Genetics Home Reference

Help Me Understand Genetics

Reprinted from https://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

Published November 22, 2016

Table of Contents

Cells and DNA 4
Cells, genes, and chromosomes

Mutations and Health 19
Gene mutations, chromosomal changes, and conditions that run in families

How Genes Work 58
Proteins, cell growth, and cell division

Gene Families 78
Groups of genes that share important characteristics

Inheriting Genetic Conditions 102
Inheritance patterns and understanding risk

Genetics and Human Traits 130
How genes influence various human characteristics

Genetic Consultation 146
Finding and visiting a genetic counselor or other genetics professional

Genetic Testing 159
Benefits, costs, risks, and limitations of genetic testing

Newborn Screening 184
Testing all babies in their first days of life for certain disorders and conditions

Gene Therapy 192
Experimental techniques, safety, ethics, and availability

The Human Genome Project 200
Sequencing and understanding the human genome

Genomic Research 206
Next steps in studying the human genome

Precision Medicine 218
Disease treatment and prevention strategies tailored to variability in genes, environment, and lifestyle

Cells and DNA

Table of Contents

What is a cell? 5

What is DNA? 10

What is mitochondrial DNA? 13

What is a gene? 14

What is a chromosome? 16

How many chromosomes do people have? 18

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 (image on page 7)

Within cells, the cytoplasm is made up of a jelly-like fluid (called the cytosol) and other structures that surround the nucleus.

Cytoskeleton

The cytoskeleton is a network of long fibers that make up the cell's structural framework. The cytoskeleton has several critical functions, including determining cell shape, participating in cell division, and allowing cells to move. It also provides a track-like system that directs the movement of organelles and other substances within cells.

Endoplasmic reticulum (ER) (image on page 7)

This organelle helps process molecules created by the cell. The endoplasmic reticulum also transports these molecules to their specific destinations either inside or outside the cell.

Golgi apparatus (image on page 8)

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

Lysosomes and peroxisomes (image on page 8)

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 (image on page 8)

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 (image on page 9)

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 (image on page 9)

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 (image on page 9)

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:

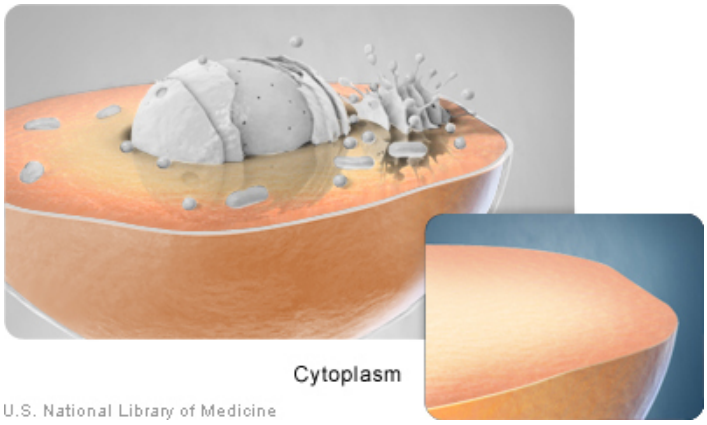
The Genetic Science Learning Center at the University of Utah offers an interactive introduction to cells (http://learn.genetics.utah.edu/content/cells/insideacell/) and their many functions.

Arizona State University's "Ask a Biologist" provides a description and illustration of each of the cell's organelles (http://askabiologist.asu.edu/content/cell-parts).

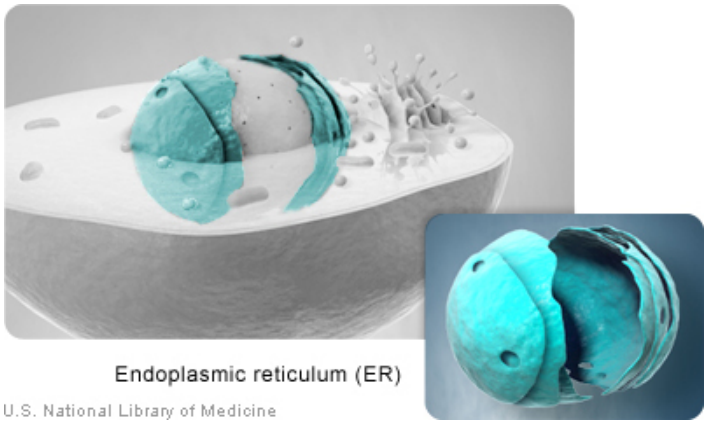
Queen Mary University of London allows you to explore a 3-D cell and its parts (https://www.centreofthecell.org/learn-play/games/explore-a-cell/).

Additional information about the cytoskeleton, including an illustration, is available from the Cytoplasm Tutorial (http://www.biology.arizona.edu/Cell_bio/tutorials/cytoskeleton/page1.html). This resource is part of The Biology Project at the University of Arizona.

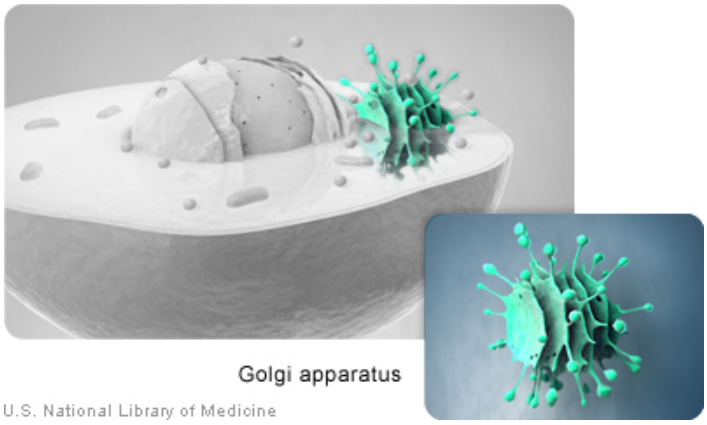
Images



The cytoplasm surrounds the cell's nucleus and organelles.



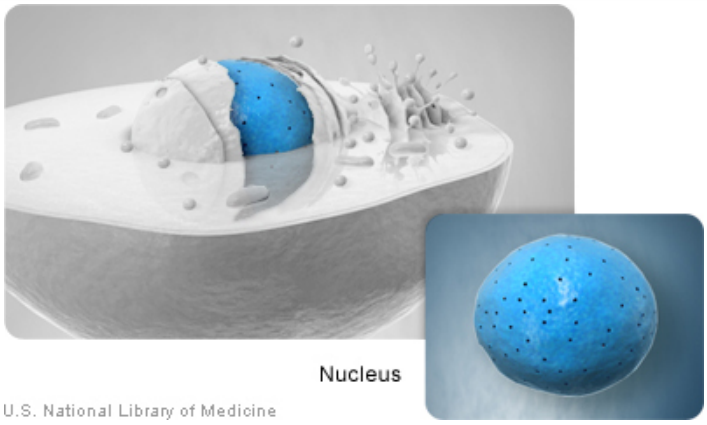
The endoplasmic reticulum is involved in molecule processing and transport.



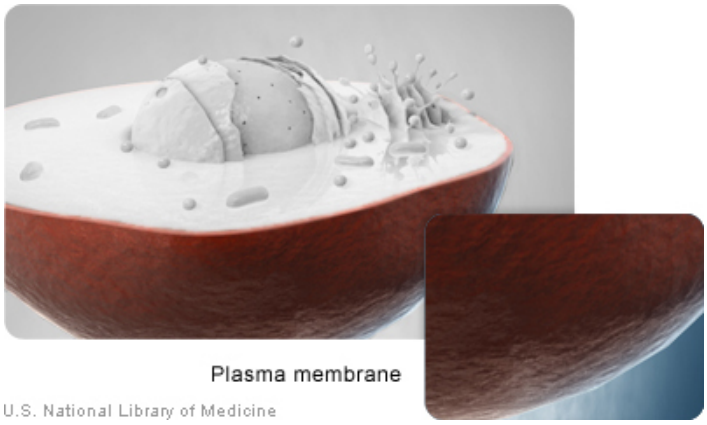
The Golgi apparatus is involved in packaging molecules for export from the cell.

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

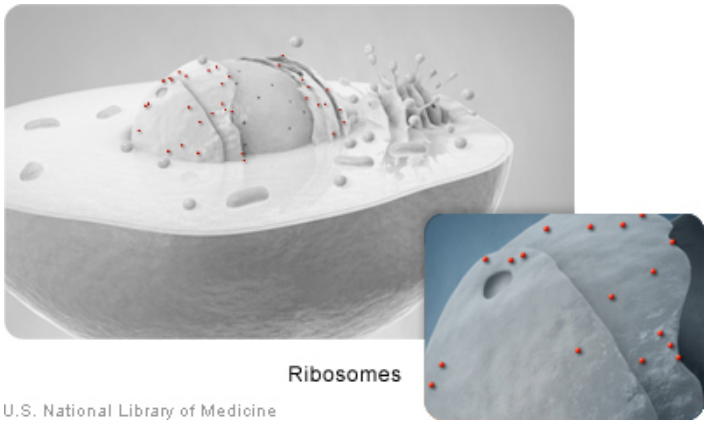
Mitochondria provide the cell's energy.



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.

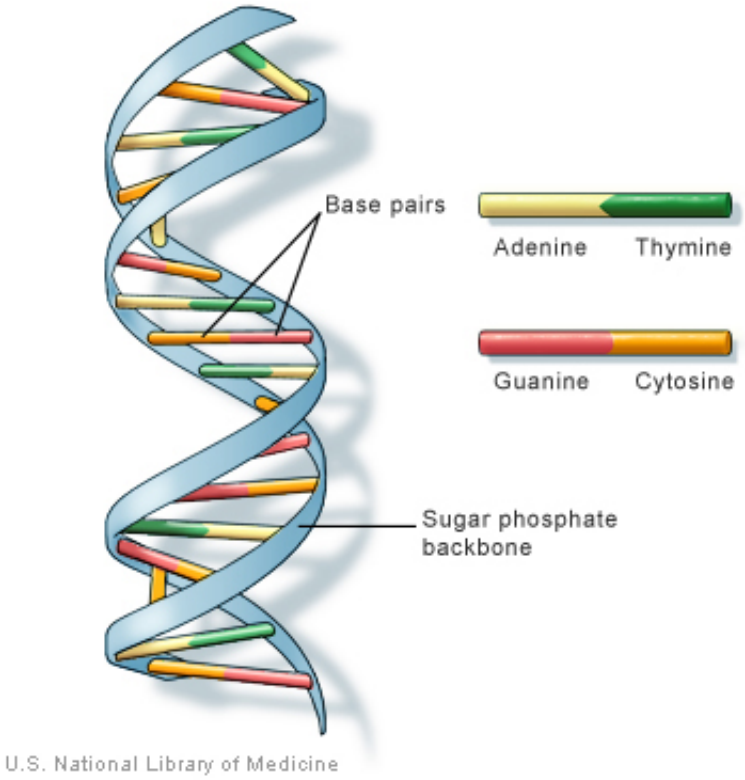
What is DNA?

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:

The National Human Genome Research Institute fact sheet Deoxyribonucleic Acid (DNA) (https://www.genome.gov/25520880) provides an introduction to this molecule.

Information about the genetic code (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=15&sid=19) and the structure of the DNA double helix (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=15&sid=16) is available from GeneEd.

The New Genetics, a publication of the National Institute of General Medical Sciences, discusses the structure of DNA and how it was discovered (https://publications.nigms.nih.gov/thenewgenetics/chapter1.html#c1).

A basic explanation and illustration of DNA (https://askabiologist.asu.edu/dna-shape-and-structure) can be found on Arizona State University's "Ask a Biologist" website.

The Virtual Genetics Education Centre, created by the University of Leicester, offers additional information on DNA, genes, and chromosomes (http://www2.le.ac.uk/departments/genetics/vgec/schoolscolleges/topics/dna-genes-chromosomes).

What is mitochondrial DNA?

Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA. This genetic material is known as mitochondrial DNA or mtDNA.

Mitochondria (image on page 8) are structures within cells that convert the energy from food into a form that cells can use. Each cell contains hundreds to thousands of mitochondria, which are located in the fluid that surrounds the nucleus (the cytoplasm).

Mitochondria produce energy through a process called oxidative phosphorylation. This process uses oxygen and simple sugars to create adenosine triphosphate (ATP), the cell's main energy source. A set of enzyme complexes, designated as complexes I-V, carry out oxidative phosphorylation within mitochondria.

In addition to energy production, mitochondria play a role in several other cellular activities. For example, mitochondria help regulate the self-destruction of cells (apoptosis). They are also necessary for the production of substances such as cholesterol and heme (a component of hemoglobin, the molecule that carries oxygen in the blood).

Mitochondrial DNA contains 37 genes, all of which are essential for normal mitochondrial function. Thirteen of these genes provide instructions for making enzymes involved in oxidative phosphorylation. The remaining genes provide instructions for making molecules called transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), which are chemical cousins of DNA. These types of RNA help assemble protein building blocks (amino acids) into functioning proteins.

For more information about mitochondria and mitochondrial DNA:

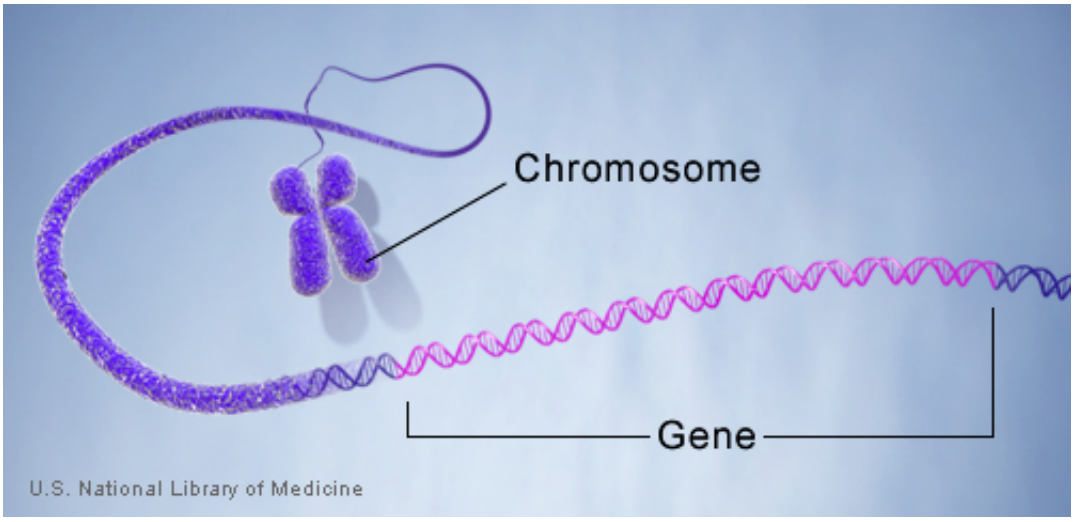
Molecular Expressions, a web site from the Florida State University Research Foundation, offers an illustrated introduction to mitochondria and mitochondrial DNA (http://micro.magnet.fsu.edu/cells/mitochondria/mitochondria.html).

An overview of mitochondrial DNA (http://neuromuscular.wustl.edu/mitosyn.html#general) is available from the Neuromuscular Disease Center at Washington University.

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 20,000 and 25,000 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 (https://ghr.nlm.nih.gov/gene) that include an explanation of each gene's normal function and how mutations in the gene cause particular genetic conditions.

The Centre for Genetics Education offers a fact sheet that introduces genes and chromosomes (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetDNAGenesChromosomes).

The Tech Museum of Innovation at Stanford University describes genes and how they were discovered (http://genetics.thetech.org/about-genetics/what-gene).

The Virtual Genetics Education Centre, created by the University of Leicester, offers additional information on DNA, genes, and chromosomes (http://

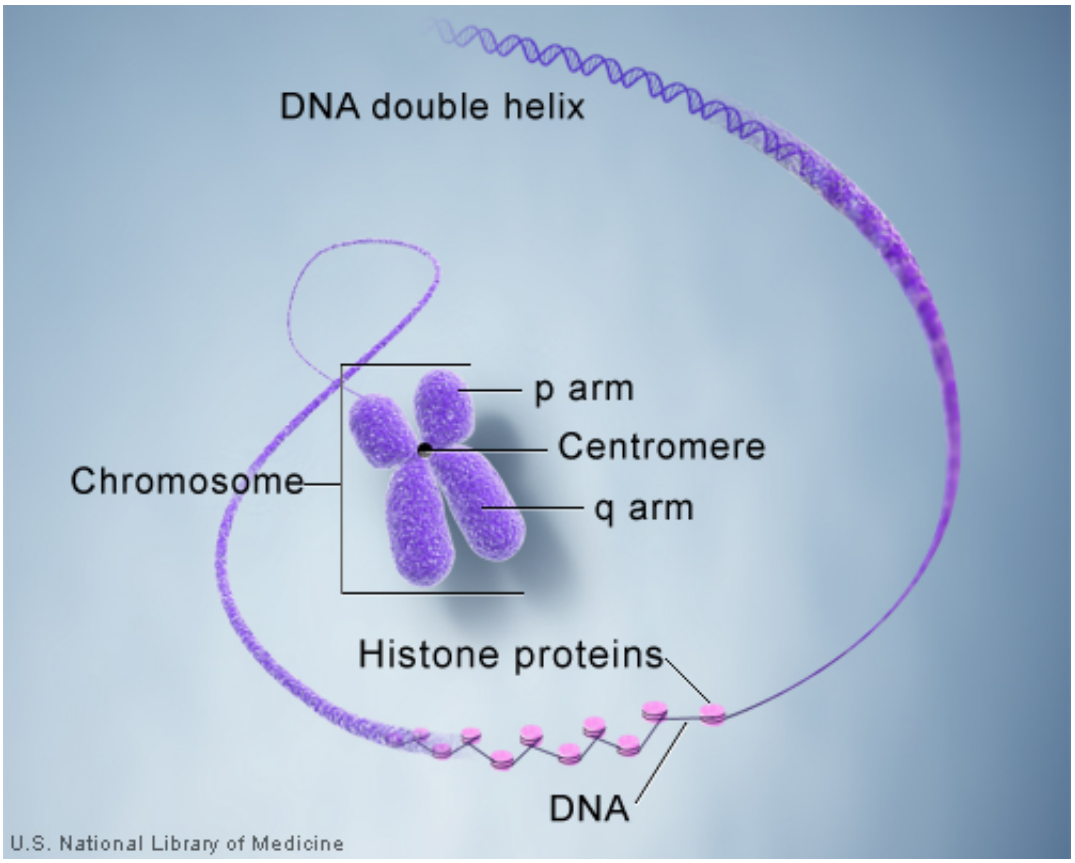
www2.le.ac.uk/departments/genetics/vgec/schoolscolleges/topics/dna-genes-chromosomes).

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 (https://ghr.nlm.nih.gov/chromosome) written in lay language.

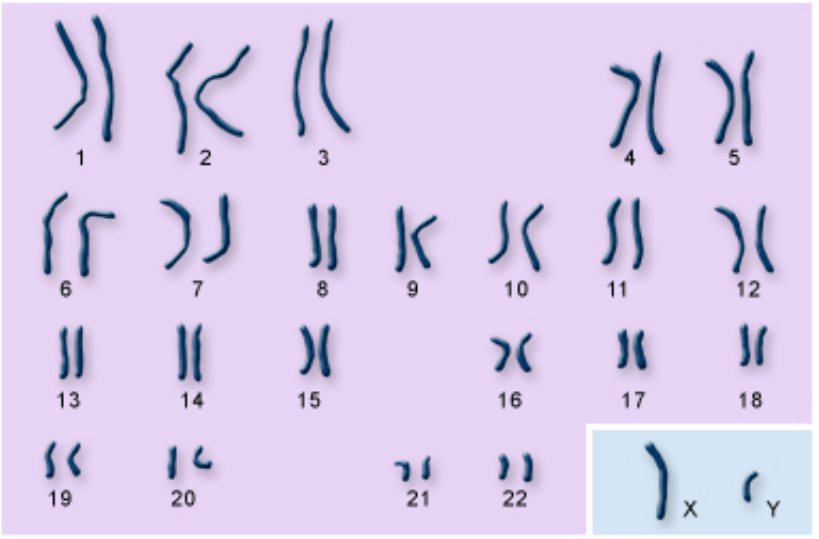
The Centre for Genetics Education offers a fact sheet that introduces genes and chromosomes (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheet1GenesandChromosomesTheGenome.pdf).

GeneEd also provides information about the basics of chromosomes (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=15&sid=17).

The University of Utah's Genetic Science Learning Center offers a description of chromosomes (http://learn.genetics.utah.edu/content/basics/readchromosomes/), including how scientists tell them apart.

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.



U.S. National Library of Medicine

The 22 autosomes are numbered by size. The other two chromosomes, X and Y, are the sex chromosomes. This picture of the human chromosomes lined up in pairs is called a karyotype.

For more information about the 23 pairs of human chromosomes:

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

The University of Utah's Genetic Science Learning Center discusses how karyotypes can be used in diagnosing genetic disorders (http://learn.genetics.utah.edu/content/basics/diagnose/).

Arizona State University's "Ask a Biologist" discusses the inheritance of human chromosomes. (http://askabiologist.asu.edu/chromosomes-and-genes)

Mutations and Health

Table of Contents

What is a gene mutation and how do mutations occur? 20

How can gene mutations affect health and development? 22

Do all gene mutations affect health and development? 23

What kinds of gene mutations are possible? 24

Can a change in the number of genes affect health and development? 30

Can changes in the number of chromosomes affect health and development? 31

Can changes in the structure of chromosomes affect health and development? 38

Can changes in mitochondrial DNA affect health and development? 49

What are complex or multifactorial disorders? 51

What does it mean to have a genetic predisposition to a disease? 52

What information about a genetic condition can statistics provide? 54

How are genetic conditions and genes named? 56

What is a gene mutation and how do mutations occur?

A gene mutation is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. Mutations range in size; they can affect anywhere from a single DNA building block (base pair) to a large segment of a chromosome that includes multiple genes.

Gene mutations can be classified in two major ways:

- Hereditary mutations are inherited from a parent and are present throughout a person's life in virtually every cell in the body. These mutations are also called germline mutations because they are present in the parent's egg or sperm cells, which are also called germ cells. When an egg and a sperm cell unite, the resulting fertilized egg cell receives DNA from both parents. If this DNA has a mutation, the child that grows from the fertilized egg will have the mutation in each of his or her cells.
- Acquired (or somatic) mutations occur at some time during a person's life and are present only in certain cells, not in every cell in the body. 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.

Genetic changes that are described as de novo (new) mutations can be either hereditary or somatic. In some cases, the mutation occurs in a person's egg or sperm cell but is not present in any of the person's other cells. In other cases, the mutation occurs in the fertilized egg shortly after the egg and sperm cells unite. (It is often impossible to tell exactly when a de novo mutation happened.) As the fertilized egg divides, each resulting cell in the growing embryo will have the mutation. De novo mutations may explain genetic disorders in which an affected child has a mutation in every cell in the body but the parents do not, and there is no family history of the disorder.

Somatic mutations that happen in a single cell early in embryonic development can lead to a situation called mosaicism. These genetic changes are not present in a parent's egg or sperm cells, or in the fertilized egg, but happen a bit later when the embryo includes several cells. As all the cells divide during growth and development, cells that arise from the cell with the altered gene will have the mutation, while other cells will not. Depending on the mutation and how many cells are affected, mosaicism may or may not cause health problems.

Most disease-causing gene mutations are uncommon in the general population. However, other genetic changes occur more frequently. Genetic alterations that occur in more than 1 percent of the population are called polymorphisms. They are common enough to be considered a normal variation in the DNA. Polymorphisms are responsible for many of the normal differences between people such as eye color, hair color, and blood type. Although many polymorphisms have no negative effects on a person’s health, some of these variations may influence the risk of developing certain disorders.

For more information about mutations:

The Centre for Genetics Education provides a fact sheet discussing variations in the genetic code (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetVariationsinCode).

More basic information about genetic mutations (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=142&sid=145) is available from GeneEd.

Additional information about genetic alterations is available from the University of Utah fact sheet "What is Mutation?" (http://learn.genetics.utah.edu/content/basics/mutation/)

How can gene mutations affect health and development?

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, it can disrupt normal development or cause a medical condition. A condition caused by mutations in one or more genes is called a genetic disorder.

In some cases, gene mutations are so severe that they prevent an embryo from surviving until birth. These changes occur in genes that are essential for development, and often disrupt the development of an embryo in its earliest stages. Because these mutations have very serious effects, they are incompatible with life.

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 Centre for Genetics Education offers a fact sheet about genetic changes that lead to disorders (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetMutations).

The Tech Museum of Innovation offers a brief overview of genetic mutations and disease (http://genetics.thetech.org/about-genetics/mutations-and-disease).

Do all gene mutations affect health and development?

No; only a small percentage of mutations cause genetic disorders—most have no impact on health or development. For example, some mutations alter a gene's DNA sequence but do not 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 and an altered protein is produced. 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, DNA repair is an important process by 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 individual better adapt to changes in his or her environment. For example, a beneficial mutation could result in a protein that protects an individual and future generations from a new strain of bacteria.

Because a person's genetic code can have a large number of mutations with no effect on health, diagnosing genetic conditions can be difficult. Sometimes, genes thought to be related to a particular genetic condition have mutations, but whether these changes are involved in development of the condition has not been determined; these genetic changes are known as variants of unknown significance (VOUS). Sometimes, no mutations are found in suspected disease-related genes, but mutations are found in other genes whose relationship to a particular genetic condition is unknown. It is difficult to know whether these variants are involved in the disease.

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

The University of Utah Genetic Science Learning Center provides information about genetic disorders (http://learn.genetics.utah.edu/content/disorders/) that explains why some mutations cause disorders but others do not.

The National Coalition for Health Professional Education in Genetics explains how mutations can be harmful, neutral, or beneficial (http://www.nchpeg.org/dentistry/index.php?option=com_content&view=article&id=22&Itemid=55&limitstart=3).

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 (image on page 26)

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 (image on page 26)

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 (image on page 27)

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 (image on page 27)

A deletion changes the number of DNA bases by removing a piece of DNA. Small deletions may remove one or a few base pairs within a gene, while larger deletions can remove an entire gene or several neighboring genes. The deleted DNA may alter the function of the resulting protein(s).

Duplication (image on page 28)

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 (image on page 28)

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 (image on page 29)

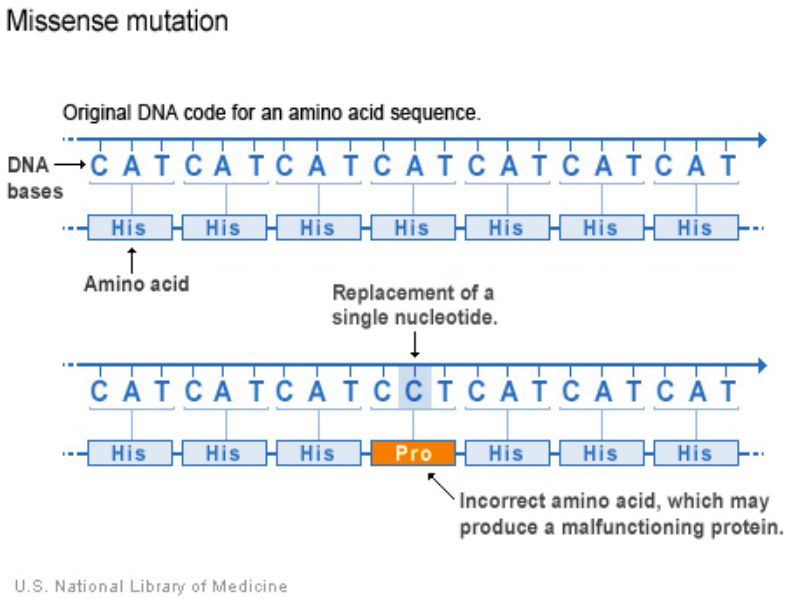
Nucleotide repeats are short DNA sequences that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of 3-base-pair sequences, and a tetranucleotide repeat is made up of 4-base-pair sequences. A repeat expansion is a mutation that increases the number of times that 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:

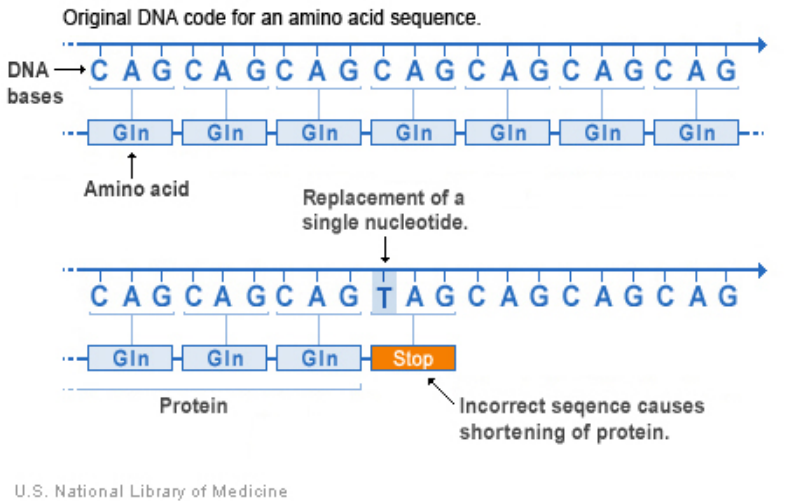
The National Human Genome Research Institute offers a Talking Glossary of Genetic Terms (https://www.genome.gov/glossary/). This resource includes definitions, diagrams, and detailed audio descriptions of several of the gene mutations listed above.

A brief explanation of different mutation types (http://www.yourgenome.org/facts/what-types-of-mutation-are-there) is available from yourgenome.org.

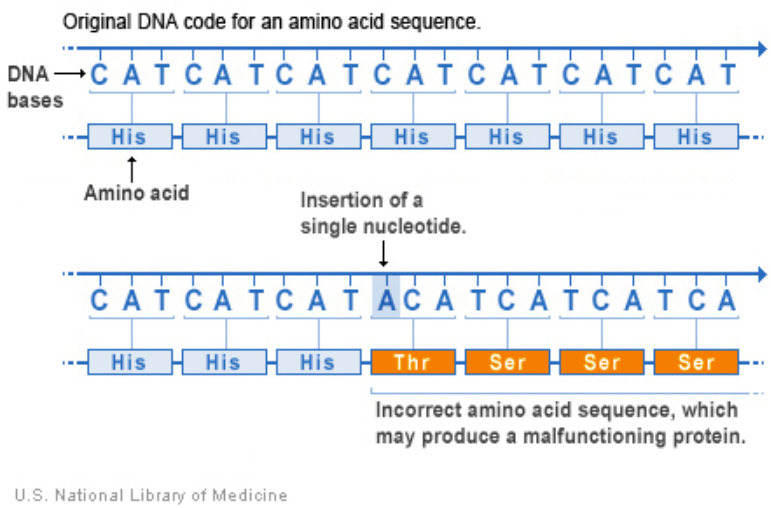
Images



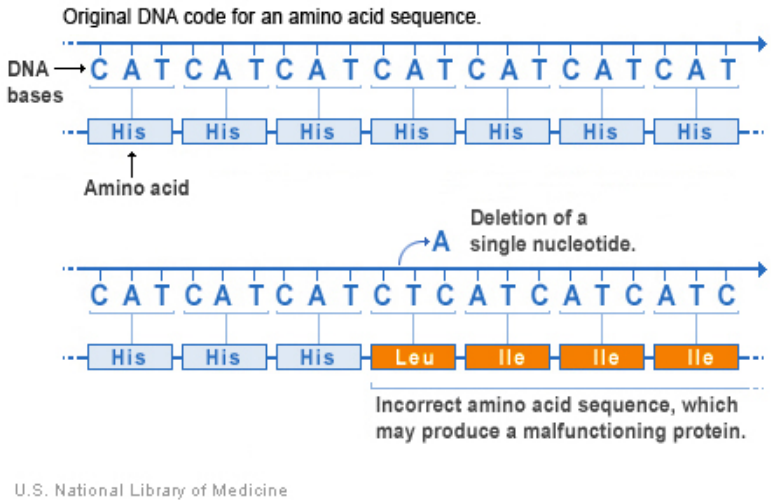
In this example, the nucleotide adenine is replaced by cytosine in the genetic code, introducing an incorrect amino acid into the protein sequence.



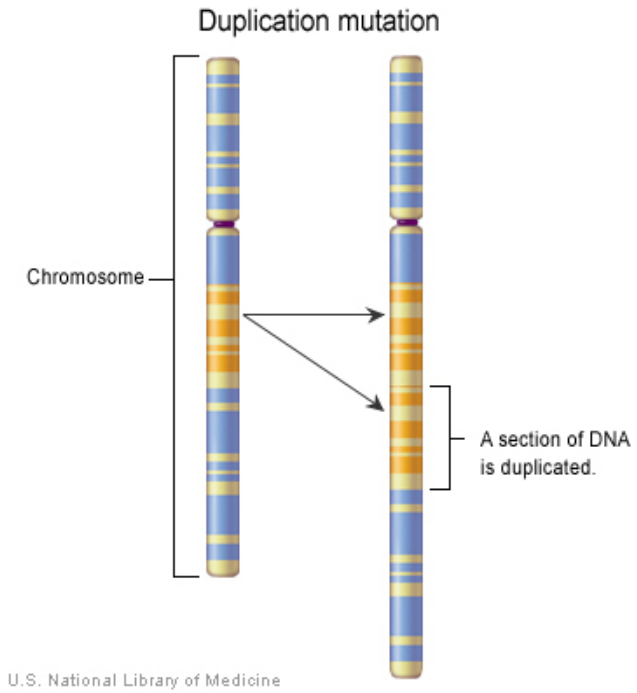
In this example, the nucleotide cytosine is replaced by thymine in the DNA code, signaling the cell to shorten the protein.



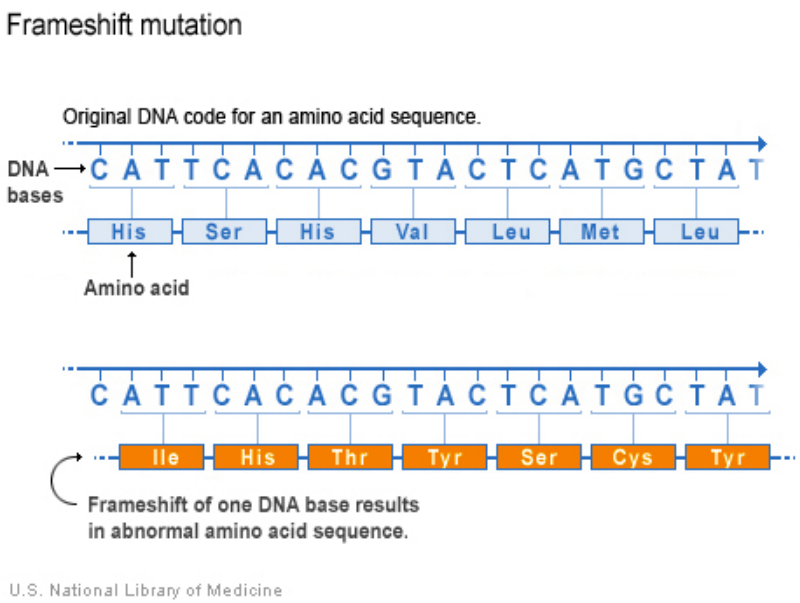
In this example, one nucleotide (adenine) is added in the DNA code, changing the amino acid sequence that follows.



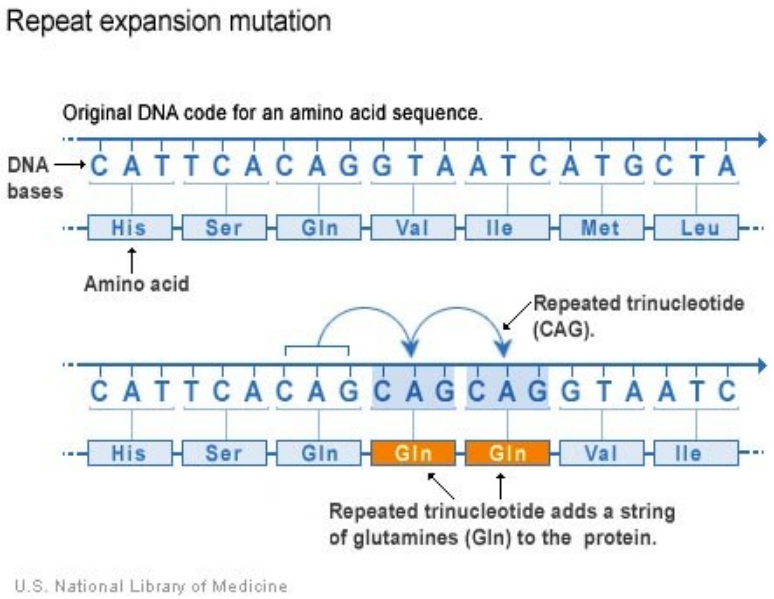
In this example, one nucleotide (adenine) is deleted from the DNA code, changing the amino acid sequence that follows.



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 a change in the number of genes affect health and development?

People have two copies of most genes, one copy inherited from each parent. In some cases, however, the number of copies varies—meaning that a person can be born with one, three, or more copies of particular genes. Less commonly, one or more genes may be entirely missing. This type of genetic difference is known as copy number variation (CNV).

Copy number variation results from insertions, deletions, and duplications of large segments of DNA. These segments are big enough to include whole genes. Variation in gene copy number can influence the activity of genes and ultimately affect many body functions.

Researchers were surprised to learn that copy number variation accounts for a significant amount of genetic difference between people. More than 10 percent of human DNA appears to contain these differences in gene copy number. While much of this variation does not affect health or development, some differences likely influence a person's risk of disease and response to certain drugs. Future research will focus on the consequences of copy number variation in different parts of the genome and study the contribution of these variations to many types of disease.

For more information about copy number variation:

The Howard Hughes Medical Institute discusses the results of recent research on copy number variation in the news release, Genetic Variation: We're More Different Than We Thought (http://www.hhmi.org/news/genetic-variation-were-more-different-we-thought).

More information about copy number variation (https://www.dnalc.org/view/552-Copy-Number-Variants.html) is available in a video from Cold Spring Harbor Laboratory.

For people interested in more technical data, several institutions provide databases of structural differences in human DNA, including copy number variation:

- Database of Genomic Variants (http://dgv.tcag.ca/dgv/app/home)
- The Sanger Institute: Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER (https://decipher.sanger.ac.uk/))

Can changes in the number of chromosomes affect health and development?

Human cells normally contain 23 pairs of chromosomes, for a total of 46 chromosomes in each cell (image on page 33). A change in the number of chromosomes can cause problems with growth, development, and function of the body's systems. These changes can occur during the formation of reproductive cells (eggs and sperm), in early fetal development, or in any cell after birth. A gain or loss of chromosomes from the normal 46 is called aneuploidy.

A common form of aneuploidy is trisomy, or the presence of an extra chromosome in cells. "Tri-" is Greek for "three"; people with trisomy have three copies of a particular chromosome in cells instead of the normal two copies. Down syndrome is an example of a condition caused by trisomy (image on page 34). 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 in cells, is another kind of aneuploidy. "Mono-" is Greek for "one"; people with monosomy have one copy of a particular chromosome in cells instead of the normal two copies. Turner syndrome is a condition caused by monosomy (image on page 35). Women with Turner syndrome usually have only one copy of the X chromosome in every cell, for a total of 45 chromosomes per cell.

Rarely, some cells end up with complete extra sets of chromosomes. Cells with one additional set of chromosomes, for a total of 69 chromosomes, are called triploid (image on page 36). Cells with two additional sets of chromosomes, for a total of 92 chromosomes, are called tetraploid. A condition in which every cell in the body has an extra set of chromosomes is not compatible with life.

