to develop NBDs become part of a crowd that includes Socrates, Newton, Beethoven, Darwin, Lincoln, Poe, Dickens, Tolstoy, van Gogh, Freud, Churchill, Einstein, Picasso, Woolf, Hemingway, and Nash.

We have not yet identified all of the interactions among genes and the environment that might tip such individuals one way or the other. But we do know about several mutant genes that predispose them to develop NBDs.

Creatively gifted people, as well as those affected by NBDs, often turn up in the same family tree—which points

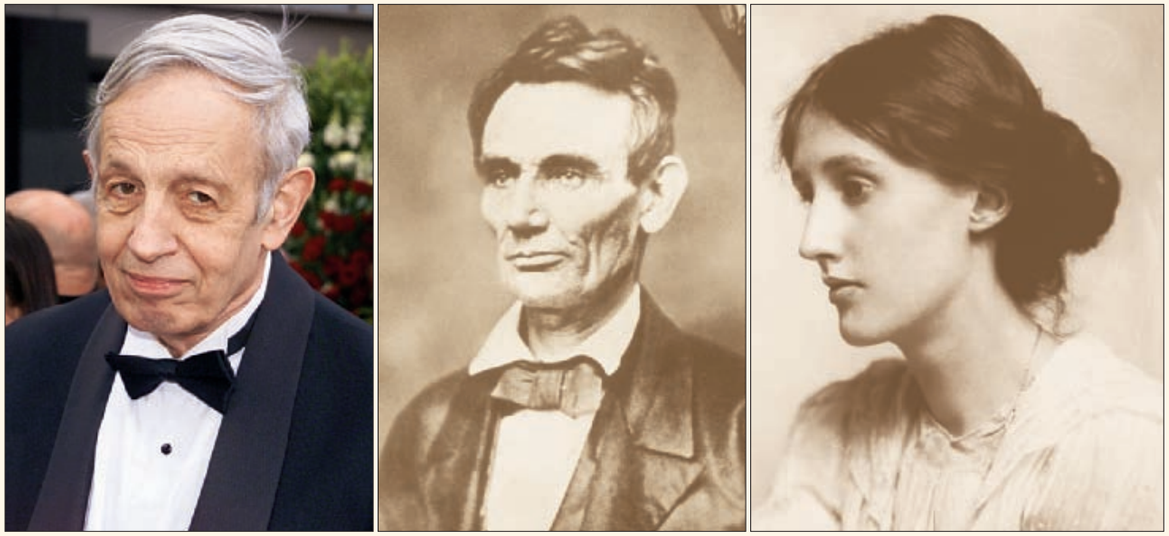


Figure 12.1 John Forbes Nash, Jr., a prodigy who solved problems that had baffled some of the greatest minds in mathematics. His early work in economic game theory won him a Nobel Prize. He is shown here at a premier of *A Beautiful Mind*, an award-winning film based on his battle with schizophrenia. His neural disorder places him in the ranks of other highly creative, distinguished, yet troubled individuals, including Abraham Lincoln, Virginia Woolf, and Pablo Picasso.

IMPACTS, ISSUES

to a genetic basis for their special traits. Also, those affected by bipolar disorder and schizophrenia show altered gene expression in certain brain regions. Cells make too many or too few of the enzymes of electron transfer phosphorylation. Remember, this stage of aerobic respiration yields the bulk of the body's ATP. Does its disruption alter brain cells in ways that boost creativity but also invite illness? Perhaps.

With this intriguing connection, we invite you to reflect on how far you have come in this unit of the book. You first surveyed mitotic and meiotic cell divisions. You looked at how chromosomes and genes become shuffled during meiosis and then during fertilization. You also became acquainted with Gregor Mendel's discovery of major patterns of inheritance. This knowledge is your portal to the chromosomal basis of human inheritance.

Watch the video online!

How Would You Vote?

Diagnostic tests for predisposition to neurobiological disorders will soon be available. Individuals might use knowledge of their susceptibility to modify choices in life-styles. Insurance companies and employers might also use that information to exclude predisposed but otherwise healthy individuals. Would you support legislation governing these tests? See BiologyNow for details, then vote online.

Key Concepts

AUTOSOMES AND SEX CHROMOSOMES

Sexually reproducing species have pairs of autosomes, which are chromosomes that are the same in length, shape, and which genes they carry. Nearly all animals also have a pair of sex chromosomes.

Karyotyping, a diagnostic tool, helps reveal changes in the structure or number of an individual's chromosomes. Section 12.1, 12.2

AUTOSOMAL INHERITANCE

Many alleles on autosomes are expressed in Mendelian patterns of simple dominance and recessiveness. Sections 12.3, 12.4

SEX-LINKED INHERITANCE

The pairing of sex chromosomes in human females (XX) differs from the pairing in males (XY). One of the genes on the Y chromosome dictates gender. Many alleles on the X chromosome are expressed in Mendelian patterns of simple dominance and recessiveness. Sections 12.5–12.7

CHANGES IN CHROMOSOME STRUCTURE

On rare occasions, a chromosome may undergo permanent change in its structure, as when a segment of it is deleted, duplicated, inverted, or translocated. Section 12.8

CHANGES IN CHROMOSOME NUMBER

Also on rare occasions, the parental number of autosomes or sex chromosomes changes. In humans, the change usually results in problems. Section 12.9

HUMAN GENETIC ANALYSIS AND OPTIONS

Various analytical and diagnostic procedures often reveal genetic disorders. Risks and benefits are associated with what individuals as well as society at large do with the information. Sections 12.10, 12.11

Links to Earlier Concepts

You will be drawing on your knowledge of chromosome structure (Sections 9.1, 9.3), meiosis (10.3, 10.4), and gamete formation (10.5). Be sure you understand dominance, recessiveness, and the homozygous and heterozygous conditions (11.1). Remember, environmental factors influence gene expression (11.6). Colchicine (4.10) will turn up again. So will glycolysis (8.2), this time in the context of a genetic disorder. You also will consider whether the hemoglobin family evolved after changes in chromosome structure (3.6).

12.1 Human Chromosomes

LINKS TO SECTIONS 4.10, 9.1, 9.5, 10.3

You already know quite a bit about chromosomes and their roles in inheritance. Let's now focus on human autosomes and sex chromosomes.

Like nearly all animals, humans normally are male or female. Also like many species, they have a diploid chromosome number ($2n$), meaning that body cells have pairs of homologous chromosomes. Remember, all but one of the pairs are alike in their length, shape, and gene sequence. One member of the last pairing is a unique sex chromosome that is present in males or females, but not in both.

For instance, a diploid cell in a human female has two X chromosomes (XX). A diploid cell in a human male has one X and one Y chromosome (XY). This is a common inheritance pattern among mammals, fruit flies, and many other animals. It is not the only one, however. Among butterflies, moths, birds, and certain fishes, the males have two identical sex chromosomes and females do not.

Human X and Y chromosomes differ physically and in which genes they carry. Recall, from Section 10.3, that each pair of homologous chromosomes synapses (zippers together tightly) in prophase I of meiosis. An X chromosome and Y chromosome synapse in a small region along their length, but that is enough to allow the two to interact as homologues during meiosis.

Human X and Y chromosomes fall into the general category of **sex chromosomes**. As you will see later, when sex chromosomes are inherited in certain combinations, they dictate the gender of the new individual—that is, whether it will become a male or a female.

All of the other chromosomes in our body cells are the same in both sexes. We categorize them as **autosomes**.

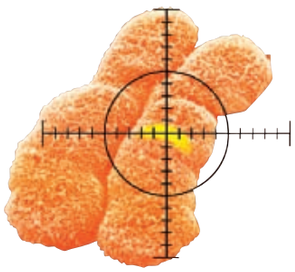


Figure 12.2 Long before the spectacular discoveries of molecular biology, researchers started identifying regions on chromosomes that probably held the genes responsible for certain genetic disorders.

The duplicated human chromosome shown in Figure 12.2 has a targeted band (*yellow*), an artistic way of introducing a key point: Molecular biology increased the power of diagnostic tools that were already in use to analyze chromosomes—as with fluorescent dyes that can label DNA regions linked to genetic disorders. In the next section, you will read about two of the diagnostic procedures.

Autosomes are pairs of chromosomes that are the same in males and females of a species. One other pairing, of sex chromosomes, differs between males and females.

12.2 What Is Karyotyping?

With karyotyping, a diagnostic tool, images are constructed to analyze the structure and number of chromosomes in an individual's cells.

How do we know about an individual's autosomes and sex chromosomes? *Karyotyping* is one of the earliest diagnostic tools. A typical **karyotype** is a preparation of an individual's metaphase chromosomes, sorted out by length, shape, centromere location, and other defining features. Gross abnormalities in chromosome structure or an altered chromosome number can be pinpointed by comparing the individual's karyotype against a standard karyotype for the species.

Making a Karyotype Human chromosomes are in their most condensed form and easiest to identify when a cell is at metaphase of mitosis (Sections 9.1 and 9.3). Technicians do not count on finding dividing cells in the body. They culture cells and induce mitosis artificially. They place a sample of cells, usually from blood, into a solution that stimulates growth and mitotic cell division. They add colchicine to the sample to arrest the cell cycle at metaphase. Colchicine, remember, is a poison that blocks spindle formation by preventing microtubules from forming (Section 4.10).

As Figure 12.3 explains, the cell culture is centrifuged to isolate all the metaphase cells. A hypotonic solution makes the cells swell, by way of osmosis, and move away from each other. The chromosomes inside them move away from each other, also. Then the cells are mounted on slides, fixed, and stained for microscopy.

Once the chromosomes are brought into focus, they are photographed. The photograph is cut with scissors or with a computer's cut-and-paste tools to separate the chromosomes. Then the chromosomes are lined up by size and shape, as in Figure 12.3*f*.

Spectral Karyotypes *Spectral karyotyping*, a more recent diagnostic tool, uses a range of colored fluorescent dyes that bind to specific parts of chromosomes. Analysis of the resulting rainbow-hued karyotype often reveals abnormalities that would not otherwise be discernible.

Figure 12.4 shows a spectral karyotype. The Philadelphia chromosome in this karyotype, named after the city where someone discovered it, was the first chromosome to be specifically correlated with cancer—one of the leukemias. The Philadelphia chromosome was already known to be longer than human chromosome 9, which is its normal counterpart. But spectral karyotyping identified the extra length as a piece of chromosome 22.

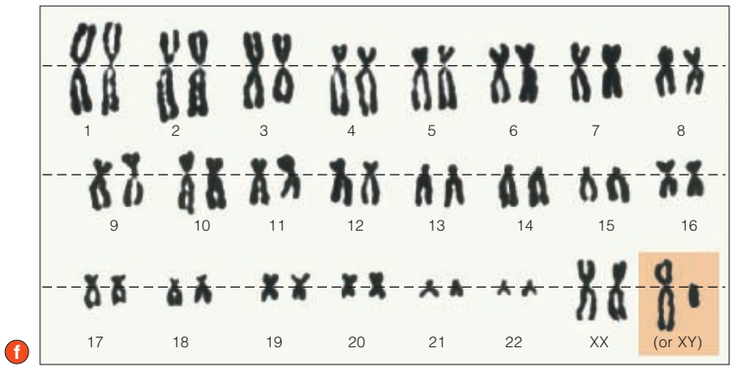
By chance, both chromosomes broke inside a stem cell in bone marrow. Such cells give rise to blood cells. Enzymes reattached the pieces—but on the wrong chromosomes. You can identify the translocated parts in the Figure 12.4 karyotype. We will be returning to this type of change in the structure of chromosomes in Section 12.8.

