Genetics Home Reference

Your Guide to Understanding Genetic Conditions

Handbook

Help Me Understand Genetics

Mutations and Genetic Disorders

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Chapter 2

Mutations and Genetic Disorders

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What is a gene mutation and how do mutations occur?

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

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

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

For more information about mutations:

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

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

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

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

How can gene mutations cause disorders?

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

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

For more information about mutations and genetic disorders:

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

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

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

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

Do all gene mutations cause disorders?

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

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

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

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

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

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

What kinds of gene mutations are possible?

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

Missense mutation (illustration on page 7)

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

Nonsense mutation (illustration on page 8)

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

Insertion (illustration on page 8)

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

Deletion (illustration on page 9)

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

Duplication (illustration on page 9)

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

Frameshift mutation (illustration on page 10)

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

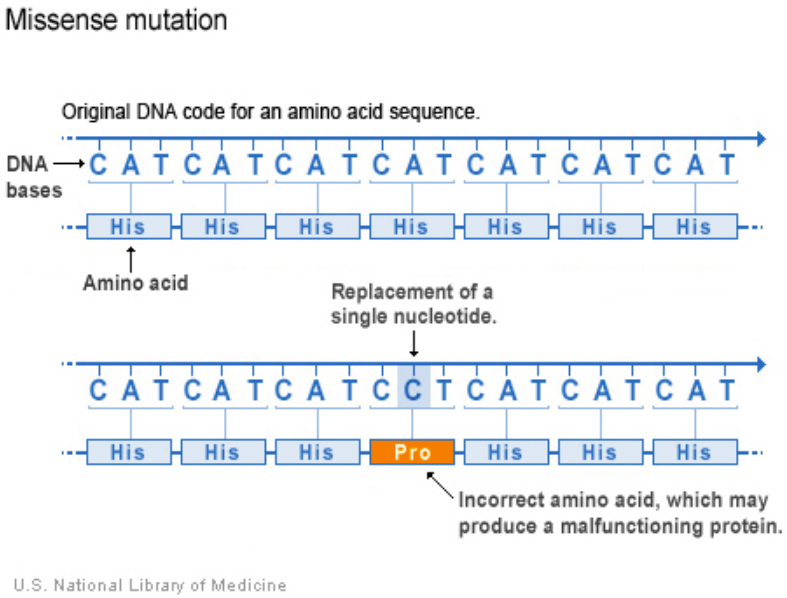
Repeat expansion (illustration on page 10)

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

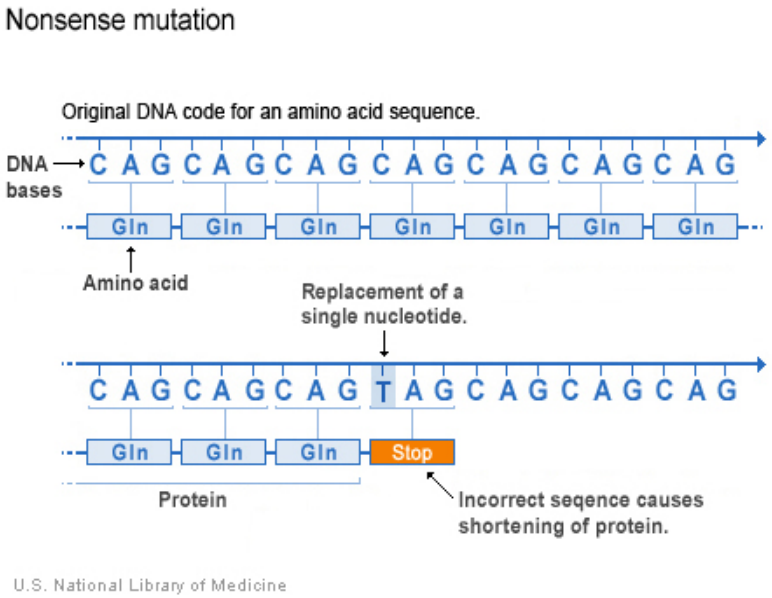
For more information about the types of gene mutations:

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

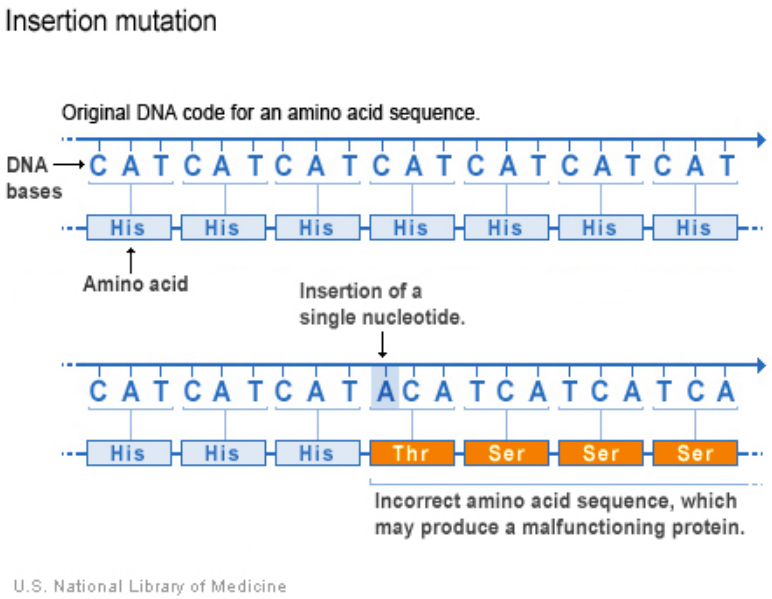
Illustrations: Types of gene mutations



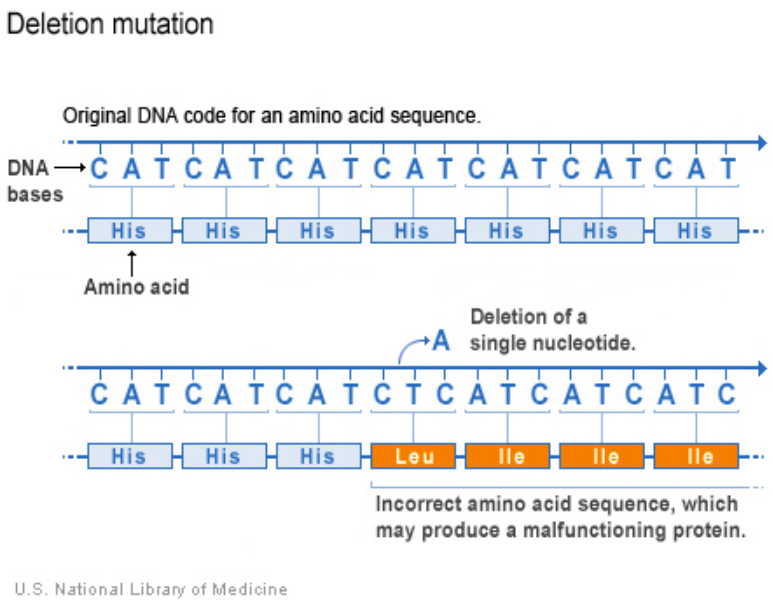
In this example, the nucleotide adenine is replaced by cytosine in the genetic code, introducing an incorrect amino acid into the protein sequence.



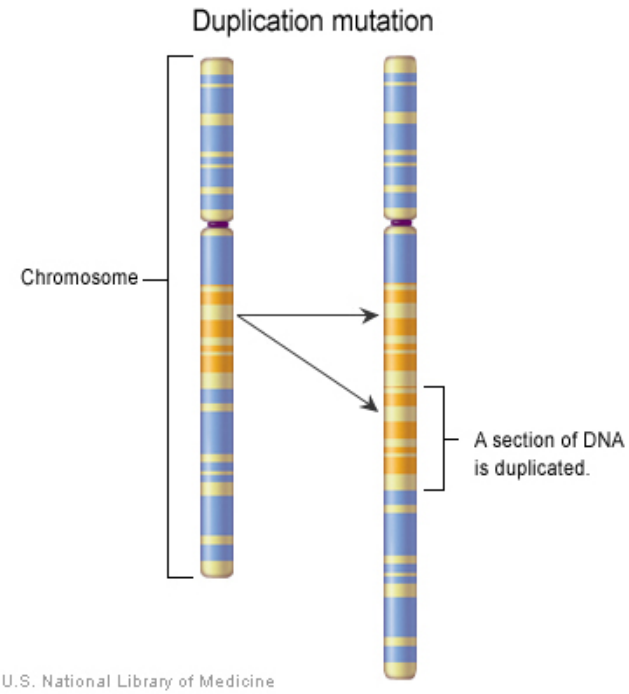
In this example, the nucleotide cytosine is replaced by thymine in the DNA code, signaling the cell to shorten the protein.