In some cases, a change in the number of chromosomes occurs only in certain cells. When an individual has two or more cell populations with a different chromosomal makeup, this situation is called chromosomal mosaicism (image on page 37). Chromosomal mosaicism occurs from an error in cell division in cells other than eggs and sperm. Most commonly, some cells end up with one extra or missing chromosome (for a total of 45 or 47 chromosomes per cell), while other cells have the usual 46 chromosomes. Mosaic Turner syndrome is one example of chromosomal mosaicism. In females with this condition, some cells have 45 chromosomes because they are missing one copy of the X chromosome, while other cells have the usual number of chromosomes.

Many cancer cells also have changes in their number of chromosomes. These changes are not inherited; they occur in somatic cells (cells other than eggs or sperm) during the formation or progression of a cancerous tumor.

For more information about chromosomal disorders:

A discussion of how chromosomal abnormalities happen (https://www.genome.gov/11508982#6) is provided by the National Human Genome Research Institute.

The Centre for Genetics Education offers a fact sheet about changes in chromosome number or size (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetChromosomeChanges).

Information about chromosomal changes (http://www.eurogentest.org/index.php?id=611), including changes in the number of chromosomes, is available from EuroGentest.

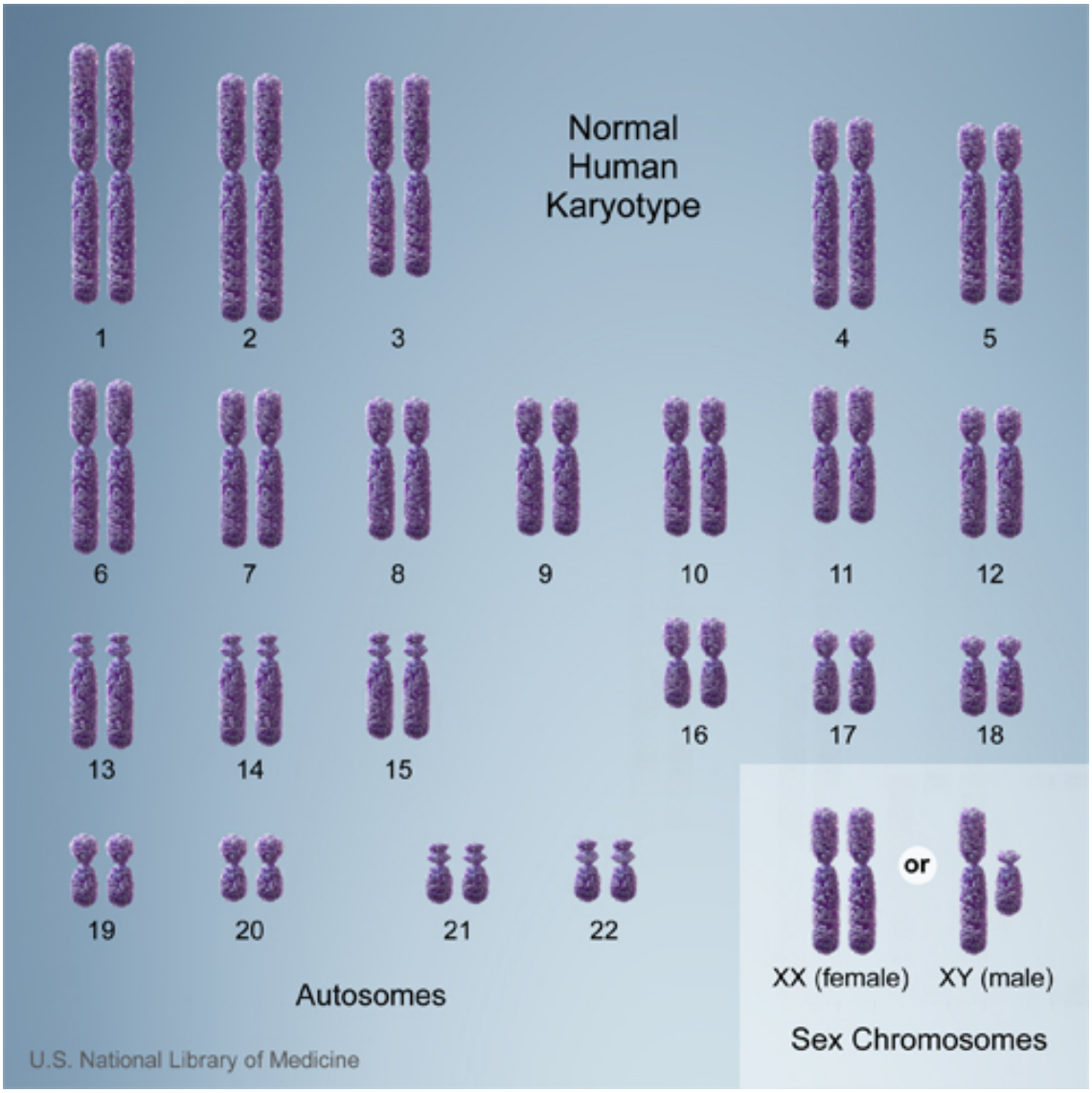
The University of Leicester's Virtual Genetics Education Center provides an explanation of numerical chromosome aberrations (http://www2.le.ac.uk/departments/genetics/vgec/healthprof/topics/patterns-of-inheritance/chromosomal-abnormalities#numerical-aberrations).

The National Organization for Rare Disorders offers an overview of triploidy (http://rarediseases.org/rare-diseases/triploidy/).

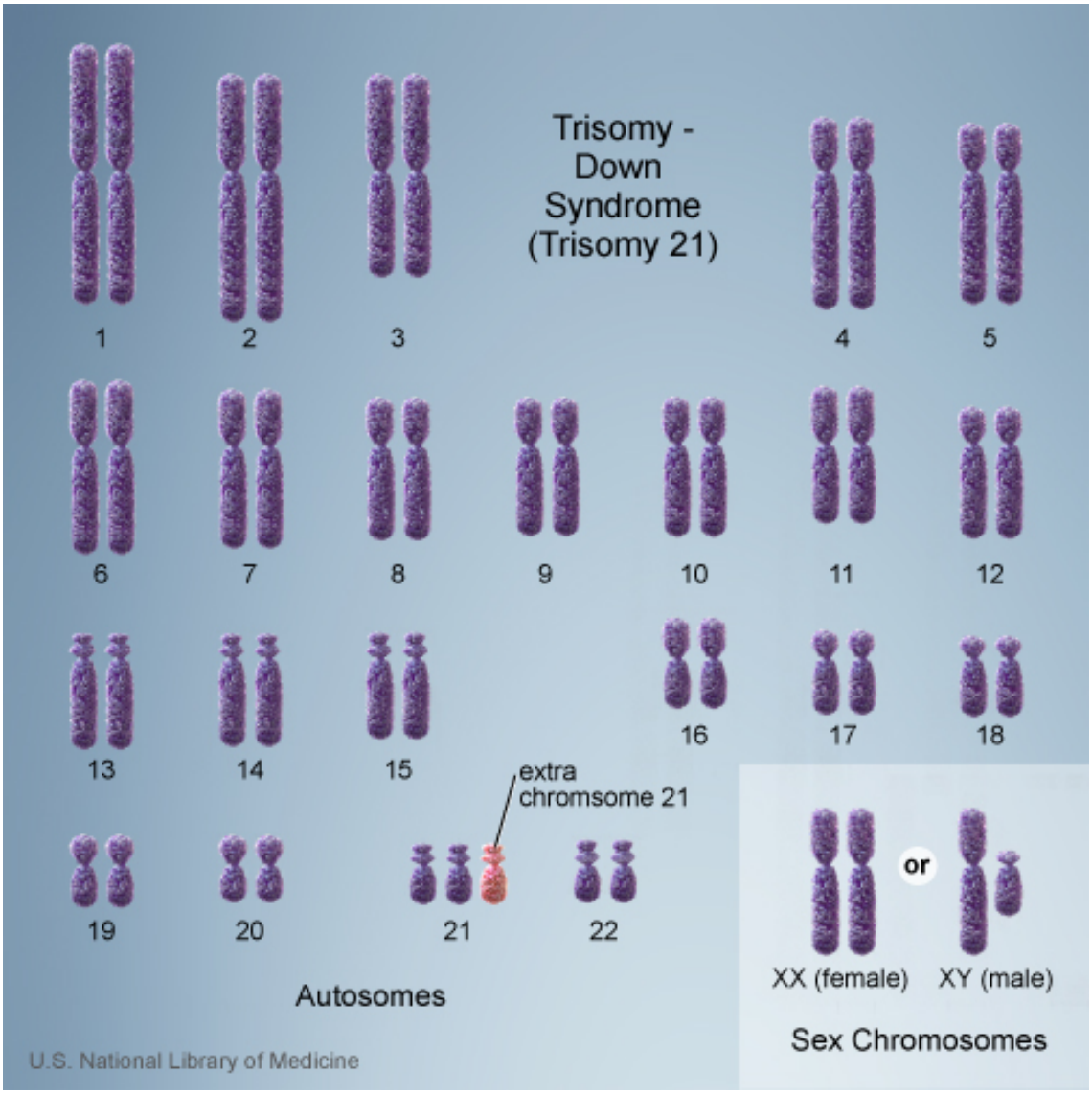
Chromosomal Mosaicism (http://mosaicism.cfri.ca/index.htm), a web site provided by the University of British Columbia, offers detailed information about mosaic chromosomal abnormalities.

MedlinePlus offers an encyclopedia article about chromosomal mosaicism (https://medlineplus.gov/ency/article/001317.htm).

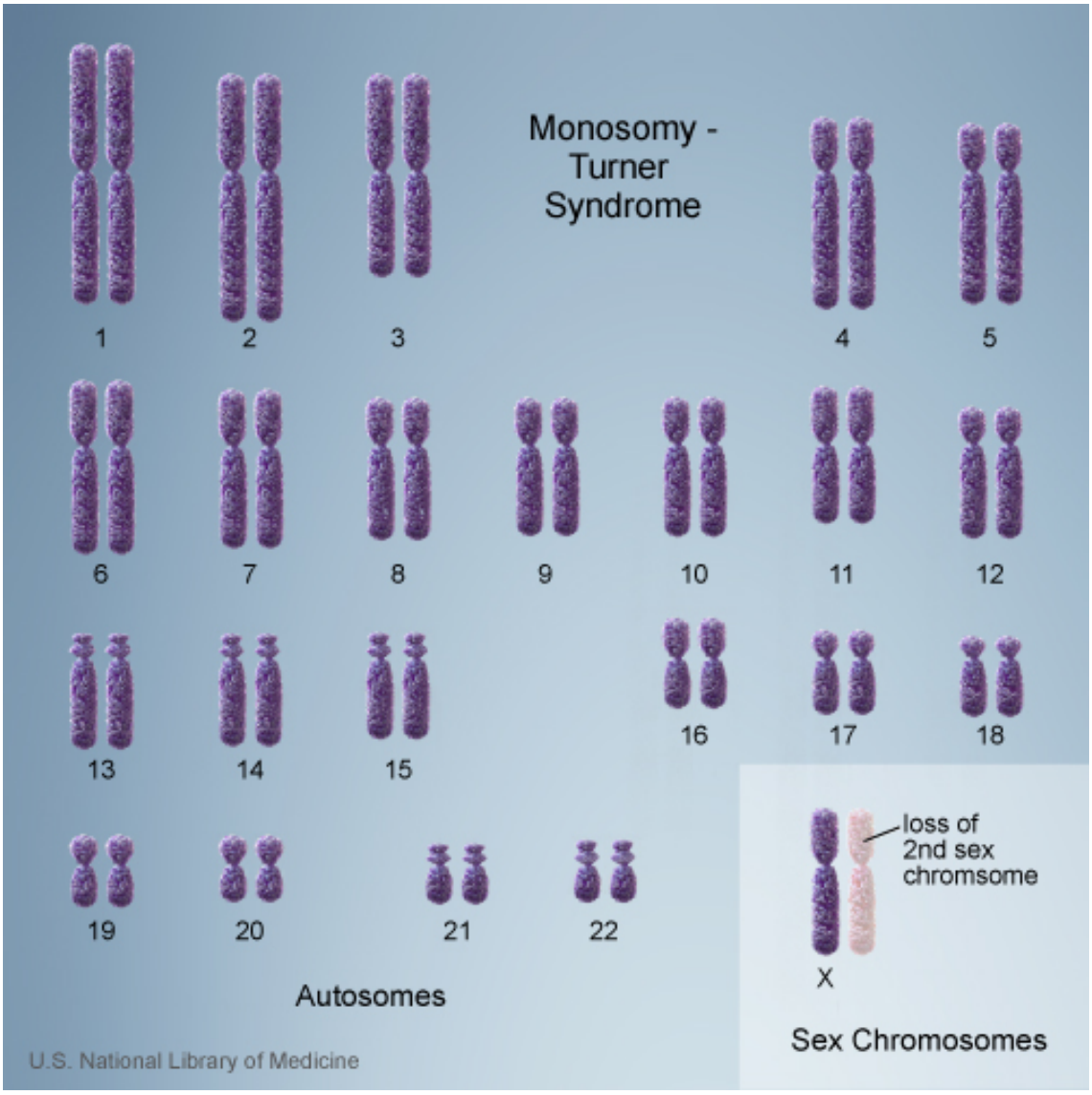
Images



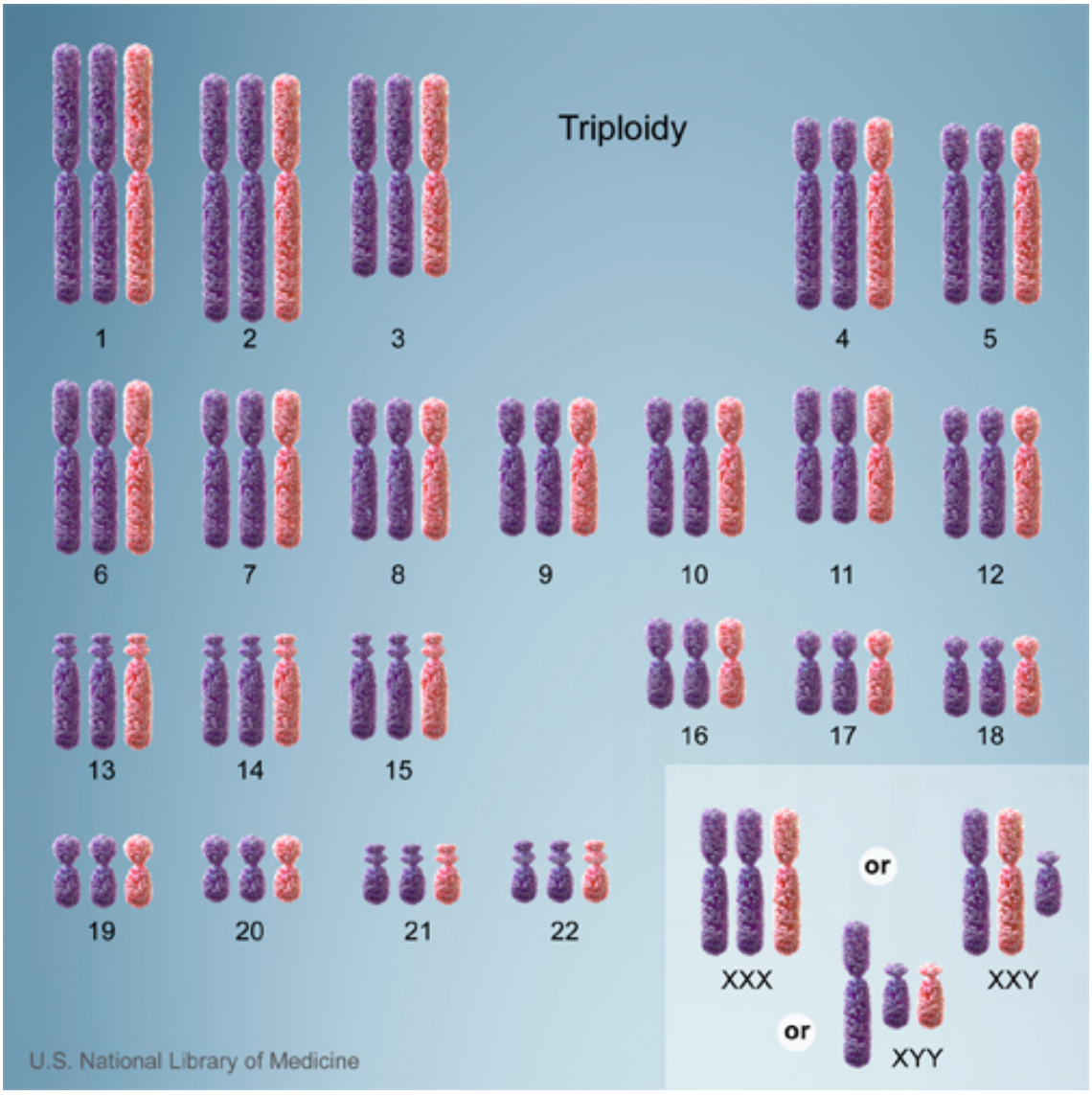
Human cells normally contain 23 pairs of chromosomes,
for a total of 46 chromosomes in each cell.



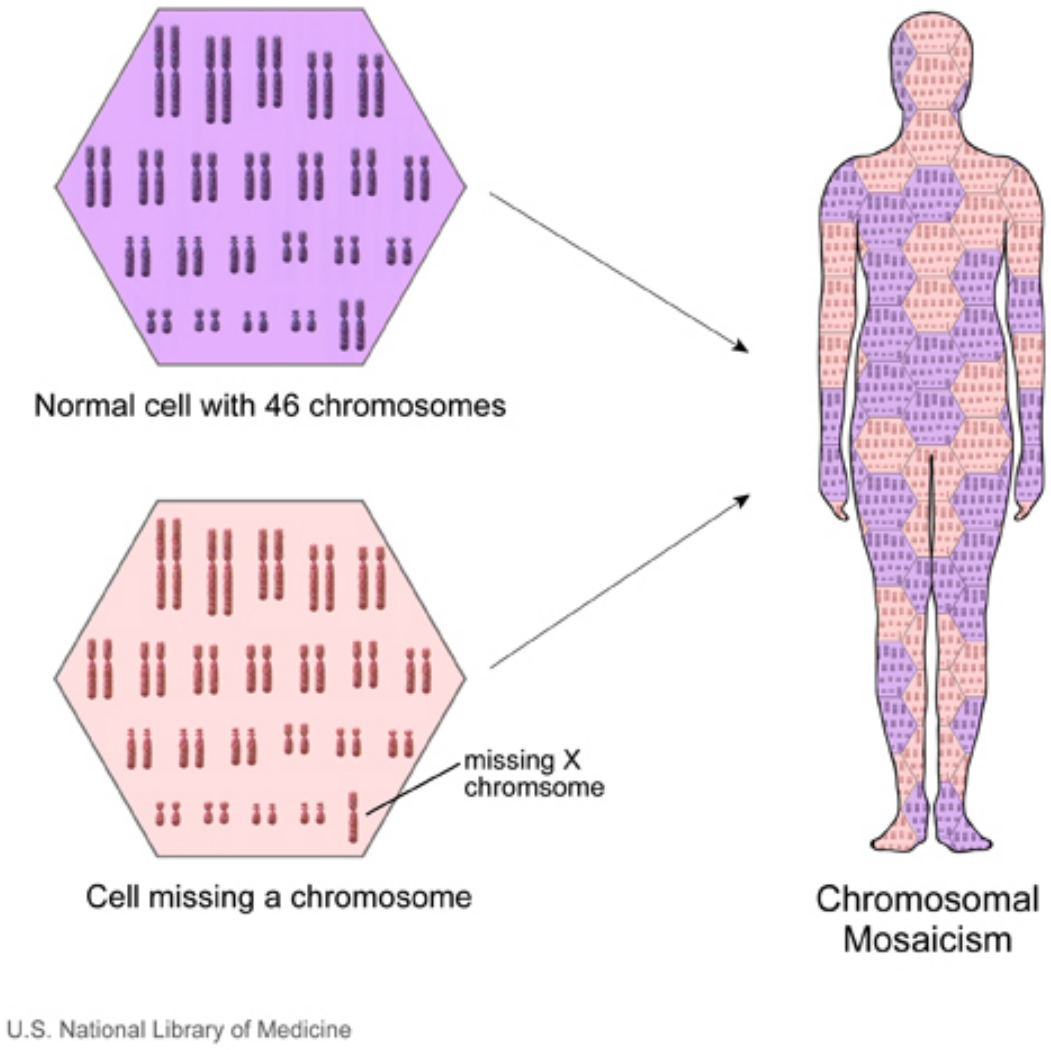
Trisomy is the presence of an extra chromosome in cells. Down syndrome is an example of a condition caused by trisomy.



Monosomy is the loss of one chromosome in cells. Turner syndrome is an example of a condition caused by monosomy.



Cells with one additional set of chromosomes,
for a total of 69 chromosomes, are called triploid.



When an individual has two or more cell populations with a different chromosomal makeup, this situation is called chromosomal mosaicism.

Can changes in the structure of chromosomes affect health and development?

Changes that affect the structure 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 disrupt the proteins made from those genes.

Structural changes can occur during the formation of egg or sperm cells, in early fetal development, or in any cell after birth. 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, and whether any genetic material is gained or lost. Some changes cause medical problems, while others may have no effect on a person's health.

Changes in chromosome structure include:

Translocations (image on page 41)**,** (image on page 42)

A translocation occurs when a piece of one chromosome breaks off and attaches to another chromosome. This type of rearrangement is described as balanced if no genetic material is gained or lost in the cell. If there is a gain or loss of genetic material, the translocation is described as unbalanced.

Deletions (image on page 43)

Deletions occur when a chromosome breaks and some genetic material is lost. Deletions can be large or small, and can occur anywhere along a chromosome.

Duplications (image on page 44)

Duplications occur when part of a chromosome is copied (duplicated) too many times. This type of chromosomal change results in extra copies of genetic material from the duplicated segment.

Inversions (image on page 45)

An inversion involves the breakage of a chromosome in two places; the resulting piece of DNA is reversed and re-inserted into the chromosome. Genetic material may or may not be lost as a result of the chromosome breaks. An inversion that involves the chromosome's constriction point (centromere) is called a pericentric inversion. An inversion that occurs in the long (q) arm or short (p) arm and does not involve the centromere is called a paracentric inversion.

Isochromosomes (image on page 46)

An isochromosome is a chromosome with two identical arms. Instead of one long (q) arm and one short (p) arm, an isochromosome has two long arms or two short arms. As a result, these abnormal chromosomes have an extra copy of some genes and are missing copies of other genes.

Dicentric chromosomes (image on page 47)

Unlike normal chromosomes, which have a single constriction point (centromere), a dicentric chromosome contains two centromeres. Dicentric chromosomes result from the abnormal fusion of two chromosome pieces, each of which includes a centromere. These structures are unstable and often involve a loss of some genetic material.

Ring chromosomes (image on page 48)

Ring chromosomes usually occur when a chromosome breaks in two places and the ends of the chromosome arms fuse together to form a circular structure. The ring may or may not include the chromosome's constriction point (centromere). In many cases, genetic material near the ends of the chromosome is lost.

Many cancer cells also have changes in their chromosome structure. These changes are not inherited; they occur in somatic cells (cells other than eggs or sperm) during the formation or progression of a cancerous tumor.

For more information about structural changes to chromosomes:

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

Chromosome Deletion Outreach offers a fact sheet on this topic titled Introduction to Chromosomes (http://chromodisorder.org/Display.aspx?ID=35). This resource includes illustrated explanations of several chromosome abnormalities.

The Centre for Genetics Education provides a fact sheet about chromosome changes (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FS4).

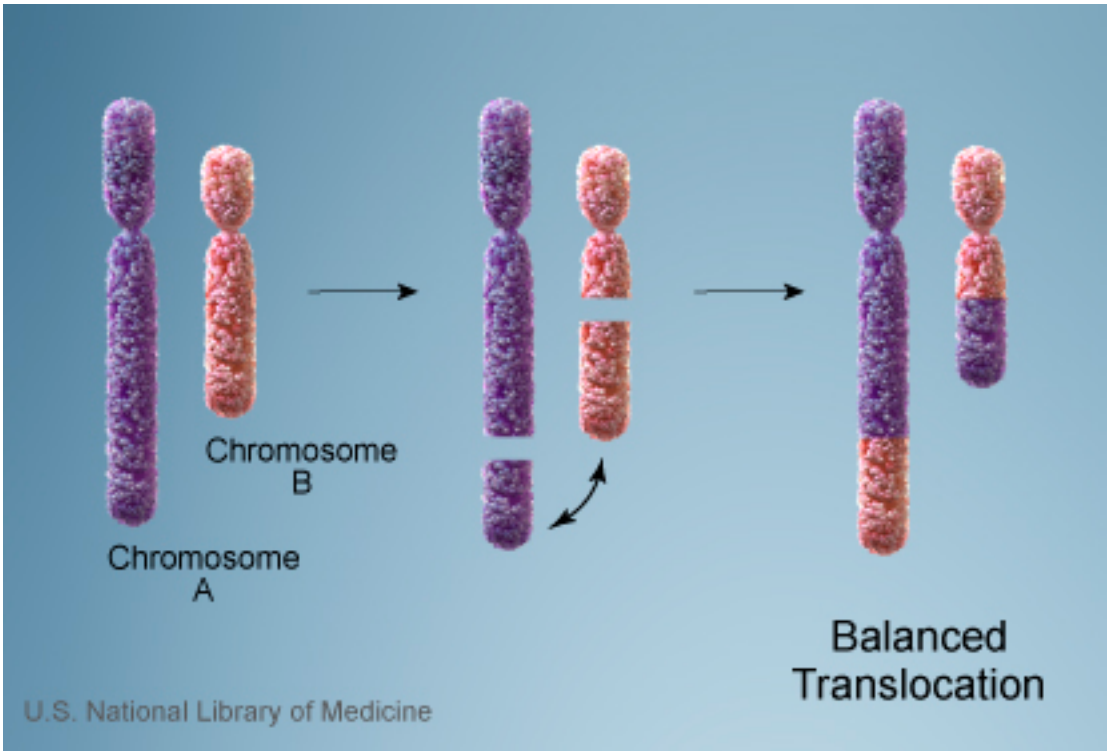
EuroGentest offers fact sheets about chromosome changes (http://www.eurogentest.org/index.php?id=611) and chromosome translocations (http://www.eurogentest.org/index.php?id=612).

The University of Leicester's Virtual Genetics Education Center provides an explanation of structural chromosome aberrations (http://www2.le.ac.uk/

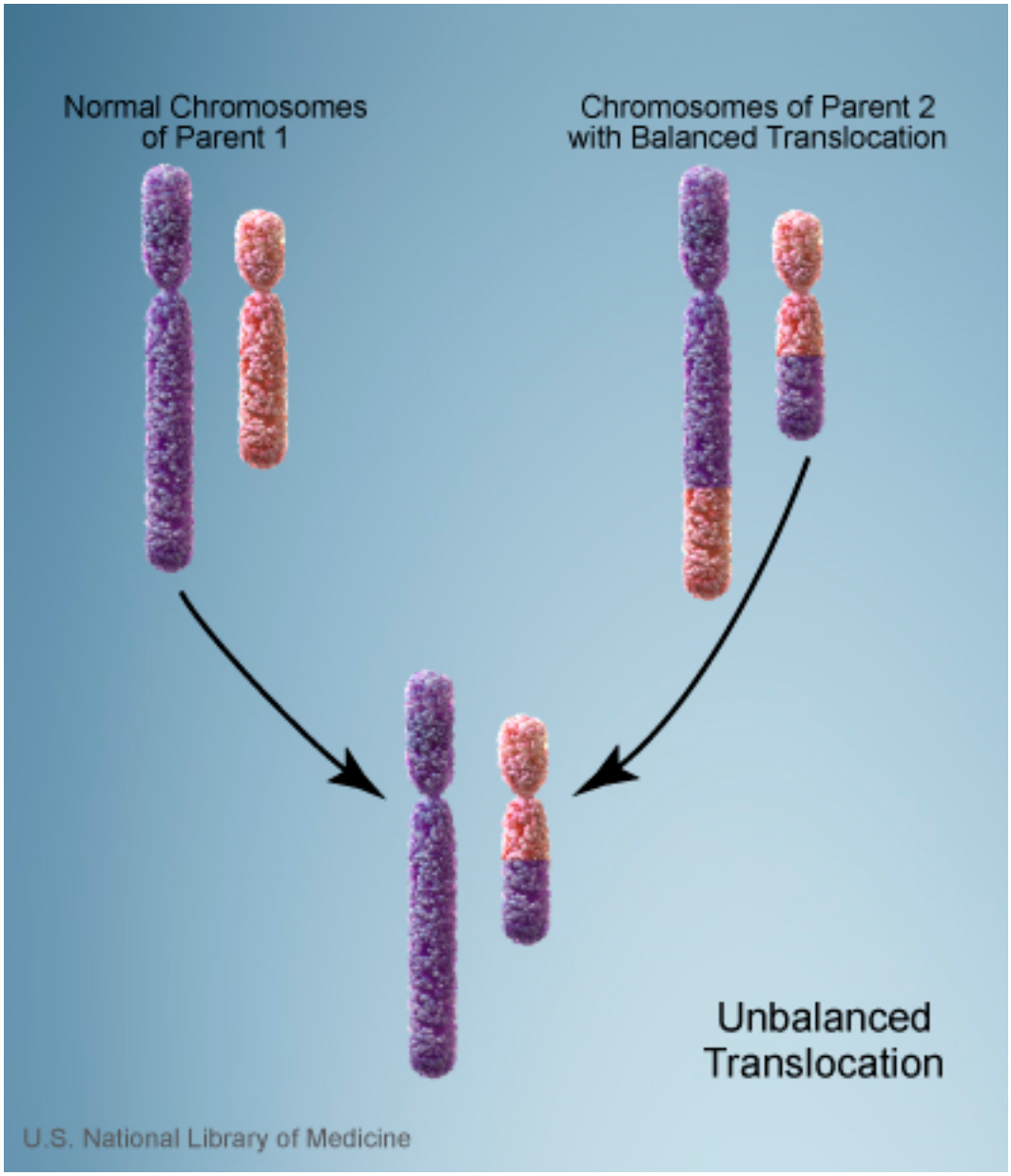
departments/genetics/vgec/healthprof/topics/patterns-of-inheritance/chromosomal-abnormalities#structural-aberrations).

The Atlas of Genetics and Cytogenetics in Oncology and Haematology provides a technical introduction to chromosomal aberrations (http://atlasgeneticsoncology.org/Deep/Chromaber.html) and a detailed discussion of ring chromosomes (http://atlasgeneticsoncology.org/Deep/RingChromosID20030.html), particularly their role in cancer.

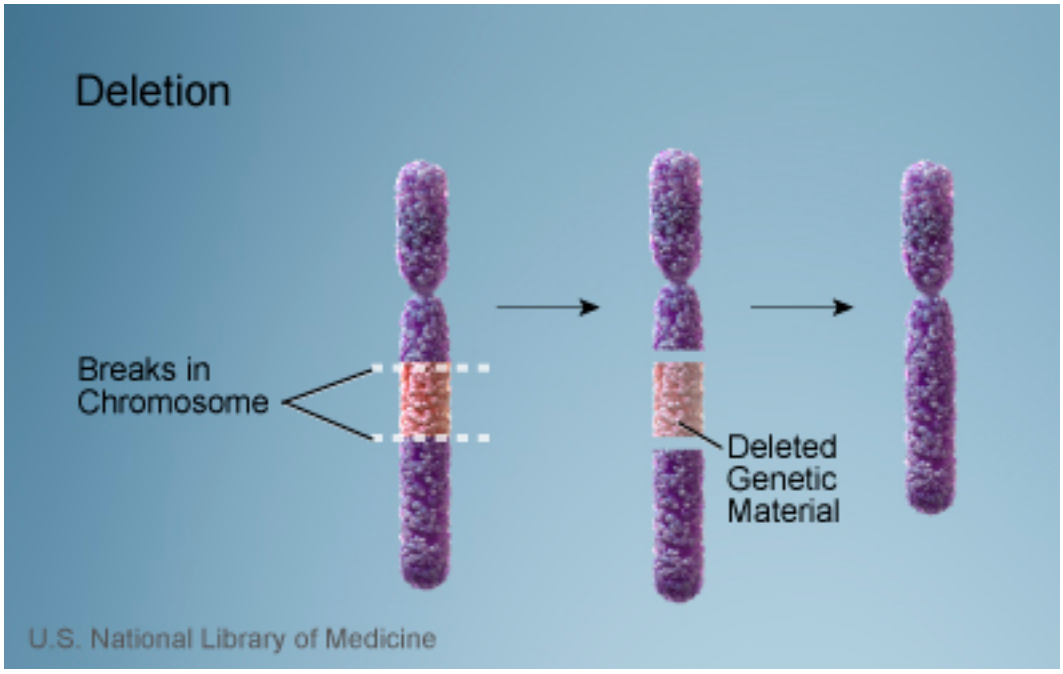
Images



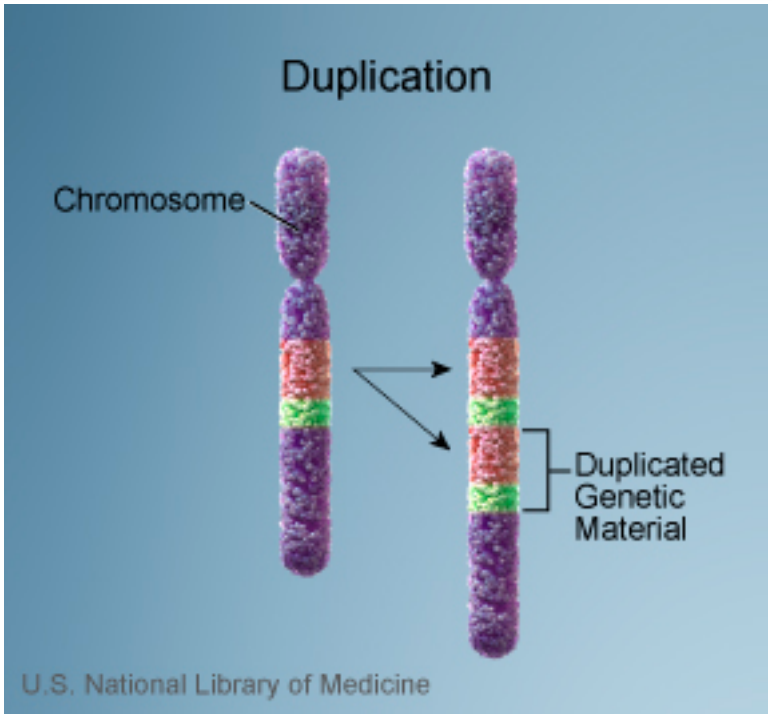
In a balanced translocation, pieces of chromosomes are rearranged but no genetic material is gained or lost in the cell.



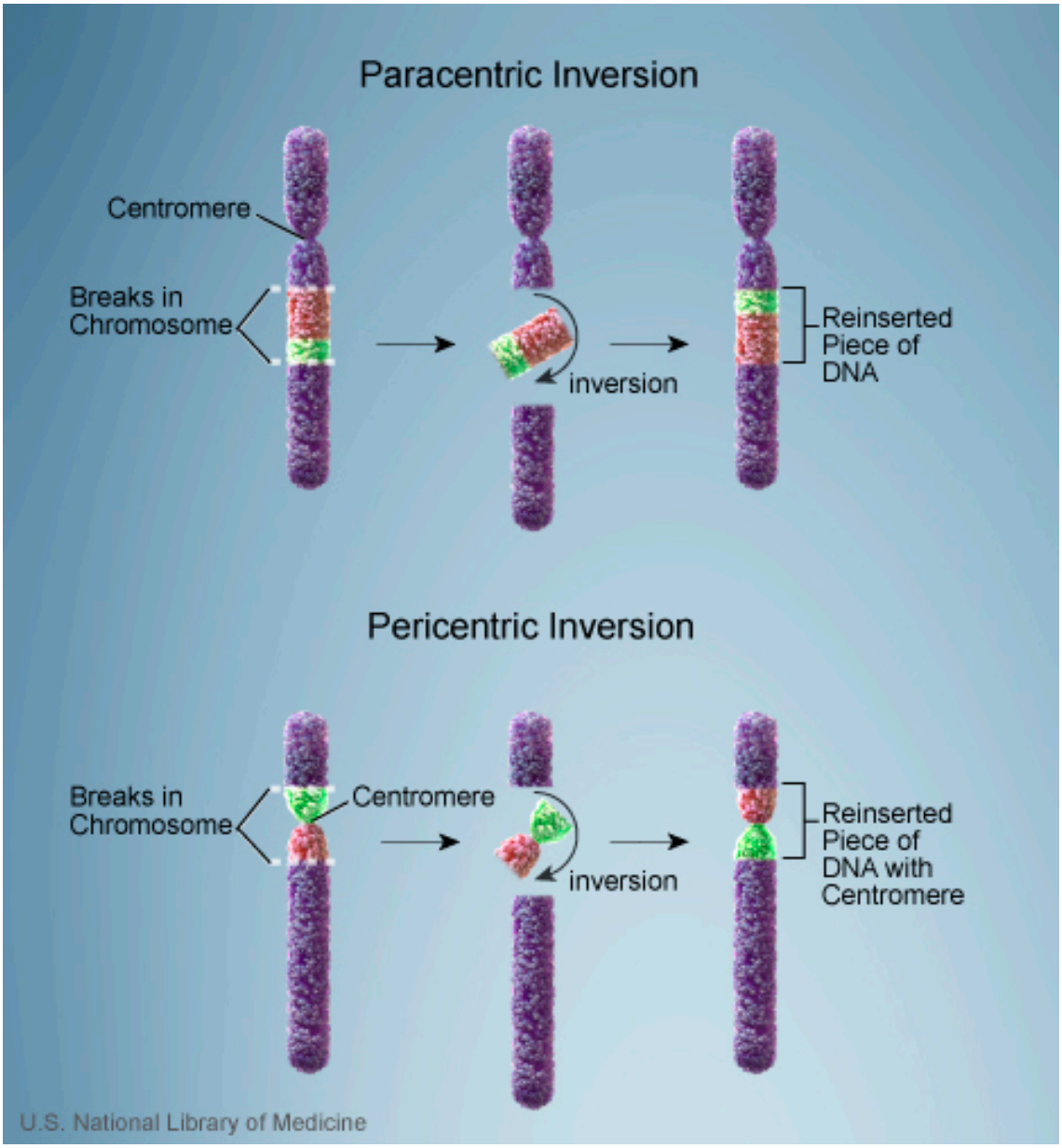
An unbalanced translocation occurs when a child inherits a chromosome with extra or missing genetic material from a parent with a balanced translocation.



