Genetics Home Reference

Your Guide to Understanding Genetic Conditions

Handbook

Help Me Understand Genetics

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Chapter 1

The Basics: Genes and How They Work

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What is a cell?

Cells are the basic building blocks of all living things. The human body is composed of trillions of cells. They provide structure for the body, take in nutrients from food, convert those nutrients into energy, and carry out specialized functions. Cells also contain the body's hereditary material and can make copies of themselves.

Cells have many parts, each with a different function. Some of these parts, called organelles, are specialized structures that perform certain tasks within the cell. Human cells contain the following major parts, listed in alphabetical order:

Cytoplasm (illustration on page 5)

The cytoplasm is fluid inside the cell that surrounds the organelles.

Endoplasmic reticulum (ER) (illustration on page 6)

This organelle helps process molecules created by the cell and transport them to their specific destinations either inside or outside the cell.

Golgi apparatus (illustration on page 6)

The golgi apparatus packages molecules processed by the endoplasmic reticulum to be transported out of the cell.

Lysosomes and peroxisomes (illustration on page 6)

These organelles are the recycling center of the cell. They digest foreign bacteria that invade the cell, rid the cell of toxic substances, and recycle worn-out cell components.

Mitochondria (illustration on page 7)

Mitochondria are complex organelles that convert energy from food into a form that the cell can use. They have their own genetic material, separate from the DNA in the nucleus, and can make copies of themselves.

Nucleus (illustration on page 7)

The nucleus serves as the cell's command center, sending directions to the cell to grow, mature, divide, or die. It also houses DNA (deoxyribonucleic acid), the cell's hereditary material. The nucleus is surrounded by a membrane called the nuclear envelope, which protects the DNA and separates the nucleus from the rest of the cell.

Plasma membrane (illustration on page 7)

The plasma membrane is the outer lining of the cell. It separates the cell from its environment and allows materials to enter and leave the cell.

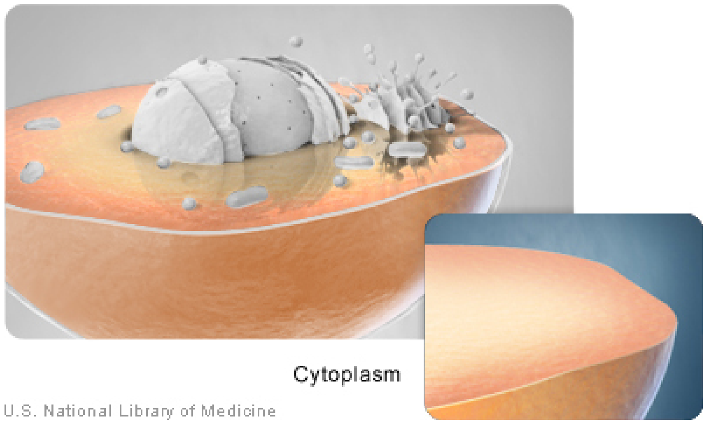
Ribosomes (illustration on page 8)

Ribosomes are organelles that process the cell’s genetic instructions to create proteins. These organelles can float freely in the cytoplasm or be connected to the endoplasmic reticulum (see above).

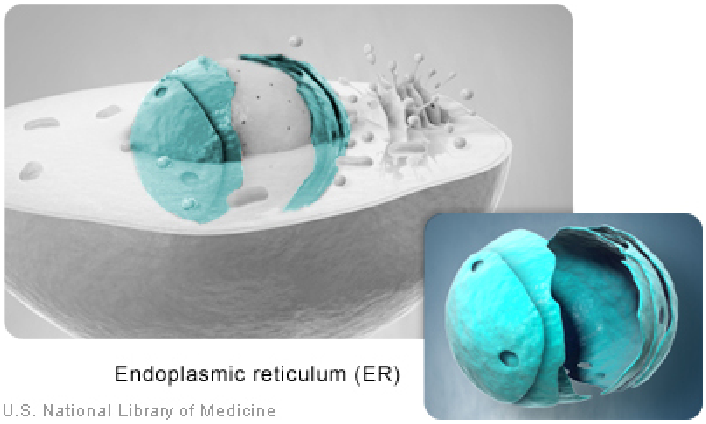
For more information about cells:

The NCBI Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html) offers additional information about the structure and function of cells under the headings “What is a Cell?” and “Cell Structures: The Basics.”

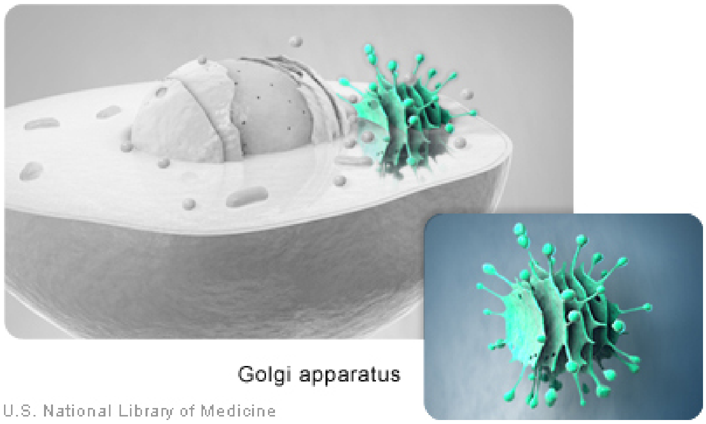
Illustrations: Major parts of a cell



The cytoplasm surrounds the cell's nucleus and organelles.



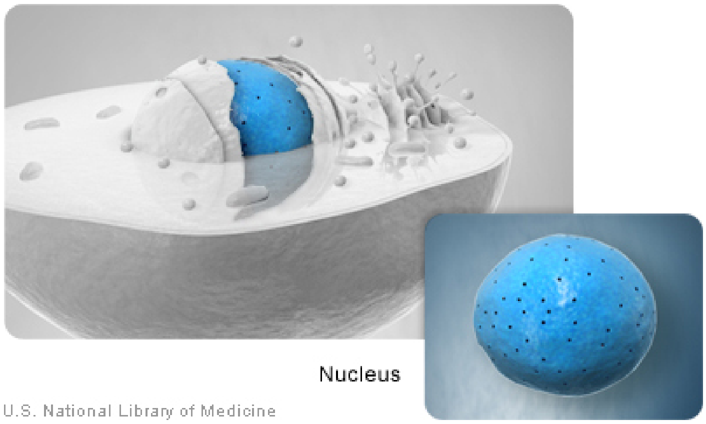
The endoplasmic reticulum is involved in molecule processing and transport.



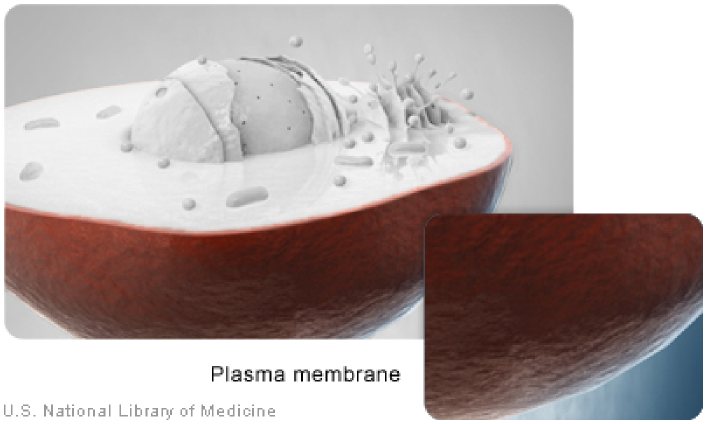
The Golgi apparatus is involved in packaging molecules for export from the cell.

Lysosomes and peroxisomes destroy toxic substances and recycle worn-out cell parts.

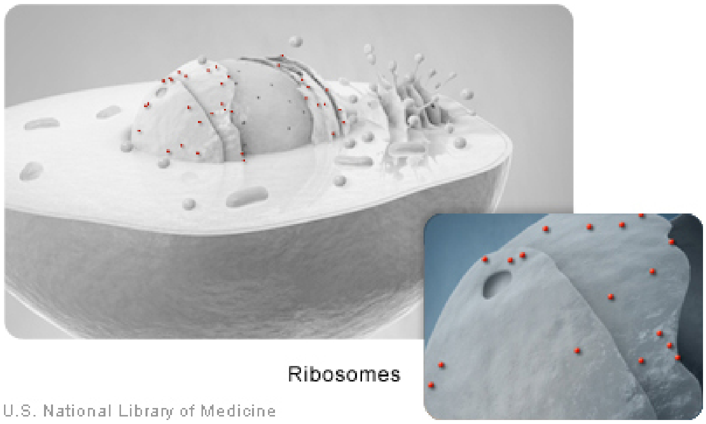
Mitochondria provide the cell's energy.



The nucleus contains most of the cell's genetic material.



The plasma membrane is the outer covering around the cell.



Ribosomes use the cell's genetic instructions to make proteins.

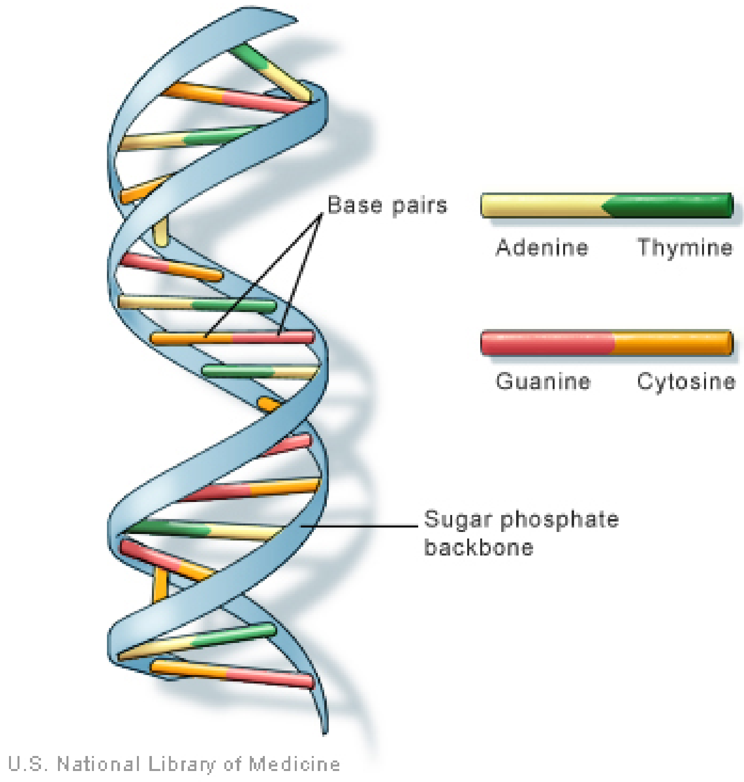
What is DNA?

DNA, or deoxyribonucleic acid, is the hereditary material in humans and almost all other organisms. Nearly every cell in a person’s body has the same DNA. Most DNA is located in the cell nucleus (where it is called nuclear DNA), but a small amount of DNA can also be found in the mitochondria (where it is called mitochondrial DNA or mtDNA).

The information in DNA is stored as a code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Human DNA consists of about 3 billion bases, and more than 99 percent of those bases are the same in all people. The order, or sequence, of these bases determines the information available for building and maintaining an organism, similar to the way in which letters of the alphabet appear in a certain order to form words and sentences.

DNA bases pair up with each other, A with T and C with G, to form units called base pairs. Each base is also attached to a sugar molecule and a phosphate molecule. Together, a base, sugar, and phosphate are called a nucleotide. Nucleotides are arranged in two long strands that form a spiral called a double helix. The structure of the double helix is somewhat like a ladder, with the base pairs forming the ladder’s rungs and the sugar and phosphate molecules forming the vertical sidepieces of the ladder.

An important property of DNA is that it can replicate, or make copies of itself. Each strand of DNA in the double helix can serve as a pattern for duplicating the sequence of bases. This is critical when cells divide because each new cell needs to have an exact copy of the DNA present in the old cell.



DNA is a double helix formed by base pairs attached to a sugar-phosphate backbone.

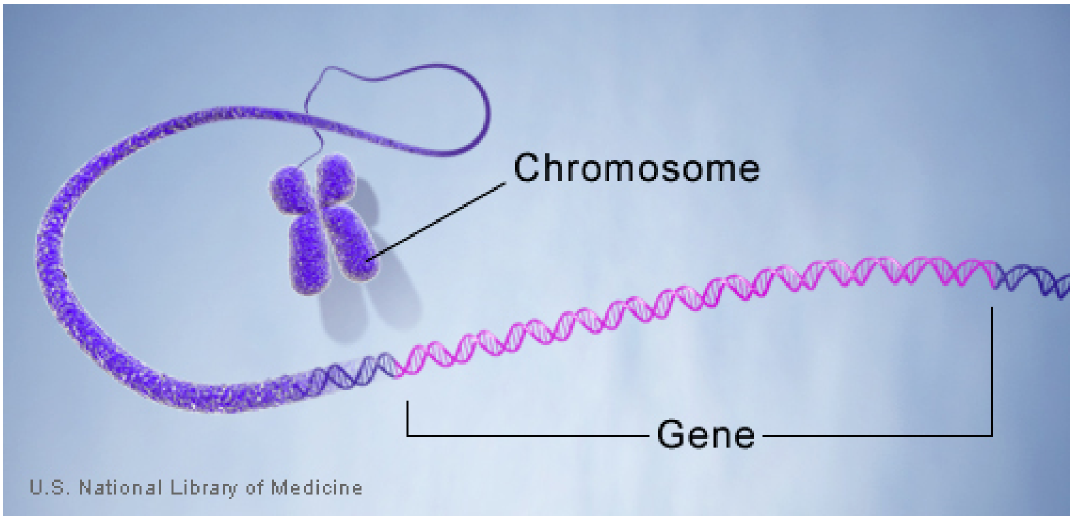
For more information about DNA:

For additional information about the structure of DNA, please refer to the NCBI Science Primer (http://www.ncbi.nih.gov/About/primer/genetics_genome.html), under the heading "The Physical Structure of the Human Genome."

What is a gene?

A gene is the basic physical and functional unit of heredity. Genes, which are made up of DNA, act as instructions to make molecules called proteins. In humans, genes vary in size from a few hundred DNA bases to more than 2 million bases. The Human Genome Project has estimated that humans have between 30,000 and 40,000 genes.

Every person has two copies of each gene, one inherited from each parent. Most genes are the same in all people, but a small number of genes (less than 1 percent of the total) are slightly different between people. Alleles are forms of the same gene with small differences in their sequence of DNA bases. These small differences contribute to each person's unique physical features.



Genes are made up of DNA. Each chromosome contains many genes.

For more information about genes:

Genetics Home Reference provides consumer-friendly gene summaries (http://ghr.nlm.nih.gov/ghr/genesBySymbol) that include an explanation of each gene's normal function and how mutations in the gene cause particular genetic conditions.

The National Institute of General Medical Sciences offers additional information about DNA and genes in its publication Genetic Basics (http://www.nigms.nih.gov/news/science_ed/genetics/). Please refer to the publication's introduction, "A Science Called Genetics."

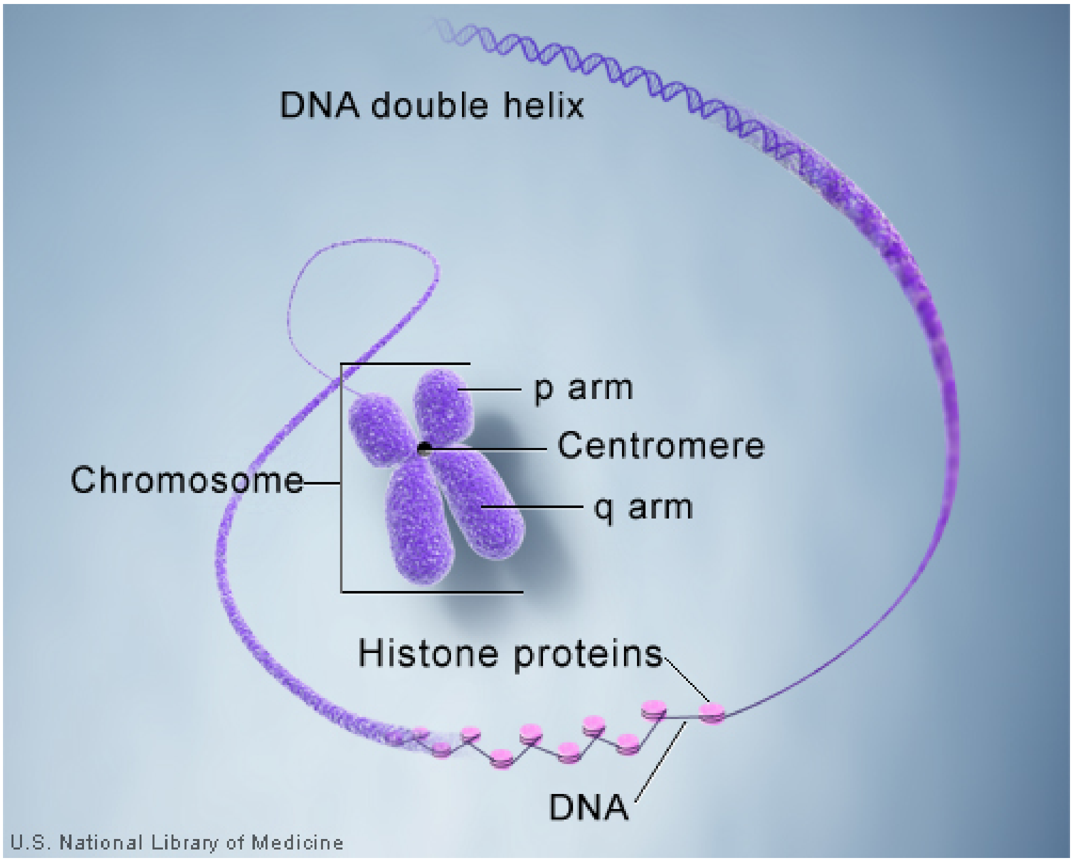
For more information about genes, please also refer to "What is a Genome?" in the NCBI Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html).

What is a chromosome?

In the nucleus of each cell, the DNA molecule is packaged into thread-like structures called chromosomes. Each chromosome is made up of DNA tightly coiled many times around proteins called histones that support its structure.

Chromosomes are not visible in the cell's nucleus—not even under a microscope—when the cell is not dividing. However, the DNA that makes up chromosomes becomes more tightly packed during cell division and is then visible under a microscope. Most of what researchers know about chromosomes was learned by observing chromosomes during cell division.

