Help Me Understand Genetics

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1
Cells and DNA

1.1 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

Within cells, the cytoplasm (Figure 1.1) is made up of a jelly-like fluid (called the cytosol) and other structures that surround the nucleus.

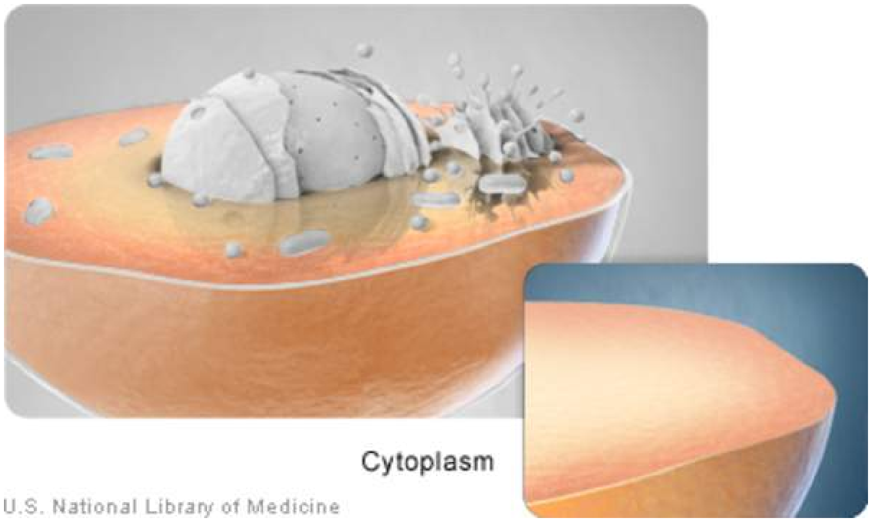

FIGURE 1.1: The cytoplasm is fluid within cells that surrounds the nucleus.

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)

This organelle helps process molecules created by the cell. The endoplasmic reticulum (Figure 1.2) also transports these molecules to their specific destinations either inside or outside the cell.

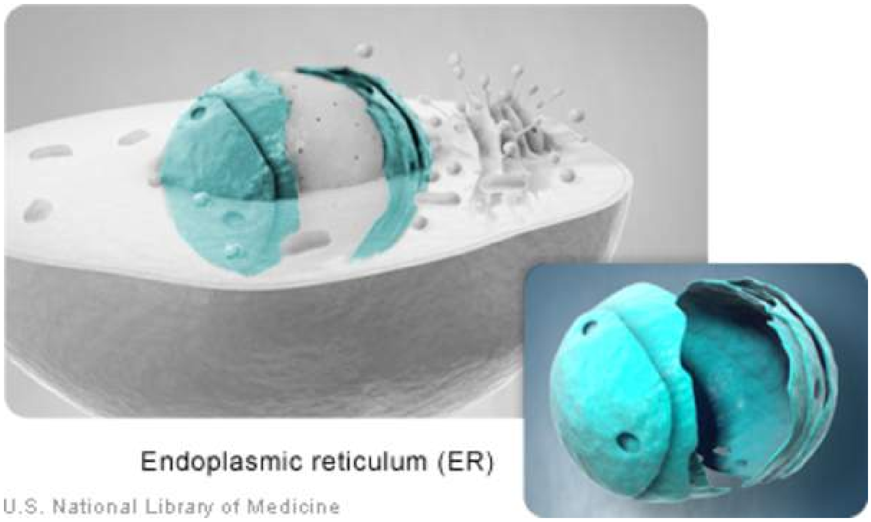

FIGURE 1.2: The endoplasmic reticulum is a structure near the cell nucleus.

Golgi apparatus

The Golgi apparatus (Figure 1.3) packages molecules processed by the endoplasmic reticulum to be transported out of the cell.

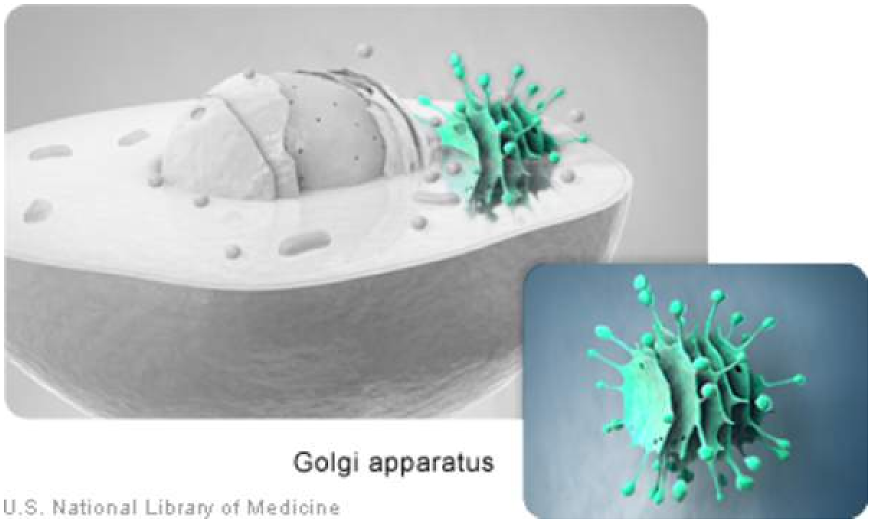

FIGURE 1.3: The Golgi apparatus is a structure in the cell cytoplasm.

Lysosomes and peroxisomes

These organelles (Figure 1.4) 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.

FIGURE 1.4: Lyosomes are cell structures in the cytoplasm.

Mitochondria

Mitochondria (Figure 1.5) 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.

FIGURE 1.5: Mitochondria are structures within the cell cytoplasm.

Nucleus

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

The plasma membrane (Figure 1.6) is the outer lining of the cell. It separates the cell from its environment and allows materials to enter and leave the cell.

FIGURE 1.6: The plasma membrane surrounds a cell.

Ribosomes

Ribosomes (Figure 1.7) 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).

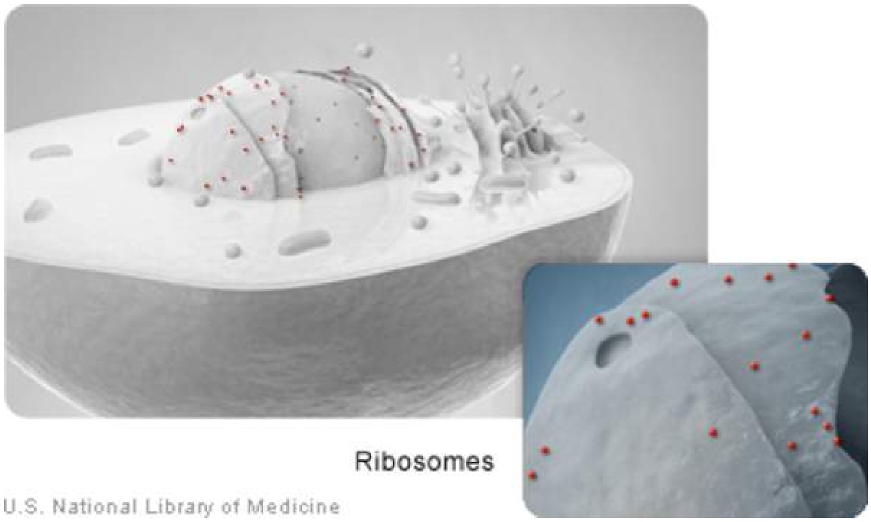

FIGURE 1.7: Ribosomes are cell structures near the nucleus.

For more information about cells:

The National Institute of General Medical Sciences has a science education booklet about cells called Inside the Cell (https://www.nigms.nih.gov/education/Booklets/Inside-the-Cell/Pages/Home.aspx).

The National Human Genome Research Institute's Talking Glossary (https://www.genome.gov/genetics-glossary/Cell) provides a definition of a cell as well as an illustration and video.

The Genetic Science Learning Center at the University of Utah offers an interactive introduction to cells (https://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 (https://askabiologist.asu.edu/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/).

1.2 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). Mitochondria (Figure 1.5) are structures within cells that convert the energy from food into a form that cells can use.

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. (Figure 1.8)

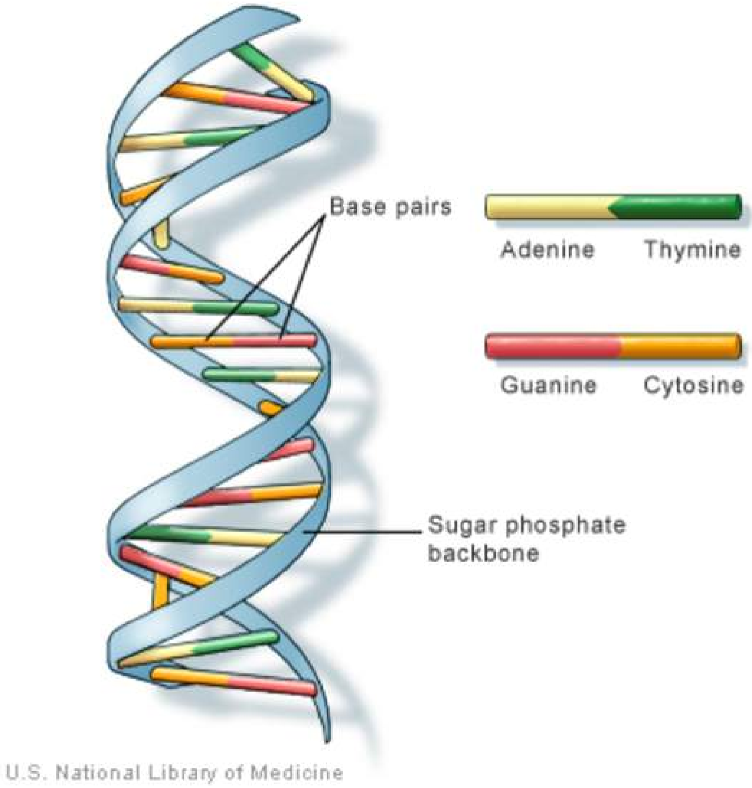

FIGURE 1.8: DNA is made up of base pairs and a sugar phosphate backbone.

For more information about DNA:

The National Human Genome Research Institute (NHGRI), a part of the National Institutes of Health (NIH), provides a fact sheet Deoxyribonucleic Acid (DNA) (https://www.genome.gov/about-genomics/fact-sheets/Deoxyribonucleic-Acid-Fact-Sheet) that gives an introduction to this molecule.

StatedClearly offers a video introduction to DNA and how it works (https://www.statedclearly.com/videos/what-is-dna/).

The New Genetics, a publication of the National Institute of General Medical Sciences, part of the NIH, discusses the structure of DNA and how it was discovered (https://www.nigms.nih.gov/education/Booklets/the-new-genetics/Pages/Home.aspx).

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 (https://www2.le.ac.uk/projects/vgec/highereducation/topics/dna-genes-chromosomes).

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

1.3 What is a gene?

A gene is the basic physical and functional unit of heredity. Genes are made up of DNA. Some genes act as instructions to make molecules called proteins. However, many genes do not code for proteins. In humans, genes vary in size from a few hundred DNA bases to more than 2 million bases. An international research effort called the Human Genome Project, which worked to determine the sequence of the human genome and identify the genes that it contains, 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.

Scientists keep track of genes by giving them unique names. Because gene names can be long, genes are also assigned symbols, which are short combinations of letters (and sometimes numbers) that represent an abbreviated version of the gene name. For example, a gene on chromosome 7 that has been associated with cystic fibrosis is called the cystic fibrosis transmembrane conductance regulator; its symbol is *CFTR*.

Genes are made up of DNA. Each chromosome contains many genes. (Figure 1.9)

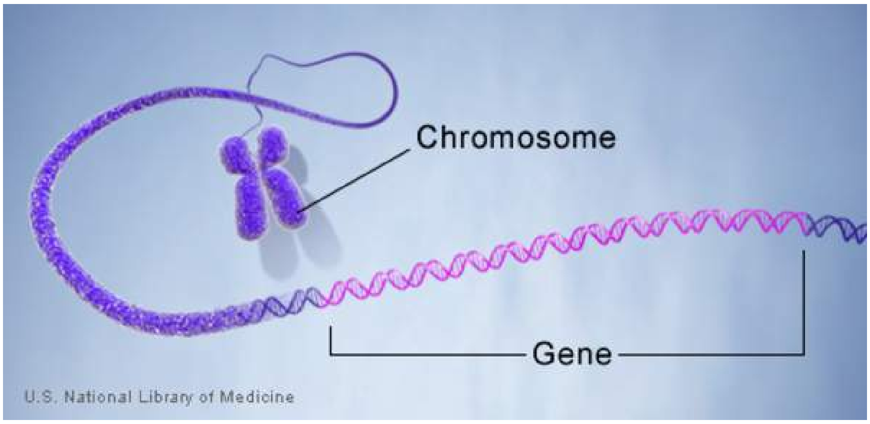

FIGURE 1.9: A gene is labeled along the length of a chromosome.

For more information about genes:

MedlinePlus Genetics provides consumer-friendly gene summaries (https://medlineplus.gov/genetics/gene/) that include an explanation of each gene's normal function and how variants in the gene cause particular genetic conditions.

More information about how genetic conditions and genes are named (https://medlineplus.gov/genetics/understanding/mutationsanddisorders/naming/) is also available from MedlinePlus Genetics.

The Centre for Genetics Education offers a fact sheet that introduces genes and chromosomes (https://www.genetics.edu.au/SitePages/DNA-RNA-genes-and-chromosomes.aspx).

The Tech Museum of Innovation at Stanford University describes genes and how they were discovered (https://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 (https://www2.le.ac.uk/projects/vgec/highereducation/topics/dna-genes-chromosomes).

1.4 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. (Figure 1.10)

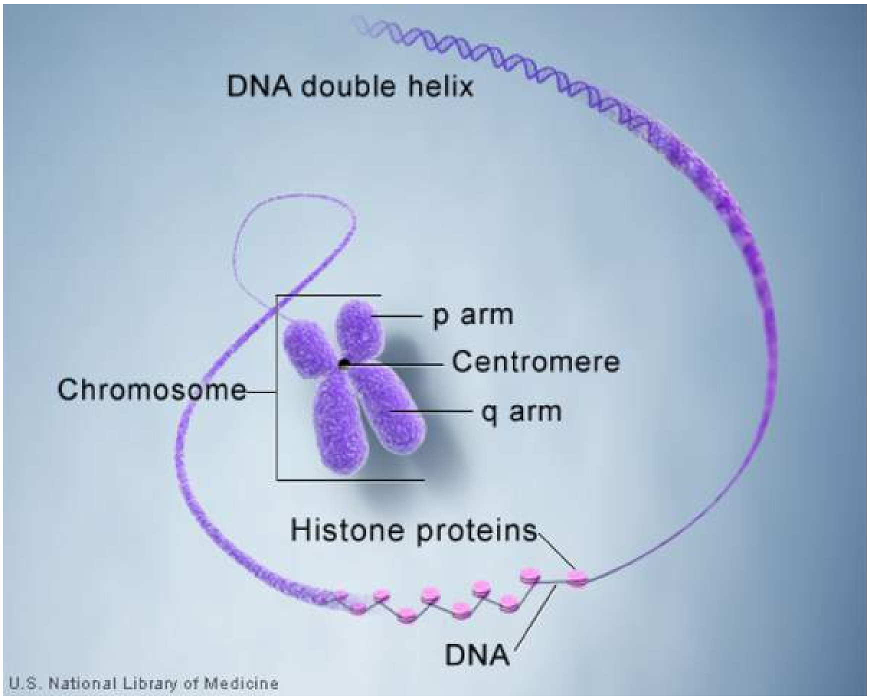

FIGURE 1.10: Chromosomes have a p arm, a q arm, and a centromere. They are made up of DNA wrapped around histone proteins.

For more information about chromosomes:

MedlinePlus Genetics provides information about each human chromosome (https://medlineplus.gov/genetics/chromosome/) written in lay language.

A basic introduction to chromosomes (https://www.genome.gov/about-genomics/fact-sheets/Chromosomes-Fact-Sheet) is available from the National Human Genome Research Institute.

The Centre for Genetics Education offers a fact sheet that introduces genes and chromosomes (https://www.genetics.edu.au/SitePages/DNA-RNA-genes-and-chromosomes.aspx).

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

1.5 How many chromosomes do people have?

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

The 22 autosomes are numbered by size. The other two chromosomes, X and Y, are the sex chromosomes. This picture of the human chromosomes lined up in pairs is called a karyotype. (Figure 1.11)

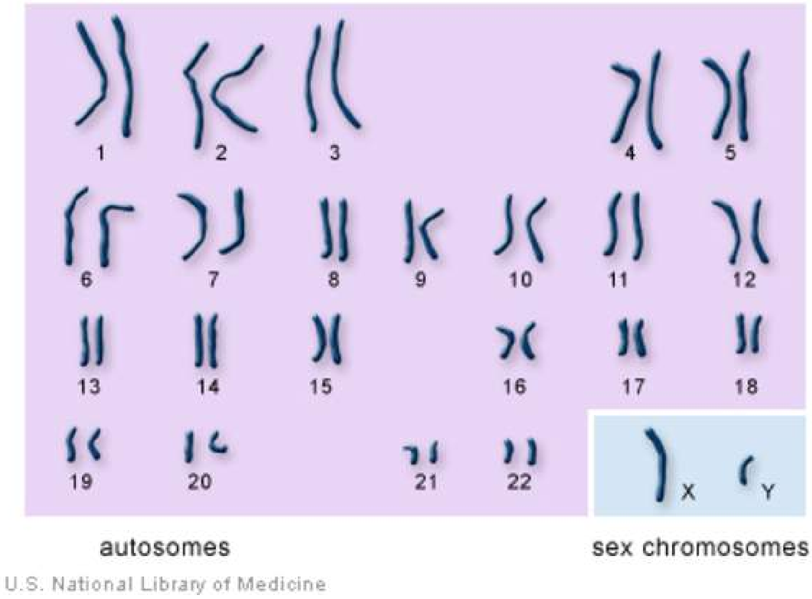

FIGURE 1.11: A normal male karyotype with 22 autosomes, one X chromosome, and one Y chromosome.

For more information about the 23 pairs of human chromosomes:

MedlinePlus Genetics provides information about each human chromosome (https://medlineplus.gov/genetics/chromosome/) written in lay language.

MedlinePlus offers additional details about karyotype genetic tests (https://medlineplus.gov/lab-tests/karyotype-genetic-test/).

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

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

1.6 What is noncoding DNA?

Only about 1 percent of DNA is made up of protein-coding genes; the other 99 percent is noncoding. Noncoding DNA does not provide instructions for making proteins. Scientists once thought noncoding DNA was “junk,” with no known purpose. However, it is becoming clear that at least some of it is integral to the function of cells, particularly the control of gene activity. For example, noncoding DNA contains sequences that act as regulatory elements, determining when and where genes are turned on and off. Such elements provide sites for specialized proteins (called transcription factors) to attach (bind) and either activate or repress the process by which the information from genes is turned into proteins (transcription). Noncoding DNA contains many types of regulatory elements:

- Promoters provide binding sites for the protein machinery that carries out transcription. Promoters are typically found just ahead of the gene on the DNA strand.
- Enhancers provide binding sites for proteins that help activate transcription. Enhancers can be found on the DNA strand before or after the gene they control, sometimes far away.
- Silencers provide binding sites for proteins that repress transcription. Like enhancers, silencers can be found before or after the gene they control and can be some distance away on the DNA strand.
- Insulators provide binding sites for proteins that control transcription in a number of ways. Some prevent enhancers from aiding in transcription (enhancer-blocker insulators). Others prevent structural changes in the DNA that repress gene activity (barrier insulators). Some insulators can function as both an enhancer blocker and a barrier.

Other regions of noncoding DNA provide instructions for the formation of certain kinds of RNA molecules. RNA is a chemical cousin of DNA. Examples of specialized RNA molecules produced from noncoding DNA include transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), which help assemble protein building blocks (amino acids) into a chain that forms a protein; microRNAs (miRNAs), which are short lengths of RNA that block the process of protein production; and long noncoding RNAs (lncRNAs), which are longer lengths of RNA that have diverse roles in regulating gene activity.

Some structural elements of chromosomes are also part of noncoding DNA. For example, repeated noncoding DNA sequences at the ends of chromosomes form telomeres. Telomeres protect the ends of chromosomes from being degraded during the copying of genetic material. Repetitive noncoding DNA sequences also form satellite DNA, which is a part of other structural elements. Satellite DNA is the basis of the centromere, which is the constriction point of the X-shaped chromosome pair. Satellite DNA also forms heterochromatin, which is densely packed DNA that is important for controlling gene activity and maintaining the structure of chromosomes.

Some noncoding DNA regions, called introns, are located within protein-coding genes but are removed before a protein is made. Regulatory elements, such as enhancers, can be located in introns. Other noncoding regions are found between genes and are known as intergenic regions.

The identity of regulatory elements and other functional regions in noncoding DNA is not completely understood. Researchers are working to understand the location and role of these genetic components.

Scientific journal articles for further reading

Maston GA, Evans SK, Green MR. Transcriptional regulatory elements in the human genome. Annu Rev Genomics Hum Genet. 2006;7:29-59. Review. PubMed: 16719718.

ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. Nature. 2012 Sep 6;489(7414):57-74. doi: 10.1038/nature11247. PubMed: 22955616; Free full text available from PubMed Central: PMC3439153.

Plank JL, Dean A. Enhancer function: mechanistic and genome-wide insights come together. Mol Cell. 2014 Jul 3;55(1):5-14. doi: 10.1016/j.molcel.2014.06.015. Review. PubMed: 24996062.

For more information about noncoding DNA:

Cold Spring Harbor Laboratory DNA Learning Center: The Human Genome: Genes and Non-coding DNA, 3D Animation with Basic Narration (https://dnalc.cshl.edu/view/15486-The-human-genome-genes-and-non-coding-DNA-3D-animation-with-basic-narration.html)

University of Leicester Virtual Genetics Education Centre: Gene Expression and Regulation (https://www2.le.ac.uk/projects/vgec/highereducation/topics/geneexpression-regulation)

National Academies Press: Noncoding DNA—Subtlety, Punctuation, or Just Plain Junk? (https://www.nap.edu/read/1859/chapter/6#99)

Khan Academy: Transcription Factors (https://www.khanacademy.org/science/biology/gene-regulation/gene-regulation-in-eukaryotes/a/eukaryotic-transcription-factors)

The Cell: A Molecular Approach (second edition, 2000): Regulation of Transcription in Eukaryotes (https://www.ncbi.nlm.nih.gov/books/NBK9904/)

Genetic Science Learning Center, University of Utah: RNA's Role in the Central Dogma (https://learn.genetics.utah.edu/content/basics/centraldogma/), Telomeres (https://learn.genetics.utah.edu/content/basics/telomeres/), and Centromeres (https://learn.genetics.utah.edu/content/basics/readchromosomes/)

2
How Genes Work

2.1 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. Amino acids are coded by combinations of three DNA building blocks (nucleotides), determined by the sequence of genes.

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

Antibody. Antibodies bind to specific foreign particles, such as viruses and bacteria, to help protect the body.

Example: Immunoglobulin G (IgG) (Figure 2.1)

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.

Example: Phenylalanine hydroxylase (Figure 2.2)

Messenger. Messenger proteins, such as some types of hormones, transmit signals to coordinate biological processes between different cells, tissues, and organs.

Example: Growth hormone (Figure 2.3)

Structural component. These proteins provide structure and support for cells. On a larger scale, they also allow the body to move.

Example: Actin (Figure 2.4)

Transport/storage. These proteins bind and carry atoms and small molecules within cells and throughout the body.

Example: Ferritin (Figure 2.5)

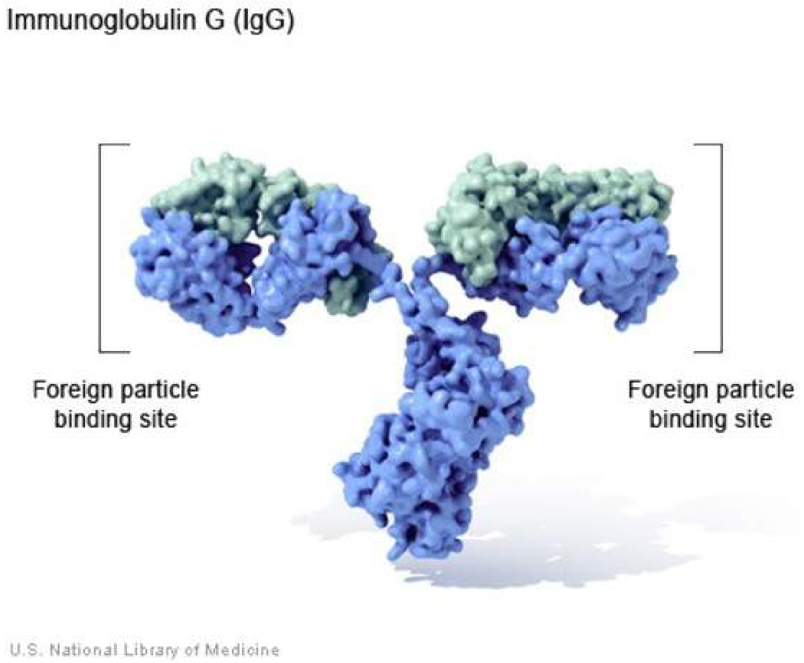

FIGURE 2.1: The structure of immunoglobulin G, including foreign particle binding sites.

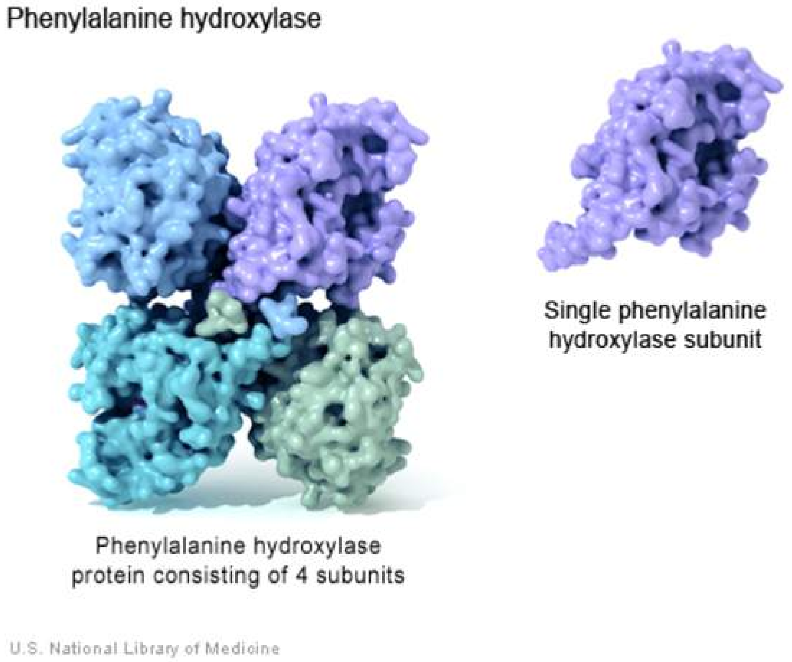

FIGURE 2.2: The phenylalanine hydroxylase protein consists of four subunits.

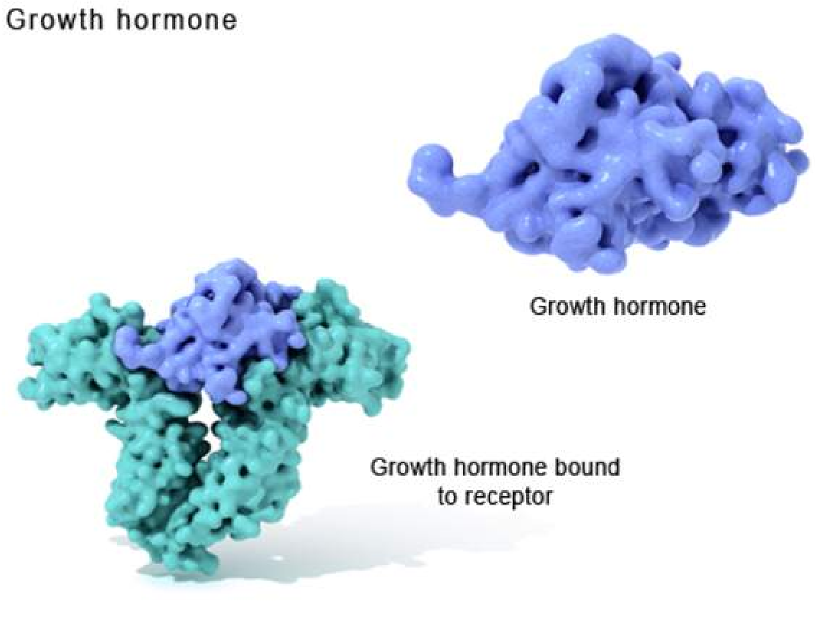

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FIGURE 2.3: The structure of growth hormone, and growth hormone bound to its receptor.

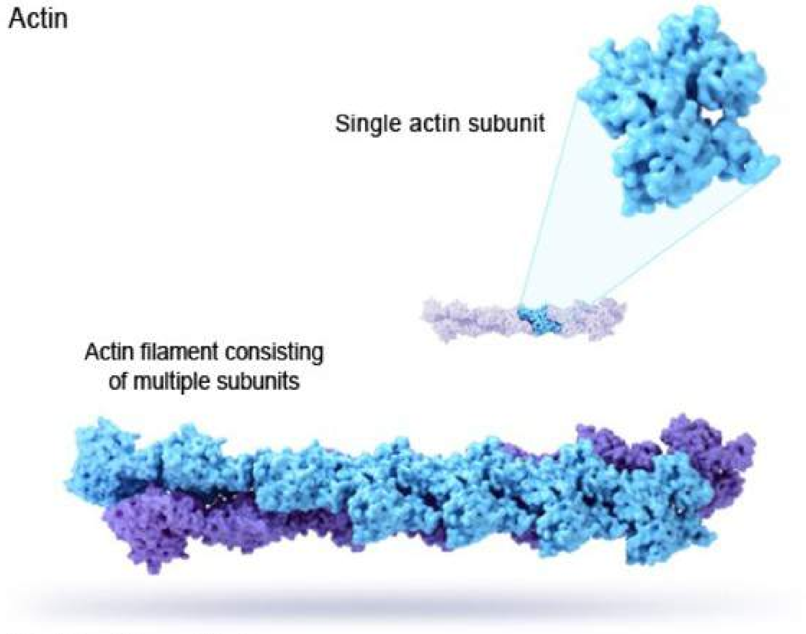

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FIGURE 2.4: An actin filament consisting of multiple subunits.

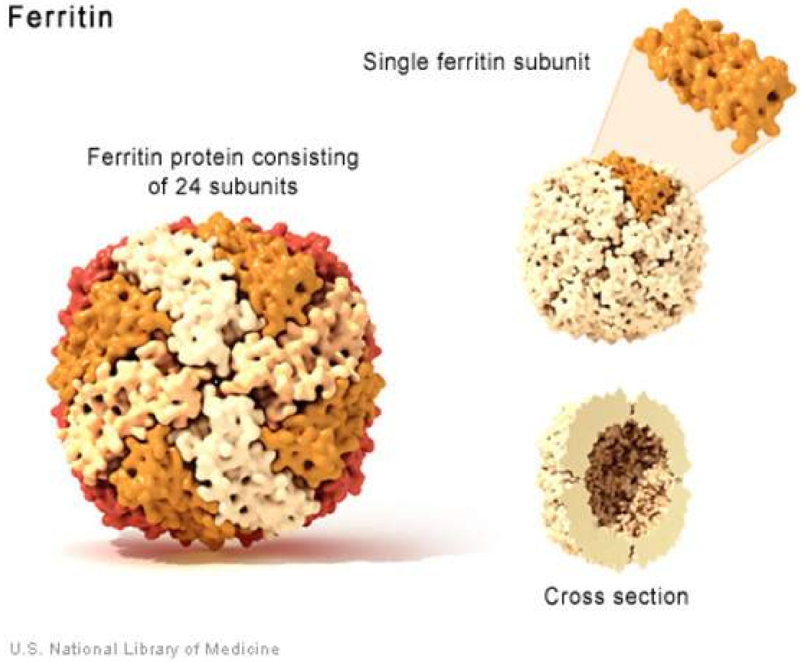


FIGURE 2.5: Ferritin protein consisting of 24 subunits.

For more information about proteins and their functions:

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

The textbook Molecular Biology of the Cell (4th edition, 2002), from the NCBI Bookshelf, offers a detailed introduction to protein function (https://www.ncbi.nlm.nih.gov/books/NBK26911/).

2.2 How do genes direct the production of proteins?

Most genes contain the information needed to make functional molecules called proteins. (A few genes produce regulatory 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 passed to a similar molecule called RNA (ribonucleic acid) in the cell nucleus. Both RNA and DNA are made up of a chain of building blocks called nucleotides, 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 nucleotides. Each sequence of three nucleotides, 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 nucleotides 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. (Figure 2.6)

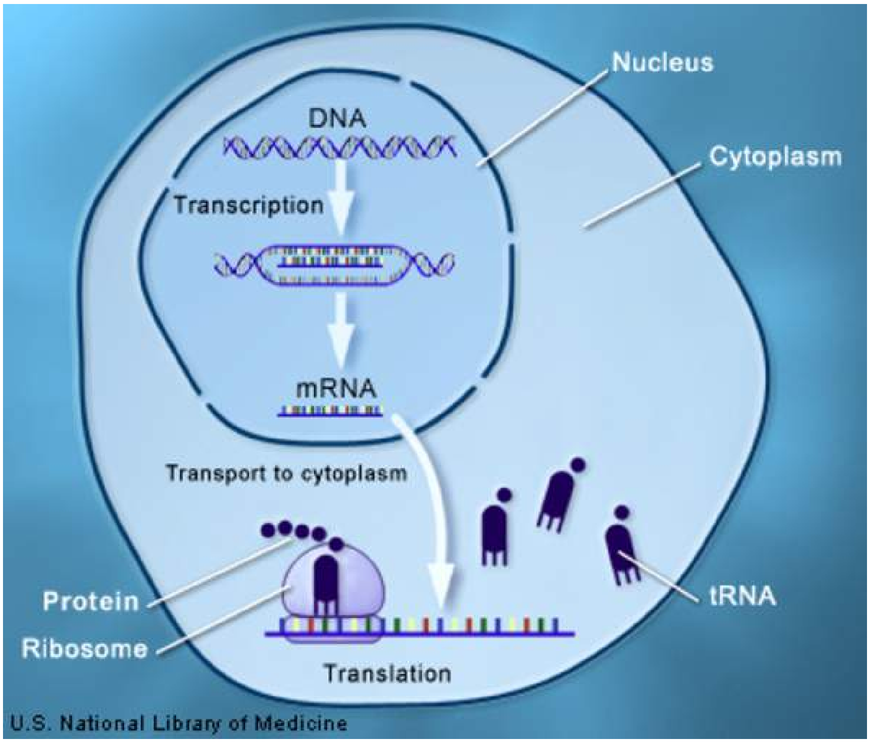


FIGURE 2.6: DNA is transcribed into mRNA, which is transported into the cell cytoplasm and translated into a protein.

For more information about making proteins:

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

The New Genetics (https://www.nigms.nih.gov/education/Booklets/the-new-genetics/Pages/Home.aspx), a publication of the National Institute of General Medical Sciences, includes discussions of transcription and translation.

Biointeractive from the Howard Hughes Medical Institute illustrates the stages in the flow of information from DNA to RNA to protein. (https://www.biointeractive.org/classroom-resources/central-dogma-and-genetic-medicine) This tool also gives examples of how modern technologies that target the different stages are used to treat genetic diseases.

2.3 Can genes be turned on and off in cells?

Each cell expresses, or turns on, only a fraction of its genes at any given time. 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 passed 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 when and how much protein product is made by a gene.

For more information about gene regulation:

The National Human Genome Research Institute provides a definition of gene regulation (https://www.genome.gov/genetics-glossary/Gene-Regulation) in their Talking Glossary of Genetic Terms.

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

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

The Khan Academy has an educational unit on gene regulation (https://www.khanacademy.org/science/biology/gene-regulation), including videos about gene regulation in bacteria and eukaryotes.

2.4 What is epigenetics?

Epigenetics is the study of how cells control gene activity without changing the DNA sequence."Epi-"means on or above in Greek,and "epigenetic" describes factors beyond the genetic code. Epigenetic changes are modifications to DNA that regulate whether genes are turned on or off. These modifications are attached to DNA and do not change the sequence of DNA building blocks. Within the complete set of DNA in a cell (genome) , all of the modifications that regulate the activity (expression) of the genes is known as the epigenome.

Because epigenetic changes help determine whether genes are turned on or off, they influence the production of proteins in cells. This regulation helps ensure that each cell produces only proteins that are necessary for its function. For example, proteins that promote bone growth are not produced in muscle cells. Patterns of epigenetic modification vary among individuals, in different tissues within an individual, and even in different cells within a tissue. Environmental influences, such as a person’s diet and exposure to pollutants, can impact the epigenome. Epigenetic modifications can be maintained from cell to cell as cells divide and, in some cases, can be inherited through the generations.

A common type of epigenetic modification is called DNA methylation. DNA methylation involves the attachment of small chemical groups called methyl groups (each consisting of one carbon atom and three hydrogen atoms) to DNA building blocks. When methyl groups are present on a gene, that gene is turned off or silenced, and no protein is produced from that gene.

