

Gene therapy: what to know

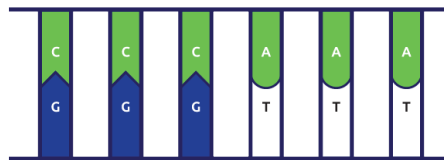
The purpose of this site is to provide information to patients and caregivers about the field of gene therapy, which is being investigated for hemophilia.

About genetic disease

Understanding genetic disease

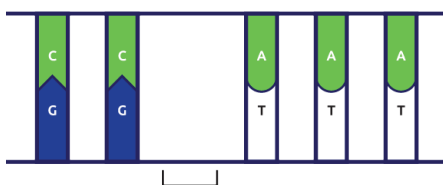
The human body is composed of trillions of cells. Cells are the basic building blocks of all living things. The command center of each cell is called the nucleus, and it contains chromosomes. Chromosomes are made up of DNA (deoxyribonucleic acid)—the body's hereditary material.

Genes are segments (pieces) of DNA. They contain instructions for making proteins. Genes are inherited (passed down) from parent to child, half from the mother and half from the father.

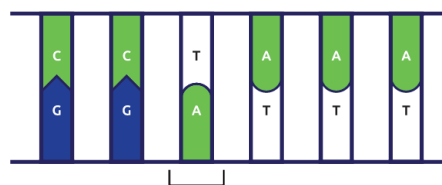


DNA has its own alphabet: A, C, G, T. The letters stand for the 4 nucleotides, which are the building blocks of DNA. Unique combinations of adenine (A), cytosine (C), guanine (G), and thymine (T) make up all of the genes in the body.

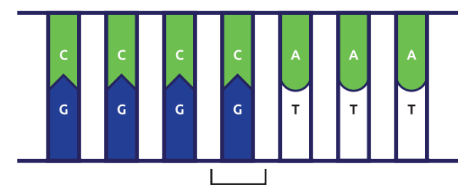
A gene mutation is a change in the sequence of DNA that makes up a gene. There are different types of gene mutations including:



Deletion: A segment of or a complete gene is deleted or lost from a chromosome



Substitution: A segment of a gene is replaced with a different segment



Duplication: A segment of a gene is repeated, resulting in multiple copies of that genetic information

Mutations can be passed from parent to child or be acquired (occurring randomly or caused by exposure to something in the environment). Some gene mutations are harmless, but others can result in a genetic disease.

NEXT LEVEL

How gene mutations can cause genetic disease

Genes contain instructions for making proteins, the large, complex molecules that do most of the work in cells. Proteins are responsible for building, regulating, and maintaining the body. For example, proteins build bones, allow muscles to move, control blood clotting, and make antibodies so our bodies can fight infections.

Gene mutations can cause:

- A protein to malfunction or stop working altogether
- No protein to be made at all

When a protein is missing or not working properly, the function in the body that protein controls will be affected, resulting in a genetic disease.

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Genes and hemophilia

Hemophilia is a rare genetic bleeding disorder that causes a delay in clot formation.

In hemophilia, there is a mutation in the gene that contains the body's instructions for creating one of several important blood-clotting proteins called "factors."



- Hemophilia A, or factor VIII deficiency, affects 1 in 5,000 males
- Hemophilia B, or factor IX deficiency, affects 1 in 25,000 males

Hemophilia is most often inherited, meaning it's passed down through a mutation in the parents' genes or DNA. However, in one-third of cases, hemophilia is caused by a new or spontaneous mutation. Because of how hemophilia is passed from parents to a child, it primarily affects men. However, in rare cases, women can have hemophilia too.

Hemophilia severity is classified based on a person's factor level in the blood:

- Mild (5% to 40%)
- Moderate (1% to 5%)
- Severe (less than 1%)

Individuals with hemophilia may bleed spontaneously (without a known cause) or due to injury, inside or outside of the body, and longer than those without hemophilia. Common sites of internal bleeding are joints and muscles; bleeding in these locations can lead to joint damage and arthritis. External bleeding may also occur, including nose bleeds, prolonged bleeding from minor cuts and dental work, and unexplained bruising.

What is gene therapy?

Introduction to gene therapy research

Gene therapy is a potential approach to treating or preventing genetic diseases. The goal of gene therapy is to address a genetic disease at its source—the gene. This can be done by modifying (changing) genes or creating new genes in a laboratory and delivering them to specific cells in the body.

What is gene therapy?

NEXT LEVEL

History of gene therapy research

Scientists have been investigating and evolving gene therapy for more than 50 years. To date, more than 2,300 gene therapy clinical trials are planned, ongoing, or have been completed for different genetic diseases.