Each chromosome has a constriction point called the centromere, which divides the chromosome into two sections, or "arms." The short arm of the chromosome is labeled the "p arm." The long arm of the chromosome is labeled the "q arm." The location of the centromere on each chromosome gives the chromosome its characteristic shape, and can be used to help describe the location of specific genes.



DNA and histone proteins are packaged into structures called chromosomes.

For more information about chromosomes:

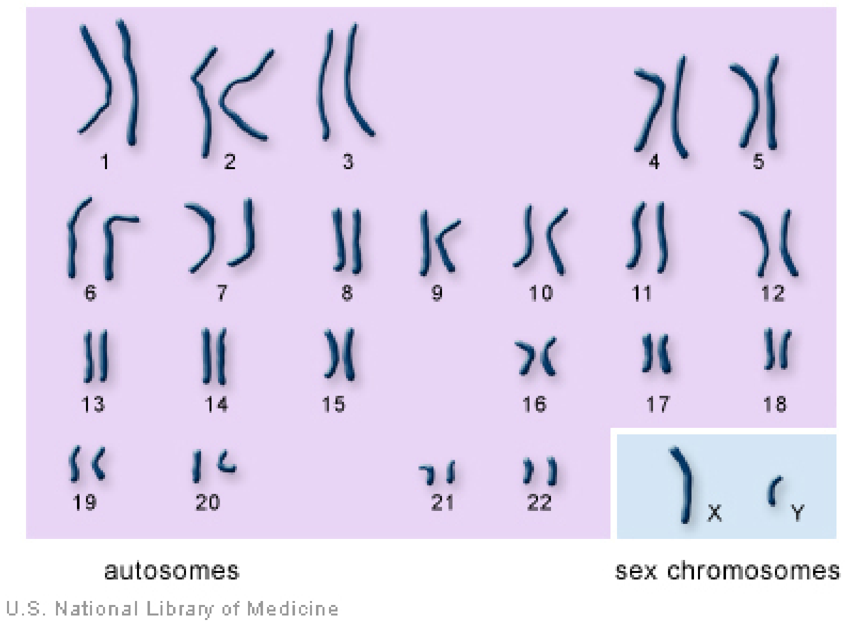
Genetics Home Reference provides information about each human chromosome (http://ghr.nlm.nih.gov/ghr/chromosomes) written in lay language.

The NCBI Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html) includes a discussion of the DNA that makes up chromosomes under the heading “Structural Genes, Junk DNA and Regulatory Sequences.”

The U.S. Department of Energy Office of Science offers a list of Chromosome FAQs (http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/faqs.shtml).

How many chromosomes do people have?

In humans, each cell normally contains 23 pairs of chromosomes, for a total of 46. Twenty-two of these pairs, called autosomes, look the same in both males and females. The 23rd pair, the sex chromosomes, differ between males and females. Females have two copies of the X chromosome, while males have one X and one Y chromosome.



The 22 autosomes are numbered by size. The other two chromosomes, X and Y, are the sex chromosomes.

For more information about the 23 pairs of human chromosomes:

Genetics Home Reference provides information about each human chromosome (http://ghr.nlm.nih.gov/ghr/chromosomes) written in lay language.

How do geneticists indicate the location of a gene?

Geneticists use a standardized way of describing the location of a particular gene on a chromosome. A gene's location is often written as a position:

17q12

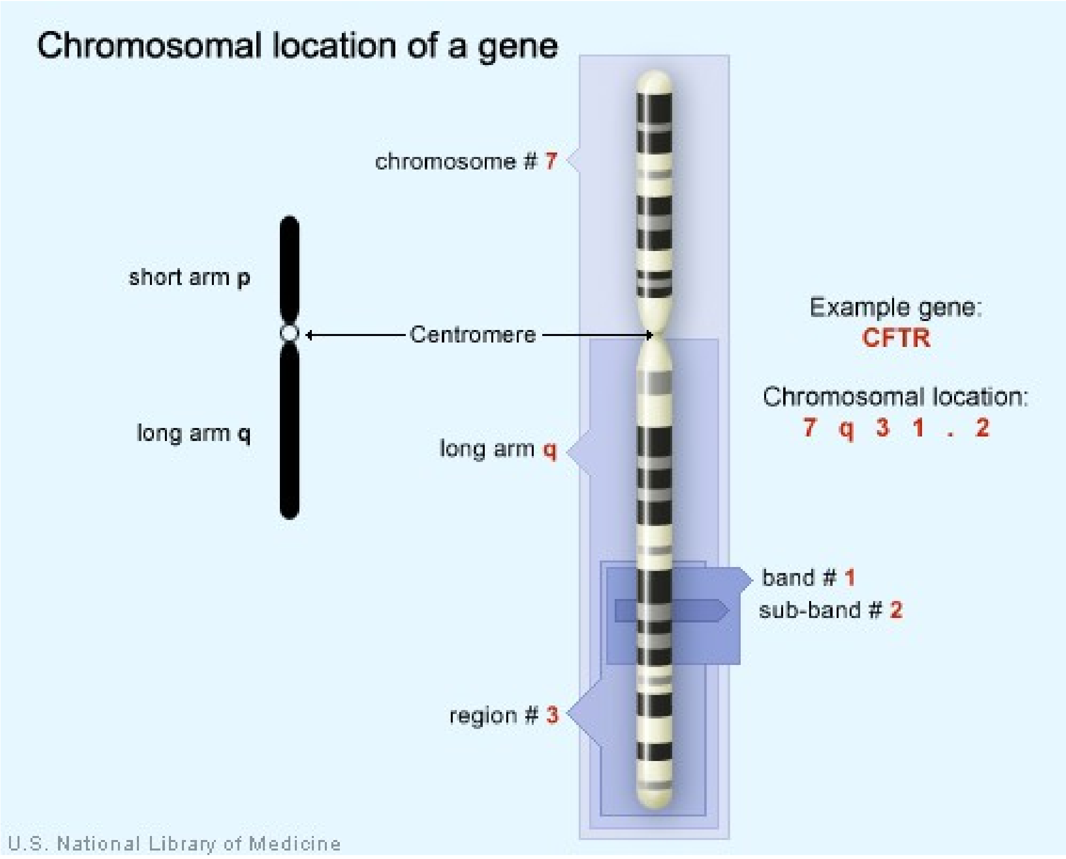
It can also be written as a range, if less is known about the exact location:

17q12-q21

These combinations of numbers and letters provide a gene's “address” on a chromosome. The address is made up of several parts:

- The chromosome on which the gene can be found. The first number or letter used to describe a gene's location represents the chromosome. Chromosomes 1 through 22 (the autosomes) are designated by their chromosome number. The sex chromosomes are designated by X or Y.
- The arm of the chromosome. Each chromosome is divided into two sections, or arms, based on the location of a narrowing (constriction) called the centromere. By convention, the shorter arm is called p, and the longer arm is called q. The chromosome arm is the second part of the gene's address. For example, 5q is the long arm of chromosome 5, and Xp is the short arm of the X chromosome.
- The position of the gene on the p or q arm. The position of a gene is based on a standard pattern of light and dark bands that appear when the chromosome is stained in a certain way. The position is usually designated by two digits (representing a region and a band), which are sometimes followed by a decimal point and one or more additional digits (representing sub-bands within a light or dark area). The number indicating gene position increases with distance from the centromere. For example: 14q21 represents the long arm of chromosome 14 at position 21. 14q21 is closer to the centromere than 14q22.

Sometimes, the abbreviations “cen” or “ter” are also used to describe a gene's location. “Cen” indicates that the gene is very close to the centromere. For example, 16pcen refers to the short arm of chromosome 16 near the centromere. “Ter” stands for terminus, which indicates that the gene is very close to the end of the p or q arm. For example, 14qter refers to tip of the long arm of chromosome 14. (“Tel” is also sometimes used to describe a gene's location. “Tel” stands for telomeres, which are at the ends of each chromosome. The abbreviations “tel” and “ter” refer to the same location.)



The CFTR gene is located on the long arm of chromosome 7 at position 7q31.2.

What are proteins and what do they do?

Proteins are large, complex molecules that play many critical roles in the body. They do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs.

Proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached to one another in long chains. There are 20 different types of amino acids that can be combined to make a protein. The sequence of amino acids determines each protein's unique 3-dimensional structure and its specific function.

Proteins can be described according to their large range of functions in the body, listed in alphabetical order:

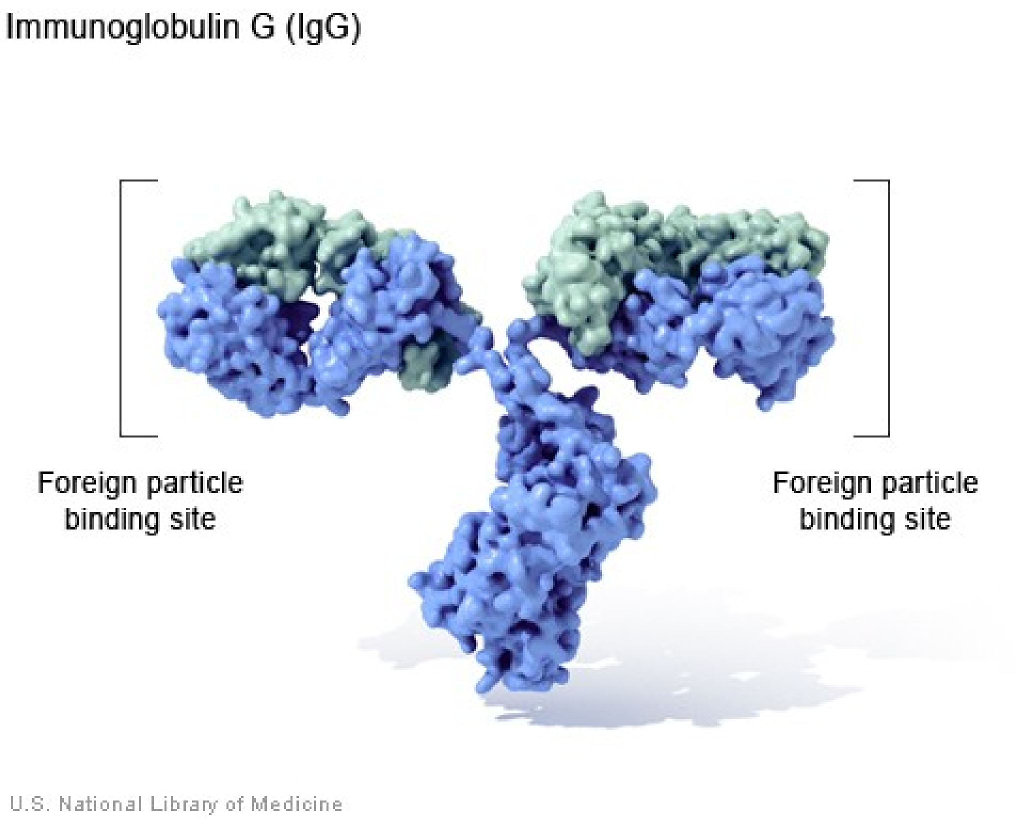
Function	Description	Examples
Antibody	Antibodies bind to specific foreign particles, such as viruses and bacteria, to help protect the body.	Immunoglobulin G (IgG) (illustration on page 18)
Enzyme	Enzymes carry out almost all of the thousands of chemical reactions that take place in cells. They also assist with the formation of new molecules by reading the genetic information stored in DNA.	Phenylalanine hydroxylase (illustration on page 19)
Messenger	Messenger proteins, such as some types of hormones, transmit signals to coordinate biological processes between different cells, tissues, and organs.	Growth hormone (illustration on page 20)
Structural component	These proteins provide structure and support for cells. On a larger scale, they also allow the body to move.	Actin (illustration on page 21)
Transport/storage molecule	These proteins bind and carry atoms and small molecules within cells and throughout the body.	Ferritin (illustration on page 22)

For more information about proteins and their functions:

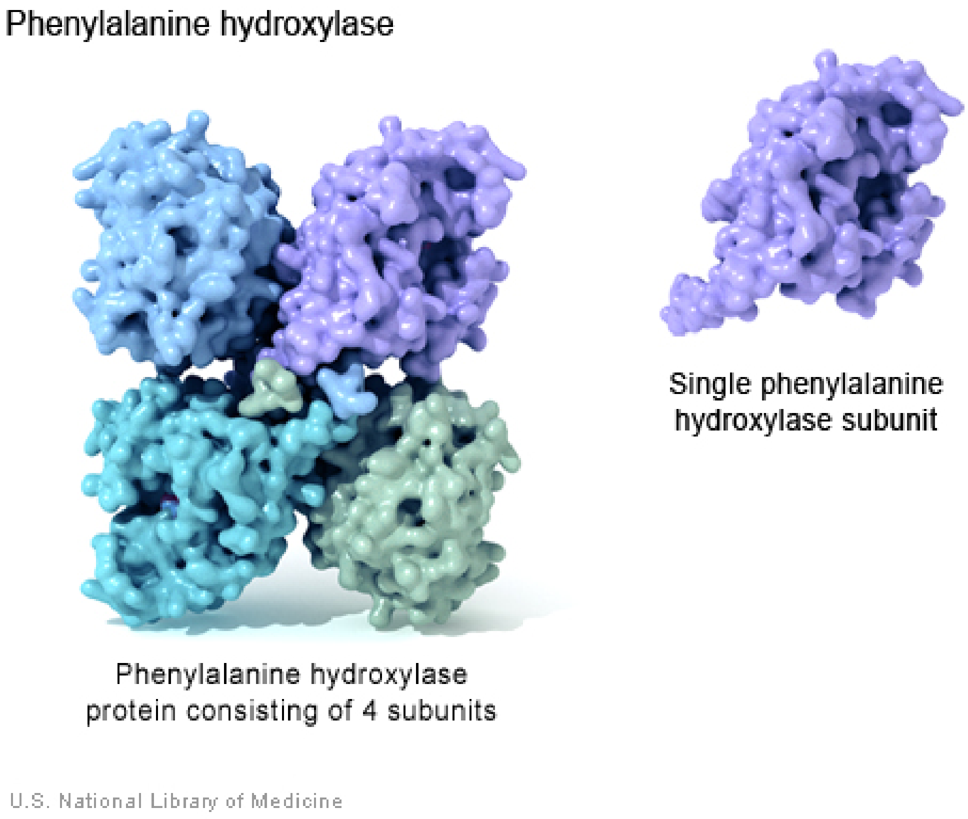
Information about proteins and what they do is available from the National Institute of General Medical Sciences publication Genetic Basics (http://www.nigms.nih.gov/news/science_ed/genetics/). Refer to the section "From Genes to Proteins" in Chapter 1 (How Genes Work).

Additional discussion of the role of proteins can be found in the NCBI Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html) under the heading "Proteins."

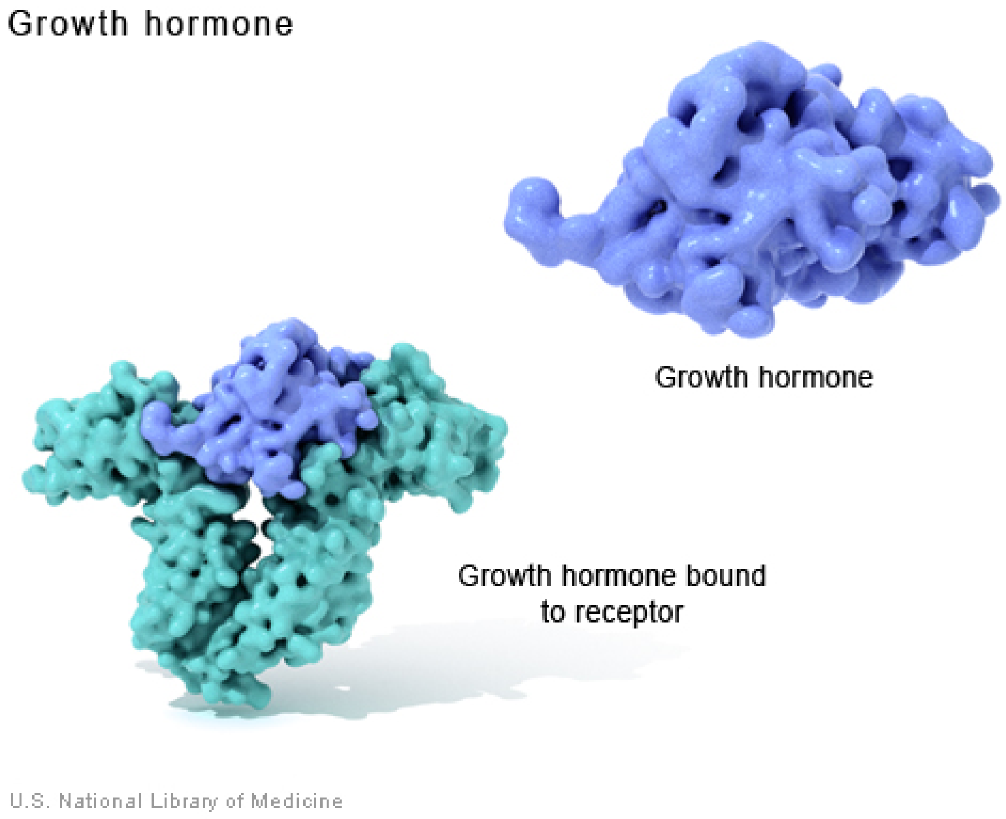
Illustrations: Proteins



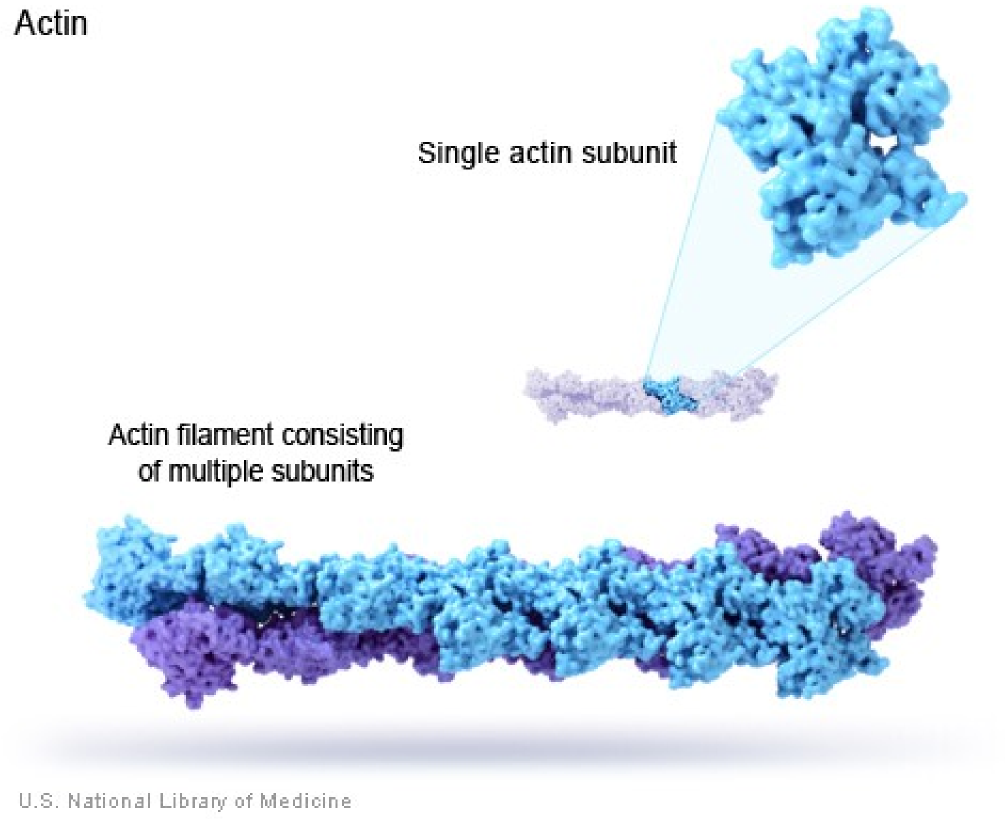
Immunoglobulin G is a type of antibody that circulates in the blood and recognizes foreign particles that might be harmful.