Another common epigenetic change is histone modification. Histones are structural proteins in the cell nucleus. DNA wraps around histones, giving chromosomes their shape. Histones can be modified by the addition or removal of chemical groups, such as methyl groups or acetyl groups (each consisting of two carbon, three hydrogen, and one oxygen atoms). The chemical groups influence how tightly the DNA is wrapped around histones, which affects whether a gene can be turned on or off.

Errors in the epigenetic process, such as modification of the wrong gene or failure to add a chemical group to a particular gene or histone, can lead to abnormal gene activity or inactivity. Altered gene activity, including that caused by epigenetic errors, is a common cause of genetic disorders. Conditions such as cancers, metabolic disorders, and degenerative disorders have 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 the effects that epigenetic modifications and errors have on gene function, protein production, and human health.

For more information about the epigenome:

Human Epigenome Toolset (http://www.genboree.org/site/epigenomics_toolset) from Baylor College of Medicine allows for comparison of the epigenomes of many species and cell types.

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

The National Human Genome Research Institute provides a fact sheet (https://www.genome.gov/about-genomics/fact-sheets/Epigenomics-Fact-Sheet) on Epigenomics.

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

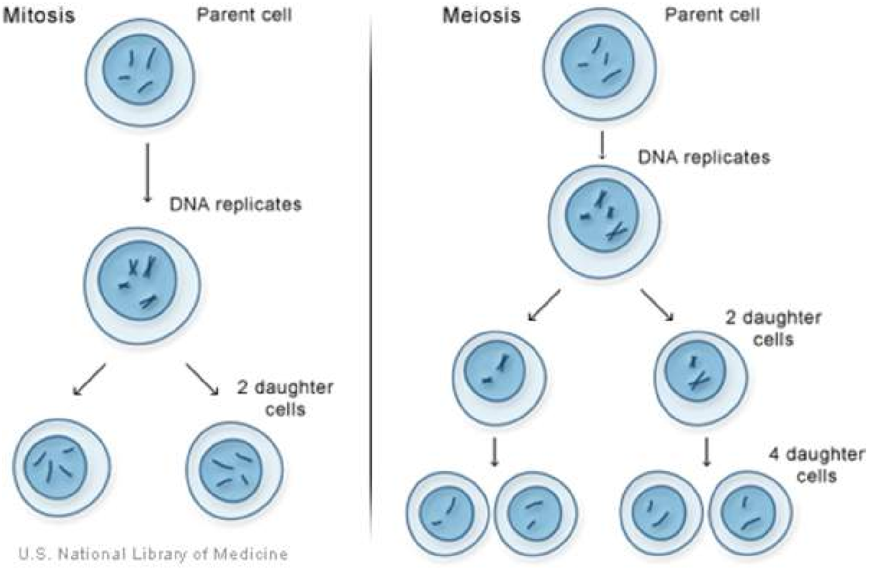
2.5 How do cells divide?

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 certain 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 gene shuffling while the cells are dividing.

Mitosis and meiosis, the two types of cell division. (Figure 2.7)



**FIGUR
E 2.7:** The cell division processes of mitosis and meiosis.

For more information about cell division:

The National Human Genome Research Institute's Talking Glossary provides information about mitosis (https://www.genome.gov/genetics-glossary/Mitosis) and meiosis (https://www.genome.gov/genetics-glossary/Meiosis).

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

2.6 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 replicates itself in an organized, step-by-step fashion known as the cell cycle. 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 cell cycle has checkpoints (also called restriction points), which allow certain genes to check for problems 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 self-destruction (apoptosis (Figure 2.8)). Apoptosis is a common process throughout life that helps the body get rid of cells that no longer work or that it doesn’t need. Cells that undergo apoptosis break apart (Figure 2.9) and are recycled by a type of white blood cell called a macrophage. 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.

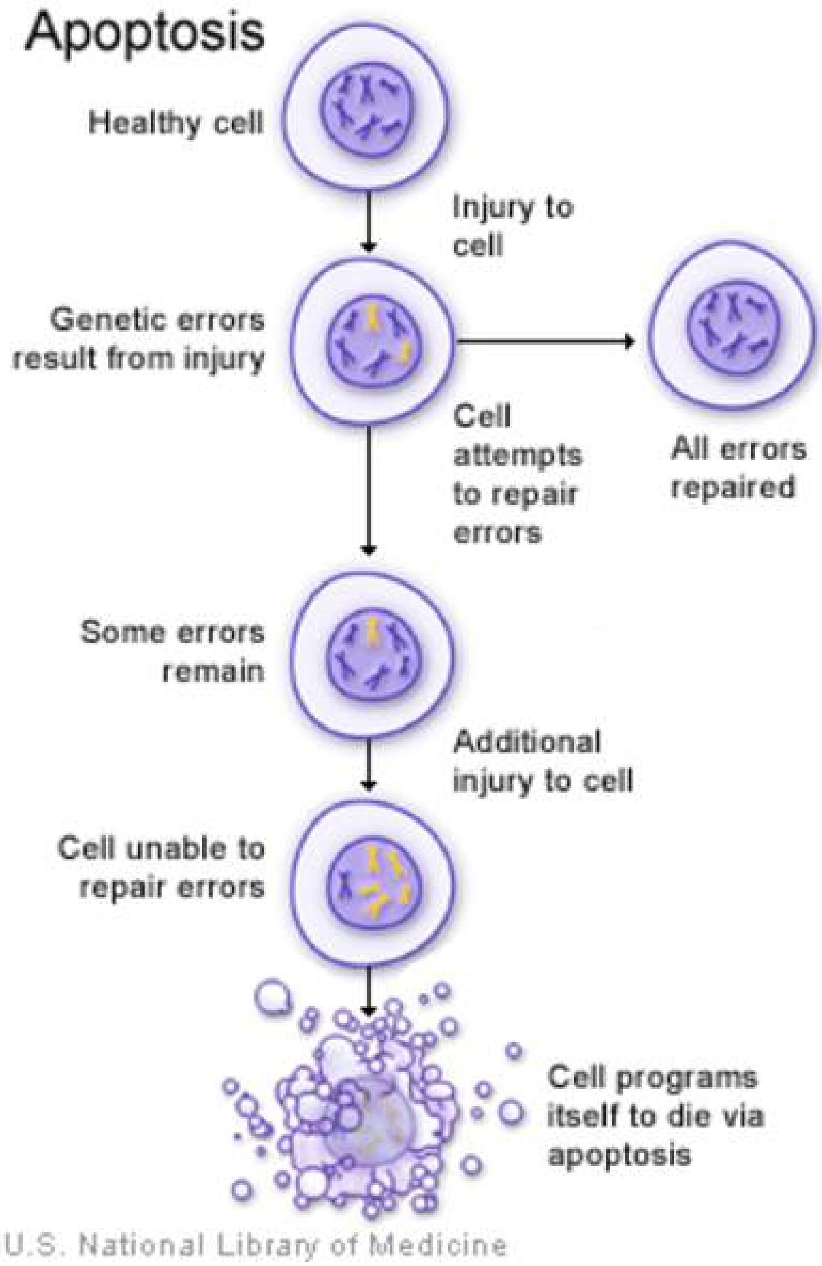


FIGURE 2.8: If a cell is unable to repair errors, it programs itself to die via apoptosis.

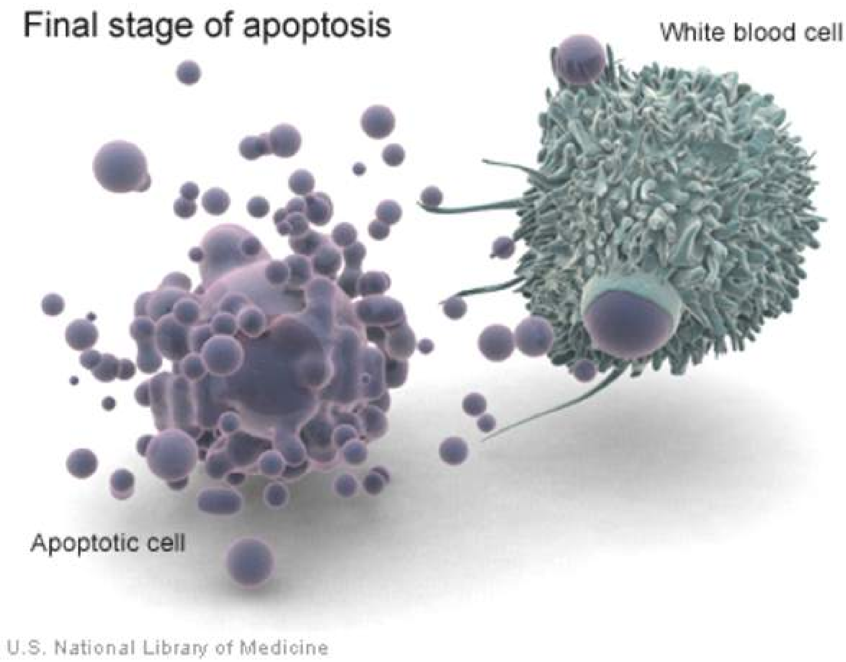


FIGURE 2.9: A white blood cell and an apoptotic cell.

Disruption of normal regulation of the cell cycle can lead to diseases such as cancer. When the cell cycle proceeds without control, cells can divide without order and accumulate genetic errors that can lead to a cancerous tumor (Figure 2.10).

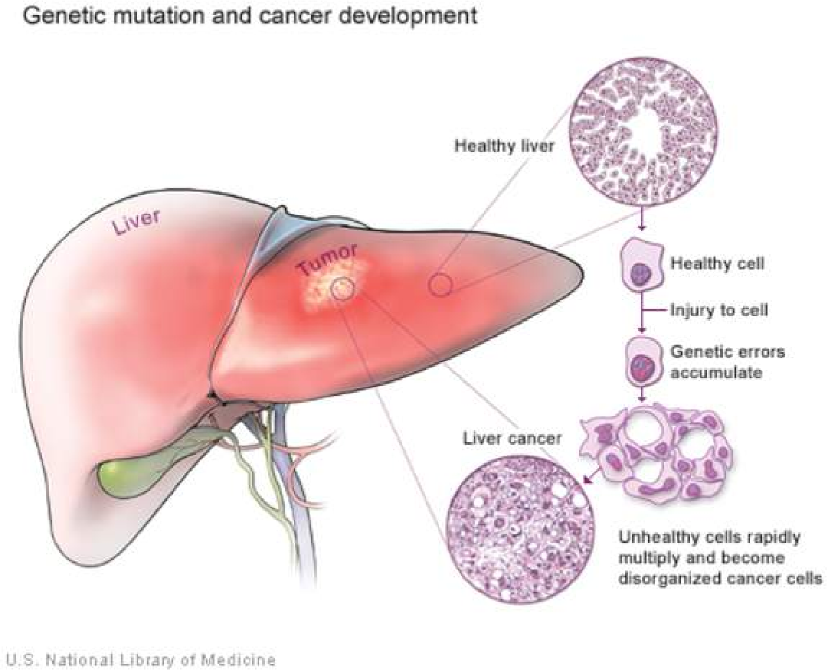


FIGURE 2.10: A tumor in the liver; inset shows the progression from a normal cell to one in which genetic changes accumulate, leading to rapid

and disorganized cell division.

For more information about cell growth and division:

The National Human Genome Research Institute's Talking Glossary provides information about the cell cycle (https://www.genome.gov/genetics-glossary/Cell-Cycle).

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

2.7 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, which is a precise description of a gene's position on a chromosome. The molecular location is based on the sequence of DNA building blocks (nucleotides) 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, or the very end, of chromosome 14.

The CFTR gene is located on the long arm of chromosome 7 at position 7q31.2. (Figure 2.11)

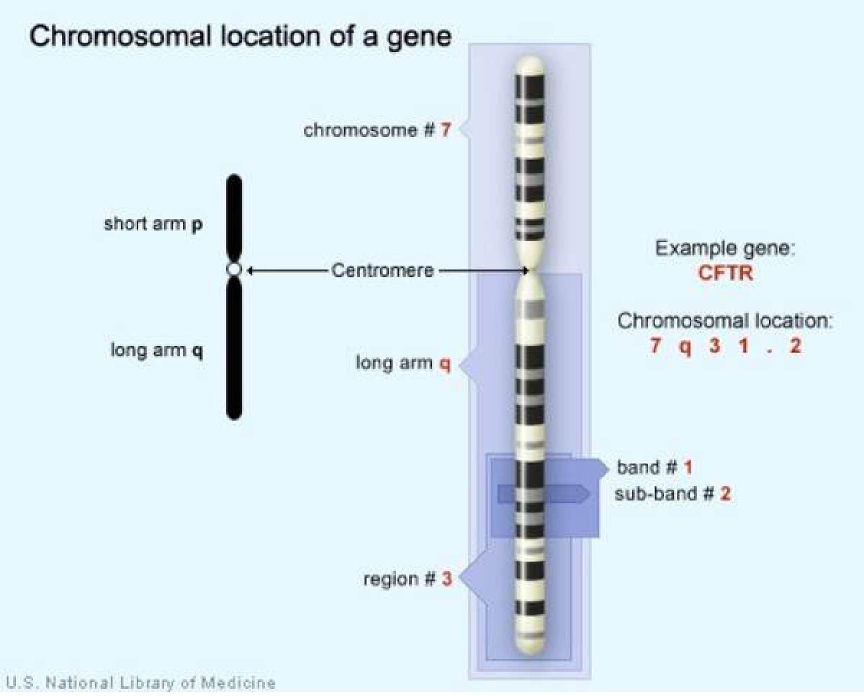


FIGURE 2.11: The CFTR gene is located on the long (q) arm of chromosome 7 at position 31.2.

Molecular location

The Human Genome Project, an international research effort completed in 2003, determined the sequence of nucleotides 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 nucleotides. 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.

For more information on genetic mapping:

The National Human Genome Research Institute explains how researchers create a genetic map (https://www.genome.gov/about-genomics/fact-sheets/Genetic-Mapping-Fact-Sheet).

Information about assembling and annotating the genome (https://www.ncbi.nlm.nih.gov/guide/genomes-maps/) is available from NCBI.

3
Variants and Health

3.1 What is a gene variant and how do variants occur?

A gene variant is a permanent change in the DNA sequence that makes up a gene. This type of genetic change used to be known as a gene mutation, but because changes in DNA do not always cause disease, it is thought that gene variant is a more accurate term. Variants can affect one or more DNA building blocks (nucleotides) in a gene.

Gene variants can be inherited from a parent or occur during a person's lifetime:

- Inherited (or hereditary) variants are passed from parent to child and are present throughout a person's life in virtually every cell in the body. These variants are also called germline variants 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 contains DNA from both parents. Any variants that are present in that DNA will be present in the cells of the child that grows from the fertilized egg.
- Non-inherited variants occur at some time during a person's life and are present only in certain cells, not in every cell in the body. Because non-inherited variants typically occur in somatic cells (cells other than sperm and egg cells), they are often referred to as somatic variants. These variants cannot be passed to the next generation. Non-inherited variants can be caused by environmental factors such as ultraviolet radiation from the sun or can occur if an error is made as DNA copies itself during cell division.

Some genetic changes are described as new (de novo) variants; these variants are recognized in a child but not in either parent. In some cases, the variant occurs in a parent's egg or sperm cell but is not present in any of their other cells. In other cases, the variant occurs in the fertilized egg shortly after the egg and sperm cells unite. (It is often impossible to tell exactly when a de novo variant happened.) As the fertilized egg divides, each resulting cell in the growing embryo will have the variant. De novo variants are one explanation for genetic disorders in which an affected child has a variant in every cell in the body, but the parents do not, and there is no family history of the disorder.

Variants acquired during development can lead to a situation called mosaicism, in which a set of cells in the body has a different genetic makeup than others. In mosaicism, the genetic change is not present in a parent's egg or sperm cells, or in the fertilized egg, but happens later, anytime from embryonic development through adulthood. As cells grow and divide, cells that arise from the cell with the altered gene will have the variant, while other cells will not. When a proportion of somatic cells have a gene variant and others do not, it is called somatic mosaicism. Depending on the variant and how many cells are affected, somatic mosaicism may or may not cause health problems. When a proportion of egg or sperm cells have a variant and others do not, it is called germline mosaicism. In this situation, an unaffected parent can pass a genetic condition to their child.

Most variants do not lead to development of disease, and those that do are uncommon in the general population. Some variants occur often enough in the population to be considered common genetic variation. Several such variants are responsible for differences between people such as eye color, hair color, and blood type. Although many of these common variations in the DNA have no negative effects on a person's health, some may influence the risk of developing certain disorders.

For more information about variants:

The Centre for Genetics Education provides a fact sheet discussing variations in the genetic code (https://www.genetics.edu.au/SitePages/Variations-in-the-Genetic-Code.aspx).

An introductory explanation of what variants are and how they occur (https://www.yourgenome.org/facts/what-is-a-mutation) is provided by Your Genome from the Wellcome Genome Campus.

KidsHealth from Nemours offers an introduction to genes, genetics, and genetic changes (https://kidshealth.org/en/parents/about-genetics.html).

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

Using animations and videos, DNA From the Beginning (Cold Spring Harbor National Laboratory) describes the early experiments that helped researchers understand genetic variants (http://www.dnaftb.org/27/).

3.2 How can gene variants 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 variants (also known as mutations) prevent one or more proteins from working properly. By changing a gene's instructions for making a protein, a variant can cause a protein to malfunction or to not be produced at all. When a variant alters a protein that plays a critical role in the body, it can disrupt normal development or cause a health condition. A condition caused by variants in one or more genes is called a genetic disorder.

In some cases, gene variants 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 variants 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 variants that alter or eliminate a gene's function. For example, when people say that someone has "the cystic fibrosis gene," they are usually referring to a version of the *CFTR* gene that contains a variant that causes the disease. All people, including those without cystic fibrosis, have a version of the *CFTR* gene.

For more information about variants and genetic disorders:

The Genetic and Rare Diseases Information Center provides information to various resources about genetic disorders (https://rarediseases.info.nih.gov/).

The Centre for Genetics Education offers a fact sheet about genetic changes that lead to disorders (https://www.genetics.edu.au/SitePages/Types-of-Genetic-variation.aspx).

3.3 Do all gene variants affect health and development?

No; only a small percentage of variants cause genetic disorders—most have no impact on health or development. For example, some variants alter a gene's DNA sequence but do not change the function of the protein made from the gene.

Often, gene variants 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 errors in DNA. Because DNA can be changed or damaged in many ways, DNA repair is an important process by which the body protects itself from disease.

A very small percentage of all variants actually have a positive effect. These variants lead to new versions of proteins that help an individual better adapt to changes in his or her environment. For example, a beneficial variant 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 many variants with no effect on health, diagnosing genetic disorders can be difficult.

When determining if a gene variant is associated with a genetic disorder, the variant is evaluated using scientific research to date, such as information on how the variant affects the function or production of the protein that is made from the gene and previous variant classification data. The variant is then classified on a spectrum based on how likely the variant is to lead to the disorder.

Gene variants, as they relate to genetic disorders, are classified into one of five groups:

- Pathogenic: The variant is responsible for causing disease. There is ample scientific research to support an association between the disease and the gene variant. These variants are often referred to as mutations.
- Likely pathogenic: The variant is probably responsible for causing disease, but there is not enough scientific research to be certain.
- Variant of uncertain significance (VUS or VOUS): The variant cannot be confirmed to play a role in the development of disease. There may not be enough scientific research to confirm or refute a disease association or the research may be conflicting.
- Likely benign: The variant is probably not responsible for causing disease, but there is not enough scientific research to be certain.
- Benign: The variant is not responsible for causing disease. There is ample scientific research to disprove an association between the disease and the gene variant.

Evaluation needs to be done for each variant. Just because a gene is associated with a disease, does not mean that all variants in that gene are pathogenic. Additionally, evaluation of a variant needs to be done for all diseases with which it is thought to be associated. A variant that is pathogenic for one disease, is not necessarily pathogenic for a different disease. It is important to re-evaluate variants periodically; the classification of a variant can change over time as more information about the effects of variants becomes known through additional scientific research.

Scientific journal article for further reading

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5): 405-24. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5. PMID: 25741868; PMCID: PMC4544753.

For more information about the health effects of gene variants:

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

The National Human Genome Research Institute provides information about human genomic variation (https://www.genome.gov/dna-day/15-ways/human-genomic-variation).

Cold Spring Harbor National Laboratory’s DNA From the Beginning explains the discovery of DNA repair mechanisms in cells (http://www.dnaftb.org/28/) and introduces the researchers who worked to understand these mechanisms.

FORCE (Facing Our Risk of Cancer Empowered) explains the significance of variants of unknown significance in cancer (https://www.facingourrisk.org/understanding-brca-and-hboc/information/hereditary-cancer/genetic-testing/basics/variants-of-uncertain-significance.php).

3.4 What kinds of gene variants are possible?

The DNA sequence of a gene can be altered in a number of ways. Gene variants (also known as mutations) can have varying effects --on health, depending on where they occur and whether they alter the function of essential proteins. Variant types include the following:

Substitution

This type of variant replaces one DNA building block (nucleotide) with another. Substitution variants can be further classified by the effect they have on the production of protein from the altered gene.

- Missense: A missense variant (Figure 3.1) is a typeof substitution in which the nucleotide change results in the replacement of one protein building block (amino acid) with another in the protein made from the gene. The amino acid change may alter the function of the protein.
- Nonsense: A nonsense variant (Figure 3.2) is another type of substitution. Instead of causing a change in one amino acid, however, the altered DNA sequence results in a stop signal that prematurely signals the cell to stop building a protein. This type of variant results in a shortened protein that may function improperly, be nonfunctional, or get broken down.

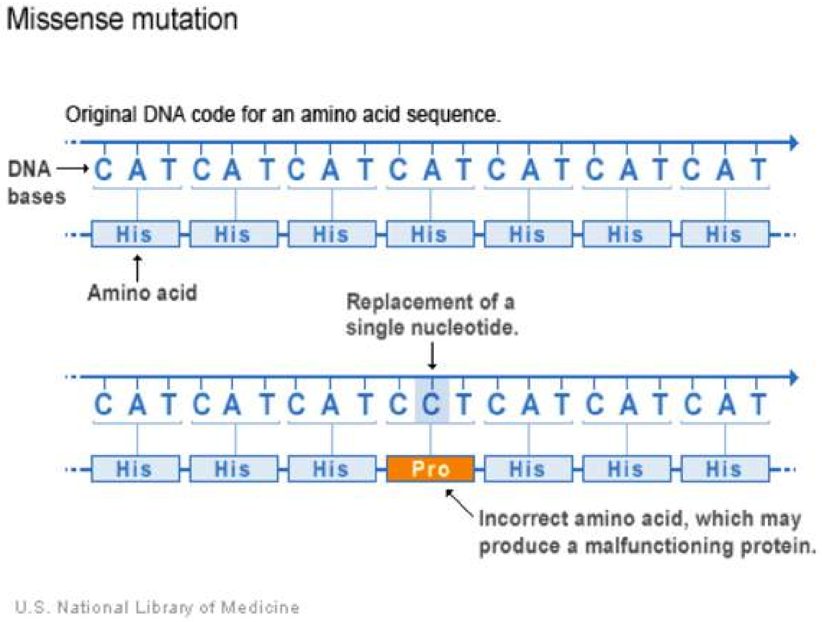


FIGURE 3.1: Replacement of a single nucleotide in the DNA sequence creates an incorrect amino acid, which may result in a malfunctioning protein.

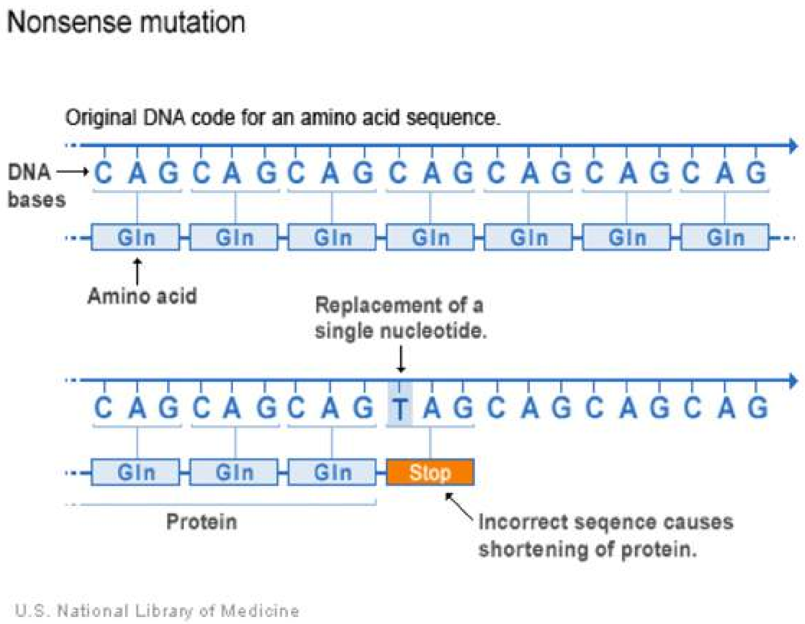


FIGURE 3.2: Replacement of a single nucleotide leads to a stop codon, which halts protein production at that point.

Insertion

An insertion (Figure 3.3) changes the DNA sequence by adding one or more nucleotides to the gene. As a result, the protein made from the gene may not function properly.

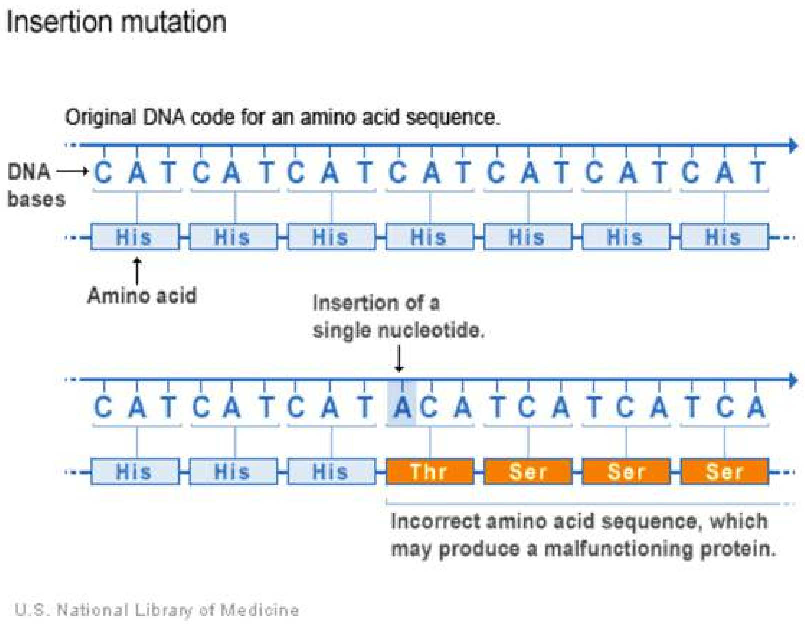
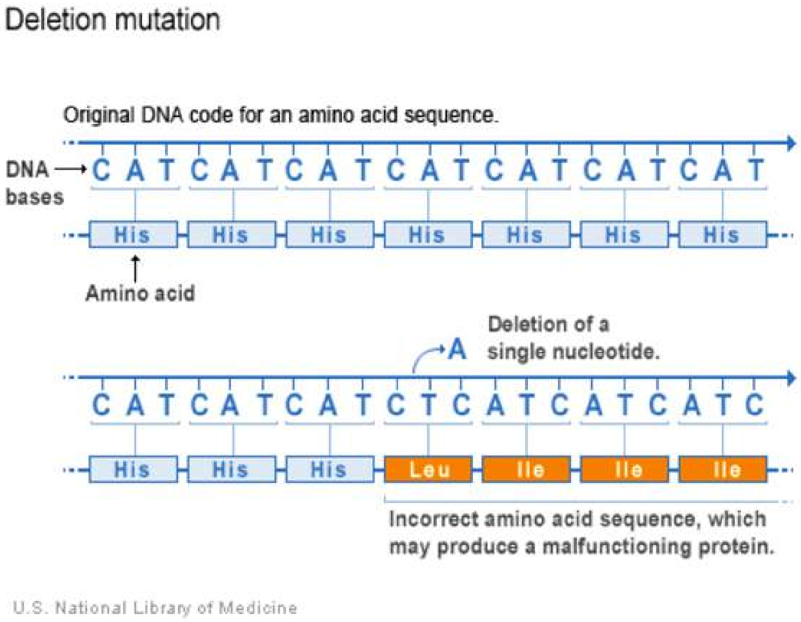


FIGURE 3.3: Insertion of a single nucleotide in the DNA sequence leads to an incorrect sequence of amino acids, which may produce a malfunctioning

protein.

Deletion

A deletion (Figure 3.4) changes the DNA sequence by removing at least one nucleotide in a gene. Small deletions remove one or a few nucleotides within a gene, while larger deletions can remove an entire gene or several neighboring genes. The deleted DNA may alter the function of the affected protein or proteins.


Deletion mutation

U.S. National Library of Medicine

FIGURE 3.4: The deletion of a single nucleotide leads to an incorrect amino acid sequence, which may produce a malfunctioning protein.

Deletion-Insertion

This variant occurs when a deletion and insertion happen at the same time in the same location in the gene. In a deletion-insertion variant, at least one nucleotide is removed and at least one nucleotide is inserted. However, the change must be complex enough to differ from a simple substitution. The resulting protein may not function properly. A deletion-insertion (delins) variant may also be known as an insertion-deletion (indel) variant.

Duplication

A duplication (Figure 3.5)occurs when a stretch of one or more nucleotides in a gene is copied and repeated next to the original DNA sequence. This type of variant may alter the function of the protein made from the gene.

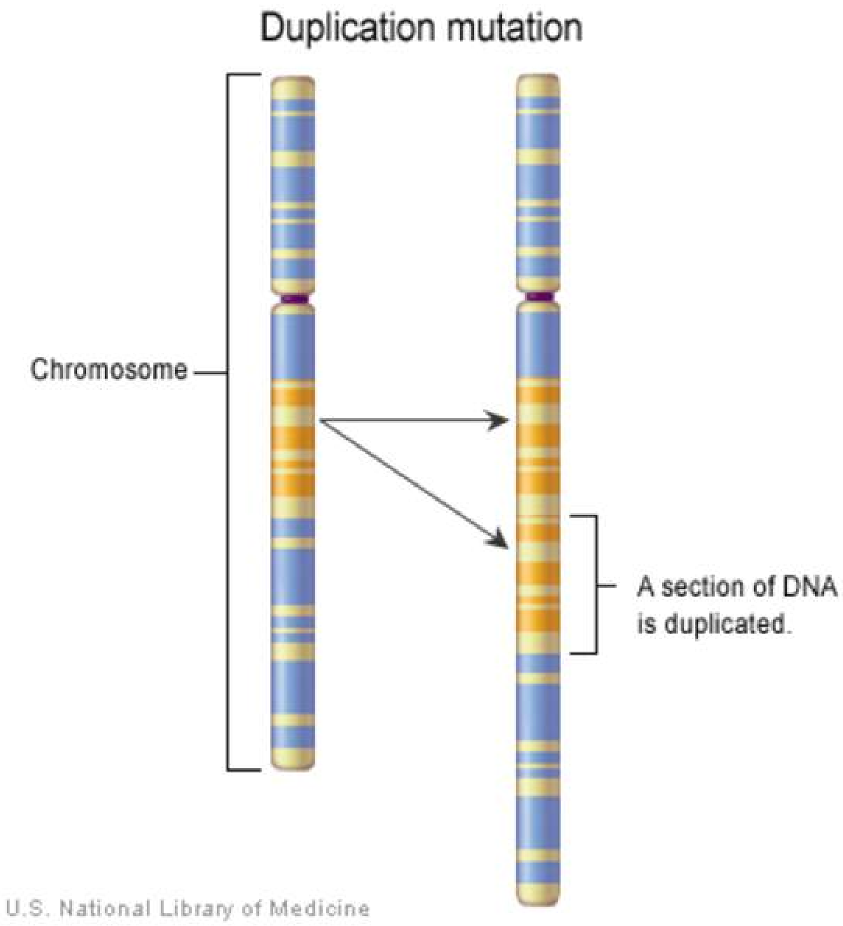


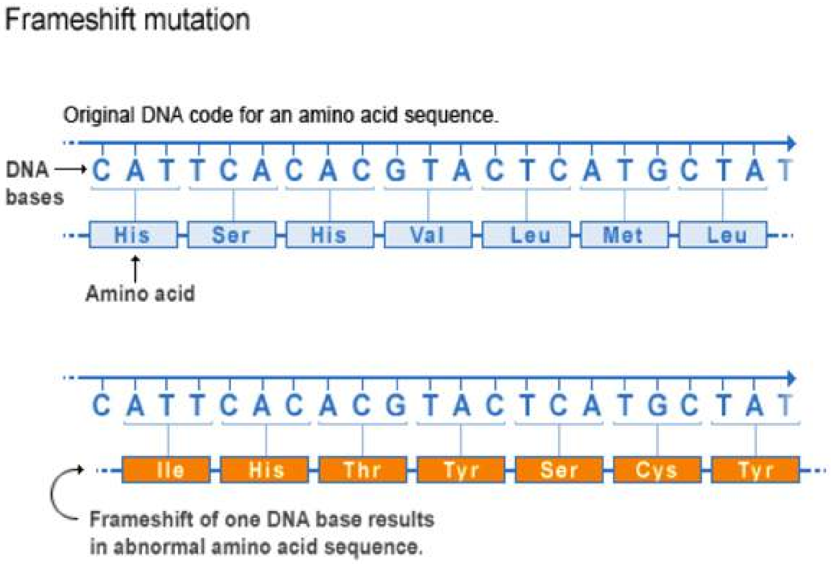
FIGURE 3.5: A section of DNA from a chromosome is duplicated.

Inversion

An inversion changes more than one nucleotide in a gene by replacing the original sequence with the same sequence in reverse order.

Frameshift

A reading frame consists of groups of three nucleotides that eachcode for one amino acid. Aframeshift variant (Figure 3.6) occurs when there is an addition or loss of nucleotides that shifts the grouping and changes the code for all downstream amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift variants.

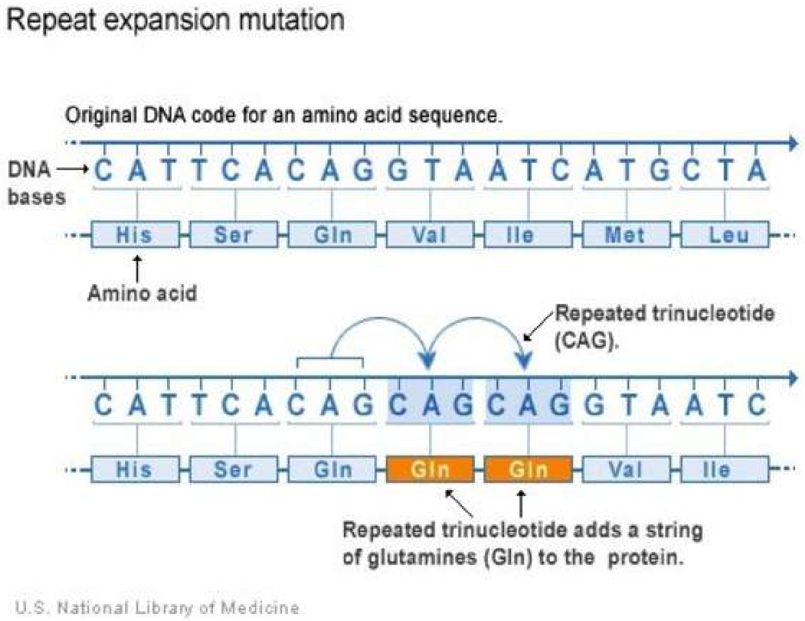


U.S. National Library of Medicine

FIGURE 3.6: A framshift of one DNA base results in an abnormal amino acid sequence.

Repeat expansion

Some regions of DNA contain short sequences of nucleotides that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of sequences of three nucleotides, and a tetranucleotide repeat is made up of sequences of four nucleotides. Arepeat expansion (Figure 3.7) is a variant that increases the number of times that the short DNA sequence is repeated. This type of variant can cause the resulting protein to function improperly.


Repeat expansion mutation

U.S. National Library of Medicine

FIGURE 3.7: A trinucleotide (CAG) is repeated multiple times in a DNA sequence, adding a string of glutamines to the protein.

For more information about the types of gene variants:

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

A brief explanation of different variants types (https://www.yourgenome.org/facts/what-types-of-mutation-are-there) is available from yourgenome.org, a service of the Wellcome Trust.

The Khan Academy has a video describing the different types of gene variants (https://www.khanacademy.org/test-prep/mcat/biomolecules/genetic-mutations/v/the-different-types-of-mutations).

3.5 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 have one, three, or more copies of particular genes. Less commonly, both copies of a gene may be missing. These types of genetic difference are known as copy number variations (CNV).

Copy number variation results from insertions, deletions, and duplications of large segments of DNA that are at least one thousand nucleotides (also called 1 kilobase or 1kb) in length. These segments are often big enough to include whole genes. Variation in gene copy number can influence the activity of genes and the functioning of proteins made from them, which may affect body processes.

Copy number variation accounts for a significant amount of genetic difference between people. More than 10 percent of the human genome appears to contain differences in gene copy number. While much of this variation does not affect health or development, some differences influence a person's risk of disease, particularly some types of cancer, or response to certain drugs.

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 (https://www.hhmi.org/news/genetic-variation-were-more-different-we-thought).

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

A definition of copy number variation (https://www.genome.gov/genetics-glossary/Copy-Number-Variation) is included in the Talking Genome Glossary from the National Human Genome Research Institute.