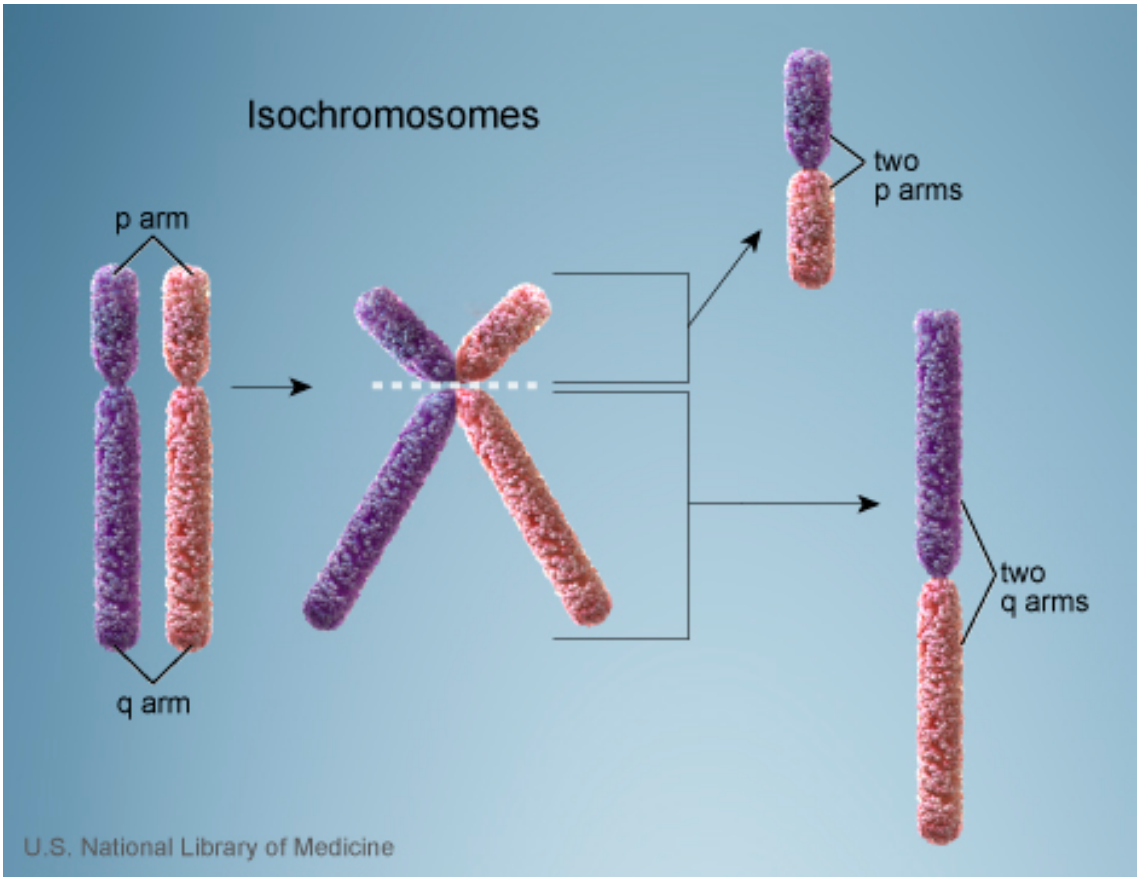
A deletion occurs when a chromosome breaks and some genetic material is lost.



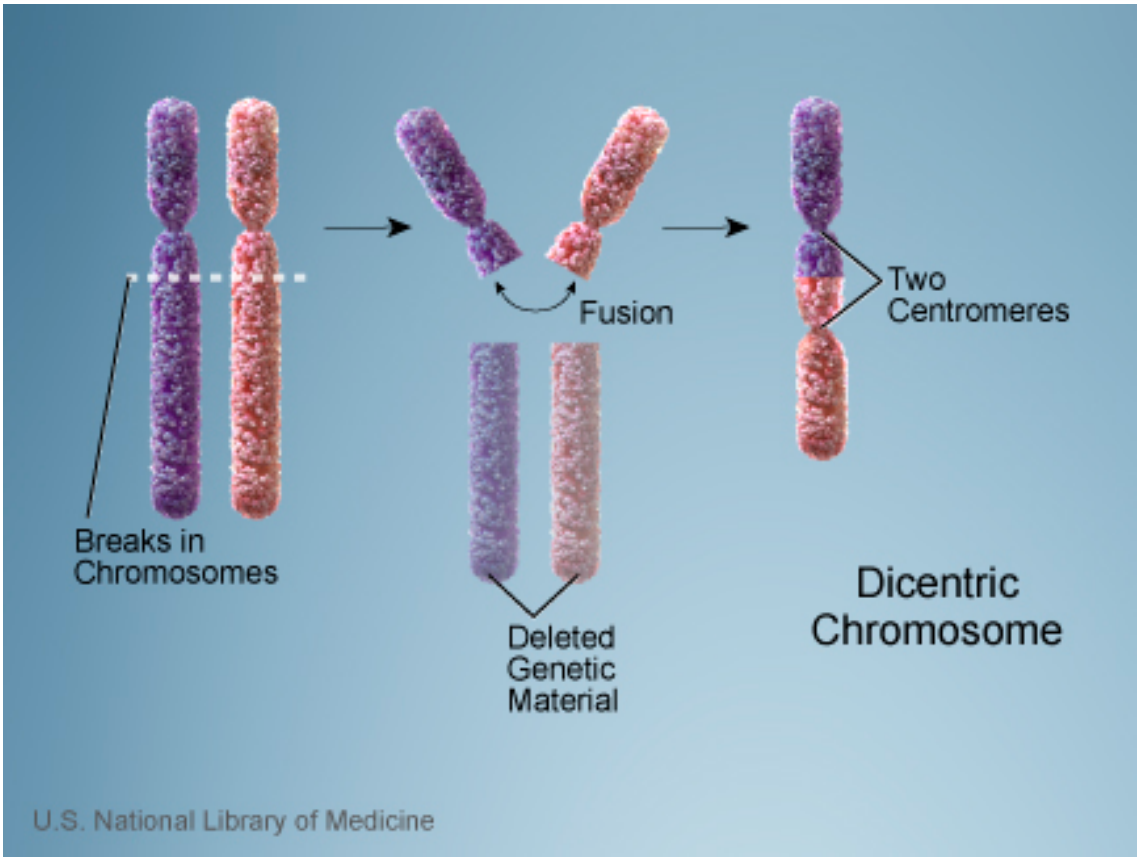
A duplication occurs when part of a chromosome is copied (duplicated) abnormally, resulting in extra genetic material from the duplicated segment.



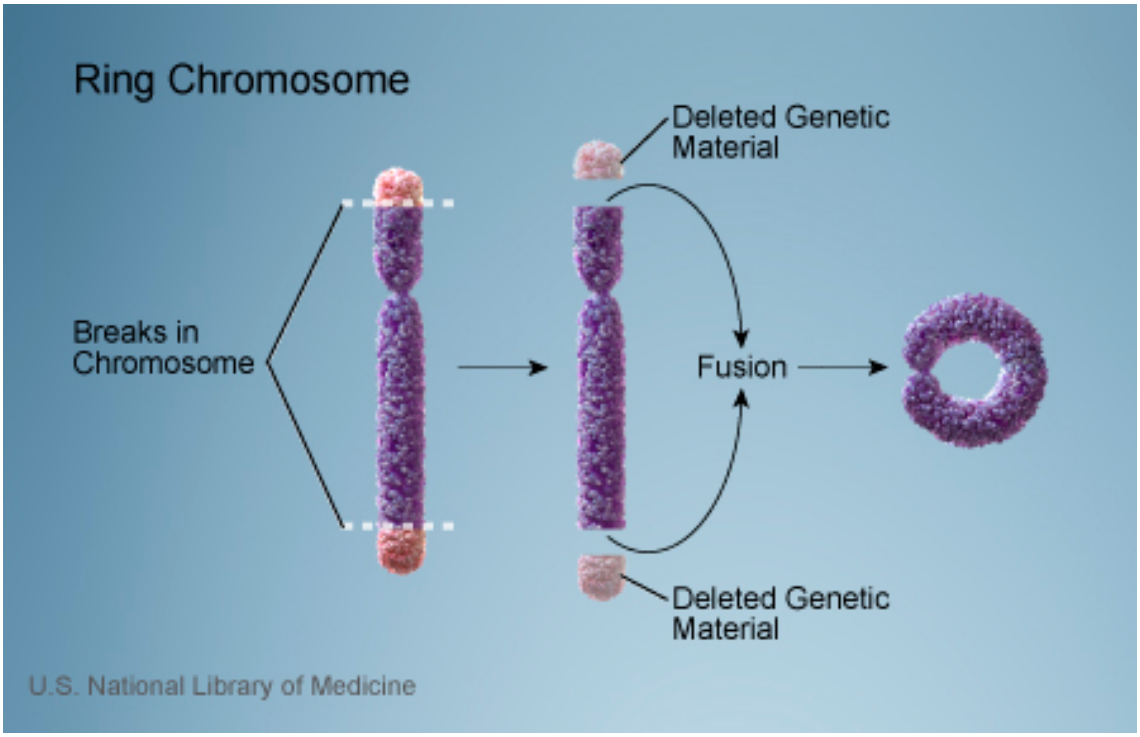
Inversions occur when a chromosome breaks in two places and the resulting piece of DNA is reversed and re-inserted into the chromosome. Inversions that involve the centromere are called pericentric inversions; those that do not involve the centromere are called paracentric inversions.



An isochromosome is an abnormal chromosome with two identical arms, either two short (p) arms or two long (q) arms.



Dicentric chromosomes result from the abnormal fusion of two chromosome pieces, each of which includes a centromere.



Ring chromosomes usually occur when a chromosome breaks in two places and the ends of the chromosome arms fuse together to form a circular structure.

Can changes in mitochondrial DNA affect health and development?

Mitochondria (image on page 8) are structures within cells that convert the energy from food into a form that cells can use. Although most DNA is packaged in chromosomes within the nucleus, mitochondria also have a small amount of their own DNA (known as mitochondrial DNA or mtDNA). In some cases, inherited changes in mitochondrial DNA can cause problems with growth, development, and function of the body's systems. These mutations disrupt the mitochondria's ability to generate energy efficiently for the cell.

Conditions caused by mutations in mitochondrial DNA often involve multiple organ systems. The effects of these conditions are most pronounced in organs and tissues that require a lot of energy (such as the heart, brain, and muscles). Although the health consequences of inherited mitochondrial DNA mutations vary widely, frequently observed features include muscle weakness and wasting, problems with movement, diabetes, kidney failure, heart disease, loss of intellectual functions (dementia), hearing loss, and abnormalities involving the eyes and vision.

Mitochondrial DNA is also prone to somatic mutations, which are not inherited. Somatic mutations occur in the DNA of certain cells during a person's lifetime and typically are not passed to future generations. Because mitochondrial DNA has a limited ability to repair itself when it is damaged, these mutations tend to build up over time. A buildup of somatic mutations in mitochondrial DNA has been associated with some forms of cancer and an increased risk of certain age-related disorders such as heart disease, Alzheimer disease, and Parkinson disease. Additionally, research suggests that the progressive accumulation of these mutations over a person's lifetime may play a role in the normal process of aging.

For more information about conditions caused by mitochondrial DNA mutations:

Genetics Home Reference provides background information about mitochondria and mitochondrial DNA on page 13 written in consumer-friendly language.

The Cleveland Clinic offers a basic introduction to mitochondrial disease (http://my.clevelandclinic.org/health/diseases_conditions/hic-what-are-mitochondrial-diseases/hic_Myths_and_Facts_About_Mitochondrial_Diseases). Additional information about mitochondrial disorders (https://www.cincinnatichildrens.org/service/m/mitochondrial-disorders/patients/) is available from Cincinnati Children's Hospital Medical Center.

An overview of mitochondrial disorders (http://www.ncbi.nlm.nih.gov/books/NBK1224/) is available from GeneReviews.

The Muscular Dystrophy Association offers an introduction to mitochondrial disorders as part of their fact sheet called Mitochondrial Myopathies (https://www.mda.org/disease/mitochondrial-myopathies).

The Neuromuscular Disease Center at Washington University provides an in-depth description of many mitochondrial conditions (http://neuromuscular.wustl.edu/mitosyn.html).

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 disease 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. Researchers continue to look for major contributing genes for many common complex disorders.

For more information about complex disorders:

A fact sheet about the inheritance of multifactorial disorders (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetEnvironmenralGeneticInteractions) is available from the Centre for Genetics Education.

The Children's Hospital of Wisconsin provides basic information about multifactorial inheritance (http://www.chw.org/medical-care/genetics-and-genomics-program/medical-genetics/multifactorial-inheritance/) and examples of multifactorial disorders.

GeneEd from the National Library of Medicine and the National Human Genome Research Institute provides a list of educational resources about multifactorial inheritance and complex disease (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=5&sid=8).

The National Human Genome Research Institute describes how researchers study complex disorders (https://www.genome.gov/10000865).

If you would like information about a specific complex disorder such as diabetes or obesity, MedlinePlus (https://medlineplus.gov/) 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/DiseasesConditions/) that links to additional information.

What does it mean to have a genetic predisposition to a disease?

A genetic predisposition (sometimes also called genetic susceptibility) is an increased likelihood of developing a particular disease based on a person's genetic makeup. A genetic predisposition results from specific genetic variations that are often inherited from a parent. These genetic changes contribute to the development of a disease but do not directly cause it. Some people with a predisposing genetic variation will never get the disease while others will, even within the same family.

Genetic variations can have large or small effects on the likelihood of developing a particular disease. For example, certain mutations in the *BRCA1* or *BRCA2* genes greatly increase a person's risk of developing breast cancer and ovarian cancer. Variations in other genes, such as *BARD1* and *BRIP1*, also increase breast cancer risk, but the contribution of these genetic changes to a person's overall risk appears to be much smaller.

Current research is focused on identifying genetic changes that have a small effect on disease risk but are common in the general population. Although each of these variations only slightly increases a person's risk, having changes in several different genes may combine to increase disease risk significantly. Changes in many genes, each with a small effect, may underlie susceptibility to many common diseases, including cancer, obesity, diabetes, heart disease, and mental illness.

In people with a genetic predisposition, the risk of disease can depend on multiple factors in addition to an identified genetic change. These include other genetic factors (sometimes called modifiers) as well as lifestyle and environmental factors. Diseases that are caused by a combination of factors are described as multifactorial on page 51. Although a person's genetic makeup cannot be altered, some lifestyle and environmental modifications (such as having more frequent disease screenings and maintaining a healthy weight) may be able to reduce disease risk in people with a genetic predisposition.

For more information about genetic predisposition to disease:

The World Health Organization offers information about genetic predisposition to several common diseases (http://www.who.int/genomics/public/geneticdiseases/en/index3.html), including cancer, diabetes, cardiovascular disease, and asthma.

The Genetic Science Learning Center at the University of Utah provides more information about calculating the risk of genetic diseases and predicting

disease based on family history (http://learn.genetics.utah.edu/content/history/geneticrisk/).

The Coriell Personalized Medicine Collaborative explains genetic and nongenetic risk factors (https://cpmc.coriell.org/genetic-education/genetic-and-non-genetic-risk) for complex diseases.

More detailed information about the genetics of breast and ovarian cancer (http://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq) is available from the National Cancer Institute.

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:

Common statistical terms

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 in a specified group at a given time who have the mutation or disorder. This term includes both newly diagnosed and pre-existing cases in people of any age. 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 understanding and interpreting statistics:

The New York Department of Health provides a basic explanation of statistical terms (http://www.health.ny.gov/diseases/chronic/basicstat.htm), including incidence, prevalence, morbidity, and mortality.

More detailed information about health statistics is available from Woloshin, Schwartz, and Welch's Know Your Chances: Understanding Health Statistics (http://www.ncbi.nlm.nih.gov/books/NBK115435/), which is available through the NCBI Bookshelf.

The National Cancer Institute offers additional tools for understanding cancer statistics (http://www.cancer.gov/about-cancer/what-is-cancer/statistics).

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, hypermanganesemia with dystonia, polycythemia, and cirrhosis);
- The parts of the body affected by the condition (for example, craniofacial-deafness-hand syndrome);
- 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 the 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.

Naming genes

The HUGO Gene Nomenclature Committee (http://www.genenames.org/) (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 20,000 to 25,000 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. For specific information about how genes are named, refer to the HGNC's Guidelines for Human Gene Nomenclature (http://www.genenames.org/about/guidelines).

How Genes Work

Table of Contents

What are proteins and what do they do? 59

How do genes direct the production of proteins? 65

Can genes be turned on and off in cells? 67

What is the epigenome? 68

How do cells divide? 70

How do genes control the growth and division of cells? 72

How do geneticists indicate the location of a gene? 75

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:

Examples of protein functions

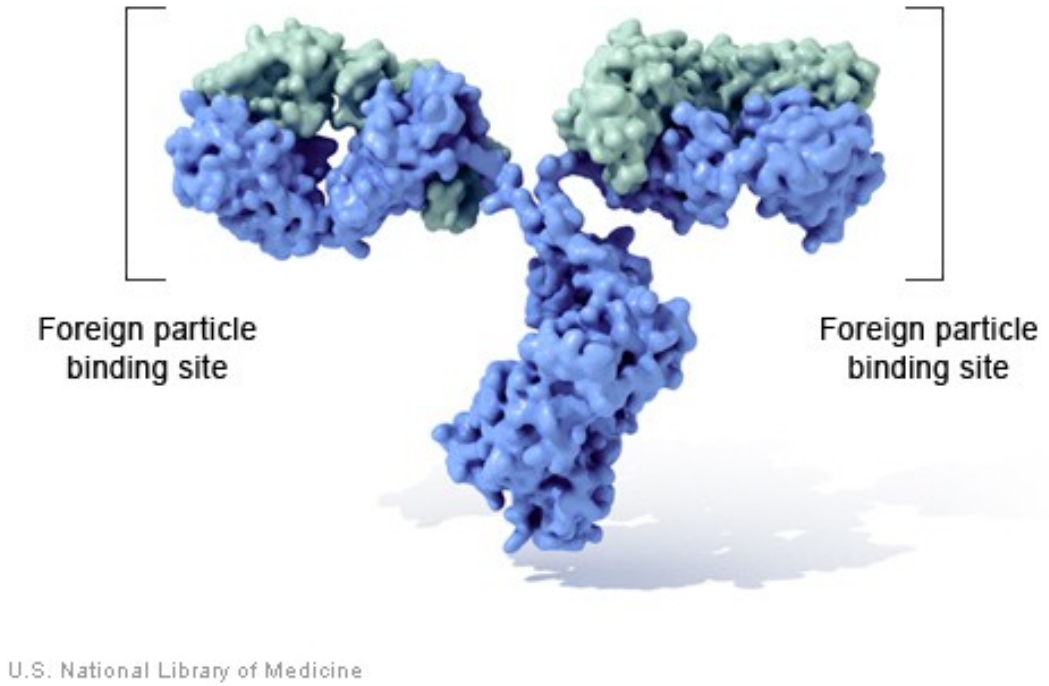
Function	Description	Example
Antibody	Antibodies bind to specific foreign particles, such as viruses and bacteria, to help protect the body.	Immunoglobulin G (IgG) (image on page 60)
Enzyme	Enzymes carry out almost all of the thousands of chemical reactions that take place in cells. They also assist with the formation of new molecules by reading the genetic information stored in DNA.	Phenylalanine hydroxylase (image on page 61)
Messenger	Messenger proteins, such as some types of hormones, transmit signals to coordinate biological processes between different cells, tissues, and organs.	Growth hormone (image on page 62)
Structural component	These proteins provide structure and support for cells. On a larger scale, they also allow the body to move.	Actin (image on page 63)
Transport/ storage	These proteins bind and carry atoms and small molecules within cells and throughout the body.	Ferritin (image on page 64)

For more information about proteins and their functions:

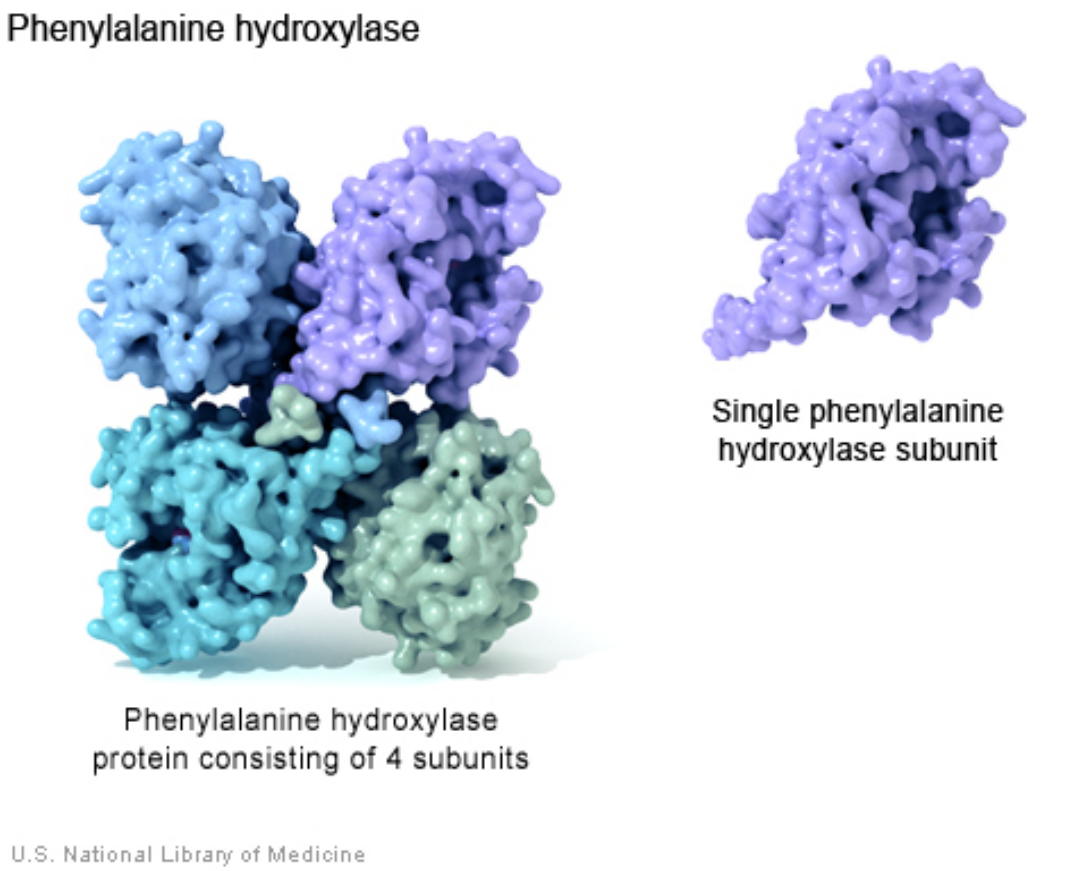
KidsHealth from Nemours offers a basic overview of proteins (http://kidshealth.org/en/kids/protein.html) and what they do.

Arizona State University's "Ask a Biologist" discusses the different kinds of proteins (http://askabiologist.asu.edu/venom/what-are-proteins) and what they do.

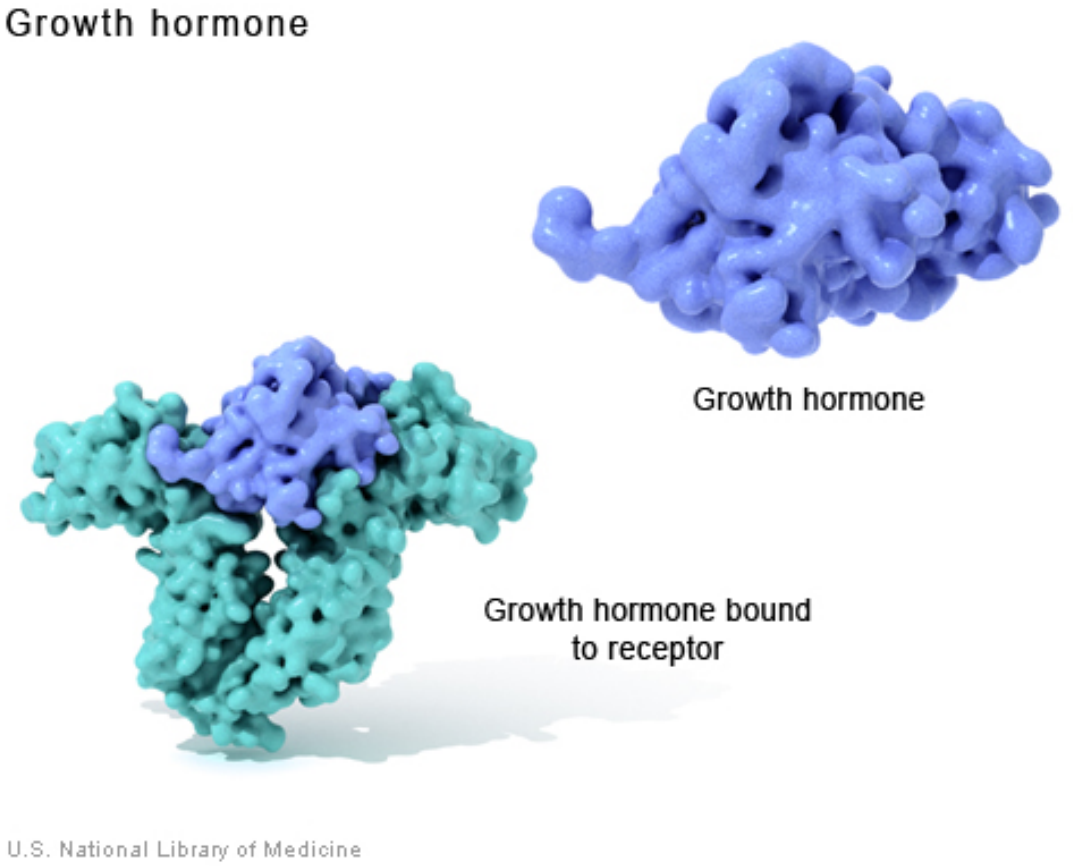
Images



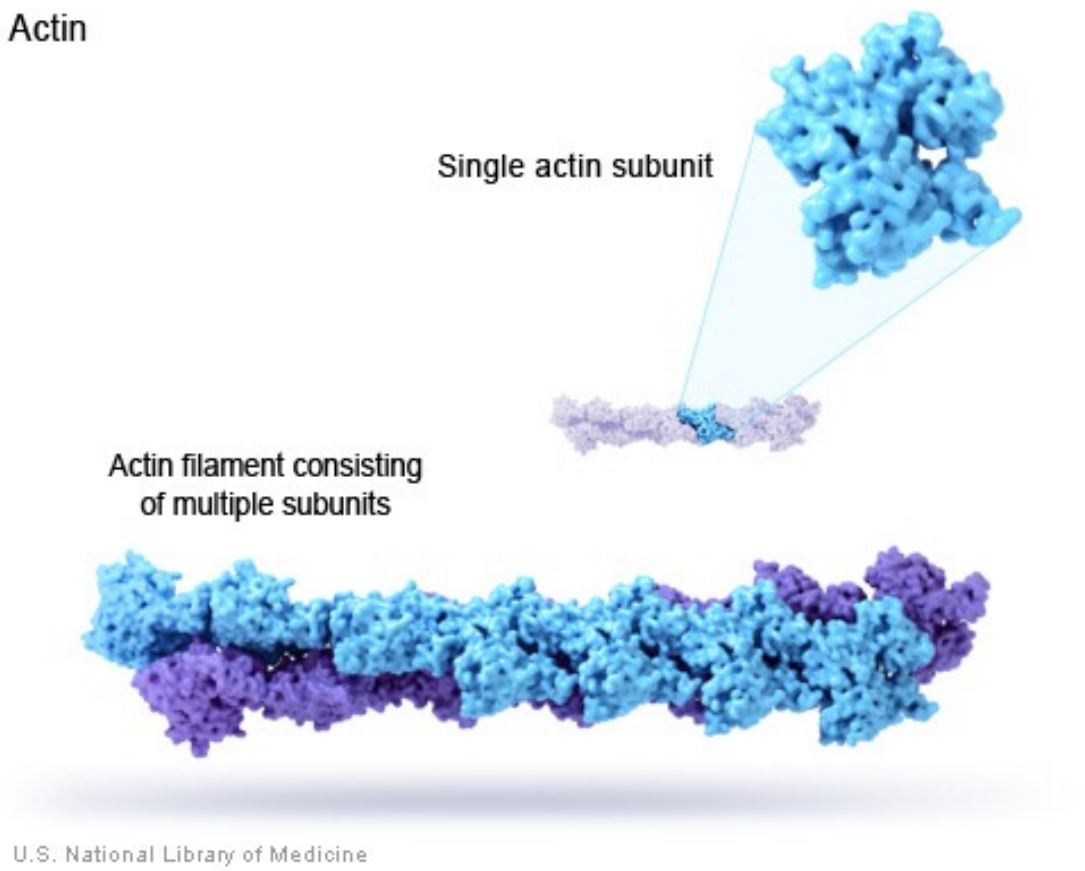
Immunoglobulin G is a type of antibody that circulates in the blood and recognizes foreign particles that might be harmful.



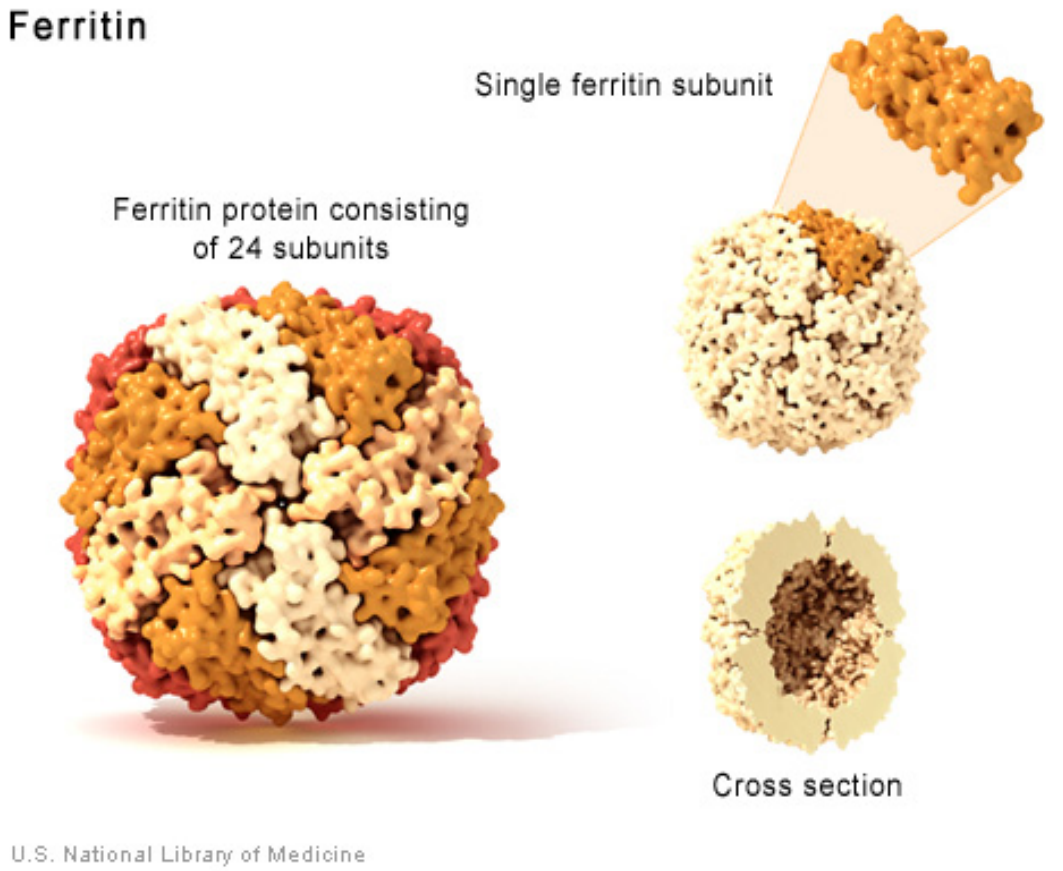
The functional phenylalanine hydroxylase enzyme is made up of four identical subunits. The enzyme converts the amino acid phenylalanine to another amino acid, tyrosine.



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.

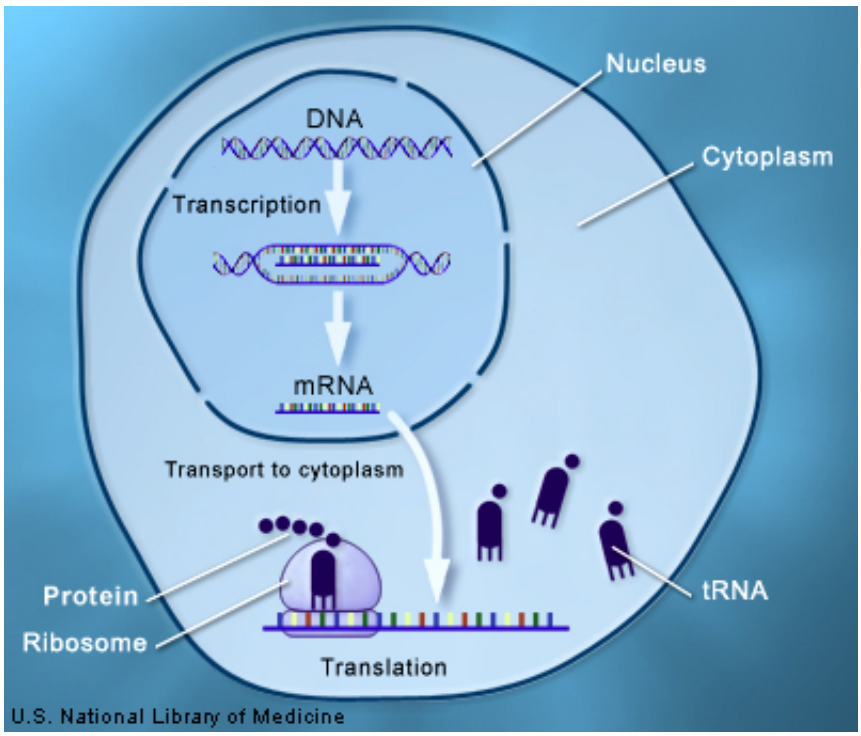
How do genes direct the production of proteins?

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:

The Genetic Science Learning Center at the University of Utah offers an interactive introduction to transcription and translation (http://learn.genetics.utah.edu/content/basics/dna).

Information about RNA (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=15&sid=18), transcription (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=15&sid=22), and translation (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=15&sid=23) is available from GeneEd.

North Dakota State University's Virtual Cell Animation Collection offers videos that illustrate the processes of transcription (http://vcell.ndsu.nodak.edu/animations/transcription/movie-flash.htm) and translation (http://vcell.ndsu.nodak.edu/animations/translation/movie-flash.htm).

The New Genetics, a publication of the National Institute of General Medical Sciences, includes discussions of transcription (https://publications.nigms.nih.gov/thenewgenetics/chapter1.html#c4) and translation (https://publications.nigms.nih.gov/thenewgenetics/chapter1.html#c7).

Can genes be turned on and off in cells?

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 is an important part of normal development. Genes are turned on and off in different patterns during development to make a brain cell look and act different from a liver cell or a muscle cell, for example. Gene regulation also allows cells to react quickly to changes in their environments. 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:

The Genetic Science Learning Center at the University of Utah offers an explanation of gene expression as it relates to disease risk (http://learn.genetics.utah.edu/content/science/expression/).

Additional information about gene expression (http://www.yourgenome.org/facts/what-is-gene-expression) is available from yourgenome.org, a service of the Wellcome Trust.

What is the epigenome?

DNA modifications that do not change the DNA sequence can affect gene activity. Chemical compounds that are added to single genes can regulate their activity; these modifications are known as epigenetic changes. The epigenome comprises all of the chemical compounds that have been added to the entirety of one's DNA (genome) as a way to regulate the activity (expression) of all the genes within the genome. The chemical compounds of the epigenome are not part of the DNA sequence, but are on or attached to DNA ("epi-" means above in Greek). Epigenomic modifications remain as cells divide and in some cases can be inherited through the generations. Environmental influences, such as a person's diet and exposure to pollutants, can also impact the epigenome.

Epigenetic changes can help determine whether genes are turned on or off and can influence the production of proteins in certain cells, ensuring that only necessary proteins are produced. For example, proteins that promote bone growth are not produced in muscle cells. Patterns of epigenome modification vary among individuals, different tissues within an individual, and even different cells.

A common type of epigenomic modification is called methylation. Methylation involves attaching small molecules called methyl groups, each consisting of one carbon atom and three hydrogen atoms, to segments of DNA. When methyl groups are added to a particular gene, that gene is turned off or silenced, and no protein is produced from that gene.

Because errors in the epigenetic process, such as modifying the wrong gene or failing to add a compound to a gene, can lead to abnormal gene activity or inactivity, they can cause genetic disorders. Conditions including cancers, metabolic disorders, and degenerative disorders have all been found to be related to epigenetic errors.

Scientists continue to explore the relationship between the genome and the chemical compounds that modify it. In particular, they are studying what effect the modifications have on gene function, protein production, and human health.

For more information about the epigenome:

The National Institutes of Health (NIH) offers the NIH Roadmap Epigenomics Project (http://www.roadmapepigenomics.org/), which provides epigenome maps of a variety of cells to begin to assess the relationship between epigenomics and human disease.

The National Center for Biotechnology Information (NCBI) provides the NCBI Epigenomics (http://www.ncbi.nlm.nih.gov/epigenomics) database of maps of the epigenomes of various species and many cell types.

Human Epigenome Atlas (http://www.genboree.org/epigenomeatlas/index.rhtml) from Baylor College of Medicine allows for comparison of the epigenomes of many species and cell types.

GeneEd from the National Library of Medicine and the National Human Genome Research Institute provides a list of educational resources about the epigenome (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=35&sid=36).

Ongoing research is being done with the Human Epigenome Project (http://www.epigenome.org/).

The University of Utah provides an interactive epigenetics tutorial (http://learn.genetics.utah.edu/content/epigenetics/).

The National Human Genome Research Institute provides a fact sheet (https://www.genome.gov/27532724) on Epigenomics.

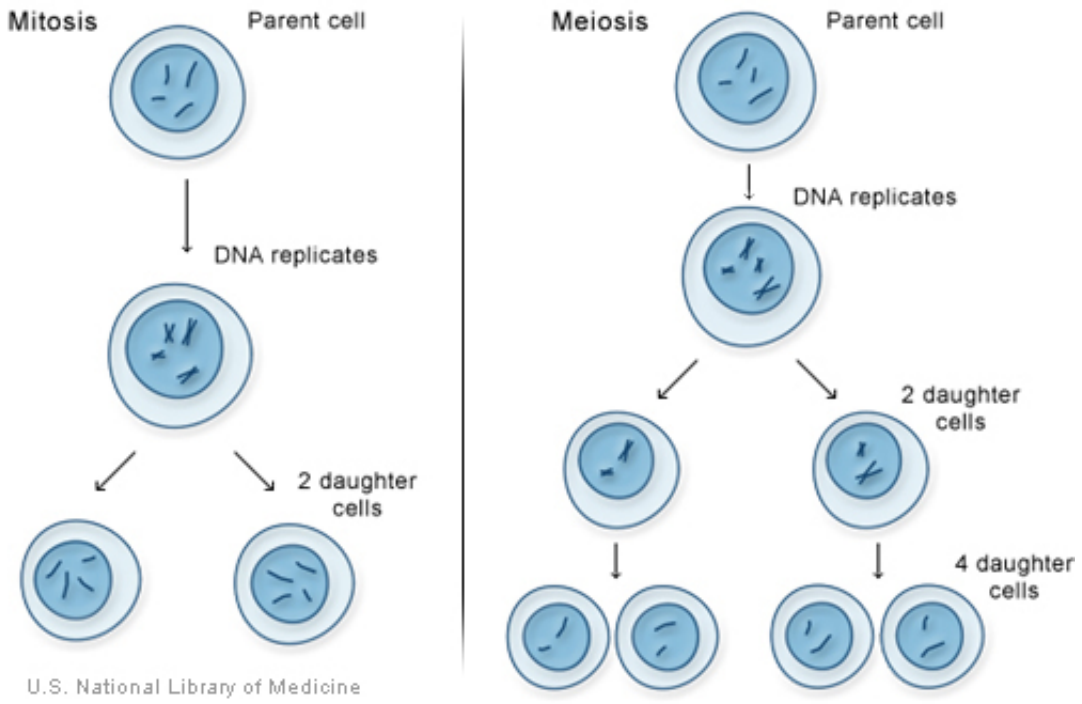
Many tools for understanding epigenomics are available through the NIH Common Fund Epigenomics Project (https://commonfund.nih.gov/epigenomics/).

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:

Information about mitosis (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=1&sid=2) and meiosis (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=1&sid=3) is available from GeneEd.

North Dakota State University's Virtual Cell Animation Collection offers videos that illustrate the processes of mitosis (http://vcell.ndsu.nodak.edu/animations/mitosis/movie-flash.htm) and meiosis (http://vcell.ndsu.nodak.edu/animations/meiosis/movie-flash.htm).

Yourgenome from the Wellcome Trust outlines the similarities and differences between mitosis and meiosis (http://www.yourgenome.org/facts/mitosis-versus-meiosis).