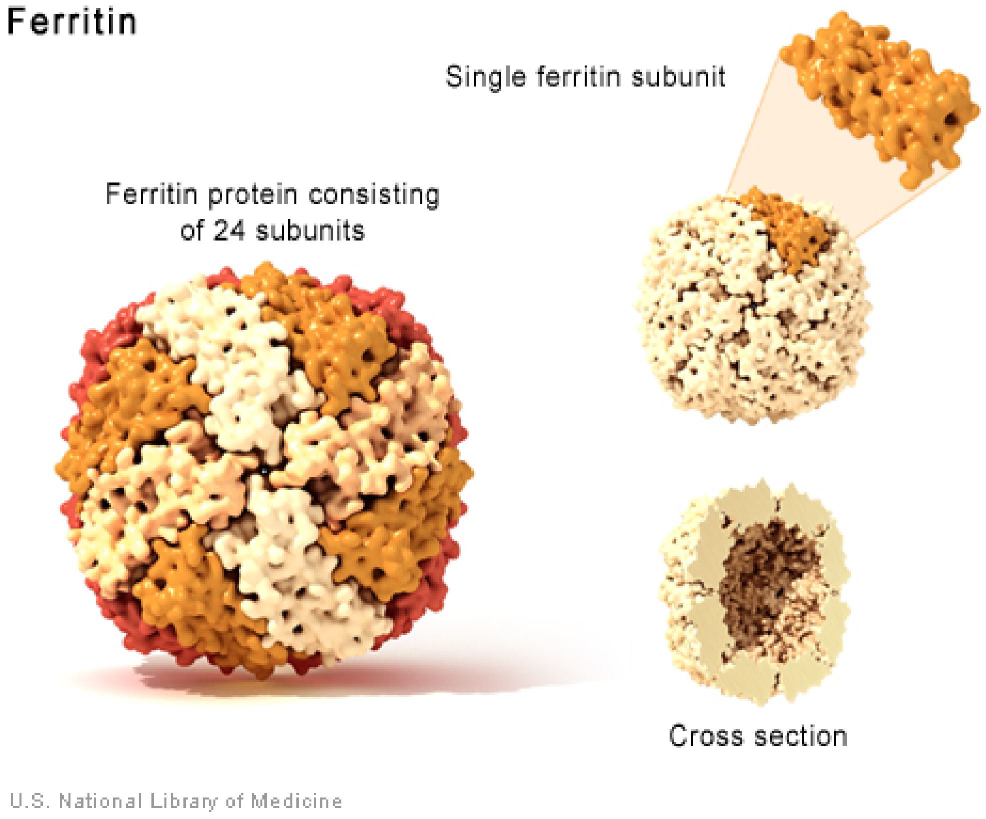
The functional phenylalanine hydroxylase enzyme is made up of four identical subunits. The enzyme converts the amino acid phenylalanine to another amino acid, tyrosine.



Growth hormone is a messenger protein made by the pituitary gland. It regulates cell growth by binding to a protein called a growth hormone receptor.



Actin filaments, which are structural proteins made up of multiple subunits, help muscles contract and cells maintain their shape.



Ferritin, a protein made up of 24 identical subunits, is involved in iron storage.

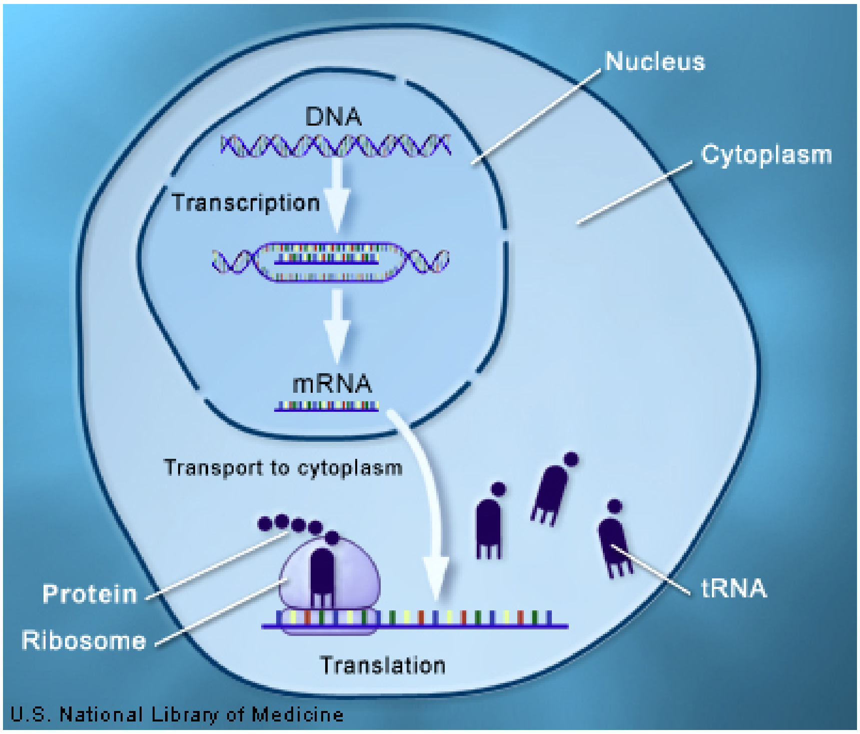
How does a gene make a protein?

Most genes contain the information needed to make functional molecules called proteins. (A few genes produce other molecules that help the cell assemble proteins.) The journey from gene to protein is complex and tightly controlled within each cell. It consists of two major steps: transcription and translation. Together, transcription and translation are known as gene expression.

During the process of transcription, the information stored in a gene's DNA is transferred to a similar molecule called RNA (ribonucleic acid) in the cell nucleus. Both RNA and DNA are made up of a chain of nucleotide bases, but they have slightly different chemical properties. The type of RNA that contains the information for making a protein is called messenger RNA (mRNA) because it carries the information, or message, from the DNA out of the nucleus into the cytoplasm.

Translation, the second step in getting from a gene to a protein, takes place in the cytoplasm. The mRNA interacts with a specialized complex called a ribosome, which "reads" the sequence of mRNA bases. Each sequence of three bases, called a codon, usually codes for one particular amino acid. (Amino acids are the building blocks of proteins.) A type of RNA called transfer RNA (tRNA) assembles the protein, one amino acid at a time. Protein assembly continues until the ribosome encounters a “stop” codon (a sequence of three bases that does not code for an amino acid).

The flow of information from DNA to RNA to proteins is one of the fundamental principles of molecular biology. It is so important that it is sometimes called the “central dogma.”



Through the processes of transcription and translation, information from genes is used to make proteins.

For more information about making proteins:

For a more detailed description of transcription and translation, please refer to the section "From Genes to Proteins: Start to Finish" in the NCBI Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html).

Can genes be turned on and off in cells?

Yes; each cell expresses, or turns on, only a fraction of its genes. The rest of the genes are repressed, or turned off. The process of turning genes on and off is known as gene regulation. Gene regulation makes a brain cell look and act different from a liver cell or a muscle cell. It also allows cells to react quickly to changes in their environments and is an important part of normal development. Although we know that the regulation of genes is critical for life, this complex process is not yet fully understood.

Gene regulation can occur at any point during gene expression, but most commonly occurs at the level of transcription (when the information in a gene's DNA is transferred to mRNA). Signals from the environment or from other cells activate proteins called transcription factors. These proteins bind to regulatory regions of a gene and increase or decrease the level of transcription. By controlling the level of transcription, this process can determine the amount of protein product that is made by a gene at any given time.

For more information about gene regulation:

More information about gene regulation can be found in the NCBI Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html). Please refer to the sections “Gene Switching: Turning Genes On and Off,” “Controlling Transcription,” and “Controlling Translation.”

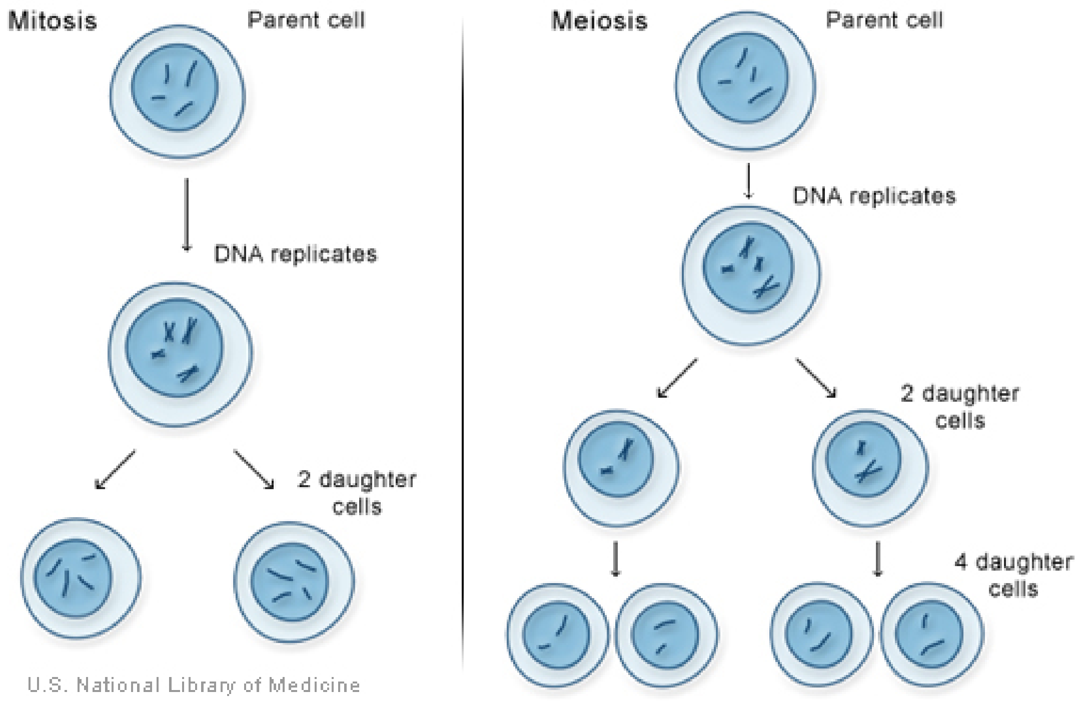
The National Institute of General Medical Science publication Genetic Basics (http://www.nigms.nih.gov/news/science_ed/genetics/) also offers a discussion of gene regulation. Refer to the section “Controlling Genes” in Chapter 1 (How Genes Work).

How do cells divide?

There are two types of cell division: mitosis and meiosis. Most of the time when people refer to “cell division,” they mean mitosis, the process of making new body cells. Meiosis is the type of cell division that creates egg and sperm cells.

Mitosis is a fundamental process for life. During mitosis, a cell duplicates all of its contents, including its chromosomes, and splits to form two identical daughter cells. Because this process is so critical, the steps of mitosis are carefully controlled by a number of genes. When mitosis is not regulated correctly, health problems such as cancer can result.

The other type of cell division, meiosis, ensures that humans have the same number of chromosomes in each generation. It is a two-step process that reduces the chromosome number by half—from 46 to 23—to form sperm and egg cells. When the sperm and egg cells unite at conception, each contributes 23 chromosomes so the resulting embryo will have the usual 46. Meiosis also allows genetic variation through a process of DNA shuffling while the cells are dividing.



Mitosis and meiosis, the two types of cell division.

For more information about cell division:

For a detailed summary of mitosis and meiosis, please refer to the section “Making New Cells and Cell Types” in the NCBI Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html).

How do genes control the growth and division of cells?

A variety of genes are involved in the control of cell growth and division. The cell cycle is the cell's way of replicating itself in an organized, step-by-step fashion. Tight regulation of this process ensures that a dividing cell's DNA is copied properly, any errors in the DNA are repaired, and each daughter cell receives a full set of chromosomes. The cycle has checkpoints (also called restriction points), which allow certain genes to check for mistakes and halt the cycle for repairs if something goes wrong.

If a cell has an error in its DNA that cannot be repaired, it may undergo programmed cell death (apoptosis) (illustration on page 29). Apoptosis is a common process throughout life that helps the body get rid of cells it doesn't need. Cells that undergo apoptosis break apart and are recycled by a type of white blood cell called a macrophage (illustration on page 29). Apoptosis protects the body by removing genetically damaged cells that could lead to cancer, and it plays an important role in the development of the embryo and the maintenance of adult tissues.

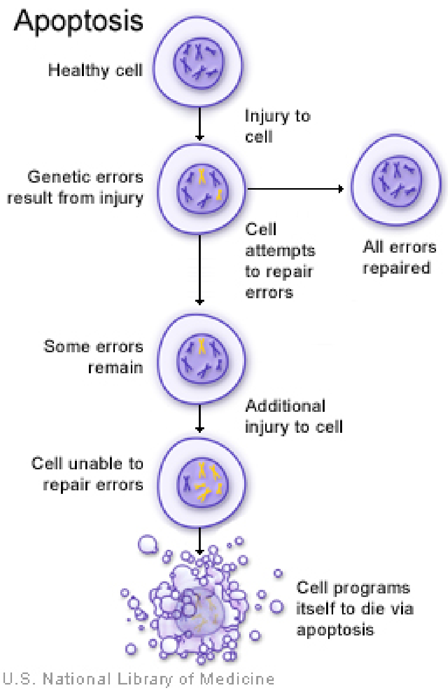
Cancer results from a disruption of the normal regulation of the cell cycle. When the cycle proceeds without control, cells can divide without order and accumulate genetic defects that can lead to a cancerous tumor (illustration on page 30).

For more information about cell growth and division:

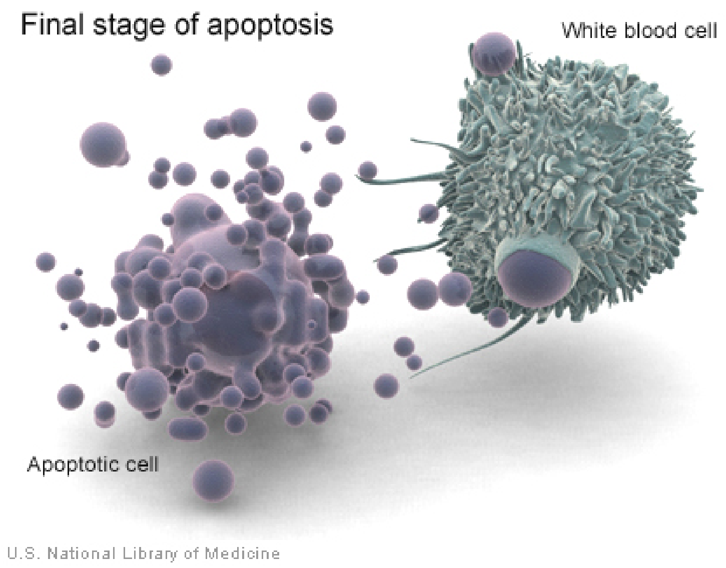
The National Institutes of Health's Apoptosis Interest Group (http://www.nih.gov/sigs/aig/Aboutapo.html) provides an introduction to programmed cell death.

The National Cancer Institute offers several publications that explain the growth of cancerous tumors. These include What You Need To Know About Cancer—An Overview (http://www.cancer.gov/cancerinfo/wyntk/overview) and Understanding Cancer (http://press2.nci.nih.gov/sciencebehind/cancer/cancer01.htm).

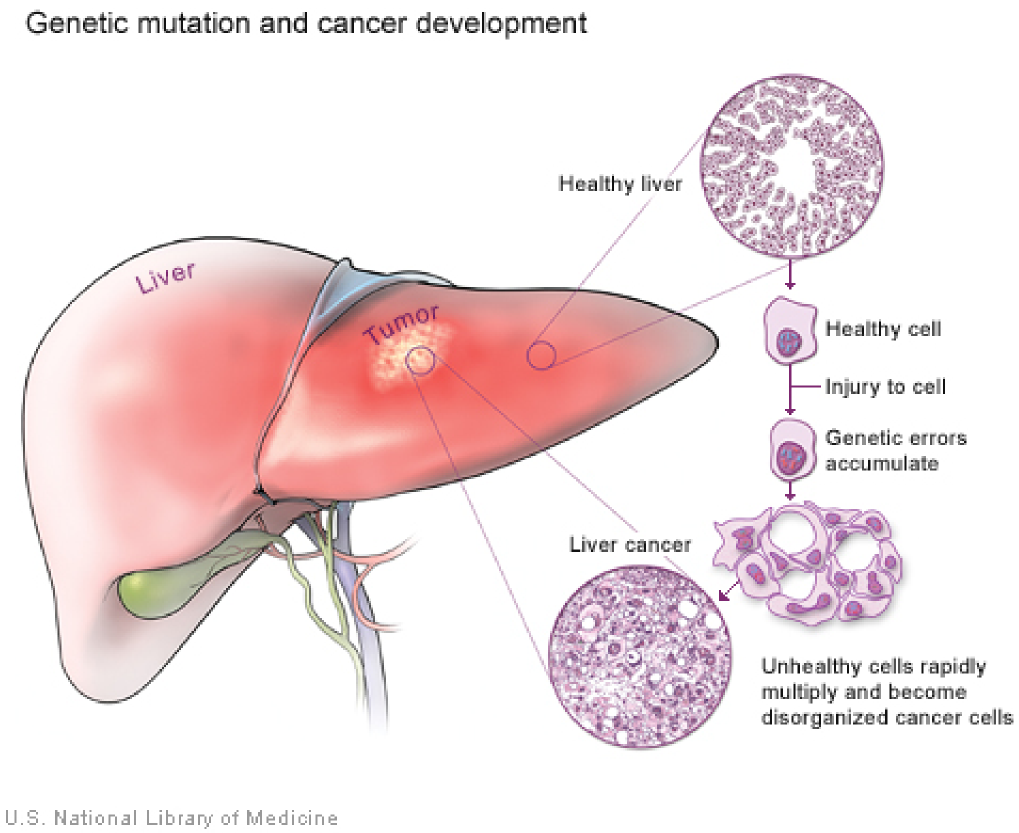
Illustrations: Control of cell growth and division



A damaged cell may undergo apoptosis if it is unable to repair genetic errors.