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

- The Centre for Applied Genomics 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/))

3.6 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 (Figure 3.8). 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 in the number of chromosomes from the normal 46 is called aneuploidy.

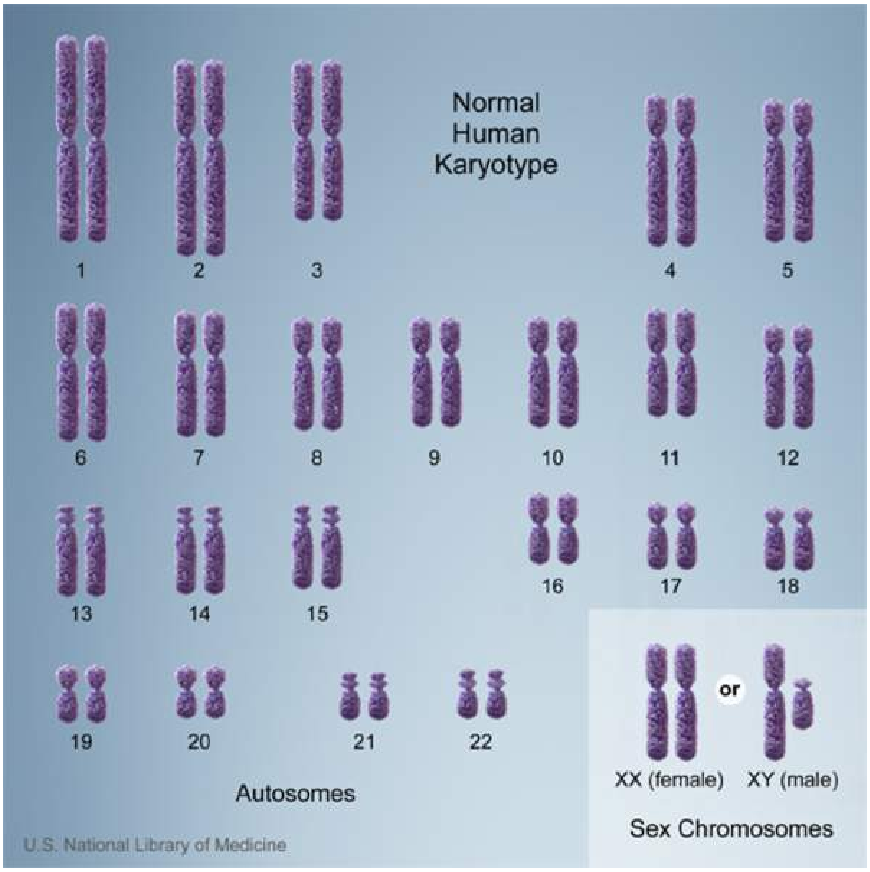


FIGURE 3.8: Normal human karyotype with 22 pairs of autosomes and two sex chromosomes, either two X chromosomes or an X and a Y chromosome.

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 (also known as trisomy 21) is an example of a condition caused by trisomy (Figure 3.9). People with Down syndrome typically have three copies of chromosome 21 in each cell, for a total of 47 chromosomes per cell.

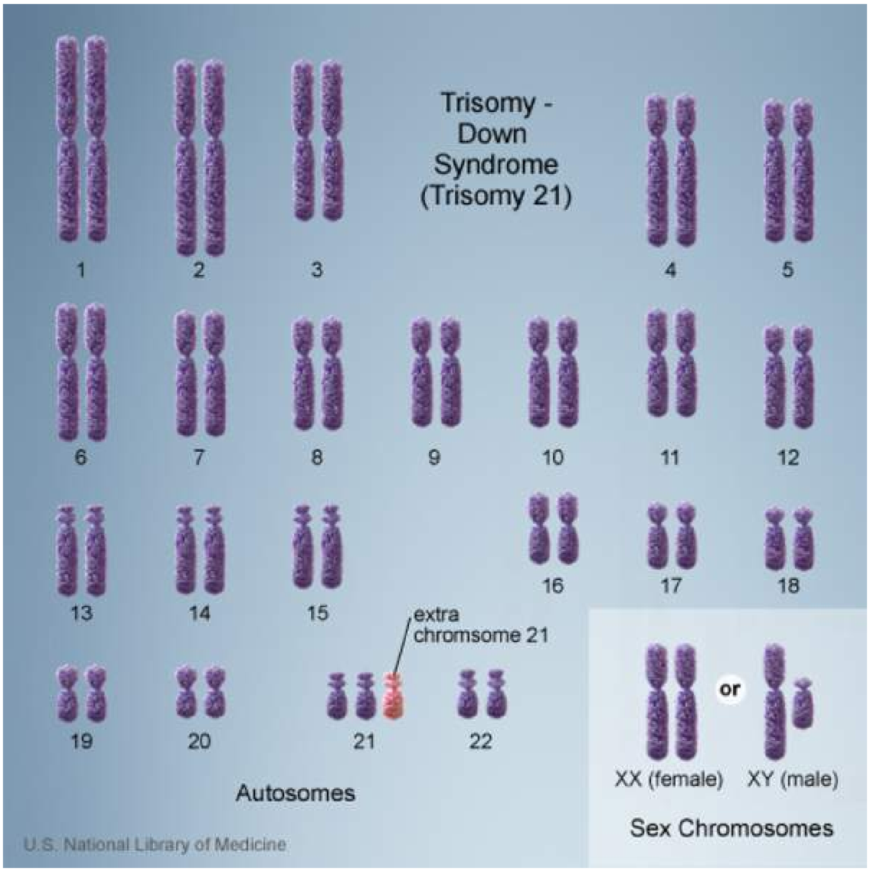


FIGURE 3.9: A karyotype showing an extra copy of chromsome 21, for a total of 47 chromosomes instead of the usual 46.

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 (also known as monosomy X) is a condition caused by monosomy (Figure 3.10). Women with Turner syndrome usually have only one copy of the X chromosome in every cell, for a total of 45 chromosomes per cell.

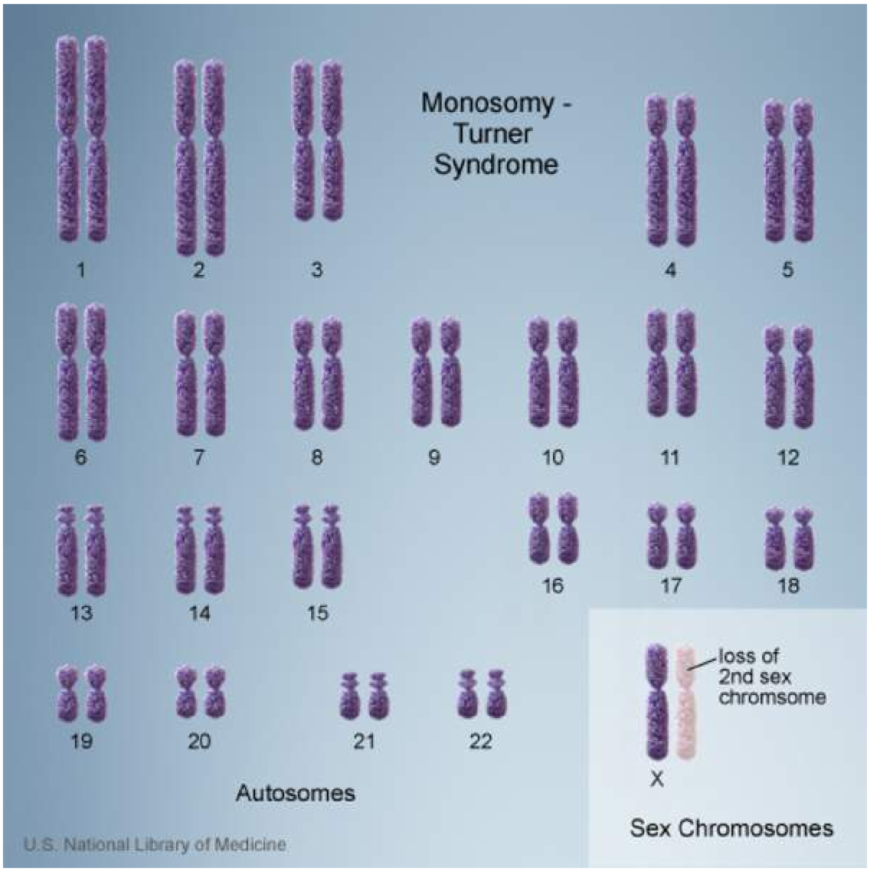


FIGURE 3.10: A karyotype showing a form of monosomy called Turner syndrome, in which the second sex chromosome is missing.

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 (Figure 3.11). 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.

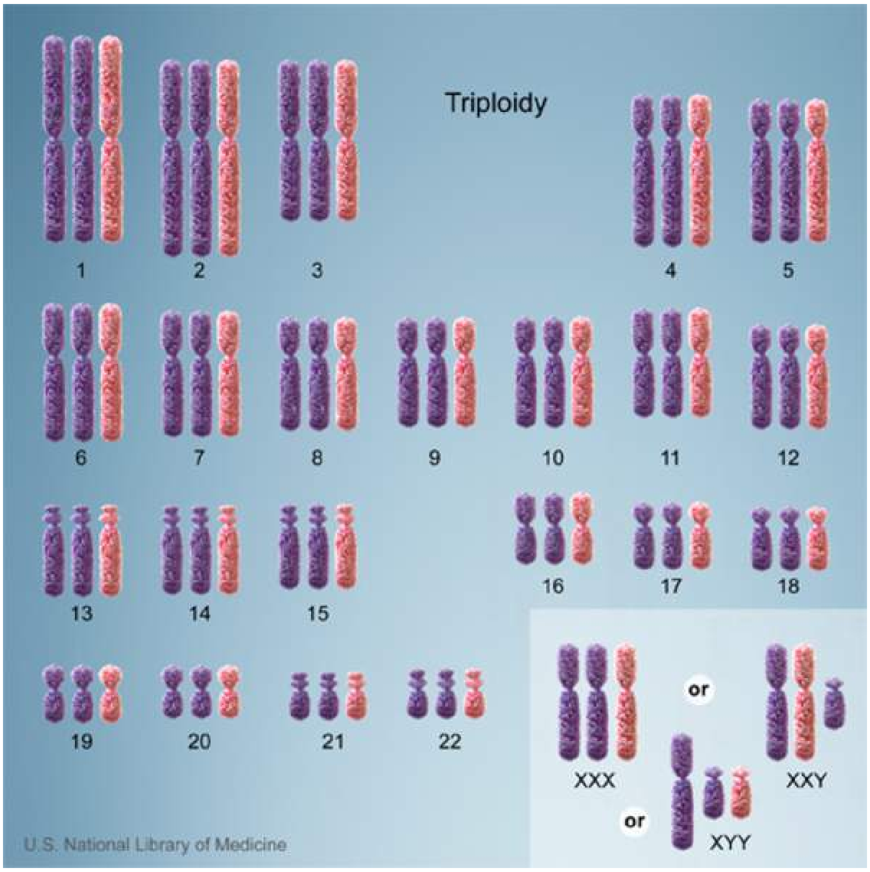


FIGURE 3.11: A karyotype with one extra copy of each chromosome, for a total of 69 chromosomes instead of the usual 46.

In some cases, a change in the number of chromosomes occurs only in certain cells. When an individual's cells differ in their chromosomal makeup, it is known as chromosomal mosaicism (Figure 3.12). 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.

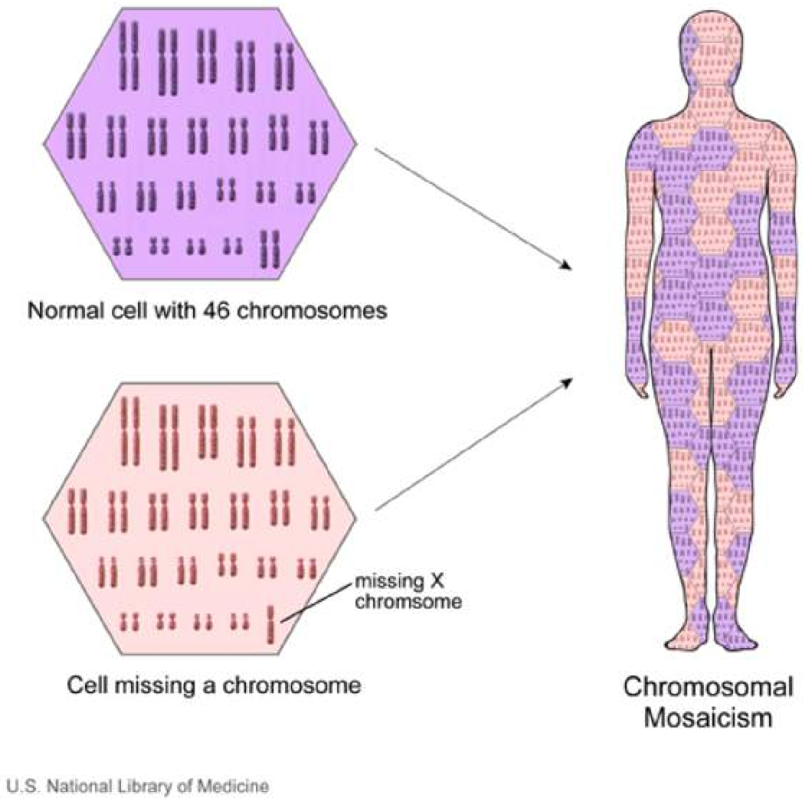


FIGURE 3.12: A person with mosaicism has some populations of cells with a chromsomal change and other cells without the change.

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:

MedlinePlus provides a medical encyclopedia article about chromosomal mosaicism (https://medlineplus.gov/ency/article/001317.htm).

A discussion of how chromosomal abnormalities happen (https://www.genome.gov/about-genomics/fact-sheets/Chromosome-Abnormalities-Fact-Sheet) 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 (https://www.genetics.edu.au/SitePages/Chromosome-changes.aspx).

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

Your Genome from the Wellcome Genome Campus discusses chromosome disorders (https://www.yourgenome.org/facts/what-is-a-chromosome-disorder), including how changes in the number of chromosomes cause genetic disorders.

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

3.7 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, whether gene function is interrupted, and whether any genetic material is gained or lost. Some changes cause health problems, while others may have no effect on a person's health.

Changes in chromosome structure include the following:

Translocations

A translocation occurs when a piece of one chromosome breaks off and attaches to another chromosome. This type of rearrangement is described as balanced (Figure 3.13) 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 (Figure 3.14).

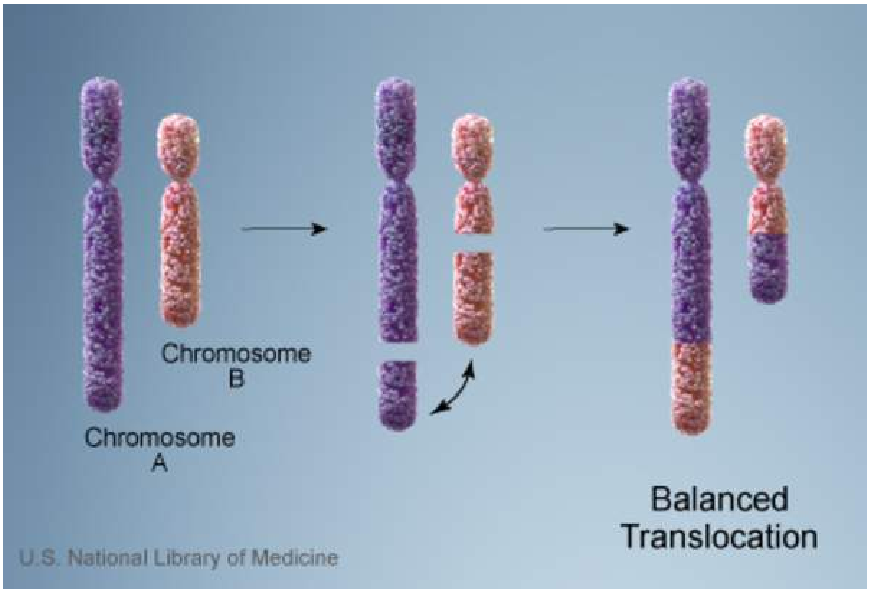


FIGURE 3.13: Two chromosomes break and swap pieces; no genetic material is gained or lost.

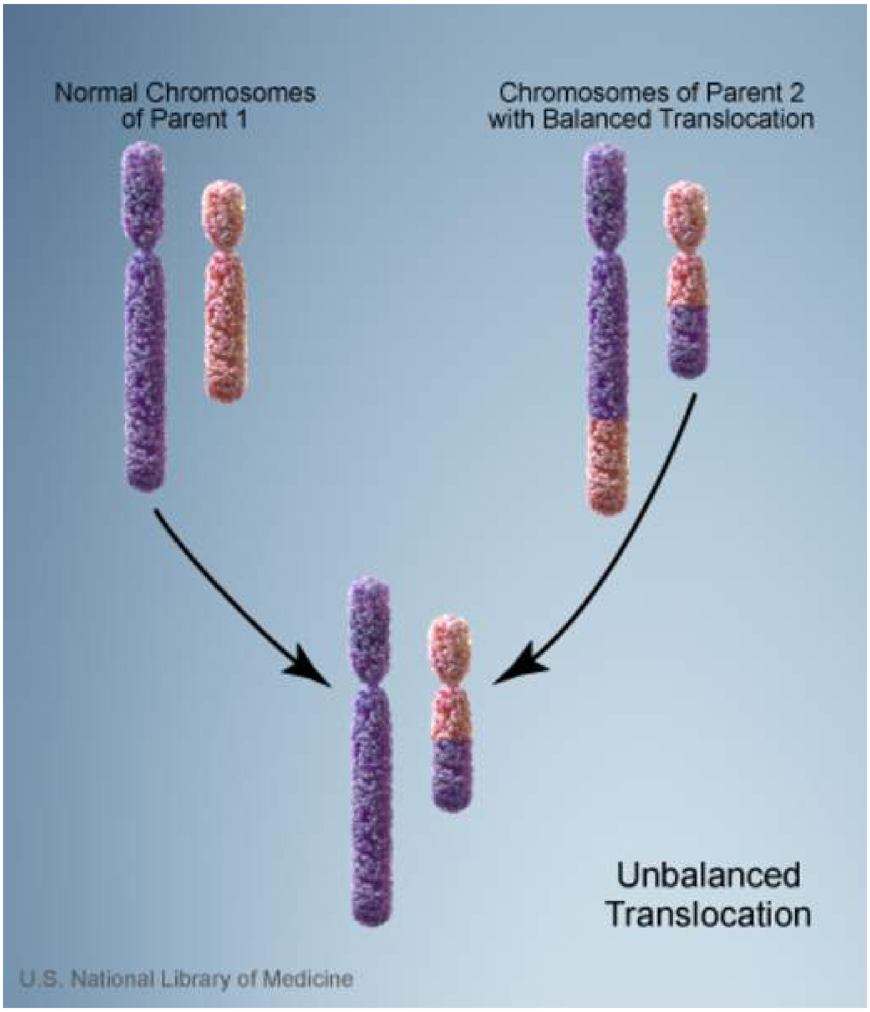


FIGURE 3.14: A balanced translocation can become unbalanced in the next generation, with extra or missing genetic material.

Deletions

Deletions (Figure 3.15) occur when a chromosome breaks and some genetic material is lost. Deletions can be large or small, and can occur anywhere along a chromosome.

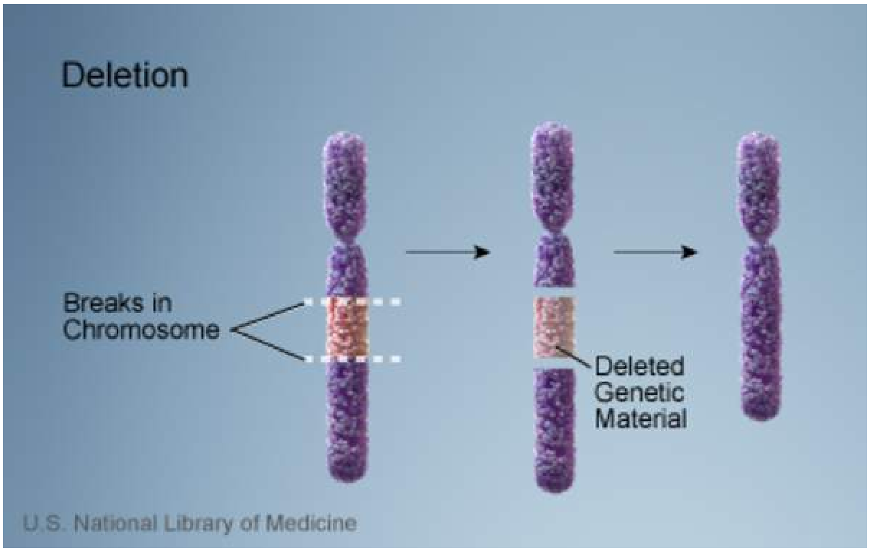


FIGURE 3.15: Genetic material is deleted from a chromosome.

Duplications

Duplications (Figure 3.16) occur when part of a chromosome is abnormally copied (duplicated). This type of chromosomal change results in extra copies of genetic material from the duplicated segment.

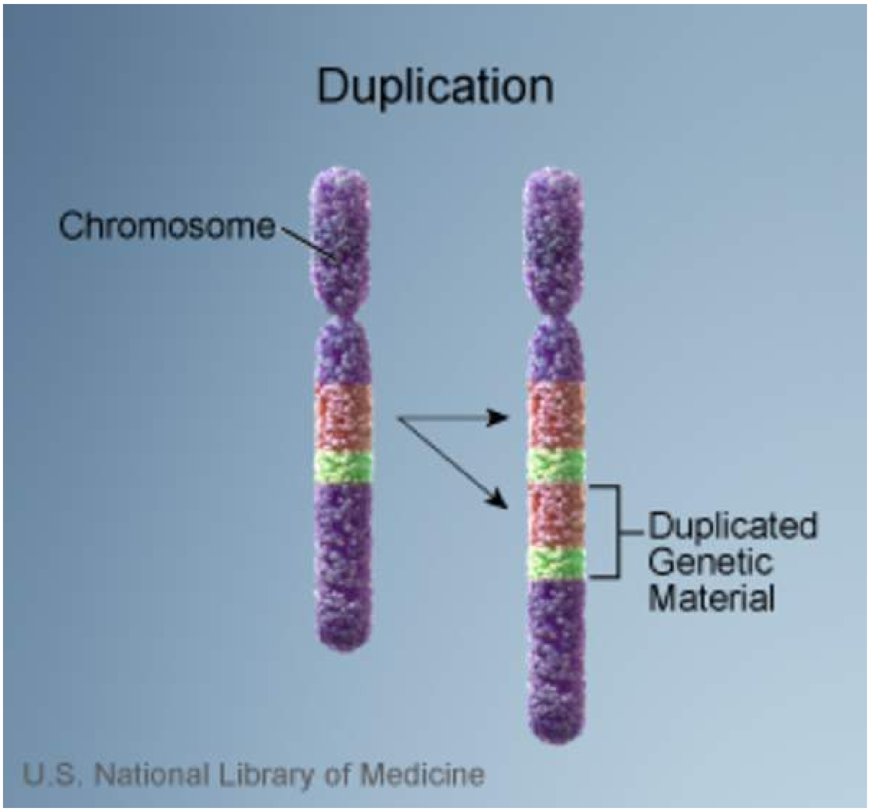


FIGURE 3.16: DNA from a chromosome is abnormally copied.

Inversions

An inversion (Figure 3.17) occurs when a chromosome breaks 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 includes 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.

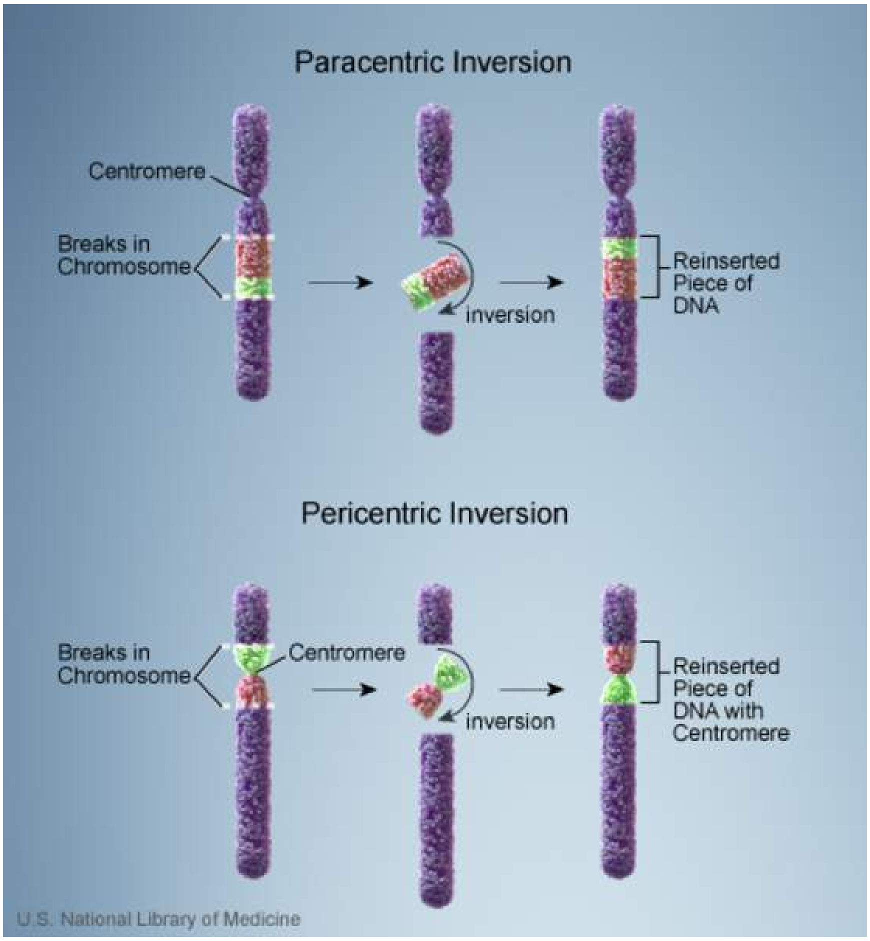


FIGURE 3.17: A paracentric inversion does not include the centromere; a pericentric inversion does include the centromere.

Isochromosomes

An isochromosome (Figure 3.18) is a chromosome with two identical arms. Instead of one q arm and one p arm, an isochromosome has two q arms or two p arms. As a result, these abnormal chromosomes have an extra copy of some genes and are lacking copies of genes on the missing arm.

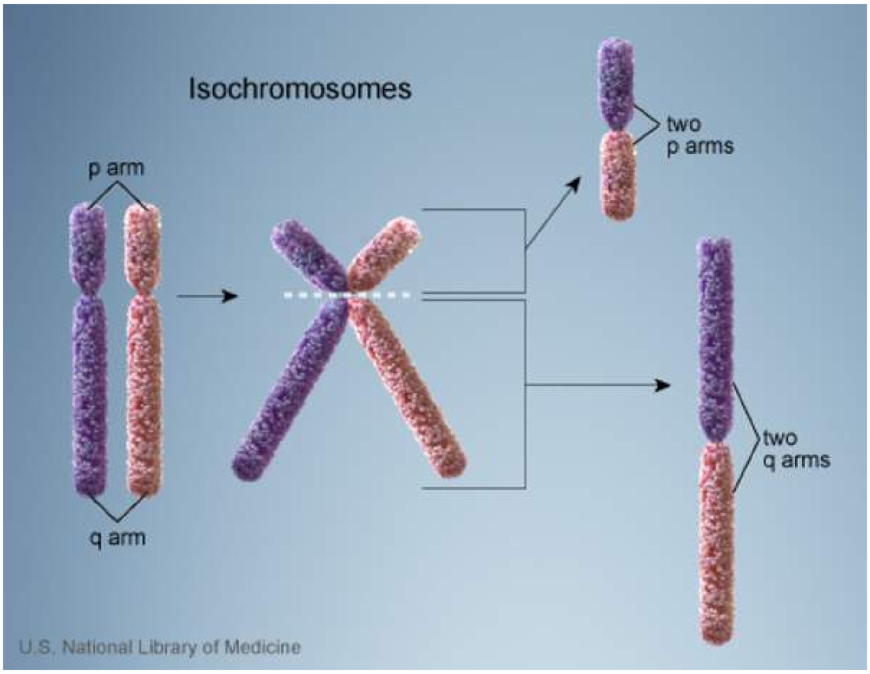


FIGURE 3.18: Isochromosomes have two p arms or two q arms instead of one p arm and one q arm.

Dicentric chromosomes

Unlike normal chromosomes, which have one centromere, a dicentric chromosome (Figure 3.19) 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.

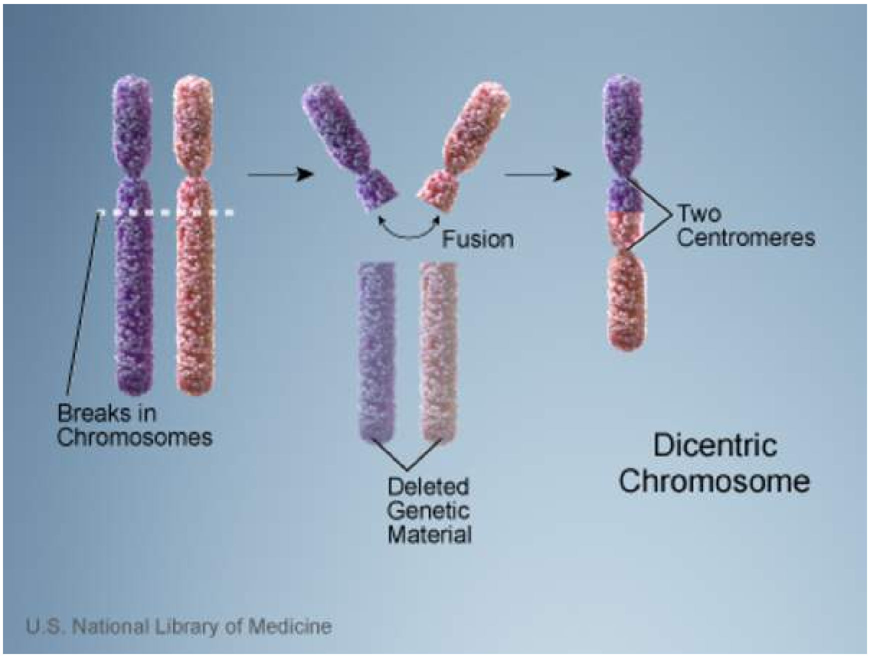


FIGURE 3.19: A dicentric chromosome results from the abnormal fusion of pieces of two chromosomes, creating a chromosome with two centromeres.

Ring chromosomes

Ring chromosomes (Figure 3.20) usually occur when a chromosome breaks in two places, typically at the ends of the p and q arms, and then the arms fuse together to form a circular structure. The ring may or may not include the centromere, depending on where on the chromosome the breaks occur. In many cases, genetic material near the ends of the chromosome is lost.

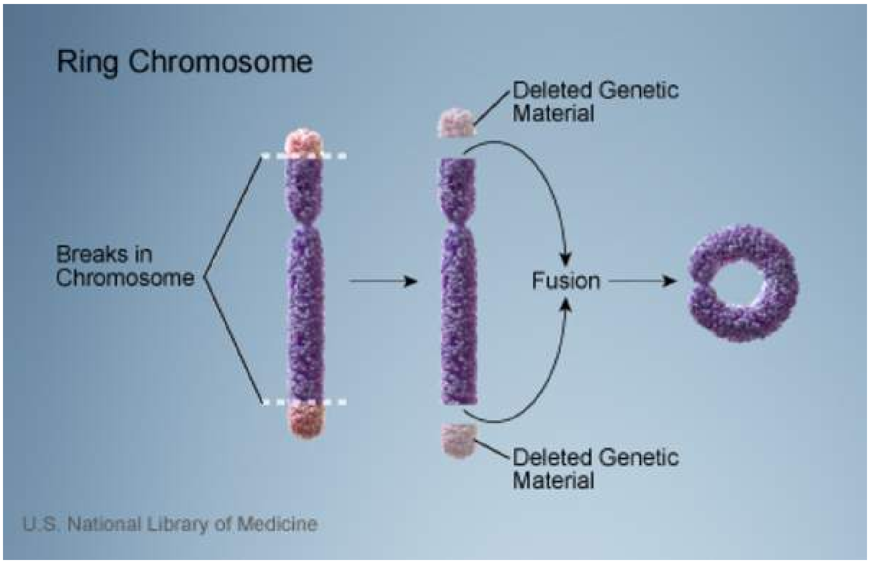


FIGURE 3.20: A ring chromosome occurs when the two ends of a chromosome break and then fuse together, creating a ring shape.

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/about-genomics/fact-sheets/Chromosome-Abnormalities-Fact-Sheet), including a glossary of related terms.

Chromosome Disorder Outreach offers a fact sheet on this topic titled Introduction to Chromosomes (https://chromodisorder.org/introduction-to-chromosomes/). This resource includes illustrated explanations of several chromosome abnormalities.

The Centre for Genetics Education provides a fact sheet about chromosome changes (https://www.genetics.edu.au/SitePages/Chromosome-changes.aspx).

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

Your Genome from the Wellcome Genome Campus discusses chromosome disorders (https://www.yourgenome.org/facts/what-is-a-chromosome-disorder), including types of structural abnormalities in chromosomes that are involved in genetic diseases.

3.8 Can changes in noncoding DNA affect health and development?

It is well established that changes in genes can alter a protein’s function in the body, potentially causing health problems. Scientists have determined that changes in regions of DNA that do not contain genes (noncoding DNA) can also lead to disease.

Many regions of noncoding DNA play a role in the control of gene activity, meaning they help determine when and where certain genes are turned on or off. Other regions of noncoding DNA are important for protein assembly. By altering one of these regions, a variant (also known as a mutation) in noncoding DNA can turn on a gene and cause a protein to be produced in the wrong place or at the wrong time. Alternatively, a variant can reduce or eliminate the production of an important protein when it is needed. Not all changes in noncoding DNA have an impact on health, but those that alter the pattern of a critical protein can disrupt normal development or cause a health problem.

Variants in noncoding DNA have been linked to several types of cancer and developmental disorders such as isolated Pierre Robin sequence. This condition is caused by changes in regions of noncoding DNA that act as enhancer elements. Enhancers attach proteins that help turn on particular genes. The enhancers altered in isolated Pierre-Robin sequence control the activity of the *SOX9* gene.

In addition to enhancer elements, variants in noncoding DNA can disrupt other regulatory elements. These other elements include promoters, where proteins that turn on genes attach; insulators, where proteins that help shape the activity of genes in different ways attach; and silencers, where proteins that turn off genes attach.

Some regions of noncoding DNA provide instructions for making certain kinds of RNA molecules that play roles in regulating gene activity or assembling proteins. Variants that interrupt these functional RNA molecules, such as transfer RNAs, microRNAs, or long noncoding RNAs, have also been implicated in disease.

The same types of genetic changes that occur in genes or that alter the structure of chromosomes can affect health and development when they occur in noncoding DNA. These alterations include changes in single DNA building blocks (substitution variants), insertions, deletions, duplications, and translocations. Noncoding DNA variants can be inherited from a parent or acquired during a person’s life.

Much is still unknown about how to identify regions of noncoding DNA that have a function in cells and the roles such regions play. As a result, linking genetic changes in noncoding DNA to their effects on certain genes and to health conditions is difficult. The roles of noncoding DNA and the effects that genetic changes in noncoding DNA have on the body are growing areas of research.

Scientific journal articles for further reading

Scacheri CA, Scacheri PC. Mutations in the noncoding genome. Curr Opin Pediatr. 2015 Dec;27(6):659-64. doi: 10.1097/MOP.0000000000000283. Review. PubMed: 26382709; Free full text from PubMed Central: PMC5084913.

Chatterjee S, Ahituv N. Gene Regulatory Elements, Major Drivers of Human Disease. Annu Rev Genomics Hum Genet. 2017 Aug 31;18:45-63. doi: 10.1146/annurev-genom-091416-035537. Epub 2017 Apr 7. Review. PubMed: 28399667.

Gordon CT, Attanasio C, Bhatia S, Benko S, Ansari M, Tan TY, Munnich A, Pennacchio LA, Abadie V, Temple IK, Goldenberg A, van Heyningen V, Amiel J, FitzPatrick D, Kleinjan DA, Visel A, Lyonnet S. Identification of novel craniofacial regulatory domains located far upstream of SOX9 and disrupted in Pierre Robin sequence. Hum Mutat. 2014 Aug;35(8):1011-20. doi: 10.1002/humu.22606. PubMed: 24934569; Free full text from PubMed Central: PMC4389788.

Read more about the role of noncoding DNA in health and disease:

University of California, San Francisco: The Mysterious 98%: Scientists Look to Shine Light on Our Dark Genome (https://www.ucsf.edu/news/2017/02/405686/mysterious-98-scientists-look-shine-light-our-dark-genome)

Duke University: Variation in “Junk” DNA Leads to Trouble (https://today.duke.edu/2016/08/variation-%E2%80%9Cjunk%E2%80%9D-dna-leads-trouble)

HEDD: Human Enhancer Disease Database (https://zdzlab.einsteinmed.edu/1/hedd.php)

3.9 Can changes in mitochondrial DNA affect health and development?

Mitochondria (Figure 1.5) 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 variants (also known as mutations) disrupt the mitochondria’s ability to generate energy efficiently for cells.

Conditions caused by variants 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 alterations 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 problems involving the eyes and vision.