Figure 12.3 ***Animated!*** Karyotyping, in which an image of metaphase chromosomes is cut apart. Individual chromosomes are aligned by their centromeres and arranged according to size, shape, and length.

(**a**) A sample of cells from an individual is put in a medium that stimulates cell growth and mitotic division. Colchicine is added to arrest the cell cycle at metaphase. (**b**) The culture is subjected to *centrifugation*, which works because cells have greater mass and density than the solution bathing them. A centrifuge's spinning force moves the cells farthest from the center of rotation, so they collect at the base of the centrifuge tubes.

(**c**) The culture medium is removed; a hypotonic solution is added. The cells swell, and chromosomes move apart. (**d**) The cells are mounted on a microscope slide and stained to make the chromosomes show up.

(**e**) A photograph of one cell's chromosomes is cut up and organized, as in the human karyotype in (**f**), which shows 22 pairs of autosomes and 1 pair of sex chromosomes—XX *or* XY. Scissors or computer tools do the cuts.



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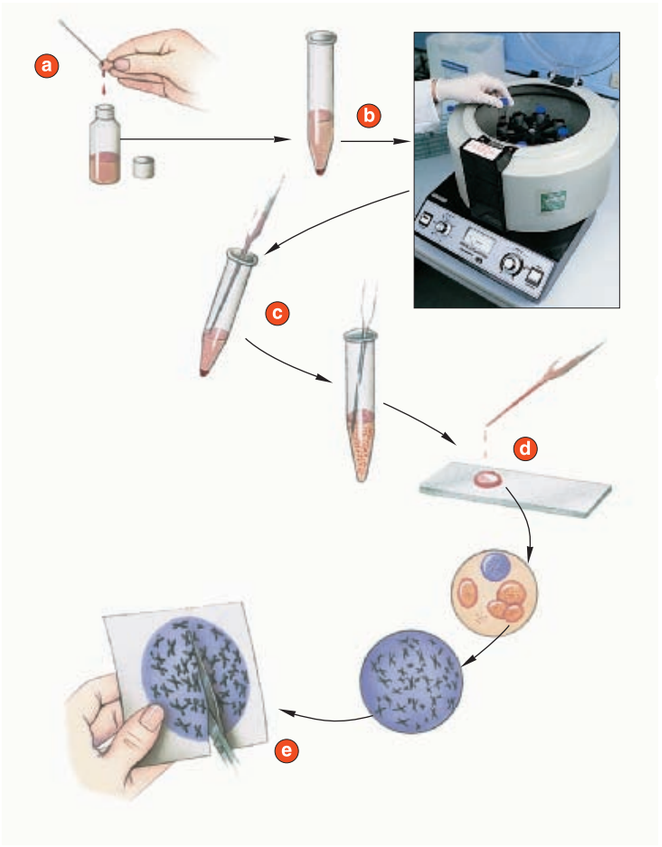


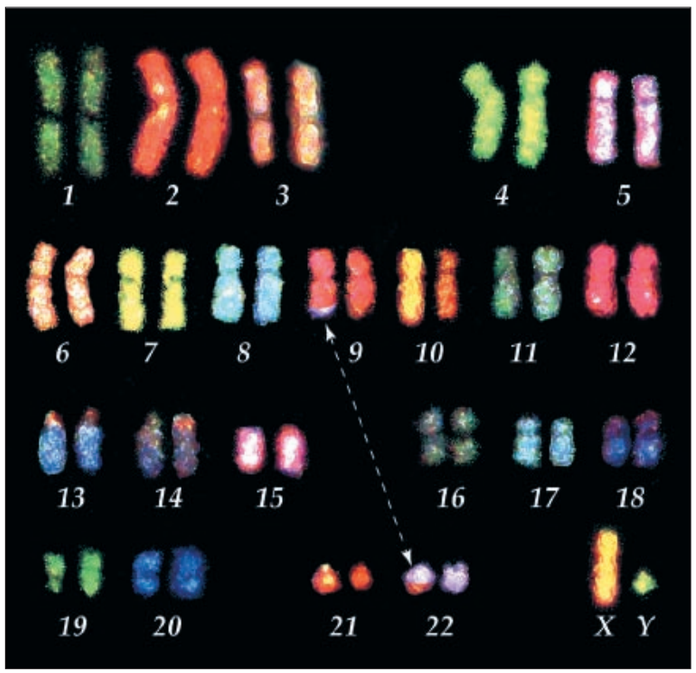


Figure 12.4 Image of a killer—the Philadelphia chromosome, as revealed by the artificial colors of spectral karyotyping. Its normal counterpart is human chromosome 9.

This chromosome exchanged a segment of itself with the nonhomologous chromosome 22. The broken end of chromosome 9 contained a gene that affects mitotic cell division. This gene fused with a DNA sequence in chromosome 22 that controls expression of another gene.

The fused gene is transcribed far more than it should be, and the cell cycle spins out of control (Section 9.5). The phenotypic outcome is *chronic myelogenous leukemia* (CML)—a rare form of leukemia in which the body produces far too many white blood cells. Uncontrolled divisions give rise to masses of malignant cells in bone tissues, where stem cells that give rise to white blood cells originate.

12.3 Examples of Autosomal Inheritance Patterns

LINKS TO SECTIONS 8.2, 8.6

Most human traits arise from complex gene interactions, but many can be traced to autosomal dominant or recessive alleles that are inherited in simple Mendelian patterns. Some of these alleles cause genetic disorders.

AUTOSOMAL DOMINANT INHERITANCE

Figure 12.5*a* shows a typical inheritance pattern for an autosomal dominant allele. If one of the parents is heterozygous and the other homozygous, any child of theirs has a 50 percent chance of being heterozygous. The trait usually appears every generation. Why? The allele is expressed even in heterozygotes.

One autosomal condition, *achondroplasia*, affects 1 in 10,000 or so people. While they were still embryos, the cartilage model on which a skeleton is constructed did not form properly. Adults have abnormally short arms and legs relative to other body parts and they are only about four feet, four inches tall (Figure 12.5*a*). Most homozygotes die before or not long after birth. The allele does not affect the capacity of the survivors to grow and reproduce.

In *Huntington's disease*, the nervous system slowly deteriorates, and involuntary muscle action increases. Symptoms often do not start until past age thirty, and those affected die during their forties or fifties. Many unknowingly transmit the mutant allele to children before then. The mutation causing the disorder alters a protein required for normal brain cell development. It is one of the *expansion* mutations, in which three nucleotides are repeated in series along the length of DNA. Hundreds of thousands of repeats occur within and between genes on human chromosomes, but this one (CAG) disrupts a gene product's function.

A few dominant alleles that cause severe problems persist in populations because expression of the allele may not interfere with reproduction, or affected people reproduce before the symptoms become severe. Also, spontaneous mutations reintroduce some of them.

AUTOSOMAL RECESSIVE INHERITANCE

Inheritance patterns also may point to a recessive allele on an autosome. First, if both of the parents are heterozygous for the allele, there is a 50 percent chance that any child of theirs will be heterozygous and a 25 percent chance it will be homozygous recessive (Figure 12.5*b*). Second, if both parents are homozygous recessive, then each child born to them will have the same condition.

Galactosemia is a heritable metabolic disorder that affects about 1 in every 100,000 newborns. This case of autosomal recessive inheritance involves alleles for an enzyme that helps digest the lactose in milk or milk products. The body normally converts lactose to glucose and galactose, then three enzymes convert the galactose to glucose–1–phosphate (Figure 12.6). This intermediate can enter glycolysis or be converted to glycogen (Sections 8.2 and 8.6). But galactosemics do not have functional copies for one of these three enzymes; they are homozygous recessive for a mutant

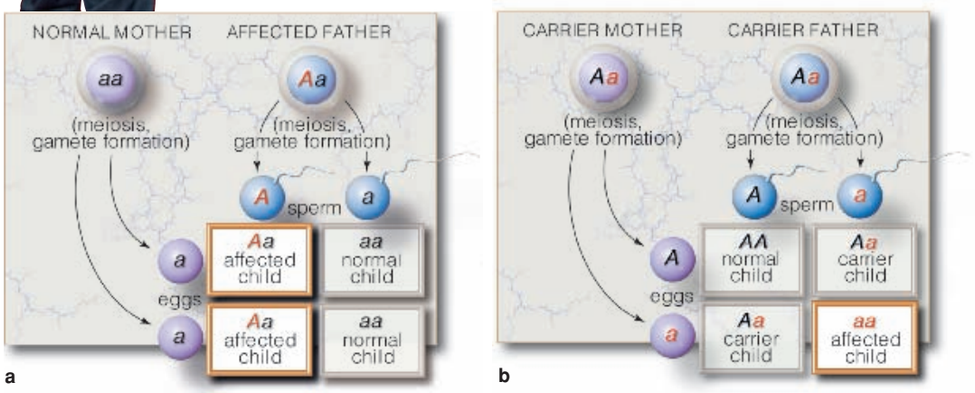


Figure 12.5 ***Animated!*** (**a**) Example of autosomal dominant inheritance. One dominant allele (*red*) is fully expressed in carriers. Achondroplasia, an autosomal dominant disorder, affects the three males shown above. At center, Verne Troyer (or Mini Me in the Mike Myers spy movies), stands two feet, eight inches tall.

(**b**) An autosomal recessive pattern. In this example, both of the parents are heterozygous carriers of the recessive allele (*red*).

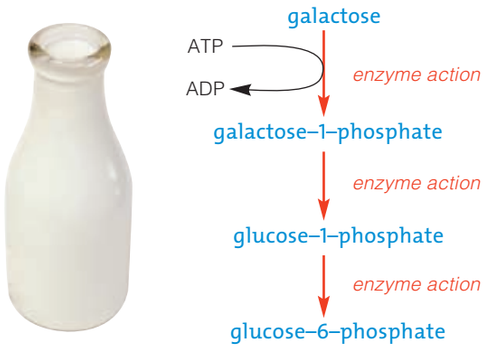


Figure 12.6 How galactose is normally converted to a form that can enter the breakdown reactions of glycolysis. A mutation that affects the second enzyme in the conversion pathway gives rise to galactosemia.

allele that encodes it. Galactose–1–phosphate builds up to toxic levels in their body. High levels of this intermediate can be detected in urine. The excess leads to malnutrition, diarrhea, vomiting, and damage to the eyes, liver, and brain.

When they do not receive treatment, galactosemics typically die young. When they are quickly placed on a diet that excludes all dairy products, the symptoms may not be as severe.

WHAT ABOUT NEUROBIOLOGICAL DISORDERS?

Those human neurobiological disorders introduced at the start of the chapter do not follow simple patterns of Mendelian inheritance. In most cases, a lone gene does not give rise to depression, schizophrenia, or bipolar disorder. Still, it is useful to search for mutations that make some people more vulnerable, as long as we recognize that many genes and environmental factors contribute in individually small ways to the outcome.