When a cell undergoes apoptosis, white blood cells called macrophages consume cell debris.



Cancer results when cells accumulate genetic errors and multiply without control.

Chapter 2

Mutations and Genetic Disorders

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What is a gene mutation and how do mutations occur?

A gene mutation is a permanent change in the DNA sequence that makes up a gene. Mutations range in size from one DNA base to a large segment of a chromosome.

Gene mutations occur in two ways: they can be inherited from a parent or acquired during a person's lifetime. Mutations that are passed from parent to child are called hereditary mutations or germline mutations (because they are present in the egg and sperm cells, which are also called germ cells). This type of mutation is present throughout a person's life in virtually every cell in the body.

Acquired (or sporadic) mutations, on the other hand, occur in the DNA of individual cells at some time during a person's life. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, or can occur if a mistake is made as DNA copies itself during cell division. Acquired mutations in somatic cells (cells other than sperm and egg cells) cannot be passed on to the next generation. If a mutation occurs in an egg or sperm cell during a person's life, however, there is a chance that the person's children will inherit the mutation.

For more information about mutations:

The National Cancer Institute offers a discussion of hereditary mutations (http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting12.htm) and information about acquired mutations (http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting13.htm).

For additional information about gene mutations, please refer to the following resources from the University of Utah Genetic Science Learning Center:

What is a Mutation? (http://gslc.genetics.utah.edu/units/disorders/mutations/)

How do Mutations Occur? (http://gslc.genetics.utah.edu/units/disorders/sloozeworm/)

How can gene mutations cause disorders?

To function correctly, each cell depends on thousands of proteins to do their jobs in the right places at the right times. Sometimes, gene mutations prevent one or more of these proteins from working properly. By changing a gene's instructions for making a protein, a mutation can cause the protein to malfunction or to be missing entirely. When a mutation alters a protein that plays a critical role in the body, a medical condition can result. A condition caused by mutations in one or more genes is called a genetic disorder.

It is important to note that genes themselves do not cause disease—genetic disorders are caused by mutations that make a gene function improperly. For example, when people say that someone has "the cystic fibrosis gene," they are usually referring to a mutated version of the CFTR gene, which causes the disease. All people, including those without cystic fibrosis, have a version of the CFTR gene.

For more information about mutations and genetic disorders:

The National Cancer Institute provides additional information about how gene mutations can trigger disease. Please refer to the following Web pages:

Gene Mutations and Disease (http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting09.htm)

Altered DNA, Altered Protein (http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting11.htm)

The University of Utah Genetic Science Learning Center also offers a discussion titled How Do Mutations Cause Genetic Disorders? (http://gslc.genetics.utah.edu/units/disorders/proteinrole/)

Do all gene mutations cause disorders?

No; only a small percentage of mutations cause genetic disorders—most have no impact on health. For example, some mutations alter a gene's DNA base sequence but don’t change the function of the protein made by the gene.

Often, gene mutations that could cause a genetic disorder are repaired by certain enzymes before the gene is expressed (makes a protein). Each cell has a number of pathways through which enzymes recognize and repair mistakes in DNA. Because DNA can be damaged or mutated in many ways, the process of DNA repair is an important way in which the body protects itself from disease.

A very small percentage of all mutations actually have a positive effect. These mutations lead to new versions of proteins that help an organism and its future generations better adapt to changes in their environment. For example, a beneficial mutation could result in a protein that protects the organism from a new strain of bacteria.

For more information about DNA repair and the health effects of gene mutations:

The University of Utah Genetic Science Learning Center's page about genetic disorders (http://gslc.genetics.utah.edu/units/disorders/whataregd/) explains why some mutations cause disorders but others do not. (Please refer to the questions in the far right column.)

Additional information about DNA repair is available from the NCBI Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html). Scroll down the page to the heading “DNA Repair Mechanisms.”

What kinds of gene mutations are possible?

The DNA sequence of a gene can be altered in a number of ways. Gene mutations have varying effects on health, depending on where they occur and whether they alter the function of essential proteins. The types of mutations include:

Missense mutation (illustration on page 36)

This type of mutation is a change in one DNA base pair that results in the substitution of one amino acid for another in the protein made by a gene.

Nonsense mutation (illustration on page 37)

A nonsense mutation is also a change in one DNA base pair. Instead of substituting one amino acid for another, however, the altered DNA sequence prematurely signals the cell to stop building a protein. This type of mutation results in a shortened protein that may function improperly or not at all.

Insertion (illustration on page 37)

An insertion changes the number of DNA bases in a gene by adding a piece of DNA. As a result, the protein made by the gene may not function properly.

Deletion (illustration on page 38)

A deletion changes the number of DNA bases in a gene by removing a piece of DNA. The deleted DNA may alter the function of the resulting protein.

Duplication (illustration on page 38)

A duplication consists of a piece of DNA that is abnormally copied one or more times. This type of mutation may alter the function of the resulting protein.

Frameshift mutation (illustration on page 39)

This type of mutation occurs when the addition or loss of DNA bases changes a gene's reading frame. A reading frame consists of groups of 3 bases that each code for one amino acid. A frameshift mutation shifts the grouping of these bases and changes the code for amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift mutations.

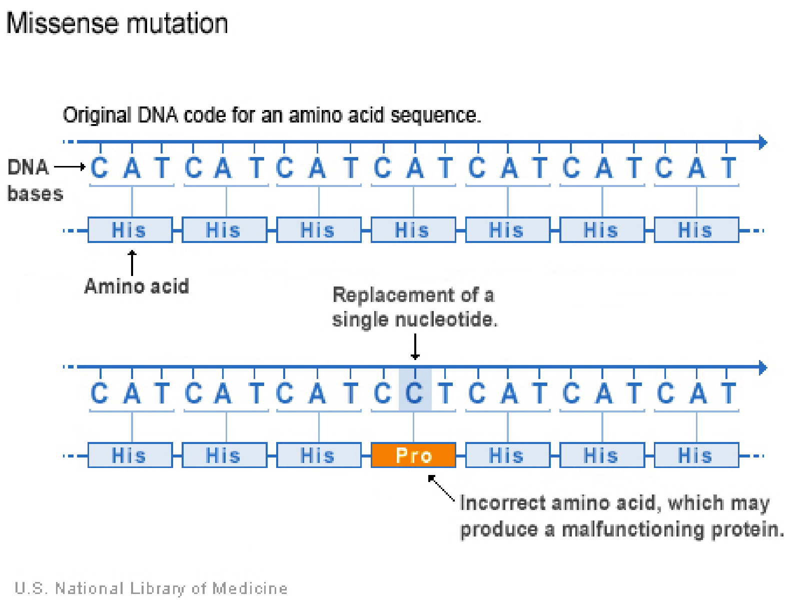
Repeat expansion (illustration on page 39)

Nucleotide repeats are short DNA sequences that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of 3-base-pair sequences, and a tetranucleotide repeat is made up of 4-base-pair sequences. A repeat expansion is a mutation that increases the number of times that the short DNA sequence is repeated. This type of mutation can cause the resulting protein to function improperly.

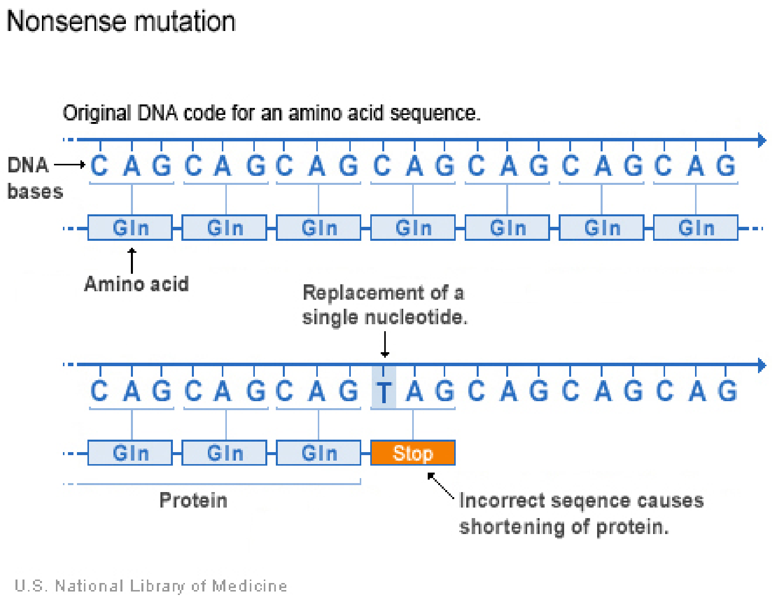
For more information about the types of gene mutations:

The National Human Genome Research Institute offers a Talking Glossary of Genetic Terms (http://www.genome.gov/10002096). This resource includes definitions, diagrams, and detailed audio descriptions of several of the gene mutations listed above.

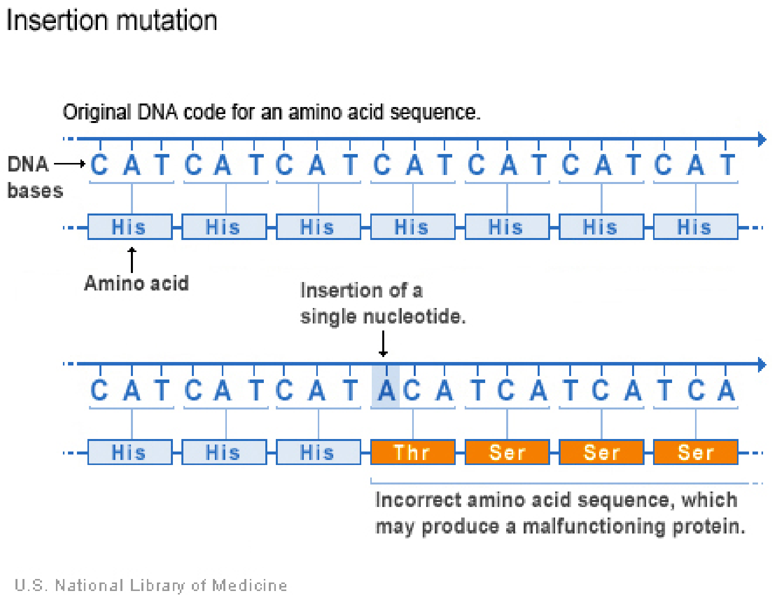
Illustrations: Types of gene mutations



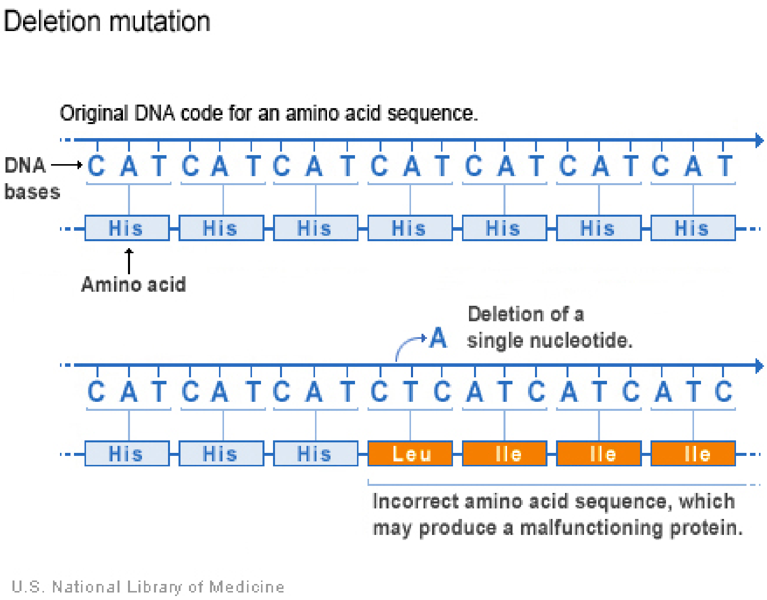
In this example, the nucleotide adenine is replaced by cytosine in the genetic code, introducing an incorrect amino acid into the protein sequence.



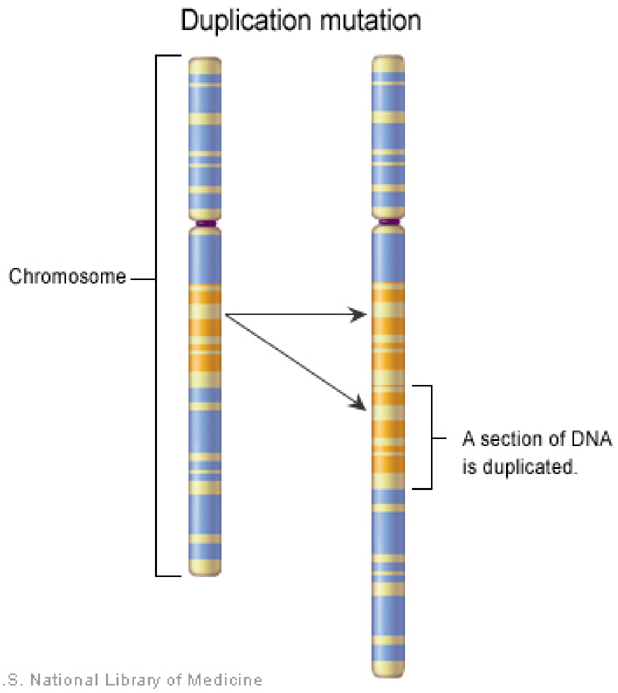
In this example, the nucleotide cytosine is replaced by thymine in the DNA code, signaling the cell to shorten the protein.



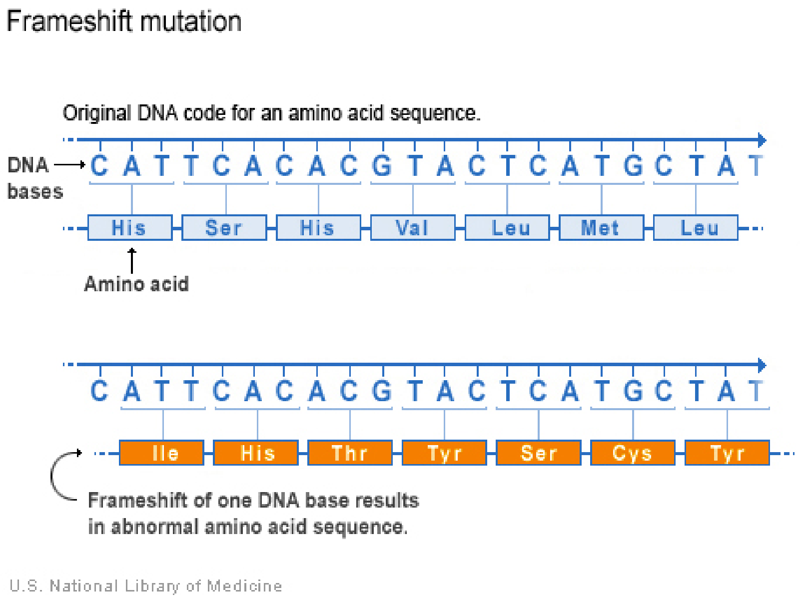
In this example, one nucleotide (adenine) is added in the DNA code, changing the amino acid sequence that follows.



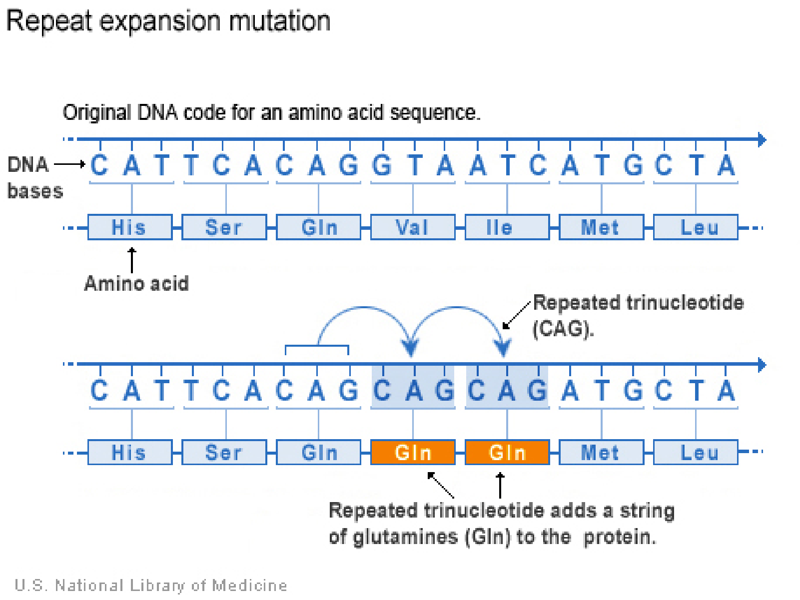
In this example, one nucleotide (adenine) is deleted from the DNA code, changing the amino acid sequence that follows.



A section of DNA is accidentally duplicated when a chromosome is copied.



A frameshift mutation changes the amino acid sequence from the site of the mutation.



In this example, a repeated trinucleotide sequence (CAG) adds a series of the amino acid glutamine to the resulting protein.

Can changes in chromosomes cause disorders?

Yes; changes that affect entire chromosomes or segments of chromosomes can cause problems with growth, development, and function of the body's systems. These changes can affect many genes along the chromosome and alter the proteins made by those genes. Conditions caused by a change in the number or structure of chromosomes are known as chromosomal disorders.

Human cells normally contain 23 pairs of chromosomes, for a total of 46 chromosomes in each cell. A change in the number of chromosomes leads to a chromosomal disorder. These changes can occur during the formation of reproductive cells (eggs and sperm) or in early fetal development. A gain or loss of chromosomes from the normal 46 is called aneuploidy.

The most common form of aneuploidy is trisomy, or the presence of an extra chromosome in each cell. “Tri-” is Greek for “three”; people with trisomy have three copies of a particular chromosome in each cell instead of the normal two copies. Down syndrome is an example of a condition caused by trisomy—people with Down syndrome typically have three copies of chromosome 21 in each cell, for a total of 47 chromosomes per cell.