Genetic changes that are not inherited (which are known as somatic variants) may also occur in mitochondrial DNA. Somatic variants occur in the DNA of certain cells (not sperm or egg cells) during a person’s lifetime and are not passed to future generations. Because mitochondrial DNA has a limited ability to repair errors, these variants tend to build up over time. A buildup of somatic variants 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's disease, and Parkinson's disease. Additionally, research suggests that the progressive accumulation of these variants over a person’s lifetime may play a role in the normal process of aging.

For more information about conditions caused by mitochondrial DNA changes:

An overview of mitochondrial disorders (https://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 in St. Louis provides an in-depth description of many mitochondrial disorders (https://neuromuscular.wustl.edu/mitosyn.html).

3.10 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 variants (also known as mutations) in single genes. The causes of many other disorders, however, are much more complex. Common health problems such as heart disease, type 2 diabetes, and obesity do not have a single genetic cause—they are influenced by multiple genes (polygenic) in combination with lifestyle and environmental factors, such as exercise, diet, or pollutant exposures. 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. It may be difficult to identify the role of genetics in these disorders, particularly because families often also share environments and may have similar lifestyles. 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:

MedlinePlus (https://medlineplus.gov/) provides additional information about specific complex disorders such as diabetes and obesity and other reliable medical information

A fact sheet about the inheritance of multifactorial disorders (https://www.genetics.edu.au/SitePages/Environmental-and-Genetic-interactions.aspx) is available from the Centre for Genetics Education.

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

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

The Centers for Disease Control and Prevention provides a list of diseases and conditions (https://www.cdc.gov/DiseasesConditions/) with additional information.

3.11 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 variants (also called mutations) in the *BRCA1* or *BRCA2* genes greatly increase a person's risk of developing breast cancer and ovarian cancer. Particular 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. Researchers are working to calculate an individual’s estimated risk for developing a common disease based on the combination of variants in many genes across their genome. This measure, known as the polygenic risk score, is expected to help guide healthcare decisions in the future.

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. 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 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 (https://learn.genetics.utah.edu/content/history/geneticrisk/).

More detailed information about the genetics of breast and ovarian cancer (https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq), as well as other cancers (https://www.cancer.gov/publications/pdq/information-summaries/genetics), is available from the National Cancer Institute.

The National Human Genome Research Institute explains the calculation of polygenic risk scores (https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores) and what information the scores can provide.

3.12 How are gene variants involved in evolution?

Evolution is the process by which populations of organisms change over generations. Genetic variations underlie these changes. Genetic variations can arise from gene variants (also called mutations) or from a normal process in which genetic material is rearranged as a cell is getting ready to divide (known as genetic recombination). Genetic variations that alter gene activity or protein function can introduce different traits in an organism. If a trait is advantageous and helps the individual survive and reproduce, the genetic variation is more likely to be passed to the next generation (a process known as natural selection). Over time, as generations of individuals with the trait continue to reproduce, the advantageous trait becomes increasingly common in a population, making the population different than an ancestral one. Sometimes the population becomes so different that it is considered a new species.

Not all variants influence evolution. Only hereditary variants, which occur in egg or sperm cells, can be passed to future generations and potentially contribute to evolution. Some variants occur during a person's lifetime in only some of the body's cells and are not hereditary, so natural selection cannot play a role. Also, many genetic changes have no impact on the function of a gene or protein and are not helpful or harmful. In addition, the environment in which a population of organisms lives is integral to the selection of traits. Some differences introduced by variants may help an organism survive in one setting but not in another—for example, resistance to a certain bacteria is only advantageous if that bacteria is found in a particular location and harms those who live there.

So why do some harmful traits, like genetic diseases, persist in populations instead of being removed by natural selection? There are several possible explanations, but in many cases, the answer is not clear. For some conditions, such as the neurological condition Huntington disease, signs and symptoms occur later in life, typically after a person has children, so the gene variant can be passed on despite being harmful. For other harmful traits, a phenomenon called reduced penetrance, in which some individuals with a disease-associated variant do not show signs and symptoms of the condition, can also allow harmful genetic variations to be passed to future generations. For some conditions, having one altered copy of a gene in each cell is advantageous, while having two altered copies causes disease. The best-studied example of this phenomenon is sickle cell disease: Having two altered copies of the *HBB* gene in each cell results in the disease, but having only one copy provides some resistance to malaria. This disease resistance helps explain why the variants that cause sickle cell disease are still found in many populations, especially in areas where malaria is prevalent.

To find out more about the role of gene variants in evolution:

National Institute of General Medical Sciences: The New Genetics Chapter 3: Life's Genetic Tree (https://www.nigms.nih.gov/education/Booklets/the-new-genetics/Pages/Home.aspx)

Learn.Genetics from the University of Utah: Evolution: DNA and the Unity of Life (https://learn.genetics.utah.edu/content/evolution/)

Cold Spring Harbor Lab: Genetic Origins (http://www.geneticorigins.org/)

Understanding Evolution from the University of California Museum of Paleontology: Huntington’s Chorea: Evolution and Genetic Disease (https://evolution.berkeley.edu/evolibrary/article/0_0_0/medicine_05)

Understanding Evolution from the University of California Museum of Paleontology: Misconceptions About Natural Selection (https://evolution.berkeley.edu/evolibrary/article/evo_32)

3.13 What information can statistics provide about a genetic condition?

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, but they do 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 the statistics and explain what they mean for an individual.

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

Incidence. The incidence of a gene variant (also called a gene mutation) or a genetic disorder is the number of people in a specified group who develop a variant or disorder during a particular time period. Incidence is often written in the form “1 in [a number]” or as a total number of a population.

> *Example: About 1 in 200,000 people in the United States are diagnosed with syndrome A each year. An estimated 15,000 people worldwide were diagnosed with syndrome B last year.*

Prevalence. The prevalence of a gene variant or a genetic disorder is the total number of people in a specified group at a given time who are living with the variant 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.

> *Example: 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.

> *Example: An estimated 12,000 people worldwide died from syndrome C in 2020.*

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.

> *Example: 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:

NIH News in Health offers an explanation of health statistics in their article "

Understanding Health Risks (https://newsinhealth.nih.gov/2016/10/understanding-health-risks)."

The New York Department of Health provides a basic explanation of statistical terms (https://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 (https://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 (https://www.cancer.gov/about-cancer/understanding/statistics).

3.14 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 new, previously unknown disorder are often the first to propose a name for the condition. Later, healthcare professionals, researchers, people affected by the condition, and other interested individuals may come together to revise the name to improve its usefulness. Naming is important because it allows accurate and effective communication about particular conditions, which will ultimately improve care and help researchers find new approaches to treatment.

Condition 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);
- The gene in which the variant (or mutation) that causes the condition occurs (for example, TUBB4A-related leukodystrophy);
- One or more major signs or symptoms of the disorder (for example, hypermanganesemia with dystonia, polycythemia vera, and cryptogenic cirrhosis);
- The parts of the body affected by the condition (for example, brain-lung-thyroid 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 is often called Lou Gehrig disease after the famous baseball player who was diagnosed with the condition).

Conditions named after a specific person are called eponyms. They can be in the possessive form (e.g., Alzheimer’s disease) or in the nonpossessive form (e.g., Down syndrome).

Naming genes

The HUGO Gene Nomenclature Committee (HGNC) designates an official name and symbol (an abbreviation of the name) for each known human gene. The HGNC is a nonprofit organization funded by the U.S. National Human Genome Research Institute and the UK's Wellcome Trust. The Committee has named more than 19,000 of the estimated 20,000 to 25,000 protein-coding genes in the human genome.

During the research process, genes often acquire several alternate names and symbols from researchers investigating the same gene. To resolve this 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.

Learn more about the naming of conditions and genes:

Common sources for finding the names of genetic conditions include PubMed (https://pubmed.ncbi.nlm.nih.gov/) , GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1116/) , OMIM (https://omim.org/), GARD (https://rarediseases.info.nih.gov/) , MeSH (https://meshb.nlm.nih.gov/) , and Orphanet (https://www.orpha.net/).

The official names and symbols of all human genes are found on the HUGO Gene Nomenclature Committee (https://www.genenames.org/) (HGNC) website.

4

Inheriting Genetic Conditions

4.1 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 variants (also known as mutations), which can be inherited (passed down from parent to child). Other conditions that appear to run in families are not caused by variants in single genes. Instead, environmental factors such as dietary habits, pollutants, 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 health 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.

First-degree relatives. Parents, children, brothers, and sisters

Second-degree relatives. Grandparents, aunts and uncles, nieces and nephews, and grandchildren

Third-degree relatives. First cousins

This condition affects members in each generation of a family. (Figure 4.1)

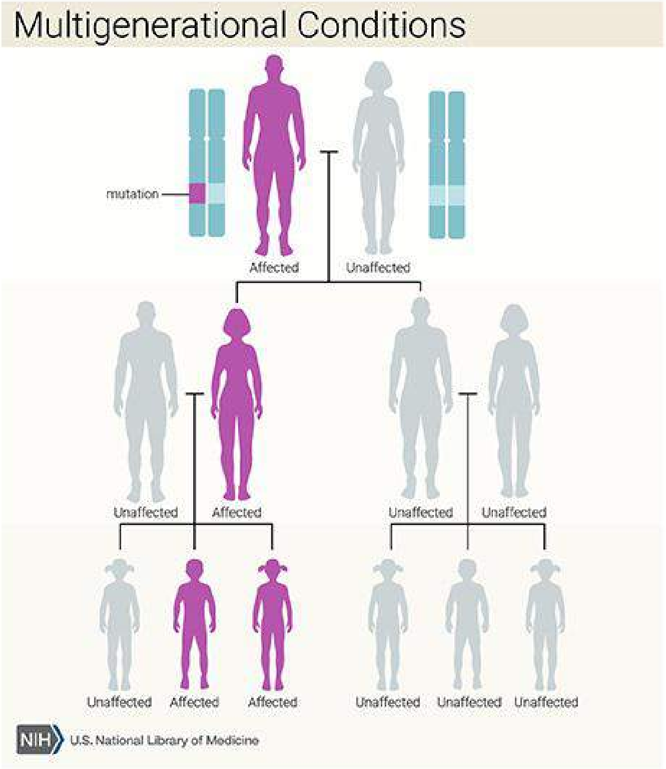


FIGURE 4.1: Three generations of a family with a genetic disorder.

For general information about disorders that run in families:

MedlinePlus Genetics provides consumer-friendly summaries of genetic conditions (https://medlineplus.gov/genetics/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 Genetic Science Learning Center at the University of Utah offers interactive tools about disorders that run in families (https://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/For-Patients-and-Families/Genetic-Disorders).

The Centre for Genetics Education provides an overview of genetic conditions (https://www.genetics.edu.au/SitePages/Genetic-conditions.aspx).

4.2 Why is it important to know my family health history?

A family health 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 similar genetic backgrounds, and often similar environments and lifestyles. Together, these factors can give clues to conditions that may run in a family. By noticing patterns of disorders among relatives, healthcare professionals can determine whether an individual, family members, or future generations may be at an increased risk of developing a particular condition.

A family health 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 type 2 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 variants (mutations) in a single gene, such as cystic fibrosis and sickle cell disease.

While a family health history provides information about the risk of specific health concerns, having relatives with a 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 the disorder.

Knowing one’s family health 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 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 health history is to talk to relatives about their health. Have they had any health 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 health 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 health history:

Additional educational resources related to information about family history (https://medlineplus.gov/familyhistory.html) is available from MedlinePlus.

The Centers for Disease Control and Prevention (CDC) provides information about the importance of family health history (https://www.cdc.gov/genomics/famhistory/index.htm). This resource also includes links to tools for recording family health information.

The American Medical Association provides family history tools (https://www.ama-assn.org/delivering-care/precision-medicine/collecting-family-history), including questionnaires and forms for collecting medical information.

The National Institute on Aging provides suggestions on how to obtain a health history form older individuals (https://www.nia.nih.gov/health/obtaining-older-patients-medical-history).

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

Some genetic conditions are caused by variants (also known as mutations) in a single gene. These conditions are usually inherited in one of several patterns, depending on the gene involved:

Autosomal dominant. One altered 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 (Figure 4.2). In others, the condition may result from a new variant (Figure 4.3) in the gene and occur in people with no history of the disorder in their family.

Example: Huntington disease, Marfan syndrome

Autosomal recessive. In autosomal recessive inheritance (Figure 4.4), variants occur in both copies of the gene in each cell. The parents of an individual with an autosomal recessive condition each carry one copy of the altered 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.

Example: cystic fibrosis, sickle cell disease

X-linked dominant. X-linked dominant (Figure 4.5) disorders are caused by variants in genes on the X chromosome. In males (who have only one X chromosome), a variant in the only copy of the gene in each cell causes the disorder. In females (who have two X chromosomes), a variant in one of the two copies of the gene in each cell is sufficient to cause the disorder. Females may experience less severe symptoms of the disorder than males. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).

Example: fragile X syndrome

X-linked recessive. X-linked recessive (Figure 4.6) disorders are also caused by variants 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 variant would have to occur in both copies of the gene to cause the disorder. 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).

Example: hemophilia, Fabry disease

X-linked. Because the inheritance pattern of many X-linked disorders is not clearly dominant or recessive, some experts suggest that conditions be considered X-linked rather than X-linked dominant or X-linked recessive. X-linked disorders are caused by variants in genes on the X chromosome, one of thetwo sex chromosomes in each cell.

In males (who have only one X chromosome), an alteration in the only copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), one altered copy of the gene usually leads to less severe health problems than those in affected males, or it may cause no signs or symptoms at all. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons (no male-to-male transmission).

Example: glucose-6-phosphate-dehydrogenase-deficiency, X-linked thrombocytopenia

Y-linked. A condition is considered Y-linked (Figure 4.7) if the altered 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 variant can only be passed from father to son.

Example: Y chromosome infertility, some cases of Swyer syndrome

Codominant. In codominant inheritance (Figure 4.8), two different versions (alleles) of a gene are expressed, and each version makes a slightly different protein. Both alleles influence the genetic trait or determine the characteristics of the genetic condition.

Example: ABO blood group, alpha-1 antitrypsin deficiency

Mitochondrial. Mitochondrial inheritance (Figure 4.9), 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 variants to their children. Conditions resulting from variants 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.

Example: Leber hereditary optic neuropathy (LHON)

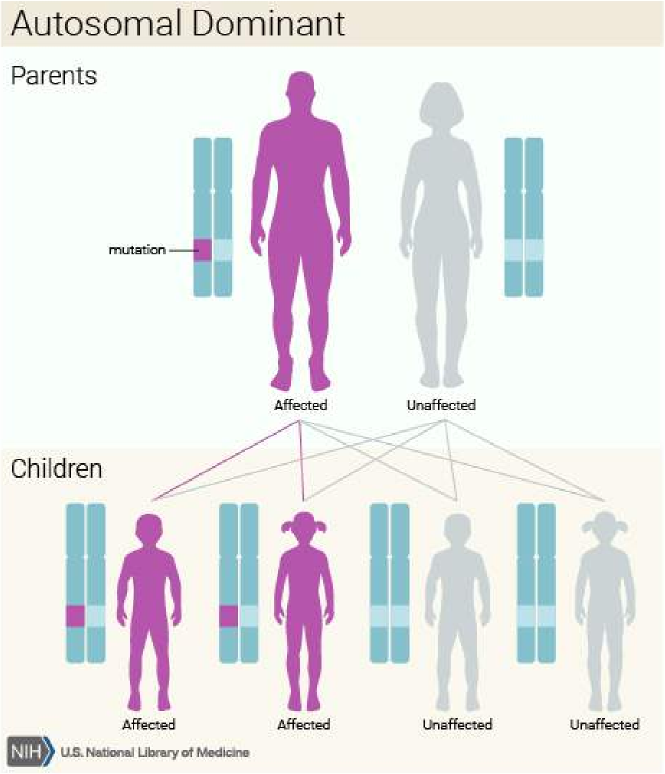


FIGURE 4.2: A parent with an autosomal dominant condition passes the altered gene to two affected children. Two other children do not receive the altered gene, and are unaffected.

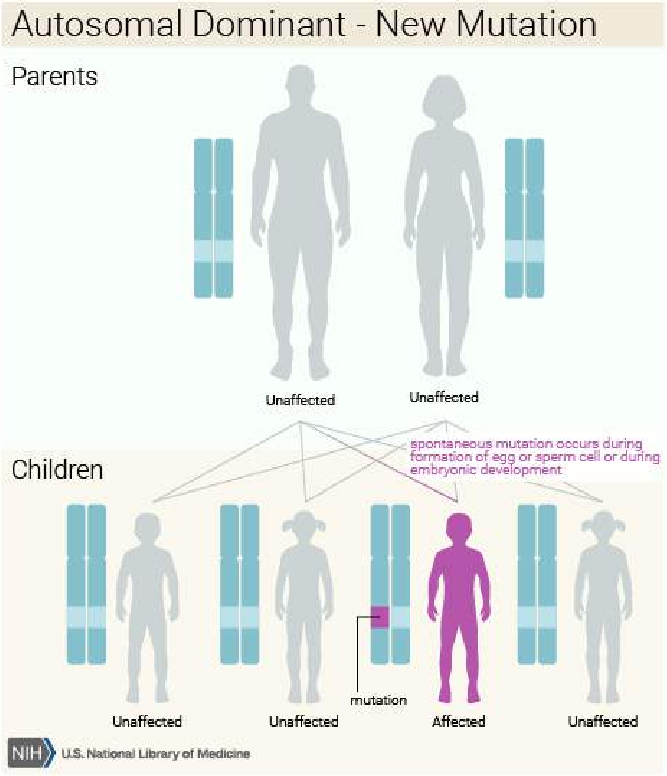


FIGURE 4.3: Neither parent has the mutated gene. A spontaneous mutation occurs during the formation of an egg or sperm cell during embryonic development, leading to an affected child.

Reprinted from MedlinePlus Genetics (https://medlineplus.gov/genetics/)

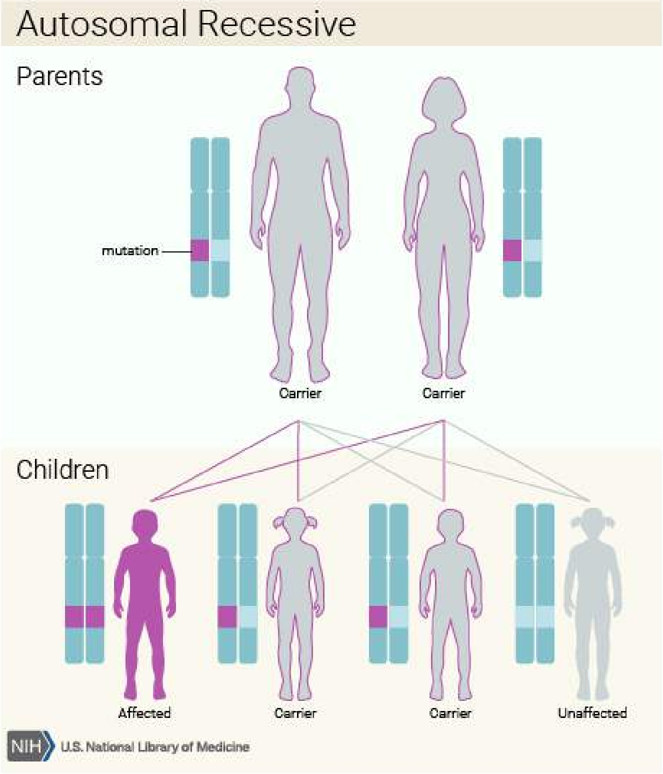


FIGURE 4.4: Both parents carry one copy of a mutated gene. In the next generation, one child is affected with the condition, two children are carriers, and one is unaffected and not a carrier.

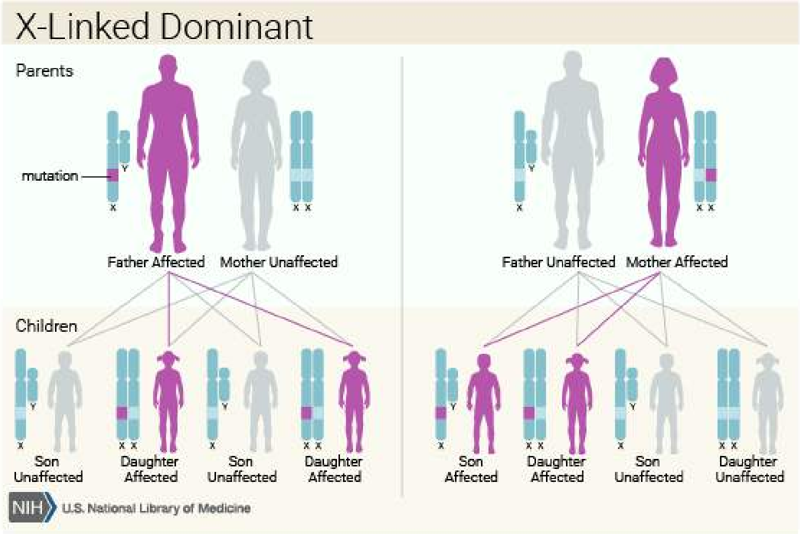


FIGURE 4.5: Inheritance of an X-linked dominant disorder depends on which parent is affected.

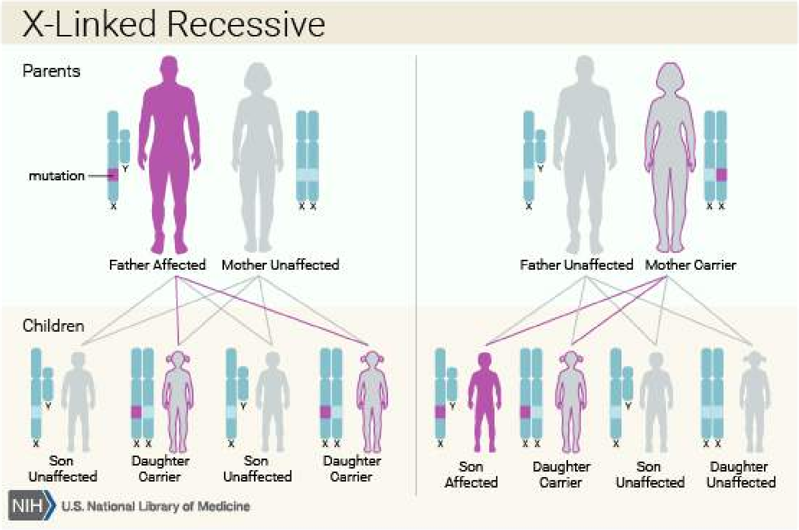


FIGURE 4.6: Two generations of a family with an X-linked recessive disorder. In this form of inheritance, the chance of being affected or being a carrier depends on whether the mother or the father has the mutated gene on the X chromosome.

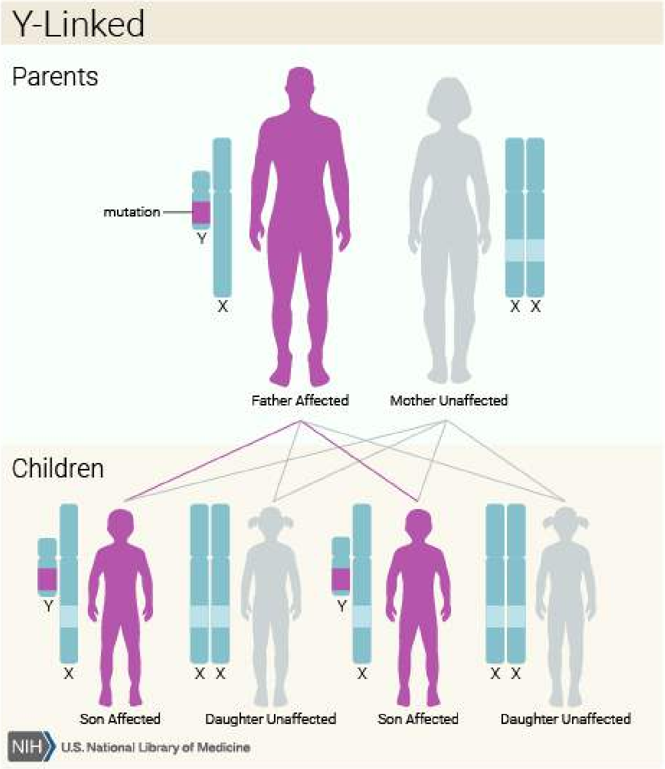


FIGURE 4.7: A father and sons are affected with a Y-linked disorder, which

is caused by a genetic mutation on the Y chromosome. Females are unaffected.

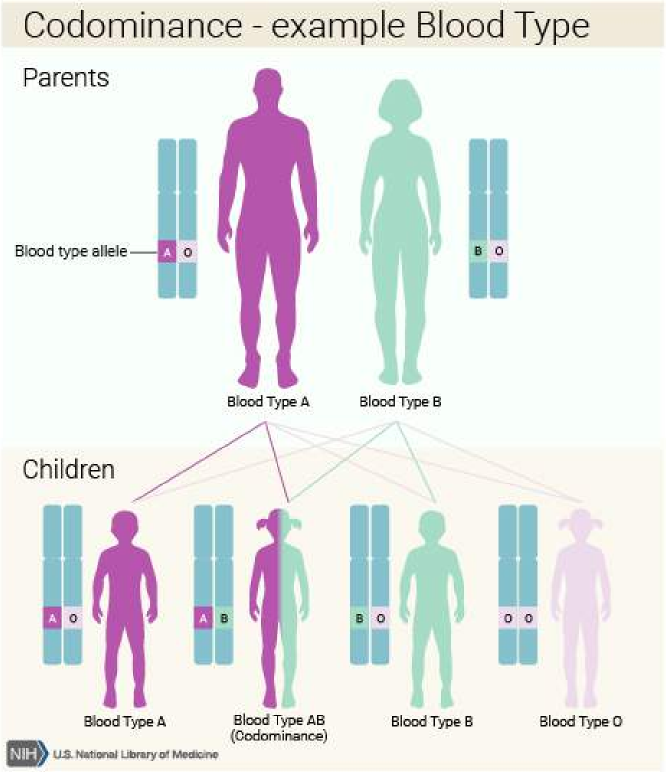


FIGURE 4.8: ABO blood type is an example of a trait with codominant inheritance.

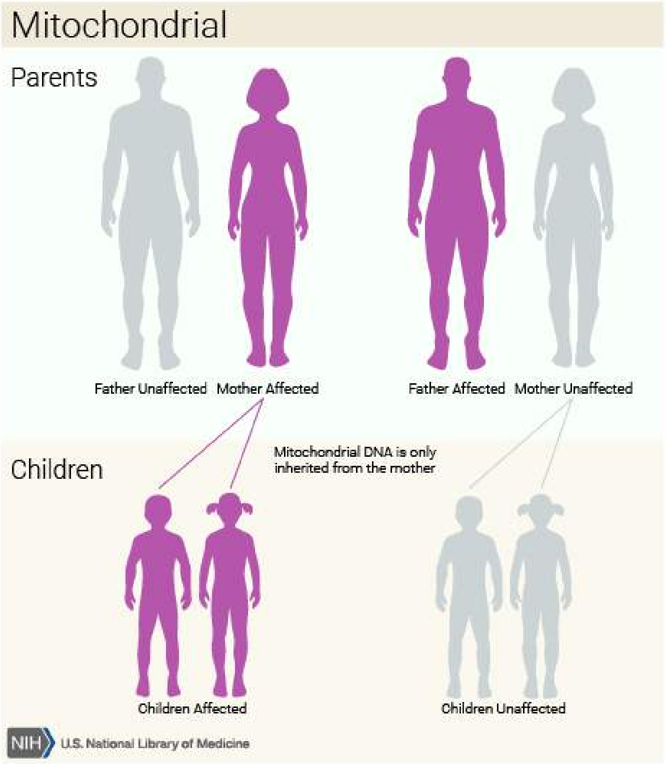


FIGURE 4.9: The inheritance of a mitochondrial disorder depends whether the mother or the father has the mutation in mitochondrial DNA.

Many health conditions are caused by the combined effects of multiple genes (described as polygenic) or by interactions between genes and the environment. Such disorders usually do not follow the patterns of inheritance listed above. Examples of conditions caused by variants in multiple genes or gene/environment interactions include heart disease, type 2 diabetes, schizophrenia, and certain types of cancer. For more information, please see What are complex or multifactorial disorders?

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?

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

For more information about inheritance patterns:

The Centre for Genetics Education provides information about different inheritance patterns:

- Autosomal dominant inheritance (https://www.genetics.edu.au/SitePages/Autosomal-dominant-inheritance.aspx)
- Autosomal recessive inheritance (https://www.genetics.edu.au/SitePages/Autosomal-recessive-inheritance.aspx)
- X-linked dominant inheritance (https://www.genetics.edu.au/SitePages/X-linked-dominant-inheritance.aspx)
- X-linked recessive inheritance (https://www.genetics.edu.au/SitePages/X-linked-recessive-inheritance.aspx)
- Mitochondrial inheritance (https://www.genetics.edu.au/SitePages/Mitochondrial-Inheritance.aspx)

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

4.4 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 (Figure 4.2) has a 50 percent chance of passing the altered gene to each child. The chance that a child will not inherit the altered gene is also 50 percent. However, in some cases an autosomal dominant disorder results from a new (de novo) variant (Figure 4.3) 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.
- Autosomal recessive inheritance: Two unaffected people who each carry one copy of the altered gene for an autosomal recessive disorder (Figure 4.4) (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. If only one parent is a carrier of the altered gene and the other parent does not carry the variant, none of their children will develop the condition, and the chance with each pregnancy of having an unaffected child who is a carrier is 50 percent.
- X-linked dominant inheritance: The chance of passing on an X-linked dominant condition (Figure 4.5) differs between men and women because men have one X chromosome and one Y chromosome, while women have two X chromosomes. A man passes on his Y chromosome to all of his sons and his X chromosome to all of his daughters. Therefore, the sons of a man with an X-linked dominant disorder will not be affected, 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 (Figure 4.6) also differs between men and women. The sons of a man with an X-linked recessive disorder will not be affected, and his daughters will carry one copy of the altered gene. With each pregnancy, a woman who carries an altered gene for X-linked recessive 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 altered gene. Females with one gene variant associated with an X-linked recessive disorder typically have no or very mild signs or symptoms of the condition.
- X-linked: Because the inheritance pattern of many X-linked disorders is not clearly dominant or recessive, some experts suggest that conditions be considered X-linked rather than X-linked dominant or X-linked recessive.As above, the probability of

passing on an X-linked disorder differs between men and women. The sons of a man with an X-linked disorder will not be affected, but all of his daughters will inherit the altered gene and may develop signs and symptoms of the condition. A woman passes on one or the other of her X chromosomes to each child. Therefore, with each pregnancy, a woman with an X-linked disorder has a 50 percent chance of having a child with the altered gene. An affected daughter may have milder signs and symptoms than an affected son.

- Y-linked inheritance: Because only males have a Y chromosome, only males can be affected by and pass on Y-linked disorders (Figure 4.7). All sons of a man with a Y-linked disorder will inherit the condition from their father.
- Codominant inheritance: In codominant inheritance (Figure 4.8), 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.
- Mitochondrial inheritance: Mitochondria, which are the energy-producing centers inside cells, each contain a small amount of DNA. Disorders with mitochondrial inheritance (Figure 4.9) result from variants in mitochondrial DNA. Although these disorders can affect both males and females, only females can pass variants in mitochondrial DNA to their children. A woman with a disorder caused by changes in mitochondrial DNA will pass the variants to all of her daughters and sons, but the children of a man with such a disorder will not inherit the variant.

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 variant 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:

MedlinePlus offers additional 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 provides an explanation of mitochondrial inheritance (https://www.genetics.edu.au/SitePages/Mitochondrial-Inheritance.aspx).

4.5 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 variant (or gene mutation) who exhibit signs and symptoms of a genetic disorder. If some people with the variant 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 variant in the *BRCA1* or *BRCA2* gene associated with an increased cancer risk will develop cancer during their lifetime, but some people will not. Doctors cannot predict which people with these variants 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 variant 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:

Additional information about penetrance and expressivity (https://www.merckmanuals.com/home/fundamentals/genetics/inheritance-of-single-gene-disorders) is available from the Merck Manual Consumer Version.

4.6 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 variant (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 Professional Version provides a brief explanation of anticipation as part of its chapter on nontraditional inheritance (https://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 (https://www.myotonic.org/digital-academy/dm-anticipation-part-1).

4.7 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 National Human Genome Research Institute provides a definition of genetic imprinting (https://www.genome.gov/genetics-glossary/Genetic-Imprinting) in its Talking Glossary of Genetic Terms.

The University of Utah offers a basic overview of genomic imprinting (https://learn.genetics.utah.edu/content/epigenetics/imprinting/).

Additional information about epigenetics, including genomic imprinting (https://www.genetics.edu.au/SitePages/Epigenetics.aspx) is available from the Centre for Genetics Education.

Geneimprint, a website about genomic imprinting, provides an introduction to imprinting (http://www.geneimprint.com/site/what-is-imprinting) as well as related articles and a list of imprinted genes (http://www.geneimprint.com/site/genes-by-species).

4.8 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/about-genomics/fact-sheets/Chromosome-Abnormalities-Fact-Sheet)

The Chromosome Disorder Outreach fact sheet Introduction to Chromosomes (https://chromodisorder.org/introduction-to-chromosomes/) explains how structural changes occur.

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.

4.9 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 variant (also known as a 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 disease, 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 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 (https://www.juf.org/cjg/Ashkenazi-Jewish-Disorders.aspx) and Sephardic Jews (https://www.juf.org/cjg/Sephardic-Jewish-Disorders.aspx).

The Centers of Disease Control and Prevention provides data on the prevalence of sickle cell disease (https://www.cdc.gov/ncbddd/sicklecell/data.html) in various populations in the United States.

4.10 What is heritability?

Heritability is a measure of how well differences in people's genes account for differences in their traits. Traits can include characteristics such as height, eye color, and intelligence, as well as disorders like schizophrenia and autism spectrum disorder. In scientific terms, heritability is a statistical concept (represented as h^2) that describes how much of the variation in a given trait can be attributed to genetic variation. An estimate of the heritability of a trait is specific to one population in one environment, and it can change over time as circumstances change.

Heritability estimates range from zero to one. A heritability close to zero indicates that almost all of the variability in a trait among people is due to environmental factors, with very little influence from genetic differences. Characteristics such as religion or language spoken have a heritability of zero because they are not under genetic control. A heritability close to one indicates that almost all of the variability in a trait comes from genetic differences, with very little contribution from environmental factors. Many disorders that are caused by variants (also known as mutations) in single genes, such as phenylketonuria (PKU), have high heritability. Most complex traits in people, such as intelligence and multifactorial diseases, have a heritability somewhere in the middle, suggesting that their variability is due to a combination of genetic and environmental factors.

Heritability has historically been estimated from studies of twins. Identical twins have almost no differences in their DNA, while fraternal twins share, on average, 50 percent of their DNA. If a trait appears to be more similar in identical twins than in fraternal twins (when they were raised together in the same environment), genetic factors likely play an important role in determining that trait. By comparing a trait in identical twins versus fraternal twins, researchers can calculate an estimate of its heritability.

Heritability can be difficult to understand, so there are many misconceptions about what it can and cannot tell us about a given trait:

- Heritability does not indicate what proportion of a trait is determined by genes and what proportion is determined by environment. So, a heritability of 0.7 does not mean that a trait is 70% caused by genetic factors; it means that 70% of the variability in the trait in a population is due to genetic differences among people.
- Knowing the heritability of a trait does not provide information about which genes or environmental influences are involved, or how important they are in determining the trait.
- Heritable is not the same as familial. A trait is described as familial if it is shared by members of a family. Traits can appear in families for many reasons in addition to genetics, such as similarities in lifestyle and environment. For example, the language that is spoken tends to be shared in families, but it has no genetic contribution and so is not heritable.
- Heritability does not give any information about how easy or difficult it is to change a trait. For example, hair color is a trait with high heritability, but it is very easy to change with dye.

If heritability provides such limited information, why do researchers study it? Heritability is of particular interest in understanding traits that are very complex with many contributing factors. Heritability can give initial clues as to the relative influences of “ nature” (genetics) and “nurture” (environment) on complex traits, and it can give researchers a place to start teasing apart the factors that influence these traits.

Scientific articles for further reading

Moore DS, Shenk D. The heritability fallacy. Wiley Interdiscip Rev Cogn Sci. 2017 Jan; 8(1-2). doi: 10.1002/wcs.1400. Epub 2016 Dec 1. Review. PubMed: 27906501.

Tenesa A, Haley CS. The heritability of human disease: estimation, uses and abuses. Nat Rev Genet. 2013 Feb;14(2):139-49. doi: 10.1038/nrg3377. Review. PubMed: 23329114.

For more information about heritability:

Indiana University Bloomington: Heritability: What It Means and Why It’s Important (https://blogs.iu.edu/sciu/2017/04/11/heritability/)

Stanford Encyclopedia of Philosophy: Heritability (https://plato.stanford.edu/entries/heredity/)

5

Genetics and Human Traits

5.1 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 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 substances taken during pregnancy and 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.

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. Free full-text available from PubMed Central: 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.

Sudha PI, Singh J, Sodhi GS. The Dermal Ridges as the Infallible Signature of Skin: An Overview. Indian J Dermatol. 2021 Nov-Dec;66(6):649-653. doi: 10.4103/ijd.ijd_1123_20. PubMed: 35283510. Free full-text available from PubMed Central: PMC8906331.

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

The Washington State Twin Registry has an FAQ about the fingerprints of identical twins (https://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).