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) (image on page 73). 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 (image on page 73). 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.

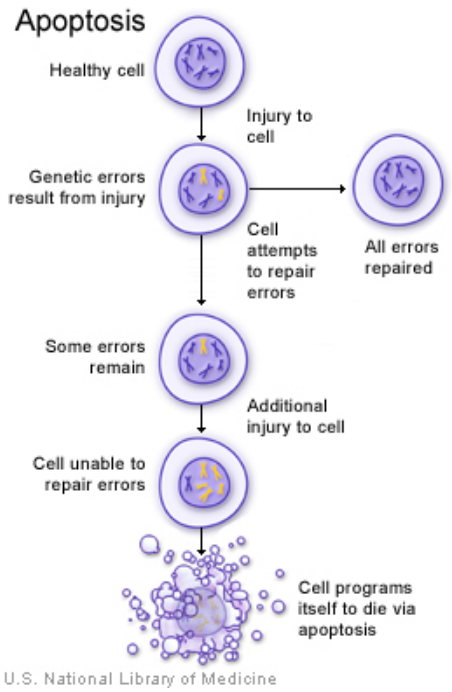
Cancer results from a disruption of the normal regulation of the cell cycle. When the cycle proceeds without control, cells can divide without order and accumulate genetic defects that can lead to a cancerous tumor (image on page 74).

For more information about cell growth and division:

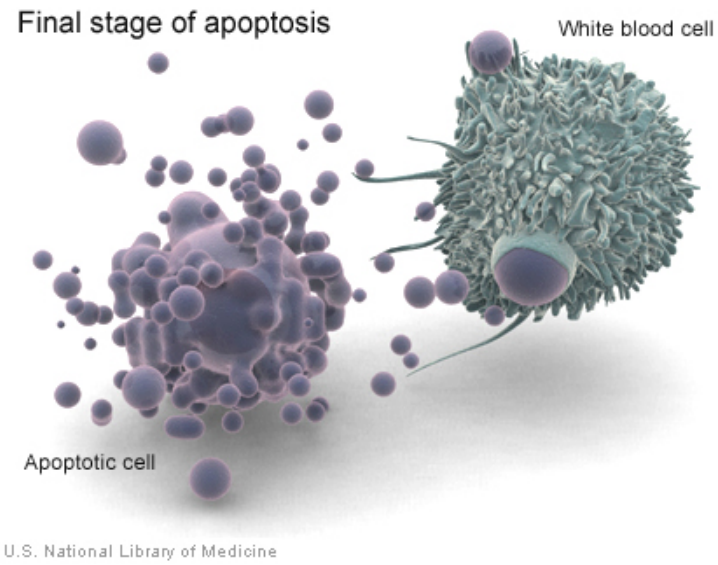
The National Institutes of Health's Apoptosis Interest Group (http://sigs.nih.gov/cell-death/Pages/Miscellaneous.aspx) provides an introduction to programmed cell death.

The National Cancer Institute's fact sheet What is Cancer? (http://www.cancer.gov/about-cancer/what-is-cancer) explains the growth of cancerous tumors.

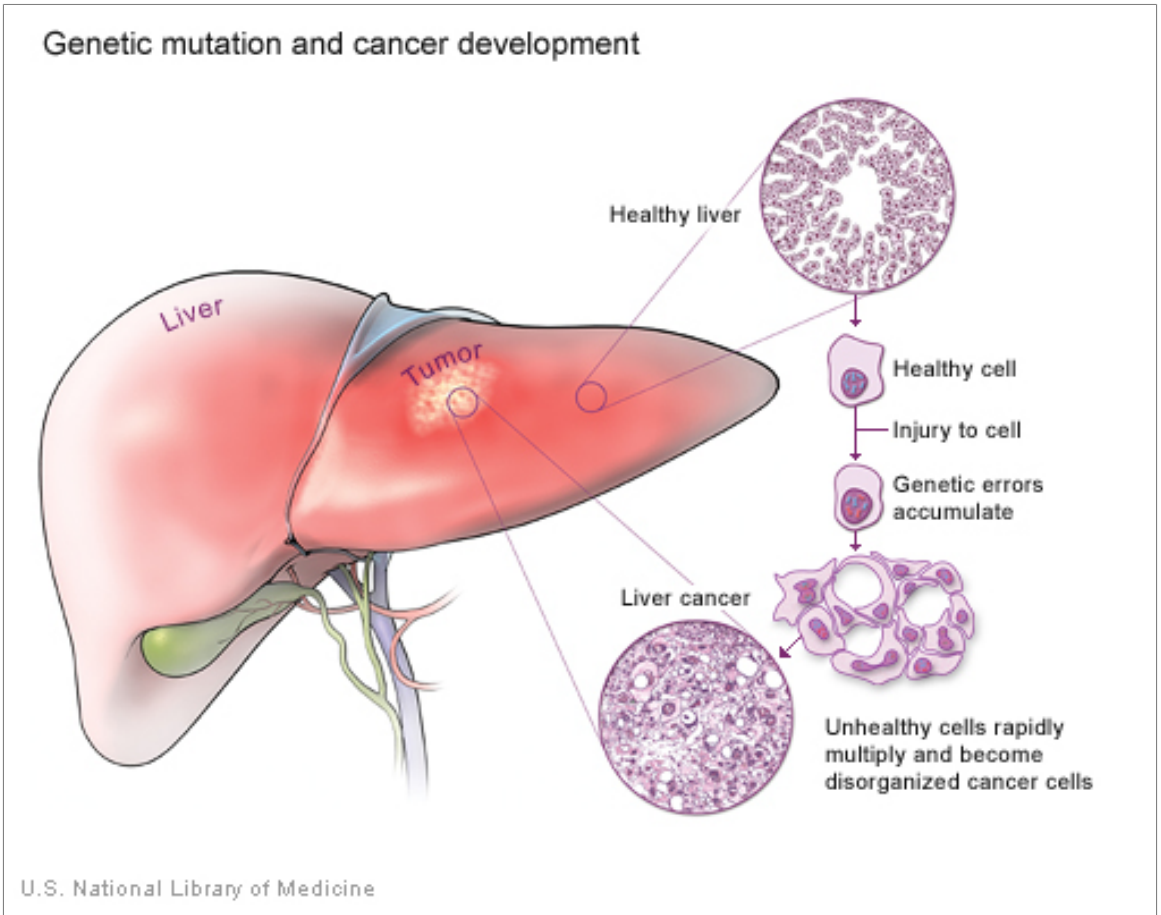
Images



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.

How do geneticists indicate the location of a gene?

Geneticists use maps to describe the location of a particular gene on a chromosome. One type of map uses the cytogenetic location to describe a gene's position. The cytogenetic location is based on a distinctive pattern of bands created when chromosomes are stained with certain chemicals. Another type of map uses the molecular location, a precise description of a gene's position on a chromosome. The molecular location is based on the sequence of DNA building blocks (base pairs) that make up the chromosome.

Cytogenetic location

Geneticists use a standardized way of describing a gene's cytogenetic location. In most cases, the location describes the position of a particular band on a stained chromosome:

17q12

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

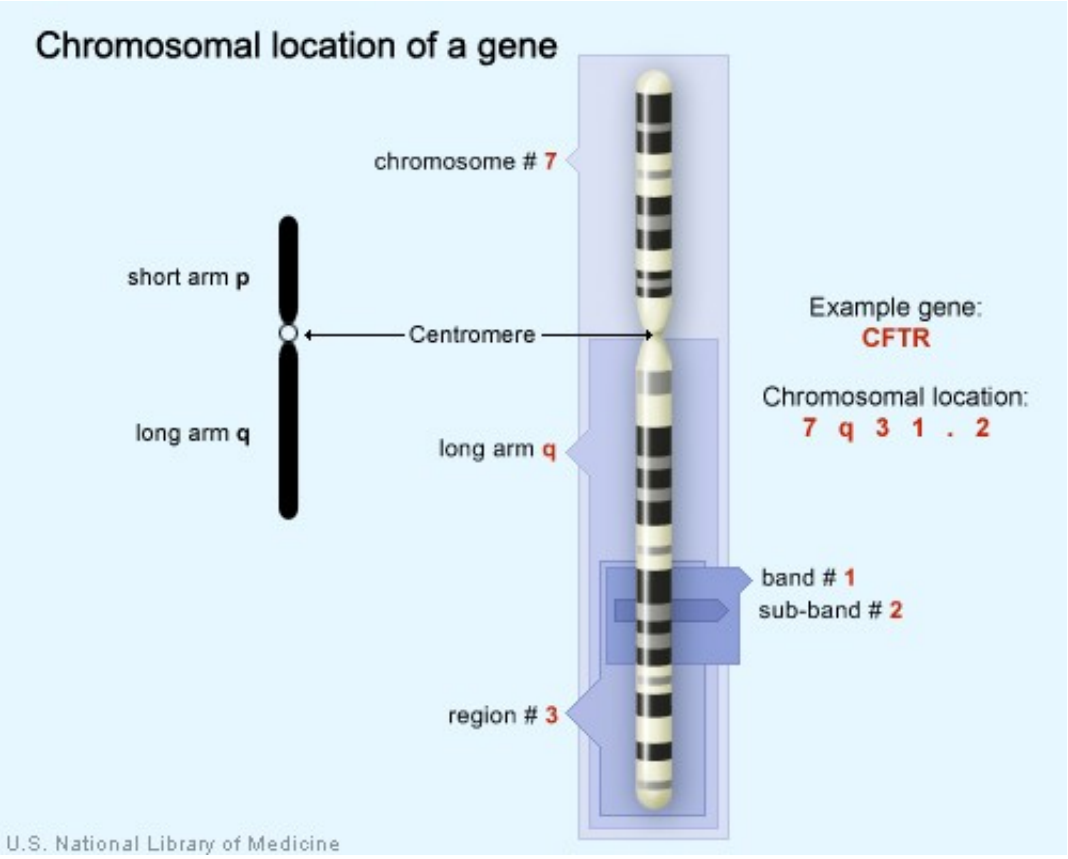
17q12-q21

The combination of numbers and letters provide a gene's “address” on a chromosome. This 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 (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 distinctive 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 the gene position increases with distance from the centromere. For example: 14q21 represents position 21 on the long arm of chromosome 14. 14q21 is closer to the centromere than 14q22.

Sometimes, the abbreviations “cen” or “ter” are also used to describe a gene's cytogenetic 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 the 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.

Molecular location

The Human Genome Project, an international research effort completed in 2003, determined the sequence of base pairs for each human chromosome. This sequence information allows researchers to provide a more specific address than the cytogenetic location for many genes. A gene's molecular address pinpoints the location of that gene in terms of base pairs. It describes the gene's precise position on a chromosome and indicates the size of the gene. Knowing the molecular location also allows researchers to determine exactly how far a gene is from other genes on the same chromosome.

Different groups of researchers often present slightly different values for a gene's molecular location. Researchers interpret the sequence of the human genome using a variety of methods, which can result in small differences in a gene's molecular address. Genetics Home Reference presents data from NCBI (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene) for the molecular location of genes.

For more information on genetic mapping:

The National Human Genome Research Institute explains how researchers create a genetic map (https://www.genome.gov/10000715).

The University of Washington provides a Cytogenetics Gallery (http://www.pathology.washington.edu/galleries/Cytogallery/main.php?file=intro) that includes a description of chromosome banding patterns (http://www.pathology.washington.edu/galleries/Cytogallery/main.php?file=banding+patterns).

Information about assembling and annotating the genome (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=handbook&part=ch14) is available from NCBI.

Gene Families

Table of Contents

What are gene families? 79

Blood group antigens 80

Collagen proteoglycans 82

Complement 83

Cytochrome p450 85

Endogenous ligands 88

Human leukocyte antigens 90

Homeoboxes 92

Keratins 94

Mitochondrial respiratory chain complex 96

Myosins 98

Transfer RNAs 100

What are gene families?

A gene family is a group of genes that share important characteristics. In many cases, genes in a family share a similar sequence of DNA building blocks (nucleotides). These genes provide instructions for making products (such as proteins) that have a similar structure or function. In other cases, dissimilar genes are grouped together in a family because proteins produced from these genes work together as a unit or participate in the same process.

Classifying individual genes into families helps researchers describe how genes are related to each other. Researchers can use gene families to predict the function of newly identified genes based on their similarity to known genes. Similarities among genes in a family can also be used to predict where and when a specific gene is active (expressed). Additionally, gene families may provide clues for identifying genes that are involved in particular diseases.

Sometimes not enough is known about a gene to assign it to an established family. In other cases, genes may fit into more than one family. No formal guidelines define the criteria for grouping genes together. Classification systems for genes continue to evolve as scientists learn more about the structure and function of genes and the relationships between them.

For more information about gene families:

The HUGO Gene Nomenclature Committee (http://www.genenames.org/cgi-bin/genefamilies/) (HGNC) has classified many human genes into families. Each grouping is given a name and symbol, and contains a table of the genes in that family.

The Gene Ontology (http://geneontology.org/) database lists the protein products of genes by their location within the cell (cellular component), biological process, and molecular function.

The Reactome (http://www.reactome.org/) database classifies the protein products of genes based on their participation in specific biological pathways. For example, this resource provides tables of genes involved in controlled cell death (apoptosis), cell division, and DNA repair.

Blood group antigens

Blood is classified into different groups according to the presence or absence of molecules called antigens on the surface of every red blood cell in a person's body. Antigens determine blood type and can either be proteins or complexes of sugar molecules (polysaccharides). The genes in the blood group antigen family provide instructions for making antigen proteins. Blood group antigen proteins serve a variety of functions within the cell membrane of red blood cells. These protein functions include transporting other proteins and molecules into and out of the cell, maintaining cell structure, attaching to other cells and molecules, and participating in chemical reactions.

Blood group antigens play a role in recognizing foreign cells in the bloodstream. For example, if a person with blood type A receives a blood transfusion with blood type B, the recipient's immune system will recognize the type B cells as foreign and mount an immune response. Antibodies against type B blood cells (anti-B antibodies) are made, which attack and destroy the type B blood cells. This sort of blood type mismatch can lead to illness. Some blood types are associated with more severe immune reactions than others. The blood type of donated cells, or tissues in the case of organ donation, is checked before being given to a recipient in order to prevent this immune response.

There are 29 recognized blood groups, most involving only one gene. Variations (polymorphisms) within the genes that determine blood group give rise to the different antigens for a particular blood group protein. For example, changes in a few DNA building blocks (nucleotides) in the *ABO* gene give rise to the A, B, and O blood types of the *ABO* blood group. The changes that occur in the genes that determine blood group typically affect only blood type and are not associated with adverse health conditions, although exceptions do occur.

Example of a gene in this gene family: *SLC4A1*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (http://www.genenames.org/cgi-bin/genefamilies/) and their member genes.

References

Byrne KM, Byrne PC. Review: other blood group systems--Diego,Yt, Xg, Scianna, Dombrock, Colton, Landsteiner-Wiener, and Indian. Immunohematology. 2004;20(1):50-8. Review. PubMed: 15373669 (http://www.ncbi.nlm.nih.gov/pubmed/15373669).

Daniels G. The molecular genetics of blood group polymorphism. Transpl Immunol. 2005 Aug;14(3-4):143-53. Epub 2005 Apr 26. Review. PubMed: 15982556 (http://www.ncbi.nlm.nih.gov/pubmed/15982556).

Daniels G. Functions of red cell surface proteins. Vox Sang. 2007 Nov;93(4):331-40. Review. PubMed: 17198846 (http://www.ncbi.nlm.nih.gov/pubmed/17198846).

Eyler CE, Telen MJ. The Lutheran glycoprotein: a multifunctional adhesion receptor. Transfusion. 2006 Apr;46(4):668-77. Review. PubMed: 16584446 (http://www.ncbi.nlm.nih.gov/pubmed/16584446).

Palacajornsuk P. Review: molecular basis of MNS blood group variants. Immunohematology. 2006;22(4):171-82. Review. Erratum in: Immunohematol. 2007;23(1):44. PubMed: 17430076 (http://www.ncbi.nlm.nih.gov/pubmed/17430076).

Quill E. Medicine. Blood-matching goes genetic. Science. 2008 Mar 14;319(5869):1478-9. doi: 10.1126/science.319.5869.1478. PubMed: 18339916 (http://www.ncbi.nlm.nih.gov/pubmed/18339916).

Westhoff CM. The structure and function of the Rh antigen complex. Semin Hematol. 2007 Jan;44(1):42-50. Review. PubMed: 17198846 (http://www.ncbi.nlm.nih.gov/pubmed/17198846). Free full-text available from PubMed Central: PMC1831834 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1831834/).

Westhoff CM, Reid ME. Review: the Kell, Duffy, and Kidd blood group systems. Immunohematology. 2004;20(1):37-49. Review. PubMed: 15373667 (http://www.ncbi.nlm.nih.gov/pubmed/15373667).

Yamamoto F. Review: *ABO* blood group system--ABH oligosaccharide antigens, anti-A and anti-B, A and B glycosyltransferases, and *ABO* genes. Immunohematology. 2004;20(1):3-22. Review. PubMed: 15373665 (http://www.ncbi.nlm.nih.gov/pubmed/15373665).

Learn more about the blood group antigens gene family:

National Library of Medicine: Blood Groups and Red Cell Antigens (2005): Blood group antigens are surface markers on the red blood cell membrane (http://www.ncbi.nlm.nih.gov/books/NBK2264/#ch2)

Emory University: The Genetics of Blood Type (http://genetics.emory.edu/documents/resources/factsheet43.pdf)

NCBI: Blood Group Antigen Gene Mutations Database (http://www.ncbi.nlm.nih.gov/gv/rbc/xslcgi.fcgi?cmd=bgmut/home)

Collagen proteoglycans

Genes in this family provide instructions for making the protein component of large molecules called collagen proteoglycans. A proteoglycan is a molecule that is made up of a core protein attached to one or more sugar molecules called glycosaminoglycan (GAG) chains. The collagen proteoglycans gene family is a subset of a larger gene family known as the proteoglycan superfamily.

The many different types of proteoglycans are classified according to their core protein. The core protein produced by members of the collagen proteoglycans gene family is collagen. Collagens are a family of proteins that strengthen and support connective tissues, such as skin, bone, cartilage, tendons, and ligaments. Collagen proteoglycans are major components of the extracellular matrix, which is an intricate lattice of proteins and other molecules that forms in the spaces between cells. The collagen proteoglycans bind to a variety of other proteins in the extracellular matrix, including other forms of collagen.

Examples of genes in this gene family: *COL9A1*, *COL9A2*, *COL9A3*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (http://www.genenames.org/cgi-bin/genefamilies/) and their member genes.

References

Amenta PS, Scivoletti NA, Newman MD, Sciancalepore JP, Li D, Myers JC. Proteoglycan-collagen XV in human tissues is seen linking banded collagen fibers subjacent to the basement membrane. J Histochem Cytochem. 2005 Feb;53(2):165-76. PubMed 15684329 (http://www.ncbi.nlm.nih.gov/pubmed/15684329).

Li D, Clark CC, Myers JC. Basement membrane zone type XV collagen is a disulfide-bonded chondroitin sulfate proteoglycan in human tissues and cultured cells. J Biol Chem. 2000 Jul 21;275(29):22339-47. PubMed: 10791950 (http://www.ncbi.nlm.nih.gov/pubmed/10791950).

van der Rest M, Mayne R. Type IX collagen proteoglycan from cartilage is covalently cross-linked to type II collagen. J Biol Chem. 1988 Feb 5;263(4):1615-8. PubMed: 3123475 (http://www.ncbi.nlm.nih.gov/pubmed/3123475).

Learn more about the collagen proteoglycan gene family:

Essentials of Glycobiology (first edition, 1999): Proteoglycans and Glycosaminoglycans (http://www.ncbi.nlm.nih.gov/books/NBK20693/)

Complement

Genes in the complement family provide instructions for making proteins involved in the complement system, an essential part of the body's immune response. The complement system is composed of more than 20 proteins that work together to destroy foreign invaders (such as bacteria and viruses), trigger inflammation, and remove debris from cells and tissues. This system must be carefully regulated so it targets only unwanted materials and does not attack the body's healthy cells.

Several diseases have been associated with changes in complement genes. Each of these genetic changes typically results in a shortage (deficiency) of a single complement system protein. These deficiencies disrupt the normal activity or regulation of the complement system, often leading to an increased risk of bacterial infection or recurrent episodes of severe swelling (angioedema). Complement system defects have also been found in autoimmune disorders such as systemic lupus erythematosus. Autoimmune disorders occur when the immune system malfunctions and attacks the body's own tissues and organs.

Examples of genes in this gene family: *C8A*, *C8B*, *CFH*, *CFHR5*, *CFI*, *ITGB2*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (http://www.genenames.org/cgi-bin/genefamilies/) and their member genes.

References

Chen M, Daha MR, Kallenberg CG. The complement system in systemic autoimmune disease. J Autoimmun. 2010 May;34(3):J276-86. doi: 10.1016/j.jaut.2009.11.014. Epub 2009 Dec 11. Review. PubMed: 20005073 (http://www.ncbi.nlm.nih.gov/pubmed/20005073).

Rus H, Cudrici C, Niculescu F. The role of the complement system in innate immunity. Immunol Res. 2005;33(2):103-12. Review. PubMed: 16234578 (http://www.ncbi.nlm.nih.gov/pubmed/16234578).

Thurman JM, Holers VM. The central role of the alternative complement pathway in human disease. J Immunol. 2006 Feb 1;176(3):1305-10. Review. PubMed: 16424154 (http://www.ncbi.nlm.nih.gov/pubmed/16424154).

Learn more about the complement gene family:

MedlinePlus Encyclopedia: Complement (https://medlineplus.gov/ency/article/003456.htm)

Merck Manual Professional Verson: Complement System (http://www.merckmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/complement-system)

Immunobiology (fifth edition, 2001): The Complement System and Innate Immunity (http://www.ncbi.nlm.nih.gov/books/NBK27100/)

Cytochrome p450

Enzymes produced from the cytochrome P450 genes are involved in the formation (synthesis) and breakdown (metabolism) of various molecules and chemicals within cells. Cytochrome P450 enzymes play a role in the synthesis of many molecules including steroid hormones, certain fats (cholesterol and other fatty acids), and acids used to digest fats (bile acids). Additional cytochrome P450 enzymes metabolize external substances, such as medications that are ingested, and internal substances, such as toxins that are formed within cells. There are approximately 60 CYP genes in humans.

Cytochrome P450 enzymes are primarily found in liver cells but are also located in cells throughout the body. Within cells, cytochrome P450 enzymes are located in a structure involved in protein processing and transport (endoplasmic reticulum) and the energy-producing centers of cells (mitochondria). The enzymes found in mitochondria are generally involved in the synthesis and metabolism of internal substances, while enzymes in the endoplasmic reticulum usually metabolize external substances, primarily medications and environmental pollutants.

Common variations (polymorphisms) in cytochrome P450 genes can affect the function of the enzymes. The effects of polymorphisms are most prominently seen in the breakdown of medications. Depending on the gene and the polymorphism, drugs can be metabolized quickly or slowly. If a cytochrome P450 enzyme metabolizes a drug slowly, the drug stays active longer and less is needed to get the desired effect. A drug that is quickly metabolized is broken down sooner and a higher dose might be needed to be effective. Cytochrome P450 enzymes account for 70 percent to 80 percent of enzymes involved in drug metabolism.

Each cytochrome P450 gene is named with CYP, indicating that it is part of the cytochrome P450 gene family. The gene is also given a number associated with a specific group within the gene family, a letter representing the gene's subfamily, and a number assigned to the specific gene within the subfamily. For example, the cytochrome P450 gene that is in group 27, subfamily A, gene 1 is written as *CYP27A1*.

Diseases caused by mutations in cytochrome P450 genes typically involve the buildup of substances in the body that are harmful in large amounts or that prevent other necessary molecules from being produced.

Examples of genes in this gene family: *CYP1B1*, *CYP2C9*, *CYP2C19*, *CYP4V2*, *CYP11B1*, *CYP11B2*, *CYP17A1*, *CYP19A1*, *CYP21A2*, *CYP27B1*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (http://www.genenames.org/cgi-bin/genefamilies/) and their member genes.

References

Guengerich FP. Cytochrome p450 and chemical toxicology. Chem Res Toxicol. 2008 Jan;21(1):70-83. Epub 2007 Dec 6. Review. PubMed: 18052394 (http://www.ncbi.nlm.nih.gov/pubmed/18052394).

Hannemann F, Bichet A, Ewen KM, Bernhardt R. Cytochrome P450 systems--biological variations of electron transport chains. Biochim Biophys Acta. 2007 Mar;1770(3):330-44. Epub 2006 Aug 2. Review. PubMed 16978787 (http://www.ncbi.nlm.nih.gov/pubmed/16978787).

Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacol Ther. 2007 Dec;116(3):496-526. Epub 2007 Oct 9. Review. PubMed: 18001838 (http://www.ncbi.nlm.nih.gov/pubmed/18001838).

Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. Am Fam Physician. 2007 Aug 1;76(3):391-6. Review. PubMed 17708140 (http://www.ncbi.nlm.nih.gov/pubmed/17708140).

Nebert DW, Russell DW. Clinical importance of the cytochromes P450. Lancet. 2002 Oct 12;360(9340):1155-62. Review. PubMed: 12387968 (http://www.ncbi.nlm.nih.gov/pubmed/12387968).

Wijnen PA, Op den Buijsch RA, Drent M, Kuijpers PM, Neef C, Bast A, Bekers O, Koek GH. Review article: The prevalence and clinical relevance of cytochrome P450 polymorphisms. Aliment Pharmacol Ther. 2007 Dec;26 Suppl 2:211-9. doi 10.1111/j.1365-2036.2007.03490.x. Review. Erratum in: Aliment Pharmacol Ther. 2009 Feb 1;29(3):350. Kuipers, P M J C [corrected to Kuijpers, P M J C]. PubMed: 18081664 (http://www.ncbi.nlm.nih.gov/pubmed/18081664).

Learn more about the cytochrome p450 gene family:

Biochemistry (fifth edition, 2002): The Cytochrome P450 System is Widespread and Performs a Protective Function (http://www.ncbi.nlm.nih.gov/books/NBK22339/#A3663)

Biochemistry (fifth edition, 2002): Cytochrome P450 Mechanism (Figure) (http://www.ncbi.nlm.nih.gov/books/NBK22339/figure/A3662/)

Indiana University: Cytochrome P450 Drug-Interaction Table (http://medicine.iupui.edu/clinpharm/ddis/clinical-table/)

Human Cytochrome P450 (CYP) Allele Nomenclature Database (http://www.cypalleles.ki.se/)

Endogenous ligands

Genes in this family provide instructions for making specialized proteins called endogenous ligands. A ligand is a protein that attaches (binds) to another protein called a receptor; receptor proteins have specific sites into which the ligands fit like keys into locks. Endogenous ligands are those that are produced in the body, not those introduced into the body, such as certain drugs.

Together, ligands and their receptors trigger signals that affect cell development and function. Alterations in ligands can impair cell signaling and change the normal activities of cells. Because ligands mediate many different functions in the body, mutations in genes in the endogenous ligands gene family can have a variety of effects.

Examples of genes in this gene family: *AMH*, *APP*, *AVP*, *BDNF*, *EDN3*, *FN1*, *GDF3*, *GH1*, *HTT*, *PROK2*, *PSAP*, *RB1*, *TGFB1*, *TGFB2*, *TSHB*, *VWF*, *WNT3*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (http://www.genenames.org/cgi-bin/genefamilies/) and their member genes.

References

Barrow JR, Thomas KR, Boussadia-Zahui O, Moore R, Kemler R, Capecchi MR, McMahon AP. Ectodermal Wnt3/beta-catenin signaling is required for the establishment and maintenance of the apical ectodermal ridge. Genes Dev. 2003 Feb 1;17(3):394-409. PubMed: 12569130 (http://www.ncbi.nlm.nih.gov/pubmed/12569130). Free full-text available from PubMed Central: PMC195987 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC195987/).

Baynash AG, Hosoda K, Giaid A, Richardson JA, Emoto N, Hammer RE, Yanagisawa M. Interaction of endothelin-3 with endothelin-B receptor is essential for development of epidermal melanocytes and enteric neurons. Cell. 1994 Dec 30;79(7):1277-85. PubMed: 8001160 (http://www.ncbi.nlm.nih.gov/pubmed/8001160).

Kristiansen K. Molecular mechanisms of ligand binding, signaling, and regulation within the superfamily of G-protein-coupled receptors: molecular modeling and mutagenesis approaches to receptor structure and function. Pharmacol Ther. 2004 Jul;103(1):21-80. Review. PubMed: 15251227 (http://www.ncbi.nlm.nih.gov/pubmed/15251227).

Learn more about the endogenous ligands gene family:

Molecular Cell Biology (fourth edition, 2000): Receptor Proteins Exhibit Ligand-Binding and Effector Specificity (http://www.ncbi.nlm.nih.gov/books/NBK21517/#A5720)

Human leukocyte antigens

The HLA gene family provides instructions for making a group of related proteins known as the human leukocyte antigen (HLA) complex. The HLA complex helps the immune system distinguish the body's own proteins from proteins made by foreign invaders such as viruses and bacteria.

HLA is the human version of the major histocompatibility complex (MHC), a gene family that occurs in many species. In humans, the MHC complex consists of more than 200 genes located close together on chromosome 6. Genes in this complex are categorized into three basic groups: class I, class II, and class III.

Humans have three main MHC class I genes, known as *HLA-A*, *HLA-B*, and *HLA-C*. The proteins produced from these genes are present on the surface of almost all cells. On the cell surface, these proteins are bound to protein fragments (peptides) that have been exported from within the cell. MHC class I proteins display these peptides to the immune system. If the immune system recognizes the peptides as foreign (such as viral or bacterial peptides), it responds by triggering the infected cell to self-destruct.

There are six main MHC class II genes in humans: HLA-DPA1, *HLA-DPB1*, *HLA-DQA1*, *HLA-DQB1*, HLA-DRA, and *HLA-DRB1*. MHC class II genes provide instructions for making proteins that are present almost exclusively on the surface of certain immune system cells. Like MHC class I proteins, these proteins display peptides to the immune system.

The proteins produced from MHC class III genes have somewhat different functions; they are involved in inflammation and other immune system activities. The functions of some MHC genes are unknown.

HLA genes have many possible variations, allowing each person's immune system to react to a wide range of foreign invaders. Some HLA genes have hundreds of identified versions (alleles), each of which is given a particular number (such as HLA-B27). Closely related alleles are categorized together; for example, at least 40 very similar alleles are subtypes of HLA-B27. These subtypes are designated as *HLA-B**2701 to *HLA-B**2743.

More than 100 diseases have been associated with different alleles of HLA genes. For example, the HLA-B27 allele increases the risk of developing an inflammatory joint disease called ankylosing spondylitis. Many other disorders involving abnormal immune function and some forms of cancer have also been associated with specific HLA alleles. However, it is often unclear what role HLA genes play in the risk of developing these diseases.

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (http://www.genenames.org/cgi-bin/genefamilies/) and their member genes.

References

Khan MA, Mathieu A, Sorrentino R, Akkoc N. The pathogenetic role of HLA-B27 and its subtypes. Autoimmun Rev. 2007 Jan;6(3):183-9. Epub 2006 Dec 8. Review. PubMed: 17289555 (http://www.ncbi.nlm.nih.gov/pubmed/17289555).

Marsh SG, Albert ED, Bodmer WF, Bontrop RE, Dupont B, Erlich HA, Geraghty DE, Hansen JA, Hurley CK, Mach B, Mayr WR, Parham P, Petersdorf EW, Sasazuki T, Schreuder GM, Strominger JL, Svejgaard A, Terasaki PI, Trowsdale J. Nomenclature for Factors of the HLA System, 2004. Hum Immunol. 2005 May;66(5):571-636. Epub 2005 Mar 3. PubMed: 15935895 (http://www.ncbi.nlm.nih.gov/pubmed/15935895).

Shiina T, Inoko H, Kulski JK. An update of the HLA genomic region, locus information and disease associations: 2004. Tissue Antigens. 2004 Dec;64(6):631-49. Review. PubMed: 15546336 (http://www.ncbi.nlm.nih.gov/pubmed/15546336).

Learn more about the human leukocyte antigens gene family:

Merck Manual for Health Care Professionals: Human Leukocyte Antigen (HLA) System (http://www.merckmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/human-leukocyte-antigen-hla-system)

Immunobiology (fifth edition 2001): The Major Histocompatibility Complex and its Functions (http://www.ncbi.nlm.nih.gov/books/NBK27156/)

Cold Spring Harbor Laboratory: Chromosome 6: HLA Genes and the Human Immune System (https://www.dnalc.org/view/15401-Chromosome-6-HLA-genes-and-the-human-immune-system-Matt-Ridley.html)

The Anthony Nolan Trust: HLA Informatics Group (https://www.anthonynolan.org/clinicians-and-researchers/anthony-nolan-research-institute/hla-informatics-group)

EMBL-EBI: IMGT/HLA Database (http://www.ebi.ac.uk/ipd/imgt/hla/)

Homeoboxes

Homeobox genes are a large family of similar genes that direct the formation of many body structures during early embryonic development. In humans, the homeobox gene family contains an estimated 235 functional genes and 65 pseudogenes (structurally similar genes that do not provide instructions for making proteins). Homeobox genes are present on every human chromosome, and they often appear in clusters. Many classes and subfamilies of homeobox genes have been described, although these groupings are used inconsistently.

Homeobox genes contain a particular DNA sequence that provides instructions for making a string of 60 protein building blocks (amino acids) known as the homeodomain. Most homeodomain-containing proteins act as transcription factors, which means they bind to and control the activity of other genes. The homeodomain is the part of the protein that attaches (binds) to specific regulatory regions of the target genes.

Genes in the homeobox family are involved in a wide range of critical activities during development. These activities include directing the formation of limbs and organs along the anterior-posterior axis (the imaginary line that runs from head to tail in animals) and regulating the process by which cells mature to carry out specific functions (differentiation). Some homeobox genes act as tumor suppressors, which means they help prevent cells from growing and dividing too rapidly or in an uncontrolled way.

Because homeobox genes have so many important functions, mutations in these genes are responsible for a variety of developmental disorders. For example, mutations in the HOX group of homeobox genes typically cause limb malformations. Changes in PAX homeobox genes often result in eye disorders, and changes in MSX homeobox genes cause abnormal head, face, and tooth development. Additionally, increased or decreased activity of certain homeobox genes has been associated with several forms of cancer later in life.

Examples of genes in this gene family: *ALX4*, *ARX*, *HOXA13*, *HOXB13*, *OTX2*, *PAX3*, *PAX6*, *POU3F4*, *SHOX*, *SIX3*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (http://www.genenames.org/cgi-bin/genefamilies/) and their member genes.

References

Boncinelli E. Homeobox genes and disease. Curr Opin Genet Dev. 1997 Jun;7(3):331-7. Review. PubMed: 9229108 (http://www.ncbi.nlm.nih.gov/pubmed/9229108).

Cillo C, Cantile M, Faiella A, Boncinelli E. Homeobox genes in normal and malignant cells. J Cell Physiol. 2001 Aug;188(2):161-9. Review. PubMed: 11424082 (http://www.ncbi.nlm.nih.gov/pubmed/11424082).

Holland PW, Booth HA, Bruford EA. Classification and nomenclature of all human homeobox genes. BMC Biol. 2007 Oct 26;5:47. PubMed: 17963489 (http://www.ncbi.nlm.nih.gov/pubmed/17963489). Free full-text available from PubMed Central: PMC2211742 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2211742/).

Zhao Y, Westphal H. Homeobox genes and human genetic disorders. Curr Mol Med. 2002 Feb;2(1):13-23. Review. PubMed: 11898846 (http://www.ncbi.nlm.nih.gov/pubmed/11898846).

Learn more about the homeoboxes gene family:

National Human Genome Research Institute, NIH: Homeodomain Resource (http://research.nhgri.nih.gov/homeodomain/)

Arizona State University: Homeobox Genes and the Homeobox (http://embryo.asu.edu/pages/homeobox-genes-and-homeobox-0)

Keratins

Genes in the KRT family provide instructions for making proteins called keratins. Keratins are a group of tough, fibrous proteins that form the structural framework of epithelial cells, which are cells that line the surfaces and cavities of the body. Epithelial cells make up tissues such as the hair, skin, and nails. These cells also line the internal organs and are an important part of many glands.

Keratins are best known for providing strength and resilience to cells that form the hair, skin, and nails. These proteins allow tissues to resist damage from friction and minor trauma, such as rubbing and scratching. Keratins are also involved in several other critical cell functions, including cell movement (migration), regulation of cell size, cell growth and division (proliferation), wound healing, and transport of materials within cells.

Humans have at least 54 functional keratin genes, which are divided into type I and type II keratins. Most of the type I keratin genes, designated *KRT9* through KRT20, are located in a cluster on chromosome 17. The type II keratin genes, designated *KRT1* through *KRT8*, are found in another cluster on chromosome 12.

Different combinations of keratin proteins are found in different tissues. In each tissue, a type I keratin pairs with a type II keratin to form a structure called a heterodimer. Heterodimers interact with one another to form strong, flexible fibers called keratin intermediate filaments. These filaments assemble into a dense network, which forms the structural framework of cells.

Mutations in at least 20 KRT genes have been found to cause human diseases affecting the skin, hair, nails, and related tissues. The most well-studied of these diseases include epidermolysis bullosa simplex (EBS) and pachyonychia congenita. Mutations in KRT genes alter the structure of keratins, which prevent them from forming an effective network of keratin intermediate filaments. Without this network, cells become fragile and are easily damaged, making tissues less resistant to friction and minor trauma. Even normal activities such as walking can cause skin cells to break down, resulting in the formation of painful blisters and calluses.

Examples of genes in this gene family: *KRT3*, *KRT4*, *KRT5*, *KRT6A*, *KRT6B*, *KRT6C*, *KRT10*, *KRT12*, *KRT13*, *KRT14*, *KRT16*, *KRT17*, *KRT81*, *KRT83*, *KRT86*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (http://www.genenames.org/cgi-bin/genefamilies/) and their member genes.

References

Lane EB, McLean WH. Keratins and skin disorders. J Pathol. 2004 Nov;204(4):355-66. Review. PubMed: 15495218 (http://www.ncbi.nlm.nih.gov/pubmed/15495218).

Magin TM, Vijayaraj P, Leube RE. Structural and regulatory functions of keratins. Exp Cell Res. 2007 Jun 10;313(10):2021-32. Epub 2007 Mar 15. Review. PubMed: 17434482 (http://www.ncbi.nlm.nih.gov/pubmed/17434482).

Rugg EL, Leigh IM. The keratins and their disorders. Am J Med Genet C Semin Med Genet. 2004 Nov 15;131C(1):4-11. Review. PubMed: 15452838 (http://www.ncbi.nlm.nih.gov/pubmed/15452838).

Schweizer J, Bowden PE, Coulombe PA, Langbein L, Lane EB, Magin TM, Maltais L, Omary MB, Parry DA, Rogers MA, Wright MW. New consensus nomenclature for mammalian keratins. J Cell Biol. 2006 Jul 17;174(2):169-74. Epub 2006 Jul 10. PubMed: 16831889 (http://www.ncbi.nlm.nih.gov/pubmed/16831889).

Smith F. The molecular genetics of keratin disorders. Am J Clin Dermatol. 2003;4(5):347-64. Review. PubMed: 12688839 (http://www.ncbi.nlm.nih.gov/pubmed/12688839).

Szeverenyi I, Cassidy AJ, Chung CW, Lee BT, Common JE, Ogg SC, Chen H, Sim SY, Goh WL, Ng KW, Simpson JA, Chee LL, Eng GH, Li B, Lunny DP, Chuon D, Venkatesh A, Khoo KH, McLean WH, Lim YP, Lane EB. The Human Intermediate Filament Database: comprehensive information on a gene family involved in many human diseases. Hum Mutat. 2008 Mar;29(3):351-60. PubMed: 18033728 (http://www.ncbi.nlm.nih.gov/pubmed/18033728).