Monosomy, or the loss of one chromosome from each cell, is another kind of aneuploidy. “Mono-” is Greek for “one”; people with monosomy have one copy of a particular chromosome in each cell instead of the normal two copies. Turner syndrome is a condition caused by monosomy. Women with Turner syndrome are often missing one copy of the X chromosome in every cell, for a total of 45 chromosomes per cell.

Chromosomal disorders can also be caused by changes in chromosome structure. These changes are caused by the breakage and reunion of chromosome segments when an egg or sperm cell is formed or in early fetal development. Pieces of DNA can be rearranged within one chromosome, or transferred between two or more chromosomes. The effects of structural changes depend on their size and location. Many different structural changes are possible; some cause medical problems, while others may have no effect on a person’s health.

Many cancer cells also have changes in their chromosome number or structure. These changes most often occur in somatic cells (cells other than eggs and sperm) during a person’s lifetime.

For more information about chromosomal disorders:

The National Human Genome Research Institute provides a list of questions and answers about chromosome abnormalities (http://www.genome.gov/11508982), including a glossary of related terms.

Chromosome Deletion Outreach offers a fact sheet on this topic titled Introduction to Chromosome Abnormalities (http://www.chromodisorder.org/intro.htm).

Georgetown University's Human Genome Education Model Project II provides a fact sheet about chromosomal disorders and their causes (http://gucchd.georgetown.edu/hugem/fs12.htm).

The Genetics and Public Policy center also offers an overview of chromosomal mutations (http://www.dnapolicy.org/genetics/geneticsAndDisease.jhtml#chromo).

Genetics Home Reference provides clear, user-friendly information about chromosomal disorders, including Down syndrome (http://ghr.nlm.nih.gov/condition=downsyndrome) and Turner syndrome (http://ghr.nlm.nih.gov/condition=turnersyndrome).

What are complex or multifactorial disorders?

Researchers are learning that nearly all conditions and diseases have a genetic component. Some disorders, such as sickle cell anemia and cystic fibrosis, are caused by mutations in a single gene. The causes of many other disorders, however, are much more complex. Common medical problems such as heart disease, diabetes, and obesity do not have a single genetic cause—they are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors. Conditions caused by many contributing factors are called complex or multifactorial disorders.

Although complex disorders often cluster in families, they do not have a clear-cut pattern of inheritance. This makes it difficult to determine a person's risk of inheriting or passing on these disorders. Complex disorders are also difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified. By 2010, however, researchers predict they will have found the major contributing genes for many common complex disorders.

For more information about complex disorders:

The University of Utah Genetic Science Learning Center provides information about multifactorial disorders (http://gslc.genetics.utah.edu/units/disorders/whataregd/multi.cfm) and a brief discussion of the complex basis of cancer.

Additional information about complex disorders (http://gucchd.georgetown.edu/hugem/fs13.htm) is available from Georgetown University's Human Genome Education Model Project II.

If you would like information about a specific complex disorder such as diabetes or obesity, the National Institutes of Health offers a searchable list of health topics (http://health.nih.gov/) that will lead you to fact sheets and other reliable medical information. In addition, the Centers for Disease Control and Prevention provides a detailed list of diseases and conditions (http://www.cdc.gov/node.do/id/0900f3ec8000e035) that links to additional information.

What information about a genetic condition can statistics provide?

Statistical data can provide general information about how common a condition is, how many people have the condition, or how likely it is that a person will develop the condition. Statistics are not personalized, however—they offer estimates based on groups of people. By taking into account a person's family history, medical history, and other factors, a genetics professional can help interpret what statistics mean for a particular patient.

Some statistical terms are commonly used when describing genetic conditions and other disorders. These terms include:

Statistical term	**Description**	**Examples**
Incidence	The incidence of a gene mutation or a genetic disorder is the number of people who are born with the mutation or disorder in a specified group per year. Incidence is often written in the form “1 in [a number]” or as a total number of live births.	About 1 in 200,000 people in the United States are born with syndrome A each year. An estimated 15,000 infants with syndrome B were born last year worldwide.
Prevalence	The prevalence of a gene mutation or a genetic disorder is the total number of people of any age who have the mutation or disorder in a specified group at a given time. This includes both newly diagnosed and pre-existing cases. Prevalence is often written in the form “1 in [a number]” or as a total number of people who have a condition.	Approximately 1 in 100,000 people in the United States have syndrome A at the present time. About 100,000 children worldwide currently have syndrome B.
Mortality	Mortality is the number of deaths from a particular disorder occurring in a specified group per year. Mortality is usually expressed as a total number of deaths.	An estimated 12,000 people worldwide died from syndrome C in 2002.

Statistical term	Description	Examples
Lifetime risk	Lifetime risk is the average risk of developing a particular disorder at some point during a lifetime. Lifetime risk is often written as a percentage or as “1 in [a number].” It is important to remember that the risk per year or per decade is much lower than the lifetime risk. In addition, other factors may increase or decrease a person's risk as compared with the average.	Approximately 1 percent of people in the United States develop disorder D during their lifetimes. The lifetime risk of developing disorder D is 1 in 100.

For more information about interpreting statistics:

The National Alliance of Breast Cancer Organizations (NABCO) offers a fact sheet titled Comments on Putting Cancer Statistics in Context (http://www.nabco.org/index.php/index.php/138). This resource lists the uses and limitations of cancer statistics. Although the fact sheet focuses on cancer, information about interpreting medical statistics can also apply to other disorders.

How are genetic conditions and genes named?

Naming genetic conditions

Genetic conditions are not named in one standard way (unlike genes, which are given an official name and symbol by a formal committee). Doctors who treat families with a particular disorder are often the first to propose a name for the condition. Expert working groups may later revise the name to improve its usefulness. Naming is important because it allows accurate and effective communication about particular conditions, which will ultimately help researchers find new approaches to treatment.

Disorder names are often derived from one or a combination of sources:

- The basic genetic or biochemical defect that causes the condition (for example, alpha-1 antitrypsin deficiency);
- One or more major signs or symptoms of the disorder (for example, sickle cell anemia);
- The parts of the body affected by the condition (for example, retinoblastoma);
- The name of a physician or researcher, often the first person to describe the disorder (for example, Marfan syndrome, which was named after Dr. Antoine Bernard-Jean Marfan);
- A geographic area (for example, familial Mediterranean fever, which occurs mainly in populations bordering the Mediterranean Sea); or
- The name of a patient or family with the condition (for example, amyotrophic lateral sclerosis, which is also called Lou Gehrig disease after a famous baseball player who had the condition).

Disorders named after a specific person or place are called eponyms. There is debate as to whether the possessive form (e.g., Alzheimer’s disease) or the nonpossessive form (Alzheimer disease) of eponyms is preferred. As a rule, medical geneticists use the nonpossessive form, and this form may become the standard for doctors in all fields of medicine. Genetics Home Reference uses the nonpossessive form of eponyms.

Genetics Home Reference consults with experts in the field of medical genetics to provide the current, most accurate name for each disorder. Alternate names are included as synonyms.

Naming genes

The HUGO Gene Nomenclature Committee (http://www.gene.ucl.ac.uk/nomenclature/) (HGNC) designates an official name and symbol (an abbreviation of the name) for each known human gene. Some official gene names include additional information in parentheses, such as related genetic conditions, subtypes of a condition, or inheritance pattern. The HGNC is a non-profit organization funded by the U.K. Medical Research Council and the U.S. National Institutes of Health. The Committee has named more than 13,000 of the estimated 30,000 to 40,000 genes in the human genome.

During the research process, genes often acquire several alternate names and symbols. Different researchers investigating the same gene may each give the gene a different name, which can cause confusion. The HGNC assigns a unique name and symbol to each human gene, which allows effective organization of genes in large databanks, aiding the advancement of research. To access the HGNC's guidelines for naming human genes, click on “Guidelines” from the HGNC home page (http://www.gene.ucl.ac.uk/nomenclature/).

Genetics Home Reference describes genes using the HGNC’s official gene names and gene symbols. Genetics Home Reference frequently presents the symbol and name separated with a colon (for example, FGFR4: fibroblast growth factor receptor 4).

Chapter 3

Inheriting Genetic Conditions

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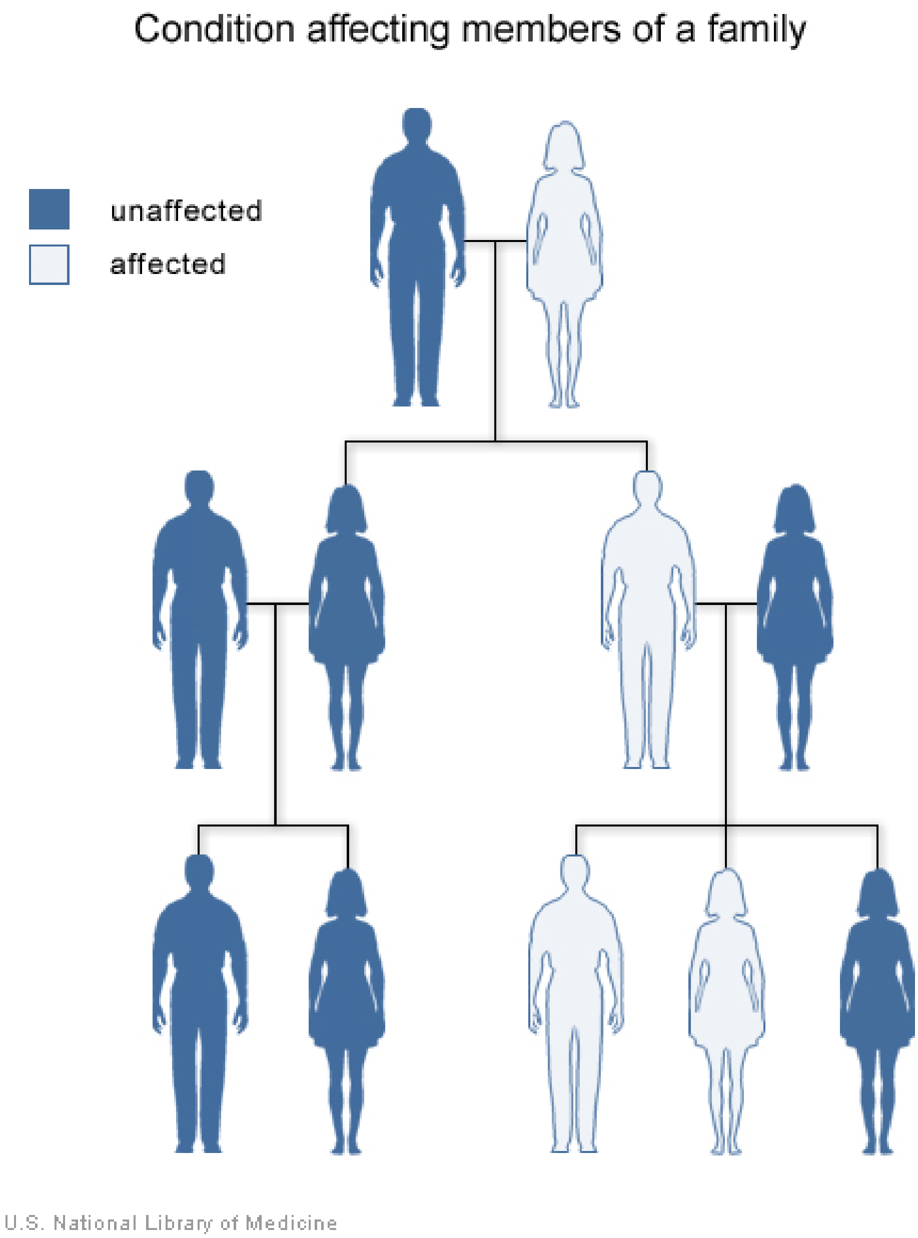
What does it mean if a disorder seems to run in my family?

A particular disorder might be described as “running in a family” if more than one person in the family has the condition. Some disorders that affect multiple family members are caused by gene mutations, which can be inherited (passed down from parent to child). Other conditions that appear to run in families are not inherited. Instead, environmental factors such as dietary habits or a combination of genetic and environmental factors are responsible for these disorders.

It is not always easy to determine whether a condition in a family is inherited. A genetics professional can use a person's family history (a record of health information about a person's immediate and extended family) to help determine whether a disorder has a genetic component.



Some disorders are seen in more than one generation of a family.

For general information about disorders that run in families:

Genetics Home Reference provides consumer-friendly summaries of genetic conditions (http://ghr.nlm.nih.gov/ghr/conditionsByName). Each summary includes a brief description of the condition, an explanation of its genetic cause, and information about the condition's frequency and pattern of inheritance.

The National Human Genome Research Institute fact sheet Frequently Asked Questions About Genetics (http://www.genome.gov/10001191) offers a general description of genetic disorders. Please refer to the first two questions, “What are genetic disorders?” and “How do I find more information about a specific disorder or learn whether a particular disease has a genetic component?”

The Department of Energy offers a fact sheet called Genetic Disease Information—Pronto! (http://www.ornl.gov/TechResources/Human_Genome/medicine/assist.html)

What are the different ways in which a genetic condition can be inherited?

Some genetic conditions are caused by mutations in a single gene. These conditions are usually inherited in one of several straightforward patterns, depending on the gene involved:

Inheritance pattern	Description	Examples
Autosomal dominant	Only one mutated copy of the gene is needed for a person to be affected by an autosomal dominant disorder. Each affected person usually has one affected parent (illustration on page 53).	Huntington disease, neurofibromatosis 1
Autosomal recessive	Two copies of the gene must be mutated for a person to be affected by an autosomal recessive disorder. An affected person usually has unaffected parents who each carry a single copy of the mutated gene (and are referred to as carriers) (illustration on page 54).	cystic fibrosis, sickle cell anemia
X-linked dominant	X-linked dominant disorders are caused by mutations in genes on the X chromosome. Only a few disorders have this inheritance pattern. Females are more frequently affected than males, and the chance of passing on an X-linked dominant disorder differs between men (illustration on page 55) and women (illustration on page 56).	X-linked hypophosphatemia
X-linked recessive	X-linked recessive disorders are also caused by mutations in genes on the X chromosome. Males are more frequently affected than females, and the chance of passing on the disorder differs between men (illustration on page 57) and women (illustration on page 58).	hemophilia A, Duchenne muscular dystrophy

Inheritance pattern	Description	Examples
Mitochondrial	This type of inheritance, also known as maternal inheritance, applies to genes in mitochondrial DNA. (Mitochondria, which are structures in each cell that convert molecules into energy, each contain a small amount of DNA.) Because only egg cells contribute mitochondria to the developing embryo, only females can pass on mitochondrial conditions to their children (illustration on page 59).	Leber's hereditary optic neuropathy (LHON)

Many other disorders are caused by a combination of the effects of multiple genes or by interactions between genes and the environment. Such disorders are more difficult to analyze because their genetic causes are often unclear, and they do not follow the patterns of inheritance described above. Examples of conditions caused by multiple genes or gene/environment interactions include heart disease, diabetes, schizophrenia, and certain types of cancer. For more information, please see "What are complex or multifactorial disorders?" on page 42.

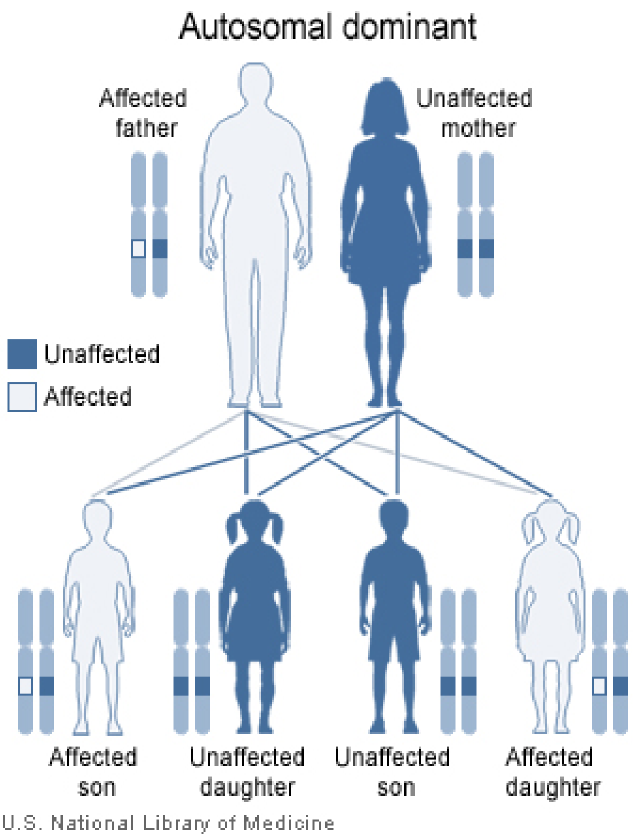
Disorders caused by changes in the number or structure of chromosomes do not follow the straightforward patterns of inheritance listed above. To read about how chromosomal conditions occur, please see "Are chromosomal disorders inherited?" on page 64.

Other genetic factors can also influence how a disorder is inherited: "What are genomic imprinting and uniparental disomy?" on page 62

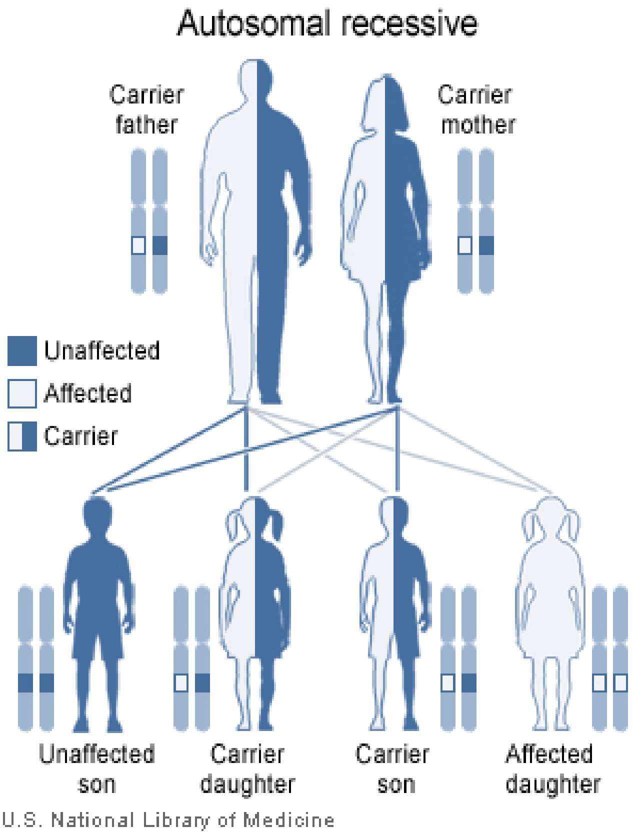
For more information about inheritance patterns:

The Genetics and Public Policy Center provides an introduction to hereditary mutations (http://www.dnapolicy.org/genetics/geneticsAndDisease.jhtml#hered), including their patterns of inheritance.