5.2 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.

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 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* and decrease P protein production, leading 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.

Eye anatomy (Figure 5.1)

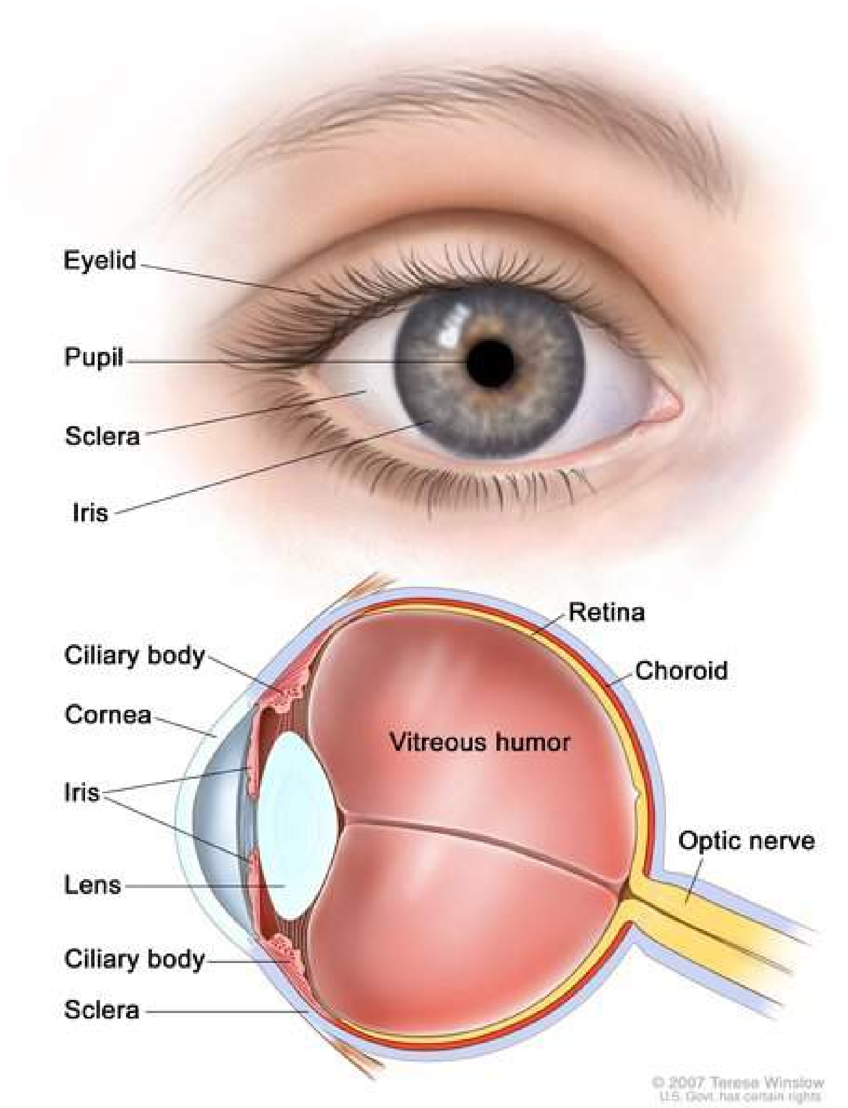


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FIGURE 5.1: Two-panel drawing shows the outside and inside of the eye. The top panel shows outside of the eye including the eyelid, pupil, sclera, and iris; the bottom panel shows inside of the eye including the cornea, lens, ciliary body, retina, choroid, optic nerve, and vitreous humor.

To learn more about the genetics of eye color:

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

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.

Additional information from MedlinePlus provides a brief description of heterochromia (https://medlineplus.gov/ency/article/003319.htm). Further information about this condition is provided by the American Academy of Ophthalmology (https://www.aao.org/eye-health/diseases/what-is-heterochromia).

5.3 Is intelligence determined by genetics?

Like most aspects of human behavior and cognition, intelligence is a complex 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. Other studies have examined variations across the entire genomes of many people (an approach called genome-wide association studies or GWAS) to determine whether any specific areas of the genome are associated with IQ. Studies have not conclusively identified any genes that have major roles in 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. Other areas that contribute to intelligence, such as memory and verbal ability, involve additional genetic factors.

Intelligence is also strongly influenced by the environment. During a child's development, factors that contribute to intelligence include their home environment and parenting, education and availability of learning resources, and healthcare and nutrition. 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 person's level of intelligence is similar to that of their 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

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Plomin R, von Stumm S. The new genetics of intelligence. Nat Rev Genet. 2018 Mar; 19(3):148-159. doi: 10.1038/nrg.2017.104. Epub 2018 Jan 8. PubMed: 29335645. Free full-text available from PubMed Central: PMC5985927.

Sniekers S, Stringer S, Watanabe K, Jansen PR, Coleman JRI, Krapohl E, Taskesen E, Hammerschlag AR, Okbay A, Zabaneh D, Amin N, Breen G, Cesarini D, Chabris CF, Iacono WG, Ikram MA, Johannesson M, Koellinger P, Lee JJ, Magnusson PKE, McGue M, Miller MB, Ollier WER, Payton A, Pendleton N, Plomin R, Rietveld CA, Tiemeier H, van Duijn CM, Posthuma D. Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. Nat Genet. 2017 Jul;49(7):1107-1112. doi: 10.1038/ng.3869. Epub 2017 May 22. Erratum in: Nat Genet. 2017 Sep 27;49(10):1558. PubMed: 28530673. Free full-text available from PubMed Central: PMC5665562

Sternberg RJ. Intelligence. Dialogues Clin Neurosci. 2012 Mar;14(1):19-27. Review. PubMed: 22577301. Free full-text available from PubMed Central: PMC3341646

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

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

Cambridge Brain Sciences discusses a recent research study that identified 22 genes that have been linked to intelligence (https://www.cambridgebrainsciences.com/more/articles/22-genes-have-been-linked-to-intelligence). (See Sniekers, et al (2017) in the ' scientific journal articles for further reading' list in the main summary to read the full research study.)

The Cold Spring Harbor Laboratory offers an interactive tool called Genes to Cognition (https://dnalc.cshl.edu/view/2251-Thinking-.html) that provides information about many aspects of the genetics of neuroscience.

5.4 Is handedness determined by genetics?

Like most aspects of human traits, handedness is complex and appears to be influenced by multiple factors, including genetics and environment.

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 worldwide, 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 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. Studies suggest that other factors also contribute to handedness. The prenatal environment and cultural influences may play a role.

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 both be 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. Free full-text available from PubMed Central: 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. Free full-text available from PubMed

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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. Free full-text available from PubMed Central: PMC3969300

de Kovel CGF, Francks C. The molecular genetics of hand preference revisited. Sci Rep. 2019 Apr 12;9(1):5986. doi: 10.1038/s41598-019-42515-0. PubMed: 30980028; Free full-text available from PubMed Central: PMC6461639.

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. Free full-text available from PubMed Central: 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 Washington State Twin Registry has an FAQ about hand preference in identical twins (https://wstwinregistry.org/2015/10/01/do-identical-twins-always-have-the-same-hand-preference/).

5.5 Is the probability of having twins determined by genetics?

The likelihood of conceiving twins is a complex trait, meaning that it is 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 to the general population, having DZ twins is about two times more likely if a close relative (for example, a sister) has had DZ twins.

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 type, 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.

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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.

Monden C, Pison G, Smits J. Twin Peaks: more twinning in humans than ever before. Hum Reprod. 2021 May 17;36(6):1666-1673. doi: 10.1093/humrep/deab029. PubMed: 33709110. Free full-text available from PubMed Central: PMC8129593.

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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.

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? (https://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? (https://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? (https://wstwinregistry.org/2015/10/01/does-mz-twinning-run-in-families/)
- What factors are related to fraternal (DZ) twinning? (https://wstwinregistry.org/2015/10/01/what-factors-are-related-to-dz-twinning/)

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

A brief overview of the factors that influence twinning (https://www.nhs.uk/conditions/pregnancy-and-baby/twins-healthy-multiple-pregnancy/) is available from the UK National Health Service.

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.

5.6 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 variants in genes that play roles in hair structure and stability, including genes associated with specialized cell structures call desmosomes that hold hair cells together, proteins called keratins 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 variants in the DSG4, LIPH, or LPAR6 gene)
- Keratoderma with woolly hair (caused by variants in the JUP, DSP, DSC2, or KANK2 gene)
- Monilethrix (caused by variants in the DSG4, KRT81, KRT83, or KRT86 gene)
- Uncombable hair syndrome (caused by variants in the PADI3, TCHH, or TGM3 gene)

Researchers speculate that the genes associated with these disorders probably also contribute to normal variations in hair texture and thickness.

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

Scientific journal articles for further reading

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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 (https://genetics.thetech.org/ask/ask107) and another on the inheritance of hair texture (https://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.

5.7 Is hair color determined by genetics?

Hair color is determined by the amount of a pigment called melanin in hair. An abundance of one type of melanin, called eumelanin, gives people black or brown hair. An abundance of another pigment, called pheomelanin, gives people red hair.

Black. Large amount of eumelanin

Brown. Moderate amount of eumelanin

Blond. Very little eumelanin

Red. Mostly pheomelanin with a little eumelanin

The type and amount of melanin in hair is determined by many genes, although little is known about most of them. The best-studied hair-color gene in humans is called *MC1R*. This gene provides instructions for making a protein called the melanocortin 1 receptor, which is involved in the pathway that produces melanin. The melanocortin 1 receptor controls which type of melanin is produced by melanocytes. When the receptor is turned on (activated), it triggers a series of chemical reactions inside melanocytes that stimulate these cells to make eumelanin. If the receptor is not activated or is blocked, melanocytes make pheomelanin instead of eumelanin. Many other genes also help to regulate this process. Most people have two functioning copies of the *MC1R* gene, one inherited from each parent. These individuals have black or brown hair, because of the high amount of eumelanin. It is estimated that more than 90 percent of people in the world have brown or black hair.

Some people have variations in one copy of the *MC1R* gene in each cell that causes the gene to be turned off (deactivated). This type of genetic change is described as loss-of-function. For these individuals, eumelanin production is lower, while pheomelanin production is higher, so they have strawberry blond, auburn, or red hair. In an even smaller percentage of people, both copies of the *MC1R* gene in each cell have loss-of-function changes, and the melanin-production pathway produces only the pheomelanin pigment. The hair of these individuals is almost always very red. Even when the melanin-production pathway is making eumelanin, changes in other genes can reduce the amount of eumelanin produced. These changes lead to blond hair.

Hair color ranges across a wide spectrum of hues, from flaxen blond to coal black. Many genes other than *MC1R* play a role in determining shades of hair color by controlling levels of eumelanin and pheomelanin. Some of these genes, including *ASIP*, *DTNBP1*, *GPR143*, *HPS3*, *KITLG*, *MLPH, MYO5A*, *MYO7A*, *OCA2*, *SLC45A2*, *SLC24A5*, *TYRP1*, TYR, *ERCC6*, *GNAS*, *HERC2*, *IRF4*, *OBSCN*, *SLC24A4*, *TPCN2*, and *MITF*, are involved in the production of melanin in hair. Some of these genes are associated with gene transcription (which is the first step in protein production), DNA repair, the transport of substances (such as calcium) across cell membranes, or the structure of hair follicles. Several of these genes contribute to eye and skin color, but the exact role they play in determining hair color is unknown.

Hair color may change over time. Particularly in people of European descent, light hair color may darken as individuals grow older. For example, blond-haired children often have darker hair by the time they are teenagers. Researchers speculate that certain hair-pigment proteins are activated as children grow older, perhaps in response to hormonal changes that occur near puberty. Almost everyone's hair will begin to turn gray as they age, although when it happens and to what extent is variable. Gray hair is partly hereditary and may vary by ethnic origin; it is also somewhat dependent on external factors such as stress. Hair becomes gray when the hair follicle loses its ability to make melanin, but exactly why that occurs is not clear.

Scientific journal articles for further reading

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Ito S, Wakamatsu K. Diversity of human hair pigmentation as studied by chemical analysis of eumelanin and pheomelanin. J Eur Acad Dermatol Venereol. 2011 Dec;25(12):1369-80. doi: 10.1111/j.1468-3083.2011.04278.x. PubMed: 22077870.

Liu F, Wen B, Kayser M. Colorful DNA polymorphisms in humans. Semin Cell Dev Biol. 2013 Jun-Jul;24(6-7):562-75. doi: 10.1016/j.semcdb.2013.03.013. Epub 2013 Apr 12. PubMed: 23587773.

Schaffer JV, Bolognia JL. The melanocortin-1 receptor: red hair and beyond. Arch Dermatol. 2001 Nov;137(11):1477-85. PubMed: 11708951.

Siewierska-Górska A, Sitek A, Zadzinska E, Bartosz G, Strapagiel D. Association of five SNPs with human hair colour in the Polish population. Homo. 2017 Mar;68(2):134-144. doi: 10.1016/j.jchb.2017.02.002. Epub 2017 Feb 4. PubMed: 28242083.

Sturm RA. Molecular genetics of human pigmentation diversity. Hum Mol Genet. 2009 Apr 15;18(R1):R9-17. doi: 10.1093/hmg/ddp003. PubMed: 19297406.

Tobin DJ. Human hair pigmentation--biological aspects. Int J Cosmet Sci. 2008 Aug;

30(4):233-57. doi: 10.1111/j.1468-2494.2008.00456.x. PubMed: 18713071.

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

The Tech Interactive at Stanford University provides a Q&A page about hair color. (https://www.thetech.org/ask-a-geneticist/hair-color-genetics)

KidsHealth from Nemours explains why hair turns gray (https://kidshealth.org/en/kids/gray-hair.html?ref=search&WT.ac=msh-p-dtop-en-search-clk).

5.8 Is height determined by genetics?

Scientists estimate that about 80 percent of an individual’s height is determined by the DNA sequence variations they have inherited, but which genes these changes are in and what they do to affect height are only partially understood. Some rare gene variants have dramatic effects on height (for example, variants in the *FGFR3* gene cause achondroplasia, a rare condition characterized by short stature). For most individuals, though, height is controlled largely by a combination of genetic variants that each have more modest effects on height, plus a smaller contribution from environmental factors (such as nutrition). More than 700 such gene variants have been discovered and many more are expected to be identified. Some of these variants are in genes that directly or indirectly affect cartilage in growth plates, which are areas in the long bones of the legs and arms where new bone is produced, lengthening the bones as children grow. The function of many other height-associated genes remains unknown.

In addition to the *FGFR3* gene, researchers have identified hundreds of other genes involved in rare disorders that have an extreme effect on height. These genes (and the conditions they are associated with) include *FBN1* (acromicric dysplasia, geleophysic dysplasia, Marfan syndrome), *GH1* (isolated growth hormone deficiency), *EVC* (Ellis-van Creveld syndrome), Weyers acrofacial dysostosis), and *GPC3* (Simpson-Golabi-Behmel syndrome). By studying the dramatic effect that altered versions of these genes have on height, scientists hope to better understand the complex interactions among genes that contribute to normal height. Some genes, such as *ACAN*, contain rare variants that cause severe growth disorders, and also other variants with milder effects on height in individuals without a related health condition. Identifying other height genes, and variants with large or small effects, is an active area of genetic research.

Because height is determined by multiple gene variants (an inheritance pattern called polygenic inheritance), it is difficult to accurately predict how tall a child will be. The inheritance of these variants from one’s parents helps explain why children usually grow to be approximately as tall as their parents, but different combinations of variants can cause siblings to be of different heights. Height is influenced by other biological mechanisms (such as hormones) that may also be determined by genetics, although the roles of these mechanisms are not fully understood.

In addition to genetic and biological determinants, height is also influenced by environmental factors, including a mother's nutrition during pregnancy, whether she smoked, and her exposure to hazardous substances. A well-nourished, healthy, and active child is likely to be taller as an adult than will be a child with a poor diet, infectious diseases, or inadequate health care. Socioeconomic factors such as income, education, and occupation can also influence height. In some cases, ethnicity plays a role in adult height, but studies on immigrant families have shown that moving to a country with better access to nutritious food, healthcare, and employment opportunities can have a substantial influence on the height of the next generation; this suggests that some differences in height between ethnicities are explained by non-genetic factors.

Scientific journal articles for further reading

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Marouli E, Graff M, Medina-Gomez C, Lo KS, et al. Rare and low-frequency coding variants alter human adult height. Nature. 2017 Feb 9;542(7640):186-190. doi: 10.1038/nature21039. Epub 2017 Feb 1. PubMed: 28146470. Free full-text available from PubMed Central: PMC5302847.

McEvoy BP, Visscher PM. Genetics of human height. Econ Hum Biol. 2009 Dec;7(3):294-306. doi: 10.1016/j.ehb.2009.09.005. Epub 2009 Sep 17. PubMed: 19818695.

Perola M. Genome-wide association approaches for identifying loci for human height genes. Best Pract Res Clin Endocrinol Metab. 2011 Feb;25(1):19-23. doi: 10.1016/j.beem.2010.10.013. PubMed: 21396572.

To learn more about the genetics of height:

The Broad Institute of the Massachusetts Institute of Technology and Harvard University published a press release about the Genetic Investigation of Anthropometric Traits (GIANT) study (https://www.broadinstitute.org/news/giant-study-reveals-giant-number-genes-linked-height), which greatly expanded understanding of the role of genetics in height determination.

OMIM.org provides a list of genes that are associated with height (https://www.omim.org/search/?index=geneMap&search=stature+height+shortness+tallness&start=1&limit=10).

5.9 Are moles determined by genetics?

Moles are very common, especially in people with fair skin. Moles are overgrowths of skin cells called melanocytes, but the genetic factors involved in their development are not well understood. Although moles, like tumors, are an overgrowth of cells, moles are almost always noncancerous (benign). Perhaps because most moles are benign, scientists have not studied them extensively, and not much is known about their genetics. Similar numbers of moles seem to occur on individuals of different generations of a family, so a tendency to develop moles seems to be inherited, but the inheritance pattern is not well understood.Most moles occur on parts of the body that are exposed to the sun (ultraviolet radiation), and the number of moles an individual has may increase after extended time in the sun. Moles usually begin to occur in childhood. These moles are called acquired melanocytic nevi (and include the subtype epidermal nevus). It is common for new moles to appear during times when hormone levels change, such as adolescence and pregnancy. During an individual's lifetime, moles may change in appearance; hair may grow out of them, and they can change in size and shape, darken, fade, or disappear. Infants and the elderly tend to have the fewest moles.

Sometimes, moles are present at birth or develop during infancy. These moles, which are called congenital nevi, are almost always benign. Rarely, a very large mole, called a giant congenital melanocytic nevus, is present at birth. In rare cases, the most serious type of skin cancer (called melanoma) may develop in this type of mole. Large, irregularly shaped and colored moles called dysplastic nevi or atypical moles can occur at any age. Although not common, they tend to be numerous, and they increase a person's risk of melanoma. Heredity contributes to the development of dysplastic nevi and to having a higher-than-average number of benign moles. Spending a lot of time in the sun can also increase the number of moles a person has. However, moles are often found on areas of the body that are not exposed, which suggests that factors other than ultraviolet radiation from the sun, perhaps hormones or other biologic processes, are involved in triggering the development of acquired melanocytic nevi and dysplastic nevi.

Although the genetics of melanoma has been widely studied, much less is known about genes involved in the development of benign moles. Variations in several genes, including *FGFR3*, *PIK3CA*, *HRAS*, and *BRAF*, are involved with benign moles. The most-studied of these is the *BRAF* gene. A variant in *BRAF* leads to the production of an altered protein that causes melanocytes to aggregate into moles. This altered protein also triggers the production of a tumor-suppressor protein called p15 that stops moles from growing too big. In rare cases, *BRAF* gene variants together with loss (deletion) of the *CDKN2A* gene causes a lack of p15, which creates the potential for mole cells to grow uncontrollably and become cancerous (malignant). The formation of cancer is increasingly likely when combined with environmental factors, such as cell damage caused by ultraviolet radiation exposure.In susceptible individuals (those with fair skin, light hair, skin that burns instead of tans, a family history of melanoma, and genetic risk factors such as deletion of or variants in the *CDKN2A* gene), ultraviolet radiation from repeated sun exposure can damage existing moles, increasing their risk of becoming malignant. Research has shown that individuals who have an abundance of moles are at an increased risk of melanoma. However, some people who are diagnosed with melanoma have few moles, and melanoma often develops in areas of the body that are not exposed to the sun. Researchers are working to identify additional susceptibility genes to better understand the genetics of moles and their relationship with cancer.

Scientific journal articles for further reading

Plasmeijer EI, Nguyen TM, Olsen CM, Janda M, Soyer HP, Green AC. The natural history of common melanocytic nevi: a systematic review of longitudinal studies in the general population. J Invest Dermatol. 2017 Sep;137(9):2017-2018. doi: 10.1016/j.jid.2017.03.040. Epub 2017 May 18. PubMed: 28528913.

Roh MR, Eliades P, Gupta S, Tsao H. Genetics of melanocytic nevi. Pigment Cell Melanoma Res. 2015 Nov;28(6):661-72. doi: 10.1111/pcmr.12412. PubMed: 26300491. Free full-text available from PubMed Central: PMC4609613.Silva JH1, Sá BC, Avila AL, Landman G, Duprat Neto JP. Atypical mole syndrome and dysplastic nevi: identification of populations at risk for developing melanoma - review article. Clinics (Sao Paulo). 2011;66(3):493-9. PubMed: 21552679. Free full-text available from PubMed Central: PMC3072014.

To learn more about the genetics of moles:

MedlinePlus offers additional resources (https://medlineplus.gov/moles.html) to learn more about moles.

A University of Pennsylvania press release describes *BRAF* and p15, factors that keep moles from turning into melanoma (https://www.pennmedicine.org/news/news-releases/2015/august/penn-scientists-identify-key-g).

5.10 Are facial dimples determined by genetics?

Dimples—indentations on the cheeks—tend to occur in families, and this trait is assumed to be inherited. Dimples are usually considered a dominant genetic trait, which means that one copy of the altered gene in each cell is sufficient to cause dimples. However, some researchers say that there is no proof that dimples are inherited. Little research has been done to explore the genetics of dimples and it is not known which gene or genes may be involved.

A dimple is an anomaly of the muscle that causes a dent in the cheek, especially when the individual smiles. Some people have dimples in both cheeks, others in just one cheek. Babies are likely to have dimples caused by baby fat in their cheeks. When they lose their baby fat as they get older, their dimples disappear. Other children do not have them at birth but may develop them later in childhood. In some people, dimples last only until adolescence or young adulthood, while in others they are a lifetime trait.

Dimples that have a similar appearance can occur in successive generations of a family. For example, in one family, it was observed that the siblings, their father, uncles, grandfather, and great-grandfather all had similar-looking dimples in both cheeks. In other families, dimples may occur in a child but are not seen in more than one generation.

Scientific articles for further reading

OMIM: Dimples, Facial (126100)

Wiedemann HR. Cheek dimples. Am J Med Genet. 1990 Jul;36(3):376. PubMed: 2363446.

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

Stanford at the Tech: Genetics of Dimples (https://genetics.thetech.org/ask/ask47)

Genetic Science Learning Center at the University of Utah: Observable Human Characteristics (https://learn.genetics.utah.edu/content/basics/observable/)

5.11 Is athletic performance determined by genetics?

Athletic performance is a complex trait that is influenced by both genetic and environmental factors. Many physical traits help determine an individual's athletic ability, primarily the strength of muscles used for movement (skeletal muscles) and the predominant type of fibers that compose them. Skeletal muscles are made up of two types of muscle fibers: slow-twitch fibers and fast-twitch fibers. Slow-twitch muscle fibers contract slowly but can work for a long time without tiring; these fibers enable endurance activities like long-distance running. Fast-twitch muscle fibers contract quickly but tire rapidly; these fibers are good for sprinting and other activities that require power or strength. Other traits related to athleticism include the maximum amount of oxygen the body can deliver to its tissues (aerobic capacity), muscle mass, height, flexibility, coordination, intellectual ability, and personality.

Studies focused on similarities and differences in athletic performance within families, including between twins, suggest that genetic factors underlie 30 to 80 percent of the differences among individuals in traits related to athletic performance. Many studies have investigated variations in specific genes thought to be involved in these traits, comparing athletes with nonathletes.

The best-studied genes associated with athletic performance are *ACTN3* and *ACE*. These genes influence the fiber type that makes up muscles, and they have been linked to strength and endurance. The *ACTN3* gene provides instructions for making a protein called alpha (α)-actinin-3, which is predominantly found in fast-twitch muscle fibers. A variant in this gene, called R577X, leads to production of an abnormally short α-actinin-3 protein that is quickly broken down. Some people have this variant in both copies of the gene; this genetic pattern (genotype) is referred to as 577XX. These individuals have a complete absence of α-actinin-3, which appears to reduce the proportion of fast-twitch muscle fibers and increase the proportion of slow-twitch fibers in the body. Some studies have found that the 577XX genotype is more common among high-performing endurance athletes (for example, cyclists and long-distance runners) than in the general population, while other studies have not supported these findings. The 577RR genotype is associated with a high proportion of fast-twitch fibers and is seen more commonly in athletes who rely on strength or speed, such as short-distance runners.

The *ACE* gene provides instructions for making a protein called angiotensin-converting enzyme, which converts a hormone called angiotensin I to another form called angiotensin II. Angiotensin II helps control blood pressure and may also influence skeletal muscle function, although this role is not completely understood. A variation in the *ACE* gene, called the ACE I/D polymorphism, alters activity of the gene. Individuals can have two copies of a version called the D allele, which is known as the DD pattern, two copies of a version called the I allele, known as the II pattern, or one copy of each version, called the ID pattern. Of the three patterns, DD is associated with the highest levels of angiotensin-converting enzyme. The DD pattern is thought to be related to a higher proportion of fast-twitch muscle fibers and greater speed.

Many other genes with diverse functions have been associated with athletic performance. Some are involved in the function of skeletal muscles, while others play roles in the production of energy for cells, communication between nerve cells, or other cellular processes.

Other studies have examined variations across the entire genomes (an approach called genome-wide association studies or GWAS) of elite athletes to determine whether specific areas of the genome are associated with athleticism. More than 150 different variations linked to athletic performance have been identified in these studies; however, most have been found in only one or a few studies, and the significance of most of these genetic changes have not been identified. It is likely that a large number of genes are involved, each of which makes only a small contribution to athletic performance.

Athletic performance is also strongly influenced by the environment. Factors such as the amount of support a person receives from family and coaches, economic and other circumstances that allow one to pursue the activity, availability of resources, and a person’s relative age compared to their peers all seem to play a role in athletic excellence. A person’s environment and genes influence each other, so it can be challenging to tease apart the effects of the environment from those of genetics. For example, if a child and his or her parent excel at a sport, is that similarity due to genetic factors passed down from parent to child, to similar environmental factors, or (most likely) to a combination of the two? It is clear that both environmental and genetic factors play a part in determining athletic ability.

Scientific journal articles for further reading

Ahmetov II, Egorova ES, Gabdrakhmanova LJ, Fedotovskaya ON. Genes and Athletic Performance: An Update. Med Sport Sci. 2016;61:41-54. doi: 10.1159/000445240. Epub 2016 Jun 10. Review. PubMed: 27287076.

Ahmetov II, Fedotovskaya ON. Current Progress in Sports Genomics. Adv Clin Chem. 2015;70:247-314. doi: 10.1016/bs.acc.2015.03.003. Epub 2015 Apr 11. Review. PubMed: 26231489.

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Yan X, Papadimitriou I, Lidor R, Eynon N. Nature versus Nurture in Determining Athletic Ability. Med Sport Sci. 2016;61:15-28. doi: 10.1159/000445238. Epub 2016 Jun 10. Review. PubMed: 27287074.

5.12 Is longevity determined by genetics?

The duration of human life (longevity) is influenced by genetics, the environment, and lifestyle. Environmental improvements beginning in the 1900s extended the average life span dramatically with significant improvements in the availability of food and clean water, better housing and living conditions, reduced exposure to infectious diseases, and access to medical care. Most significant were public health advances that reduced premature death by decreasing the risk of infant mortality, increasing the chances of surviving childhood, and avoiding infection and communicable disease. Now people in the United States live about 80 years on average, but some individuals survive for much longer.

Scientists are studying people in their nineties (called nonagenarians) and hundreds (called centenarians, including semi-supercentenarians of ages 105-109 years and supercentenarians, ages 110+) to determine what contributes to their long lives. They have found that long-lived individuals have little in common with one another in education, income, or profession. The similarities they do share, however, reflect their lifestyles—many are nonsmokers, do not have obesity, and cope well with stress. Also, most are women. Because of their healthy habits, these older adults are less likely to develop age-related chronic diseases, such as high blood pressure, heart disease, cancer, and diabetes, than their same-age peers.

The siblings and children (collectively called first-degree relatives) of long-lived individuals are more likely to remain healthy longer and to live to an older age than their peers. People with centenarian parents are less likely at age 70 to have the age-related diseases that are common among older adults. The brothers and sisters of centenarians typically have long lives, and if they develop age-related diseases (such as high blood pressure, heart disease, cancer, or type 2 diabetes), these diseases appear later than they do in the general population. Longer life spans tend to run in families, which suggests that shared genetics, lifestyle, or both play an important role in determining longevity.

The study of longevity genes is a developing science. It is estimated that about 25 percent of the variation in human life span is determined by genetics, but which genes, and how they contribute to longevity, are not well understood. A few of the common variations (called polymorphisms) associated with long life spans are found in the *APOE*, *FOXO3*, and *CETP* genes, but they are not found in all individuals with exceptional longevity. It is likely that variants in multiple genes, some of which are unidentified, act together to contribute to a long life.

Whole genome sequencing studies of supercentenarians have identified the same gene variants that increase disease risk in people who have average life spans. The supercentenarians, however, also have many other newly identified gene variants that possibly promote longevity. Scientists speculate that for the first seven or eight decades, lifestyle is a stronger determinant of health and life span than genetics. Eating well, not drinking too much alcohol, avoiding tobacco, and staying physically active enable some individuals to attain a healthy old age; genetics then appears to play a progressively important role in keeping individuals healthy as they age into their eighties and beyond.

Many nonagenarians and centenarians are able to live independently and avoid age-related diseases until the very last years of their lives.

Some of the gene variants that contribute to a long life are involved with the basic maintenance and function of the body's cells. These cellular functions include DNA repair, maintenance of the ends of chromosomes (regions called telomeres), and protection of cells from damage caused by unstable oxygen-containing molecules (free radicals). Other genes that are associated with blood fat (lipid) levels, inflammation, and the cardiovascular and immune systems contribute significantly to longevity because they reduce the risk of heart disease (the main cause of death in older people), stroke, and insulin resistance.

In addition to studying the very old in the United States, scientists are also studying a handful of communities in other parts of the world where people often live into their nineties and older—Okinawa (Japan), Ikaria (Greece), and Sardinia (Italy). These three regions are similar in that they are relatively isolated from the broader population in their countries, are lower income, have little industrialization, and tend to follow a traditional (non-Western) lifestyle. Unlike other populations of the very old, the centenarians on Sardinia include a significant proportion of men. Researchers are studying whether hormones, sex-specific genes, or other factors may contribute to longer lives among men as well as women on this island.

Scientific journal articles for further reading

Martin GM, Bergman A, Barzilai N. Genetic determinants of human health span and life span: progress and new opportunities. PLoS Genet. 2007 Jul;3(7):e125. PubMed: 17677003. Free full-text available from PubMed Central: PMC1934400.

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Young RD. Validated living worldwide supercentenarians, living and recently deceased: February 2018. Rejuvenation Res. 2018 Feb 1. doi: 10.1089/rej.2018.2057. [Epub ahead of print] PubMed: 29390945.

To learn more about the genetics of longevity:

Boston University School of Medicine provides a description of the New England Centenarian Study (http://www.bumc.bu.edu/centenarian/).

The Institute for Aging Research at Albert Einstein College of Medicine describes the Longevity Genes Project (https://www.einsteinmed.edu/centers/aging/longevity-genes-project/about-the-study/).

The Duke University Center for Population Health & Aging provides descriptions of studies of long lives (https://cpha.duke.edu/life-course-studies).

The National Institute on Aging offers a video about the Baltimore Longitudinal Study of Aging (https://www.nia.nih.gov/research/labs/blsa/about).

The SardiNIA Project has several pages describing research investigating longevity genes (https://sardinia.irp.nia.nih.gov/index.html) among Italians living on the Mediterranean island of Sardinia.

The Okinawa Centenarian Study (https://orcls.org/) describes the genetics, healthy aging, and longevity of Japanese living on the island of Okinawa.

5.13 Is temperament determined by genetics?

Temperament includes behavioral traits such as sociability (outgoing or shy), emotionality (easy-going or quick to react), activity level (high or low energy), attention level (focused or easily distracted), and persistence (determined or easily discouraged). These examples represent a spectrum of common characteristics, each of which may be advantageous in certain circumstances. Temperament remains fairly consistent, particularly throughout adulthood.

Similar temperaments within a family may be attributable to shared genetics and to the environment in which an individual is raised. Studies of identical twins (who share 100 percent of their DNA) and their non-twin siblings (who share about 50 percent of their DNA) show that genetics play a large role. Identical twins typically have very similar temperaments when compared with their other siblings. Even identical twins who were raised apart from one another in separate households share such traits.

Scientists estimate that 20 to 60 percent of temperament is determined by genetics. Temperament, however, does not have a clear pattern of inheritance and there are not specific genes that confer specific temperamental traits. Instead, many (perhaps thousands) of common gene variations (polymorphisms) combine to influence individual characteristics of temperament. Other DNA modifications that do not alter DNA sequences (epigenetic changes) also likely contribute to temperament.

Large studies have identified several genes that play a role in temperament. Many of these genes are involved in communication between cells in the brain. Certain gene variations may contribute to particular traits related to temperament. For example, variants in the *DRD2* and *DRD4* genes have been linked to a desire to seek out new experiences, and *KATNAL2* gene variants are associated with self-discipline and carefulness. Variants affecting the *PCDH15* and *WSCD2* genes are associated with sociability, while some *MAOA* gene variants may be linked to introversion, particularly in certain environments. Variants in several genes, such as *SLC6A4*, *AGBL2*, *BAIAP2*, *CELF4*, *L3MBTL2*, *LINGO2*, *XKR6*, *ZC3H7B*, *OLFM4*, *MEF2C*, and *TMEM161B* contribute to anxiousness or depression.

Environmental factors also play a role in temperament by influencing gene activity. In children raised in an adverse environment (such as one of child abuse and violence), genes that increase the risk of impulsive temperamental characteristics may be turned on (activated). However, a child who grows up in a positive environment (for example a safe and loving home) may have a calmer temperament, in part because a different set of genes is activated

Scientific journal articles for further reading

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Manuck SB, McCaffery JM. Gene-environment interaction. Annu Rev Psychol. 2014;65: 41-70. doi: 10.1146/annurev-psych-010213-115100. PubMed: 24405358

Power RA, Pluess M. Heritability estimates of the big five personality traits based on common genetic variants. Translational Psychiatry (2015) 5, e604; doi:10.1038/tp.2015.96; published online 14 July 2015. PubMed: 26171985 PubMed Central: PMC5068715

To find out more about the role of genetics in temperament:

The Dana Foundation. One of a Kind: The Neurobiology of Individuality (https://www.dana.org/article/one-of-a-kind-the-neurobiology-of-individuality/).

6

Genetic Consultation

6.1 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 conditions. 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. Additionally, genetic consultations may be carried out using telemedicine (also known as telehealth), in which the meeting is done from a distance using computers, cameras, videoconferencing tools, or the telephone.

For more information about genetic consultations:

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

MedlinePlus also offers information about telehealth (https://medlineplus.gov/telehealth.html).

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

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 (https://www.ncbi.nlm.nih.gov/books/NBK115508/).

The National Society of Genetic Counselors discusses what happens during an appointment (https://www.aboutgeneticcounselors.org/Prepare-for-an-Appointment/What-Happens-During-an-Appointment).

The Centre for Genetics Education also offers an introduction to genetic counseling (https://www.genetics.edu.au/publications-and-resources/facts-sheets/fact-sheet-6-genetic-counselling).

6.2 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 person received results from direct-to-consumer genetic testing and they want to discuss the implications of the results.

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 (https://www.ncbi.nlm.nih.gov/books/NBK115554/) is available from The Genetic Alliance booklet "Understanding Genetics: A Guide for Patients and Professionals."

The Centers for Disease Control and Prevention (CDC) Office of Public Health Genomics has a list of reasons why people go for genetic counseling (https://www.cdc.gov/genomics/gtesting/genetic_counseling.htm).

The National Society of Genetic Counselors details the reasons to see a genetic counselor, including pregnancy and family planning (https://www.aboutgeneticcounselors.org/Reasons-to-See-a-Genetic-Counselor/Pregnancy-and-Family-Planning), cancer (https://www.aboutgeneticcounselors.org/Reasons-to-See-a-Genetic-Counselor/Cancer), childhood conditions (https://www.aboutgeneticcounselors.org/Reasons-to-See-a-Genetic-Counselor/Childhood-Conditions), and at-home genetic testing (https://www.aboutgeneticcounselors.org/Reasons-to-See-a-Genetic-Counselor/At-Home-Genetic-Testing).