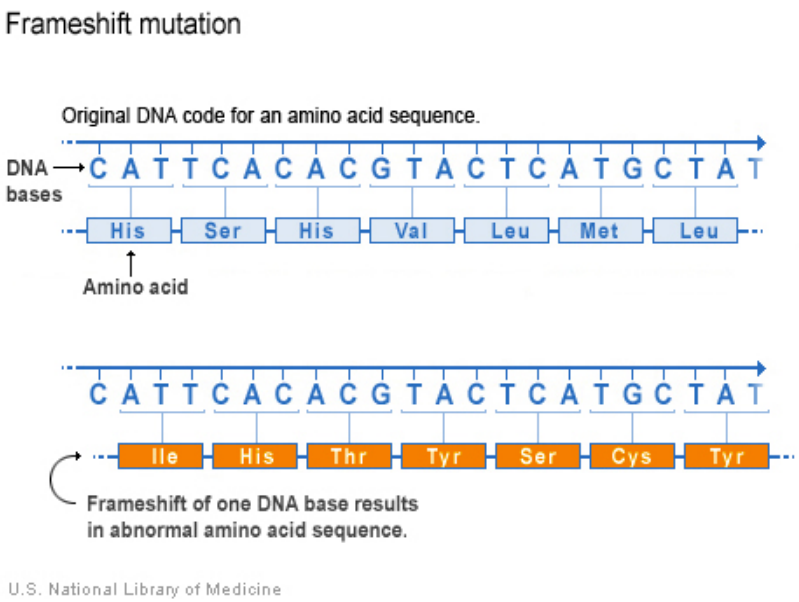
In this example, one nucleotide (adenine) is added in the DNA code, changing the amino acid sequence that follows.



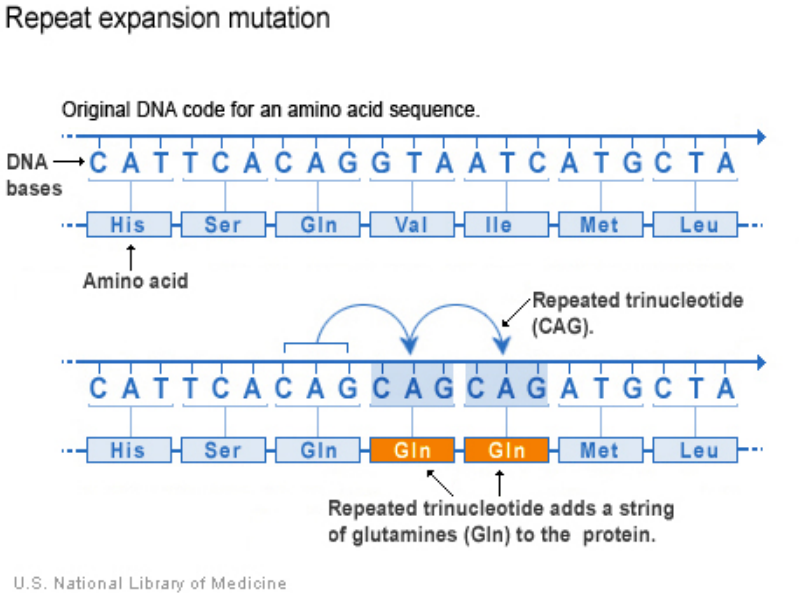
In this example, one nucleotide (adenine) is deleted from the DNA code, changing the amino acid sequence that follows.



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



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



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

Can changes in chromosomes cause disorders?

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

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

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

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

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

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

For more information about chromosomal disorders:

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

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

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

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

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

What are complex or multifactorial disorders?

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

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

For more information about complex disorders:

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

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

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

What information about a genetic condition can statistics provide?

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

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

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

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

For more information about interpreting statistics:

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

How are genetic conditions and genes named?

Naming genetic conditions

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

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

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

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

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

Naming genes

The HUGO Gene Nomenclature Committee (http://www.gene.ucl.ac.uk/nomenclature/) (HGNC) designates an official name and symbol (an abbreviation of

the name) for each known human gene. Some official gene names include additional information in parentheses, such as related genetic conditions, subtypes of a condition, or inheritance pattern. The HGNC is a non-profit organization funded by the U.K. Medical Research Council and the U.S. National Institutes of Health. The Committee has named more than 13,000 of the estimated 30,000 to 40,000 genes in the human genome.

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

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

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