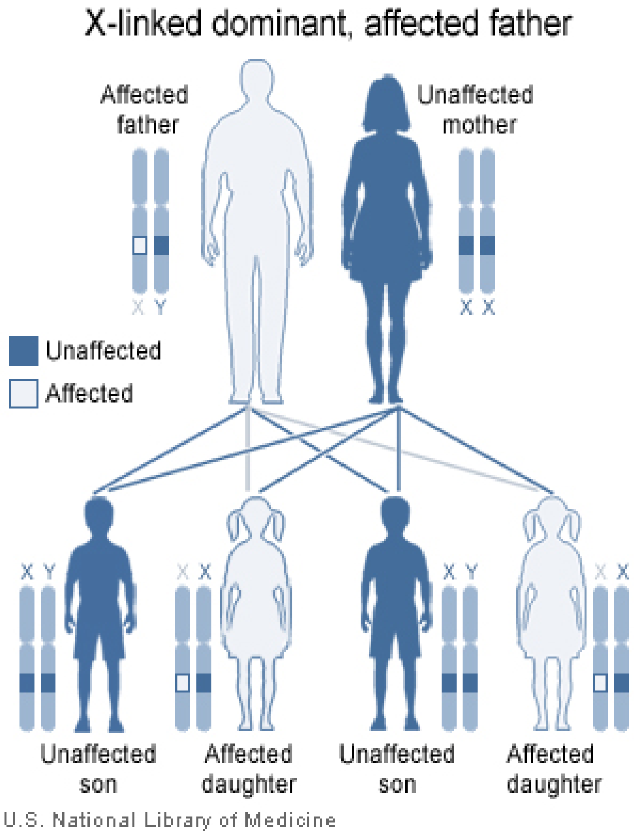
Illustrations: Inheritance patterns



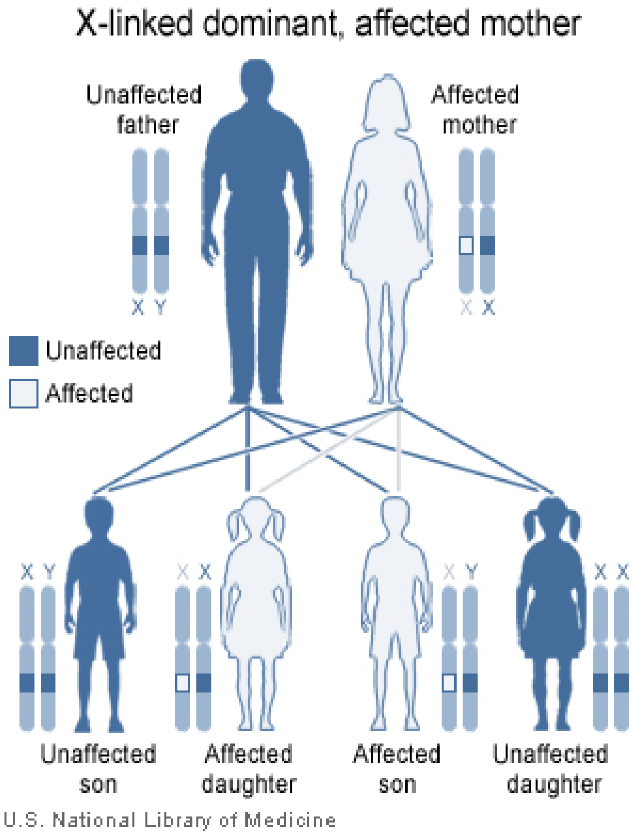
In this example, a man with an autosomal dominant disorder has two affected children and two unaffected children.



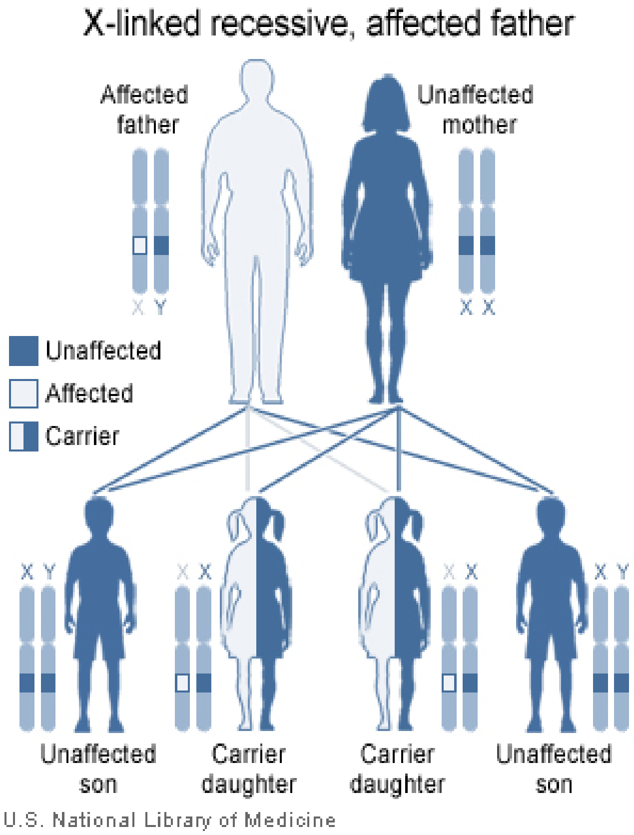
In this example, two unaffected parents each carry one copy of a gene mutation for an autosomal recessive disorder. They have one affected child and three unaffected children, two of which carry one copy of the gene mutation.



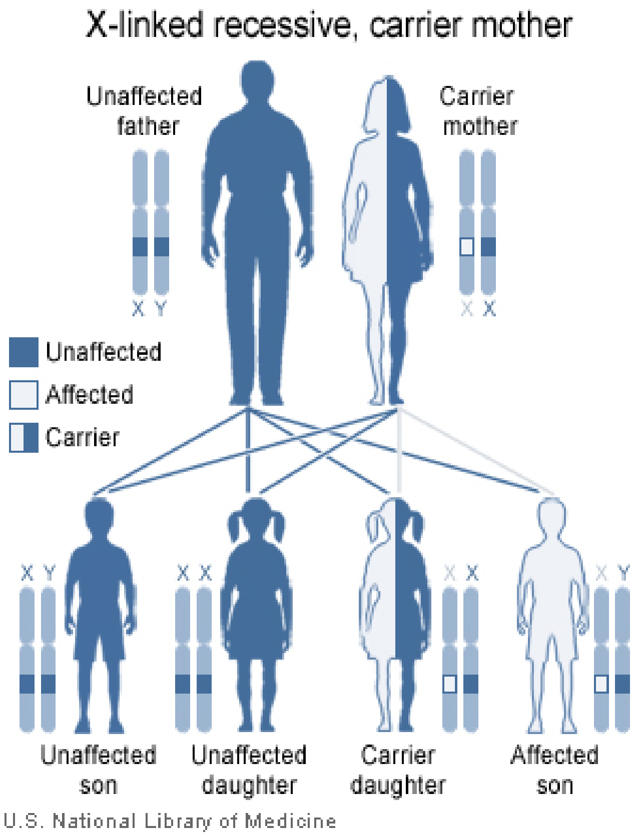
In this example, a man with an X-linked dominant condition has two affected daughters and two unaffected sons.



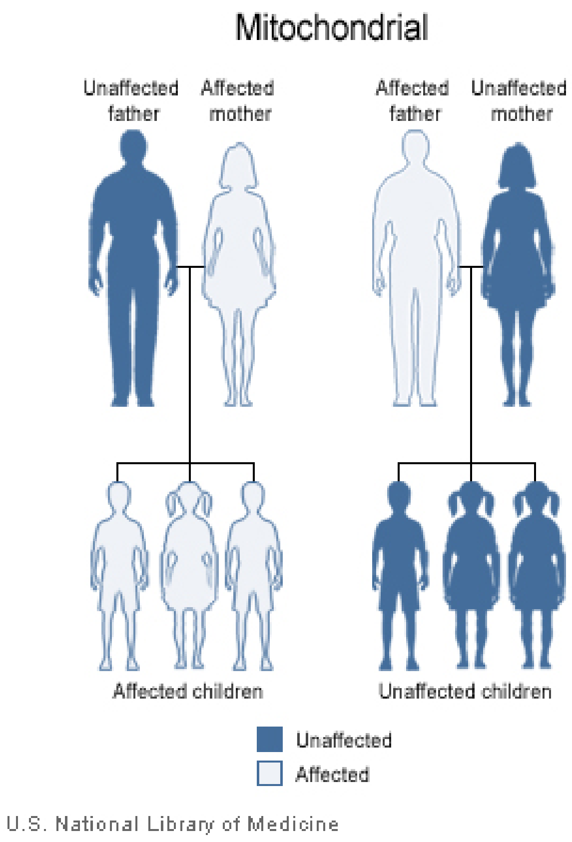
In this example, a woman with an X-linked dominant condition has an affected daughter, an affected son, an unaffected daughter, and an unaffected son.



In this example, a man with an X-linked recessive condition has two unaffected daughters who each carry one copy of the gene mutation, and two unaffected sons who do not have the mutation.



In this example, an unaffected woman carries one copy of a gene mutation for an X-linked recessive disorder. She has an affected son, an unaffected daughter who carries one copy of the mutation, and two unaffected children who do not have the mutation.



In one family, a woman with a mitochondrial disorder and her unaffected husband have only affected children. In another family, a man with a mitochondrial condition and his unaffected wife have no affected children.

If a genetic disorder runs in my family, what are the chances that my children will have the condition?

When a genetic disorder is diagnosed in a family, family members often want to know the likelihood that they or their children will develop the condition. This can be difficult to predict in some cases because many factors influence a person's chances. One important factor is how the condition is inherited. For example:

- A person affected by an autosomal dominant disorder has a 50-percent chance of passing the mutated gene to each child. There is also a 50-percent chance that a child will not inherit the mutated gene (illustration on page 53).
- For an autosomal recessive disorder, two unaffected people who each carry one copy of the mutated gene (carriers) have a 25-percent chance with each pregnancy of having a child affected by the disorder. There is a 75-percent chance with each pregnancy that a child will be unaffected (illustration on page 54).
- The chance of passing on an X-linked dominant condition differs between men and women because men have one X and one Y chromosome, while women have two X chromosomes. A man passes on his Y chromosome to all of his sons and his X chromosome to all of his daughters. Therefore, the sons of a man with an X-linked dominant disorder will not be affected, and his daughters will all inherit the condition (illustration on page 55). A woman passes on one or the other of her X chromosomes to each child. Therefore, a woman with an X-linked dominant disorder has a 50-percent chance of having an affected daughter or son with each pregnancy (illustration on page 56).
- Because of the difference in sex chromosomes, the probability of passing on an X-linked recessive disorder also differs between men and women. The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the mutated gene (illustration on page 57). With each pregnancy, a woman who carries an X-linked recessive disorder has a 50-percent chance of having sons who are affected and a 50-percent chance of having daughters who carry one copy of the mutated gene (illustration on page 58).

It is important to note that the chance of passing on a genetic condition applies equally to each pregnancy. For example, if a couple has a child with an autosomal recessive disorder, the chance of having another child with the disorder is still 25 percent (or

1 in 4). Having one child with a disorder does not “protect” future children from inheriting the condition. Conversely, having a child without the condition does not mean that future children will definitely be affected.

Although the chances of inheriting a genetic condition appear straightforward, in some cases factors such as a person's family history and the results of genetic testing can modify those chances. In addition, some people with a disease-causing mutation never develop any health problems or may experience only mild symptoms of the disorder. If a disease that runs in a family does not have a clear-cut inheritance pattern, predicting the likelihood that a person will develop the condition can be particularly difficult.

Because estimating the chance of developing or passing on a genetic disorder can be complex, genetics professionals can help people understand these chances and make informed decisions about their health.

For more information about passing on a genetic disorder in a family:

The National Library of Medicine MedlinePlus web site offers information about the chance of developing a genetic disorder on the basis of its inheritance pattern. Scroll down to the section “Statistical Chances of Inheriting a Trait” for each of the following inheritance patterns:

Autosomal dominant (http://www.nlm.nih.gov/medlineplus/ency/article/002049.htm)

Autosomal recessive (http://www.nlm.nih.gov/medlineplus/ency/article/002052.htm)

X-linked dominant (http://www.nlm.nih.gov/medlineplus/ency/article/002050.htm)

X-linked recessive (http://www.nlm.nih.gov/medlineplus/ency/article/002051.htm)

What are genomic imprinting and uniparental disomy?

Genomic imprinting and uniparental disomy are factors that influence how some genetic conditions are inherited.

Genomic imprinting

People inherit two copies of their genes—one from their mother and one from their father. Usually both copies of each gene are active, or "turned on," in cells. In some cases, however, only one of the two copies is normally turned on. Which copy is active depends on the parent of origin: some genes are normally active only when they are inherited from a person's father; others are active only when inherited from a person's mother. This phenomenon is known as genomic imprinting.

In genes that undergo genomic imprinting, the parent of origin is often marked, or "stamped," on the gene during the formation of egg and sperm cells. This stamping process, called methylation, is a chemical reaction that attaches small molecules called methyl groups to certain segments of DNA. These molecules identify which copy of a gene was inherited from the mother and which was inherited from the father. The addition and removal of methyl groups can be used to control the activity of genes.

Only a small percentage of all human genes undergo genomic imprinting. Researchers are not yet certain why some genes are imprinted and others are not. They do know that imprinted genes tend to cluster together in the same regions of chromosomes. Two major clusters of imprinted genes have been identified in humans, one on the short (p) arm of chromosome 11 (at position 11p15) and another on the long (q) arm of chromosome 15 (in the region 15q11 to 15q13).

Uniparental disomy

Uniparental disomy (UPD) occurs when a person receives two copies of a chromosome, or part of a chromosome, from one parent and no copies from the other parent. UPD can occur as a random event during the formation of egg or sperm cells or may happen in early fetal development.

In many cases, UPD likely has no effect on health or development. Because most genes are not imprinted, it doesn't matter if a person inherits both copies from one parent instead of one copy from each parent. In some cases, however, it does make a difference whether a gene is inherited from a person's mother or father. A person with UPD may lack any active copies of essential genes that undergo genomic imprinting. This loss of gene function can lead to delayed development, mental retardation, or other medical problems.

Several genetic disorders can result from UPD or a disruption of normal genomic imprinting. The most well-known conditions include Prader-Willi syndrome, which is characterized by uncontrolled eating and obesity, and Angelman syndrome, which causes mental retardation and impaired speech. Both of these disorders can be caused by UPD or other errors in imprinting involving genes on the long arm of chromosome 15. Other conditions, such as Beckwith-Wiedemann syndrome (a disorder characterized by accelerated growth and an increased risk of cancerous tumors), are associated with abnormalities of imprinted genes on the short arm of chromosome 11.

For more information about genomic imprinting and UPD:

The University of British Columbia's web site about chromosomal mosaicism provides an explanation of UPD and genomic imprinting (http://www.medgen.ubc.ca/wrobinson/mosaic/upd.htm), including diagrams illustrating how UPD can occur.

A fact sheet (http://gucchd.georgetown.edu/hugem/fs16.htm)from Georgetown University's Human Genome Education Model Project II offers a brief discussion of UPD, genomic imprinting, and other forms of nontraditional inheritance.

Genetics Home Reference provides clear, user-friendly information about Prader-Willi syndrome (http://ghr.nlm.nih.gov/condition=praderwillisyndrome) and Angelman syndrome (http://ghr.nlm.nih.gov/condition=angelmansyndrome).

Are chromosomal disorders inherited?

Although it is possible to inherit some types of chromosomal abnormalities, most chromosomal disorders are not passed from one generation to the next.

Some chromosomal conditions are caused by changes in the number of chromosomes. These changes are not inherited, but occur as random events during the formation of reproductive cells (eggs and sperm). An error in cell division called nondisjunction results in reproductive cells with an abnormal number of chromosomes. For example, a reproductive cell may accidentally gain or lose one copy of a chromosome. If one of these atypical reproductive cells contributes to the genetic makeup of a child, the child will have an extra or missing chromosome in each of the body's cells.

Changes in chromosome structure can also cause chromosomal disorders. Some changes in chromosome structure can be inherited, while others occur as random accidents during the formation of reproductive cells or in early fetal development. Because the inheritance of these changes can be complex, people concerned about this type of chromosomal abnormality may want to talk with a genetics professional.

Some cancer cells also have changes in the number or structure of their chromosomes. Because these changes occur in somatic cells (cells other than eggs and sperm), they cannot be passed from one generation to the next.

For more information about how chromosomal changes occur:

As part of its fact sheet on chromosome abnormalities, the National Human Genome Research Institute provides a discussion of how chromosome abnormalities happen (http://www.genome.gov/11508982#6).

The University of British Columbia's web site about chromosomal mosaicism explains chromosomal changes, including a detailed description of how trisomy (the presence of an extra chromosome in each cell) happens.

Changes to the Chromosomes (http://www.medgen.ubc.ca/wrobinson/mosaic/changes.htm)

How Does Trisomy Arise? (http://www.medgen.ubc.ca/wrobinson/mosaic/tri_how.htm)

The Chromosome Deletion Outreach fact sheet Introduction to Chromosome Abnormalities (http://www.chromodisorder.org/intro.htm) explains how structural changes occur.

Why are some genetic conditions more common in particular ethnic groups?

Some genetic disorders are more likely to occur among people who trace their ancestry to a particular geographic area. People in an ethnic group often share certain versions of their genes, which have been passed down from common ancestors. If one of these shared genes contains a disease-causing mutation, a particular genetic disorder may be more frequently seen in the group.

Examples of genetic conditions that are more common in particular ethnic groups are sickle cell anemia, which is more common in people of African, African-American, or Mediterranean heritage; and Tay-Sachs disease, which is more likely to occur among people of Ashkenazi (eastern and central European) Jewish or French Canadian ancestry. It is important to note, however, that these disorders can occur in any ethnic group.

For more information about genetic disorders that are more common in certain groups:

The National Institute of General Medical Sciences (NIGMS) fact sheet Genes & Populations (http://www.nigms.nih.gov/news/science_ed/genepop/faq.html) offers additional discussion on this topic. Scroll down to the question “Why do researchers sometimes study ethnic and racial groups?”