6.3 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 health 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 medical 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.
- Coerce a couple about whether or 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 (https://www.aboutgeneticcounselors.org/Prepare-for-an-Appointment/What-Happens-During-an-Appointment), what happens during a prenatal genetic counseling appointment (https://www.aboutgeneticcounselors.org/Reasons-to-See-a-Genetic-Counselor/Pregnancy-and-Family-Planning), and insurance coverage for genetic counseling (https://www.aboutgeneticcounselors.org/Prepare-for-an-Appointment/Insurance-Billing-and-Protecting-Your-Privacy).

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

6.4 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 organizations have tips for finding a healthcare professional:

- The Genetic and Rare Diseases Information Center, a service of the National Institutes of Health, provides a guide to finding specialists in particular genetic and rare conditions.
- The Tuberous Sclerosis Alliance provides advice on finding and choosing a doctor. Although this advice is written for adults with tuberous sclerosis, much of it applies to people with any chronic health condition.

Additional 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. You can search by location, name, area of practice/specialization, and/or ZIP Code.
- The American Board of Genetic Counseling (ABGC) provides a searchable directory of certified genetic counselors worldwide. You can search by practice area, name, organization, or location.
- The Canadian Association of Genetic Counsellors (CAGC) has a searchable directory of genetic counselors in Canada. You can search by name, distance from an address, province, or services.
- The American College of Medical Genetics and Genomics (ACMG) has a searchable database of medical genetics clinic services in the United States.
- The National Cancer Institute provides a Cancer Genetics Services 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.

If you have a health condition that has not been diagnosed, you may be interested in the Undiagnosed Diseases Network. They have information about how to apply for this multicenter research study.

6.5 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)
- When signs and symptoms develop and whether they worsen (and how quickly) or are stable over time
- Quality of life, such as independence in daily activities
- Potential for complications and associated health issues

The prognosis of a genetic condition depends on many factors, including the specific diagnosis and an individual's particular signs and symptoms. Sometimes the associated genetic variant, 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 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. This variability is likely caused by a combination of genetic, environmental, and lifestyle factors, many of which can be difficult to identify.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:

MedlinePlus Genetics provides an additional list of resources that can help you locate a genetics professional (https://medlineplus.gov/genetics/understanding/consult/findingprofessional/) in your area.

A discussion of the prognosis of disorders with a neurological basis (https://www.ninds.n ih.gov/Disorders/All-Disorders) is available from the National Institute of Neurological Disorders and Stroke (NINDS).

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

Local and national support and advocacy groups are also excellent resources for information about specific genetic conditions, including disease prognosis. Patient support resources related to specific genetic conditions can be identified through the Genetic Alliance's Disease InfoSearch (https://www.diseaseinfosearch.org/).

6.6 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 health 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 or genomic 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, sequencing the entire genome may result in locating the responsible genetic variant. Additionally, 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 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:

MedlinePlus Genetics provides additional information about genetic testing (https://medlineplus.gov/genetics/understanding/testing/) (https://medlineplus.gov/genetics/understanding/inheritance/familyhistory/).

The National Center for Biotechnology Information (NCBI) provides an in-depth guide called Understanding Genetics (https://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 (https://www.cdc.gov/ncbddd/birthdefects/diagnosis.html), including information about screening and diagnostic test.

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

GeneReviews (https://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.

The Undiagnosed Diseases Network (https://undiagnosed.hms.harvard.edu/) is a research study that helps people with diseases that have not been diagnosed. They have information about applying to participate (https://undiagnosed.hms.harvard.edu/apply/) in this study.

The Genetic and Rare Diseases Information Center (GARD), a service of the National Institutes of Health, also provides tips for the undiagnosed (https://rarediseases.info.nih.gov/guides/pages/24/tips-for-the-undiagnosed).

6.7 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 make up for the enzyme shortage. These treatments are used to manage existing signs and symptoms and may help prevent future complications. An example of an inborn error of metabolism is phenylketonuria (PKU).

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:

GeneReviews (https://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.

MedlinePlus provides additional information related to the treatment of genetic conditions:

- 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)
- Gene Therapy (https://medlineplus.gov/genetics/understanding/therapy/)
- Precision Medicine (https://medlineplus.gov/genetics/understanding/precisionmedicine/definition/)

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

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)).

7
Genetic Testing

7.1 What is genetic testing?

Genetic testing is a type of medical test that identifies changes in genes, chromosomes, 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 77,000 genetic tests are currently in use, and others are being developed.

Genetic testing involves looking for changes in:

- Genes: Gene tests study DNA sequences to identify variations (mutations) in genes that can cause or increase the risk of a genetic disorder. Gene tests can be narrow or large in scope, analyzing an individual DNA building block (nucleotide), one or more genes, or all of a person's DNA (which is known as their genome).
- Chromosomes: 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.
- Proteins: Biochemical genetic tests study the amount or activity level of proteins or enzymes; 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 Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/) is a service from the National Library of Medicine that provides a searchable database of genetic tests that have submitted by providers and laboratories.

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

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.

7.2 What are the different types of genetic tests?

Many types of genetic tests are available to analyze changes in genes, chromosomes, or proteins. A health care provider will consider several factors when selecting the appropriate test, including what condition or conditions are suspected and the genetic variations typically associated with those conditions. If a diagnosis is unclear, a test that looks at many genes or chromosomes may be used. However, if a specific condition is suspected, a more focused test may be done.

There are several types of genetic tests:

Molecular tests look for changes in one or more genes. These types of tests determine the order ofDNA (Figure 7.1) building blocks (nucleotides) in an individual's genetic code, a process called DNA sequencing. These tests can vary in scope:

- Targeted single variant: Single variant tests look for a specific variant in one gene. The selected variant is known to cause a disorder (for example, the specific variant in the HBB gene that causes sickle cell disease). This type of test is often used to test family members of someone who is known to have a particular variant, to determine whether they have a familial condition. Also, direct-to-consumer genetic testing companies typically analyze a number of specific variants in particular genes (rather than finding all the variants in those genes) when providing health or disease risk information.
- Single gene: Single gene tests look for any genetic changes in one gene. These tests are typically used to confirm (or rule out) a specific diagnosis, particularly when there are many variants in the gene that can cause the suspected condition.
- Gene panel: Panel tests look for variants in more than one gene. This type of test is often used to pinpoint a diagnosis when a person has symptoms that may fit a wide array of conditions, or when the suspected condition can be caused by variants in many genes. (For example, there are hundreds of genetic causes of epilepsy.)
- Whole exome sequencing/whole genome sequencing: These tests analyze the bulk of an individual’s DNA to find genetic variations. Whole exome or whole genome sequencing is typically used when single gene or panel testing has not provided a diagnosis, or when the suspected condition or genetic cause is unclear. Whole exome or whole genome sequencing is often more cost- and time-effective than performing multiple single gene or panel tests.

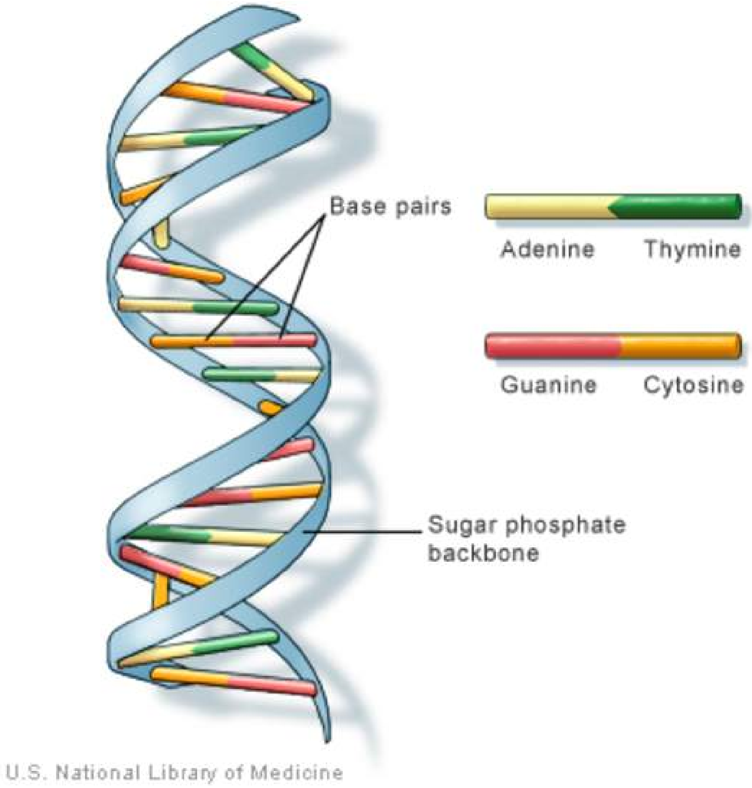

FIGURE 7.1: DNA is made up of base pairs and a sugar phosphate backbone.

Chromosomal tests analyze whole chromosomes or long lengths of DNA to identify large-scale changes. Changes that can be found include an extra or missing copy of a chromosome (trisomy or monosomy, respectively), a large piece of a chromosome that is added (duplicated) or missing (deleted), or rearrangements (translocations) of segments of chromosomes. Certain genetic conditions are associated with specific chromosomal changes, and a chromosomal test can be used when one of these conditions is suspected. (For example, Williams syndrome is caused by a deletion of a section of chromosome 7.)

Gene expression tests look at which genes are turned on or off (expressed) in different types of cells. When a gene is turned on (active), the cell produces a molecule called mRNA from the instructions in the genes, and the mRNA molecule is used as a blueprint to make proteins. Gene expression tests study the mRNA in cells to determine which genes are active. Too much activity (overexpression) or too little activity (underexpression) of certain genes can be suggestive of particular genetic disorders, such as many types of cancer.

Biochemical tests do not directly analyze DNA, but they study the amount or activity level of proteins or enzymes that are produced from genes. Abnormalities in these substances can indicate that there are changes in the DNA that underlie a genetic disorder. (For example, low levels of biotinidase enzyme activity is suggestive of biotinidase deficiency, which is caused by *BTD* gene variants.)

For information about types of genetic testing:

The Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/) is available from the National Center of Biotechnology and Information at the National Library of Medicine. The Genetic Testing Registry is a database of laboratory-submitted genetic tests.

The Centers of Disease Control and Prevention provides a page discussing genetic testing (https://www.cdc.gov/genomics/gtesting/genetic_testing.htm).

The Jackson Laboratory compares different types of genetic tests (https://www.jax.org/education-and-learning/clinical-and-continuing-education/cancer-resources/genetic-testing-technology-comparison).

GeneReviews compares whole genome sequencing, whole exome sequencing, and the sequencing of a selection of individual genes (https://www.ncbi.nlm.nih.gov/books/NBK279899/), particularly their use in the diagnosis of genetic conditions.

7.3 What are the uses of genetic testing?

Genetic testing can provide information about a person's genetic background. The uses of genetic 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. The U. S. Health Services and Resource Administration recommends that states screen for a set of 35 conditions, which many states exceed.

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 (ART) such as in-vitro fertilization (IVF). 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:

Johns Hopkins Medicine provides additional information about genetic carrier screening (https://www.hopkinsmedicine.org/gynecology_obstetrics/specialty_areas/fertility-center/infertility-services/genetic-screening.html).

The Centre for Genetics Education offers an overview of prenatal testing (https://www.genetics.edu.au/SitePages/Prenatal-testing-overview.aspx), as well as fact sheets about preimplantation genetic diagnosis (https://www.genetics.edu.au/SitePages/Preimplantation-genetic-diagnosis.aspx), screening tests during pregnancy, (https://www.genetics.edu.au/SitePages/Screening-tests-during-pregnancy.aspx) and diagnostic tests during pregnancy (https://www.genetics.edu.au/SitePages/Diagnostic-tests-during-pregnancy.aspx).

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).

Baby's First Test (https://www.babysfirsttest.org/newborn-screening/screening-101) offers detailed information about newborn screening.

For information about forensic DNA testing, refer to a page about forensic DNA analysis (https://learn.genetics.utah.edu/content/science/forensics/) from the Genetic Science Learning Center at the University of Utah.

7.4 How is genetic testing done?

Once a person decides to proceed with genetic testing, a health care provider can arrange testing. 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 to understand 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.

Individuals interested in direct-to-consumer genetic testing do not need to go through a health care provider to obtain a test, but they can get it directly from the testing company. After undergoing direct-to-consumer genetic testing, people who test positive for a condition or are found to be at higher risk of developing a disorder are encouraged to follow-up with a genetic counselor or other health care provider.

For more information about genetic testing procedures:

A brief overview of how genetic testing is done (https://www.cancer.gov/about-cancer/causes-prevention/genetics/genetic-testing-fact-sheet#how-is-genetic-testing-done) is also available from The National Cancer Institute.

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

7.5 What is informed consent?

Before a person has a genetic test, it is important to fully understand 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 health care 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 (for example, a blood sample).
- What the test results mean, 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.
- Whether the results can be used for research purposes.
- 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 undergoing testing has had the opportunity to discuss the test with a health care provider.
- 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 their 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 health care provider if the decision has been made to not 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 (https://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/about-genomics/policy-issues/Informed-Consent) and policies and legislation related to informed consent for genetic research studies and testing (https://www.genome.gov/about-genomics/policy-issues/Informed-Consent/Required-Elements-of-Consent-Form).

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

7.6 How can I 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 helpful information about diagnosis, treatment, management, or prevention of a disease.

All laboratories that perform health-related testing for disease prevention, diagnosis, or treatment, 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, particularly those tests that can influence a person's medical care. Additionally, states may require additional information on clinical validity for laboratory tests performed for people living in that state. Test takers, health care 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 genetic tests sold directly to the public. Some providers of direct-to-consumer genetic tests are not CLIA-certified, and many direct-to-consumer genetic tests are not regulated by the FDA, so it can be difficult to tell whether the 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 people make more informed decisions. It may also be helpful to discuss any concerns with a health care provider before ordering a direct-to-consumer genetic test and after receiving test results.

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 (https://www.cdc.gov/genomics/gtesting/ACCE/), including analytical validity, clinical validity, and clinical utility, as part of their ACCE project.

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.

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/index) as well as information on their role in regulating laboratory developed tests (https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf).

7.7 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, health care providers 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 variant, identify an increased risk of developing a disease (such as cancer), 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 care providers typically cannot use a positive test result to predict the course or severity of a condition. Rarely, tests results can be false positive, which occur when results indicate an increased risk for a genetic condition when the person is unaffected.

A negative test result means that the laboratory did not find a change that is known to affect health or development 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 variant, 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, or re-testing at a later date, may be required to confirm a negative result. Rarely, tests results can be false negative, which occur when the results indicate a decreased risk or a genetic condition when the person is actually affected.

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 confirmed to play a role in the development of disease, known as a variant of uncertain significance (VUS or VOUS), it can be difficult to tell whether it is a natural polymorphism or a disease-causing variant. For these variants, there may not be enough scientific research to confirm or refute a disease association or the research may be conflicting. 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 (https://www.cancer.gov/about-cancer/causes-prevention/genetics/genetic-testing-fact-sheet#q6) provides an explanation of positive and negative genetic test results.

The Centers for Disease Control and Prevention (CDC) offers a fact sheet about genetic testing (https://www.cdc.gov/genomics/gtesting/genetic_testing.htm), including an explantion of the types of genetic test results.

7.8 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 $30 to $150 per infant.

From the date that a sample is taken, it may take a few days to weeks 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:

The National Human Genome Research Institute discusses the coverage and reimbursement of genetic tests (https://www.genome.gov/about-genomics/policy-issues/Coverage-Reimbursement-of-Genetic-Tests).

7.9 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 may wish to contact their insurance company before testing to ask about coverage.

Some people may choose not to use their insurance to pay for testing. Instead, they may opt to pay out-of-pocket for the test or pursue direct-to-consumer genetic testing, if available. 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? 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/about-genomics/policy-issues/Coverage-Reimbursement-of-Genetic-Tests).

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.

7.10 What are the benefits of genetic testing?

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

For more information about the benefits of genetic testing:

The Centers for Disease Control and Prevention (CDC) offers a fact sheet about genetic testing (https://www.cdc.gov/genomics/gtesting/genetic_testing.htm).

7.11 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 method that samples cells from the inside surface of the cheek). The procedures used for prenatal diagnostic testing (called amniocentesis and chorionic villus sampling) 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? 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).

7.12 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. 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 detailed discussions of genetic discrimination and current laws that address this issue:

- Genetic Discrimination (https://www.genome.gov/about-genomics/policy-issues/Genetic-Discrimination)
- NHGRI Genome Statute and Legislation Database (https://www.genome.gov/about-genomics/policy-issues/Genome-Statute-Legislation-Database)
- Genetic Information Nondiscrimination Act (GINA) of 2008 (https://www.genome.gov/24519851/genetic-information-nondiscrimination-act-of-2008)

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

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/)

7.13 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 about the Supreme Court case (https://www.scotusblog.com/case-files/cases/association-for-molecular-pathology-v-myriad-genetics-inc/) and ruling 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 (https://www.ama-assn.org/delivering-care/precision-medicine/gene-patenting) 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/about-genomics/policy-issues/Intellectual-Property)

7.14 How are genetic screening tests different from genetic diagnostic tests?

Screening tests evaluate an individual’s risk of developing a genetic condition, while diagnostic tests identify genetic conditions. All genetic tests have both benefits and limitations.

Genetic screening tests are generally used in people who do not have signs or symptoms of a disorder. These tests estimate whether an individual’s risk of having a certain condition is increased or decreased compared with the risk in other people in a similar population. A positive result means that a person’s risk of developing the condition is higher than average. A negative screening test means that a person’s risk is lower than average. However, having a positive screening result does not mean the individual has the condition. Because screening tests are only estimates, in some cases the results indicate an increased risk for a genetic abnormality when the person is actually unaffected (false positive), or the results indicate a decreased risk for a genetic abnormality when the person is really affected (false negative). While genetic screening tests do not provide a conclusive answer, they can help guide next steps, such as whether additional, diagnostic testing is needed.

Genetic diagnostic tests are often used in people who have signs and symptoms. These tests are used to confirm or rule out suspected genetic conditions. Diagnostic tests can also help inform a person’s chance of developing a genetic condition or of passing on a genetic condition to their children. Diagnostic testing can be performed before birth or at any time during a person's life, but it is not available for all genes or all genetic conditions. The results of a diagnostic test can be used to guide a person's choices about health care and the management of the disorder.

Examples of genetic screening tests include:

Noninvasive prenatal testing/screening (NIPT/NIPS): This screening test is performed before birth to help determine the risk that a fetus will be born with certain genetic abnormalities, such as Down syndrome and other chromosomal disorders.

Newborn screening: In the United States, a screening test is performed on all newborns shortly after birth. This test can assess the risk for developing more than 35 genetic conditions. For many of these conditions, the test analyzes various protein and enzyme levels, which would be abnormal in affected individuals.

Examples of genetic diagnostic tests include:

Molecular gene tests: These tests determine the order of DNA building blocks (nucleotides) in an individual's genetic code, a process called DNA sequencing. The purpose of these tests is to identify genetic changes that can cause disease.

Chromosomal tests: These tests analyze whole chromosomes or long lengths of DNA to identify large-scale changes, such as an extra or missing copy of a chromosome (trisomy or monosomy, respectively) or abnormalities of large segments of chromosomes, that underlie certain genetic conditions.

For more information about the difference between screening and diagnostic genetic tests:

The Centers for Disease Control and Prevention (CDC) provides information about genetic testing (https://www.cdc.gov/genomics/gtesting/genetic_testing.htm).

The American Medical Association provides details on genetic testing (https://www.ama-assn.org/delivering-care/precision-medicine/genetic-testing).

Genes In Life discusses diagnostic genetic testing (http://www.genesinlife.org/testing-services/testing-genetic-conditions/diagnostic-testing).

MedlinePlus has additional information on newborn screening (https://medlineplus.gov/newbornscreening.html).

7.15 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 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://wexnermedical.osu.edu/genetics/facts-about-testing).

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

7.16 What are whole exome sequencing and whole genome 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 technique used to test for genetic disorders. Two methods, whole exome sequencing and whole genome sequencing, are increasingly used in healthcare and research to identify genetic variations; both methods rely on new technologies that allow rapid sequencing of large amounts of DNA. These approaches are known as next-generation sequencing (or next-gen sequencing).

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). Next-generation sequencing has 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 in only 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:

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

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

GeneReviews compares whole genome sequencing, whole exome sequencing, and the sequencing of a selection of individual genes (https://www.ncbi.nlm.nih.gov/books/NBK279899/), particularly their use in the diagnosis of genetic conditions.

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

7.17 What are secondary findings from genetic testing?

Secondary findings are genetic test results that provide information about changes (variants) in a gene unrelated to the primary purpose for the testing.

When a clinician orders a genetic test to discover the genetic cause of a particular condition, the test will often sequence one or a few genes that seem most likely to be associated with that individual's set of signs and symptoms. However, if the individual's signs and symptoms do not have an obvious genetic cause, a clinician might order a test that sequences all of the pieces of an individual's DNA that provide instructions for making proteins (called an exome) or a test that sequences all of an individual's DNA building blocks (nucleotides), called a genome. These tests are called whole exome sequencing and whole genome sequencing, respectively.

Many more genetic changes can be identified with whole exome and whole genome sequencing than by sequencing just one or a few genes. Sometimes, testing finds a variant that is associated with a condition other than the one for which testing was originally indicated. This is called a secondary finding. Some individuals with a secondary finding may not yet have any of the symptoms associated with the condition, but may be at risk of developing it later in life. For example, a person with a variant in the *BRCA1*gene, which is associated with an increased risk of breast cancer and ovarian cancer, may not have developed cancer. Other individuals with secondary findings may have a known medical condition, such as extremely high cholesterol, but receive results that indicate a genetic cause for that condition, such as a variant in the *LDLR* gene.

In 2013, then again in 2017 and 2021, the American College of Medical Genetics and Genomics (ACMG) recommended that all labs performing whole exome and whole genome sequencing tests report particular secondary findings, in addition to any variants that are found related to the primary purpose of the testing. In the 2021 updated recommendations, ACMG proposed a list of 73 genes that are associated with a variety of conditions, from cancer to heart disease. The 73 genes for which secondary findings are reported were chosen because they are associated with conditions that have a definable set of clinical features, the possibility of early diagnosis, a reliable clinical genetic test, and effective intervention or treatment. The goal of reporting these secondary findings to an individual is to provide medical benefit by preventing or better managing health conditions. The variants that are reported are known to cause disease. Variants of unknown significance, whose involvement in disease at the current time is unclear, are not reported.

The information provided by secondary findings can be very important because it may help prevent a disease from occurring or guide the management of signs and symptoms if the disease develops or is already present. However, as with any type of medical diagnosis, the news of an unexpected potential health problem may lead to additional health costs and stress for individuals and their families. On the basis of secondary findings, additional testing to confirm results, ongoing screening tests, or preventive care may be advised. Individuals receiving whole exome or whole genome sequencing can choose to “opt out” of analysis of the 73 secondary finding genes and not receive variant results. As whole exome and whole genome sequencing become more common, it is important for individuals to understand what type of information they may learn and how it can impact their medical care.

Scientific journal articles for further reading

Robert C. Green MD, MPH, Jonathan S. Berg MD, PhD, Wayne W. Grody MD, PhD, Sarah S. Kalia ScM, CGC, Bruce R. Korf MD, PhD, Christa L. Martin PhD, FACMG, Amy L. McGuire JD, PhD, Robert L. Nussbaum MD, Julianne M. O’Daniel MS, CGC, Kelly E. Ormond MS, CGC, Heidi L. Rehm PhD, FACMG, Michael S. Watson PhD, FACMG, Marc S. Williams MD, FACMG & Leslie G. Biesecker MD. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013 Jul;15(7):565-74. doi: 10.1038/gim.2013.73. Epub 2013 Jun 20. PubMed: 23788249. Free full-text article from PubMed Central: 3727274.

Sarah S. Kalia ScM, Kathy Adelman, Sherri J. Bale PhD, Wendy K. Chung MD, PhD, Christine Eng MD, James P. Evans MD, PhD, Gail E. Herman MD, PhD, Sophia B. Hufnagel MD, Teri E. Klein PhD, Bruce R. Korf MD, PhD, Kent D. McKelvey MD, Kelly E. Ormond MS, C. Sue Richards PhD, Christopher N. Vlangos PhD, Michael Watson PhD, Christa L. Martin PhD & David T. Miller MD, PhD ; on behalf of the ACMG Secondary Findings Maintenance Working Group. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017 Feb;19(2):249-255. doi: 10.1038/gim.2016.190. Epub 2016 Nov 17. PubMed: 27854360.

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Learn more about secondary genetic findings:

The Columbia University Medical Center has videos giving an Introduction to Secondary Findings (http://www.learninggenetics.org/secondary-findings.html) as well as discussing the Pros and Cons of Secondary Findings (http://www.learninggenetics.org/pros-cons.html) and Decisions about Secondary Findings (http://www.learninggenetics.org/decisions.html).

The American College of Medical Genetics and Genomics provides ACT Sheets (https://www.ncbi.nlm.nih.gov/books/NBK553548/) on secondary findings for mutliple genes, which is available through the NCBI Bookshelf.

MedlinePlus Genetics has information on many of the genetic conditions (https://vsearch.nlm.nih.gov/vivisimo/cgi-bin/query-meta?&v:project=medlineplus&v:sources=medlineplus-bundle&query=secondary%20findings&binning-state=group%3d%3dGenetics%0aalpha%3d%3dGenetic%20Conditions&) and genes (https://vsearch.nlm.nih.gov/vivisimo/cgi-bin/query-meta?&v:project=medlineplus&v:sources=medlineplus-bundle&query=secondary%20findings&binning-state=group%3d%3dGenetics%0aalpha%3d%3dGenes&)that are associated with the 73 ACMG-recommended secondary finding genes.

The U.S. National Library of Medicine provides a list of the ACMG-recommended secondary finding genes and their associated conditions (https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/).

7.18 What is noninvasive prenatal testing (NIPT) and what disorders can it screen for?

Noninvasive prenatal testing (NIPT), sometimes called noninvasive prenatal screening (NIPS), is a method of determining the risk that the fetus will be born with certain genetic abnormalities. This testing analyzes small fragments of DNA that are circulating in a pregnant woman’s blood. Unlike most DNA, which is found inside a cell’s nucleus, these fragments are free-floating and not within cells, and so are called cell-free DNA (cfDNA). These small fragments usually contain fewer than 200 DNA building blocks (base pairs) and arise when cells die off and get broken down and their contents, including DNA, are released into the bloodstream.

During pregnancy, the mother’s bloodstream contains a mix of cfDNA that comes from her cells and cells from the placenta. The placenta is tissue in the uterus that links the fetus and the mother’s blood supply. These cells are shed into the mother’s bloodstream throughout pregnancy. The DNA in placental cells is usually identical to the DNA of the fetus. Analyzing cfDNA from the placenta provides an opportunity for early detection of certain genetic abnormalities without harming the fetus.

NIPT is most often used to look for chromosomal disorders that are caused by the presence of an extra or missing copy (aneuploidy) of a chromosome. NIPT primarily looks for Down syndrome (trisomy 21, caused by an extra chromosome 21), trisomy 18 (caused by an extra chromosome 18), trisomy 13 (caused by an extra chromosome 13), and extra or missing copies of the X chromosome and Y chromosome (the sex chromosomes). The accuracy of the test varies by disorder.

NIPT may include screening for additional chromosomal disorders that are caused by missing (deleted) or copied (duplicated) sections of a chromosome. NIPT is beginning to be used to test for genetic disorders that are caused by changes (variants) in single genes. As technology improves and the cost of genetic testing decreases, researchers expect that NIPT will become available for many more genetic conditions.

NIPT is considered noninvasive because it requires drawing blood only from the pregnant woman and does not pose any risk to the fetus. NIPT is a screening test, which means that it will not give a definitive answer about whether or not a fetus has a genetic condition. The test can only estimate whether the risk of having certain conditions is increased or decreased. In some cases, NIPT results indicate an increased risk for a genetic abnormality when the fetus is actually unaffected (false positive), or the results indicate a decreased risk for a genetic abnormality when the fetus is actually affected (false negative). Because NIPT analyzes both fetal and maternal cfDNA, the test may detect a genetic condition in the mother.

There must be enough fetal cfDNA in the mother’s bloodstream to be able to identify fetal chromosome abnormalities. The proportion of cfDNA in maternal blood that comes from the placenta is known as the fetal fraction. Generally, the fetal fraction must be above 4 percent, which typically occurs around the tenth week of pregnancy. Low fetal fractions can lead to an inability to perform the test or a false negative result. Reasons for low fetal fractions include testing too early in the pregnancy, sampling errors, maternal obesity, and fetal abnormality.

There are multiple NIPT methods to analyze fetal cfDNA. To determine chromosomal aneuploidy, the most common method is to count all cfDNA fragments (both fetal and maternal). If the percentage of cfDNA fragments from each chromosome is as expected, then the fetus has a decreased risk of having a chromosomal condition (negative test result). If the percentage of cfDNA fragments from a particular chromosome is more than expected, then the fetus has an increased likelihood of having a trisomy condition (positive test result). A positive screening result indicates that further testing (called diagnostic testing, because it is used to diagnose a disease) should be performed to confirm the result.

Scientific journal articles for further reading

Committee Opinion No. 640: Cell-Free DNA Screening For Fetal Aneuploidy. Obstet Gynecol. 2015 Sep;126(3):e31-7. doi: 10.1097/AOG.0000000000001051. PubMed: 26287791.

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Goldwaser T, Klugman S. Cell-free DNA for the detection of fetal aneuploidy. Fertil Steril. 2018 Feb;109(2):195-200. doi: 10.1016/j.fertnstert.2017.12.019. PubMed: 29447662.

Gregg AR, Skotko BG, Benkendorf JL, Monaghan KG, Bajaj K, Best RG, Klugman S, Watson MS. Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics. Genet Med. 2016 Oct;18(10):1056-65. doi: 10.1038/gim.2016.97. Epub 2016 Jul 28. PubMed: 27467454.Rose NC, Kaimal AJ, Dugoff L, Norton ME; American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics; Committee on Genetics; Society for Maternal-Fetal Medicine. Screening for Fetal Chromosomal Abnormalities: ACOG Practice Bulletin, Number 226. Obstet Gynecol. 2020 Oct;136(4):e48-e69. doi: 10.1097/AOG.0000000000004084. PubMed: 32804883. Skrzypek H, Hui L. Noninvasive prenatal testing for fetal aneuploidy and single gene disorders. Best Pract Res Clin Obstet Gynaecol. 2017 Jul;42:26-38. doi: 10.1016/j.bpobgyn.2017.02.007. Epub 2017 Feb 28. PubMed: 28342726.

For more information about NIPT:

MedlinePlus Medical Test: Prenatal Cell-Free DNA Screening (https://medlineplus.gov/lab-tests/prenatal-cell-free-dna-screening/)

Genomics Education Programme (UK): What is NIPT? (https://www.genomicseducation.hee.nhs.uk/blog/what-is-nipt/)

National Human Genome Research Institute: Noninvasive Prenatal Genetic Testing (https://www.genome.gov/dna-day/15-ways/noninvasive-prenatal-genetic-testing)

Centre for Genetics Education (Australia): Fact Sheet: Non-Invasive Prenatal Testing (NIPT) (https://www.genetics.edu.au/SitePages/Non-invasive-prenatal-testing.aspx)

National Society of Genetic Counselors: Questions Expectant Mothers Should Ask Before Prenatal Screening (https://www.aboutgeneticcounselors.org/Resources-to-Help-You/Post/questions-expectant-mothers-should-ask-before-prenatal-screening)

Eunice Kennedy Shriver National Institute of Child Health and Human Development: How do Health Care Providers Diagnose Birth Defects? (https://www.nichd.nih.gov/health/topics/birthdefects/conditioninfo/diagnosed)

Genetic Support Foundation: Prenatal Cell-free DNA (cfDNA) Screening (https://www.geneticsupport.org/genetics-pregnancy/prenatal-screening-tests/cell-free-dna-screening/)

7.19 What is circulating tumor DNA and how is it used to diagnose and manage cancer?

Circulating tumor DNA (ctDNA) is found in the bloodstream and refers to DNA that comes from cancerous cells and tumors. Most DNA is inside a cell's nucleus. As a tumor grows, cells die and are replaced by new ones. The dead cells get broken down and their contents, including DNA, are released into the bloodstream. ctDNA are small pieces of DNA, usually comprising fewer than 200 building blocks (nucleotides) in length.

The quantity of ctDNA varies among individuals and depends on the type of tumor, its location, and for cancerous tumors, the cancer stage.

Detection of ctDNA can be helpful in the following cases:

- Detecting and diagnosing a tumor. Because tumor DNA has acquired multiple genetic changes (variants), leading to tumor development, ctDNA is not an exact match to the individual's DNA. Finding DNA with genetic differences aids in tumor detection. Diagnosing the type of tumor using ctDNA can reduce the need for getting a sample of the tumor tissue (tumor biopsy), which can be challenging when a tumor is difficult to access, such as a tumor in the brain or lung.
- Guiding tumor-specific treatment. Analyzing the genome of tumor cells using ctDNA can help doctors determine which treatment will be most effective. Currently, however, approval from the U.S. Food and Drug Administration for ctDNA testing to personalize cancer treatment is limited.
- Monitoring treatment. A decrease in the quantity of ctDNA suggests the tumor is shrinking and treatment is successful.
- Monitoring periods with no symptoms (remission of cancer). A lack of ctDNA in the bloodstream indicates that the cancer has not returned.

Scientists have discovered that dying tumor cells release small pieces of their DNA into the bloodstream. These pieces are called cell-free circulating tumor DNA (ctDNA). (Figure 7.2)

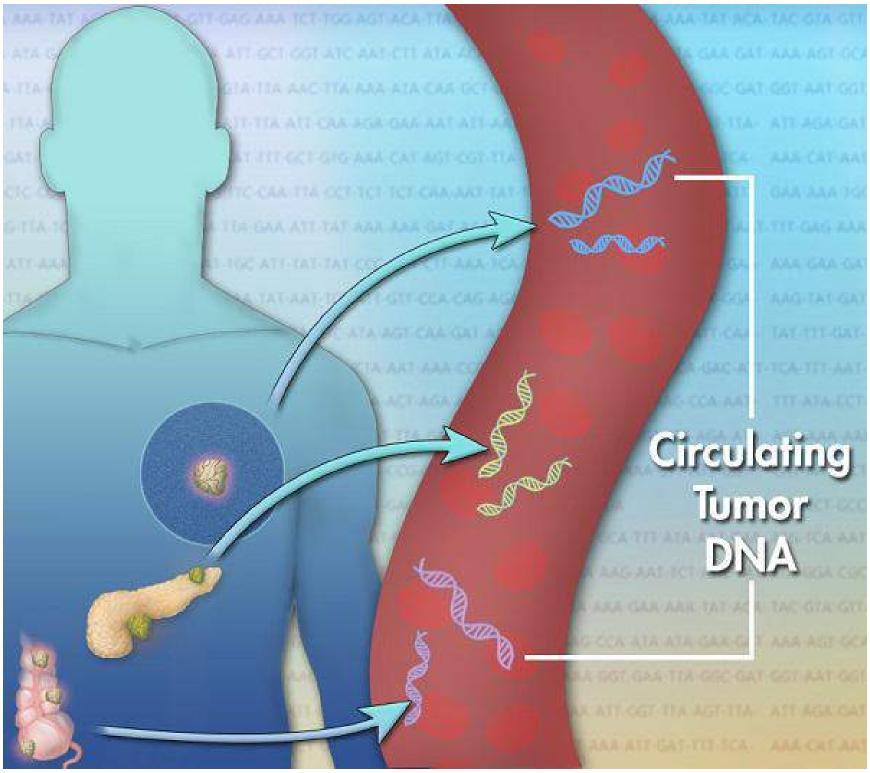


FIGURE 7.2: Illustration of DNA fragments in a blood vessel with arrows indicating the fragments originated from tumors in body organs.

Scientific journal articles for further reading

Merker JD, Oxnard GR, Compton C, Diehn M, Hurley P, Lazar AJ, Lindeman N, Lockwood CM, Rai AJ, Schilsky RL, Tsimberidou AM, Vasalos P, Billman BL, Oliver TK, Bruinooge SS, Hayes DF, Turner NC. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. J Clin Oncol. 2018 Jun 1;36(16):1631-1641. doi: 10.1200/JCO.2017.76.8671. Epub 2018 Mar 5. PubMed: 29504847.

Stewart CM, Kothari PD, Mouliere F, Mair R, Somnay S, Benayed R, Zehir A, Weigelt B, Dawson SJ, Arcila ME, Berger MF, Tsui DW. The value of cell-free DNA for molecular pathology. J Pathol. 2018 Apr;244(5):616-627. doi: 10.1002/path.5048. Epub 2018 Mar 12. PubMed: 29380875.

For more information about ctDNA:

National Human Genome Research Institute: Cancer Genomics (https://www.genome.gov/dna-day/15-ways/cancer-genomics)

PHG Foundation (UK): Circulating Tumour DNA Technology: The Future of Cancer

Management? (https://www.phgfoundation.org/briefing/ctDNA-the-future-of-cancer-management)

8

Direct-to-Consumer Genetic Testing

8.1 What is direct-to-consumer genetic testing?

Most of the time, genetic testing is done through healthcare providers such as physicians, nurse practitioners, or genetic counselors. Healthcare providers determine which test is needed, order the test from a laboratory, collect the DNA sample, send the DNA sample to the lab for testing and interpretation, and share the results with the patient. Often, a health insurance company covers part or all of the cost of testing. This type of testing is known as clinical genetic testing.