Learn more about the keratins gene family:

Molecular Biology of the Cell (fourth edition, 2002): Keratin Filaments in Epithelial Cells (Image) (http://www.ncbi.nlm.nih.gov/books/NBK26862/figure/A2988/)

The Cell: A Molecular Approach (second edition, 2000): Intermediate Filaments (http://www.ncbi.nlm.nih.gov/books/NBK9834/)

Mitochondrial respiratory chain complex

Genes in the mitochondrial respiratory chain complex gene family provide instructions for proteins involved in oxidative phosphorylation, also called the respiratory chain. Oxidative phosphorylation is an important cellular process that uses oxygen and simple sugars to create adenosine triphosphate (ATP), the cell's main energy source. Five protein complexes, made up of several proteins each, are involved in this process. The complexes are named complex I, complex II, complex III, complex IV, and complex V.

Oxidative phosphorylation occurs in mitochondria, which are specialized, energy-producing structures inside cells. Within mitochondria, the five protein complexes are embedded in a tightly folded membrane called the inner mitochondrial membrane. During oxidative phosphorylation, the protein complexes carry out chemical reactions that drive the production of ATP. Specifically, they create an unequal electrical charge on either side of the inner mitochondrial membrane through a step-by-step transfer of negatively charged particles called electrons. This difference in electrical charge provides the energy for ATP production.

Most DNA is contained in a cell's nucleus and is called nuclear DNA. Mitochondria also contain a small amount of DNA, known as mitochondrial DNA. The mitochondrial respiratory chain complex gene family includes genes found in nuclear DNA as well as genes found in mitochondrial DNA. Mutations in either nuclear or mitochondrial genes in the mitochondrial respiratory chain complex gene family can cause disease.

Examples of genes in this gene family: *MT-ATP6*, *MT-CYB*, *SDHA*, *SDHB*, *SDHC*, *SDHD*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (http://www.genenames.org/cgi-bin/genefamilies/) and their member genes.

References

Hanna MG, Nelson IP. Genetics and molecular pathogenesis of mitochondrial respiratory chain diseases. Cell Mol Life Sci. 1999 May;55(5):691-706. Review. PubMed: 10379358 (http://www.ncbi.nlm.nih.gov/pubmed/10379358).

Hatefi Y. The mitochondrial electron transport and oxidative phosphorylation system. Annu Rev Biochem. 1985;54:1015-69. Review. No abstract available. PubMed: 2862839 (http://www.ncbi.nlm.nih.gov/pubmed/2862839).

Saraste M. Oxidative phosphorylation at the fin de siècle. Science. 1999 Mar 5;283(5407):1488-93. Review. PubMed: 10066163 (http://www.ncbi.nlm.nih.gov/pubmed/10066163).

Shoubridge EA. Nuclear genetic defects of oxidative phosphorylation. Hum Mol Genet. 2001 Oct 1;10(20):2277-84. Review. PubMed: 11673411 (http://www.ncbi.nlm.nih.gov/pubmed/11673411).

Learn more about the mitochondrial respiratory chain complex gene family:

Biochemistry (5th Edition, 2002): Oxidative Phosphorylation in Eukaryotes Takes Place in Mitochondria (http://www.ncbi.nlm.nih.gov/books/NBK22422/#A2570)

Molecular Cell Biology (4th Edition, 2000): Electrons Flow from FADH2 and NADH to O2 via a Series of Multiprotein Complexes (http://www.ncbi.nlm.nih.gov/books/NBK21528/#A4383)

Myosins

Genes in this family provide instructions for making related proteins called myosins. Myosins are often referred to as molecular motors because they use energy to move. They interact with another protein called actin; actin proteins are organized into filaments to form a network (the cytoskeleton) that gives structure to cells and can act as a track for myosin to move along. Some myosin proteins attach (bind) to other proteins and transport them within and between cells along the actin track.

Some myosins are involved in muscle contraction. These myosins interact with other myosin proteins, forming thick filaments. In muscle cells, thick filaments made up of myosin and thin filaments made up of actin compose structures called sarcomeres, which are the basic units of muscle contraction. The overlapping thick and thin filaments bind to each other and release, which allows the filaments to move relative to one another so that muscles can contract. Mutations in genes that provide instructions for making muscle myosins can cause severe abnormalities in the muscles used for movement (skeletal muscles) or in the heart (cardiac) muscle. Cardiac muscle abnormalities can lead to heart failure and sudden death.

Myosin proteins are involved in many cellular functions. Their ability to transport materials and create force through contractions make them important in the process of cell division. Myosins are also involved in cell movement. Some myosins are found in specialized structures in the inner ear known as stereocilia. These myosins are thought to help properly organize the stereocilia. Abnormalities in these myosins can cause deafness.

Examples of genes in this gene family: *MYH3*, *MYH6*, *MYH7*, *MYH9*, *MYH11*, *MYO5A*, *MYO5B*, *MYO7A*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (http://www.genenames.org/cgi-bin/genefamilies/) and their member genes.

References

Dantzig JA, Liu TY, Goldman YE. Functional studies of individual myosin molecules. Ann N Y Acad Sci. 2006 Oct;1080:1-18. Review. PubMed: 17132771 (http://www.ncbi.nlm.nih.gov/pubmed/17132771).

Hartman MA, Spudich JA. The myosin superfamily at a glance. J Cell Sci. 2012 Apr 1;125(Pt 7):1627-32. doi: 10.1242/jcs.094300. PubMed: 22566666 (http://www.ncbi.nlm.nih.gov/pubmed/22566666). Free full-text available from PubMed Central: PMC3346823 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3346823/).

Syamaladevi DP, Spudich JA, Sowdhamini R. Structural and functional insights on the Myosin superfamily. Bioinform Biol Insights. 2012;6:11-21. doi: 10.4137/BBI.S8451. Epub 2012 Feb 1. PubMed: 22399849 (http://www.ncbi.nlm.nih.gov/pubmed/22399849). Free full-text available from PubMed Central: PMC3290112 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3290112/).

Learn more about the myosins gene family:

Biochemistry (fifth edition, 2002): Myosins Move Along Actin Filaments (http://www.ncbi.nlm.nih.gov/books/NBK22418/)

Molecular Biology of the Cell (fourth edition, 2002): Actin-Based Motor Proteins Are Part of the Myosin Superfamily (http://www.ncbi.nlm.nih.gov/books/NBK26888/#A3042)

Molecular Cell Biology (fourth edition, 2000): Myosin: The Actin Motor Protein (http://www.ncbi.nlm.nih.gov/books/NBK21724/)

Transfer RNAs

Genes in the TRNA gene family provide instructions for making molecules called transfer RNAs (tRNAs). Transfer RNAs are a particular type of RNA, which is a chemical cousin of DNA. These molecules help assemble protein building blocks (amino acids) into functioning proteins. Each tRNA attaches to a particular amino acid. During protein assembly, the tRNA recognizes a specific three-letter sequence (a codon) in the genetic blueprint for making proteins and inserts the amino acid into the appropriate location in the growing protein.

There are two classes of tRNA: cytoplasmic and mitochondrial. Cytoplasmic tRNAs are found in the fluid inside cells (the cytoplasm). These tRNAs help produce proteins from genes located in the DNA in the nucleus of the cell (nuclear DNA). Although most DNA is nuclear, cellular structures called mitochondria have a small amount of their own DNA, called mitochondrial DNA. Proteins produced from genes located in mitochondrial DNA are assembled by mitochondrial tRNAs.

Mutations in TRNA genes reduce the ability of the tRNA to add amino acids to proteins, slowing protein production. Mutations that affect mitochondrial tRNAs impair the ability of mitochondria to provide energy for cells or to control blood sugar levels. These mutations can cause a variety of signs and symptoms, including muscle weakness, seizures, neurological problems, hearing loss, and diabetes. Mutations in genes that provide instructions for cytoplasmic tRNAs do not appear to cause disease.

Examples of genes in this gene family: *MT-TE*, *MT-TH*, *MT-TK*, *MT-TL1*, *MT-TS1*, *MT-TV*

The HUGO Gene Nomenclature Committee (HGNC) provides an index of gene families (http://www.genenames.org/cgi-bin/genefamilies/) and their member genes.

References

McClain WH. Transfer RNA identity. FASEB J. 1993 Jan;7(1):72-8. Review. PubMed: 8422977 (http://www.ncbi.nlm.nih.gov/pubmed/8422977).

Rich A, RajBhandary UL. Transfer RNA: molecular structure, sequence, and properties. Annu Rev Biochem. 1976;45:805-60. Review. PubMed: 60910 (http://www.ncbi.nlm.nih.gov/pubmed/60910).

Suzuki T, Nagao A, Suzuki T. Human mitochondrial tRNAs: biogenesis, function, structural aspects, and diseases. Annu Rev Genet. 2011;45:299-329. Epub 2011 Sep 6. Review. PubMed: 21910628 (http://www.ncbi.nlm.nih.gov/pubmed/21910628).

Learn more about the transfer RNAs gene family:

Biochemistry (fifth edition, 2002): Protein Synthesis Requires the Translation of Nucleotide Sequences into Amino Acid Sequences (http://www.ncbi.nlm.nih.gov/books/NBK22421/)

The Cell: A Molecular Approach (second edition, 2000): Translation of mRNA (http://www.ncbi.nlm.nih.gov/books/NBK9849/)

Molecular Biology of the Cell (fourth edition, 2002): From RNA to Protein (http://www.ncbi.nlm.nih.gov/books/NBK26829/)

Inheriting Genetic Conditions

Table of Contents

What does it mean if a disorder seems to run in my family? 103

Why is it important to know my family medical history? 106

What are the different ways in which a genetic condition can be inherited? 108

If a genetic disorder runs in my family, what are the chances that my children will have the condition? 120

What are reduced penetrance and variable expressivity? 123

What do geneticists mean by anticipation? 125

What are genomic imprinting and uniparental disomy? 126

Are chromosomal disorders inherited? 128

Why are some genetic conditions more common in particular ethnic groups? 129

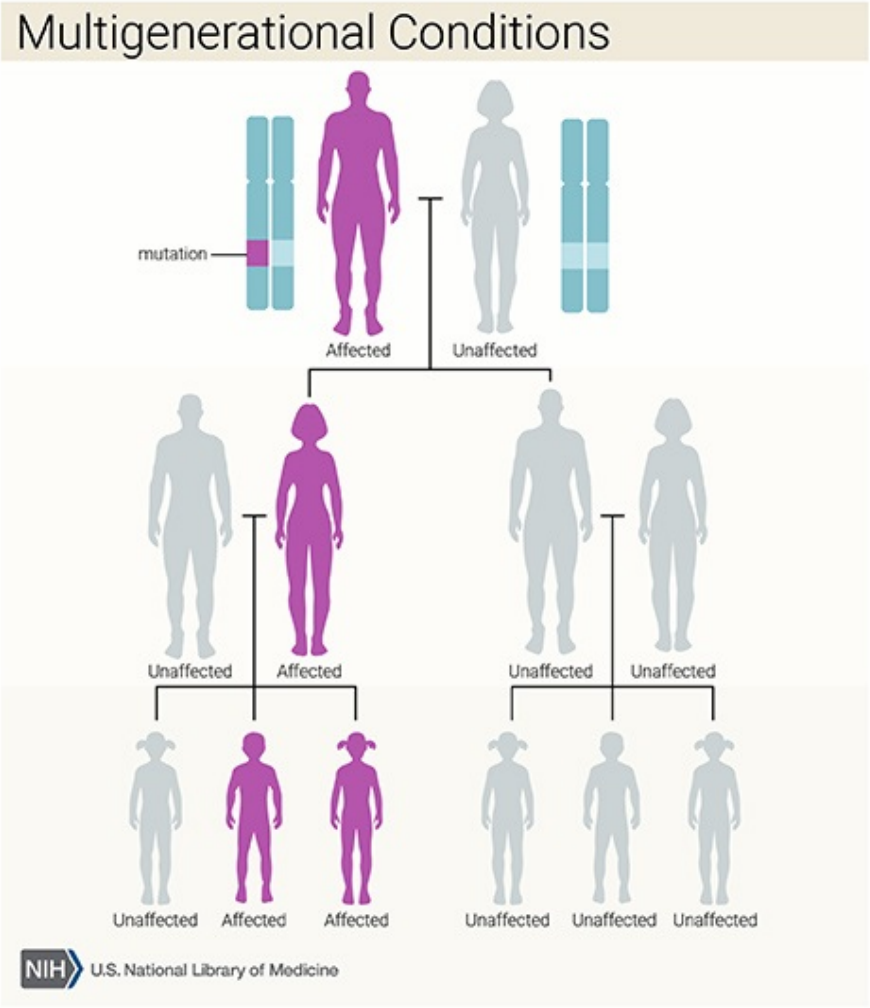
What does it mean if a disorder seems to run in my family?

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 caused by mutations in single genes. 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. He or she will ask about the health of people from several generations of the family, usually first-, second-, and third-degree relatives.

Degrees of relationship

Degrees of relationship	Examples
First-degree relatives	Parents, children, brothers, and sisters
Second-degree relatives	Grandparents, aunts and uncles, nieces and nephews, and grandchildren
Third-degree relatives	First cousin



This condition affects members in each generation of a family.

For general information about disorders that run in families:

Genetics Home Reference provides consumer-friendly summaries of genetic conditions (https://ghr.nlm.nih.gov/condition). 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 Coriell Personalized Medicine Collaborative provides a brief introduction to heritable diseases in the article Heredity: It Runs in the Family (https://cpmc.coriell.org/genetic-education/it-runs-in-the-family).

The Genetic Science Learning Center at the University of Utah offers interactive tools about disorders that run in families (http://learn.genetics.utah.edu/content/history).

The National Human Genome Research Institute offers a brief fact sheet called Frequently Asked Questions About Genetic Disorders (https://www.genome.gov/19016930).

The Centre for Genetics Education provides an overview of genetic conditions (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetGeneticConditions).

Why is it important to know my family medical history?

A family medical history is a record of health information about a person and his or her close relatives. A complete record includes information from three generations of relatives, including children, brothers and sisters, parents, aunts and uncles, nieces and nephews, grandparents, and cousins.

Families have many factors in common, including their genes, environment, and lifestyle. Together, these factors can give clues to medical conditions that may run in a family. By noticing patterns of disorders among relatives, healthcare professionals can determine whether an individual, other family members, or future generations may be at an increased risk of developing a particular condition.

A family medical history can identify people with a higher-than-usual chance of having common disorders, such as heart disease, high blood pressure, stroke, certain cancers, and diabetes. These complex disorders are influenced by a combination of genetic factors, environmental conditions, and lifestyle choices. A family history also can provide information about the risk of rarer conditions caused by mutations in a single gene, such as cystic fibrosis and sickle cell disease.

While a family medical history provides information about the risk of specific health concerns, having relatives with a medical condition does not mean that an individual will definitely develop that condition. On the other hand, a person with no family history of a disorder may still be at risk of developing that disorder.

Knowing one’s family medical history allows a person to take steps to reduce his or her risk. For people at an increased risk of certain cancers, healthcare professionals may recommend more frequent screening (such as mammography or colonoscopy) starting at an earlier age. Healthcare providers may also encourage regular checkups or testing for people with a medical condition that runs in their family. Additionally, lifestyle changes such as adopting a healthier diet, getting regular exercise, and quitting smoking help many people lower their chances of developing heart disease and other common illnesses.

The easiest way to get information about family medical history is to talk to relatives about their health. Have they had any medical problems, and when did they occur? A family gathering could be a good time to discuss these issues. Additionally, obtaining medical records and other documents (such as obituaries and death certificates) can help complete a family medical history. It is important to keep this information up-to-date and to share it with a healthcare professional regularly.

For more information about family medical history:

NIHSeniorHealth, a service of the National Institutes of Health, provides information and tools (http://nihseniorhealth.gov/creatingafamilyhealthhistory/whycreateafamilyhealthhistory/01.html) for documenting family health history. Additional information about family history (https://medlineplus.gov/familyhistory.html) is available from MedlinePlus.

Educational resources related to family health history (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=5&sid=13) are available from GeneEd.

The Centers for Disease Control and Prevention's (CDC) of Public Health Genomics provides information about the importance of family medical history (http://www.cdc.gov/genomics/famhistory/famhist.htm). This resource also includes links to publications, reports, and tools for recording family health information.

The Office of the Surgeon General offers a tool called My Family Health Portrait (https://familyhistory.hhs.gov/) that allows you to enter, print, and update your family health history.

The American Medical Association provides family history tools (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/family-history.page), including questionnaires and forms for collecting medical information.

Links to additional resources (http://www.kumc.edu/gec/pedigree.html) are available from the University of Kansas Medical Center. The Genetic Alliance also offers a list of links to family history resources (http://www.geneticalliance.org/programs/genesinlife/fhh).

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 patterns, depending on the gene involved:

Patterns of inheritance

Inheritance pattern	Description	Examples
Autosomal dominant	One mutated copy of the gene in each cell is sufficient for a person to be affected by an autosomal dominant disorder. In some cases, an affected person inherits the condition from an affected parent (image on page 112). In others, the condition may result from a new mutation in the gene and occur in people with no history of the disorder in their family (image on page 113).	Huntington disease, Marfan syndrome
Autosomal recessive	In autosomal recessive inheritance, both copies of the gene in each cell have mutations (image on page 114). The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. Autosomal recessive disorders are typically not seen in every generation of an affected family.	cystic fibrosis, sickle cell disease

Inheritance pattern	Description	Examples
X-linked dominant	X-linked dominant disorders are caused by mutations in genes on the X chromosome, one of the two sex chromosomes in each cell. In females (who have two X chromosomes), a mutation in one of the two copies of the gene in each cell is sufficient to cause the disorder. In males (who have only one X chromosome), a mutation in the only copy of the gene in each cell causes the disorder (image on page 115). In most cases, males experience more severe symptoms of the disorder than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).	fragile X syndrome
X-linked recessive	X-linked recessive disorders are also caused by mutations in genes on the X chromosome. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder (image on page 116). Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked recessive disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).	hemophilia, Fabry disease
Y-linked	A condition is considered Y-linked if the mutated gene that causes the disorder is located on the Y chromosome, one of the two sex chromosomes in each of a male's cells. Because only males have a Y chromosome, in Y-linked inheritance, a mutation can only be passed from father to son (image on page 117).	Y chromosome infertility, some cases of Swyer syndrome

Inheritance pattern	Description	Examples
Codominant	In codominant inheritance, two different versions (alleles) of a gene are expressed, and each version makes a slightly different protein (image on page 118). Both alleles influence the genetic trait or determine the characteristics of the genetic condition.	*ABO* blood group, alpha-1 antitrypsin deficiency
Mitochondrial	Mitochondrial 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 mutations to their children (image on page 119). Conditions resulting from mutations in mitochondrial DNA can appear in every generation of a family and can affect both males and females, but fathers do not pass these disorders to their daughters or sons.	Leber hereditary optic neuropathy (LHON)

Many health conditions are caused by the combined effects of multiple genes or by interactions between genes and the environment. Such disorders usually 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 51

Disorders caused by changes in the number or structure of chromosomes also 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 128

Other genetic factors sometimes influence how a disorder is inherited. For an example, please see What are genomic imprinting and uniparental disomy? on page 126

For more information about inheritance patterns:

Resources related to heredity/inheritance patterns (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=5) and Mendelian inheritance (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=5&sid=6) are available from GeneEd.

The Centre for Genetics Education provides information about many of the inheritance patterns outlined above:

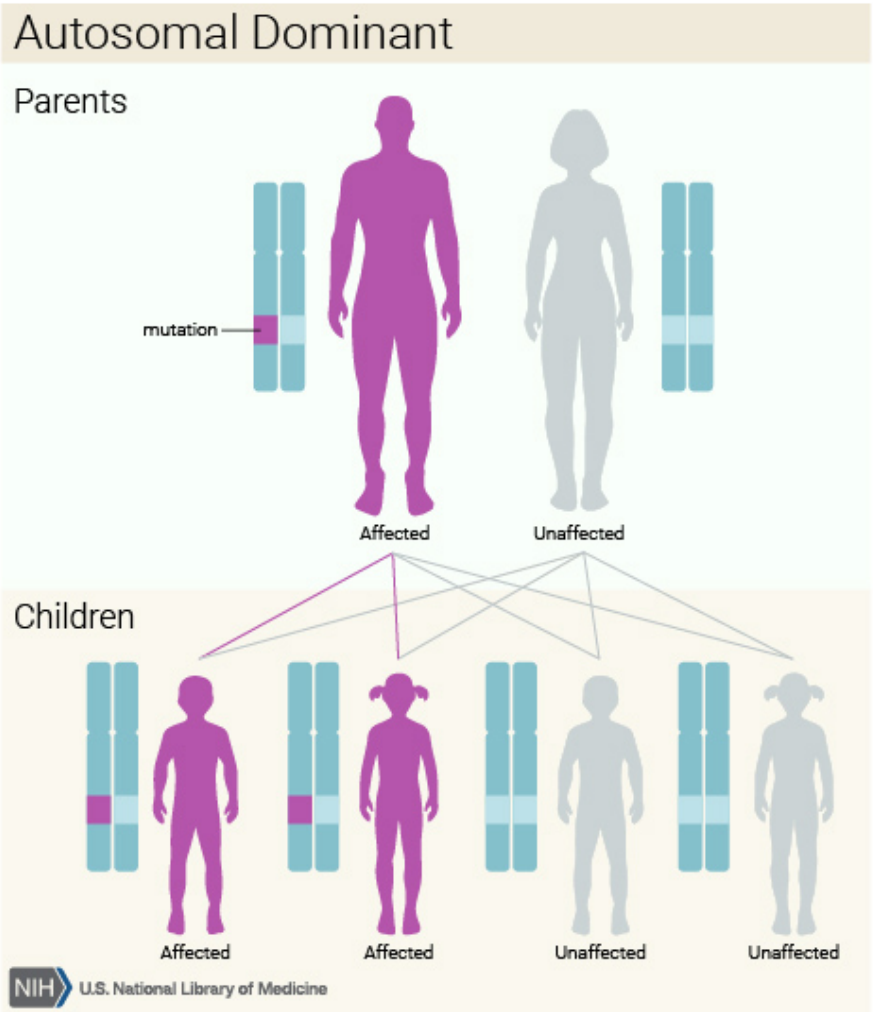
- Autosomal dominant inheritance (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetADInheritance)
- Autosomal recessive inheritance (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetARInheritance)
- X-linked dominant inheritance (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetXLDInheritance)
- X-linked recessive inheritance (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetXLRInheritance)
- Mitochondrial inheritance (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetMitochondria)

EuroGentest also offers explanations of Mendelian inheritance patterns:

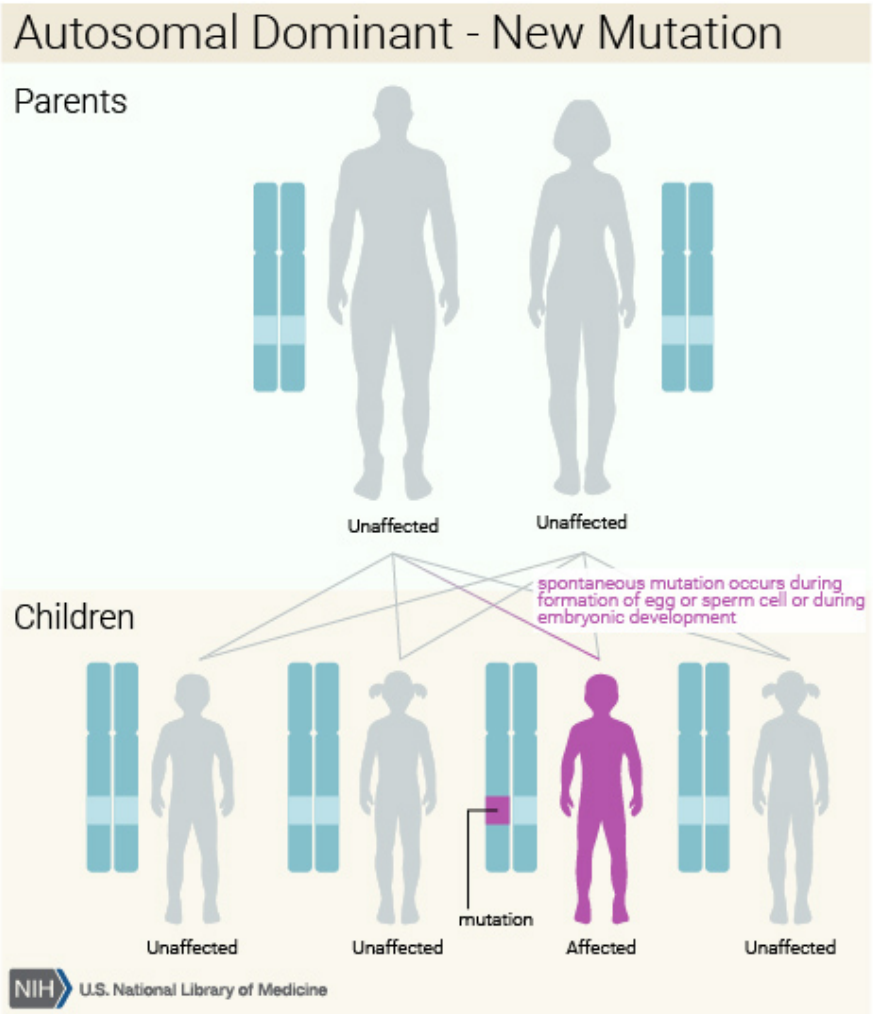
- Autosomal dominant inheritance (http://www.eurogentest.org/index.php?id=614)
- Autosomal recessive inheritance (http://www.eurogentest.org/index.php?id=619)
- X-linked inheritance (http://www.eurogentest.org/index.php?id=623)

Additional information about inheritance patterns is available from The Merck Manual (http://www.merckmanuals.com/professional/special-subjects/general-principles-of-medical-genetics/single-gene-defects).

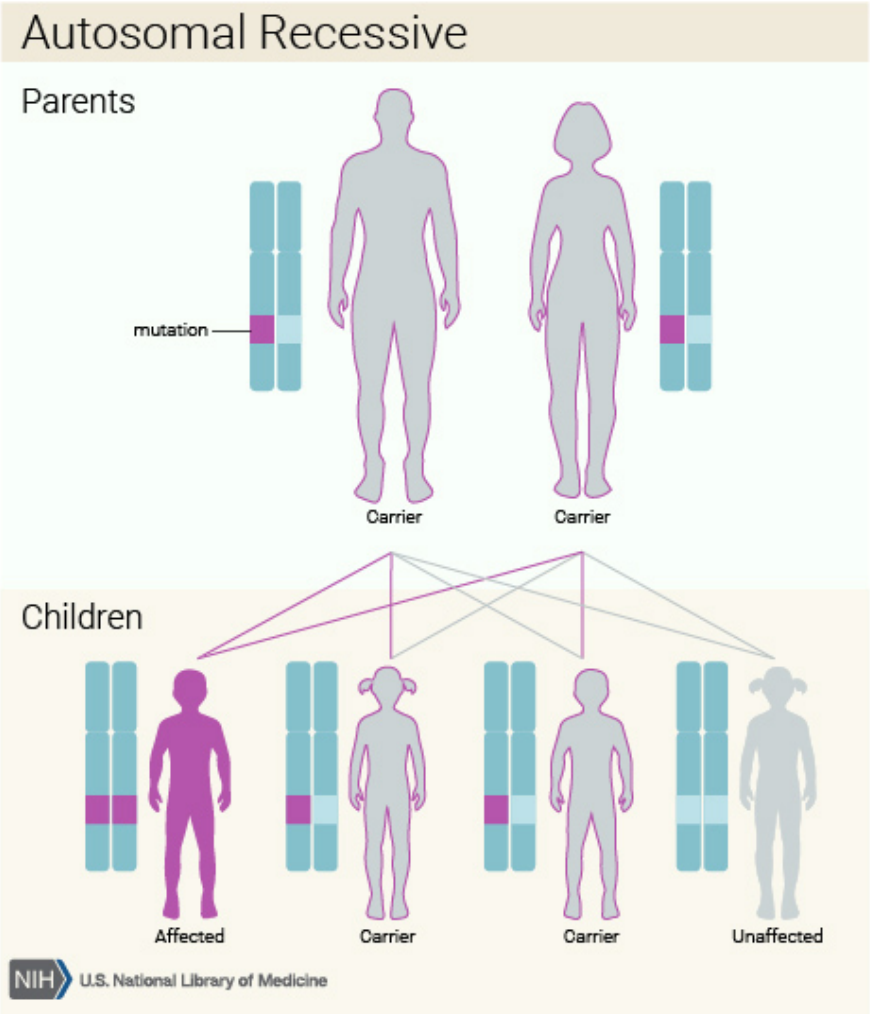
Images



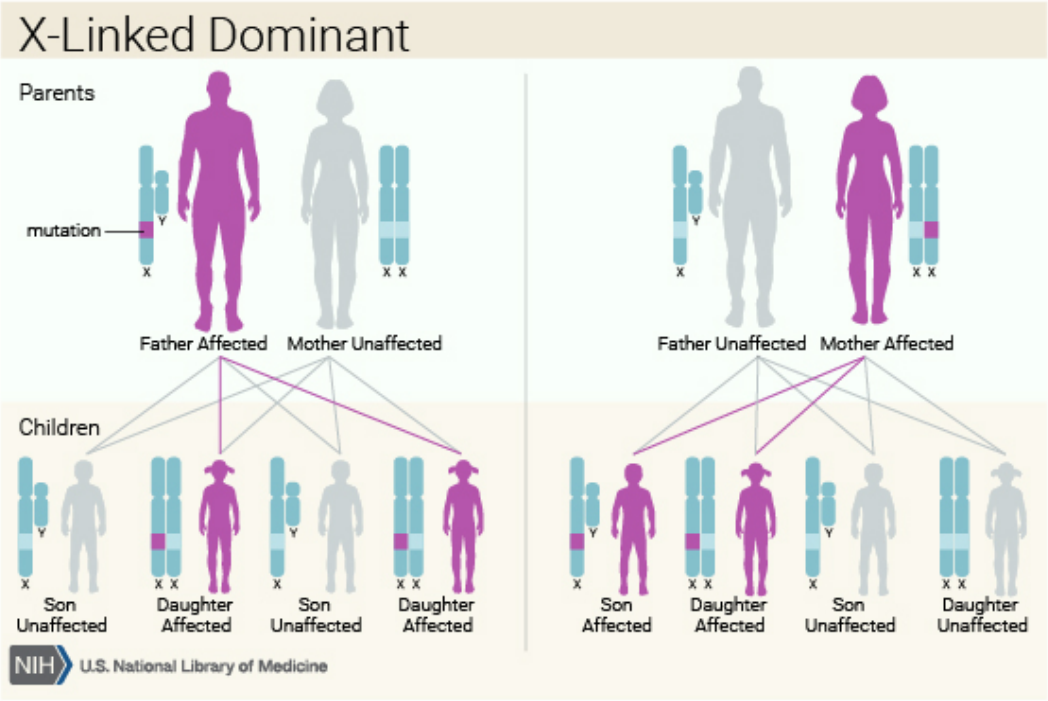
In this example, a man with an autosomal dominant disorder has two affected children and two unaffected children.



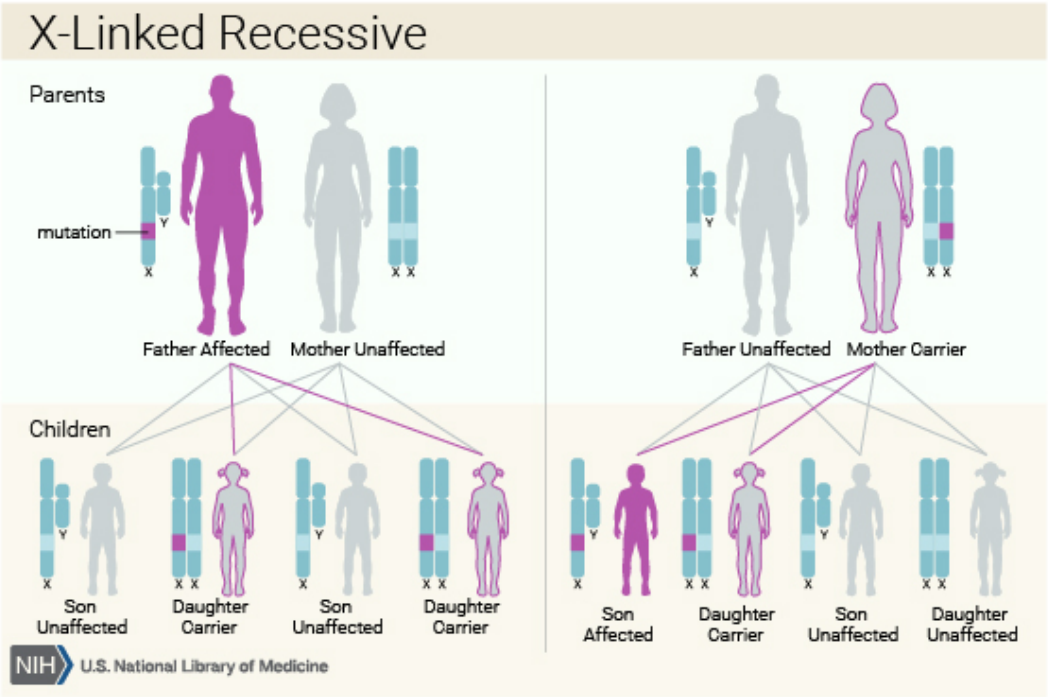
In this example, a child with an autosomal dominant condition has the disorder as a result of a new (de novo) mutation that occurred during the formation of an egg or sperm cell or early in embryonic development.



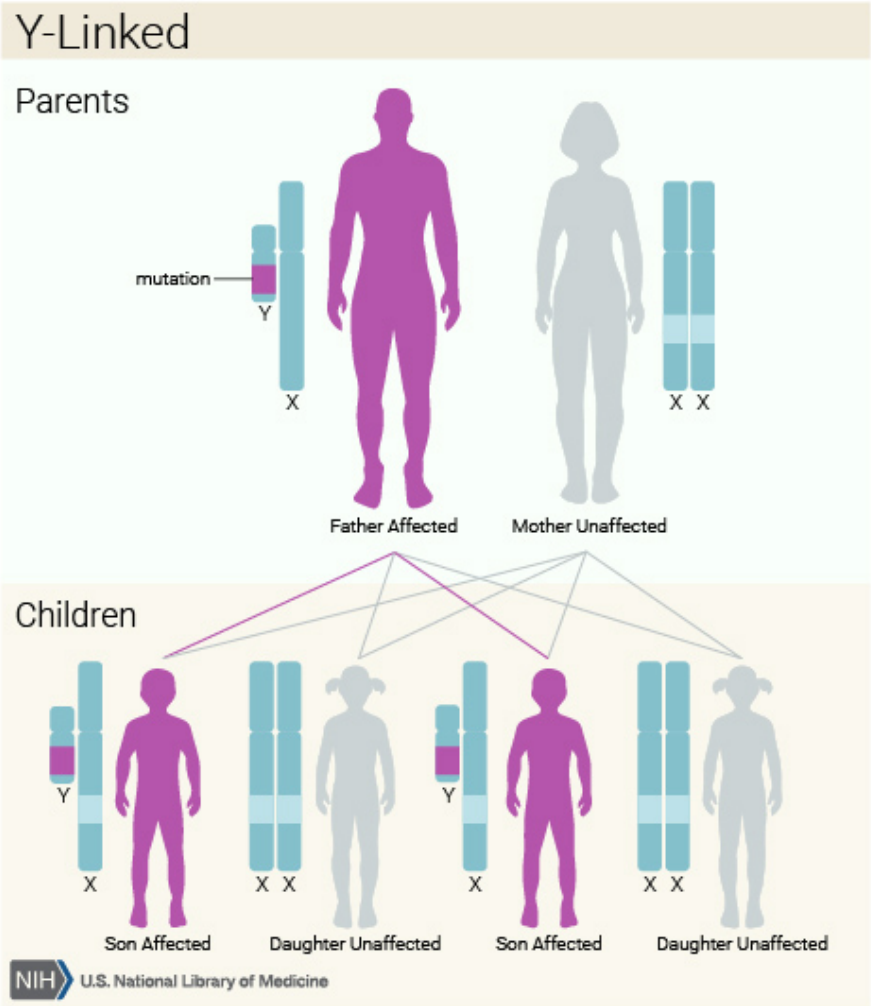
In this example, two unaffected parents each carry one copy of a gene mutation for an autosomal recessive disorder. They have one affected child and three unaffected children, two of which carry one copy of the gene mutation.



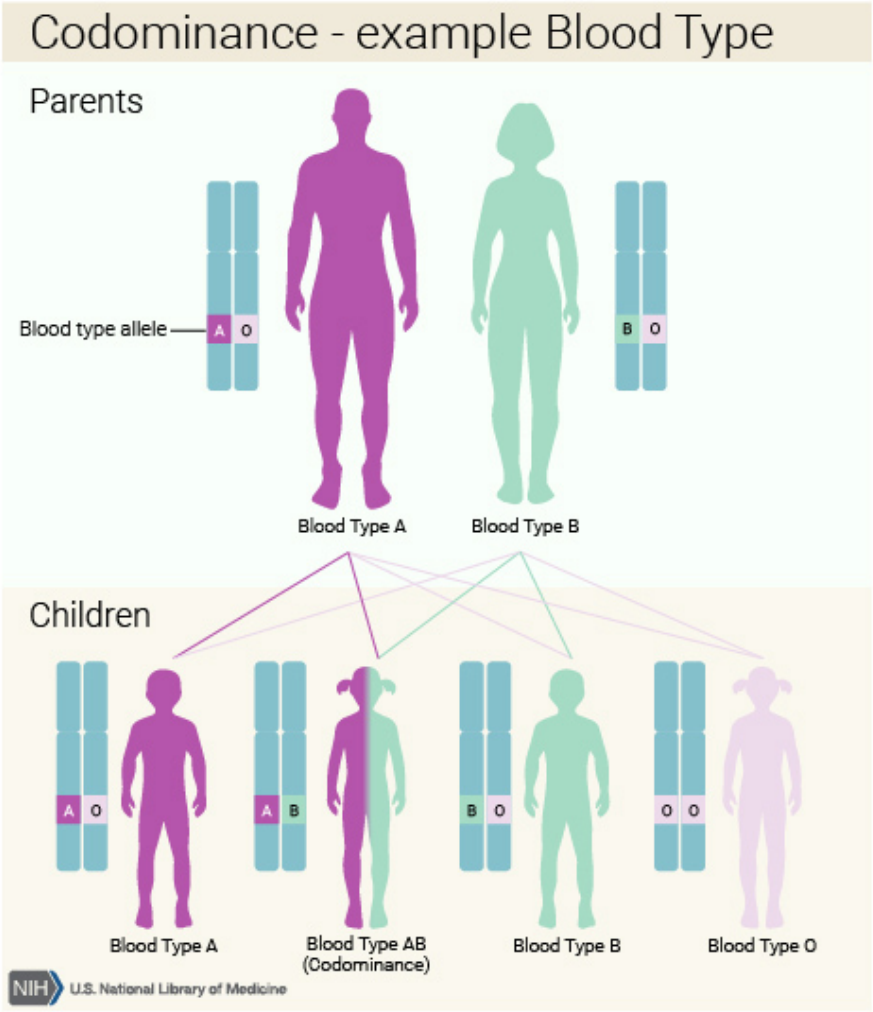
In the example on the left, a father with an X-linked dominant disorder has two affected daughters and two unaffected sons. On the right, a mother with an X-linked dominant disorder has two affected children and two unaffected children.