Chapter 4

Genetic Consultation

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What is a genetic consultation?

A genetic consultation is a health service that provides information and support to people who have, or may be at risk for, genetic disorders. During a consultation, a genetics professional meets with an individual or family to discuss genetic risks or to diagnose, confirm, or rule out a genetic condition.

Genetics professionals include medical geneticists (doctors who specialize in genetics) and genetic counselors (certified healthcare workers with experience in medical genetics and counseling). Other healthcare professionals such as nurses, psychologists, and social workers trained in genetics can also provide genetic consultations.

Consultations usually take place in a doctor's office, hospital, genetics center, or other type of medical center. These meetings are most often in-person visits with individuals or families, but they are occasionally conducted in a group or over the telephone.

For more information about genetic consultations:

MedlinePlus offers a list of links to information about genetic counseling (http://www.nlm.nih.gov/medlineplus/geneticcounseling.html).

GeneTests (http://www.genetests.org/) offers additional information about genetic consultations. Choose "Educational Materials" at the top of the GeneTests home page and scroll down to the question "What is a Genetic Consultation?"

Why might someone have a genetic consultation?

Individuals or families who are concerned about an inherited condition may benefit from a genetic consultation. The reasons that a person might be referred to a genetic counselor, medical geneticist, or other genetics professional include:

- A personal or family history of a genetic condition, birth defect, chromosomal disorder, or hereditary cancer.
- Two or more pregnancy losses (miscarriages), a stillbirth, or a baby who died.
- A child with a known inherited disorder, a birth defect, mental retardation, or developmental delay.
- A woman who is pregnant or plans to become pregnant at or after age 35. (Some chromosomal disorders occur more frequently in children born to older women.)
- Abnormal test results that suggest a genetic or chromosomal condition.
- An increased risk of developing or passing on a particular genetic disorder on the basis of a person's ethnic background.
- People related by blood (for example, cousins) who plan to have children together. (A child whose parents are related may be at an increased risk of inheriting certain genetic disorders.)

A genetic consultation is also an important part of the decision-making process for genetic testing. A visit with a genetics professional may be helpful even if testing is not available for a specific condition, however.

For more information about the reasons for having a genetic consultation:

GeneTests (http://www.genetests.org/) provides a detailed list of common reasons for a genetic consultation. Click on "Educational Materials" at the top of the GeneTests home page and scroll down to the question "Who Should Have a Genetics Consultation?"

The National Women's Health Information Center offers a fact sheet about genetic counseling (http://www.4woman.gov/editor/jul99/jul99.htm). Scroll down to the question "Why might I want to consult a genetic counselor?"

What happens during a genetic consultation?

A genetic consultation provides information, offers support, and addresses a patient's specific questions and concerns. To help determine whether a condition has a genetic component, a genetics professional asks about a person's medical history and takes a detailed family history (a record of health information about a person's immediate and extended family). The genetics professional may also perform a physical examination and recommend appropriate tests.

If a person is diagnosed with a genetic condition, the genetics professional provides information about the diagnosis, how the condition is inherited, the chance of passing the condition to future generations, and the options for testing and treatment.

During a consultation, a genetics professional will:

- Interpret and communicate complex medical information.
- Help each person make informed, independent decisions about their health care and reproductive options.
- Respect each person's individual beliefs, traditions, and feelings.

A genetics professional will NOT:

- Tell a person which decision to make.
- Advise a couple not to have children.
- Recommend that a woman continue or end a pregnancy.
- Tell someone whether to undergo testing for a genetic disorder.

For more information about what to expect during a genetic consultation:

A detailed list of topics that are discussed during a genetics consultation is available from GeneTests (http://www.genetests.org/). Click on "Educational Materials" at the top of the GeneTests home page and scroll down to the question "What is a Genetic Consultation?"

The National Society of Genetic Counselors offers information about what to expect from a genetic counseling session as part of its FAQs About Genetic Counselors and the NSGC (http://www.nsgc.org/about/faq_about.asp). Scroll down to question 5, "This is my first visit to a genetic counselor. What can I expect from this visit?"

How can I find a genetics professional in my area?

To find a genetics professional in your community, you may wish to ask your doctor for a referral. If you have health insurance, you can also contact your insurance company to find a medical geneticist or genetic counselor in your area who participates in your plan.

Several resources for locating a genetics professional in your community are available online:

- GeneTests (http://www.genetests.org/) provides a list of genetics clinics around the United States and internationally. You can access the list by clicking on “Clinic Directory” at the top of the GeneTests home page. Clinics can be chosen by state or country, by service, and/or by specialty. State maps can help you locate a clinic in your area.
- The National Society of Genetic Counselors offers a searchable directory of genetic counselors in the United States (http://www.nsgc.org/resourcelink.asp). You can search by location, name, area of practice/specialization, and/or ZIP Code.
- The National Cancer Institute provides a Cancer Genetics Services Directory (http://cancer.gov/search/genetics_services/), which lists professionals who provide services related to cancer genetics. You can search by type of cancer or syndrome, location, and/or provider name.

Chapter 5

Genetic Testing

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What is genetic testing?

Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins. Most of the time, testing is used to find changes that are associated with inherited disorders. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder. Several hundred genetic tests are currently in use, and more are being developed.

Genetic testing is voluntary. Because testing has both benefits and limitations, the decision about whether to be tested is a personal and complex one. A genetic counselor can help by providing information about the pros and cons of the test and discussing the social and emotional aspects of testing.

For general information about genetic testing:

MedlinePlus offers a list of links to information about genetic testing (http://www.nlm.nih.gov/medlineplus/genetictesting.html).

The National Human Genome Research Institute provides an overview of this topic as part of its Frequently Asked Questions About Genetics (http://www.genome.gov/10001191#3).

The Genetics and Public Policy Center also offers information about genetic testing (http://www.dnapolicy.org/genetics/testing.jhtml).

What are the uses of genetic testing?

Genetic testing can provide information about a person's genes and chromosomes throughout life. Available types of testing include:

Newborn screening

Newborn screening is used just after birth to identify genetic disorders that can be treated early in life. The routine testing of infants for certain disorders is the most widespread use of genetic testing—millions of babies are tested each year in the United States. All states currently test infants for phenylketonuria (a genetic disorder that causes mental retardation if left untreated) and hypothyroidism (a disorder of the thyroid gland). Some states also test for other genetic disorders.

Diagnostic testing

Diagnostic testing is used to diagnose or rule out a particular genetic or chromosomal condition. It is usually offered to people who have signs of a particular disorder. This type of testing can be performed at any time during a person's life, but is not available for all genetic conditions. The results of a diagnostic test can influence a person's choices about health care and the management of symptoms.

Carrier testing

Carrier testing is used to identify people who carry one copy of a gene mutation that, when present in two copies, causes a genetic disorder. This type of testing is offered to individuals who have a family history of a genetic disorder and to people in ethnic groups with an increased risk of specific genetic conditions. If both parents are tested, the test can provide information about a couple's risk of having a child with a genetic condition.

Prenatal testing

Prenatal testing is used to detect changes in a fetus's genes or chromosomes before birth. This type of testing is offered to couples with an increased risk of having a baby with a genetic or chromosomal disorder. In some cases, prenatal testing can lessen a couple's uncertainty or help them make decisions about a pregnancy. It cannot identify all possible inherited disorders and birth defects, however.

Predictive and presymptomatic testing

These types of testing are used to detect gene mutations associated with disorders that appear later in life. Predictive testing can identify mutations that increase a person's risk of developing disorders with a genetic basis, such as certain types of cancer. Presymptomatic testing can determine whether a person will develop a genetic disorder, such as Huntington disease (an inherited brain disorder that appears during mid-life), before any symptoms appear. The results of predictive and presymptomatic testing can help people make decisions about medical care.

Forensic testing

Forensic testing uses DNA sequences to identify an individual for legal purposes. Unlike the tests described above, forensic testing is not used to detect gene mutations associated with disease. This type of testing can identify crime or catastrophe victims, rule out or implicate a crime suspect, or establish biological relationships between people (for example, paternity).

For more information about the uses of genetic testing:

Information about the types of genetic testing is available from GeneTests (http://www.genetests.org/). Click on “Educational Materials” at the top of the GeneTests home page and scroll down to “Uses of Genetic Testing.”

The National Newborn Screening and Genetics Resource Center (http://genes-r-us.uthscsa.edu/) offers detailed information about newborn screening.

For information about forensic DNA testing, refer to the fact sheet DNA Forensics (http://www.ornl.gov/TechResources/Human_Genome/elsi/forensics.html) from the U.S. Department of Energy Office of Science.

How is genetic testing done?

Once a person decides to proceed with genetic testing, a medical geneticist, genetic counselor, primary care doctor, or specialist can order the test. Genetic testing is often done as part of a genetic consultation.

Genetic tests are performed on a sample of blood, hair, skin, amniotic fluid (the fluid that surrounds a fetus during pregnancy), or other tissue. For example, a procedure called a buccal smear uses a small brush or cotton swab to collect a sample of cells from the inside surface of the cheek. The sample is sent to a laboratory where technicians look for specific changes in chromosomes, DNA, or proteins, depending on the suspected disorder. The laboratory reports the test results in writing to a person's doctor or genetic counselor.

Newborn screening tests are done on a small blood sample, which is taken by pricking the baby's heel. Unlike other types of genetic testing, a parent will usually only receive the result if it is positive. If the test result is positive, additional testing is needed to determine whether the baby has a genetic disorder.

Before a person has a genetic test, it is important that he or she understands the testing procedure, the benefits and limitations of the test, and the possible consequences of the test results. The process of educating a person about the test and obtaining permission is called informed consent.

For more information about genetic testing procedures:

GeneTests (http://www.genetests.org/) explains the testing process and informed consent. Click on “Educational Materials” at the top of the GeneTests home page and scroll down to “Ordering Genetic Testing.”

For information about how newborn screening tests are performed, refer to Genetic Testing of Newborn Infants (http://gslc.genetics.utah.edu/units/newborn/samples.cfm) from the University of Utah Genetic Science Learning Center.

What is the cost of genetic testing, and how long does it take to get the results?

The cost of genetic testing can range from under $100 to more than $2,000, depending on the nature and complexity of the test. The cost increases if more than one test is necessary or if multiple family members must be tested to obtain a meaningful result. For newborn screening, costs vary by state. Some states cover part of the total cost, but most charge a fee of $15 to $60 per infant.

From the date that a sample is taken, it may take a few weeks to several months to receive the test results. Results for prenatal testing are usually available more quickly because time is an important consideration in making decisions about a pregnancy. The doctor or genetic counselor who orders a particular test can provide specific information about the cost and time frame associated with that test.

For more information about the costs and turnaround time for genetic tests:

GeneTests (http://www.genetests.org/) provides a list of factors that influence the turnaround time and costs of genetic testing. Click on “Educational Materials” at the top of the GeneTests home page and scroll down to “Ordering Genetic Testing.” In this section, “Turn-Around Time” and “Cost” are found under the heading “Choosing a Laboratory.”

Will health insurance cover the costs of genetic testing?

In many cases, health insurance plans will cover the costs of genetic testing when it is recommended by a person's doctor. Health insurance providers have different policies about which tests are covered, however. A person interested in submitting the costs of testing may wish to contact his or her insurance company beforehand to ask about coverage.

Some people may choose not to use their insurance to pay for testing because the results of a genetic test can affect a person's health insurance coverage. Instead, they may opt to pay out-of-pocket for the test. People considering genetic testing may want to find out more about their state's privacy protection laws before they ask their insurance company to cover the costs. (Refer to "What is genetic discrimination?" on page 81 for more information.)

What are the benefits of genetic testing?

Genetic testing has potential benefits whether the results are positive or negative for a gene mutation. Test results can provide a sense of relief from uncertainty and help people make informed decisions about managing their health care. For example, a negative result can eliminate the need for unnecessary checkups and screening tests in some cases. A positive result can direct a person toward available prevention, monitoring, and treatment options. Some test results can also help people make decisions about having children. Newborn screening can identify genetic disorders early in life so treatment can be started as early as possible.

For more information about the benefits of genetic testing:

The National Cancer Institute provides a brief discussion of the benefits of genetic testing (http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting30.htm).

Additional information on this topic is available in the fact sheet Gene Testing (http://www.ornl.gov/TechResources/Human_Genome/medicine/genetest.html#procon) from the U.S. Department of Energy Office of Science.

What are the risks and limitations of genetic testing?

The physical risks associated with most genetic tests are very small, particularly for those tests that require only a blood sample or buccal smear (a procedure that samples cells from the inside surface of the cheek). The procedures used for prenatal testing carry a small but real risk of losing the pregnancy (miscarriage) because they require a sample of amniotic fluid or tissue from around the fetus.

Many of the risks associated with genetic testing involve the emotional, social, or financial consequences of the test results. People may feel angry, depressed, anxious, or guilty about their results. In some cases, genetic testing creates tension within a family because the results can reveal information about other family members in addition to the person who is tested. The possibility of genetic discrimination in employment or insurance is also a concern. (Refer to "What is genetic discrimination?" on page 81 for additional information.)

Genetic testing can provide only limited information about an inherited condition. The test often can't determine if a person will show symptoms of a disorder, how severe the symptoms will be, or whether the disorder will progress over time. Another major limitation is the lack of treatment strategies for many genetic disorders once they are diagnosed.

A genetics professional can explain in detail the benefits, risks, and limitations of a particular test. It is important that any person who is considering genetic testing understand and weigh these factors before making a decision.

For more information about the risks and limitations of genetic testing:

The National Cancer Institute provides a brief discussion of the limitations of genetic testing:

Limitations of Gene Testing (http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting31.htm)

Major Limitations of Gene Testing (http://press2.nci.nih.gov/sciencebehind/genetesting/genetesting32.htm)

Additional information about the risks and benefits of genetic testing can be found in the publication Genomics and Its Impact on Science and Society: The Human Genome Project and Beyond (http://www.ornl.gov/TechResources/Human_Genome/publicat/primer2001/6.html) from the U.S. Department of Energy Office of Science. Scroll down to the section “Gene Testing.”

GeneTests (http://www.genetests.org/) outlines points to consider for each type of genetic testing. Click on “Educational Materials” at the top of the GeneTests home page and scroll down to “Uses of Genetic Testing.”

What is genetic discrimination?

Genetic discrimination occurs when people are treated differently by their employer or insurance company because they have a gene mutation that causes or increases the risk of an inherited disorder. People who undergo genetic testing may be at risk for genetic discrimination.

The results of a genetic test are normally included in a person's medical records. When a person applies for life, disability, or health insurance, the insurance company may ask to look at these records before making a decision about coverage. An employer may also have the right to look at an employee's medical records. As a result, genetic test results could affect a person's insurance coverage or employment. People making decisions about genetic testing should be aware that when test results are placed in their medical records, the results might not be kept private.

Fear of discrimination is a common concern among people considering genetic testing. Several laws at the federal and state levels help protect people against genetic discrimination; however, genetic testing is a fast-growing field and these laws don't cover every situation.

For more information about privacy and genetic discrimination:

The National Human Genome Research Institute provides a detailed discussion of genetic discrimination and current laws that address this issue:

Genetic Discrimination in Health Insurance or Employment (http://www.genome.gov/11510227)

Privacy and Discrimination in Genetics (http://www.genome.gov/10002077)

Policy and Legislation Database (http://www.genome.gov/PolicyEthics/LegDatabase/pubsearch.cfm)

The Genetic Alliance offers links to resources and policy statements on genetic discrimination (http://www.geneticalliance.org/geneticissues/discrimresources.html).

Additional information about policy and legislation related to genetic privacy (http://www.ornl.gov/TechResources/Human_Genome/elsi/legislat.html) is available from the U.S. Department of Energy Office of Science.

How does genetic testing in a research setting differ from clinical genetic testing?

The main differences between clinical genetic testing and research testing are the purpose of the test and who receives the results. The goals of research testing include finding unknown genes, learning how genes work, and advancing our understanding of genetic conditions. The results of testing done as part of a research study are usually not available to patients or their healthcare providers. Clinical testing, on the other hand, is done to find out about an inherited disorder in an individual patient or family. People receive the results of a clinical test and can use them to help them make decisions about medical care or reproductive issues.

It is important for people considering genetic testing to know whether the test is available on a clinical or research basis. Clinical and research testing both involve a process of informed consent in which patients learn about the testing procedure, the risks and benefits of the test, and the potential consequences of testing.

For more information about the differences between clinical and research testing:

GeneTests (http://www.genetests.org/) outlines the major differences between clinical tests and research tests. Click on “Educational Materials” at the top of the GeneTests home page and scroll down to the question “What is Genetic Testing?”

The Genetic Alliance fact sheet Informed Consent: Participation in Genetic Research Studies (http://www.geneticalliance.org/geneticissues/informedconsent.html) provides information about informed consent and questions to ask genetic researchers.

Chapter 6

Gene Therapy

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What is gene therapy?

Gene therapy is an experimental technique that uses genes to treat or prevent disease. In the future, this technique may allow doctors to treat a disorder by inserting a gene into a patient's cells instead of using drugs or surgery. Researchers are testing several approaches to gene therapy, including:

- Replacing a mutated gene that causes disease with a healthy copy of the gene.
- Inactivating, or "knocking out," a mutated gene that is functioning improperly.
- Introducing a new gene into the body to help fight a disease.

Although gene therapy is a promising treatment option for a number of diseases (including inherited disorders, some types of cancer, and certain viral infections), the technique remains risky and is still under study to make sure that it will be safe and effective. Gene therapy is currently only being tested for the treatment of diseases that have no other cures.

For general information about gene therapy:

MedlinePlus (from the National Library of Medicine) offers a list of links to information about genes and gene therapy (http://www.nlm.nih.gov/medlineplus/genesandgenetherapy.html).

The fact sheet Gene Therapy (http://www.ornl.gov/TechResources/Human_Genome/medicine/genetherapy.html) from the U.S. Department of Energy Office of Science offers an overview of this topic.