For example, researchers who conducted extensive family studies and twin studies have predicted that mutant alleles in specific regions of autosomes 1, 3, 5, 6, 8, 11 through 15, 18, and 22 increase the chance of developing schizophrenia. Similarly, several mutant alleles have been reportedly linked to bipolar disorder and depression.

Some traits can be traced to dominant or recessive alleles on autosomes because they are inherited in simple Mendelian patterns. Certain alleles on these chromosomes give rise to genetic abnormalities and genetic disorders.

12.4 Too Young, Too Old

FOCUS ON HEALTH

Sometimes textbook examples of the human condition seem a bit abstract, so take a moment to think about two boys who were too young to be old.

Imagine being ten years old with a mind trapped in a body that is getting a bit more shriveled, more frail—*old*—every day. You are barely tall enough to peer over the top of the kitchen counter. You weigh less than thirty-five pounds. Already you are bald and have a crinkled nose. Possibly you have a few more years to live. Would you, like Mickey Hays and Fransie Geringer, still be able to laugh?

On average, of every 8 million newborn humans, one will grow old far too soon. On one of its autosomes, that rare individual carries a mutant allele that gives rise to *Hutchinson–Gilford progeria syndrome*. While that new individual was still an embryo in its mother, billions of DNA replications and mitotic cell divisions distributed the information encoded in that gene to each newly formed body cell. Its legacy will be an accelerated rate of aging and a sharply reduced life span.

The mutation grossly disrupts gene interactions that are essential for growth and development. Observable symptoms start before age two. Skin that should be plump and resilient starts to thin. Skeletal muscles weaken. Limb bones that should lengthen and grow stronger soften. Premature baldness is inevitable (Figure 12.7). There are no documented cases of progeria running in families, so spontaneous mutation must be the cause. In one recent study, researchers examined twenty affected children. All the children carried a mutant gene that specifies lamin A, a structural protein that helps organize the nucleus.

Most progeriacs can expect to die in their early teens as a result of strokes or heart attacks. These final insults are brought on by a hardening of the wall of arteries, a condition typical of advanced age. Fransie was seventeen when he died. Before Mickey died at age twenty, he was the oldest living progeriac.

Figure 12.7 Two boys who met at a gathering of progeriacs at Disneyland, California, when they were not yet ten years old.

12.5 Sex Determination in Humans

Expression of one of the genes on the Y chromosome—that is what it takes to become a human male.

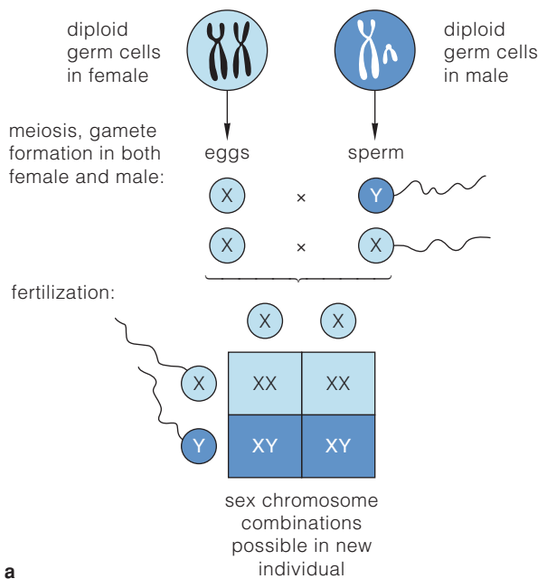
Every normal egg produced by a human female has one X chromosome. Half of the sperm cells formed in a male carry an X chromosome, and half carry a Y. If an X-bearing sperm fertilizes an X-bearing egg, then the resulting zygote will develop into a female. If the sperm carries a Y chromosome, it will develop into a male (Figure 12.8*a*).

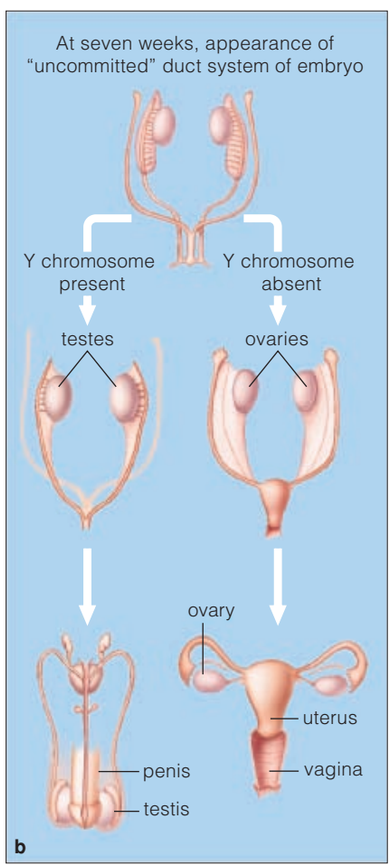
With only 255 genes, the human Y chromosome might seem relatively puny. But one of them is the *SRY* gene—which happens to be the master gene for male sex determination. Its expression in XY embryos triggers the formation of testes, or male gonads, as shown in Figure 12.8*b*. What do these primary male reproductive organs do? For one thing, some of their cells make testosterone, a sex hormone that controls the emergence of male secondary sexual traits.

An XX embryo has no Y chromosome, no *SRY* gene, and much less testosterone. Therefore, primary female reproductive organs—ovaries—form instead. Ovaries make estrogens and other sex hormones that govern the development of female secondary sexual traits.

The human X chromosome carries 1,141 genes. Like other chromosomes, it includes some genes associated with sexual traits, such as the distribution of body fat and hair. But most of its genes deal with *nonsexual* traits, such as blood-clotting functions. Such genes can be expressed in males as well as in females. Males, remember, also inherit one X chromosome.

Expression of the SRY gene on the human Y chromosome triggers testosterone synthesis, which makes a developing embryo become a male. In the absence of the Y chromosome (and the SRY gene), a developing embryo becomes a female.





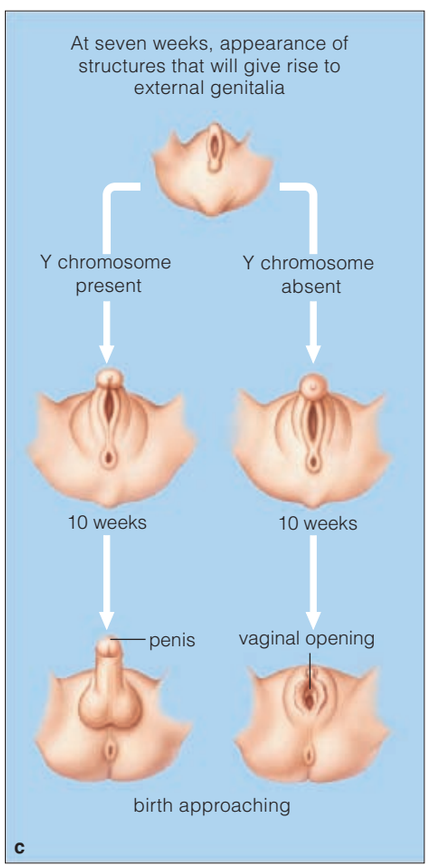


Figure 12.8 ***Animated!*** (**a**) Punnett-square diagram showing the sex determination pattern in humans.

(**b**) Early on, a human embryo is neither male nor female. Then tiny ducts and other structures that can develop into male *or* female reproductive organs start forming. In an XX embryo, ovaries form *in the absence of the Y chromosome and its SRY gene*. In an XY embryo, the gene product triggers the formation of testes. A hormone secreted from testes calls for development of male traits. (**c**) External reproductive organs in human embryos.

12.6 What Mendel Didn't Know: X-Linked Inheritance

FOCUS ON SCIENCE

After Mendel passed away in 1884, his paper on pea plants gathered dust in a hundred libraries. Then microscopists discovered chromosomes, and interest in the cellular basis of inheritance was rekindled. In 1900 researchers came across Mendel's paper while checking literature on genetic crosses. Their results confirmed what Mendel had already found out. Later, other researchers went on to discover something Mendel did not know about—genes on sex chromosomes.

By the early 1900s, researchers suspected that each gene has a specific location on a chromosome. Thomas Morgan and his coworkers confirmed it through their hybridization experiments with mutant forms of a fruit fly, *Drosophila melanogaster*. For instance, they found evidence that this fly's X chromosome has a gene for eye color and another gene for body color. They asked: Were the two genes linked on the same chromosome? That is, do they stay together during meiosis and end up in the same gamete?

Thomas Morgan, an embryologist, already had come across a relationship between sex determination and some *nonsexual* traits. For instance, human males and females both have blood-clotting factors. And yet, males are far more likely to develop hemophilia, which is a blood-clotting disorder. This sex-linked outcome was probably related to recessive forms of genes. But it was not like anything that Mendel identified in the results from his experimental crosses of pea plants. For pea plants, it made no difference which parent carried a recessive allele.

Morgan decided to study eye color and other nonsexual traits in *D. melanogaster*. This type of fruit fly has since become a favorite experimental organism. It can live in small bottles on nothing more expensive than a bit of agar, cornmeal, molasses, and yeast. A female lays hundreds of eggs in a few days, and her offspring reproduce in less than two weeks. Morgan knew that in a single year, he could use experimental tests to track observable traits for nearly thirty generations of thousands of fruit flies.

At first, all of the fruit flies in Morgan's bottles were wild type for eye color; they had brick-red eyes (Figure 12.9). Then Morgan got lucky. A gene that controls eye color mutated, and a white-eyed male appeared in a bottle, and Morgan quickly conducted **reciprocal crosses**. In the second of such paired crosses, a trait of each sex is reversed compared to the original cross to determine the role of parental sex on inheritance. In this case:

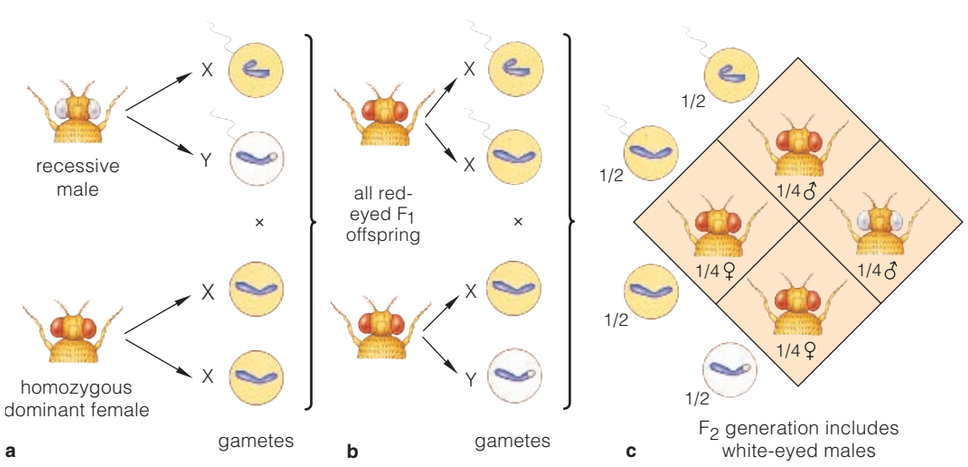
First cross: white-eyed male × red-eyed female
Second cross: red-eyed male × white-eyed female

White-eyed males mated with homozygous red-eyed females. All of the F_1 offspring had red eyes, and after the F_1 individuals had mated with each other, some of their F_2 offspring were males with white eyes (Figure 12.9*c*).