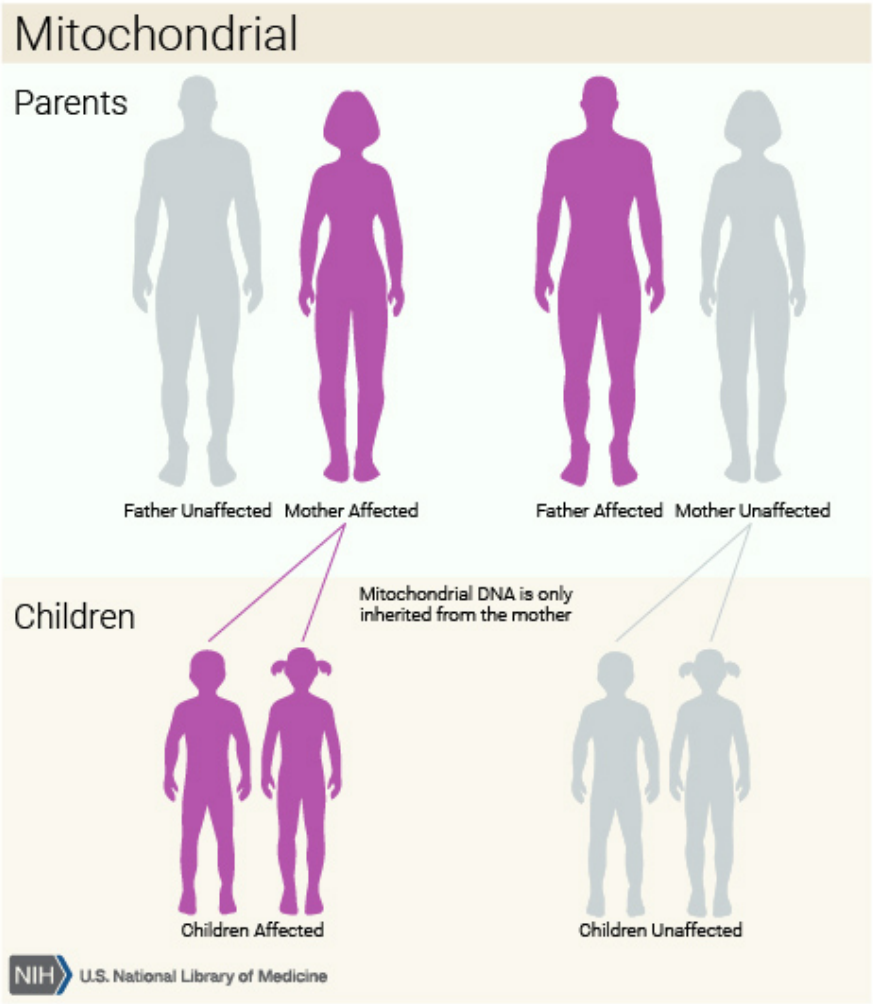
In the example on the left, a father with an X-linked recessive condition has two daughters that are carriers of the causative mutation. On the right, a mother who is a carrier of an X-linked recessive disorder has one affected son and one daughter who is also a carrier.



In this example, a father with a Y-linked condition has two affected sons. His daughters are unaffected.



The ABO blood group is a major system for classifying blood types in humans. Blood type AB is inherited in a codominant pattern. In this example, a father with blood type A and a mother with blood type B have four children, each with a different blood type: A, AB, B, and O.



In the family on the left, a woman with a disorder caused by a mutation in mitochondrial DNA and her unaffected husband have children who are all affected by the condition. In the family on the right, a man with a condition resulting from a mutation in mitochondrial DNA 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 of developing a genetic condition. One important factor is how the condition is inherited. For example:

- Autosomal dominant inheritance: A person affected by an autosomal dominant disorder has a 50 percent chance of passing the mutated gene to each child. The chance that a child will not inherit the mutated gene is also 50 percent (image on page 112). However, in some cases an autosomal dominant disorder results from a new (de novo) mutation that occurs during the formation of egg or sperm cells or early in embryonic development. In these cases, the child's parents are unaffected, but the child may pass on the condition to his or her own children (image on page 113).
- Autosomal recessive inheritance: Two unaffected people who each carry one copy of the mutated gene for an autosomal recessive disorder (carriers) have a 25 percent chance with each pregnancy of having a child affected by the disorder. The chance with each pregnancy of having an unaffected child who is a carrier of the disorder is 50 percent, and the chance that a child will not have the disorder and will not be a carrier is 25 percent (image on page 114).
- X-linked dominant inheritance: The chance of passing on an X-linked dominant condition differs between men and women because men have one X chromosome and one Y chromosome, while women have two X chromosomes (image on page 115). 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, but all of his daughters will inherit the condition. 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.

- X-linked recessive inheritance: Because of the difference in sex chromosomes, the probability of passing on an X-linked recessive disorder also differs between men and women (image on page 116). 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. 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.
- Y-linked inheritance: Because only males have a Y chromosome, only males can be affected by and pass on Y-linked disorders. All sons of a man with a Y-linked disorder will inherit the condition from their father (image on page 117).
- Codominant inheritance: In codominant inheritance, each parent contributes a different version of a particular gene, and both versions influence the resulting genetic trait. The chance of developing a genetic condition with codominant inheritance, and the characteristic features of that condition, depend on which versions of the gene are passed from parents to their child (image on page 118).
- Mitochondrial inheritance: Mitochondria, which are the energy-producing centers inside cells, each contain a small amount of DNA. Disorders with mitochondrial inheritance result from mutations in mitochondrial DNA. Although these disorders can affect both males and females, only females can pass mutations in mitochondrial DNA to their children. A woman with a disorder caused by changes in mitochondrial DNA will pass the mutation to all of her daughters and sons, but the children of a man with such a disorder will not inherit the mutation (image on page 119).

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, factors such as a person's family history and the results of genetic testing can sometimes 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.

Estimating the chance of developing or passing on a genetic disorder can be complex. Genetics professionals can help people understand these chances and help them 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:

- Autosomal dominant (https://medlineplus.gov/ency/article/002049.htm)
- Autosomal recessive (https://medlineplus.gov/ency/article/002052.htm)
- X-linked dominant (https://medlineplus.gov/ency/article/002050.htm)
- X-linked recessive (https://medlineplus.gov/ency/article/002051.htm)

The Centre for Genetics Education (Australia) provides an explanation of mitochondrial inheritance (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/Fact%20Sheet%2012).

The Muscular Dystrophy Association explains patterns and probabilities (https://www.mda.org/sites/default/files/publications/Facts_Genetics_P-210_1.pdf) of inheritance.

What are reduced penetrance and variable expressivity?

Reduced penetrance and variable expressivity are factors that influence the effects of particular genetic changes. These factors usually affect disorders that have an autosomal dominant pattern of inheritance, although they are occasionally seen in disorders with an autosomal recessive inheritance pattern.

Reduced penetrance

Penetrance refers to the proportion of people with a particular genetic change (such as a mutation in a specific gene) who exhibit signs and symptoms of a genetic disorder. If some people with the mutation do not develop features of the disorder, the condition is said to have reduced (or incomplete) penetrance. Reduced penetrance often occurs with familial cancer syndromes. For example, many people with a mutation in the *BRCA1* or *BRCA2* gene will develop cancer during their lifetime, but some people will not. Doctors cannot predict which people with these mutations will develop cancer or when the tumors will develop.

Reduced penetrance probably results from a combination of genetic, environmental, and lifestyle factors, many of which are unknown. This phenomenon can make it challenging for genetics professionals to interpret a person's family medical history and predict the risk of passing a genetic condition to future generations.

Variable expressivity

Although some genetic disorders exhibit little variation, most have signs and symptoms that differ among affected individuals. Variable expressivity refers to the range of signs and symptoms that can occur in different people with the same genetic condition. For example, the features of Marfan syndrome vary widely— some people have only mild symptoms (such as being tall and thin with long, slender fingers), while others also experience life-threatening complications involving the heart and blood vessels. Although the features are highly variable, most people with this disorder have a mutation in the same gene (*FBN1*).

As with reduced penetrance, variable expressivity is probably caused by a combination of genetic, environmental, and lifestyle factors, most of which have not been identified. If a genetic condition has highly variable signs and symptoms, it may be challenging to diagnose.

For more information about reduced penetrance and variable expressivity:

The PHG Foundation offers an interactive tutorial on penetrance (http://www.phgfoundation.org/tutorials/penetrance/index.html) that explains the differences between reduced penetrance and variable expressivity.

Additional information about penetrance and expressivity (http://www.merckmanuals.com/home/fundamentals/genetics/inheritance-of-single-gene-disorders) is available from the Merck Manual Home Health Handbook for Patients & Caregivers.

What do geneticists mean by anticipation?

The signs and symptoms of some genetic conditions tend to become more severe and appear at an earlier age as the disorder is passed from one generation to the next. This phenomenon is called anticipation. Anticipation is most often seen with certain genetic disorders of the nervous system, such as Huntington disease, myotonic dystrophy, and fragile X syndrome.

Anticipation typically occurs with disorders that are caused by an unusual type of mutation called a trinucleotide repeat expansion. A trinucleotide repeat is a sequence of three DNA building blocks (nucleotides) that is repeated a number of times in a row. DNA segments with an abnormal number of these repeats are unstable and prone to errors during cell division. The number of repeats can change as the gene is passed from parent to child. If the number of repeats increases, it is known as a trinucleotide repeat expansion. In some cases, the trinucleotide repeat may expand until the gene stops functioning normally. This expansion causes the features of some disorders to become more severe with each successive generation.

Most genetic disorders have signs and symptoms that differ among affected individuals, including affected people in the same family. Not all of these differences can be explained by anticipation. A combination of genetic, environmental, and lifestyle factors is probably responsible for the variability, although many of these factors have not been identified. Researchers study multiple generations of affected family members and consider the genetic cause of a disorder before determining that it shows anticipation.

For more information about anticipation:

The Merck Manual for Healthcare Professionals provides a brief explanation of anticipation as part of its chapter on nontraditional inheritance (http://www.merckmanuals.com/professional/special-subjects/general-principles-of-medical-genetics/unusual-aspects-of-inheritance).

The Myotonic Dystrophy Foundation describes anticipation in the context of myotonic dystrophy (http://www.myotonic.org/what-dm/disease-mechanism). (Click on the tab that says "Anticipation.")

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, intellectual disability, or other health 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 intellectual disability 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 Utah offers a basic overview of genomic imprinting (http://learn.genetics.utah.edu/content/epigenetics/imprinting/).

Additional information about epigenetics, including genomic imprinting (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetEpigenetics) is available from the Centre for Genetics Education.

An animated tutorial from the University of Miami illustrates how uniparental disomy occurs (http://hihg.med.miami.edu/code/http/modules/education/Design/animate/uniDisomy.htm).

Are chromosomal disorders inherited?

Although it is possible to inherit some types of chromosomal abnormalities, most chromosomal disorders (such as Down syndrome and Turner syndrome) 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. (https://www.genome.gov/11508982#6)

The Chromosome Deletion Outreach fact sheet Introduction to Chromosomes (http://chromodisorder.org/Display.aspx?ID=35) explains how structural changes occur.

The March of Dimes discusses the causes of chromosomal abnormalities in their fact sheet Chromosomal Abnormalities (http://www.marchofdimes.org/baby/chromosomal-conditions.aspx).

Additional information about how chromosomal changes happen (https://www.urmc.rochester.edu/Encyclopedia/Content.aspx?ContentTypeID=90&ContentID=P02126) is available from the University of Rochester Medical Center.

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 Coalition for Health Professional Education in Genetics offers Some Frequently Asked Questions and Answers About Race, Genetics, and Healthcare (http://www.nchpeg.org/index.php?option=com_content&view=article&id=142&Itemid=64).

The Norton & Elaine Sarnoff Center for Jewish Genetics provides information on disorders that occur more frequently in people with Jewish ancestry, including genetic traits that tend to be more common in Ashkenazi Jews (http://www.jewishgenetics.org/cjg/Ashkenazi-Jewish-Disorders.aspx) and Sephardic Jews (http://www.jewishgenetics.org/cjg/Sephardic-Jewish-Disorders.aspx).

Genetics and Human Traits

Table of Contents

Are fingerprints determined by genetics? 131

Is eye color determined by genetics? 133

Is intelligence determined by genetics? 136

Is handedness determined by genetics? 138

Is the probability of having twins determined by genetics? 141

Is hair texture determined by genetics? 144

Are fingerprints determined by genetics?

Each person's fingerprints are unique, which is why they have long been used as a way to identify individuals. Surprisingly little is known about the factors that influence a person's fingerprint patterns. Like many other complex on page 51 traits, studies suggest that both genetic and environmental factors play a role.

A person's fingerprints are based on the patterns of skin ridges (called dermatoglyphs) on the pads of the fingers. These ridges are also present on the toes, the palms of the hands, and the soles of the feet. Although the basic whorl, arch, and loop patterns may be similar, the details of the patterns are specific to each individual.

Dermatoglyphs develop before birth and remain the same throughout life. The ridges begin to develop during the third month of fetal development, and they are fully formed by the sixth month. The function of these ridges is not entirely clear, but they likely increase sensitivity to touch.

The basic size, shape, and spacing of dermatoglyphs appear to be influenced by genetic factors. Studies suggest that multiple genes are involved, so the inheritance pattern is not straightforward. Genes that control the development of the various layers of skin, as well as the muscles, fat, and blood vessels underneath the skin, may all play a role in determining the pattern of ridges. The finer details of the patterns of skin ridges are influenced by other factors during fetal development, including the environment inside the womb. These developmental factors cause each person's dermatoglyphs to be different from everyone else's. Even identical twins, who have the same DNA, have different fingerprints.

Few genes involved in dermatoglyph formation have been identified. Rare diseases characterized by abnormal or absent dermatoglyphs provide some clues as to their genetic basis. For example, a condition known as adermatoglyphia is characterized by an absence of dermatoglyphs, sometimes with other abnormalities of the skin. Adermatoglyphia is caused by mutations in a gene called *SMARCAD1*. Although this gene is clearly important for the formation of dermatoglyphs, its role in their development is unclear.

Scientific journal articles for further reading

Burger B, Fuchs D, Sprecher E, Itin P. The immigration delay disease: adermatoglyphia-inherited absence of epidermal ridges. J Am Acad Dermatol. 2011 May;64(5):974-80. doi: 10.1016/j.jaad.2009.11.013. Epub 2010 Jul 8.PubMed: 20619487 (http://www.ncbi.nlm.nih.gov/pubmed/20619487).

Nousbeck J, Burger B, Fuchs-Telem D, Pavlovsky M, Fenig S, Sarig O, Itin P, Sprecher E. A mutation in a skin-specific isoform of *SMARCAD1* causes autosomal-dominant adermatoglyphia. Am J Hum Genet. 2011 Aug 12;89(2):302-7. doi: 10.1016/j.ajhg.2011.07.004. Epub 2011 Aug 4. PubMed: 21820097 (http://www.ncbi.nlm.nih.gov/pubmed/21820097). Free full-text available from PubMed Central: PMC3155166 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3155166/).

Warman PH, Ennos A.R. Fingerprints are unlikely to increase the friction of primate fingerpads. J Exp Biol. 2009 Jul;212(Pt 13):2016-22. doi: 10.1242/jeb.028977. PubMed: 19525427 (http://www.ncbi.nlm.nih.gov/pubmed/19525427).

To find out more about the influence of genetics on the formation of fingerprints:

The UCSB Science Line from the University of California, Santa Barbara provides information about how fingerprints are formed (http://scienceline.ucsb.edu/getkey.php?key=2650).

The Mad Sci Network offers many Q&As related to fingerprints (http://www.madsci.org/FAQs/body/fingerprints.html), including the genetics and development of dermatoglyphs. The questions were asked by students and answered by scientists.

The Washington State Twin Registry has an FAQ about the fingerprints of identical twins (http://wstwinregistry.org/2015/10/01/do-identical-twins-have-identical-fingerprints/).

OMIM.org provides more detailed genetic information about dermatoglyphs (http://omim.org/entry/125590) and adermatoglyphia (http://omim.org/entry/136000).

Is eye color determined by genetics?

A person's eye color results from pigmentation of a structure called the iris, which surrounds the small black hole in the center of the eye (the pupil) and helps control how much light can enter the eye. The color of the iris ranges on a continuum from very light blue to dark brown. Most of the time eye color is categorized as blue, green/hazel, or brown. Brown is the most frequent eye color worldwide. Lighter eye colors, such as blue and green, are found almost exclusively among people of European ancestry.

Eye color is determined by variations in a person's genes. Most of the genes associated with eye color are involved in the production, transport, or storage of a pigment called melanin. Eye color is directly related to the amount and quality of melanin in the front layers of the iris. People with brown eyes have a large amount of melanin in the iris, while people with blue eyes have much less of this pigment.

A particular region on chromosome 15 plays a major role in eye color. Within this region, there are two genes located very close together: *OCA2* and *HERC2*. The protein produced from the *OCA2* gene, known as the P protein, is involved in the maturation of melanosomes, which are cellular structures that produce and store melanin. The P protein therefore plays a crucial role in the amount and quality of melanin that is present in the iris. Several common variations (polymorphisms) in the *OCA2* gene reduce the amount of functional P protein that is produced. Less P protein means that less melanin is present in the iris, leading to blue eyes instead of brown in people with a polymorphism in this gene.

A region of the nearby *HERC2* gene known as intron 86 contains a segment of DNA that controls the activity (expression) of the *OCA2* gene, turning it on or off as needed. At least one polymorphism in this area of the *HERC2* gene has been shown to reduce the expression of *OCA2*, which leads to less melanin in the iris and lighter-colored eyes.

Several other genes play smaller roles in determining eye color. Some of these genes are also involved in skin and hair coloring. Genes with reported roles in eye color include *ASIP*, *IRF4*, *SLC24A4*, *SLC24A5*, *SLC45A2*, *TPCN2*, *TYR*, and *TYRP1*. The effects of these genes likely combine with those of *OCA2* and *HERC2* to produce a continuum of eye colors in different people.

Researchers used to think that eye color was determined by a single gene and followed a simple inheritance pattern in which brown eyes were dominant to blue eyes. Under this model, it was believed that parents who both had blue eyes could not have a child with brown eyes. However, later studies showed that this model was too simplistic. Although it is uncommon, parents with blue eyes can

have children with brown eyes. The inheritance of eye color is more complex than originally suspected because multiple genes are involved. While a child's eye color can often be predicted by the eye colors of his or her parents and other relatives, genetic variations sometimes produce unexpected results.

Several disorders that affect eye color have been described. Ocular albinism is characterized by severely reduced pigmentation of the iris, which causes very light-colored eyes and significant problems with vision. Another condition called oculocutaneous albinism affects the pigmentation of the skin and hair in addition to the eyes. Affected individuals tend to have very light-colored irises, fair skin, and white or light-colored hair. Both ocular albinism and oculocutaneous albinism result from mutations in genes involved in the production and storage of melanin. Another condition called heterochromia is characterized by different-colored eyes in the same individual. Heterochromia can be caused by genetic changes or by a problem during eye development, or it can be acquired as a result of a disease or injury to the eye.

Scientific journal articles for further reading

Sturm RA, Duffy DL, Zhao ZZ, Leite FP, Stark MS, Hayward NK, Martin NG, Montgomery GW. A single SNP in an evolutionary conserved region within intron 86 of the *HERC2* gene determines human blue-brown eye color. Am J Hum Genet. 2008 Feb;82(2):424-31. doi: 10.1016/j.ajhg.2007.11.005. Epub 2008 Jan 24. PubMed: 18252222 (http://www.ncbi.nlm.nih.gov/pubmed/18252222). Free full-text available from PubMed Central: PMC2427173 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2427173/).

Sturm RA, Larsson M. Genetics of human iris colour and patterns. Pigment Cell Melanoma Res. 2009 Oct;22(5):544-62. doi: 10.1111/j.1755-148X.2009.00606.x. Epub 2009 Jul 8. Review. PubMed: 19619260 (http://www.ncbi.nlm.nih.gov/pubmed/19619260).

White D, Rabago-Smith M. Genotype-phenotype associations and human eye color. J Hum Genet. 2011 Jan;56(1):5-7. doi: 10.1038/jhg.2010.126. Epub 2010 Oct 14. Review. PubMed: 20944644 (http://www.ncbi.nlm.nih.gov/pubmed/20944644)

To learn more about the genetics of eye color:

John H. McDonald at the University of Delaware discusses the myth that eye color is determined by a single gene (http://udel.edu/~mcdonald/mytheyecolor.html).

The Tech Museum of Innovation at Stanford University provides a Q&A explaining how brown-eyed parents can have blue-eyed children (http://genetics.thetech.org/ask-a-geneticist/brown-eyed-parents-blue-eyed-kids).

The University of Kansas Medical Center offers links to additional resources (https://www.kumc.edu/gec/support/eyecolor.html) about the genetics of eye and hair color.

More detailed information about ocular albinism (http://omim.org/entry/300500) and oculocutaneous albinism (http://omim.org/entry/203100), as well as the genetics of eye, hair, and skin color variation (http://omim.org/entry/227220), is available from OMIM.org.

A brief description of heterochromia (https://medlineplus.gov/ency/article/003319.htm) is available from MedlinePlus.

Is intelligence determined by genetics?

Like most aspects of human behavior and cognition, intelligence is a complex on page 51 trait that is influenced by both genetic and environmental factors.

Intelligence is challenging to study, in part because it can be defined and measured in different ways. Most definitions of intelligence include the ability to learn from experiences and adapt to changing environments. Elements of intelligence include the ability to reason, plan, solve problems, think abstractly, and understand complex ideas. Many studies rely on a measure of intelligence called the intelligence quotient (IQ).

Researchers have conducted many studies to look for genes that influence intelligence. Many of these studies have focused on similarities and differences in IQ within families, particularly looking at adopted children and twins. These studies suggest that genetic factors underlie about 50 percent of the difference in intelligence among individuals. Other studies have examined variations across the entire genomes of many people (an approach called genome-wide association studies on page 209 or GWAS) to determine whether any specific areas of the genome are associated with IQ. These studies have not conclusively identified any genes that underlie differences in intelligence. It is likely that a large number of genes are involved, each of which makes only a small contribution to a person's intelligence.

Intelligence is also strongly influenced by the environment. Factors related to a child's home environment and parenting, education and availability of learning resources, and nutrition, among others, all contribute to intelligence. A person's environment and genes influence each other, and it can be challenging to tease apart the effects of the environment from those of genetics. For example, if a child's IQ is similar to that of his or her parents, is that similarity due to genetic factors passed down from parent to child, to shared environmental factors, or (most likely) to a combination of both? It is clear that both environmental and genetic factors play a part in determining intelligence.

Scientific journal articles for further reading

Deary IJ. Intelligence. Curr Biol. 2013 Aug 19;23(16):R673-6. doi: 10.1016/j.cub.2013.07.021. PubMed: 23968918 (http://www.ncbi.nlm.nih.gov/pubmed/23968918). Free full-text available from the publisher: http://www.sciencedirect.com/science/article/pii/S0960982213008440

Deary IJ, Johnson W, Houlihan LM. Genetic foundations of human intelligence. Hum Genet. 2009 Jul;126(1):215-32. doi: 10.1007/s00439-009-0655-4. Epub 2009 Mar 18. Review. PubMed: 19294424 (http://www.ncbi.nlm.nih.gov/pubmed/19294424).

Plomin R, Deary IJ. Genetics and intelligence differences: five special findings. Mol Psychiatry. 2015 Feb;20(1):98-108. doi: 10.1038/mp.2014.105. Epub 2014 Sep 16. Review. PubMed: 25224258 (http://www.ncbi.nlm.nih.gov/pubmed/25224258). Free full-text available from PubMed Central: PMC4270739 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4270739/).

Sternberg RJ. Intelligence. Dialogues Clin Neurosci. 2012 Mar;14(1):19-27. Review. PubMed: 22577301 (http://www.ncbi.nlm.nih.gov/pubmed/22577301). Free full-text available from PubMed Central: PMC3341646 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3341646/)

To find out more about the influence of genetics on intelligence:

This news release from the journal Nature explains why it is so difficult to identify genes associated with IQ: “'Smart genes' prove elusive” (http://www.nature.com/news/smart-genes-prove-elusive-1.15858) (September 8, 2014)

The Tech Museum of Innovation at Stanford University provides a Q&A about the influence of genes and environment on IQ (http://genetics.thetech.org/ask-a-geneticist/intelligence-and-genetics).

The Cold Spring Harbor Laboratory offers an interactive tool called Genes to Cognition (http://www.g2conline.org/) that provides information about many aspects of the genetics of neuroscience.

Is handedness determined by genetics?

Like most aspects of human behavior, handedness is a complex on page 51 trait that appears to be influenced by multiple factors, including genetics, environment, and chance.

Handedness, or hand preference, is the tendency to be more skilled and comfortable using one hand instead of the other for tasks such as writing and throwing a ball. Although the percentage varies by culture, in Western countries 85 to 90 percent of people are right-handed and 10 to 15 percent of people are left-handed. Mixed-handedness (preferring different hands for different tasks) and ambidextrousness (the ability to perform tasks equally well with either hand) are uncommon.

Hand preference begins to develop before birth. It becomes increasingly apparent in early childhood and tends to be consistent throughout life. However, little is known about its biological basis. Hand preference probably arises as part of the developmental process that differentiates the right and left sides of the body (called right-left asymmetry). More specifically, handedness appears to be related to differences between the right and left halves (hemispheres) of the brain. The right hemisphere controls movement on the left side of the body, while the left hemisphere controls movement on the right side of the body.

It was initially thought that a single gene controlled handedness. However, more recent studies suggest that multiple genes, perhaps up to 40, contribute to this trait. Each of these genes likely has a weak effect by itself, but together they play a significant role in establishing hand preference. Studies suggest that at least some of these genes help determine the overall right-left asymmetry of the body starting in the earliest stages of development.

So far, researchers have identified only a few of the many genes thought to influence handedness. For example, the PCSK6 gene has been associated with an increased likelihood of being right-handed in people with the psychiatric disorder schizophrenia. Another gene, LRRTM1, has been associated with an increased chance of being left-handed in people with dyslexia (a condition that causes difficulty with reading and spelling). It is unclear whether either of these genes is related to handedness in people without these conditions.

Studies suggest that other factors also contribute to handedness. The prenatal environment and cultural influences may play a role. Additionally, a person’s hand preference may be due partly to random variation among individuals.

Like many complex traits, handedness does not have a simple pattern of inheritance. Children of left-handed parents are more likely to be left-handed than are children of right-handed parents. However, because the overall chance of

being left-handed is relatively low, most children of left-handed parents are right-handed. Identical twins are more likely than non-identical twins (or other siblings) to be either right-handed or left-handed, but many twins have opposite hand preferences.

Scientific journal articles for further reading

Armour JA, Davison A, McManus IC. Genome-wide association study of handedness excludes simple genetic models. Heredity (Edinb). 2014 Mar;112(3):221-5. doi:10.1038/hdy.2013.93. Epub 2013 Sep 25. PubMed: 24065183 (http://www.ncbi.nlm.nih.gov/pubmed/24065183). Free full-text available from PubMed Central: PMC3931166 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3931166/).

Brandler WM, Morris AP, Evans DM, Scerri TS, Kemp JP, Timpson NJ, St Pourcain B, Smith GD, Ring SM, Stein J, Monaco AP, Talcott JB, Fisher SE, Webber C, Paracchini S. Common variants in left/right asymmetry genes and pathways are associated with relative hand skill. PLoS Genet. 2013;9(9):e1003751. doi: 10.1371/journal.pgen.1003751. Epub 2013 Sep 12. PubMed: 24068947 (http://www.ncbi.nlm.nih.gov/pubmed/24068947). Free full-text available from PubMed Central: PMC3772043 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3772043/).

Brandler WM, Paracchini S. The genetic relationship between handedness and neurodevelopmental disorders. Trends Mol Med. 2014 Feb;20(2):83-90. doi: 10.1016/j.molmed.2013.10.008. Epub 2013 Nov 23. Review. PubMed: 24275328 (http://www.ncbi.nlm.nih.gov/pubmed/24275328). Free full-text available from PubMed Central: PMC3969300 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3969300/).

McManus IC, Davison A, Armour JA. Multilocus genetic models of handedness closely resemble single-locus models in explaining family data and are compatible with genome-wide association studies. Ann N Y Acad Sci. 2013 Jun;1288:48-58. doi:10.1111/nyas.12102. Epub 2013 Apr 30. PubMed: 23631511 (http://www.ncbi.nlm.nih.gov/pubmed/23631511). Free full-text available from PubMed Central: PMC4298034 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4298034/).

To find out more about how handedness is determined:

General information about left-handedness, including its causes, is available from the Better Health Channel (https://www.betterhealth.vic.gov.au/health/healthyliving/left-handedness) (Australia).

The Genetic Literacy Project provides a discussion of genetic factors related to handedness (http://www.geneticliteracyproject.org/2014/12/02/left-handedness-genes-and-a-matter-of-chance/).

The Washington State Twin Registry has an FAQ about hand preference in identical twins (http://wstwinregistry.org/2015/10/01/do-identical-twins-always-have-the-same-hand-preference/).

The Max Planck Institute for Psycholinguistics in the Netherlands is carrying out a study of genetics and handedness in the general population (http://www.mpi.nl/departments/language-and-genetics/projects/brain-and-behavioural-asymmetries/genetics-of-handedness).

Is the probability of having twins determined by genetics?

The likelihood of conceiving twins is a complex on page 51 trait. It is probably affected by multiple genetic and environmental factors, depending on the type of twins. The two types of twins are classified as monozygotic and dizygotic.

Monozygotic (MZ) twins, also called identical twins, occur when a single egg cell is fertilized by a single sperm cell. The resulting zygote splits into two very early in development, leading to the formation of two separate embryos. MZ twins occur in 3 to 4 per 1,000 births worldwide. Research suggests that most cases of MZ twinning are not caused by genetic factors. However, a few families with a larger-than-expected number of MZ twins have been reported, which indicates that genetics may play a role. It is possible that genes involved in sticking cells together (cell adhesion) may contribute to MZ twinning, although this hypothesis has not been confirmed. Most of the time, the cause of MZ twinning is unknown.

Dizygotic (DZ) twins, also called fraternal twins, occur when two egg cells are each fertilized by a different sperm cell in the same menstrual cycle. DZ twins are about twice as common as MZ twins, and they are much more likely to run in families. Compared with the general population, women with a mother or sister who have had DZ twins are about twice as likely to have DZ twins themselves.

DZ twinning is thought to be a result of hyperovulation, which is the release of more than one egg in a single menstrual cycle. To explain how DZ twinning can run in families, researchers have looked for genetic factors that increase the chance of hyperovulation. However, studies examining the contributions of specific genes have had mixed and conflicting results. Few specific genes in humans have been definitively linked with hyperovulation or an increased probability of DZ twinning.

Other factors known to influence the chance of having DZ twins include the mother’s age, ethnic background, diet, body composition, and number of other children. Assisted reproductive technologies such as in vitro fertilization (IVF) are also associated with an increased frequency of DZ twins.

Scientific journal articles for further reading

Hoekstra C, Zhao ZZ, Lambalk CB, Willemsen G, Martin NG, Boomsma DI, Montgomery GW. Dizygotic twinning. Hum Reprod Update. 2008 Jan-Feb;14(1):37-47. Epub 2007 Nov 16. Review. PubMed: 18024802 (http://www.ncbi.nlm.nih.gov/pubmed/18024802).

Machin G. Familial monozygotic twinning: a report of seven pedigrees. Am J Med Genet C Semin Med Genet. 2009 May 15;151C(2):152-4. doi:

10.1002/ajmg.c.30211. PubMed: 19363801 (http://www.ncbi.nlm.nih.gov/pubmed/19363801).

Mbarek H, Steinberg S, Nyholt DR, Gordon SD, Miller MB, McRae AF, Hottenga JJ, Day FR, Willemsen G, de Geus EJ, Davies GE, Martin HC, Penninx BW, Jansen R, McAloney K, Vink JM, Kaprio J, Plomin R, Spector TD, Magnusson PK, Reversade B, Harris RA, Aagaard K, Kristjansson RP, Olafsson I, Eyjolfsson GI, Sigurdardottir O, Iacono WG, Lambalk CB, Montgomery GW, McGue M, Ong KK, Perry JR, Martin NG, Stefánsson H, Stefánsson K, Boomsma DI. Identification of Common Genetic Variants Influencing Spontaneous Dizygotic Twinning and Female Fertility. Am J Hum Genet. 2016 May 5;98(5):898-908. doi: 10.1016/j.ajhg.2016.03.008. Epub 2016 Apr 28. Pubmed: 27132594 (http://www.ncbi.nlm.nih.gov/pubmed/27132594).

Painter JN, Willemsen G, Nyholt D, Hoekstra C, Duffy DL, Henders AK, Wallace L, Healey S, Cannon-Albright LA, Skolnick M, Martin NG, Boomsma DI, Montgomery GW. A genome wide linkage scan for dizygotic twinning in 525 families of mothers of dizygotic twins. Hum Reprod. 2010 Jun;25(6):1569-80. doi: 10.1093/humrep/deq084. Epub 2010 Apr 8. PubMed: 20378614 (http://www.ncbi.nlm.nih.gov/pubmed/20378614). Free full-text available from PubMed Central: PMC2912534 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2912534/).

Shur N. The genetics of twinning: from splitting eggs to breaking paradigms. Am J Med Genet C Semin Med Genet. 2009 May 15;151C(2):105-9. doi: 10.1002/ajmg.c.30204. PubMed: 19363800 (http://www.ncbi.nlm.nih.gov/pubmed/19363800).

To learn more about the genetics of twinning:

Information about factors influencing MZ and DZ twinning is available from the Washington State Twin Registry:

- Twins run in my family. Do I have an increased chance of having twins? (http://wstwinregistry.org/2015/10/01/twins-run-in-my-family-do-i-have-an-increased-chance-of-having-twins/)
- I am a twin. Do I have an increased chance of having twins? (http://wstwinregistry.org/2015/10/01/i-am-a-twin-do-i-have-an-increased-chance-of-having-twins/)
- Does identical (MZ) twinning run in families? (http://wstwinregistry.org/2015/10/01/does-mz-twinning-run-in-families/)
- What factors are related to fraternal (DZ) twinning? (http://wstwinregistry.org/2015/10/01/what-factors-are-related-to-dz-twinning/)

The Tech from Stanford University offers a discussion of why twins can run in families (http://genetics.thetech.org/ask-a-geneticist/twin-genetics).

A brief overview of the factors that influence twinning (http://www.nhs.uk/chq/Pages/2550.aspx?CategoryID=54) is available from the UK National Health Service.

The Netherlands Twin Register provides an overview of international research on the genetics of DZ and MZ twinning (http://www.tweelingenregister.org/en/research/current-research/searching-for-twinning-genes/).

More detailed information about genetic factors related to MZ twinning (http://www.omim.org/entry/276410) and DZ twinning (http://www.omim.org/entry/276400) is available from OMIM.org.

The International Society for Twin Studies provides a list of twin registries worldwide (http://www.twinstudies.org/information/twinregisters/) and other organizations for twins and their families (http://www.twinstudies.org/information/worldwide-organizations/).

Is hair texture determined by genetics?

Genetic factors appear to play a major role in determining hair texture—straight, wavy, or curly—and the thickness of individual strands of hair. Studies suggest that different genes influence hair texture and thickness in people of different ethnic backgrounds. For example, normal variations (polymorphisms) in two genes, *EDAR* and *FGFR2*, have been associated with differences in hair thickness in Asian populations. A polymorphism in another gene, TCHH, appears to be related to differences in hair texture in people of northern European ancestry. It is likely that many additional genes contribute to hair texture and thickness in various populations.

Several genetic syndromes are characterized by unusual hair texture. These syndromes are caused by mutations in genes that play roles in hair structure and stability, including genes associated with desmosomes (specialized cell structures that hold hair cells together), keratins (proteins that provide strength and resilience to hair strands), and chemical signaling pathways involving a molecule called lysophosphatidic acid (LPA), which promotes hair growth. Genetic syndromes that feature altered hair texture include:

- Autosomal recessive hypotrichosis (caused by mutations in the *DSG4*, *LIPH*, or *LPAR6* gene)
- Keratoderma with woolly hair (caused by mutations in the *JUP*, *DSP*, *DSC2*, or *KANK2* gene)
- Monilethrix (caused by mutations in the *DSG4*, *KRT81*, *KRT83*, or *KRT86* gene)

Researchers speculate that the genes associated with these disorders probably also contribute to normal variations in hair texture and thickness, although little is known about the roles these genes play in normal hair.

Factors other than genetics can also influence hair texture and thickness. Hormones, certain medications, and chemicals such as hair relaxers can alter the characteristics of a person’s hair. Hair texture and thickness can also change with age.

Scientific journal articles for further reading

Fujimoto A, Kimura R, Ohashi J, Omi K, Yuliwulandari R, Batubara L, Mustofa MS, Samakkarn U, Settheetham-Ishida W, Ishida T, Morishita Y, Furusawa T, Nakazawa M, Ohtsuka R, Tokunaga K. A scan for genetic determinants of human hair morphology: *EDAR* is associated with Asian hair thickness. Hum Mol Genet. 2008 Mar 15;17(6):835-43. Epub 2007 Dec 8. PubMed: 18065779 (http://www.ncbi.nlm.nih.gov/pubmed/18065779).

Fujimoto A, Nishida N, Kimura R, Miyagawa T, Yuliwulandari R, Batubara L, Mustofa MS, Samakkarn U, Settheetham-Ishida W, Ishida T, Morishita Y, Tsunoda T, Tokunaga K, Ohashi J. *FGFR2* is associated with hair thickness in Asian populations. J Hum Genet. 2009 Aug;54(8):461-5. doi: 10.1038/jhg.2009.61. Epub 2009 Jul 10. PubMed: 19590514 (http://www.ncbi.nlm.nih.gov/pubmed/19590514).

Medland SE, Nyholt DR, Painter JN, McEvoy BP, McRae AF, Zhu G, Gordon SD, Ferreira MA, Wright MJ, Henders AK, Campbell MJ, Duffy DL, Hansell NK, Macgregor S, Slutske WS, Heath AC, Montgomery GW, Martin NG. Common variants in the trichohyalin gene are associated with straight hair in Europeans. Am J Hum Genet. 2009 Nov;85(5):750-5. doi: 10.1016/j.ajhg.2009.10.009. Epub 2009 Nov 5. PubMed: 19896111 (http://www.ncbi.nlm.nih.gov/pubmed/19896111); PubMed Central: PMC2775823 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2775823/).

Shimomura Y, Christiano AM. Biology and genetics of hair. Annu Rev Genomics Hum Genet. 2010;11:109-32. doi: 10.1146/annurev-genom-021610-131501. Review. PubMed: 20590427 (http://www.ncbi.nlm.nih.gov/pubmed/20590427).

To find out more about the influence of genetics on hair texture:

The Tech Museum of Innovation at Stanford University provides a Q&A on the differences in hair texture among ethnic groups (http://genetics.thetech.org/ask/ask107) and another on the inheritance of hair texture (http://genetics.thetech.org/ask/ask368).

More detailed information about the genetics of hair thickness (http://omim.org/entry/612630) and hair texture (http://omim.org/entry/139450) is available from OMIM.org.

Genetic Consultation

Table of Contents

What is a genetic consultation? 147

Why might someone have a genetic consultation? 148

What happens during a genetic consultation? 149

How can I find a genetics professional in my area? 151

What is the prognosis of a genetic condition? 152

How are genetic conditions diagnosed? 154

How are genetic conditions treated or managed? 156

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 (https://medlineplus.gov/geneticcounseling.html).

Additional background information is provided by the National Genome Research Institute in its Frequently Asked Questions About Genetic Counseling (https://www.genome.gov/19016905).

Information about genetic counseling, including the different types of counseling, is available from the National Center for Biotechnology Information (NCBI) in the booklet Making Sense of Your Genes: A Guide to Genetic Counseling (http://www.ncbi.nlm.nih.gov/books/NBK115508/).

An introduction to genetic counseling (http://aboutgeneticcounselors.com/Genetic-Counseling) is provided by the National Society of Genetic Counselors.