What is gene therapy?

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Types of gene therapy being studied

Researchers are investigating potential gene therapy approaches that may be used to treat or prevent genetic diseases by:

- Replacing a healthy copy of a mutated gene that causes disease
- Introducing an entirely new gene (created in a laboratory) into the body
- Inactivating, or “knocking out,” a mutated gene that is functioning improperly

What is gene therapy meant to do?

Gene therapy step by step

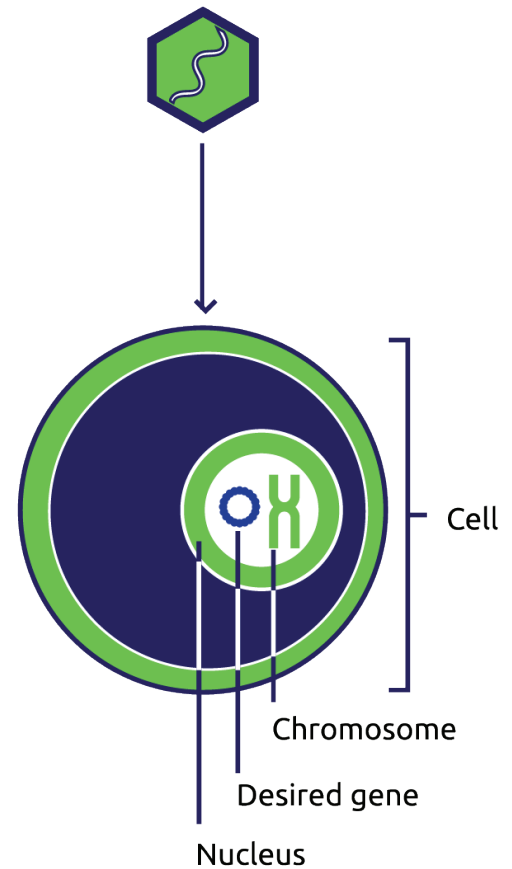
First, a healthy replacement gene is placed in a delivery vehicle, called a vector. This step occurs outside of the body. Then, the vector is inserted into the body and carries the healthy gene into specific cells where it is needed.

Viruses are commonly used as vectors because of their natural ability to enter specific cells in the body. Viruses used as vectors, or viral vectors, are modified (changed) before use in gene therapy. Once the virus is modified to be used as a vector, it is intended to transport the replacement gene to target cells without causing disease.

The viral vector can then carry and deliver the healthy gene into targeted cells. When the healthy gene is delivered to the cell, it is released from the viral vector with the goal of replacing a mutated gene, introducing a new gene, or “knocking out” a mutated gene.

If transferred successfully, the healthy gene is intended to:

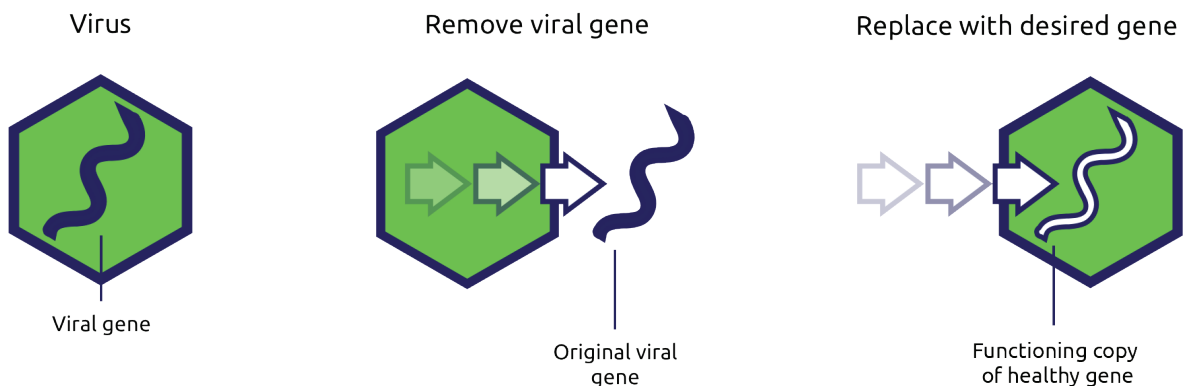
- Provide the correct instructions for the cell to make a functioning protein or stop producing a harmful protein
- Reduce the harmful effects of a genetic disease or even make it go away altogether



What is gene therapy meant to do?