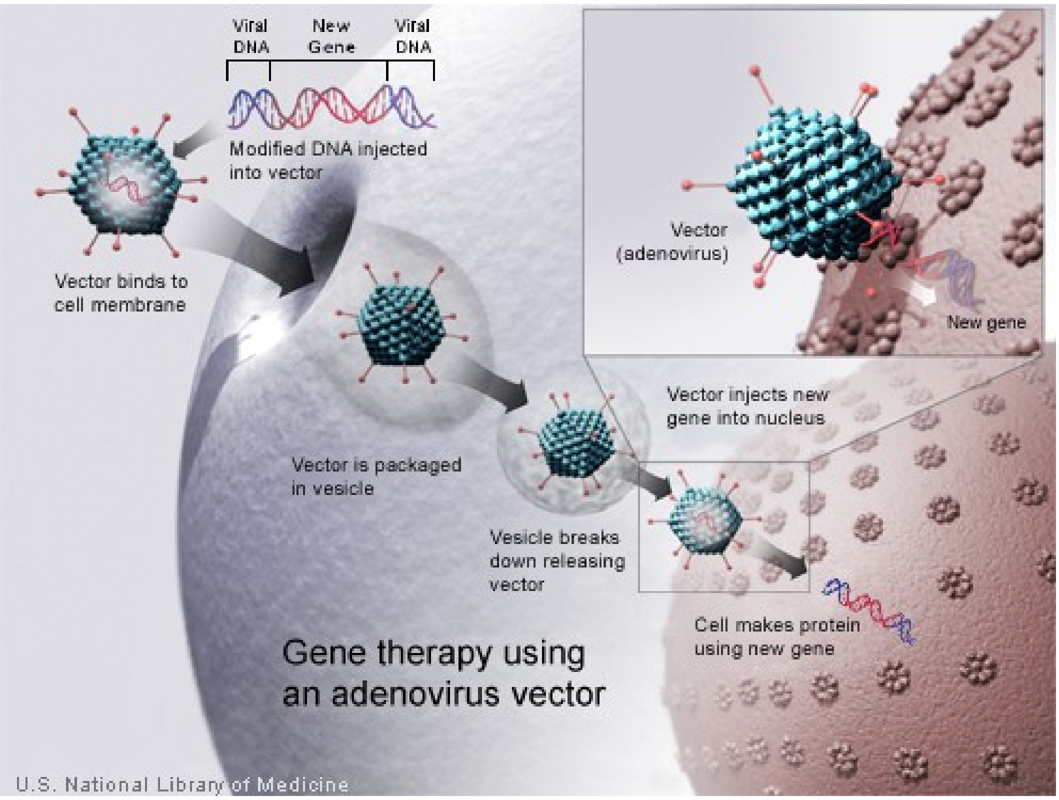
How does gene therapy work?

Gene therapy is designed to introduce genetic material into cells to compensate for abnormal genes or to make a beneficial protein. If a mutated gene causes a necessary protein to be faulty or missing, gene therapy may be able to introduce a normal copy of the gene to restore the function of the protein.

A gene that is inserted directly into a cell usually does not function. Instead, a carrier called a vector is genetically engineered to deliver the gene. Certain viruses are often used as vectors because they can deliver the new gene by infecting the cell. The viruses are modified so they can't cause disease when used in people. Some types of virus, such as retroviruses, integrate their genetic material (including the new gene) into a chromosome in the human cell. Other viruses, such as adenoviruses, introduce their DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome.

The vector can be injected or given intravenously (by IV) directly into a specific tissue in the body, where it is taken up by individual cells. Alternately, a sample of the patient's cells can be removed and exposed to the vector in a laboratory setting. The cells containing the vector are then returned to the patient. If the treatment is successful, the new gene delivered by the vector will make a functioning protein.

Researchers must overcome many technical challenges before gene therapy will be a practical approach to treating disease. For example, scientists must find better ways to deliver genes and target them to particular cells. They must also ensure that new genes are precisely controlled by the body.



A new gene is injected into an adenovirus vector, which is used to introduce the modified DNA into a human cell. If the treatment is successful, the new gene will make a functional protein.

For more information about how gene therapy works:

The National Cancer Institute fact sheet Questions and Answers About Gene Therapy (http://cis.nci.nih.gov/fact/7_18.htm) includes a discussion of the technical aspects of gene therapy. In particular, refer to question 3, “How are genes transferred into cells so that gene therapy can take place?” and question 5, “What are the basic steps involved in gene therapy?”

A short description and diagram of gene therapy is available in the article Fundamentals of Gene Therapy (http://www.fda.gov/fdac/features/2000/gene.html) from the September-October 2000 issue of FDA Consumer magazine.

Is gene therapy safe?

Gene therapy is under study to determine whether it could be used to treat disease. Current research is evaluating the safety of gene therapy; future studies will test whether it is an effective treatment option. Several studies have already shown that this approach can have very serious health risks, such as toxicity, inflammation, and cancer. Because the techniques are relatively new, some of the risks may be unpredictable; however, medical researchers, institutions, and regulatory agencies are working to ensure that gene therapy research is as safe as possible.

Comprehensive federal laws, regulations, and guidelines help protect people who participate in research studies (called clinical trials). The U.S. Food and Drug Administration (FDA) regulates all gene therapy products in the United States and oversees research in this area. Researchers who wish to test an approach in a clinical trial must first obtain permission from the FDA. The FDA has the authority to reject or suspend clinical trials that are suspected of being unsafe for participants.

The National Institutes of Health (NIH) also plays an important role in ensuring the safety of gene therapy research. NIH provides guidelines for investigators and institutions (such as universities and hospitals) to follow when conducting clinical trials with gene therapy. These guidelines state that clinical trials at institutions receiving NIH funding for this type of research must be registered with the NIH Office of Biotechnology Activities. The protocol, or plan, for each clinical trial is then reviewed by the NIH Recombinant DNA Advisory Committee (RAC) to determine whether it raises medical, ethical, or safety issues that warrant further discussion at one of the RAC's public meetings.

An Institutional Review Board (IRB) and an Institutional Biosafety Committee (IBC) must approve each gene therapy clinical trial before it can be carried out. An IRB is a committee of scientific and medical advisors and consumers that reviews all research within an institution. An IBC is a group that reviews and approves an institution's potentially hazardous research studies. Multiple levels of evaluation and oversight ensure that safety concerns are a top priority in the planning and carrying out of gene therapy research.

For more information about the safety and oversight of gene therapy:

A discussion of the safety concerns surrounding gene therapy research is available in the article Human Gene Therapy: Harsh Lessons, High Hopes (http://www.fda.gov/fdac/features/2000/500_gene.html) from the September-October 2000 issue of FDA Consumer magazine.

Additional information about the FDA's role in overseeing the safety of gene therapy research can be found in the fact sheet Human Gene Therapy and The Role of the Food and Drug Administration. (http://www.fda.gov/cber/infosheets/genezn.htm)

The NIH provides several resources about its role in the safety of gene therapy research:

Office of Biotechnology Activities (http://www4.od.nih.gov/oba/)

Frequently Asked Questions: Recombinant DNA and Gene Transfer (http://www4.od.nih.gov/oba/RAC/RAC_FAQs.htm)

What are the ethical issues surrounding gene therapy?

Because gene therapy involves making changes to the body's set of basic instructions, it raises many unique ethical concerns. The ethical questions surrounding gene therapy include:

- How can "good" and "bad" uses of gene therapy be distinguished?
- Who decides which traits are normal and which constitute a disability or disorder?
- Will the high costs of gene therapy make it available only to the wealthy?
- Could the widespread use of gene therapy make society less accepting of people who are different?
- Should people be allowed to use gene therapy to enhance basic human traits such as height, intelligence, or athletic ability?

Current gene therapy research has focused on treating individuals by targeting the therapy to body cells such as bone marrow or blood cells. This type of gene therapy cannot be passed on to a person's children. Gene therapy could be targeted to egg and sperm cells (germ cells), however, which would allow the inserted gene to be passed on to future generations. This approach is known as germline gene therapy.

The idea of germline gene therapy is controversial. While it could spare future generations in a family from having a particular genetic disorder, it might affect the development of a fetus in unexpected ways or have long-term side effects that are not yet known. Because people who would be affected by germline gene therapy are not yet born, they can't choose whether to have the treatment. Because of these ethical concerns, the U.S. Government does not allow federal funds to be used for research on germline gene therapy in people.

For more information about the ethical issues raised by gene therapy:

The National Cancer Institute fact sheet Questions and Answers About Gene Therapy (http://cis.nci.nih.gov/fact/7_18.htm) offers information on this topic. Refer to Question 12, "What are some of the social and ethical issues surrounding human gene therapy?" and Question 13, "What is being done to address these social and ethical issues?"

Information about the ethics of germline gene therapy is provided in chapter 7 of the publication Your Genes, Your Choices (http://www.ornl.gov/TechResources/Human_Genome/publicat/genechoice/7_dr.html). Scroll down to the section "Germ-Line Therapy."

The Genetics and Public Policy Center also outlines scientific issues and ethical concerns regarding gene therapy (http://www.dnapolicy.org/genetics/transfer.jhtml).

Is gene therapy available to treat my disorder?

Gene therapy is currently available only in a research setting. The U.S. Food and Drug Administration (FDA) has not yet approved any gene therapy products for sale in the United States.

Hundreds of research studies (clinical trials) are under way to test gene therapy as a treatment for genetic conditions, cancer, and HIV/AIDS. If you are interested in participating in a clinical trial, talk with your doctor or a genetics professional about how to participate.

You can also search for clinical trials online. ClinicalTrials.gov (http://clinicaltrials.gov/), a service of the National Institutes of Health, provides easy access to information on clinical trials. You can search for specific trials or browse by condition or trial sponsor. You may wish to refer to a list of gene therapy trials (http://clinicaltrials.gov/search/term=gene+therapy) that are accepting (or will accept) patients.

Chapter 7

The Human Genome Project and Genomic Research

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What is a genome?

A genome is an organism's complete set of DNA, including all of its genes. Each genome contains all of the information needed to build and maintain that organism. In humans, a copy of the entire genome—more than 3 billion DNA base pairs—is contained in all cells that have a nucleus.

For more information about genomes:

The U.S. Department of Energy Office of Science provides background information about the human genome in its fact sheet The Science Behind the Human Genome Project (http://www.ornl.gov/TechResources/Human_Genome/project/info.html).

The NCBI Science Primer (http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html) offers more detailed information about the structure and function of the human genome under the heading "What Is a Genome?"

What was the Human Genome Project and why has it been important?

The Human Genome Project was an international research effort to determine the sequence of the human genome and identify the genes that it contains. The Project was coordinated by the National Institutes of Health and the U.S. Department of Energy. Additional contributors included universities across the United States and international partners in the United Kingdom, France, Germany, Japan, and China. The Human Genome Project formally began in 1990 and was completed in 2003, 2 years ahead of its original schedule.

The work of the Human Genome Project has allowed researchers to begin to understand the blueprint for building a person. As researchers learn more about the functions of genes and proteins, this knowledge will have a major impact in the fields of medicine, biotechnology, and the life sciences.

For more information about the Human Genome Project:

The National Human Genome Research Institute offers a fact sheet about the Human Genome Project (http://www.genome.gov/10001772) and a list of frequently asked questions (http://www.genome.gov/11006943).

A brief description of the Project and links to many additional resources are available from the Human Genome Project Information web site (http://www.ornl.gov/TechResources/Human_Genome/home.html), a service of the U.S. Department of Energy Office of Science.

The U.S. Department of Energy Office of Science also provides a fact sheet called Potential Benefits of Human Genome Project Research (http://www.ornl.gov/sci/techresources/Human_Genome/project/benefits.shtml).

What were the goals of the Human Genome Project?

The main goals of the Human Genome Project were to provide a complete and accurate sequence of the 3 billion DNA base pairs that make up the human genome and to find all of the estimated 30,000 to 40,000 human genes. The Project also aimed to sequence the genomes of several other organisms that are important to medical research, such as the mouse and the fruit fly.

In addition to sequencing DNA, the Human Genome Project sought to develop new tools to obtain and analyze the data and to make this information widely available. Also, because advances in genetics have consequences for individuals and society, the Human Genome Project committed to exploring the consequences of genomic research through its Ethical, Legal, and Social Implications (ELSI) program.

For more information about the Human Genome Project's goals:

The U.S. Department of Energy Office of Science offers an overview of the Human Genome Project's 5-year goals (http://www.ornl.gov/TechResources/Human_Genome/hg5yp/), including a table outlining the goals and when they were achieved.

The National Human Genome Research Institute provides a fact sheet about DNA sequencing (http://www.genome.gov/10001177).

What did the Human Genome Project accomplish?

In April 2003, researchers announced that the Human Genome Project had completed a high-quality sequence of essentially the entire human genome. This sequence closed the gaps from a working draft of the genome, which was published in 2001. It also identified the locations of many human genes and provided information about their structure and organization. The Project made the sequence of the human genome and tools to analyze the data freely available via the Internet.

In addition to the human genome, the Human Genome Project sequenced the genomes of several other organisms, including brewers' yeast, the roundworm, and the fruit fly. In 2002, researchers announced that they had also completed a working draft of the mouse genome. By studying the similarities and differences between human genes and those of other organisms, researchers can discover the functions of particular genes and identify which genes are critical for life.

The Project's Ethical, Legal, and Social Implications (ELSI) program became the world's largest bioethics program and a model for other ELSI programs worldwide. For additional information about ELSI and the program's accomplishments, please refer to "What were some of the ethical, legal, and social implications addressed by the Human Genome Project?" on page 97

For more information about the accomplishments of the Human Genome Project:

An overview of the Project's accomplishments is available in the National Human Genome Research Institute press release International Consortium Completes Human Genome Project (http://www.genome.gov/11006929).

The U.S. Department of Energy Office of Science provides links to information about the Project's activities as part of its fact sheet Human Genome Project Completion: 1990-2003 (http://www.ornl.gov/TechResources/Human_Genome/project/50yr.html).

The complete sequence of the human genome and articles analyzing the sequence were published in early 2003. The Human Genome Project Information web site provides an index of these landmark scientific papers (http://www.ornl.gov/TechResources/Human_Genome/project/journals/journals.html).

What were some of the ethical, legal, and social implications addressed by the Human Genome Project?

The Ethical, Legal, and Social Implications (ELSI) program was founded in 1990 as an integral part of the Human Genome Project. The mission of the ELSI program was to identify and address issues raised by genomic research that would affect individuals, families, and society. A percentage of the Human Genome Project budget at the National Institutes of Health and the U.S. Department of Energy was devoted to ELSI research.

The ELSI program focused on the possible consequences of genomic research in four main areas:

- Privacy and fairness in the use of genetic information, including the potential for genetic discrimination in employment and insurance.
- The integration of new genetic technologies, such as genetic testing, into the practice of clinical medicine.
- Ethical issues surrounding the design and conduct of genetic research with people, including the process of informed consent.
- The education of healthcare professionals, policy makers, students, and the public about genetics and the complex issues that result from genomic research.

For more information about the ELSI program:

Information about the ELSI program at the National Institutes of Health, including program goals and activities, is available in the fact sheet Ethical, Legal and Social Implications (ELSI) Research Program (http://www.genome.gov/10001618) from the National Human Genome Research Institute. The About ELSI web page (http://www.genome.gov/10001754) provides a more detailed discussion of the program.

The U.S. Department of Energy Office of Science offers two fact sheets on the ELSI program, each of which includes links to many additional resources:

Ethical, Legal, and Social Issues (http://www.ornl.gov/TechResources/Human_Genome/elsi/elsi.html)

Ethical, Legal, and Social Issues Research (http://www.ornl.gov/TechResources/Human_Genome/research/elsi.html)

What are the next steps in genomic research?

Discovering the sequence of the human genome was only the first step in understanding how the instructions coded in DNA lead to a functioning human being. The next stage of genomic research will begin to derive meaningful knowledge from the DNA sequence. Research studies that build on the work of the Human Genome Project are under way worldwide.

The objectives of continued genomic research include the following:

- Determine the function of genes and the elements that regulate genes throughout the genome.
- Find variations in the DNA sequence among people and determine their significance. These variations may one day provide information about a person's disease risk and response to certain medications.
- Discover the 3-dimensional structures of proteins and identify their functions.
- Explore how DNA and proteins interact with one another and with the environment to create complex living systems.
- Develop and apply genome-based strategies for the early detection, diagnosis, and treatment of disease.
- Sequence the genomes of other organisms, such as the rat, cow, and chimpanzee, in order to compare similar genes between species.
- Develop new technologies to study genes and DNA on a large scale and store genomic data efficiently.
- Continue to explore the ethical, legal, and social issues raised by genomic research.

For more information about the genomic research following the Human Genome Project:

The National Human Genome Research Institute supports research in many of the areas described above. The Institute provides detailed information about its research initiatives at NIH and nationwide (http://www.genome.gov/Research/). In addition, the NIH Roadmap (http://nihroadmap.nih.gov/) outlines major initiatives in biomedical research.

The U.S. Department of Energy's Genomes to Life program will use genomic data and new technologies to obtain a fundamental understanding of living systems. The

Genomes to Life web site (http://doegenomestolife.org/) offers information about the program.

The U.S. Department of Energy Office of Science provides a look at the possible benefits and applications of future research in the article Fast Forward to 2020: What to Expect in Molecular Medicine (http://www.ornl.gov/hgmis/medicine/tnty.html).

What is pharmacogenomics?

Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.

Many drugs that are currently available are "one size fits all," but they don't work the same way for everyone. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects (called adverse drug reactions). Adverse drug reactions are a significant cause of hospitalizations and deaths in the United States. With the knowledge gained from the Human Genome Project, researchers are learning how inherited differences in genes affect the body's response to medications. These genetic differences will be used to predict whether a medication will be effective for a particular person and to help prevent adverse drug reactions.

The field of pharmacogenomics is still in its infancy. Its use is currently quite limited, but new approaches are under study in clinical trials. In the future, pharmacogenomics will allow the development of tailored drugs to treat a wide range of health problems, including cardiovascular disease, Alzheimer disease, cancer, HIV/AIDS, and asthma.

For more information about pharmacogenomics:

The U.S Department of Energy Office of Science offers a fact sheet on pharmacogenomics (http://www.ornl.gov/TechResources/Human_Genome/medicine/pharma.html). This resource outlines the anticipated benefits of this approach and lists barriers to progress.

The National Center for Biotechnology Information provides a discussion of this topic as part of its Science Primer: One Size Does Not Fit All: The Promise of Pharmacogenomics (http://www.ncbi.nlm.nih.gov/About/primer/pharm.html).

A list of clinical trials involving pharmacogenomics (http://clinicaltrials.gov/search/term=pharmacogenomics+OR+pharmacogenetics) is available from ClinicalTrials.gov, a service of the National Institutes of Health.

Genetics Home Reference
Your Guide to Understanding Genetic Conditions

http://ghr.nlm.nih.gov/

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services

Help Me Understand Genetics
Handbook

Chapter	Last Comprehensive Review
The Basics: Genes and How They Work	January 2003
Mutations and Genetic Disorders	January 2003
Inheriting Genetic Conditions	January 2003
Genetic Consultation	February 2003
Genetic Testing	February 2003
Gene Therapy	February 2003
The Human Genome Project and Genomic Research	March 2003

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