The Tuberous Sclerosis Alliance provides an overview of geneticists and genetic counselors (http://www.tsalliance.org/pages.aspx?content=607).

The Centre for Genetics Education also offers an introduction to genetic counseling (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetGeneticCounselling).

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, intellectual disability, 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:

An overview of indications for a genetics referral (http://www.ncbi.nlm.nih.gov/books/NBK115554/) is available from The Genetic Alliance booklet "Understanding Genetics: A Guide for Patients and Professionals."

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

The National Society of Genetic Counselors offers information about what to expect from a genetic counseling session (http://aboutgeneticcounselors.com/Genetic-Counseling/What-Does-Genetic-Counseling-Involve) and insurance coverage for genetic counseling (http://aboutgeneticcounselors.com/Genetic-Counseling/Does-Insurance-Cover-Genetic-Counseling-and-Testing).

EuroGentest explains what a person can expect during a visit with a genetic specialist (http://www.eurogentest.org/index.php?id=620) and offers frequently asked questions that may be helpful during an appointment (http://www.eurogentest.org/index.php?id=615).

Information about the role of genetic counselors and the process of genetic counseling (http://www.ncbi.nlm.nih.gov/books/NBK115552/) are available from the Genetic Alliance publication "Understanding Genetics: A Guide for Patients and Professionals."

The Illinois Department of Public Health discusses genetic counseling services and provides a list of questions to ask a genetic counselor (http://www.idph.state.il.us/HealthWellness/gencounselor.htm).

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:

- The National Society of Genetic Counselors (NSGC) offers a searchable directory of genetic counselors in the United States and Canada (http://www.findageneticcounselor.com/). You can search by location, name, area of practice/specialization, and/or ZIP Code.
- The American College of Medical Genetics and Genomics (ACMG) has a searchable database of medical genetics clinic services (https://www.acmg.net/ACMG/Find_Genetic_Services/ACMG/ISGweb/FindaGeneticService.aspx) in the United States.
- The Genetic and Rare Diseases Information Center, a service of the National Institutes of Health, provides a guide to finding specialists (https://rarediseases.info.nih.gov/resources/pages/25/how-to-find-a-disease-specialist) in particular genetic and rare conditions.
- The National Cancer Institute provides a Cancer Genetics Services Directory (http://www.cancer.gov/about-cancer/causes-prevention/genetics/directory), which lists professionals who provide services related to cancer genetics. You can search by type of cancer or syndrome, location, and/or provider name.

What is the prognosis of a genetic condition?

The prognosis of a genetic condition includes its likely course, duration, and outcome. When health professionals refer to the prognosis of a disease, they may also mean the chance of recovery; however, most genetic conditions are life-long and are managed rather than cured.

Disease prognosis has multiple aspects, including:

- How long a person with the disorder is likely to live (life expectancy)
- Whether the signs and symptoms worsen (and how quickly) or are stable over time
- Quality of life, such as independence in daily activities
- Potential for complications and associated health

The prognosis of a genetic condition depends on many factors, including the specific diagnosis on page 154 and an individual's particular signs and symptoms. Sometimes the associated genetic change, if known, can also give clues to the prognosis. Additionally, the course and outcome of a condition depends on the availability and effectiveness of treatment and management on page 156 approaches. The prognosis of very rare diseases can be difficult to predict because so few affected individuals have been identified. Prognosis may also be difficult or impossible to establish if a person's diagnosis is unknown.

The prognoses of genetic disorders vary widely, often even among people with the same condition. Some genetic disorders cause physical and developmental problems that are so severe they are incompatible with life. These conditions may cause a miscarriage of an affected embryo or fetus, or an affected infant may be stillborn or die shortly after birth. People with less severe genetic conditions may live into childhood or adulthood but have a shortened lifespan due to health problems related to their disorder. Genetic conditions with a milder course may be associated with a normal lifespan and few related health issues.

The prognosis of a disease is based on probability, which means that it is likely but not certain that the disorder will follow a particular course. Your healthcare provider is the best resource for information about the prognosis of your specific genetic condition. He or she can assess your medical history and signs and symptoms to give you the most accurate estimate of your prognosis.

Learn more about the prognosis of genetic conditions:

This list of resources on page 151 can help you locate a genetics professional in your area.

The A.D.A.M. Medical Encyclopedia (https://medlineplus.gov/encyclopedia.html) on MedlinePlus offers brief descriptions about many health problems, including some genetic conditions. Each page includes a section on Outlook (prognosis).

A discussion of the prognosis of disorders with a neurological basis (http://www.ninds.nih.gov/disorders/disorder_index.htm) is available from the National Institute of Neurological Disorders and Stroke (NINDS).

The National Cancer Institute (NCI) provides an overview of cancer prognosis (http://www.cancer.gov/about-cancer/diagnosis-staging/prognosis).

Nemours' KidsHealth has a fact sheet, When Your Baby is Born With a Health Problem (http://www.nemours.org/content/nemours/wwwv2/service/medical/geneticdisorders.html?tab=about&kidshealth=22895), that outlines what parents can expect when their infant has a genetic condition.

Local and national support and advocacy groups are also excellent resources for information about specific genetic conditions, including disease prognosis. Each condition summary (https://ghr.nlm.nih.gov/condition) on Genetics Home Reference provides links to support and advocacy resources under the heading "Patient Support." Additionally, patient support resources related to specific genetic conditions can be identified through the Genetic Alliance's Disease InfoSearch (http://www.diseaseinfosearch.org/).

How are genetic conditions diagnosed?

A doctor may suspect a diagnosis of a genetic condition on the basis of a person's physical characteristics and family history, or on the results of a screening test.

Genetic testing is one of several tools that doctors use to diagnose genetic conditions. The approaches to making a genetic diagnosis include:

- A physical examination: Certain physical characteristics, such as distinctive facial features, can suggest the diagnosis of a genetic disorder. A geneticist will do a thorough physical examination that may include measurements such as the distance around the head (head circumference), the distance between the eyes, and the length of the arms and legs. Depending on the situation, specialized examinations such as nervous system (neurological) or eye (ophthalmologic) exams may be performed. The doctor may also use imaging studies including x-rays, computerized tomography (CT) scans, or magnetic resonance imaging (MRI) to see structures inside the body.
- Personal medical history: Information about an individual's health, often going back to birth, can provide clues to a genetic diagnosis. A personal medical history includes past health issues, hospitalizations and surgeries, allergies, medications, and the results of any medical or genetic testing that has already been done.
- Family medical history: Because genetic conditions often run in families, information about the health of family members can be a critical tool for diagnosing these disorders. A doctor or genetic counselor will ask about health conditions in an individual's parents, siblings, children, and possibly more distant relatives. This information can give clues about the diagnosis and inheritance pattern of a genetic condition in a family.
- Laboratory tests, including genetic testing: Molecular, chromosomal, and biochemical genetic testing are used to diagnose genetic disorders. Other laboratory tests that measure the levels of certain substances in blood and urine can also help suggest a diagnosis.

Genetic testing is currently available for many genetic conditions. However, some conditions do not have a genetic test; either the genetic cause of the condition is unknown or a test has not yet been developed. In these cases, a combination of the approaches listed above may be used to make a diagnosis. Even when genetic testing is available, the tools listed above are used to narrow down the possibilities (known as a differential diagnosis) and choose the most appropriate genetic tests to pursue.

A diagnosis of a genetic disorder can be made anytime during life, from before birth to old age, depending on when the features of the condition appear and the availability of testing. Sometimes, having a diagnosis can guide treatment and management on page 156 decisions. A genetic diagnosis can also suggest whether other family members may be affected by or at risk of a specific disorder. Even when no treatment is available for a particular condition, having a diagnosis can help people know what to expect and may help them identify useful support and advocacy resources.

For more information about diagnosing genetic conditions:

Genetics Home Reference provides information about genetic testing on page 159 and the importance of family medical history on page 106. Additionally, links to information about the diagnosis of specific genetic disorders are available in each condition summary (https://ghr.nlm.nih.gov/condition) under the heading "Diagnosis & Management."

The National Center for Biotechnology Information (NCBI) provides an in-depth guide called Understanding Genetics (http://www.ncbi.nlm.nih.gov/books/NBK132142/), which includes a chapter about how genetics professionals diagnose many types of genetic disorders.

The Centers for Disease Control and Prevention (CDC) offers a fact sheet about the diagnosis of birth defects (http://www.cdc.gov/ncbddd/birthdefects/diagnosis.html), including information about screening and diagnostic tests.

Boston Children’s Hospital provides this brief overview of testing for genetic disorders (http://www.childrenshospital.org/conditions-and-treatments/conditions/genetic-disorders).

The American College of Medical Genetics offers practice guidelines (https://www.acmg.net/ACMG/Publications/Practice_Guidelines/ACMG/Publications/Practice_Guidelines.aspx), including diagnostic criteria, for several genetic disorders. These guidelines are designed for geneticists and other healthcare providers.

The Agency for Healthcare Research and Quality’s (AHRQ) National Guideline Clearinghouse has compiled screening, diagnosis, treatment, and management guidelines (https://www.guideline.gov/search?f_Clinical_Specialty=Medical+Genetics&fLockTerm=Medical+Genetics) for many genetic disorders.

GeneReviews (http://www.ncbi.nlm.nih.gov/books/NBK1116/), a resource from the University of Washington and the NCBI, provides detailed information about the diagnosis of specific genetic disorders as part of each peer-reviewed disease description.

How are genetic conditions treated or managed?

Many genetic disorders result from gene changes that are present in essentially every cell in the body. As a result, these disorders often affect many body systems, and most cannot be cured. However, approaches may be available to treat or manage some of the associated signs and symptoms.

For a group of genetic conditions called inborn errors of metabolism, which result from genetic changes that disrupt the production of specific enzymes, treatments sometimes include dietary changes or replacement of the particular enzyme that is missing. Limiting certain substances in the diet can help prevent the buildup of potentially toxic substances that are normally broken down by the enzyme. In some cases, enzyme replacement therapy can help compensate for the enzyme shortage. These treatments are used to manage existing signs and symptoms and may help prevent future complications.

For other genetic conditions, treatment and management strategies are designed to improve particular signs and symptoms associated with the disorder. These approaches vary by disorder and are specific to an individual's health needs. For example, a genetic disorder associated with a heart defect might be treated with surgery to repair the defect or with a heart transplant. Conditions that are characterized by defective blood cell formation, such as sickle cell disease, can sometimes be treated with a bone marrow transplant. Bone marrow transplantation can allow the formation of normal blood cells and, if done early in life, may help prevent episodes of pain and other future complications.

Some genetic changes are associated with an increased risk of future health problems, such as certain forms of cancer. One well-known example is familial breast cancer related to mutations in the *BRCA1* and *BRCA2* genes. Management may include more frequent cancer screening or preventive (prophylactic) surgery to remove the tissues at highest risk of becoming cancerous.

Genetic disorders may cause such severe health problems that they are incompatible with life. In the most severe cases, these conditions may cause a miscarriage of an affected embryo or fetus. In other cases, affected infants may be stillborn or die shortly after birth. Although few treatments are available for these severe genetic conditions, health professionals can often provide supportive care, such as pain relief or mechanical breathing assistance, to the affected individual.

Most treatment strategies for genetic disorders do not alter the underlying genetic mutation; however, a few disorders have been treated with gene therapy. This experimental technique involves changing a person's genes to prevent or treat

a disease. Gene therapy, along with many other treatment and management approaches for genetic conditions, are under study in clinical trials.

Find out more about the treatment and management of genetic conditions:

Links to information about the treatment of specific genetic disorders are available in each Genetics Home Reference condition summary (https://ghr.nlm.nih.gov/condition) under the heading "Where can I find information about diagnosis or management of...?"

GeneReviews (http://www.ncbi.nlm.nih.gov/books/NBK1116/), a resource from the University of Washington and the National Center for Biotechnology Information (NCBI), provides detailed information about the management of specific genetic disorders as part of each peer-reviewed disease description.

The Genetic and Rare Diseases Information Center, a service of the National Institutes of Health, provides this video with suggestions for finding information about treatment (https://www.youtube.com/watch?v=by4nQriQcKs&list=PLtOMdJ_3bSnzIDTV_tD2qOKLraENN9PLv&index=3) for genetic and rare conditions.

The Agency for Healthcare Research and Quality's (AHRQ) National Guideline Clearinghouse has compiledscreening, diagnosis, treatment, and management guidelines (https://www.guideline.gov/search?f_Clinical_Specialty=Medical+Genetics&fLockTerm=Medical+Genetics) for many diseases, including genetic disorders.

Information related to the approaches discussed above is available from MedlinePlus:

- Inborn Errors of Metabolism (https://medlineplus.gov/ency/article/002438.htm)
- Bone Marrow Transplantation (https://medlineplus.gov/bonemarrowtransplantation.html)
- Palliative care (https://medlineplus.gov/palliativecare.html) (also known as supportive care)

The Fetal Treatment Center at the University of California, San Francisco describes stem cell treatments for inherited diseases (http://fetus.ucsf.edu/stem-cells).

Genetics Home Reference offers consumer-friendly information about gene therapy on page 192, including safety, ethical issues, and availability. Information is also available about precision medicine on page 219, an approach to disease diagnosis and treatment that takes into account variations in genes, environment, and lifestyle.

ClinicalTrials.gov (https://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 (https://www.clinicaltrials.gov/ct2/search/browse?brwse=cond_alpha_all),trial sponsor (https://www.clinicaltrials.gov/ct2/search/browse?brwse=spns_cat), location (https://www.clinicaltrials.gov/ct2/search/browse?brwse=locn_cat), or treatment approach (for example, drug interventions (https://www.clinicaltrials.gov/ct2/search/browse?brwse=intr_cat)).

Genetic Testing

Table of Contents

What is genetic testing? 160

What are the types of genetic tests? 162

How is genetic testing done? 165

What is informed consent? 166

What is direct-to-consumer genetic testing? 168

How can consumers be sure a genetic test is valid and useful? 170

What do the results of genetic tests mean? 172

What is the cost of genetic testing, and how long does it take to get the results? 174

Will health insurance cover the costs of genetic testing? 175

What are the benefits of genetic testing? 176

What are the risks and limitations of genetic testing? 177

What is genetic discrimination? 178

Can genes be patented? 180

How does genetic testing in a research setting differ from clinical genetic testing? 181

What is genetic ancestry testing? 182

What is genetic testing?

Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins. 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. More than 1,000 genetic tests are currently in use, and more are being developed.

Several methods can be used for genetic testing:

- Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.
- Chromosomal genetic tests analyze whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition.
- Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder.

Genetic testing is voluntary. Because testing has benefits as well as limitations and risks, the decision about whether to be tested is a personal and complex one. A geneticist or 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 (https://medlineplus.gov/genetictesting.html).

The National Human Genome Research Institute provides an overview of this topic in its Frequently Asked Questions About Genetic Testing (https://www.genome.gov/19516567). Additional information about genetic testing legislation, policy, and oversight (https://www.genome.gov/10002335) is available from the Institute.

The National Institutes of Health fact sheet Genetic Testing: What It Means for Your Health and for Your Family's Health (https://www.genome.gov/pages/health/patientspublicinfo/genetictestingfactsheet.pdf) provides a brief overview for people considering genetic testing.

Educational resources related to genetic testing (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=41&sid=42) are available from GeneEd.

You can also search for clinical trials involving genetic testing. ClinicalTrials.gov (https://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 studies related to genetic testing (https://clinicaltrials.gov/search?term=%22genetic+testing%22) that are accepting (or will accept) participants.

What are the types of genetic tests?

Genetic testing can provide information about a person's genes and chromosomes. 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. Millions of babies are tested each year in the United States. All states currently test infants for phenylketonuria (a genetic disorder that causes intellectual disability if left untreated) and congenital hypothyroidism (a disorder of the thyroid gland). Most states also test for other genetic disorders.

Diagnostic testing

Diagnostic testing is used to identify or rule out a specific genetic or chromosomal condition. In many cases, genetic testing is used to confirm a diagnosis when a particular condition is suspected based on physical signs and symptoms. Diagnostic testing can be performed before birth or at any time during a person's life, but is not available for all genes or all genetic conditions. The results of a diagnostic test can influence a person's choices about health care and the management of the disorder.

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 certain 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 during pregnancy if there is an increased risk that the baby will have 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.

Preimplantation testing

Preimplantation testing, also called preimplantation genetic diagnosis (PGD), is a specialized technique that can reduce the risk of having a child with a particular genetic or chromosomal disorder. It is used to detect genetic changes in embryos that were created using assisted reproductive techniques such as in-vitro fertilization. In-vitro fertilization involves removing egg cells from a woman’s ovaries and fertilizing them with sperm cells outside the body. To perform preimplantation testing, a small number of cells are taken from these embryos and tested for certain genetic changes. Only embryos without these changes are implanted in the uterus to initiate a pregnancy.

Predictive and presymptomatic testing

Predictive and presymptomatic types of testing are used to detect gene mutations associated with disorders that appear after birth, often later in life. These tests can be helpful to people who have a family member with a genetic disorder, but who have no features of the disorder themselves at the time of testing. 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 hereditary hemochromatosis (an iron overload disorder), before any signs or symptoms appear. The results of predictive and presymptomatic testing can provide information about a person’s risk of developing a specific disorder and help with making 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:

A Brief Primer on Genetic Testing (https://www.genome.gov/10506784), which outlines the different kinds of genetic tests, is available from the National Human Genome Research Institute.

Educational resources related to patient genetic testing/carrier screening (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=52&sid=55) are available from GeneEd. Johns Hopkins Medicine provides additional information about

genetic carrier screening (http://www.hopkinsmedicine.org/fertility/resources/genetic_screening.html).

The National Society of Genetic Counselors provides an overview of the different types of genetic testing (http://aboutgeneticcounselors.com/Genetic-Testing) that are available.

The Centre for Genetics Education offers an overview of prenatal testing (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FACTSHEETPRENATALTESTINGOVERVIEW), as well as fact sheets about preimplantation genetic diagnosis (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetPREIMPLANTATIONGENETICDIAGNOSISPGD.pdf), screening tests during pregnancy, (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetSCREENINGTESTSDURINGPREGNANCY.pdf) and diagnostic tests during pregnancy (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetDIAGNOSTICTESTSDURINGPREGNANCY.pdf).

EuroGentest provides fact sheets about predictive testing (http://www.eurogentest.org/index.php?id=617) and carrier testing (http://www.eurogentest.org/index.php?id=610).

The University of Pennsylvania offers an explanation of preimplantation genetic diagnosis (https://www.pennmedicine.org/for-patients-and-visitors/find-a-program-or-service/penn-fertility-care/embryo-screening).

Genetics Home Reference provides information and links related to newborn screening (https://ghr.nlm.nih.gov/primer#newbornscreening).

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 about forensic genetic testing (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetForensicPaternityAncestry) from the Centre for Genetics Education and a page about forensic DNA analysis (http://learn.genetics.utah.edu/content/science/forensics/) from the Genetic Science Learning Center at the Univeristy of Utah.

How is genetic testing done?

Once a person decides to proceed with genetic testing, a medical geneticist, primary care doctor, specialist, or nurse practitioner 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, or directly to the patient if requested.

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 on page 166.

For more information about genetic testing procedures:

The National Society of Genetic Counselors offers an overview of the genetic testing process (http://aboutgeneticcounselors.com/Genetic-Testing/How-Does-the-Testing-Process-Work).

The Genetic Science Learning Center at the University of Utah provides an interactive animation of DNA extraction techniques (http://learn.genetics.utah.edu/content/labs/extraction/).

What is informed consent?

Before a person has a genetic test, it is important that he or she fully 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 to carry out testing is called informed consent. "Informed" means that the person has enough information to make an educated decision about testing; "consent" refers to a person's voluntary agreement to have the test done.

In general, informed consent can only be given by adults who are competent to make medical decisions for themselves. For children and others who are unable to make their own medical decisions (such as people with impaired mental status), informed consent can be given by a parent, guardian, or other person legally responsible for making decisions on that person's behalf.

Informed consent for genetic testing is generally obtained by a doctor or genetic counselor during an office visit. The healthcare provider will discuss the test and answer any questions. If the person wishes to have the test, he or she will then usually read and sign a consent form.

Several factors are commonly included on an informed consent form:

- A general description of the test, including the purpose of the test and the condition for which the testing is being performed.
- How the test will be carried out on page 165 (for example, a blood sample).
- What the test results mean on page 172, including positive and negative results, and the potential for uninformative results or incorrect results such as false positives or false negatives.
- Any physical or emotional risks associated with the test on page 177.
- Whether the results can be used for research purposes on page 181.
- Whether the results might provide information about other family members' health, including the risk of developing a particular condition or the possibility of having affected children.
- How and to whom test results will be reported and under what circumstances results can be disclosed (for example, to health insurance providers).
- What will happen to the test specimen after the test is complete.
- Acknowledgement that the person requesting testing has had the opportunity to discuss the test with a healthcare professional.
- The individual's signature, and possibly that of a witness.

The elements of informed consent may vary, because some states have laws that specify factors that must be included. (For example, some states require

disclosure that the test specimen will be destroyed within a certain period of time after the test is complete.)

Informed consent is not a contract, so a person can change his or her mind at any time after giving initial consent. A person may choose not to go through with genetic testing even after the test sample has been collected. A person simply needs to notify the healthcare provider if he or she decides not to continue with the testing process.

For more information about informed consent:

MedlinePlus offers general information about informed consent by adults (https://medlineplus.gov/ency/patientinstructions/000445.htm).

The National Cancer Institute discusses informed consent for genetic testing in the context of inherited cancer syndromes (http://www.cancer.gov/about-cancer/causes-prevention/genetics/risk-assessment-pdq).

The National Human Genome Research Institute provides information about informed consent in genomics research (https://www.genome.gov/27026588) and policies and legislation related to informed consent for genetic research studies and testing (https://www.genome.gov/10002332).

The Centers for Disease Control and Prevention offers several examples of state-required components of informed consent for genetic testing (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5806a3.htm).

Additional information about informed consent (http://www.phgfoundation.org/tutorials/informedConsent/) is available in a tutorial from the PHG Foundation (UK).

What is direct-to-consumer genetic testing?

Traditionally, genetic tests have been available only through healthcare providers such as physicians, nurse practitioners, and genetic counselors. Healthcare providers order the appropriate test from a laboratory, collect and send the samples, and interpret the test results. Direct-to-consumer genetic testing refers to genetic tests that are marketed directly to consumers via television, print advertisements, or the Internet. This form of testing, which is also known as at-home genetic testing, provides access to a person's genetic information without necessarily involving a doctor or insurance company in the process.

If a consumer chooses to purchase a genetic test directly, the test kit is mailed to the consumer instead of being ordered through a doctor's office. The test typically involves collecting a DNA sample at home, often by swabbing the inside of the cheek, and mailing the sample back to the laboratory. In some cases, the person must visit a health clinic to have blood drawn. Consumers are notified of their results by mail or over the telephone, or the results are posted online. In some cases, a genetic counselor or other healthcare provider is available to explain the results and answer questions. The price for this type of at-home genetic testing ranges from several hundred dollars to more than a thousand dollars.

The growing market for direct-to-consumer genetic testing may promote awareness of genetic diseases, allow consumers to take a more proactive role in their health care, and offer a means for people to learn about their ancestral origins. At-home genetic tests, however, have significant risks and limitations. Consumers are vulnerable to being misled by the results of unproven or invalid tests. Without guidance from a healthcare provider, they may make important decisions about treatment or prevention based on inaccurate, incomplete, or misunderstood information about their health. Consumers may also experience an invasion of genetic privacy if testing companies use their genetic information in an unauthorized way.

Genetic testing provides only one piece of information about a person's health —other genetic and environmental factors, lifestyle choices, and family medical history also affect a person's risk of developing many disorders. These factors are discussed during a consultation with a doctor or genetic counselor, but in many cases are not addressed by at-home genetic tests. More research is needed to fully understand the benefits and limitations of direct-to-consumer genetic testing.

For more information about direct-to-consumer genetic testing:

The American College of Medical Genetics, which is a national association of doctors specializing in genetics, has issued a statement on direct-to-consumer genetic testing (https://www.acmg.net/StaticContent/StaticPages/Direct_Consumer.pdf).

The American Society of Human Genetics, a professional membership organization for specialists in genetics, has also issued a statement on direct-to-consumer genetic testing in the United States (http://www.ashg.org/pdf/dtc_statement.pdf).

The Federal Trade Commission (FTC) works to protect consumers and promote truth in advertising. The FTC offers an overview of direct-to-consumer genetic testing (https://www.consumer.ftc.gov/articles/0166-direct-consumer-genetic-tests) and a fact sheet for older people (https://www.consumer.ftc.gov/articles/0325-home-genetic-tests-health-information-older-people) about the benefits and risks of at-home genetic tests.

The National Society of Genetic Counselors offers information about at-home genetic testing (http://aboutgeneticcounselors.com/Genetic-Testing/What-is-At-Home-Genetic-Testing).

The Genetic Alliance also provides information about genetic testing (http://www.geneticalliance.org/advocacy/policyissues/genetictesting), including issues surrounding direct-to-consumer genetic testing.

Additional information about direct-to-consumer marketing of genetic tests (https://www.genome.gov/12010659) is available from the National Human Genome Research Institute.

EuroGentest offers a list of publications related to direct-to-consumer genetic testing in Europe (http://www.eurogentest.org/index.php?id=678).

How can consumers be sure a genetic test is valid and useful?

Before undergoing genetic testing, it is important to be sure that the test is valid and useful. A genetic test is valid if it provides an accurate result. Two main measures of accuracy apply to genetic tests: analytical validity and clinical validity. Another measure of the quality of a genetic test is its usefulness, or clinical utility.

- Analytical validity refers to how well the test predicts the presence or absence of a particular gene or genetic change. In other words, can the test accurately detect whether a specific genetic variant is present or absent?
- Clinical validity refers to how well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease.
- Clinical utility refers to whether the test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to a consumer.

All laboratories that perform health-related testing, including genetic testing, are subject to federal regulatory standards called the Clinical Laboratory Improvement Amendments (CLIA) or even stricter state requirements. CLIA standards cover how tests are performed, the qualifications of laboratory personnel, and quality control and testing procedures for each laboratory. By controlling the quality of laboratory practices, CLIA standards are designed to ensure the analytical validity of genetic tests.

CLIA standards do not address the clinical validity or clinical utility of genetic tests. The Food and Drug Administration (FDA) requires information about clinical validity for some genetic tests. Additionally, the state of New York requires information on clinical validity for all laboratory tests performed for people living in that state. Consumers, health providers, and health insurance companies are often the ones who determine the clinical utility of a genetic test.

It can be difficult to determine the quality of a genetic test sold directly to the public. Some providers of direct-to-consumer genetic tests on page 168 are not CLIA-certified, so it can be difficult to tell whether their tests are valid. If providers of direct-to-consumer genetic tests offer easy-to-understand information about the scientific basis of their tests, it can help consumers make more informed decisions. It may also be helpful to discuss any concerns with a health professional before ordering a direct-to-consumer genetic test.

For more information about determining the quality of genetic tests:

The Centers for Disease Control and Prevention (CDC) provides an explanation of the factors used to evaluate genetic tests (http://www.cdc.gov/genomics/gtesting/ACCE/index.htm), including analytical validity, clinical validity, and clinical utility, as part of their ACCE project. Additional information about the ACCE framework (http://www.phgfoundation.org/tutorials/acce/) is available in an interactive tutorial from the PHG Foundation.

The Genetic Alliance offers information about the quality of genetic tests and current public policy issues (http://www.geneticalliance.org/advocacy/policyissues/genetictesting) surrounding their regulation.

Interactive tutorials about analytical validity (http://www.phgfoundation.org/tutorials/acce/2.html), clinical validity (http://www.phgfoundation.org/tutorials/acce/3.html), and clinical utility (http://www.phgfoundation.org/tutorials/acce/5.html) are available from the PHG Foundation.

The World Health Organization discusses quality and safety in genetic testing (http://www.who.int/genomics/policy/quality_safety/en/index1.html).

The U.S. Centers for Medicare and Medicaid Services (CMS) provide an overview of the Clinical Laboratory Improvement Amendments (CLIA) (https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/).

What do the results of genetic tests mean?

The results of genetic tests are not always straightforward, which often makes them challenging to interpret and explain. Therefore, it is important for patients and their families to ask questions about the potential meaning of genetic test results both before and after the test is performed. When interpreting test results, healthcare professionals consider a person's medical history, family history, and the type of genetic test that was done.

A positive test result means that the laboratory found a change in a particular gene, chromosome, or protein of interest. Depending on the purpose of the test, this result may confirm a diagnosis, indicate that a person is a carrier of a particular genetic mutation, identify an increased risk of developing a disease (such as cancer) in the future, or suggest a need for further testing. Because family members have some genetic material in common, a positive test result may also have implications for certain blood relatives of the person undergoing testing. It is important to note that a positive result of a predictive or presymptomatic genetic test usually cannot establish the exact risk of developing a disorder. Also, health professionals typically cannot use a positive test result to predict the course or severity of a condition.

A negative test result means that the laboratory did not find a change in the gene, chromosome, or protein under consideration. This result can indicate that a person is not affected by a particular disorder, is not a carrier of a specific genetic mutation, or does not have an increased risk of developing a certain disease. It is possible, however, that the test missed a disease-causing genetic alteration because many tests cannot detect all genetic changes that can cause a particular disorder. Further testing may be required to confirm a negative result.

In some cases, a test result might not give any useful information. This type of result is called uninformative, indeterminate, inconclusive, or ambiguous. Uninformative test results sometimes occur because everyone has common, natural variations in their DNA, called polymorphisms, that do not affect health. If a genetic test finds a change in DNA that has not been associated with a disorder in other people, it can be difficult to tell whether it is a natural polymorphism or a disease-causing mutation. An uninformative result cannot confirm or rule out a specific diagnosis, and it cannot indicate whether a person has an increased risk of developing a disorder. In some cases, testing other affected and unaffected family members can help clarify this type of result.

For more information about interpreting genetic test results:

The National Cancer Institute fact sheet Genetic Testing for Hereditary Cancer Syndromes (http://www.cancer.gov/about-cancer/causes-prevention/genetics/

genetic-testing-fact-sheet) provides an explanation of positive and negative genetic test results. (Scroll down to question 6, "What do the results of genetic testing mean?")

Fact sheets including "What can genetic testing tell you and how can it help? (http://aboutgeneticcounselors.com/Genetic-Testing/What-Can-Genetic-Testing-Can-Tell-You-and-How-Can-It-Help)" and "How do I understand my test results? (http://aboutgeneticcounselors.com/Genetic-Testing/How-Do-I-Understand-My-Test-Results)" are available from the National Society of Genetic Counselors.

The National Coalition for Health Professional Education in Genetics (NCHPEG) offers more information in their fact sheet Interpreting the Results of a Genetic or Genomic Test (http://www.nchpeg.org/index.php?option=com_content&view=article&id=172&Itemid=64).

The National Women’s Health Resource Center offers a list of questions about genetic testing (http://www.healthywomen.org/condition/genetic-testing#hc-tab-1), including the meaning of test results, that patients and families can ask their healthcare professional.

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 logistics of genetic testing:

EuroGentest offers a fact sheet about genetic testing laboratories (http://www.eurogentest.org/index.php?id=621), including the reasons why some genetic test results take longer than others.

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 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 178 for more information.)

For more information about insurance coverage of genetic testing:

The National Human Genome Research Institute provides information about Coverage and Reimbursement of Genetic Tests (https://www.genome.gov/19016729).

Genes In Life discusses insurance coverage (http://www.genesinlife.org/after-diagnosis/plan-future/insurance-and-financial-planning) and reimbursement (http://www.genesinlife.org/testing-services/testing-genetic-conditions/reimbursement-genetic-testing) for genetic testing.

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:

EuroGentest offers a fact sheet about genetic testing (http://www.eurogentest.org/index.php?id=622), including a section on its benefits.

Additional information about the potential benefits of genetic testing (http://www.ucdenver.edu/academics/colleges/medicalschool/programs/Adult%20Medical%20Genetics/GeneticTestingInfo/Pages/GeneticTestingInfo.aspx#tab-2) is available from the University of Colorado.

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 178 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 American College of Medical Genetics and Genomics (ACMG) published a policy statement about the risks associated with incorrect genetic test results or interpretation (https://www.acmg.net/docs/LDT_Release.pdf).

EuroGentest offers a fact sheet about genetic testing (http://www.eurogentest.org/index.php?id=622), including a section on its possible risks and limitations.

Additional information about the risks and limitations of genetic testing (http://www.ucdenver.edu/academics/colleges/medicalschool/programs/Adult%20Medical%20Genetics/GeneticTestingInfo/Pages/GeneticTestingInfo.aspx#tab-3) is available from the University of Colorado.

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. 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. In particular, a federal law called the Genetic Information Nondiscrimination Act (GINA) is designed to protect people from this form of discrimination.

GINA has two parts: Title I, which prohibits genetic discrimination in health insurance, and Title II, which prohibits genetic discrimination in employment. Title I makes it illegal for health insurance providers to use or require genetic information to make decisions about a person's insurance eligibility or coverage. This part of the law went into effect on May 21, 2009. Title II makes it illegal for employers to use a person's genetic information when making decisions about hiring, promotion, and several other terms of employment. This part of the law went into effect on November 21, 2009.

GINA and other laws do not protect people from genetic discrimination in every circumstance. For example, GINA does not apply when an employer has fewer than 15 employees. It does not cover people in the U.S. military or those receiving health benefits through the Veterans Health Administration or Indian Health Service. GINA also does not protect against genetic discrimination in forms of insurance other than health insurance, such as life, disability, or long-term care insurance.

For more information about genetic discrimination and GINA:

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

- Genetic Discrimination (https://www.genome.gov/10002077)
- NHGRI Genome Statute and Legislation Database (https://www.genome.gov/PolicyEthics/LegDatabase/pubsearch.cfm)
- Genetic Information Nondiscrimination Act (GINA) of 2008 (https://www.genome.gov/24519851)

The Genetic Alliance offers links to resources and policy statements on genetic discrimination (http://www.geneticalliance.org/advocacy/policyissues/geneticdiscrimination).

The Smithsonian National Museum of Natural History's exhibit 'Genome: Unlocking Life's Code' discusses GINA's implementation (http://

unlockinglifescode.org/explore/genomics-society/feature-story-gina-protection-misuse-genetic-information).

More detailed information about GINA is available from these resources

- Coalition for Genetic Fairness (http://www.geneticfairness.org/ginaresource.html)
- GINAHelp.org (http://www.ginahelp.org/)

Can genes be patented?

A gene patent is the exclusive rights to a specific sequence of DNA (a gene) given by a government to the individual, organization, or corporation who claims to have first identified the gene. Once granted a gene patent, the holder of the patent dictates how the gene can be used, in both commercial settings, such as clinical genetic testing, and in noncommercial settings, including research, for 20 years from the date of the patent. Gene patents have often resulted in companies having sole ownership of genetic testing for patented genes.

On June 13, 2013, in the case of the Association for Molecular Pathology v. Myriad Genetics, Inc., the Supreme Court of the United States ruled that human genes cannot be patented in the U.S. because DNA is a "product of nature." The Court decided that because nothing new is created when discovering a gene, there is no intellectual property to protect, so patents cannot be granted. Prior to this ruling, more than 4,300 human genes were patented. The Supreme Court's decision invalidated those gene patents, making the genes accessible for research and for commercial genetic testing.

The Supreme Court's ruling did allow that DNA manipulated in a lab is eligible to be patented because DNA sequences altered by humans are not found in nature. The Court specifically mentioned the ability to patent a type of DNA known as complementary DNA (cDNA). This synthetic DNA is produced from the molecule that serves as the instructions for making proteins (called messenger RNA).

For more information about gene patenting and the Supreme Court ruling:

Read the Supreme Court ruling (https://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf) against gene patenting.

The National Institutes of Health (https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-director-francis-collins-us-supreme-court-ruling-gene-patenting), the American College of Medical Genetics and Genomics (https://www.acmg.net/docs/GenePatientsDecision.pdf), and the American Medical Association (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/related-policy-topics/gene-patenting.page) voice their support for the Supreme Court's ruling on gene patents.

The National Human Genome Research Institute discusses the relationship between Intellectual Property and Genomics (https://www.genome.gov/19016590)

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, developing tests for future clinical use, 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 on page 166 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:

The Ohio State University's Wexner Medical Center describes the difference between clinical and research genetic testing (https://internalmedicine.osu.edu/genetics/patient-care/genetic-testing-facts/index.cfm).

The Sudden Arrhythmia Death Syndromes (SADS) Foundation also outlines the major differences between clinical tests and research tests (http://www.sads.org/Living-with-SADS/Genetic-Testing/Genetic-Testing---Clinical-vs--Research).

The Columbia University Medical Center offers a table that summarizes the major differences between clinical genetic testing and genetic research (http://columbianeurology.org/research/divisions-and-programs/movement-disorders/genetic-research).

Additional information about clinical and research tests (http://www.ncbi.nlm.nih.gov/gtr/docs/about/#tests) is available from the Genetic Testing Registry.

What is genetic ancestry testing?

Genetic ancestry testing, or genetic genealogy, is a way for people interested in family history (genealogy) to go beyond what they can learn from relatives or from historical documentation. Examination of DNA variations can provide clues about where a person's ancestors might have come from and about relationships between families. Certain patterns of genetic variation are often shared among people of particular backgrounds. The more closely related two individuals, families, or populations are, the more patterns of variation they typically share.

Three types of genetic ancestry testing are commonly used for genealogy:

- Y chromosome testing: Variations in the Y chromosome, passed exclusively from father to son, can be used to explore ancestry in the direct male line. Y chromosome testing can only be done on males, because females do not have a Y chromosome. However, women interested in this type of genetic testing sometimes recruit a male relative to have the test done. Because the Y chromosome is passed on in the same pattern as are family names in many cultures, Y chromosome testing is often used to investigate questions such as whether two families with the same surname are related.
- Mitochondrial DNA testing: This type of testing identifies genetic variations in mitochondrial DNA. Although most DNA is packaged in chromosomes within the cell nucleus, cell structures called mitochondria also have a small amount of their own DNA (known as mitochondrial DNA). Both males and females have mitochondrial DNA, which is passed on from their mothers, so this type of testing can be used by either sex. It provides information about the direct female ancestral line. Mitochondrial DNA testing can be useful for genealogy because it preserves information about female ancestors that may be lost from the historical record because of the way surnames are often passed down.
- Single nucleotide polymorphism on page 208 testing: These tests evaluate large numbers of variations (single nucleotide polymorphisms or SNPs) across a person’s entire genome. The results are compared with those of others who have taken the tests to provide an estimate of a person's ethnic background. For example, the pattern of SNPs might indicate that a person's ancestry is approximately 50 percent African, 25 percent European, 20 percent Asian, and 5 percent unknown. Genealogists use this type of test because Y chromosome and mitochondrial DNA test results, which represent only single ancestral lines, do not capture the overall ethnic background of an individual.

Genetic ancestry testing has a number of limitations. Test providers compare individuals' test results to different databases of previous tests, so ethnicity estimates may not be consistent from one provider to another. Also, because most human populations have migrated many times throughout their history and mixed with nearby groups, ethnicity estimates based on genetic testing may differ from an individual's expectations. In ethnic groups with a smaller range of genetic variation due to the group's size and history, most members share many SNPs, and it may be difficult to distinguish people who have a relatively recent common ancestor, such as fourth cousins, from the group as a whole.

Genetic ancestry testing is offered by several companies and organizations. Most companies provide online forums and other services to allow people who have been tested to share and discuss their results with others, which may allow them to discover previously unknown relationships. On a larger scale, combined genetic ancestry test results from many people can be used by scientists to explore the history of populations as they arose, migrated, and mixed with other groups.

For more information about genetic ancestry testing:

The University of Utah provides video tutorials (http://learn.genetics.utah.edu/content/basics/molgen/) on molecular genealogy.

The International Society of Genetic Genealogy (http://www.isogg.org/) promotes the use of DNA testing in genealogy.