Then Morgan allowed true-breeding red-eyed males to mate with white-eyed females. *Half* of the F_1 offspring of this cross turned out to be red-eyed females, and *half* were white-eyed males. Later, the phenotypes of F_2 offspring were 1/4 red-eyed females, 1/4 white-eyed females, 1/4 red-eyed males, and 1/4 white-eyed males. The results did not fit with the straightforward inheritance patterns of pea plants. Could Mendel's theories explain them?

They could if the locus of an eye-color gene were on a sex chromosome. But which one? Because females (XX) could be white-eyed, the recessive allele had to be on one of their X chromosomes. What if white-eyed males (XY) had the recessive allele on their X chromosome and their Y chromosome had no corresponding eye-color allele? In that case, they would have white eyes. They would have no dominant allele to mask the effect of the recessive one, as the Punnett-square diagram in Figure 12.9*c* shows.

And so Morgan's idea of an X-linked gene dovetailed with Mendel's concept of segregation. By proposing that a specific gene is located on an X chromosome but not on the Y chromosome, Morgan explained his reciprocal crosses. His experimental results matched predicted outcomes.



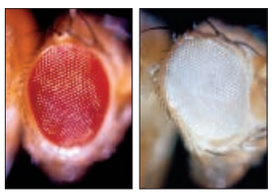


Figure 12.9 One of the experiments that pointed to sex-linked genes in *Drosophila melanogaster*. In this fruit fly, a wild-type allele specifies red eyes, and a mutant allele for the same locus specifies white eyes. *Wild-type* refers to a gene's most common form (either in nature or in standardized, laboratory-bred strains of a species) compared to less common, *mutant* alleles.

12.7 Examples of X-Linked Inheritance Patterns

LINK TO SECTION 4.10

Alleles on an X chromosome give rise to phenotypes that also reflect simple Mendelian patterns of inheritance. Many of the recessive ones cause problems.

A recessive allele on an X chromosome often leaves certain clues when it causes a genetic disorder. First, more males than females are affected. Heterozygous females still have a dominant allele on their other X chromosome that masks the recessive allele's effects.

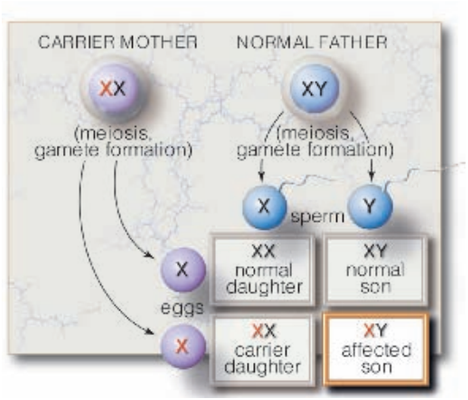


Figure 12.10 ***Animated!*** One pattern for X-linked recessive inheritance. In this case, the mother carries a recessive allele on one of her X chromosomes (*red*).

Males are not protected, because they inherit only one X chromosome along with one Y chromosome. Figure 12.10 reinforces this point. Second, a heterozygous female must be the bridge between an affected male and an affected grandson; an affected father cannot pass on the recessive allele to his son.

HEMOPHILIA A

Hemophilia A, a type of blood-clotting disorder, is one of the classic cases of X-linked recessive inheritance. Most of us have a functional clotting mechanism that quickly puts a stop to bleeding from minor injuries, in the manner explained in Section 38.9. The mechanism involves the synthesis of proteins that are products of genes on the X chromosome. Bleeding is prolonged in males who carry a mutant form of one of these X-linked genes. The affected males bruise easily, and the internal bleeding can cause problems in their muscles and joints.

This disorder affects 1 in 7,000 males, on average, but new mutations may account for a third of them. In heterozygous females, clotting time is close to normal. The disorder's frequency was relatively high among royal families of Europe and Russia in the nineteenth century. Figure 12.11 is a classic example of a pedigree for hemophilia A.

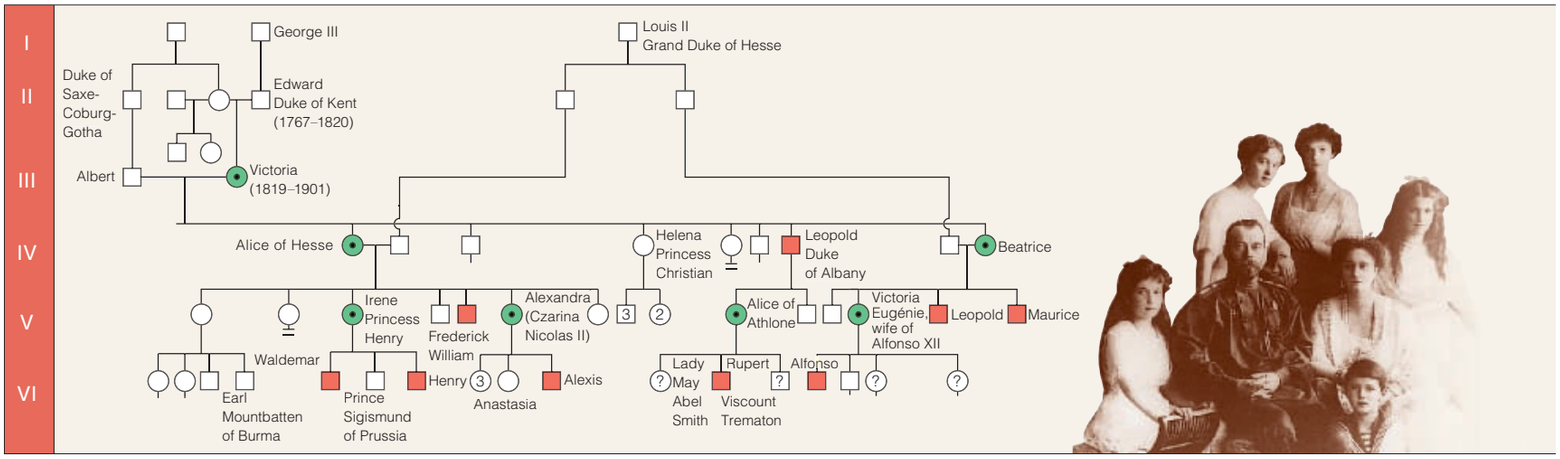


Figure 12.11 A classic case of X-linked recessive inheritance. This is a partial pedigree, or a chart of genetic connections, among descendants of Queen Victoria of England. It focuses on carriers and affected males who inherited the X-linked allele for hemophilia A (*white* circles and squares). At one time, the recessive allele was present in eighteen of Victoria's sixty-nine descendants, who sometimes intermarried. Of the Russian royal family members shown, the mother was a carrier. Through her obsession with the vulnerability of Crown Prince Alexis, a hemophiliac, she was sucked into political intrigue that helped trigger the Russian Revolution of 1917.

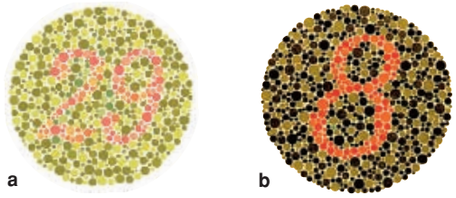


Figure 12.12 *Left,* what red–green color blindness means, using ripe red cherries on a green-leafed tree as an example. In this case, the perception of blues and yellows is normal, but the affected individual has difficulty distinguishing red from green.

Above, two of many Ishihara plates, which are standardized tests for different forms of color blindness. (**a**) You may have one form of red–green color blindness if you see the numeral "7" instead of "29" in this circle. (**b**) You may have another form if you see a "3" instead of an "8."

RED–GREEN COLOR BLINDNESS

The pattern of X-linked recessive inheritance shows up among individuals who have some degree of *color blindness*. The term refers to a range of conditions in which an individual cannot distinguish among some or all of the colors in the spectrum of visible light. Mutant gene products alter the structure and function of photoreceptors (light-sensitive receptors) in eyes.

Normally, humans can sense the differences among 150 colors. A person who is *red–green* color blind sees fewer than 25 because some or all of the receptors that respond to red and green wavelengths are weakened or absent. Other people confuse red and green colors. Still others see shades of gray instead of green but see blues and yellows quite well. Figure 12.12*a* represents this condition. Figure 12.12*b* is part of a standardized set of tests for color blindness.

Color blindness is more common in men, who are about twelve times more likely than women to develop the condition. Heterozygous women show symptoms as well. Can you explain why?

DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is one of a group of X-linked recessive disorders characterized by rapid degeneration of muscles, starting early in life. About 1 in every 3,500 boys is affected.

The recessive allele encodes dystrophin. This is the protein that structurally supports fused-together cells in muscle fibers. It anchors much of the cell cortex to the plasma membrane (Section 4.10). In cases where dystrophin is abnormal or absent, the cell cortex weakens and muscle cells die. The debris left behind in tissues triggers inflammation that becomes chronic.

Most individuals are diagnosed between ages three and seven. The progression of the disorder cannot be stopped. When the affected boy is about twelve years old, he will start using a wheelchair. His heart muscles will start to break down. Even with the best managed care, he usually will die before age twenty-five, most often as a result of respiratory failure.

Recently, researchers mapped all of the genes on the X chromosome. They discovered two things. First, only 5 percent of all of the genes we have reside on this sex chromosome. Second, the mutant alleles that cause or contribute to many known genetic disorders can occur at locations along this chromosome. More than 300 such connections have been identified.

Diverse recessive alleles on the human X chromosome are implicated in more than 300 genetic disorders.

A heterozygous female may not show symptoms if she has a dominant allele on her other X chromosome, which masks the effect of the recessive allele. Males (XY) cannot transmit any X-linked allele to their sons.

12.8 Heritable Changes in Chromosome Structure

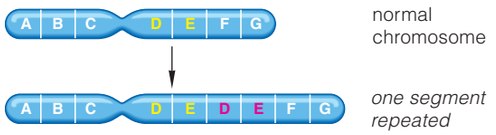
LINK TO SECTION 10.3

On rare occasions, a chromosome's structure changes. Many of the alterations have severe or lethal outcomes.

MAIN CATEGORIES OF STRUCTURAL CHANGE

One or more changes in the physical structure of a chromosome may give rise to a genetic disorder or abnormality. Such changes are rare, but they do occur spontaneously in nature. Some also can be induced by exposure to certain chemicals or irradiation. Either way, the alteration may be detected by microscopic examination and karyotype analysis of cells during mitosis or meiosis. Four kinds of structural changes are chromosomal duplications, deletions, inversions, and translocations.

Duplication Even normal chromosomes have DNA sequences that are repeated two or more times. These are called **duplications**:



Duplications can occur through unequal crossovers at prophase I. Homologous chromosomes align side by side, but their DNA sequences misalign at some point along their length. The probability of this happening is greater in regions where DNA has long repeats of the same series of nucleotides. A stretch of DNA gets deleted from one chromosome and is spliced into the partner chromosome. Some duplications cause neural problems and physical abnormalities. As you will see, others apparently were important in the evolution of primates that were ancestral to humans.