NEXT LEVEL

Viral vectors



Many factors are considered when determining which viruses should be modified for use as a vector to deliver a healthy gene in gene therapy research. An ideal vector for use in gene therapy research should be able to do the following:

- Target a specific type of cell and deliver a gene into it
- Protect the gene from getting broken down in the body before it reaches the target cell
- Have the right effect with low risk of causing an immune response (the body’s reaction to what it recognizes as a foreign invader)
 - Immune responses can result in short- and long-term consequences, including the viral vector and the gene it’s carrying being attacked before the replacement gene is delivered to the target cells

Introducing viral vectors into the body

To deliver a healthy gene to targeted cells, a viral vector may be administered to the body intravenously (by IV) or by injection into specific tissues. Other procedures, such as surgery, can be used to deliver vectors into specific areas of the body.

What is gene therapy meant to do?

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Types of viral vectors

Several types of viruses are used by researchers to create viral vectors for potential gene therapy. Different viruses are being developed as vectors because each of them can enter different types of cells, express genes (make the desired protein) at different levels, and interact with the immune system in different ways.

Some of the most common viral vectors used in gene therapy research are lentiviruses (LVs), adenoviruses (AVs), and adeno-associated viruses (AAVs).

The type of viral vector used depends on the following:

- Size of the gene it can carry
- Ability to bind (attach) to and enter specific types of cells
- Ability to allow the delivered healthy gene to exist independently of a person's own DNA
- Potential for causing an immune response in the body

Integrating vs nonintegrating viral vectors

An integrating vector permanently inserts a new, healthy copy of a gene into a cell where a mutation had caused the previously existing gene to not work properly. Once in the cell, the healthy gene is inserted (or integrated) into the native (original) DNA in the cell. That means that once the healthy gene is inserted, it will be passed on to new cells when the cell divides. Integrating viral vectors are preferred for cell types that divide frequently, ensuring that the healthy gene isn't lost during cell division.

Nonintegrating viral vectors deliver a healthy copy of a mutated gene into targeted cells, but the healthy gene does not get inserted into the native DNA and instead remains episomally (separate from the native DNA). By existing independently of the cell's native DNA, the healthy gene is not passed on to new cells when the cell divides. Nonintegrating vectors are ideal for cell types, such as liver cells, that divide slowly, infrequently, or not at all.

Potential risks of modifying DNA in human cells

There are potential risks to investigational gene therapy. Some of these potential risks include:

- Unintended immune system reaction
 - The body's immune system may recognize the viral vector as foreign and attack it. This could cause inflammation and, in severe cases, organ failure
- Affecting unintended cells
 - Viruses can affect more than one type of cell; therefore, it is possible the viral vector may infect different cells than those that were intended/targeted. If this happens, healthy cells may be damaged, causing other illnesses or diseases, such as cancer

Potential risks of modifying DNA in human cells (continued)

- Viral infection
 - It is possible that once introduced to the body, viruses may recover their original ability to cause disease
- Causing a tumor
 - If the new gene is unintentionally integrated into a different place in the DNA, there is a chance that the insertion might lead to tumor formation

To ensure patient safety concerns are a top priority during research, investigational clinical trials of gene therapy conducted in the United States are closely monitored by the Food and Drug Administration and the National Institutes of Health.

What is the potential of gene therapy?

Genetic diseases that may be treated using a gene therapy approach

Gene therapy has the potential to treat many diseases, including some that are caused in part or in full by gene mutations. Some of these diseases include:



**Blood-clotting diseases,
such as hemophilia**



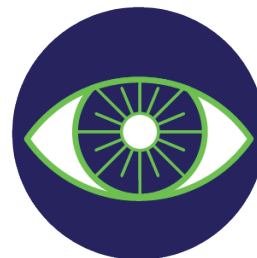
Cardiovascular diseases



Infectious diseases



Neurodegenerative diseases



Vision disorders

Gene therapy research for hemophilia

Gene therapy research for hemophilia seeks to replace the mutated gene that is causing a clotting factor deficiency with a new, healthy gene. The healthy gene would be delivered to liver cells, allowing the body to begin making clotting factor.

There are two forms of gene therapy currently being investigated for hemophilia:

- Gene transfer with vector AAV, or adeno-associated virus, to deliver a healthy and functioning new gene
- Genome editing, to change, remove, or add new DNA to the cell's native (built-in) DNA

The pioneering research of gene therapy for hemophilia began in the late 1990s. To date, more than 20 clinical studies of gene therapy to treat hemophilia have been conducted, are underway, or are planned. Recently, results of investigational gene therapy trials for hemophilia A and B were published.

If you're interested in learning more about gene therapy clinical trials for hemophilia, visit ClinicalTrials.gov.