Direct-to-consumer genetic testing is different: these genetic tests are marketed directly to customers via television, radio, print advertisements, or the Internet, and the tests can be bought online or in stores. After purchasing a test kit, customers send the company a DNA sample and receive their results directly from a secure website or app or in a written report. Direct-to-consumer genetic testing provides people access to their genetic information without necessarily involving a healthcare provider or health insurance company in the process.

Many companies currently offer direct-to-consumer genetic tests for a variety of purposes. The most popular tests use a limited set of genetic variations to make predictions about a certain aspects of health, provide information about common traits, and offer clues about a person's ancestry. The number of companies providing direct-to-consumer genetic testing is growing, along with the range of health information provided by these tests. Because there is currently little regulation of direct-to-consumer genetic testing services, it is important to assess the quality of available services before pursuing any testing.

Other names for direct-to-consumer genetic testing include DTC genetic testing, direct-access genetic testing, at-home genetic testing, and home DNA testing. Ancestry testing (also called genealogy testing) is also considered a form of direct-to-consumer genetic testing.

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

Centers for Disease Control and Prevention (CDC) Genomics and Health Impact Blog: Direct to Consumer Genetic Testing: Think Before You Spit, 2017 Edition! (https://blogs.cdc.gov/genomics/2017/04/18/direct-to-consumer-2/)

National Human Genome Research Institute: Direct-to-Consumer Genomic Testing (https://www.genome.gov/dna-day/15-ways/direct-to-consumer-genomic-testing)

National Society of Genetic Counselors: What is At-Home Genetic Testing? (https://www.aboutgeneticcounselors.org/Reasons-to-See-a-Genetic-Counselor/At-Home-Genetic-Testing)

American Medical Association: Direct-to-Consumer Genetic Testing (https://www.ama-assn.org/delivering-care/precision-medicine/direct-consumer-genetic-testing)

The Federal Trade Commission: Direct to Consumer Genetic Tests (https://www.consumer.ftc.gov/articles/0166-direct-consumer-genetic-tests)

Genes in Life: Direct-to-Consumer Genetic Testing (http://www.genesinlife.org/testing-services/testing-genetic-conditions/direct-consumer-genetic-testing)

Johns Hopkins Medicine: Five Things to Know about Direct-to-Consumer Genetic Tests (https://www.hopkinsmedicine.org/news/articles/five-things-to-know-about-direct-to-consumer-genetic-tests)

8.2 What kinds of direct-to-consumer genetic tests are available?

With direct-to-consumer genetic testing companies offering a variety of tests, it can be challenging to determine which tests will be most informative and helpful to you. When considering testing, think about what you hope to get out of the test. Some direct-to-consumer genetic tests are very specific (such as paternity tests), while other services provide a broad range of health, ancestry, and lifestyle information.

Major types of direct-to-consumer genetic tests include:

Disease risk and health

The results of these tests estimate your genetic risk of developing several common diseases that are caused by environmental factors and multiple variants in several genes. These common diseases include such as celiac disease, Parkinson's disease, and Alzheimer's disease. Some companies also include a person’s carrier status for less common conditions, including cystic fibrosis and sickle cell disease. A carrier is someone who has a gene variant in one copy of the gene that, when present in both copies of the gene, causes a genetic disorder. The tests may also look for certain genetic variations that could be related to other health-related traits, such as weight and metabolism (how a person’s body converts the nutrients from food into energy). These tests may also provide information about how a person may respond to certain drugs (pharmacogenomics).

Ancestry or genealogy

The results of these tests provide clues about where a person's ancestors might have come from, their ethnicity, and genetic connections between families. For more information, see What is genetic ancestry testing?

Kinship

The results of these tests can indicate whether tested individuals are biologically related to one another. For example, kinship testing can establish whether one person is the biological father of another (paternity testing).

Lifestyle

The results of these tests claim to provide information about lifestyle factors, such as nutrition, fitness, weight loss, skincare, sleep, and even your wine preferences, based on variations in your DNA. Many of the companies that offer this kind of testing also sell services, products, or programs that they customize on the basis of your test results.

Before choosing a direct-to-consumer genetic test, find out what kinds of health, ancestry, or other information will be reported to you. Most direct-to-consumer genetic tests do not sequence whole genes, but look at only a subset of variants within the genes associated with the conditions or traits they report on. For more comprehensive genetic testing, see a genetics professional. Think about whether there is any information you would rather not know. In some cases, you can decline to find out specific information if you tell the company before it delivers your results.

Learn more about the available types of direct-to-consumer genetic testing:

National Society of Genetic Counselors: What is At-Home Genetic Testing? (https://www.aboutgeneticcounselors.org/Reasons-to-See-a-Genetic-Counselor/At-Home-Genetic-Testing)

GeneReviews: Resources for Genetics Professionals--Direct-to-Consumer Genetic Testing (https://www.ncbi.nlm.nih.gov/books/NBK542335/)

Applied & Translational Genomics (free full-text via PubMed Central): Only a click away — DTC genetics for ancestry, health, love…and more: A view of the business and regulatory landscape (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4796702/)

Stanford at the Tech: Kinship Testing (https://genetics.thetech.org/ask-a-geneticist/best-half-sibling-dna-test)

8.3 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 can be used to explore ancestry in the direct male line. Only individuals with a Y chromosome (typically males) can have this type of testing done. However, people interested in this type of genetic testing sometimes recruit a relative to have the test done. Because the Y chromosome is passed on in the same pattern as are family names (surnames) 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 so this type of testing can be used by either sex. Mitochondria DNA is passed on solely from egg cells so 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 testing

These tests evaluate large numbers of individual variations (single nucleotide polymorphisms or SNPs) across a person’s entire genome. The results are compared to similar SNPs in a testing database 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. (Sometimes, more regional specificity can be provided.) 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 ancestral background of an individual.

Genetic ancestry testing has a number of limitations. Test providers compare individuals' test results to different databases of SNPs, so ethnicity estimates may not be consistent from one provider to another. Additionally, these databases do not have equal coverage of SNPs for all ethnic populations; so results for minority populations may be nonspecific or inaccurate. 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 (https://learn.genetics.utah.edu/content/basics/molgen/) on molecular genealogy.

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

The National Human Genome Research Institute discusses human origins and ancestry (https://www.genome.gov/dna-day/15-ways/human-origins-ancestry).

The Tech Museum of Innovation provides information about how ancestry testing works (https://genetics.thetech.org/ask-a-geneticist/how-ancestry-tests-work).

The Smithsonian National Museum of Natural History's exhibit 'Genome: Unlocking Life's Code' discusses the difference between ancestry and race (https://www.unlockinglifescode.org/genomics-insights/ancestry-vs-race-implications-society). The exhibit also discusses the Great Human Migration (https://www.unlockinglifescode.org/genomics-insights/hominid-development-great-human-migration-and-concept-race) and its influence on heredity and genealogy.

8.4 What are the benefits and risks of direct-to-consumer genetic testing?

Direct-to-consumer genetic testing has both benefits and limitations, as they are somewhat different than those of genetic testing ordered by a healthcare provider.

Benefits

- Direct-to-consumer genetic testing promotes awareness of genetic diseases.
- It provides personalized information about your health, disease risk, and other traits.
- It may help you be more proactive about your health.
- It does not require approval from a healthcare provider or health insurance company.
- As results are provided directly to the individual, they are not in your insurance or medical record (unless you share results with your healthcare professional).
- It is often less expensive than genetic testing obtained through a healthcare provider, which can make testing more accessible to people with no or limited health insurance.
- DNA sample collection is usually simple and noninvasive, and results are available quickly.
- Your anonymous data is added to a large database that can be used to further medical research. Depending on the company, the database may represent up to several million participants.

Risks and limitations

- Tests may not be available for the health conditions or traits that interest you.
- This type of testing cannot tell definitively whether you will or will not get a particular disease. Results often need to be confirmed with genetic tests administered by a healthcare professional.
- The tests look only at a subset of variants within genes, so disease-causing variants can be missed.
- Unexpected information that you receive about your health, family relationships, or ancestry may be stressful or upsetting.
- As testing is done outside of a healthcare clinic, individuals often are not provided with genetic counseling or thorough informed consent.
- People may make important decisions about disease treatment or prevention based on inaccurate, incomplete, or misunderstood information from their test results.
- There is currently little oversight or regulation of testing companies.
- Unproven or invalid tests can be misleading. There may not be enough scientific evidence to link a particular genetic variation with a given disease or trait.
- Genetic privacy may be compromised if testing companies use your genetic

information in an unauthorized way or if your data is stolen.

- The results of genetic testing may impact your ability to obtain life, disability, or long-term care insurance.

Direct-to-consumer genetic testing provides only partial information about your health. Other genetic and environmental factors, lifestyle choices, and family medical history also affect the likelihood of developing many disorders. These factors would be discussed during a consultation with a doctor or genetic counselor, but in many cases they are not addressed when using at-home genetic tests.

Learn more about the pros and cons of direct-to-consumer genetic testing:

National Human Genome Research Institute: Direct-to-Consumer Genetic Testing FAQ (https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources/Healthcare-Provider-Direct-to-Consumer-Genetic-Testing-FAQ)

Washington State Department of Health: Purchasing Genetic Testing- Buyers Beware! (https://www.doh.wa.gov/YouandYourFamily/InfantsandChildren/HealthandSafety/GeneticServices/PurchasingGeneticTestingBuyersBeware)

GeneReviews: Resources for Genetics Professionals--Direct-to-Consumer Genetic Testing (https://www.ncbi.nlm.nih.gov/books/NBK542335/#dtc_testing.Advantages)

Yale Medicine: Is an At-Home DNA Test an Ideal Gift, Really? (https://www.yalemedicine.org/stories/at-home-genetic-test-kit-holiday-gift/)

American College of Medical Genetics and Genomics (ACMG): Position statement on direct-to-consumer genetic testing (https://www.acmg.net/docs/ACMG%20Revised%20DTC%20Statement%20AOP%20Dec%202015.pdf)

8.5 How do I choose a direct-to-consumer genetic testing company?

If you are interested in direct-to-consumer genetic testing, do some research into the companies that offer these services. Questions that can help you assess the quality and credibility of a testing company include:

- Does the company's website appear professional? Do they have an app? Are both secure? Does the company provide adequate information about the services it offers, including sample reports, pricing, and methodology?
- Does the company have experienced genetics professionals, such as medical geneticists and genetic counselors, on its staff? Does the company offer consultation with a genetics professional if you have questions about your test results?
- Does the company explain which genetic variations it is testing for? Does it include the scientific evidence linking those variations with a particular disease or trait? Are the limitations of the test and the interpretation of results made clear?
- What kind of laboratory does the genetic testing, and is the laboratory inside or outside the United States? Is the laboratory certified or accredited? For example, does the laboratory meet U.S. federal regulatory standards called the Clinical Laboratory Improvement Amendments (CLIA)? Is the test approved by the U.S. Food and Drug Administration (FDA)?
- Does the company indicate how it will protect your privacy and keep your genetic data safe? Does that information include both current privacy practices and what may happen to your genetic data in the future?
- Does the company indicate who will have access to your data and how it may be shared? Does it share or sell their customers' genetic data for research or other purposes? For some companies, much of their profit comes from selling large amounts of participant data for research and drug development, not from selling individual test kits.

Be sure to read and understand the "fine print" on the company's website before purchasing a direct-to-consumer genetic test. This detailed information, which is often called the "terms of use" or "terms of service," is a legally binding agreement between you and the company providing the testing. It spells out what is included and excluded in the service and details your rights and the company's responsibilities. If you still have questions, contact the company to get more information before you make a decision about testing.

More information about factors to consider when choosing a direct-to-consumer genetic testing company:

Harvard Law Bill of Health Blog: Considering Direct-to-Consumer Genetic Testing? Spit with Caution. (https://blog.petrieflom.law.harvard.edu/2017/12/21/considering-direct-to-consumer-genetic-testing-spit-with-caution/)

National Human Genome Research Institute: Regulation of Genetic Tests (https://www.

genome.gov/about-genomics/policy-issues/Regulation-of-Genetic-Tests)

Personal Genetics Education Project: What is Consumer Genetics? (https://pged.org/direct-to-consumer-genetic-testing/)

8.6 How is direct-to-consumer genetic testing done?

For most types of direct-to-consumer genetic testing, the process involves:

1. Purchasing a test

Test kits can be purchased online (and are shipped to your home) or at a store. The price of some test kits includes the analysis and interpretation, while in other cases this information is purchased separately.

2. Collecting the sample

Collection of the DNA sample usually involves spitting saliva into a tube or swabbing the inside of your cheek and putting that swab into a tube. You then mail the sample as directed by the company. In some cases, you will need to visit a health clinic to have blood drawn.

3. Analyzing the sample

A laboratory will analyze the sample to look for particular genetic variations. The variations included in the test depend on the purpose of the test.

4. Receiving results

In most cases, you will be able to access your results on a secure website or app. (You will likely need to create an account on the testing company website to access results.) Other test companies share results in the mail or over the phone. The results usually include interpretation of what specific genetic variations may mean for your health or ancestry. At some companies, you can request additional explanation from a genetic counselor or other healthcare provider. This additional service may or may not involve an extra cost. Some testing companies may update your results over time based on new scientific information, such as a new genetic variant associated with a trait on their test.

The test kit will include step-by-step instructions, so be sure you understand them before you begin. If you have questions, contact the company before collecting your sample.

Learn more about the direct-to-consumer genetic testing process:

National Society of Genetic Counselors: At-Home Genetic Testing (https://www.aboutgeneticcounselors.org/Reasons-to-See-a-Genetic-Counselor/At-Home-Genetic-Testing)

National Human Genome Research Institute: Direct-to-Consumer Genetic Testing FAQ (https://www.genome.gov/For-Health-Professionals/Provider-Genomics-Education-Resources/Healthcare-Provider-Direct-to-Consumer-Genetic-Testing-FAQ)

8.7 How much does direct-to-consumer genetic testing cost, and is it covered by health insurance?

The price of direct-to-consumer genetic testing ranges from under a hundred dollars to thousands dollars. The cost depends on how many genetic variations are analyzed (and it will cost more if whole genome or whole exome sequencing is used), how extensive the interpretation of results is, and whether other products, programs, or services are included. Some companies charge separately for the sample collection kit and the analysis, while others offer the sample collection and analysis as part of a package. In some cases, consultation with a healthcare professional (such as a genetic counselor) is included in the cost of testing; in others, it can be added for an additional fee. Before you proceed with testing, make sure you know the total cost for all of the results, support, and other services you expect to receive.

Direct-to-consumer genetic tests, even tests that provide information about health and disease risk, are not covered by most health insurance plans. Because this testing is done without a referral from a healthcare provider and is not considered “diagnostic” (that is, it cannot be used to diagnose any disease or condition), health insurance companies generally will not pay for it. However, the tests may be eligible for reimbursement through flexible spending accounts (FSA) or health spending accounts (HSA) if the testing included health information. If you decide to share your results with your healthcare provider and he or she recommends additional testing or management, that follow-up care may be covered by insurance.

Direct-to-consumer genetic tests that are unrelated (or indirectly related) to health, such as ancestry testing and paternity testing, are typically not covered by FSAs, HSAs, or health insurance plans.

Learn more about the costs of direct-to-consumer genetic testing:

MedlinePlus Genetics provides information about:

- What is the cost of genetic testing and how long does it take to get the results? (https://medlineplus.gov/genetics/understanding/testing/costresults/)
- Will health insurance cover the costs of genetic testing? (https://medlineplus.gov/genetics/understanding/testing/insurancecoverage/)

8.8 What do the results of direct-to-consumer genetic testing mean?

Direct-to-consumer genetic testing can provide interesting information about your health, traits, and ancestry. However, the results may not be clear-cut. Companies that provide these tests often tell their customers that the results are for information, education, and research purposes only—they are not meant to diagnose, prevent, or treat any disease or health condition. It is useful to keep this distinction in mind when interpreting your own test results.

Health and disease risk

The results of these genetic tests provide information about your chance of developing certain diseases (such as celiac disease or Parkinson's disease) and the likelihood that you have particular traits (such as dimples or lactose intolerance). These tests may also provide information about how a person may respond to certain drugs (pharmacogenomics). Test results are usually based on an analysis of one or more genetic variations that are known or suspected to be associated with the disease or trait. Direct-to-consumer genetic tests do not look at all genetic variants associated with diseases or traits.

The results of tests to predict disease risk do not provide a “yes or no” answer about whether a person will develop a given disease. Other factors, including genetic variations that were not tested, environmental factors, and lifestyle choices (such as diet and exercise) also contribute to disease risk in ways that may not be fully understood. Therefore, a result showing an increased risk does not mean you will definitely develop the disease, and a result showing a reduced risk does not mean you will never develop the disease.

Ancestry or genealogy

The results of these tests give clues about major geographic areas that are your family’s origins. These results are calculated on the basis of genetic variations that are more common in people from certain areas of the world than in others.

Sometimes the results of ancestry testing are unexpected or inconsistent with what a person understands about his or her family history. People who are closely related, such as siblings, may receive slightly different information about their ancestry because results are limited by the number and diversity of people who have submitted DNA samples to a given direct-to-consumer genetic testing company. It is important to be aware that receiving unexpected or ambiguous information about your background is a potential risk with this type of testing.

Kinship

The results of these tests give information about individuals who are likely related to you.

(These individuals have also undergone testing, and the predictions are based on similarities among DNA sequences.) These tests can uncover previously unknown information about biological relationships among people (such as paternity). It is important to be aware that receiving unexpected or ambiguous information about your background or family is a potential risk with this type of testing.

Lifestyle

In most cases, direct-to-consumer lifestyle tests assess genetic variations related to very specific traits, such as how your body converts the nutrients from food into energy (metabolism), day/night (circadian) rhythm, or the senses of taste and smell. The company may recommend specific diet or fitness programs, dietary supplements, skincare products, or other products and services on the basis of your results. However, in most cases the link between a given genetic variation and a complex trait like weight, athletic performance, or sleep is indirect or unknown. Therefore, the results of these tests can be challenging to interpret, and it can be difficult to predict whether a recommended product or service will be helpful to you.

If you have questions about the meaning of your test results, professional support (such as guidance from a genetic counselor) may be available from the company that provided the test. You can also share questions about your results with your own healthcare provider. Talk to your doctor before making any major changes in managing your health, diet, or fitness after you receive results of a direct-to-consumer genetic test.

Read more about the issues raised by direct-to-consumer genetic test results:

Kaiser Health News: My Grandmother Was Italian. Why Aren’t My Genes Italian? (https://khn.org/news/my-grandmother-was-italian-why-arent-my-genes-italian/)

PLOS DNA Science Blog: DNA Testing Kits as Holiday Gifts Can Bring Surprises (https://dnascience.plos.org/2017/12/14/dna-testing-kits-as-holiday-gifts-can-bring-surprises/)

British Journal of Sports Medicine (free full text from PubMed Central): Direct-to-Consumer Genetic Testing for Predicting Sports Performance and Talent Identification: Consensus Statement (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4680136/)

Stanford at the Tech: Going From DNA to Health Risk (https://genetics.thetech.org/ask-a-geneticist/how-gwas-works)

Stanford at the Tech: Why Can’t a Genetic Test Predict Whether I Will Get Type 2 Diabetes? (https://genetics.thetech.org/ask-a-geneticist/genetic-tests-imprecise-complex-disease)

8.9 What can raw data from a direct-to-consumer genetic test tell me?

In addition to providing various reports and analyses based on your genetics, some direct-to-consumer genetic testing companies make your raw data available to download. The raw data are your genotype—the particular A’s, C’s, T’s, and G’s of your DNA—extracted from the sample you provided. These data are unique to you. Most companies caution that the raw data are only for research or education and are not suitable for medical purposes, such as diagnosing a disease.

It is challenging to interpret raw genotype data on your own. To help with this, several online “third-party interpretation” services offer analysis and interpretation of the raw data collected by another company. Third-party interpretation services can potentially use your genetic data to provide you with more information about your disease risk, traits, and ancestry. However, these services also have some risks and limitations:

- Relatively often, test results indicate an increased risk of disease when your risk is not actually higher than that of the general population. These errors can cause stress and anxiety.
- The results may include unexpected or upsetting information about your disease risk or family relationships without any context or guidance.
- The raw data, once you download it and send it by e-mail or store it on your computer, is no longer protected by the original service’s privacy measures.
- There is little regulation of third-party interpretation services.

As with any kind of genetic testing, it is important to assess the credibility of any company you are considering and find out how it protects your privacy before submitting your genetic information. Your healthcare provider can help you understand your results and determine whether any follow-up testing would be useful.

Learn more about the interpretation of raw genetic data:

KQED/NPR: You Can Transform Your Genetic Ancestry Data Into Health Info, But Your Results May Vary (https://www.kqed.org/science/18728/you-can-transform-your-genetic-ancestry-data-into-health-info-but-your-results-may-vary)

Futurity: Home DNA Tests Put Gene Experts in an Awkward Spot (https://www.futurity.org/home-dna-tests-1695142/)

Stanford at the Tech: Dangers of Converting Ancestry Data Into Health Data (https://genetics.thetech.org/ask-a-geneticist/dangers-converting-ancestry-data-health-data)

8.10 Can a direct-to-consumer genetic test tell me whether I will develop cancer?

While a direct-to-consumer genetic test can estimate your risk, it cannot tell you for certain whether you will or will not develop certain forms of cancer. Many other factors, including sex, age, diet and exercise, ethnic background, a history of previous cancer, hormonal and reproductive factors, and family history also contribute to a person's overall cancer risk.

The U.S. Food and Drug Administration (FDA) has allowed at least one direct-to-consumer genetic testing company, 23andMe, to offer a test for cancer risk. The test identifies specific genetic changes that are associated with particular cancers. For example, it looks for three specific genetic variants (also known as mutations) in two genes: *BRCA1* and *BRCA2*. These variants are associated with an increased risk of breast cancer, ovarian cancer, and potentially other forms of cancer in people of Ashkenazi (eastern European) Jewish ancestry.

Researchers estimate that 5 to 10 percent of all cancers run in families. Some of these cancers are associated with inherited mutations in particular genes, such as *BRCA1* or *BRCA2*. More than 1,000 variants in each of these genes have been associated with an increased risk of cancer. However, the FDA-approved direct-to-consumer genetic test analyzes only three of these genetic changes. The variants included in the test are much more common in people of Ashkenazi Jewish background than in people of other ethnicities, so if you are not of Ashkenazi Jewish heritage, the results may not be useful to you.

The test offered by 23andMe also looks for two variants in the *MUTYH* gene. These variants can cause a condition called MUTYH-associated polyposis (MAP; also known as autosomal recessive familial adenomatous polyposis). MAP greatly increases a person's risk of developing colorectal cancer, but it accounts for less than 1 percent of colorectal cancer cases. The two variants included in the test are the most common MAP-associated changes in people of European descent; however there are more than 100 variants in the *MUTYH* gene known to be associated with an increased risk of developing cancer.

Because the variants included in these tests are uncommon, most people will have a negative result. A negative result does not mean that you will never get cancer. Similarly, a positive result (one that indicates a cancer-related genetic variation) does not mean that you will definitely develop cancer.

Direct-to-consumer genetic testing for cancer risk can be stressful and anxiety-producing. Health professional organizations and patient advocacy groups strongly recommend that people considering genetic testing for cancer-associated gene variants, including those included in direct-to-consumer genetic tests, talk with a genetic counselor about the reasons they want to undergo testing and what the results could mean for their health.

Learn more about direct-to-consumer genetic testing for cancer risk:

U.S. Food and Drug Administration: FDA Authorizes, with Special Controls, Direct-to-Consumer Test that Reports Three Mutations in the BRCA Breast Cancer Genes (https://www.fda.gov/news-events/press-announcements/fda-authorizes-special-controls-direct-consumer-test-reports-three-mutations-brca-breast-cancer)

American Cancer Society: What to Know Before Buying a Home DNA Test (https://www.cancer.org/latest-news/what-to-know-before-buying-a-home-dna-test.html)

American Cancer Society: Should I Get Genetic Testing for Cancer Risk? (https://www.cancer.org/cancer/cancer-causes/genetics/should-i-get-genetic-testing-for-cancer-risk.html)

8.11 Can a direct-to-consumer genetic test tell me whether I will develop Alzheimer's disease?

While a direct-to-consumer genetic test can estimate your risk, it cannot tell you for certain whether you will or will not develop Alzheimer's disease. Variations in multiple genes, together with lifestyle factors such as diet and exercise, all play a role in determining a person’s risk.

The U.S. Food and Drug Administration (FDA) has allowed at least one direct-to-consumer genetic testing company, 23andMe, to offer a test for Alzheimer's disease risk. The test analyzes a gene called *APOE*. Certain variations in this gene are associated with the likelihood of developing late-onset Alzheimer's disease (the most common form of the condition, which begins after age 65). Specifically, the test allows you to find out how many copies (zero, one, or two) you have of a version of the gene called the e4 allele. People who have zero copies of the e4 allele have the same risk of late-onset Alzheimer's disease as the general population. The risk increases with the number of copies of the e4 allele, so people with one copy have an increased chance of developing the disease, and people with two copies have an even greater risk. However, many people who have one or two copies of the e4 allele never develop Alzheimer's disease, and many people with no copies of this allele ultimately get the disease.

Variations in the *APOE* gene are among many factors that influence a person’s overall risk of developing Alzheimer's disease. Variations in many other genes, which are not reported in the FDA-approved direct-to-consumer genetic test, also contribute to disease risk. Additionally, there are risk factors for Alzheimer's disease that have yet to be discovered. Therefore the *APOE* e4 allele represents only one piece of your overall Alzheimer's disease risk.

Currently, there are no effective approaches for preventing Alzheimer's disease, and while the disease can be treated, it has no cure. For these reasons, the National Institute on Aging and patient advocacy groups strongly recommend that people considering genetic testing for Alzheimer's disease, including direct-to-consumer genetic testing, talk with a doctor or genetic counselor about the reasons they want to undergo testing and how they would cope with the results.

Learn more about direct-to-consumer genetic testing for Alzheimer's disease:

U.S. Food and Drug Administration: FDA Allows Marketing of First Direct-to-Consumer Tests that Provide Genetic Risk Information for Certain Conditions (https://www.fda.gov/news-events/press-announcements/fda-allows-marketing-first-direct-consumer-tests-provide-genetic-risk-information-certain-conditions)

National Institute on Aging: Alzheimer’s Disease Genetics Fact Sheet (https://www.nia.nih.gov/health/alzheimers-disease-genetics-fact-sheet#testing)

Alzheimer’s Association: Genetic Testing (https://www.alz.org/media/Documents/alzhei mers-dementia-genetic-testing-ts.pdf)

Alzheimer’s Society (UK): Genetics of Dementia: Genetic Testing (https://www.alzheimers.org.uk/about-dementia/risk-factors-and-prevention/types-genetic-testing)

8.12 What does it mean to have Neanderthal or Denisovan DNA?

Several direct-to-consumer genetic testing companies report how much DNA a person has inherited from prehistoric humans, such as Neanderthals and Denisovans. This information is generally reported as a percentage that suggests how much DNA an individual has inherited from these ancestors. The percentage of Neanderthal DNA in modern humans is zero or close to zero in people from African populations, and is about 1 to 2 percent in people of European or Asian background. The percentage of Denisovan DNA is highest in the Melanesian population (4 to 6 percent), lower in other Southeast Asian and Pacific Islander populations, and very low or undetectable elsewhere in the world.

Neanderthals were very early (archaic) humans who lived in Europe and Western Asia from about 400,000 years ago until they became extinct about 40,000 years ago. Denisovans are another population of early humans who lived in Asia and were distantly related to Neanderthals. (Much less is known about the Denisovans because scientists have uncovered fewer fossils of these ancient people.) The precise way that modern humans, Neanderthals, and Denisovans are related is still under study. However, research has shown that modern humans overlapped with Neanderthal and Denisovan populations for a period, and that they had children together (interbred). As a result, many people living today have a small amount of genetic material from these distant ancestors.

Scientists have sequenced Neanderthal and Denisovan genomes from fossils discovered in Europe and Asia. This genetic information is helping researchers learn more about these early humans. Determining which areas of the genome are shared with archaic humans, and which areas are different, will also help researchers find out what differentiates modern humans from our closest extinct relatives.

In addition to the percentage of Neanderthal or Denisovan DNA, direct to-consumer testing reports may include information about a few genetic variants inherited from these ancestors that influence specific traits. Some studies have suggested that certain genetic variations inherited from archaic humans may play roles in hair texture, height, sensitivity of the sense of smell, immune responses, adaptations to high altitude, and other characteristics in modern humans. These variations may also influence the risk of developing certain diseases. However, other studies have not found the same associations. The significance of Neanderthal or Denisovan genetic variants on disease risk is still an area of active study, and most direct-to-consumer test results currently do not include them.

While knowing how much DNA a person has in common with his or her Neanderthal or Denisovan ancestors may be interesting, these data do not provide practical information about a person’s current health or chances of developing particular diseases. Having more or less DNA in common with archaic humans says nothing about how “evolved” a person is, nor does it give any indication of strength or intelligence. For now, knowing which specific genetic variants a person inherited from Neanderthal or Denisovan ancestors provides only limited information about a few physical traits.

Scientific journal articles for further reading

Meyer M, Kircher M, Gansauge MT, Li H, Racimo F, Mallick S, Schraiber JG, Jay F, Prüfer K, de Filippo C, Sudmant PH, Alkan C, Fu Q, Do R, Rohland N, Tandon A, Siebauer M, Green RE, Bryc K, Briggs AW, Stenzel U, Dabney J, Shendure J, Kitzman J, Hammer MF, Shunkov MV, Derevianko AP, Patterson N, Andrés AM, Eichler EE, Slatkin M, Reich D, Kelso J, Pääbo S. A high-coverage genome sequence from an archaic Denisovan individual. Science. 2012 Oct 12;338(6104):222-6. doi: 10.1126/science.1224344. Epub 2012 Aug 30. PubMed: 22936568; Free full-text article from PubMed Central: PMC3617501.

Pääbo S. The diverse origins of the human gene pool. Nat Rev Genet. 2015 Jun;16(6):313-4. doi: 10.1038/nrg3954. PubMed: 25982166.

Sankararaman S, Mallick S, Dannemann M, Prüfer K, Kelso J, Pääbo S, Patterson N, Reich D. The genomic landscape of Neanderthal ancestry in present-day humans. Nature. 2014 Mar 20;507(7492):354-7. doi: 10.1038/nature12961. Epub 2014 Jan 29. PubMed: 24476815. Free full-text article from PubMed Central: PMC4072735.

Skov L, Coll Macià M, Sveinbjörnsson G, Mafessoni F, Lucotte EA, Einarsdóttir MS, Jonsson H, Halldorsson B, Gudbjartsson DF, Helgason A, Schierup MH, Stefansson K. The nature of Neanderthal introgression revealed by 27,566 Icelandic genomes. Nature. 2020 Jun;582(7810):78-83. doi: 10.1038/s41586-020-2225-9. Epub 2020 Apr 22. PubMed: 32494067.

Learn more about the genetics of Neanderthals and Denisovans:

The Smithsonian's Human Origins Program provides information about the genetics of archaic humans and its relevance to modern humans:

- Homo neanderthalensis (https://humanorigins.si.edu/evidence/human-fossils/species/homo-neanderthalensis)
- Ancient DNA and Neanderthals (https://humanorigins.si.edu/evidence/genetics/ancient-dna-and-neanderthals)

A news release about the complete sequencing of the Neanderthal genome (https://www.genome.gov/27539119/2010-release-complete-neanderthal-genome-sequenced) is available from the National Human Genome Research Institute.

The Max Planck Institute for Evolutionary Anthropology provides information and data about the Denisovan genome (https://www.eva.mpg.de/genetics/genome-projects/denisova/index.html).

8.13 How do direct-to-consumer genetic testing companies protect their customers' privacy?

A person's genetic data represent personal, private health information. If you are considering direct-to-consumer genetic testing, it is important to know how the testing company will protect your information. In particular, you should know how the company will handle your sample (for example, saliva), how it plans to safeguard your data, and whether and how your data will be used for secondary purposes (such as research or advertising).

Most direct-to-consumer genetic testing companies provide detailed information on their websites about their privacy and security practices. This information may be included in a "privacy policy," "privacy statement," or "privacy center." Be sure to read, understand, and agree with this information before you start the testing process. If you have questions, contact the company to get more information.

Questions that can help you assess a company's privacy practices include:

- What does the company do with your sample once it has completed the analysis? Will the sample be stored, shared, sold, or destroyed?
- Once you take the test, who owns your genetic data?
- How does the company safeguard your genetic data and other personal information that you provide? Is it stored in a database that is protected from unauthorized access? What happens if the database is hacked or otherwise compromised?
- Can you delete your results from the company's database if you wish?
- Does the company use your information for internal research, advertising, or other secondary purposes?
- Will the company share your genetic data or sell it to pharmaceutical or biotechnology companies, academic institutions, or nonprofit organizations? If so, will the shared data include other information that could identify you (such as your name or date of birth)? For what purposes will your data be used? Will you be informed when your data are shared or sold?
- If you do not want your genetic data shared, sold, or used for research, can you opt out? What happens if you agree to share your information but want to opt out later?
- Will you be notified in the future if the company changes its privacy policies?
- What would happen to your sample and your genetic information if the company is sold or goes out of business?

In some cases, even if a testing service promises not to share your genetic information with others, they may be required by law to disclose the information to authorities in response to a warrant, court order, or other legal requirement. Many companies now provide explicit information about whether and how your genetic data may be accessed by law enforcement officials. If you upload your data to public databases, such as those administered by some third-party interpretation services, that information will be available to law enforcement. Be sure to read and understand how your data may be accessed by authorities before you submit your sample. Because everyone shares genetic similarities with their relatives, it may have implications not only for your own privacy but for that of people who are related to you.

Scientific journal articles for further reading

Berkman BE, Miller WK, Grady C. Is It Ethical to Use Genealogy Data to Solve Crimes? Ann Intern Med. 2018 May 29. doi: 10.7326/M18-1348. [Epub ahead of print] PubMed: 29809242.

Ram N, Guerrini CJ, McGuire AL. Genealogy databases and the future of criminal investigation. Science. 2018 Jun 8;360(6393):1078-1079. doi:10.1126/science.aau1083. PubMed: 29880677.

Shen H, Ma J. Privacy Challenges of Genomic Big Data. Adv Exp Med Biol. 2017;1028: 139-148. doi: 10.1007/978-981-10-6041-0_8. Review. PubMed: 29058220.

Learn more about privacy issues related to direct-to-consumer genetic testing:

Coalition for Genetic Data Protection: Privacy Best Practices for Consumer Genetic Testing Services (https://fpf.org/wp-content/uploads/2018/07/Privacy-Best-Practices-for-Consumer-Genetic-Testing-Services-FINAL.pdf)

Moffitt Cancer Center: Do DNA Test Kits Put Your Privacy on the Line? (https://moffitt.org/endeavor/archive/do-dna-test-kits-put-your-privacy-on-the-line/)

Harvard Law Bill of Health Blog: Transparency and Direct-to-Consumer Genetic Testing Companies (https://blog.petrieflom.law.harvard.edu/2016/11/22/transparency-and-direct-to-consumer-genetic-testing-companies/)

The Hastings Center: Addressing Questions About DTC Genetic Tests and Privacy (https://www.thehastingscenter.org/addressing-questions-dtc-genetic-tests-privacy/)

Proceedings of the National Academy of Sciences: Study uncovers new privacy worries for direct-to-consumer DNA testing (https://www.pnas.org/post/journal-club/study-uncovers-new-privacy-worries-for-direct-to-consumer-dna-testing)

Personal Genetics Education Project: Genetics, Law Enforcement, and Crime (https://pged.org/genetics-and-crime/)

8.14 Can the results of direct-to-consumer genetic testing affect my ability to get insurance?

Passed in 2008, a federal law called the Genetic Information Nondiscrimination Act (GINA) made it illegal for health insurance providers in the United States to use genetic information in decisions about a person's health insurance eligibility or coverage. This means that health insurance companies cannot use the results of a direct-to-consumer genetic test (or any other genetic test) to deny coverage or require you to pay higher premiums. However, GINA does not apply when an employer has fewer than 15 employees.

GINA does not apply to other forms of insurance, such as disability insurance, long-term care insurance, or life insurance. However, some states have laws that cover these forms of insurance. Unless prohibited by state laws, companies that offer these policies have the right to request medical information, including the results of any genetic testing, when making decisions about coverage and rates. Some of these companies request information about genetic testing as part of their application process, but others do not. It is unclear whether genetic information, including the results of direct-to-consumer genetic testing, will become a standard part of the risk assessment that insurance companies undertake when making coverage decisions.

You should weigh the possible benefits and risks of direct-to-consumer genetic testing, including potential impacts on insurance eligibility and coverage, before you start the testing process.

Learn more about the implications of direct-to-consumer genetic testing in insurance coverage:

National Human Genome Research Institute: Genetic Discrimination (https://www.genome.gov/about-genomics/policy-issues/Genetic-Discrimination)

Genome Statute and Legislation Database (https://www.genome.gov/about-genomics/policy-issues/Genome-Statute-Legislation-Database)

Genetic Alliance: Genetic Discrimination (http://www.geneticalliance.org/advocacy/policyissues/geneticdiscrimination)

Wharton Public Policy Podcast: Why Genetic Testing Is a ‘Perfect Storm’ for Insurers (https://knowledge.wharton.upenn.edu/article/why-genetic-testing-is-a-perfect-storm-for-insurers/)

8.15 Where can I read more about the diseases and traits covered in my direct-to-consumer genetic testing report?

Learn more from MedlinePlus Genetics about some of the health conditions and traits that may be included in your report. Each plain-language summary provides information about the condition's major features, frequency, causes, and inheritance. You will also find links to other reputable sources of online health information.