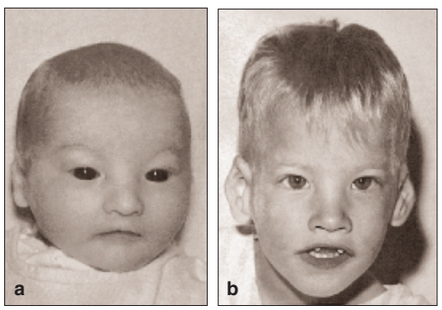
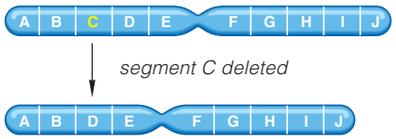


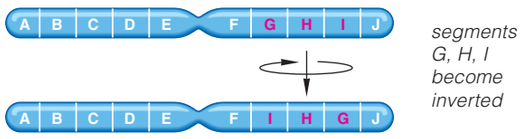
Figure 12.13 (**a**) A male infant who developed cri-du-chat syndrome. His ears are low on the side of the head relative to the eyes. (**b**) Same boy, four years later. By this age, affected humans stop making the mewing sounds typical of the syndrome.

Deletion A **deletion** is the loss of some portion of a chromosome, as by unequal crossovers, inversions, or chemical attacks:



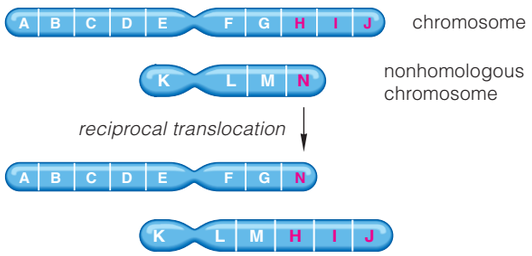
In mammals, most deletions cause serious disorders or death. Missing or broken genes disrupt the body's growth, development, and metabolism. For instance, a tiny deletion from human chromosome 5 results in an abnormally shaped larynx and mental impairment. Crying infants sound like cats meowing (Figure 12.13). Hence the name of the disorder, *cri-du-chat* (cat-cry in French). Inversions and deletions often occur together as an outcome of unequal recombination events.

Inversion With an **inversion**, part of the sequence of DNA within the chromosome becomes oriented in the reverse direction, with no molecular loss:



An inversion is not a problem for a carrier if it does not alter a crucial gene region. It can cause problems in meiosis. Chromosomes may mispair, and deletions may occur that can reduce the viability of gametes. Some individuals do not even know that they have an inverted chromosome region until a genetic disorder or abnormality surfaces in one or more children.

Translocation In Section 12.2, you came across a case of a broken part of one chromosome becoming attached to another chromosome. This type of change in chromosome structure is known as a **translocation**. Most translocations are reciprocal, in that both of the two chromosomes exchange broken parts:



Translocations often cause reduced fertility, because affected chromosomes have difficulty segregating in meiosis. Severe problems are rare, but they do arise. They include some sarcomas, lymphomas, myelomas, and leukemias.

DOES CHROMOSOME STRUCTURE EVOLVE?

Alterations in the structure of chromosomes generally are not good and may be selected against. Even so, many alterations with neutral effects have been built into the DNA of all species over evolutionary time.

Duplicates of genes could have bestowed adaptive advantages on descendants of their original bearers. Two or more copies of some gene means that one is free to mutate while the other continues to carry out its normal function. The slightly modified products of mutant genes can behave in slightly different or novel ways, some of which are beneficial.

Some duplications have proved adaptive. Reflect on the four globin chains of hemoglobin (Section 3.6). In humans and other primates, several genes for these polypeptide chains are strikingly similar. Apparently they evolved through duplications, mutations, and transpositions. They have slightly different molecular structures and slightly different capacities to bind and transport oxygen under a range of cellular conditions.

Alterations in chromosome structure might have contributed to the differences among closely related organisms, such as apes and humans. Eighteen of the twenty-three pairs of human chromosomes are almost identical with chimpanzee and gorilla chromosomes. The other five differ only at inverted and translocated regions. Figure 12.14 shows the striking similarities between some gibbon and human chromosomes that may have arisen by duplications and translocations.

To give one more example, human body cells have twenty-three pairs of chromosomes, but those of a chimpanzee, gorilla, or orangutan have twenty-four. Compare the banding patterns of these chromosomes. During human evolution, two chromosomes in an early ancestor fused, end to end, to form chromosome 2. In the fused region, researchers have discovered remnants of a telomere—the signature DNA sequence that caps the *ends* of all chromosomes (Figure 12.15).

A segment of a chromosome may be duplicated, deleted, inverted, or moved to a new location. Such changes can be harmful or lethal. Others have been conserved over time; they confer advantages or have had neutral effects.

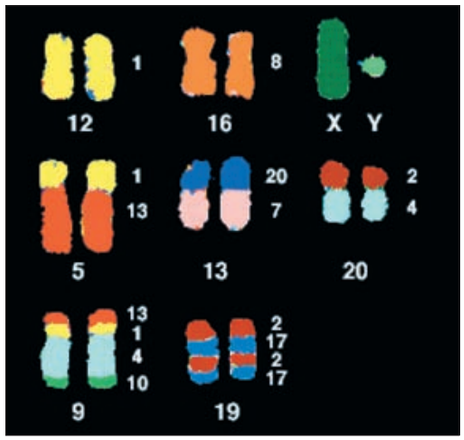


Figure 12.14 Spectral karyotype of duplicated chromosomes of the gibbon, one of the apes. The colors identify regions of gibbon chromosomes that are structurally identical with human chromosomes.

Top row: Chromosomes 12, 16, X, and Y are structurally the same in both primates. *Second row:* Translocations are present in gibbon chromosomes 5, 13, and 20, and they correspond to regions of human chromosomes 1, 13, 20, 7, 2, and 4.

Third row: Gibbon chromosome 9 corresponds to several human chromosome regions. In addition, duplications in gibbon chromosome 19 are present in human chromosomes 2 and 17.

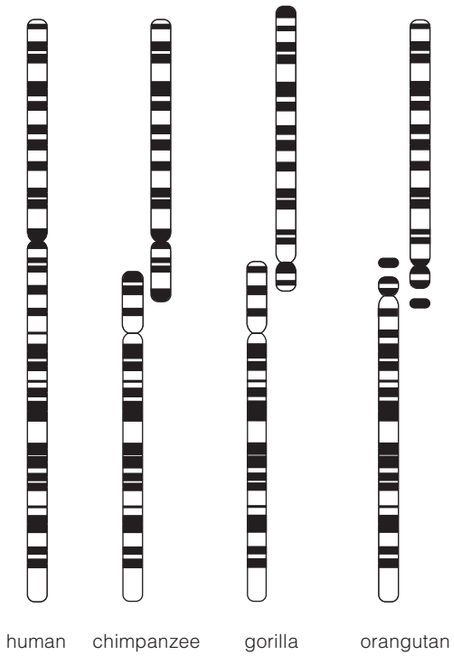


Figure 12.15 Banding patterns of human chromosome 2 (*left*), compared with the patterns on two of the chromosomes in cells of the chimpanzee, gorilla, and orangutan. Such bands appear because different chromosome regions preferentially take up different kinds of stains. Their response to a given stain depends on their base composition and packing organization.

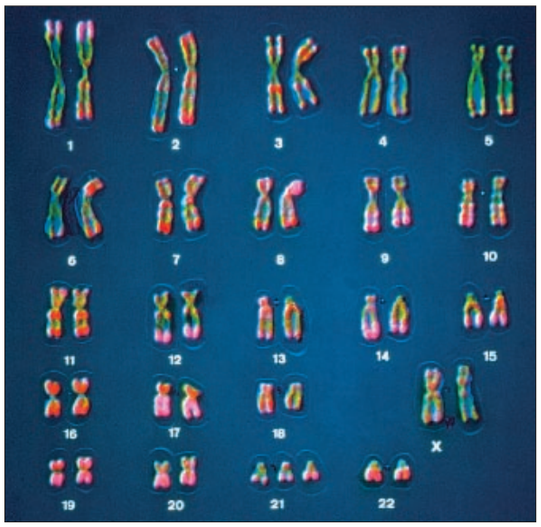
12.9 Heritable Changes in the Chromosome Number

LINKS TO SECTIONS 9.3, 10.3

Occasionally, abnormal events occur before or during cell division, and gametes and new individuals end up with the wrong chromosome number. Consequences range from minor to lethal changes in form and function.

In **aneuploidy**, cells usually have one extra or one less chromosome. Autosomal aneuploidy is usually fatal for humans and is linked to most miscarriages. Aneuploidy typically arises through **nondisjunction**, whereby one or more pairs of chromosomes do not separate as they should during mitosis or meiosis. Figure 12.16 shows an example. In **polyploidy**, cells have three or more of each type of chromosome. Half of all species of flowering plants, some insects, fishes, and other animals are polyploid.

Such changes affect the chromosome number at fertilization. Suppose a normal gamete fuses with an $n+1$ gamete, with one extra chromosome. The new individual will be trisomic ($2n+1$), with three of one type of chromosome and two of every other type. Or what if an $n-1$ gamete and a normal n gamete fuse? In this case, the new individual will be monosomic, or $2n-1$. Mitotic divisions perpetuate such mistakes when an embryo is growing in size and developing.



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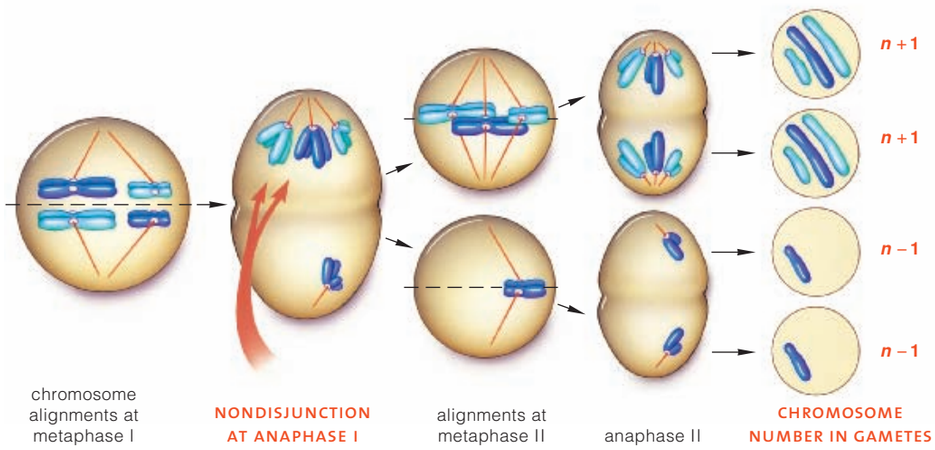


b

Figure 12.16 (**a**) A case of nondisjunction. This karyotype reveals the trisomic 21 condition of a human female. (**b**) One example of how nondisjunction arises. Of the two pairs of homologous chromosomes shown here, one fails to separate during anaphase I of meiosis. The chromosome number is altered in the gametes that form after meiosis.