The American Society of Human Genetics (ASHG) developed a position paper on ancestry testing (http://www.ashg.org/pdf/ASHGAncestryTestingStatement_FINAL.pdf).

Detailed information about genetic ancestry testing (http://archive.senseaboutscience.org/pages/genetic-ancestry-testing.html) is available from Sense About Science.

The Smithsonian National Museum of Natural History's exhibit 'Genome: Unlocking Life's Code' discusses genetic ancestry testing (http://unlockinglifescode.org/explore/our-genomic-journey/our-origins-and-ancestry). The exhibit also discusses the African Diaspora (http://unlockinglifescode.org/explore/our-genomic-journey/feature-story-african-diaspora) and its influence on heredity and genealogy.

Newborn Screening

Table of Contents

What is newborn screening? 185

How is newborn screening done? 186

What disorders are included in newborn screening? 188

Who pays for newborn screening? 189

What happens if a newborn screening test comes back negative? 190

What happens if a newborn screening test comes back positive? 191

What is newborn screening?

Newborn screening is the practice of testing all babies in their first days of life for certain disorders and conditions that can hinder their normal development. This testing is required in every state and is typically performed before the baby leaves the hospital. The conditions included in newborn screening can cause serious health problems starting in infancy or childhood. Early detection and treatment can help prevent intellectual and physical disabilities and life-threatening illnesses.

To learn more about newborn screening:

MedlinePlus from the National Library of Medicine can point you to resources related to newborn screening (https://medlineplus.gov/newbornscreening.html).

The following websites and organizations also provide information about newborn screening:

- National Newborn Screening & Global Resource Center (http://genes-r-us.uthscsa.edu/)
- Baby's First Test (http://www.babysfirsttest.org/)
- Save Babies Through Screening Foundation (http://www.savebabies.org/)
- KidsHealth from Nemours (http://kidshealth.org/en/parents/newborn-screening-tests.html)
- Newborn Screening Coding and Terminology Guide (https://newbornscreeningcodes.nlm.nih.gov/) from the U.S. National Library of Medicine

How is newborn screening done?

Newborn screening usually begins with a blood test 24 to 48 hours after a baby is born, while he or she is still in the hospital. In some states, a second blood test is performed at a check-up appointment with the baby's pediatrician when the baby is 1 to 2 weeks old. Newborn screening is part of standard care; parents do not need to request to have the test done.

The test is performed by pricking the baby's heel to collect a few drops of blood. There are very few risks associated with this procedure, and it involves minimal discomfort to the baby. The blood is placed on a special type of paper and sent to a laboratory for analysis. Within 2 to 3 weeks, the test results are sent to the baby's doctor's office or clinic.

If a baby is born outside a hospital (for example, at home or in a birthing center), a doula or midwife may collect the blood sample needed for the newborn screening test. Otherwise, the required testing can be performed at the baby's doctor's office or at a hospital.

In addition to the blood test, most states also screen newborns for hearing loss and critical congenital heart disease. These tests are also done shortly after birth. The hearing test uses earphones and sensors to determine whether the baby's inner ear or brain respond to sound. The test for critical congenital heart disease, called pulse oximetry, uses a sensor on the skin to measure how much oxygen is in the blood. Low oxygen levels suggest that an infant may have heart problems. The hearing and pulse oximetry tests are painless and can be done while the baby is sleeping.

To learn more about how newborn screening tests are performed:

Additional information about newborn screening procedures (https://www.nichd.nih.gov/health/topics/newborn/conditioninfo/pages/how-done.aspx) is available from the Eunice Kennedy Shriver National Institute of Child Health and Human Development at NIH.

Baby’s First Test provides more details about newborn screening procedures (http://www.babysfirsttest.org/newborn-screening/screening-procedures) overall, as well as the screening tests for hearing loss (http://www.babysfirsttest.org/newborn-screening/conditions/hearing-loss) and critical congenital heart disease (http://www.babysfirsttest.org/newborn-screening/conditions/critical-congenital-heart-disease-cchd) in particular.

These resources offer specific information about the tests used to screen for hearing loss:

- It's Important to Have Your Baby's Hearing Screened (https://www.nidcd.nih.gov/health/has-your-babys-hearing-been-screened) from the National Institute on Deafness and Other Communication Disorders at NIH
- Purpose of Newborn Hearing Screening (https://www.healthychildren.org/English/ages-stages/baby/pages/Purpose-of-Newborn-Hearing-Screening.aspx) from Healthychildren.org, a service of the American Academy of Pediatrics

What disorders are included in newborn screening?

The disorders included in newborn screening vary from state to state. Most states test for the 32 conditions specified by the Health Resources and Services Administration (HRSA) in their Recommended Uniform Screening Panel. These conditions include phenylketonuria (PKU), cystic fibrosis, sickle cell disease, critical congenital heart disease, hearing loss, and others. Some states test for additional disorders that are not part of the HRSA panel.

Most of the conditions included in newborn screening can cause serious health problems if treatment is not started shortly after birth. Prompt identification and management of these conditions may be able to prevent life-threatening complications.

Parents can ask their baby's healthcare provider about expanded (supplemental) screening if they live in a state that screens for a smaller number of disorders. Supplemental screening is typically done by commercial laboratories. It is separate from the testing done by the state, although it often uses a blood sample drawn at the same time.

To find out more about the disorders included in newborn screening:

The Health Resources and Services Administration (HRSA) lists all of the disorders in its Recommended Uniform Screening Panel (http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/).

These resources list the disorders included in each state's newborn screening panel:

- Baby's First Test: Conditions Screened by State (http://www.babysfirsttest.org/newborn-screening/states)
- National Newborn Screening & Global Resource Center: Newborn Screening by State (http://genes-r-us.uthscsa.edu/resources/consumer/statemap.htm)

Additional information about supplemental newborn screening is available:

- Baby's Baby's First Test: What is additional screening? (http://www.babysfirsttest.org/newborn-screening/conditions#2)
- National Newborn Screening & Global Resource Center: Commercial and Non-Profit Organizations Offering Expanded Newborn Screening Tests (http://genes-r-us.uthscsa.edu/resources/newborn/commercial.htm)

Who pays for newborn screening?

Newborn screening is performed on every infant regardless of the parents' health insurance status or ability to pay. The fees for newborn screening vary by state, from less than $15 to about $150. Some states do not charge a fee for this testing. When there is a fee, it is often covered by private health insurance plans. This testing is also covered under the Children's Health Insurance Program (CHIP) and Medicaid for those who are eligible.

If a parent chooses to have supplemental screening done through a private laboratory, that testing is not covered under the fees charged by each state for newborn screening. The costs of supplemental testing are charged by the laboratory that performs the tests. Parents should check with their health insurer to find out whether supplemental newborn screening is a covered service.

If a newborn screening test comes back positive, further testing needs to be done to determine whether the baby has a particular condition. This additional testing involves separate costs that may be covered by health insurance plans.

To find out more about the costs of newborn screening:

The National Newborn Screening & Global Resource Center lists the cost of newborn screening in each state (http://genes-r-us.uthscsa.edu/resources/consumer/statemap.htm).

Additional information about the cost of newborn screening (https://www.nichd.nih.gov/health/topics/newborn/conditioninfo/how-used/pages/pays.aspx) is available from the Eunice Kennedy Shriver National Institute of Child Health and Human Development at NIH.

What happens if a newborn screening test comes back negative?

Within 2 to 3 weeks after newborn screening tests are performed, results are sent to the baby's doctor's office or clinic. A negative result means that all of the tests are in the normal range, and they do not indicate any increased risk. Other words for a negative test result are "passing," "in-range," or "normal."

In most cases, families are not notified of negative results. Parents can contact their baby's healthcare provider if they wish to confirm that the results were negative. Usually no follow-up testing is necessary.

Rarely, the results of a newborn screening test can be a false negative. "False negative" means that a disease was missed by the screen; the test results came back negative, but the child actually has the disease. Possible reasons for a false negative result include laboratory errors, such as mixing up samples, and doing the test too early. Because false negatives are possible, further testing should be done if a baby has a family history of a particular disease or shows signs and symptoms, regardless of the newborn screening result.

Learn more about negative newborn screening test results:

Baby’s First Test provides more information about test results and what they mean (http://www.babysfirsttest.org/newborn-screening/responding-to-results).

The Minnesota Department of Health provides details about interpreting the results of several types of newborn screening tests (http://www.health.state.mn.us/divs/phl/newborn/families/screeningresults.html).

What happens if a newborn screening test comes back positive?

Within 2 to 3 weeks after newborn screening tests are performed, results are sent to the baby's doctor’s office or clinic. A positive result means that at least one of the tests came back outside the normal range. Other words for a positive result are "failing," "out-of-range," or "abnormal."

The healthcare provider will notify parents of a positive test result. A positive result does not mean that a baby definitely has a disease, but it indicates that further testing (called diagnostic testing on page 154, because it is used to diagnose a disease) should be performed as soon as possible. If the baby does have the disease, quick follow-up testing can allow treatment or management on page 156, such as a special diet, to begin very soon after birth.

Often when there is a positive screening test result, follow-up diagnostic testing shows that the baby does not have the disease. In these cases, the results of the newborn screening test are described as "false positive," meaning that the test suggested an increased risk of the disease when the baby does not actually have the disease. False positive test results occur because screening tests are designed to identify as many babies affected with treatable diseases as possible. Because it is critical not to miss affected babies, some babies who are unaffected also have a positive screening result.

Occasionally, the results of a newborn screening test are reported as "borderline." These results are not quite normal, but they are not clearly abnormal, either. In these cases, the baby’s healthcare provider may repeat the test.

Learn more about positive newborn screening test results:

Baby's First Test provides more information about test results and what they mean (http://www.babysfirsttest.org/newborn-screening/responding-to-results).

The Minnesota Department of Health provides details about interpreting the results of several types of newborn screening tests (http://www.health.state.mn.us/divs/phl/newborn/families/screeningresults.html) and a fact sheet about borderline test results (http://www.health.state.mn.us/divs/phl/newborn/families/familyfsnewborderline.pdf).

Save Babies Through Screening offers more information about positive test results and follow-up testing (http://www.savebabies.org/ips_faqs.html).

A description of false positive results is available from Baby's First Test (http://www.babysfirsttest.org/newborn-screening/false-positives).

Gene Therapy

Table of Contents

What is gene therapy? 193

How does gene therapy work? 194

Is gene therapy safe? 196

What are the ethical issues surrounding gene therapy? 198

Is gene therapy available to treat my disorder? 199

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 (https://medlineplus.gov/genesandgenetherapy.html).

Educational resources related to gene therapy (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=142&sid=144) are available from GeneEd.

The Genetic Science Learning Center at the University of Utah provides an interactive introduction to gene therapy (http://learn.genetics.utah.edu/content/genetherapy/intro/) and a discussion of several diseases for which gene therapy has been successful (http://learn.genetics.utah.edu/content/genetherapy/success/).

The Centre for Genetics Education provides an introduction to gene therapy (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetGeneTherapy), including a discussion of ethical and safety considerations.

KidsHealth from Nemours offers a fact sheet called Gene Therapy and Children (http://kidshealth.org/en/parents/gene-therapy.html).

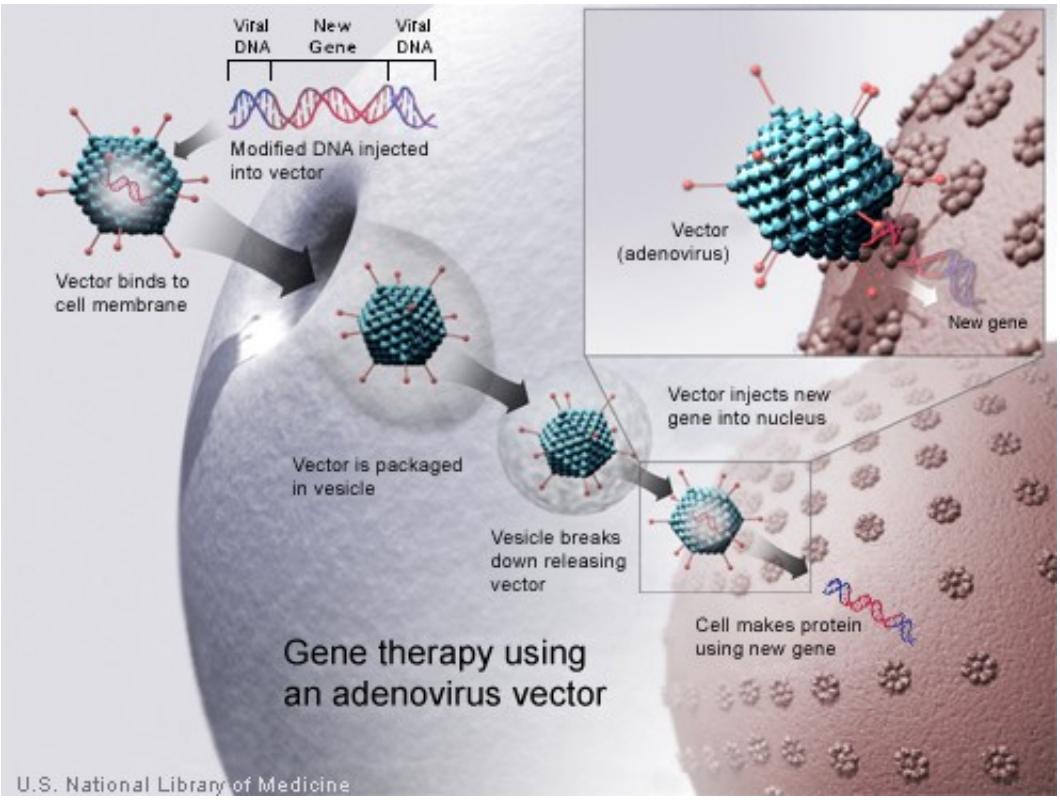
How does gene therapy work?

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 Genetic Science Learning Center at the University of Utah provides information about various technical aspects of gene therapy in Gene Delivery: Tools of the Trade (http://learn.genetics.utah.edu/content/genetherapy/tools/). They also discuss other approaches to gene therapy (http://learn.genetics.utah.edu/content/genetherapy/approaches/) and offer a related learning activity called Space Doctor (http://learn.genetics.utah.edu/content/genetherapy/doctor/).

The Better Health Channel from the State Government of Victoria (Australia) provides a brief introduction to gene therapy (https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/gene-therapy), including the gene therapy process and delivery techniques.

Penn Medicine's Oncolink describes how gene therapy works and how it is administered to patients (http://www.oncolink.org/treatment/article.cfm?aid=585&id=323&c=15).

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:

Information about the development of new gene therapies and the FDA’s role in overseeing the safety of gene therapy research can be found in the fact sheet Human Gene Therapies: Novel Product Development Q&A (http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm103331.htm).

The Genetic Science Learning Center at the University of Utah explains challenges related to gene therapy (http://learn.genetics.utah.edu/content/genetherapy/challenges/).

The NIH's Office of Biotechnology Activities provides NIH guidelines for biosafety (http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines).

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 Human Genome Research Institute discusses scientific issues and ethical concerns surrounding germline gene therapy (https://www.genome.gov/10004764).

A discussion of the ethics of gene therapy and genetic engineering (http://ethics.missouri.edu/gene-therapy.html) is available from the University of Missouri Center for Health Ethics.

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 (https://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 (https://clinicaltrials.gov/search?term=%22gene+therapy%22) that are accepting (or will accept) participants.

The Human Genome Project

Table of Contents

What is a genome? 201

What was the Human Genome Project and why has it been important? 202

What were the goals of the Human Genome Project? 203

What did the Human Genome Project accomplish? 204

What were some of the ethical, legal, and social implications addressed by the Human Genome Project? 205

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 Wellcome Trust Sanger Institute offers basic and in-depth explanations of the genome (http://www.yourgenome.org/facts/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 (https://www.genome.gov/10001772) and a list of frequently asked questions (https://www.genome.gov/11006943). Additionally, the booklet From the Blueprint to You provides an overview of the project (https://www.genome.gov/Pages/Education/Modules/BluePrintToYou/Blueprint7to8.pdf).

Additional information can be found in the National Library of Medicine fact sheet Understanding the Human Genome Project (https://medlineplus.gov/magazine/issues/summer13/articles/summer13pg15.html).

GeneEd from the National Library of Medicine and the National Human Genome Research Institute provides a list of educational resources related to the Human Genome Project (https://geneed.nlm.nih.gov/topic_subtopic.php?tid=52&sid=54).

The Wellcome Trust Sanger Institute offers an overview of the Human Genome Project, including a timeline (http://www.yourgenome.org/facts/timeline-the-human-genome-project) and approaches to sequencing (http://www.yourgenome.org/video/how-the-human-genome-was-sequenced).

The Smithsonian National Museum of Natural History's exhibit 'Genome: Unlocking Life's Code' provides a timeline (http://unlockinglifescode.org/timeline) of the Human Genome Project.

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 20,000 to 25,000 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 National Human Genome Research Institute provides a fact sheet about DNA sequencing (https://www.genome.gov/10001177).

The National Human Genome Research Institute details the goals and accomplishments (https://www.genome.gov/11006945) of the Human Genome Project.

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 205

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 news release International Consortium Completes Human Genome Project (https://www.genome.gov/11006929).

A 2004 news release (https://www.genome.gov/12513430) about the finished human genome sequence is available from the National Human Genome Research Institute.

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 on page 166.
- 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 (https://www.genome.gov/10001618) from the National Human Genome Research Institute. The ELSI Planning and Evaluation History web page (https://www.genome.gov/10001754) provides a more detailed discussion of the program.

More discussion about ethical issues in human genetics (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetELSI), including genetic discrimination, the cloning of organisms, and the patenting of genes is available from the Centre for Genetics Education.

The World Health Organization provides further discussion of the ELSI implications (http://www.who.int/genomics/elsi/en/) of human genomic research.

Genomic Research

Table of Contents

What are the next steps in genomic research? 207

What are single nucleotide polymorphisms (SNPs)? 208

What are genome-wide association studies? 209

What is the International HapMap Project? 210

What is the Encyclopedia of DNA Elements (ENCODE) Project? 212

What is pharmacogenomics? 214

What advances are being made in DNA sequencing? 216

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. The most common type of genetic variation is known as a single nucleotide polymorphism or SNP (pronounced “snip”). These small differences may help predict a person's risk of particular diseases 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 (https://www.genome.gov/ResearchAtNHGRI/).

The Genome Institute at Washington University explains the 1000 Genomes Project (http://genome.wustl.edu/projects/detail/1000-genomes-project/), which furthers the work of the HapMap Project.

The Wellcome Trust Sanger Institute discusses the 1000 Genomes Project (https://wellcome.ac.uk/press-release/1000-genomes-project-publishes-most-comprehensive-map-date-human-genetic-variation) in a press release that describes the key objectives of the project.

What are single nucleotide polymorphisms (SNPs)?

Single nucleotide polymorphisms, frequently called SNPs (pronounced “snips”), are the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, called a nucleotide. For example, a SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T) in a certain stretch of DNA.

SNPs occur normally throughout a person’s DNA. They occur once in every 300 nucleotides on average, which means there are roughly 10 million SNPs in the human genome. Most commonly, these variations are found in the DNA between genes. They can act as biological markers, helping scientists locate genes that are associated with disease. When SNPs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by affecting the gene’s function.

Most SNPs have no effect on health or development. Some of these genetic differences, however, have proven to be very important in the study of human health. Researchers have found SNPs that may help predict an individual’s response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing particular diseases. SNPs can also be used to track the inheritance of disease genes within families. Future studies will work to identify SNPs associated with complex diseases such as heart disease, diabetes, and cancer.

For more information about SNPs:

An audio definition of SNPs (https://www.genome.gov/glossary/?id=185) is available from the National Human Genome Research Institute’s Talking Glossary of Genetic Terms.

How scientists locate SNPs in the genome (http://learn.genetics.utah.edu/content/precision/snips/) is explained by the University of Utah Genetic Science Learning Center.

For people interested in more technical data, several databases of known SNPs are available:

- NCBI database of single nucleotide polymorphisms (dbSNP) (http://www.ncbi.nlm.nih.gov/SNP/)
- National Bioscience Database Center (NBDC) of the Japan Science and Technology Agency (JST) (http://biosciencedbc.jp/en/)

What are genome-wide association studies?

Genome-wide association studies are a relatively new way for scientists to identify genes involved in human disease. This method searches the genome for small variations, called single nucleotide polymorphisms or SNPs (pronounced “snips”), that occur more frequently in people with a particular disease than in people without the disease. Each study can look at hundreds or thousands of SNPs at the same time. Researchers use data from this type of study to pinpoint genes that may contribute to a person’s risk of developing a certain disease.

Because genome-wide association studies examine SNPs across the genome, they represent a promising way to study complex, common diseases in which many genetic variations contribute to a person’s risk. This approach has already identified SNPs related to several complex conditions including diabetes, heart abnormalities, Parkinson disease, and Crohn disease. Researchers hope that future genome-wide association studies will identify more SNPs associated with chronic diseases, as well as variations that affect a person’s response to certain drugs and influence interactions between a person’s genes and the environment.

For more information about genome-wide association studies:

The National Human Genome Research Institute provides a detailed explanation of genome-wide association studies (https://www.genome.gov/20019523).

You can also search for clinical trials of genome-wide association studies online. ClinicalTrials.gov (https://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 genome-wide association studies (https://clinicaltrials.gov/search?term=GWAS+OR+%22Genome+Wide+Association%22) that are accepting (or will accept) participants.

For people interested in more technical information, the NCBI’s Database of Genotype and Phenotype (dbGaP) (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap) contains data from genome-wide association studies. An introduction to this database, as well as information about study results, is available from the dbGaP press release (https://www.nlm.nih.gov/archive//20120510/news/press_releases/dbgap_launchPR06.html). In addition, the National Human Genome Research Institute and the European Bioinformatics Institute jointly provide a Catalog of Published Genome-Wide Association Studies (http://www.ebi.ac.uk/gwas/).

What is the International HapMap Project?

The International HapMap Project is an international scientific effort to identify common genetic variations among people. This project represents a collaboration of scientists from public and private organizations in six countries. Data from the project is freely available to researchers worldwide. Researchers can use the data to learn more about the relationship between genetic differences and human disease.

The HapMap (short for “haplotype map”) is a catalog of common genetic variants called single nucleotide polymorphisms or SNPs (pronounced “snips”). Each SNP represents a difference in a single DNA building block, called a nucleotide. These variations occur normally throughout a person’s DNA. When several SNPs cluster together on a chromosome, they are inherited as a block known as a haplotype. The HapMap describes haplotypes, including their locations in the genome and how common they are in different populations throughout the world.

The human genome contains roughly 10 million SNPs. It would be difficult, time-consuming, and expensive to look at each of these changes and determine whether it plays a role in human disease. Using haplotypes, researchers can sample a selection of these variants instead of studying each one. The HapMap will make carrying out large-scale studies of SNPs and human disease (called genome-wide association studies) cheaper, faster, and less complicated.

The main goal of the International HapMap Project is to describe common patterns of human genetic variation that are involved in human health and disease. Additionally, data from the project will help researchers find genetic differences that can help predict an individual’s response to particular medicines or environmental factors (such as toxins.)

For more information about the International HapMap Project:

The National Human Genome Research Institute provides an overview of the project in their International HapMap Project fact sheet (https://www.genome.gov/10001688). The fact sheet also includes a link to a more in-depth online tutorial on HapMap usage.

Cold Springs Harbor Laboratory provides a step-by-step guide (http://cshlpress.com/pdf/sample/GenVa-06.pdf) to using the International HapMap Project web site.

You can also search for clinical trials involving haplotypes or associated with the International HapMap Project. ClinicalTrials.gov (https://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 haplotype-related studies (https://clinicaltrials.gov/search?term=HAPMAP+OR+haplotype) that are accepting (or will accept) participants.

What is the Encyclopedia of DNA Elements (ENCODE) Project?

The ENCODE Project was planned as a follow-up to the Human Genome Project. The Human Genome Project sequenced the DNA that makes up the human genome; the ENCODE Project seeks to interpret this sequence. Coinciding with the completion of the Human Genome Project in 2003, the ENCODE Project began as a worldwide effort involving more than 30 research groups and more than 400 scientists.

The approximately 20,000 genes that provide instructions for making proteins account for only about 1 percent of the human genome. Researchers embarked on the ENCODE Project to figure out the purpose of the remaining 99 percent of the genome. Scientists discovered that more than 80 percent of this non-gene component of the genome, which was once considered “junk DNA,” actually has a role in regulating the activity of particular genes (gene expression).

Researchers think that changes in the regulation of gene activity may disrupt protein production and cell processes and result in disease. A goal of the ENCODE Project is to link variations in the expression of certain genes to the development of disease.

The ENCODE Project has given researchers insight into how the human genome functions. As researchers learn more about the regulation of gene activity and how genes are expressed, the scientific community will be able to better understand how the entire genome can affect human health.

For more information about the ENCODE Project:

The University of California at Santa Cruz provides detailed information about the findings of the ENCODE Project (https://www.encodeproject.org/) as well as the Project’s experimental procedures and many other types of data.

Published research findings are available through Nature Magazine’s Nature Encode Explorer (http://www.nature.com/encode/#/threads), which gives the public access to scientific information collected from the ENCODE Project.

The Broad Institute describes the purpose (http://www.broadinstitute.org/news/4326) of the ENCODE Project.

The National Human Genome Research Institute announces results of the ENCODE Project in a Press Release (https://www.genome.gov/27549810) and provides an overview (https://www.genome.gov/10005107) of the ENCODE Project.

Some of the outcomes of the ENCODE Project (http://www.cshl.edu/news-a-features/massive-genome-analysis-by-encode-redefines-the-gene-and-sheds-new-light-on-complex-disease.html) are detailed by Cold Springs Harbor Laboratory.

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 National Institute of General Medical Sciences offers a list of Frequently Asked Questions about Pharmacogenomics (https://www.nigms.nih.gov/education/Pages/factsheet-pharmacogenomics.aspx).

A list of Frequently Asked Questions about Pharmacogenomics (https://www.genome.gov/27530645) is also offered by the National Human Genome Research Institute.

Additional information about pharmacogenetics is available from the Centre for Genetics Education (http://www.genetics.edu.au/Publications-and-Resources/Genetics-Fact-Sheets/FactSheetPHARMACOGENETICSPHARMACOGENOMICS.pdf) as well as Genes In Life (http://www.genesinlife.org/testing-services/testing-genetic-conditions/pharmacogenomic-testing).

The Smithsonian National Museum of Natural History's exhibit 'Genome: Unlocking Life's Code' discusses the utility of pharmacogenomics (http://unlockinglifescode.org/explore/genomic-medicine/pharmacogenomics).

An interactive tutorial (http://www.phgfoundation.org/tutorials/pharmacogenomics/) about pharmacogenomics is available from the PHG Foundation.

The American Medical Association explains what pharmacogenomics is and provides a list of practical applications (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/current-topics/pharmacogenomics.page).

PharmGKB (https://www.pharmgkb.org/) is a pharmacogenomics resource sponsored by the National Institutes of Health that collects information on human genetic variation and drug responses.

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

What advances are being made in DNA sequencing?

Determining the order of DNA building blocks (nucleotides) in an individual's genetic code, called DNA sequencing, has advanced the study of genetics and is one method used to test for genetic disorders.

New technologies that allow rapid sequencing of large amounts of DNA are being developed. The original sequencing technology, called Sanger sequencing (named after the scientist who developed it, Frederick Sanger), was a breakthrough that helped scientists determine the human genetic code, but it is time-consuming and expensive. The Sanger method has been automated to make it faster and is still used in laboratories today to sequence short pieces of DNA, but it would take years to sequence all of a person's DNA (known as the person's genome). Several technologies have been developed more recently, called next-generation sequencing (or next-gen sequencing), that have sped up the process (taking only days to weeks to sequence a human genome) while reducing the cost.

With next-generation sequencing, it is now feasible to sequence large amounts of DNA, for instance all the pieces of an individual's DNA that provide instructions for making proteins. These pieces, called exons, are thought to make up 1 percent of a person's genome. Together, all the exons in a genome are known as the exome, and the method of sequencing them is known as whole exome sequencing. This method allows variations in the protein-coding region of any gene to be identified, rather than a select few genes. Because most known mutations that cause disease occur in exons, whole exome sequencing is thought to be an efficient method to identify possible disease-causing mutations.

However, researchers have found that DNA variations outside the exons can affect gene activity and protein production and lead to genetic disorders--variations that whole exome sequencing would miss. Another method, called whole genome sequencing, determines the order of all the nucleotides in an individual's DNA and can determine variations in any part of the genome.

While many more genetic changes can be identified with whole exome and whole genome sequencing than with select gene sequencing, the significance of much of this information is unknown. Because not all genetic changes affect health, it is difficult to know whether identified variants are involved in the condition of interest. Sometimes, an identified variant is associated with a different genetic disorder that has not yet been diagnosed (these are called incidental or secondary findings).

In addition to being used in the clinic, whole exome and whole genome sequencing are valuable methods for researchers. Continued study of exome

and genome sequences can help determine whether new genetic variations are associated with health conditions, which will aid disease diagnosis in the future.

For more information about DNA sequencing technologies and their use:

Genetics Home Reference discusses whether all genetic changes affect health and development on page 23.

A scientist at the Genome Institute at the University of Washington describes the different sequencing technologies (http://genome.wustl.edu/articles/detail/dna-sequencing-technology-a-perspective-from-dr-elaine-mardis/) and what the new technologies have meant for the study of the genetic code.

An illustration of the decline in the cost of DNA sequencing (https://www.genome.gov/sequencingcosts/), including that caused by the introduction of new technologies, is provided by the National Human Genome Research Institute (NHGRI).

The American College of Medical Genetics and Genomics (ACMG) has laid out their policies regarding whole exome and whole genome sequencing (https://www.acmg.net/StaticContent/PPG/Clinical_Application_of_Genomic_Sequencing.pdf), including when these methods should be used, what results may arise, and what the results might indicate.

The PHG Foundation (UK) provides an overview of whole genome sequencing (http://www.phgfoundation.org/file/10365/) and how it can be used in healthcare.

The Mount Sinai School of Medicine Genomics Core Facility describes the techniques used in whole exome sequencing (http://icahn.mssm.edu/research/genomics/core-facility/whole-exome).

The Smithsonian National Museum of Natural History's exhibit 'Genome: Unlocking Life's Code' discusses the advancements (http://unlockinglifescode.org/explore/genome-within-us/reading-lifes-code) made in DNA sequencing.

Precision Medicine

Table of Contents

What is precision medicine? 219

What is the difference between precision medicine and personalized medicine? What about pharmacogenomics? 221

What is the Precision Medicine Initiative? 222

What are some potential benefits of precision medicine and the Precision Medicine Initiative? 224

What are some of the challenges facing precision medicine and the Precision Medicine Initiative? 226

What is precision medicine?

According to the National Institutes of Health (NIH), precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." This approach will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people. It is in contrast to a "one-size-fits-all" approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals.

Although the term "precision medicine" is relatively new, the concept has been a part of healthcare for many years. For example, a person who needs a blood transfusion is not given blood from a randomly selected donor; instead, the donor's blood type is matched to the recipient to reduce the risk of complications. Although examples can be found in several areas of medicine, the role of precision medicine in day-to-day healthcare is relatively limited. Researchers hope that this approach will expand to many areas of health in coming years.

Learn more about precision medicine:

The NIH offers a resource focused on precision medicine (https://www.nih.gov/precision-medicine-initiative-cohort-program).

The White House also provides information about precision medicine (https://www.whitehouse.gov/blog/2015/01/30/precision-medicine-initiative-data-driven-treatments-unique-your-own-body).

Information about Genetics Home Reference and precision medicine is available from the interactive Journal of Medical Research (i-JMR) article, "Information Needs in the Precision Medicine Era: How Genetics Home Reference Can Help (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4917728/)."

The Centers for Disease Control and Prevention covers precision medicine in its Genomics and Health Impact Blog (http://blogs.cdc.gov/genomics/category/precision-medicine/).

A 2011 press release from the National Academies (http://www8.nationalacademies.org/onpinews/newsitem.aspx?recordid=13284) discusses the National Research Council report that introduced the term "precision medicine."

Information about precision medicine (http://learn.genetics.utah.edu/content/precision/) is also available from the Genetic Science Learning Center at the University of Utah.

The American Cancer Society provides information about precision medicine in cancer (http://www.cancer.org/research/acsresearchupdates/more/personalized-medicine-redefining-cancer-and-its-treatment).

What is the difference between precision medicine and personalized medicine? What about pharmacogenomics?

There is a lot of overlap between the terms "precision medicine" and "personalized medicine." According to the National Research Council, "personalized medicine" is an older term with a meaning similar to "precision medicine." However, there was concern that the word "personalized" could be misinterpreted to imply that treatments and preventions are being developed uniquely for each individual; in precision medicine, the focus is on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors. The Council therefore preferred the term "precision medicine" to "personalized medicine." However, some people still use the two terms interchangeably.

Pharmacogenomics on page 214 is a part of precision medicine. Pharmacogenomics is the study of how genes affect a person’s response to particular 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 variations in a person’s genes.

Read more about precision medicine, personalized medicine, and pharmacogenomics:

A 2011 report from the National Research Council (http://www.plengegen.com/wp-content/uploads/4_Toward-Precision-Medicine.pdf) (downloadable as a PDF) provides a detailed overview of precision medicine, including the reasoning behind the Council’s preference for the term "precision medicine" over "personalized medicine."

The journal Nature Medicine published an article on this topic called "Momentum grows to make 'personalized' medicine more 'precise'" (http://www.nature.com/nm/journal/v19/n3/full/nm0313-249.html).

Genetics Home Reference provides an introduction to pharmacogenomics on page 214. Additional information about pharmacogenomics (https://www.genome.gov/27530645) is available from the National Human Genome Research Institute (NHGRI).

What is the Precision Medicine Initiative?

In early 2015, President Obama announced a research effort focusing on bringing precision medicine to many aspects of healthcare. The President's budget for fiscal year 2016 included $216 million in funding for the initiative for the NIH, the National Cancer Institute (NCI; the NIH institute focused on cancer research), and the Food and Drug Administration (FDA).

The Precision Medicine Initiative has both short-term and long-term goals. The short-term goals involve expanding precision medicine in the area of cancer research. Researchers at the NCI hope to use this approach to find new, more effective treatments for various kinds of cancer based on increased knowledge of the genetics and biology of the disease. The long-term goals of the Precision Medicine Initiative focus on bringing precision medicine to all areas of health and healthcare on a large scale. To this end, the NIH plans to launch a study involving a group (cohort) of at least 1 million volunteers from around the United States. Participants will provide genetic data, biological samples, and other information about their health. These data will be used by researchers to study a large range of diseases, with the goals of better predicting disease risk, understanding how diseases occur, and finding improved diagnosis and treatment strategies.

Learn more about the Precision Medicine Initiative:

The NIH website about precision medicine (https://www.nih.gov/precision-medicine-initiative-cohort-program) provides information about the goals of and participants in the Precision Medicine Initiative. This infographic (http://www.nih.gov/precisionmedicine/infographic-printable.pdf) (downloadable as a PDF) gives a visual overview of the project. Additionally, the NIH Precision Medicine Initiative channel (https://www.youtube.com/channel/UCQId1TfpwPaYiDIGlxEhlkA) on YouTube includes talks by scientists and others about various aspects of the initiative.

The NCI offers information about the Precision Medicine Initiative and its role in cancer research (http://www.cancer.gov/news-events/cancer-currents-blog/2015/precision-medicine-initiative-2016).

The White House provides a fact sheet on President Obama's Precision Medicine Initiative (https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative) that explains the project's plans and objectives.

Dr. Francis Collins, director of the NIH, and Dr. Harold Varmus, former director of the NCI, wrote more about their vision for the Precision Medicine Initiative (http://

www.nejm.org/doi/full/10.1056/NEJMp1500523) in the New England Journal of Medicine.

What are some potential benefits of precision medicine and the Precision Medicine Initiative?

Precision medicine holds promise for improving many aspects of health and healthcare. Some of these benefits will be apparent soon, as the Precision Medicine Initiative's research cohort is set up and new tools and approaches for managing data are developed. Other benefits will result from long-term research in precision medicine and may not be realized for years.

Potential benefits of the Precision Medicine Initiative:

- New approaches for protecting research participants, particularly patient privacy and the confidentiality of their data.
- Design of new tools for building, analyzing, and sharing large sets of medical data.
- Improvement of FDA oversight of tests, drugs, and other technologies to support innovation while ensuring that these products are safe and effective.
- New partnerships of scientists in a wide range of specialties, as well as people from the patient advocacy community, universities, pharmaceutical companies, and others.
- Opportunity for a million people to contribute to the advancement of scientific research.

Potential long-term benefits of research in precision medicine:

- Wider ability of doctors to use patients' genetic and other molecular information as part of routine medical care.
- Improved ability to predict which treatments will work best for specific patients.
- Better understanding of the underlying mechanisms by which various diseases occur.
- Improved approaches to preventing, diagnosing, and treating a wide range of diseases.
- Better integration of electronic health records (EHRs) in patient care, which will allow doctors and researchers to access medical data more easily.

Read more about the promise of precision medicine and the Precision Medicine Initiative:

Dr. Francis Collins, director of the NIH, and Dr. Harold Varmus, former director of the NCI, wrote about their vision for the Precision Medicine Initiative (http://www.nejm.org/doi/full/10.1056/NEJMp1500523) in the New England Journal of Medicine. Dr. Collins also gave a talk about his vision (https://www.youtube.com/

watch?v=ObBYk0MOuDM) for the project, which is available on the NIH Precision Medicine Initiative channel (https://www.youtube.com/channel/UCQId1TfpwPaYiDIGlxEhlkA) on YouTube.

The White House website offers examples of how precision medicine is helping Americans (https://www.whitehouse.gov/blog/2015/01/29/precision-medicine-already-working-cure-americans-these-are-their-stories).

What are some of the challenges facing precision medicine and the Precision Medicine Initiative?

Precision medicine is still a young and growing field. Many of the technologies that will be needed to meet the goals of the Precision Medicine Initiative are in the early stages of development or have not yet been developed. For example, researchers will need to find ways to standardize collection of data from more than 1 million volunteers from hospitals and clinics around the country. They will also need to find efficient ways to store large amounts of this patient data in databases.

The Precision Medicine Initiative also raises ethical, social, and legal issues. With health data on such a large number of people, it will be critical to find ways to protect participants' privacy and the confidentiality of their health information. Participants will need to understand the risks and benefits of participating in research, which means researchers will have to develop a rigorous process of informed consent on page 166.

Cost is also an issue with precision medicine. The Precision Medicine Initiative itself will cost many millions of dollars, and the ongoing initiative will require Congress to approve funding over multiple years. Technologies such as sequencing large amounts of DNA on page 216 are still expensive to carry out (although the cost of sequencing is decreasing quickly). Additionally, drugs that are developed to target a person's genetic or molecular characteristics are likely to be expensive. Reimbursement from third-party payers (such as private insurance companies) for these targeted drugs is also likely to become an issue.

If precision medicine approaches are to become part of routine healthcare, doctors and other healthcare providers will need to know more about molecular genetics and biochemistry. They will increasingly find themselves needing to interpret the results of genetic tests on page 172, understand how that information is relevant to treatment or prevention approaches, and convey this knowledge to patients.

Learn more about challenges related to precision medicine:

The NIH Precision Medicine Initiative channel on YouTube (https://www.youtube.com/channel/UCQId1TfpwPaYiDIGlxEhlkA) offers videos of talks by leading experts on various aspects of the project, including issues related to data collection and sharing, storing data in electronic health records, and participant protection.

The Genetic Literacy Project provides the editorial "That 'Precision Medicine' initiative? A Reality Check" (http://www.geneticliteracyproject.org/2015/02/03/

that-precision-medicine-initiative-a-reality-check/) outlining some of the possible challenges and limitations of the Precision Medicine Initiative.

Genetics
Home
Reference

https://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

Published on November 22, 2016