Health conditions

BRCA1- or *BRCA2*-related breast cancer and ovarian cancer

Familial adenomatous polyposis, including MUTYH-associated polyposis

Age-related macular degeneration

Alpha-1 antitrypsin deficiency

Celiac disease

Familial hypercholesterolemia

Glucose-6-phosphate dehydrogenase deficiency, also called *G6PD* deficiency

Hereditary hemochromatosis

Transthyretin amyloidosis

Hereditary thrombophilia: prothrombin thrombophilia and factor V Leiden thrombophilia

Alzheimer's disease

Parkinson's disease

Wellness

Lactose intolerance

Traits

Cheek dimples

Eye color

Hair texture

Hair color (light or dark hair)

Carrier status

Autosomal recessive spastic ataxia of Charlevoix-Saguenay, also called ARSACS

Andermann syndrome, also called agenesis of the corpus callosum with peripheral neuropathy

Polycystic kidney disease

Beta thalassemia

Bloom syndrome

Canavan disease

PMM2-congenital disorder of glycosylation, also called *PMM2*-CDG

Cystic fibrosis

D-bifunctional protein deficiency

Dihydrolipoamide dehydrogenase deficiency

Familial dysautonomia

Congenital hyperinsulinism, also called familial hyperinsulinism

Familial Mediterranean fever

Fanconi anemia

GRACILE syndrome

Gaucher disease

Glycogen storage disease type I

Hereditary fructose intolerance

Junctional epidermolysis bullosa

Leigh syndrome

Limb-girdle muscular dystrophy

Medium-chain acyl-CoA dehydrogenase deficiency, also called MCAD deficiency

Maple syrup urine disease

Mucolipidosis type IV

CLN5 disease, also called neuronal ceroid lipofuscinosis (*CLN5*-related)

CLN1 disease, also called neuronal ceroid lipofuscinosis (*PPT1*-related)

Niemann-Pick disease

Nijmegen breakage syndrome

Nonsyndromic hearing loss

Pendred syndrome

Phenylketonuria

Primary hyperoxaluria

Pyruvate kinase deficiency

Rhizomelic chondrodysplasia punctata

Sialic acid storage disease, including Salla disease

Sickle cell disease, also called sickle cell anemia

Sjögren-Larsson syndrome

Tay-Sachs disease

Tyrosinemia

Usher syndrome

Zellweger spectrum disorder, also called Zellweger syndrome spectrum

Pharmacogenetics

CYP2C19 drug metabolism

For more help understanding your test results:

MedlinePlus Genetics provides information about:

- How can I find a genetics professional in my area? (https://medlineplus.gov/genetics/understanding/consult/findingprofessional/)
- What happens during a genetic consultation? (https://medlineplus.gov/genetics/understanding/consult/expectations/)

9
Gene Therapy and Other Medical Advances

9.1 What is gene therapy?

Gene therapy is a medical approach that treats or prevents disease by correcting the underlying genetic problem. Gene therapy techniques allow doctors to treat a disorder by altering a person's genetic makeup instead of using drugs or surgery.

The earliest method of gene therapy, often called gene transfer or gene addition, was developed to:

- Introduce a new gene into cells to help fight a disease.
- Introduce a non-faulty copy of a gene to stand in for the altered copy causing disease.

Later studies led to advances in gene therapy techniques. A newer technique, called genome editing (an example of which is CRISPR-Cas9), uses a different approach to correct genetic differences. Instead of introducing new genetic material into cells, genome editing introduces molecular tools to change the existing DNA in the cell. Genome editing is being studied to:

- Fix a genetic alteration underlying a disorder, so the gene can function properly.
- Turn on a gene to help fight a disease.
- Turn off a gene that is functioning improperly.
- Remove a piece of DNA that is impairing gene function and causing disease.

Gene therapies are being used to treat a small number of diseases, including an eye disorder called Leber congenital amaurosis and a muscle disorder called spinal muscular atrophy. Many more gene therapies are undergoing research to make sure that they will be safe and effective. Genome editing is a promising technique also under study that doctors hope to use soon to treat disorders in people.

For general information about gene therapy:

MedlinePlus offers a list of links to information about genes and gene therapy (https://medlineplus.gov/genesandgenetherapy.html).

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

The Centre for Genetics Education provides an introduction to gene therapy and other therapeutics (https://www.genetics.edu.au/SitePages/Gene-therapy-advanced-therapeutics.aspx), including a discussion of ethical and safety considerations.

The National Heart, Lung, and Blood Institute describes the approaches to gene therapy and how they work (https://www.nhlbi.nih.gov/health-topics/genetic-therapies).

Your Genome from the Wellcome Genome Campus provides an introduction to gene therapy and describes several techniques (https://www.yourgenome.org/facts/what-is-gene-therapy).

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

9.2 How does gene therapy work?

Gene therapy works by altering the genetic code to recover the functions of critical proteins. Proteins are the workhorses of the cell and the structural basis of the body’s tissues. The instructions for making proteins are carried in a person’s genetic code, and variants (or mutations) in this code can impact the production or function of proteins that may be critical to how the body works. Fixing or compensating for disease-causing genetic changes may recover the role of these important proteins and allow the body to function as expected.

Gene therapy can compensate for genetic alterations in a couple different ways.

- Gene transfer therapy introduces new genetic material into cells. If an altered gene causes a necessary protein to be faulty or missing, gene transfer therapy can introduce a normal copy of the gene to recover the function of the protein. Alternatively, the therapy can introduce a different gene that provides instructions for a protein that helps the cell function normally, despite the genetic alteration.
- Genome editing is a newer technique that may potentially be used for gene therapy. Instead of adding new genetic material, genome editing introduces gene-editing tools that can change the existing DNA in the cell. Genome editing technologies allow genetic material to be added, removed, or altered at precise locations in the genome. CRISPR-Cas9 is a well-known type of genome editing.

Genetic material or gene-editing tools that are inserted directly into a cell usually do not function. Instead, a carrier called a vector is genetically engineered to carry and deliver the material. Certain viruses are used as vectors because they can deliver the material 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. Viruses can also deliver the gene-editing tools to the nucleus of the cell.

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 or the editing molecules will correct a DNA error and restore protein function.

Gene therapy with viral vectors has been successful, but it does carry some risk. Sometimes the virus triggers a dangerous immune response. In addition, vectors that integrate the genetic material into a chromosome can cause errors that lead to cancer. Researchers are developing newer technologies that can deliver genetic material or gene-editing tools without using viruses. One such technique uses special structures called nanoparticles as vectors to deliver the genetic material or gene-editing components into cells. Nanoparticles are incredibly small structures that have been developed for many uses. For gene therapy, these tiny particles are designed with specific characteristics to target them to particular cell types. Nanoparticles are less likely to cause immune reactions than viral vectors, and they are easier to design and modify for specific purposes.

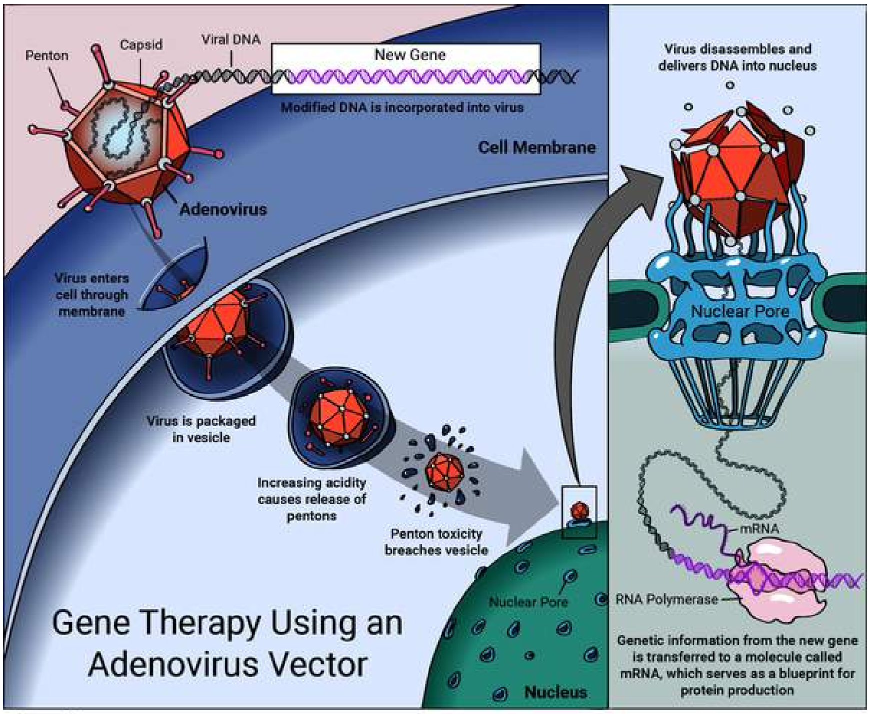
Researchers continue to work to overcome the many technical challenges of gene therapy. For example, scientists are finding better ways to deliver genes or gene-editing tools and target them to particular cells. They are also working to more precisely control when the treatment is functional in the body.

Scientific journal articles for further reading

Bulcha JT, Wang Y, Ma H, Tai PWL, Gao G. Viral vector platforms within the gene therapy landscape. Signal Transduct Target Ther. 2021 Feb 8;6(1):53. doi: 10.1038/s41392-021-00487-6. PMID: 33558455. Free full-text article from PubMed Central: PMC7868676.

Duan L, Ouyang K, Xu X, Xu L, Wen C, Zhou X, Qin Z, Xu Z, Sun W, Liang Y. Nanoparticle Delivery of CRISPR/Cas9 for Genome Editing. Front Genet. 2021 May 12; 12:673286. doi: 10.3389/fgene.2021.673286. PubMed: 34054927. Free full-text article from PubMed Central: PMC8149999.

A new gene is inserted directly into a cell. A carrier called a vector is genetically engineered to deliver the gene. An adenovirus introduces the DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome. (Figure 9.1)



NIH U.S. National Library of Medicine

FIGURE 9.1: A new gene is inserted directly into a cell. A carrier called a vector is genetically engineered to deliver the gene. An adenovirus introduces the DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome.

For more information about how gene therapy works:

Boston Children’s Hospital summarizes the evolution of gene therapy techniques (https://answers.childrenshospital.org/gene-therapy-history/).

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 (https://learn.genetics.utah.edu/content/genetherapy/tools/). They also discuss other approaches to gene therapy (https://learn.genetics.utah.edu/content/genetherapy/approaches/) and offer a related learning activity called Space Doctor (https://learn.genetics.utah.edu/content/genetherapy/doctor/).

The American Society of Gene and Cell Therapy offers an in-depth description of the different types of viral vectors used in gene therapy (https://patienteducation.asgct.org/gene-therapy-101/vectors-101).

Penn Medicine's OncoLink describes how gene therapy works and how it is administered to patients (https://www.oncolink.org/cancer-treatment/immunotherapy/what-is-gene-therapy).

The basics of nanoparticles and their use in medicine (https://askabiologist.asu.edu/tiny-medicine) are explained in the Ask a Biologist feature from Arizona State University.

Your Genome from the Wellcome Genome campus explains the first gene therapy trial to treat a condition called severe combined immunodeficiency (SCID) (https://www.yourgenome.org/stories/treating-the-bubble-babies-gene-therapy-in-use). It also describes other applications for gene therapy.

9.3 Is gene therapy safe?

The first gene therapy trial was run more than thirty years ago. The earliest studies showed that gene therapy could have very serious health risks, such as toxicity, inflammation, and cancer. Since then, researchers have studied the mechanisms and developed improved techniques that are less likely to cause dangerous immune reactions or cancer. Because gene therapy techniques are relatively new, some risks may be unpredictable; however, medical researchers, institutions, and regulatory agencies are working to ensure that gene therapy research, clinical trials, and approved treatments are 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 a RAC public meeting.

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.

The clinical trial process occurs in three phases. Phase I studies determine if a treatment is safe for people and identify its side effects. Phase II studies determine if the treatment is effective, meaning whether it works. Phase III studies compare the new treatment to the current treatments available. Doctors want to know whether the new treatment works better or has fewer side effects than the standard treatment. The FDA reviews the results of the clinical trial. If it determines that the benefits of the new treatment outweigh the side effects, it approves the therapy, and doctors can use it to treat a disorder.

Successful clinical trials have led to the approval of a small number of gene therapies, including therapies to treat inherited disorders like spinal muscular atrophy and Leber congenital amaurosis.

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

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

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

9.4 What are the ethical issues surrounding gene therapy?

Because gene therapy involves making changes to the body's basic building blocks (DNA), it raises many unique ethical concerns. The ethical questions surrounding gene therapy and genome editing include:

- How can "good" and "bad" uses of these technologies 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 research on gene therapy treatment has focused on targeting body (somatic) cells such as bone marrow or blood cells. This type of genetic alteration cannot be passed to a person's children. Gene therapy could be targeted to egg and sperm cells (germ cells), however, which would allow the genetic changes to be passed to future generations. This approach is known as germline gene therapy.

The idea of these germline alterations 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 the ethical concerns of genome editing (https://www.genome.gov/about-genomics/policy-issues/Genome-Editing/ethical-concerns).

A debate of the ethics of germline gene therapy (https://www.yourgenome.org/debates/is-germline-gene-therapy-ethical) is presented by yourgenome.org from the Wellcome Genome Campus.

A discussion of the ethics of gene therapy and genetic engineering (https://medicine.missouri.edu/centers-institutes-labs/health-ethics/faq/gene-therapy) is available from the University of Missouri Center for Health Ethics.

9.5 Is gene therapy available to treat my disorder?

Gene therapy is currently available primarily in a research setting. The U.S. Food and Drug Administration (FDA) has approved only a small number of gene therapy products for sale in the United States. For example, FDA-approved gene therapies are available for conditions that include a rare eye disorder called Leber congenital amaurosis, a form of skin cancer known as melanoma, and a genetic muscle condition called spinal muscular atrophy. Other genetic therapies have been approved for blood cell cancers such as lymphoma and multiple myeloma. Gene therapies to treat additional conditions have been approved in other countries.

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.

For information about gene therapy clinical trials:

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 about clinical trials. You can search for a specific clinical trial or browse by health condition or sponsor. You may wish to refer to a list of gene therapy clinical trials (https://clinicaltrials.gov/search?term=%22gene+therapy%22) or gene or genome editing clinical trials (https://clinicaltrials.gov/ct2/results?cond=&term=%22gene+editing%22+OR+%22genome+editing%22) that are accepting (or will accept) participants.

An explanation of the clinical trial process and how to find a clinical trial is presented by the American Society of Gene and Cell Therapy (https://patienteducation.asgct.org/gene-therapy-101/clinical-trials-process).

9.6 What are CAR T cell therapy, RNA therapy, and other genetic therapies?

Several treatments have been developed that involve genetic material but are typically not considered gene therapy. Some of these methods alter DNA for a slightly different use than gene therapy. Others do not alter genes themselves, but they change whether or how a gene's instructions are carried out to make proteins.

Cell-based gene therapy

CAR T cell therapy (or chimeric antigen receptor T cell therapy) is an example of cell-based gene therapy. This type of treatment combines the technologies of gene therapy and cell therapy. Cell therapy introduces cells to the body that have a particular function to help treat a disease. In cell-based gene therapy, the cells have been genetically altered to give them the special function. CAR T cell therapy introduces a gene to a person's T cells, which are a type of immune cell. This gene provides instructions for making a protein, called the chimeric antigen receptor (CAR), that attaches to cancer cells. The modified immune cells can specifically attack cancer cells.

RNA therapy

Several techniques, called RNA therapies, use pieces of RNA, which is a type of genetic material similar to DNA, to help treat a disorder. In many of these techniques, the pieces of RNA interact with a molecule called messenger RNA (or mRNA for short). In cells, mRNA uses the information in genes to create a blueprint for making proteins. By interacting with mRNA, these therapies influence how much protein is produced from a gene, which can compensate for the effects of a genetic alteration. Examples of these RNA therapies include antisense oligonucleotide (ASO), small interfering RNA (siRNA), and microRNA (miRNA) therapies. An RNA therapy called RNA aptamer therapy introduces small pieces of RNA that attach directly to proteins to alter their function.

Epigenetic therapy

Another gene-related therapy, called epigenetic therapy, affects epigenetic changes in cells. Epigenetic changes are specific modifications (often called "tags") attached to DNA that control whether genes are turned on or off. Abnormal patterns of epigenetic modifications alter gene activity and, subsequently, protein production. Epigenetic therapies are used to correct epigenetic errors that underlie genetic disorders.

Scientific journal articles for further reading

Kim YK. RNA Therapy: Current Status and Future Potential. Chonnam Med J. 2020 May;56(2):87-93. doi: 10.4068/cmj.2020.56.2.87. Epub 2020 May 25. PubMed: 32509554. Free full-text article from PubMed Central: PMC7250668.

Lu Y, Chan YT, Tan HY, Li S, Wang N, Feng Y. Epigenetic regulation in human cancer: the potential role of epi-drug in cancer therapy. Mol Cancer. 2020 Apr 27;19(1):79. doi: 10.1186/s12943-020-01197-3. 32340605. Free full-text article from PubMed Central:

PMC7184703.

9.7 What are mRNA vaccines and how do they work?

Vaccines help prevent infection by preparing the body to fight foreign invaders (such as bacteria, viruses, or other pathogens). All vaccines introduce into the body a harmless piece of a particular bacteria or virus, triggering an immune response. Most vaccines contain a weakened or dead bacteria or virus. However, scientists have developed a new type of vaccine that uses a molecule called messenger RNA (mRNA) rather than part of an actual bacteria or virus. Messenger RNA is a type of RNA that is necessary for protein production. Once cells finish making a protein, they quickly break down the mRNA. mRNA from vaccines does not enter the nucleus and does not alter DNA.

mRNA vaccines work by introducing a piece of mRNA that corresponds to a viral protein, usually a small piece of a protein found on the virus's outer membrane. (Individuals who get an mRNA vaccine are not exposed to the virus, nor can they become infected with the virus by the vaccine.) By using this mRNA, cells can produce the viral protein. As part of a normal immune response, the immune system recognizes that the protein is foreign and produces specialized proteins called antibodies. Antibodies help protect the body against infection by recognizing individual viruses or other pathogens, attaching to them, and marking the pathogens for destruction. Once produced, antibodies remain in the body, even after the body has rid itself of the pathogen, so that the immune system can quickly respond if exposed again. If a person is exposed to a virus after receiving mRNA vaccination for it, antibodies can quickly recognize it, attach to it, and mark it for destruction before it can cause serious illness.

Like all vaccines in the United States, mRNA vaccines require authorization or approval from the Food and Drug Administration (FDA) before they can be used. Currently vaccines for COVID-19, the disease caused by the SARS-CoV-2 coronavirus, are the only authorized or approved mRNA vaccines. These vaccines use mRNA that directs cells to produce copies of a protein on the outside of the coronavirus known as the " spike protein". Researchers are studying how mRNA might be used to develop vaccines for additional diseases.

Scientific journal articles for further reading

Jain S, Venkataraman A, Wechsler ME, Peppas NA. Messenger RNA-based vaccines: Past, present, and future directions in the context of the COVID-19 pandemic. Adv Drug Deliv Rev. 2021 Oct 9;179:114000. doi: 10.1016/j.addr.2021.114000. Epub ahead of print. PMID: 34637846; PMCID: PMC8502079.

Verbeke R, Lentacker I, De Smedt SC, Dewitte H. The dawn of mRNA vaccines: The COVID-19 case. J Control Release. 2021 May 10;333:511-520. doi: 10.1016/j.jconrel.2021.03.043. Epub 2021 Mar 30. PMID: 33798667; PMCID: PMC8008785.

Microscopic image of SARS-CoV-2, the virus that causes COVID-19. Spike proteins are seen surrounding the outer membrane of each virus particle. (Figure 9.2)

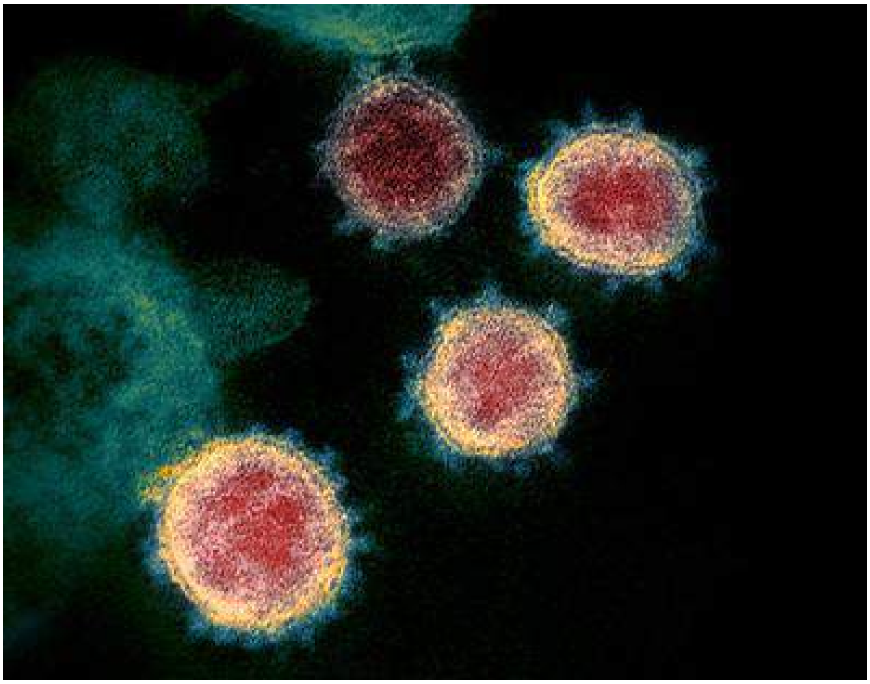


FIGURE 9.2: Microscopic image of four SARS-CoV-2 virus particles, the virus that causes COVID-19. Spike proteins are seen surrounding the outer membrane of each virus particle.

For more information about mRNA vaccines:

MedlinePlus offers many additional resources with information about mRNA vaccines, specifically relating to their use in COVID-19

- MedlinePlus: Health Topic: COVID-19 Vaccines (https://medlineplus.gov/covid19vaccines.html)
- MedlinePlus: Encyclopedia: COVID-19 vaccines (https://medlineplus.gov/ency/article/007775.htm)
- MedlinePlus: Drugs and Supplements: COVID-19 Vaccine, mRNA (Pfizer-BioNTech) (https://medlineplus.gov/druginfo/meds/a621003.html)
- MedlinePlus: Drugs and Supplements: COVID-19 Vaccine, mRNA (Moderna) (https://medlineplus.gov/druginfo/meds/a621002.html)

The National Institute of Allergy and Infectious Diseases provides in-depth information (https://www.niaid.nih.gov/diseases-conditions/coronavirus-vaccines-prevention) about the COVID-19 vaccines.

The Centers for Disease Control and Prevention has a fact sheet (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mRNA.html) on mRNA vaccines.

10

Genomic Research

10.1 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 almost once in every 1, 000 nucleotides on average, which means there are roughly 4 to 5 million SNPs in a person's genome. These variations occur in many individuals; to be classified as a SNP, a variant is found in at least 1 percent of the population. Scientists have found more than 600 million SNPs in populations around the world.

Most commonly, SNPs 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. SNPs help predict an individual’s response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing diseases. SNPs can also be used to track the inheritance of disease-associated genetic variants within families. Research is ongoing 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/genetics-glossary/Single-Nucleotide-Polymorphisms) is available from the National Human Genome Research Institute’s Talking Glossary of Genetic Terms.

How scientists locate SNPs in the genome (https://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, the National Library of Medicine maintains a frequently updated resource at NCBI of a database of single nucleotide polymorphisms (dbSNP) (https://www.ncbi.nlm.nih.gov/SNP/)

10.2 What are genome-wide association studies?

Genome-wide association studies (GWAS) help scientists identify genes associated with a particular disease (or another trait). This method studies the entire set of DNA (the genome) of a large group of people, searching for small variations, called single nucleotide polymorphisms or SNPs (pronounced “snips”). Each study can look at hundreds or thousands of SNPs at the same time. Scientists can then identify SNPs that occur more frequently in people with a certain disease than in people without it. These SNPs are said to be associated with the disease, and they can help researchers pinpoint genes that are likely involved in disease development. 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 identified SNPs associated with several complex conditions including diabetes, heart disease, Parkinson's disease, and Crohn's disease. SNPs have also been associated with a person’s response to certain drugs and susceptibility to certain environmental factors such as toxins. Researchers hope that future genome-wide association studies will identify additional SNPs associated with chronic diseases and drug effects.

Through genome-wide association studies, individual SNPs are identified that account for only a small percentage of disease risk. Together, large numbers of SNPs across the genome can help determine the overall risk of developing a disease or responding to particular drugs. Researchers can use information learned from genome-wide association studies to predict more accurately which prevention and treatment strategies will work in which groups of people, an important step in precision medicine.

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/about-genomics/fact-sheets/Genome-Wide-Association-Studies-Fact-Sheet). In addition, the National Human Genome Research Institute and the European Bioinformatics Institute jointly provide a Catalog of Published Genome-Wide Association Studies (https://www.ebi.ac.uk/gwas/).

ClinicalTrials.gov (https://clinicaltrials.gov/), a service of the National Institutes of Health, provides easy access to information about clinical trials. This site offers the option to search for a specific clinical trial or browse by health condition or sponsor. They also provide 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 more technical information, the NCBI’s Database of Genotypes and Phenotypes (dbGaP) (https://www.ncbi.nlm.nih.gov/gap/) contains data from genome-wide association studies.

10.3 What is pharmacogenomics?

Pharmacogenomics is the study of how genes affect a person’s response to drugs. This field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications that can be prescribed based on 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.

Researchers are learning how variants 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 which dose will help prevent adverse drug reactions. Conditions that affect a person’s response to certain drugs include clopidogrel resistance, warfarin sensitivity, warfarin resistance, malignant hyperthermia, Stevens-Johnson syndrome/toxic epidermal necrolysis, and thiopurine S-methyltransferase deficiency.

The field of pharmacogenomics is growing, and new approaches are under study in clinical trials. In the future, pharmacogenomics will be used to develop tailored drugs to treat a wide range of health problems, including cardiovascular disease, Alzheimer's disease, cancer, and asthma.

For more information about pharmacogenomics:

MedlinePlus provides additional details about pharmacogenetic tests (https://medlineplus.gov/lab-tests/pharmacogenetic-tests/).

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

A pharmacogenomics fact sheet (https://www.genome.gov/dna-day/15-ways/pharmacogenomics) and a list of Frequently Asked Questions about Pharmacogenomics (https://www.genome.gov/FAQ/Pharmacogenomics) is offered by the National Human Genome Research Institute.

Medical Genetics Summaries (https://www.ncbi.nlm.nih.gov/books/NBK61999/), provided by the National Center for Biotechnology Information at the National Library of Medicine, provides information about specific genetic variants and how they can impact drug responses.

Additional information about pharmacogenetics is available from the Centre for Genetics Education (https://www.genetics.edu.au/SitePages/Pharmacogenomics.aspx) as well as Genes In Life (http://www.genesinlife.org/testing-services/testing-genetic-conditions/pha rmacogenomic-testing).

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.

10.4 What are genome editing and CRISPR-Cas9?

Genome editing (also called gene editing) is a group of technologies that give scientists the ability to change an organism's DNA. These technologies allow genetic material to be added, removed, or altered at particular locations in the genome. Several approaches to genome editing have been developed. A well-known one is called CRISPR-Cas9, which is short for clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9. The CRISPR-Cas9 system has generated a lot of excitement in the scientific community because it is faster, cheaper, more accurate, and more efficient than other genome editing methods.

CRISPR-Cas9 was adapted from a naturally occurring genome editing system that bacteria use as an immune defense. When infected with viruses, bacteria capture small pieces of the viruses' DNA and insert them into their own DNA in a particular pattern to create segments known as CRISPR arrays. The CRISPR arrays allow the bacteria to " remember" the viruses (or closely related ones). If the viruses attack again, the bacteria produce RNA segments from the CRISPR arrays that recognize and attach to specific regions of the viruses' DNA. The bacteria then use Cas9 or a similar enzyme to cut the DNA apart, which disables the virus.

Researchers adapted this immune defense system to edit DNA. They create a small piece of RNA with a short "guide" sequence that attaches (binds) to a specific target sequence in a cell's DNA, much like the RNA segments bacteria produce from the CRISPR array. This guide RNA also attaches to the Cas9 enzyme. When introduced into cells, the guide RNA recognizes the intended DNA sequence, and the Cas9 enzyme cuts the DNA at the targeted location, mirroring the process in bacteria. Although Cas9 is the enzyme that is used most often, other enzymes (for example Cpf1) can also be used. Once the DNA is cut, researchers use the cell's own DNA repair machinery to add or delete pieces of genetic material, or to make changes to the DNA by replacing an existing segment with a customized DNA sequence.

Genome editing is of great interest in the prevention and treatment of human diseases. Currently, genome editing is used in cells and animal models in research labs to understand diseases. Scientists are still working to determine whether this approach is safe and effective for use in people. It is being explored in research and clinical trials for a wide variety of diseases, including single-gene disorders such as cystic fibrosis, hemophilia, and sickle cell disease. It also holds promise for the treatment and prevention of more complex diseases, such as cancer, heart disease, mental illness, and human immunodeficiency virus (HIV) infection.

Ethical concerns arise when genome editing, using technologies such as CRISPR-Cas9, is used to alter human genomes. Most of the changes introduced with genome editing are limited to somatic cells, which are cells other than egg and sperm cells (germline cells). These changes are isolated to only certain tissues and are not passed from one generation to the next. However, changes made to genes in egg or sperm cells or to the genes of an embryo could be passed to future generations. Germline cell and embryo genome editing bring up a number of ethical challenges, including whether it would be permissible to use this technology to enhance normal human traits (such as height or intelligence). Based on concerns about ethics and safety, germline cell and embryo genome editing are currently illegal in the United States and many other countries.

Scientific journal articles for further reading

Ormond KE(1), Mortlock DP(2), Scholes DT(3), Bombard Y(4), Brody LC(5), Faucett WA(6), Garrison NA(7), Hercher L(8), Isasi R(9), Middleton A(10), Musunuru K(11), Shriner D(12), Virani A(13), Young CE(3). Human Germline Genome Editing. Am J Hum Genet. 2017 Aug 3;101(2):167-176. PubMed: 28777929. Free full-text available from PubMed Central: PMC5544380.

Gupta RM, Musunuru K. Expanding the genetic editing tool kit: ZFNs, TALENs, and CRISPR-Cas9. J Clin Invest. 2014 Oct;124(10):4154-61. doi: 10.1172/JCI72992. Epub 2014 Oct 1. Review. PubMed: 25271723. Free full-text available from PubMed Central: PMC4191047.

Hsu PD, Lander ES, Zhang F. Development and applications of CRISPR-Cas9 for genome engineering. Cell. 2014 Jun 5;157(6):1262-78. doi:10.1016/j.cell.2014.05.010. Review. PubMed: 24906146. Free full-text available from PubMed Central: PMC4343198.

Komor AC, Badran AH, Liu DR. CRISPR-Based Technologies for the Manipulation of Eukaryotic Genomes. Cell. 2017 Apr 20;169(3):559. doi:10.1016/j.cell.2017.04.005. PubMed: 28431253.

For more information about CRISPR-Cas9 and other genome editing technologies:

The National Human Genome Research Institute has a series of fact sheets about genome editing:

- Overview of genome editing (https://www.genome.gov/about-genomics/policy-issues/what-is-Genome-Editing)
- How does genome editing work? (https://www.genome.gov/about-genomics/policy-issues/Genome-Editing/How-genome-editing-works)
- How is genome editing used? (https://www.genome.gov/about-genomics/policy-issues/Genome-Editing/How-genome-editing-is-used)
- What are the ethical concerns about genome editing? (https://www.genome.gov/about-genomics/policy-issues/Genome-Editing/ethical-concerns)
- What do people think about genome editing? (https://www.genome.gov/about-genomics/policy-issues/Genome-Editing/public-opinion)
- What’s happening in genome editing right now? (https://www.genome.gov/about-genomics/policy-issues/Genome-Editing/happening-right-now)

Questions and answers about CRISPR (https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/questions-and-answers-about-crispr) are available from the

Broad Institute.

The Personal Genetics Education Project has a fact sheet, Genetic Modification, Genome Editing, and CRISPR (https://pged.org/genetic-modification-genome-editing-and-crispr/), that provides an introduction to genome editing.

Yourgenome.org (from the Wellcome Genome Campus) provides information for the public about CRISPR-Cas9 (https://www.yourgenome.org/facts/what-is-crispr-cas9).

A video illustrating how CRISPR-Cas9 works (https://www.youtube.com/watch?v=2pp17E4E-O8) is available from the McGovern Institute for Brain Research at MIT.

ClinicalTrials.gov has a list of human studies using genome editing (https://clinicaltrials.gov/ct2/results?cond=&term=CRISPR+OR+genome+editing+OR+gene+editing) related to various diseases.

11

Precision Medicine

11.1 What is precision medicine?

According to the Precision Medicine Initiative, 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 and healthcare in coming years.

Learn more about precision medicine:

Information is available about precision medicine (https://obamawhitehouse.archives.gov/blog/2015/01/30/precision-medicine-initiative-data-driven-treatments-unique-your-own-body) as data-driven treatment.

Information about precision medicine and Genetics Home Reference, the former home of MedlinePlus Genetics content, 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 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4917728/)."(Available through PubMed Central)

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

Information about precision medicine (https://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 (https://www.cancer.org/latest-news/personalized-medicine-redefining-cancer-and-its-treatment.html).

11.2 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 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 are 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 (https://www.ncbi.nlm.nih.gov/books/NBK91503/) provides a detailed overview of precision medicine, including the reasoning behind the Council’s preference for the term "precision medicine" over "personalized medicine."

The National Human Genome Research Institute (NHGRI) has information on Frequently Asked Questions about pharmacogenomics (https://www.genome.gov/FAQ/Pharmacogenomics).

11.3 What is the Precision Medicine Initiative?

The Precision Medicine Initiative is a long-term research endeavor, involving the National Institutes of Health (NIH) and multiple other research centers, which aims to understand how a person's genetics, environment, and lifestyle can help determine the best approach to prevent or treat disease.

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 National Cancer Institute (NCI) hope to use an increased knowledge of the genetics and biology of cancer to find new, more effective treatments for various forms of this 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 has launched a study, known as the All of Us Research Program, which involves a group (cohort) of at least 1 million volunteers from around the United States. Participants are providing genetic data, biological samples, and other information about their health. To encourage open data sharing, participants can access their health information, as well as research that uses their data, during the study. Researchers can use these data 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 the All of Us Research Program (https://allofus.nih.gov/) provides information about the goals of and participants in the Precision Medicine Initiative. A visual overview of the program partners (https://allofus.nih.gov/funding-and-program-partners) is also available. 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 (https://www.cancer.gov/news-events/cancer-currents-blog/2015/precision-medicine-initiative-2016).

A fact sheet on President Obama’s Precision Medicine Initiative (https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative) explains the project's plans and objectives.

Dr. Francis Collins, former director of the NIH, and Dr. Harold Varmus, former director of the NCI, wrote more about their vision for the Precision Medicine Initiative (https://www.nejm.org/doi/full/10.1056/NEJMp1500523) in the New England Journal of Medicine.

11.4 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 All of Us Research Program continues 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 patients' 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, former director of the NIH, and Dr. Harold Varmus, former director of the NCI, wrote about their vision for the Precision Medicine Initiative (https://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.

Examples are available of how precision medicine is helping Americans (https://obama whitehouse.archives.gov/blog/2015/01/29/precision-medicine-already-working-cure-americans-these-are-their-stories). Other examples are available from the Genetic Science Learning Center at the University of Utah (learn.genetics.utah.edu/content/precision/action/).

Data about participants of the All of Us Research Program can be viewed on their Research Hub (https://www.researchallofus.org/).

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

Precision medicine is a growing field. Many of the technologies that are needed to meet the goals of the Precision Medicine Initiative have only recently been developed. For example, researchers needed to standardize the collection of clinic and hospital data from more than 1 million volunteers around the country. They also needed databases to store large amounts of patient data efficiently.

The Precision Medicine Initiative also raises ethical, social, and legal issues. It is critical to protect participants' privacy and the confidentiality of their personal and health information. Participants need to understand the risks and benefits of participating in research, which means researchers must have a rigorous process of informed consent.

Cost is also an issue with precision medicine. The Precision Medicine Initiative itself will cost many millions of dollars in federal funding, and the ongoing initiative will require Congress to approve funding over multiple years. Technologies such as sequencing large amounts of DNA are expensive to carry out (although the cost of sequencing is decreasing). Additionally, drugs that are developed to treat conditions based on molecular or genetic variations 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 need to interpret the results of genetic tests, 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.

HealthIT.gov describes the technology needs for Precision Medicine Initiative (//https://www.healthit.gov/buzz-blog/precision-medicine/health-it-advances-precision-medicine) and advances that have been made.

The Precision Medicine Initiative has information about its Privacy and Trust Principles (https://allofus.nih.gov/protecting-data-and-privacy/precision-medicine-initiative-privacy-and-trust-principles) and Data Security Policy Principles and Framework (https://allofus.nih.gov/protecting-data-and-privacy/precision-medicine-initiative-data-security-policy-principles-and-framework-overview).