AUTOSOMAL CHANGE AND DOWN SYNDROME

A few trisomics are born alive, but only trisomy 21 individuals reach adulthood. A newborn with three chromosomes 21 will develop *Down syndrome*. This autosomal disorder is the most frequent type of altered chromosome number in humans; it occurs once in every 800 to 1,000 births. It affects more than 350,000 people in the United States. Figure 12.16*a* shows a karyotype for a trisomic 21 female. About 95 percent of all cases arise through nondisjunction at meiosis. Affected individuals have upward-slanting eyes, a fold of skin that starts at the inner corner of each eye, a deep crease across each palm and foot sole, one (not two) horizontal furrows on their fifth fingers, and somewhat flattened facial features.

Not all of the outward symptoms develop in every individual. That said, trisomic 21 individuals do have moderate to severe mental impairment and heart problems. Also, their skeleton develops abnormally, so older children have shortened body parts, loose joints, and misaligned bones in hips, fingers, and toes. Their muscles and reflexes are weak. Motor skills, including speech, develop very slowly. With medical care, individuals can live for fifty-five years, on average.

The incidence of nondisjunction rises with increasing age of potential mothers (Figure 12.17). Nondisjunction might occur in the father, although less often. Trisomy 21 is just one of hundreds of conditions that can be detected through prenatal diagnosis (Section 12.11). With early training and medical intervention, individuals still can take part in normal activities. As a group, trisomics 21 tend to be cheerful and sociable.

CHANGE IN THE SEX CHROMOSOME NUMBER

Nondisjunction also causes most of the alterations in the number of X and Y chromosomes. The frequency of such changes is 1 in 400 live births. Usually, they lead to difficulties in learning and motor skills, such as speech, although problems can be so subtle that the underlying cause is not even diagnosed.

Female Sex Chromosome Abnormalities *Turner syndrome* individuals have an X chromosome and no corresponding X or Y chromosome (XO). About 1 in 2,500 to 10,000 newborn girls are XO. Nondisjunction originating with the father accounts for 75 percent of the cases. Yet cases are few, compared with other sex chromosome abnormalities. At least 98 percent of XO embryos may spontaneously abort early in pregnancy.

Despite the near lethality, XO survivors are not as disadvantaged as other aneuploids. On average, they are well proportioned, as shown here, but only four feet, eight inches tall. Most cannot make enough sex hormones; they do not have functional ovaries. The condition affects the development of secondary sexual traits, such as breast development. A few eggs form in the ovaries but degenerate by the time the girls are two years old.

A few females inherit three to five X chromosomes. An *XXX syndrome* occurs in about 1 of 1,000 live births. Adults are fertile. Except for slight learning difficulties, most fall in the normal range of social behavior.

Male Sex Chromosome Abnormalities About 1 of every 500 males has an XXY karyotype, with an extra chromosome inherited from the mother. Two-thirds of the cases are an outcome of nondisjunction at meiosis. Among the remainder, failure of the Y chromosome to separate at mitosis gave rise to a mosaic karyotype (XY in some cells and XXY in other cells).

The resulting *Klinefelter syndrome* develops during puberty. XXY males tend to be overweight and tall. The testes and the prostate gland usually are smaller than average. Many XXY males are within the normal range of intelligence, although some have short-term memory loss and learning disabilities. They make less testosterone and more estrogen than normal males, with feminizing effects. Sperm counts are low. Hair is sparse, the voice is pitched high, and the breasts are enlarged somewhat. When affected individuals enter puberty, they can receive testosterone injections that can reverse the feminized traits.

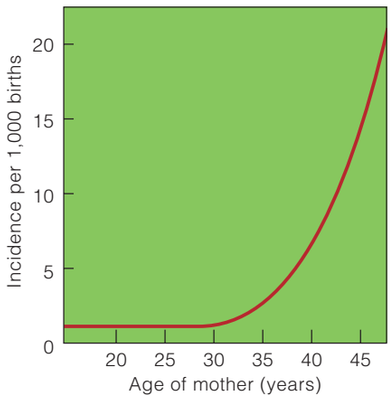


Figure 12.17 Relationship between the frequency of Down syndrome and mother's age at childbirth. The data are from a study of 1,119 affected children. The risk of having a trisomic 21 baby rises with the mother's age. This may seem odd, because about 80 percent of trisomic 21 individuals are born to women not yet thirty-five years old. But these women are in the age categories with the highest fertility rates, and they simply have more babies.

About 1 in 500 to 1,000 males has one X and two Y chromosomes, an *XYY condition*. They tend to be taller than average, with mild mental impairment, but most fall in the normal phenotypic range. They were once thought to be genetically predisposed to a life of crime. This misguided view was based on a sampling error (too few cases of narrowly chosen groups, such as prison inmates) and were biased (the same researchers gathered karyotypes *and* personal histories). Fanning the stereotype was a report that a mass murderer of young nurses was XYY. He wasn't.

In 1976 a Danish geneticist reported results from his study of 4,139 tall males, all twenty-six years old, who had registered at their draft board. Besides their data from physical examinations and intelligence tests, the draft records offered clues to social and economic status, education, and criminal convictions, if there were any. Twelve of the males studied were XYY, which meant the "control group" had more than 4,000 males. The only finding was that mentally impaired, tall males who engage in criminal deeds are just more likely to get caught—irrespective of karyotype.

The majority of XXY, XXX, and XYY children may not even be diagnosed. Some are dismissed unfairly as being underachievers.

Nondisjunction in germ cells, gametes, or early embryonic cells changes the number of autosomes or the number of sex chromosomes. The change affects development and the resulting phenotypes.

Nondisjunction at meiosis causes most sex chromosome abnormalities, which typically lead to subtle difficulties with learning, and speech and other motor skills.

12.10 Human Genetic Analysis

Some organisms, including pea plants and fruit flies, are ideal for genetic analysis. They do not have very many chromosomes. They can grow and reproduce fast in small spaces, under controlled conditions. It does not take long to track a trait through many generations. Humans, however, are another story.

Unlike the flies in laboratory bottles, we humans live under variable conditions in diverse environments, and we live as long as the geneticists who study us. Most of us select our own mates and reproduce if and when we want to. Most families are not large, which means that there are not enough offspring available for researchers to make easy inferences.

Geneticists often gather information from several generations to increase the numbers for analysis. If a trait follows a simple Mendelian inheritance pattern, geneticists can be more confident about predicting the probability of its showing up again. The pattern also can be a clue to the past (Figure 12.18).

Such information is often displayed in **pedigrees**, or charts of genetic connections among individuals. Standardized methods, definitions, and symbols that represent different kinds of individuals are used to construct these charts. You already came across one in Section 12.7. Figures 12.19 and 12.20 are two more.

Figure 12.18 An intriguing pattern of inheritance. Eight percent of the men in Central Asia carry nearly identical Y chromosomes, which implies descent from a shared ancestor. If so, then 16 million males living between northeastern China and Afghanistan—close to 1 of every 200 men alive today—belong to a lineage that started with the warrior and notorious womanizer Genghis Khan. In time, his offspring ruled an empire that stretched from China all the way to Vienna.

Those who analyze pedigrees rely on knowledge of probability and patterns of Mendelian inheritance that may yield clues to a trait. Such researchers have traced many genetic abnormalities and disorders to a dominant or recessive allele and often to its location on an autosome or a sex chromosome. Table 12.1 is a list of the ones used as examples in this book.

As individuals and as members of society, what do we do with the information? The next section gets into options. When considering them, keep in mind some important distinctions. First, a genetic *abnormality* is only a rare or uncommon version of a trait, as when a person is born with six digits on each hand or foot instead of the usual five. Whether you view such an abnormality as disfiguring or merely interesting is subjective only; there is nothing inherently life-threatening about it. By contrast, a genetic *disorder* is a heritable condition that sooner or later gives rise to mild to severe medical problems. Each

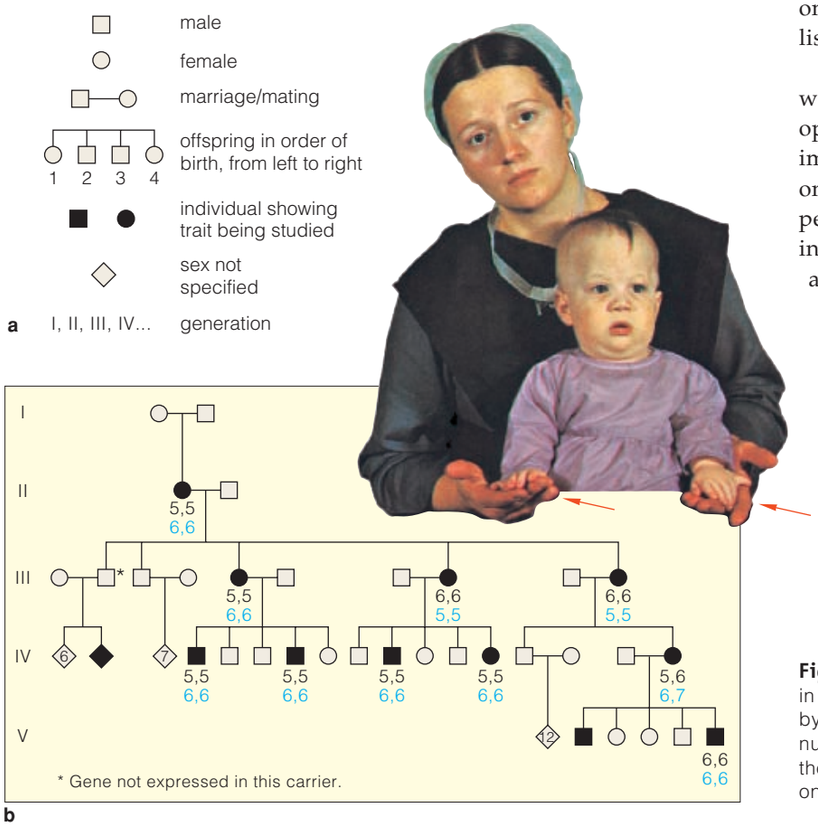


Figure 12.19 ***Animated!*** (**a**) Standardized symbols used in pedigrees. (**b**) A pedigree for *polydactyly*, characterized by extra fingers, toes, or both. *Black* numerals signify the number of fingers on each hand; *blue* numerals signify the number of toes on each foot. This condition recurs as one symptom of Ellis–van Creveld syndrome.

Table 12.1 Examples of Human Genetic Disorders and Genetic Abnormalities

Disorder or Abnormality	Main Symptoms
Autosomal recessive inheritance	
Albinism	Absence of pigmentation
Blue offspring	Bright blue skin coloration
Cystic fibrosis	Abnormal glandular secretions leading to tissue, organ damage
Ellis–van Creveld syndrome	Extra fingers, toes, short limbs
Fanconi anemia	Physical abnormalities, bone marrow failure
Galactosemia	Brain, liver, eye damage
Phenylketonuria (PKU)	Mental impairment
Sickle-cell anemia	Adverse pleiotropic effects on organs throughout body
Autosomal dominant inheritance	
Achondroplasia	One form of dwarfism
Camptodactyly	Rigid, bent fingers
Familial hypercholesterolemia	High cholesterol levels in blood; eventually clogged arteries
Huntington's disease	Nervous system degenerates progressively, irreversibly
Marfan syndrome	Abnormal or no connective tissue
Polydactyly	Extra fingers, toes, or both
Progeria	Drastic premature aging
Neurofibromatosis	Tumors of nervous system, skin

Disorder or Abnormality	Main Symptoms
X-linked recessive inheritance	
Androgen insensitivity syndrome	XY individual but having some female traits; sterility
Red–green color blindness	Inability to distinguish among some or all shades of red and green
Fragile X syndrome	Mental impairment
Hemophilia	Impaired blood-clotting ability
Muscular dystrophies	Progressive loss of muscle function
X-linked anhidrotic dysplasia	Mosaic skin (patches with or without sweat glands); other effects
Changes in chromosome structure	
Chronic myelogenous leukemia (CML)	Overproduction of white blood cells in bone marrow; organ malfunctions
Cri-du-chat syndrome	Mental impairment; abnormally shaped larynx
Changes in chromosome number	
Down syndrome	Mental impairment; heart defects
Turner syndrome	Sterility; abnormal ovaries, abnormal sexual traits
Klinefelter syndrome	Sterility; mild mental impairment
XXX syndrome	Minimal abnormalities
XYY condition	Mild mental impairment or no effect

genetic disorder is characterized by a specific set of symptoms—a **syndrome**.

One more point to keep in mind: Alleles that give rise to severe genetic disorders are generally rare in populations, because they put their bearers at risk. Why don't they disappear entirely? Rare mutations introduce new ones. In addition, in heterozygotes, a normal allele masks harmful effects that may result from expression of the mutant recessive allele. This means that heterozygotes can transmit harmful alleles to their offspring. The next section addresses how we may address the consequences.

Pedigree analysis may reveal simple patterns of Mendelian inheritance. From such patterns, specialists can infer the probability that offspring will inherit certain alleles.

A genetic abnormality is a rare or less common version of a heritable trait. A genetic disorder is a heritable condition that results in mild to severe medical problems.

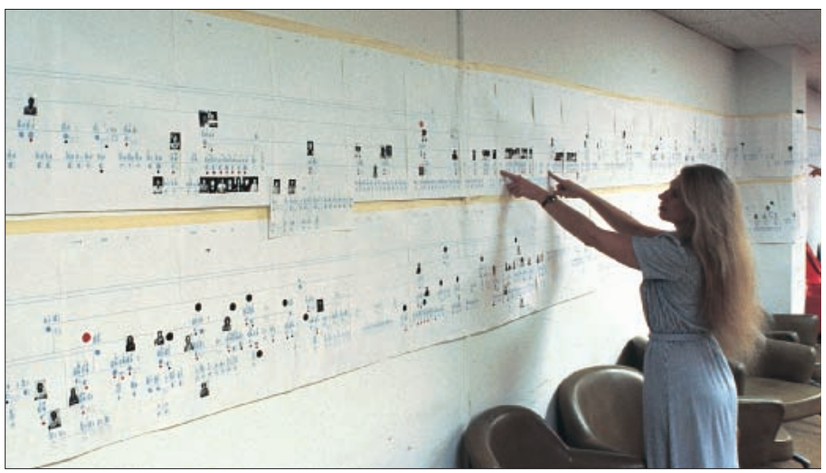


Figure 12.20 Pedigree for Huntington's disease, a progressive degeneration of the nervous system. Researcher Nancy Wexler and her team constructed this extended family tree for nearly 10,000 Venezuelans. Their analysis of unaffected and affected individuals revealed that a dominant allele on human chromosome 4 is the culprit. Wexler has a special interest in the disease; it runs in her family.

12.11 Prospects in Human Genetics

With the arrival of their newborn, parents typically ask, "Is our baby all right?" Quite naturally, they want their baby to be free of genetic disorders, and most babies are. But what are the options when something goes wrong?

Many prospective parents have difficulty coming to terms with the possibility that a child of theirs might develop a severe genetic disorder. What are their options?

Phenotypic Treatments Surgery, prescription drugs, hormone replacement therapy, and often dietary controls can minimize and in some cases eliminate the symptoms of many genetic disorders.

For instance, strict dietary controls work in cases of *phenylketonuria*, or PKU. Individuals affected by this genetic disorder are homozygous for a recessive allele on an autosome. They cannot make a functional form of an enzyme that catalyzes the conversion of the amino acid phenylalanine to tyrosine. Because the conversion is blocked, phenylalanine accumulates and is diverted into other metabolic pathways. The outcome is an impairment of brain function.

Affected people who restrict phenylalanine intake can lead essentially normal lives. They must avoid soft drinks and other products that are sweetened with aspartame, a compound that contains phenylalanine.

Genetic Screening The idea behind genetic screening is to detect alleles that cause genetic disorders, provide information on reproductive risks, and help families who are already affected. Often, carriers or affected individuals are detected early enough to start countermeasures for minimizing the damage before symptoms develop.

A few large-scale screening programs are operational. Besides helping individuals, the information they generate is being used to estimate the prevalence and distribution of harmful alleles in populations. In the United States, for instance, most hospitals routinely screen newborns for PKU, so we now see fewer individuals with symptoms of the disorder.

There are social risks that must be considered. How would you feel if you were labeled as someone with "bad" alleles? Would the knowledge invite chronic anxiety? Would potential employers or insurance companies turn you down? How would you interact with an affected child that you brought into the world if you had known about the risk in advance? No easy answers here.

Prenatal Diagnosis Doctors and clinicians commonly use methods of *prenatal diagnosis* to determine the sex of embryos or fetuses and to screen for more than 100 known genetic problems. *Prenatal* means before birth. *Embryo* is a term that applies until eight weeks after fertilization, after which the term *fetus* is appropriate.

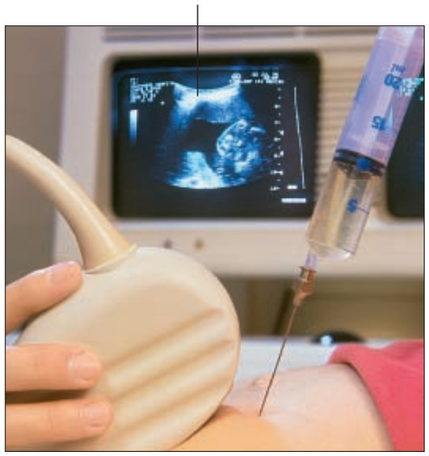


Figure 12.21 ***Animated!*** Amniocentesis, a prenatal diagnostic tool. A pregnant woman's doctor holds an ultrasound emitter against her abdomen while drawing a sample of amniotic fluid into a syringe. He monitors the path of the needle with an ultrasound screen, in the background. Then he directs the needle into the amniotic sac that holds the developing fetus and withdraws twenty milliliters or so of amniotic fluid. The fluid contains fetal cells and wastes that can be analyzed for genetic disorders.

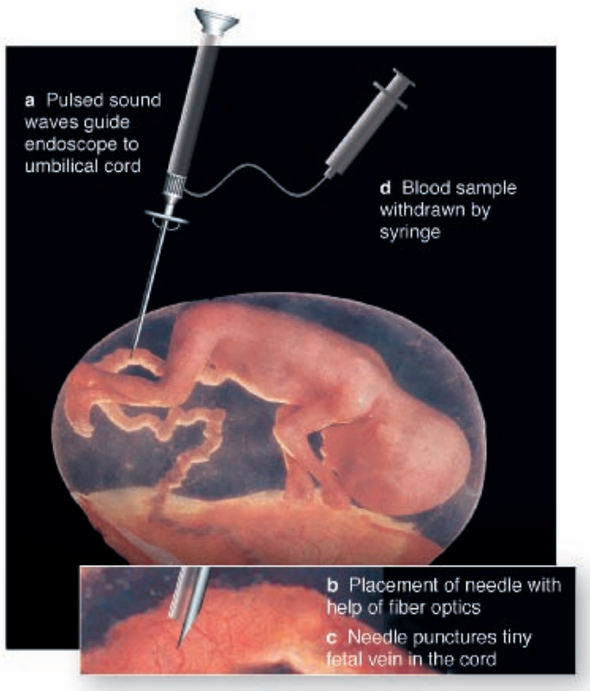


Figure 12.22 Fetoscopy for prenatal diagnosis.

Suppose a forty-five-year-old woman is pregnant and worries about Down syndrome. Between eight and twelve weeks after conception, she might opt for *amniocentesis* (Figure 12.21). By this diagnostic procedure, a clinician uses a syringe to withdraw a small sample of fluid from the amniotic cavity. The "cavity" is a fluid-filled sac, bounded by a membrane—the amnion—that encloses the fetus. The fetus normally sheds some cells into the fluid. Cells suspended in the fluid sample can be analyzed for many genetic disorders, including Down syndrome, cystic fibrosis, and sickle-cell anemia.

Chorionic villi sampling (CVS) is a similar diagnostic procedure. A clinician withdraws a few cells from the chorion, a membrane that surrounds the amnion and helps form the placenta. Unlike amniocentesis, however, CVS can be requested to find out information as early as eight weeks into pregnancy.

It is now possible to see a live, developing fetus with the aid of an endoscope, a fiber-optic device. In *fetoscopy*, sound waves are pulsed across the mother's uterus. Images of parts of the fetus, umbilical cord, or placenta show up on a computer screen that is connected to the endoscope (Figure 12.22). A sample of fetal blood is often drawn at the same time. This procedure can be used to diagnose many blood cell disorders, such as sickle-cell anemia and hemophilia.

There are risks to a fetus associated with all three procedures, including punctures or infections. Also, if the amnion does not reseal itself quickly, too much fluid can leak out of the amniotic cavity and endanger the fetus. Amniocentesis increases the risk of miscarriage by 1 to 2 percent. CVS may disrupt the placenta's development, which can cause missing or underdeveloped fingers and toes in 0.3 percent of newborns. Fetoscopy raises the risk of a miscarriage by 2 to 10 percent.

Genetic Counseling Parents-to-be commonly ask genetic counselors to compare the risks associated with diagnostic procedures against the likelihood that their future child will be affected by a severe genetic disorder. At the time of counseling, they also should discuss the small overall risk (3 percent) that complications can affect *any* child during the birth process. They should talk about how old they are. The older either prospective parent is, the greater the risk may be.

As a case in point, suppose a first child or a close relative has a severe disorder. Genetic counselers come up with a program of diagnosis of parental genotypes, pedigrees, and genetic testing for known disorders. Using this information, counselors can predict risks for disorders in future children. They should remind prospective parents that the same risk usually applies to each pregnancy.

Regarding Abortion What happens after prenatal diagnosis reveals a severe problem? Do prospective parents opt for an induced abortion? An *abortion* is an expulsion of a pre-term embryo or fetus from the uterus. We can only say here that individuals must weigh awareness of the severity of the genetic disorder against their ethical and religious beliefs. Worse, today they must play out their personal tragedy on a larger stage that is dominated by a nationwide battle between highly vocal "pro-life" and "pro-choice" factions. We return to this volatile topic in Section 44.15, after explaining the stages of human embryonic development.

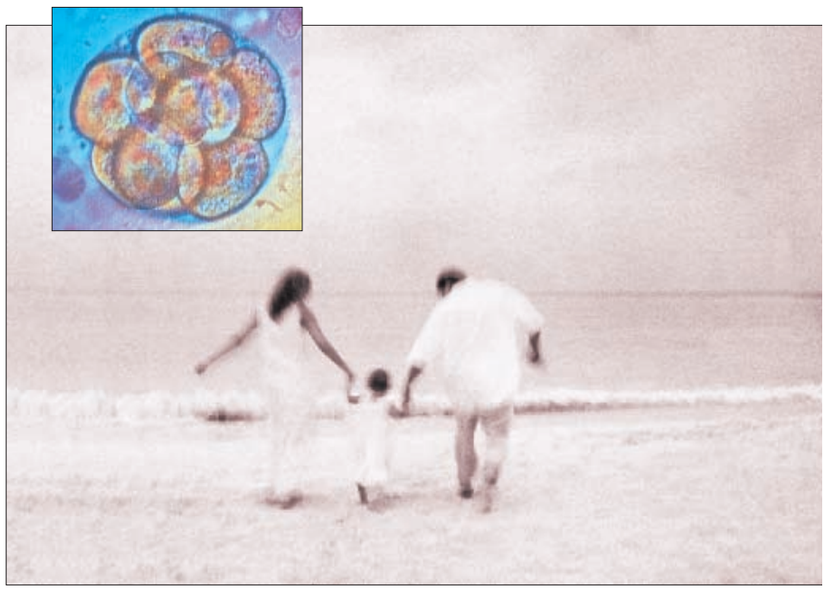


Figure 12.23 Eight-cell and multicelled stages of human development.

Preimplantation Diagnosis This procedure relies on *in vitro fertilization*. Sperm and eggs from prospective parents are mixed in a sterile culture medium. One or more eggs may get fertilized. If this happens, mitotic cell divisions can turn an egg into a ball of eight cells within forty-eight hours (Figure 12.23).

According to one view, the tiny, free-floating ball is a pre-pregnancy stage. Like all of the unfertilized eggs that a woman's body discards monthly during her reproductive years, it has not attached to the uterus. All of its cells have the same genes. However, its cells are not yet committed to being specialized one way or another. Doctors carefully remove one of these undifferentiated cells and analyze its genes. If it has no detectable genetic defects, the ball is inserted into the uterus. The withdrawn cell will not be missed. Many of the resulting "test-tube babies" are born in good health.

Some couples who are at risk of passing on the alleles for cystic fibrosis, muscular dystrophy, or some other genetic disorder have opted for this procedure.

Summary

Section 12.1 Of twenty-three pairs of homologous chromosomes in human body cells, one is a pairing of sex chromosomes. The other chromosomes are called autosomes; in both sexes, they are the same length and shape, have the same centromere location, and carry the same genes along their length.

Section 12.2 In karyotyping, a diagnostic tool, an individual's metaphase chromosomes are prepared for microscopy, photographed, and arranged in sequence in a chart on the basis of their defining features.

Biology Now
Learn how to create a karyotype with the animation on BiologyNow.

Sections 12.3, 12.4 Some dominant and recessive alleles on autosomes are inherited in simple Mendelian patterns that can be predictably connected with specific phenotypes. Some mutant forms of these alleles give rise to genetic abnormalities or genetic disorders.

Biology Now
Investigate autosomal inheritance with the interaction on BiologyNow.

Sections 12.5, 12.6 Human females have identical sex chromosomes (XX) and males have nonidentical ones (XY). The *SRY* gene on the Y chromosome is the basis of sex determination. Its expression starts the synthesis of testosterone, a hormone that causes a human embryo to develop into a male. If an embryo has no Y chromosome (no *SRY* gene), it develops into a female.

Experiments with fruit flies yielded the first evidence that specific genes that give rise to nonsexual traits are located on the X chromosome.

Biology Now
See how gender is determined in humans with the interaction on BiologyNow.

Section 12.7 Certain dominant and recessive alleles on the X chromosome are inherited in simple patterns. A number of alleles on the X chromosome contribute to more than 300 known genetic disorders. Males cannot transmit a recessive X-linked allele to their sons; an affected female must be the bridge of inheritance.

Biology Now
Investigate X-linked inheritance with the interaction on BiologyNow.

Section 12.8 On rare occasions, a chromosome's physical structure undergoes abnormal alterations. Part of it may be duplicated, deleted, inverted, or moved to a new location (translocated) in the same chromosome or a different one.

Most alterations are harmful or lethal. Even so, many have accumulated in the chromosomes of all species over evolutionary time. Either they had neutral effects or they later proved to be useful. Many duplications, inversions, and translocations are built into primate chromosomes. They are strikingly similar among human, chimpanzee, gorilla, orangutan, and gibbon chromosomes, which is strong evidence of divergences from a common ancestor.

Section 12.9 The parental chromosome number can change permanently. Most often, this is an outcome of nondisjunction: the failure of one or more pairs of duplicated chromosomes to separate from each other, most often during meiosis.

Aneuploids have inherited one extra or one less chromosome than their parents. In the human population, trisomy 21, the most well-known form of aneuploidy, results in Down syndrome. Most human autosomal aneuploids die before birth.

Polyploids inherited three or more of each type of chromosome from their parents. About half of all flowering plants and some insects, fishes, and other animals are polyploid.

Changes in the number of sex chromosomes usually cause problems with learning and motor skills. Problems can be so subtle that the underlying cause may not be diagnosed, as among XXY, XXX, and XYY children.

Sections 12.10, 12.11 Traditionally, geneticists have constructed pedigrees, or charts of genetic connections among individuals, to estimate the probability that offspring will inherit a trait of interest. Phenotypic treatments, genetic screening, genetic counseling, prenatal diagnosis, and preimplantation diagnosis are options available for potential parents who are at risk of transmitting a harmful allele to offspring.

Biology Now
Examine a human pedigree with the animation on BiologyNow.
Explore amniocentesis with the animation on BiologyNow.

Self-Quiz

Answers in Appendix II

1. The _____ of chromosomes in a cell are compared to construct karyotypes.
   a. length and shape
   b. centromere location
   c. gene sequence
   d. both a and b

2. The _____ determines gender in humans.
   a. X chromosome
   b. *Dll* gene
   c. *SRY* gene
   d. both b and c

3. If one parent is heterozygous for a dominant allele on an autosome and the other parent is homozygous, any child of theirs has a _____ chance of being heterozygous.
   a. 25 percent
   b. 50 percent
   c. 75 percent
   d. no chance; it will die

4. Expansion mutations occur _____ within and between genes in human chromosomes.
   a. only rarely
   b. frequently
   c. not at all
   d. only in multiples of ten

5. Galactosemia is a case of _____ inheritance.
   a. autosomal dominant
   b. autosomal recessive
   c. X-linked dominant
   d. X-linked recessive

6. Is this statement true or false: A son can inherit an X-linked recessive allele from his father.

7. Color blindness is a case of _____ inheritance.
   a. autosomal dominant
   b. autosomal recessive
   c. X-linked dominant
   d. X-linked recessive

8. A (An) _____ can alter chromosome structure.
   a. deletion
   b. duplication
   c. inversion
   d. translocation
   e. all of the above

9. Nondisjunction may occur during _____ .
   a. mitosis
   b. meiosis
   c. fertilization
   d. both a and b

10. Is this statement false: Body cells sometimes inherit three or more of each type of chromosome characteristic of the species, a condition called aneuploidy.

11. The karyotype for Klinefelter syndrome is _____ .
   a. XO
   b. XXX
   c. XXY
   d. XYY

12. A recognized set of symptoms that characterize a specific disorder is a _____ .
   a. syndrome
   b. disease
   c. pedigree

13. Match the chromosome terms appropriately.

____ polyploidy	a. number and defining features of an individual's metaphase chromosomes
____ deletion	b. segment of a chromosome moves to a nonhomologous chromosome
____ nondisjunction	c. extra chromosome sets
____ translocation	d. one outcome: gametes with wrong chromosome number
____ karyotype	e. a chromosome segment lost
____ aneuploidy	f. change by one chromosome

Additional questions are available on Biology Now™

Genetics Problems

Answers in Appendix III

1. Human females are XX and males are XY.
   a. Does a male inherit the X from his mother or father?
   b. With respect to X-linked alleles, how many different types of gametes can a male produce?
   c. If a female is homozygous for an X-linked allele, how many types of gametes can she produce with respect to that allele?
   d. If a female is heterozygous for an X-linked allele, how many types of gametes might she produce with respect to that allele?

2. In Section 11.4, you read about a mutation that causes a serious genetic disorder, *Marfan syndrome*. A mutant allele responsible for the disorder follows a pattern of autosomal dominant inheritance. What is the chance that any child will inherit it if one parent does not carry the allele and the other is heterozygous for it?

3. Somatic cells of individuals with Down syndrome usually have an extra chromosome 21; they contain forty-seven chromosomes.
   a. At which stages of meiosis I and II could a mistake alter the chromosome number?
   b. A few individuals with Down syndrome have forty-six chromosomes, two of which are normal-appearing chromosomes 21 and a longer-than-normal chromosome 14. Speculate on how this chromosome abnormality may have arisen.

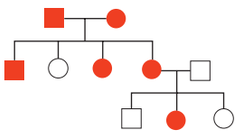
Figure 12.24 A case of Klinefelter syndrome. Until his teenage years, Stefan was shy, reserved, and prone to rage for no apparent reason. Psychologists and doctors assumed he had learning disabilities that affected comprehension, auditory processing, memory, and abstract thinking. One told Stefan he was stupid and lazy, and would be lucky to graduate from high school. In time, Stefan was graduated from college with degrees in business administration and sports management. He never discussed his learning disabilities. Instead, he took pride in doing the work on his own and not being treated differently.

Stefan was twenty-five years old before laboratory tests as well as karyotyping revealed a 46XY/47XXY mosaic condition. That same year, he started a job as a software engineer. Having a full-time position helped him open doors to volunteer work with the Klinefelter syndrome network. During his volunteer work, he met his future fiancée, whose son also has the syndrome.

4. As you read earlier, *Duchenne muscular dystrophy* is a genetic disorder that arises through the expression of a recessive X-linked allele. Usually, symptoms start in childhood. Gradual, progressive loss of muscle function leads to death, usually by age twenty or so. Unlike color blindness, the disorder is nearly always restricted to males. Suggest why.

5. In the human population, mutation of two genes on the X chromosome causes two types of X-linked *hemophilia* (A and B). In a few cases, a woman is heterozygous for both mutant alleles (one on each of the X chromosomes). All of her sons should have either hemophilia A or B.
   However, on very rare occasions, one of these women gives birth to a son who does not have hemophilia, and his one X chromosome does not have either mutant allele. Explain how such an X chromosome could arise.

6. Does the phenotype indicated by red circles and squares in this pedigree show a Mendelian inheritance pattern that is autosomal dominant, autosomal recessive, or X-linked?



7. When it comes to acceptance of a genetic condition that is out of the ordinary, people tend to be subjective. As an example, consider the individual described in Figure 12.24. How would you have categorized him without knowing the genetic basis of his early behavior? How would you categorize him now in terms of what we as a society consider to be "ideal" phenotypes?