

GENETICS AND NEUROMUSCULAR DISEASE

Many neuromuscular diseases are genetic disorders. A genetic disorder is caused by changes in one or more genes. These are called gene **variants**. Some gene variants are inherited from parents, and some occur spontaneously.

Every person has about 30,000 different genes. In recent decades, scientists have made progress in identifying genes that cause certain conditions when they have a variant. Researchers have discovered more than 500 genes that can cause neuromuscular diseases, and the number is still growing.

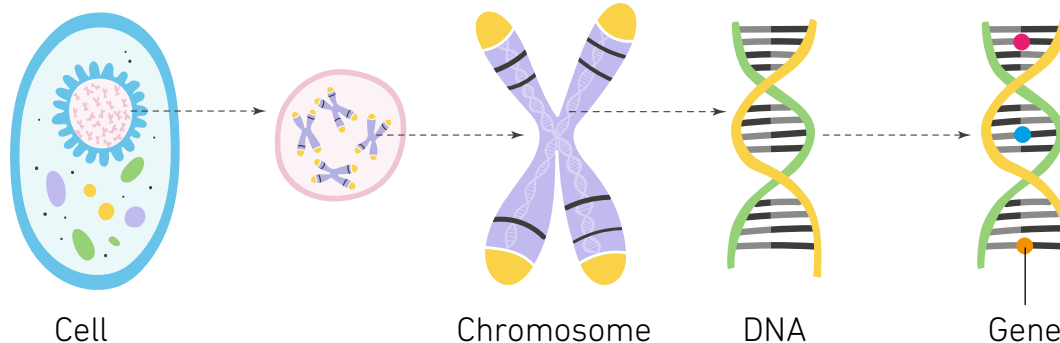
These advances make it possible for more individuals living with neuromuscular disease to get a specific diagnosis through genetic testing and gain access to high-quality care.



How genes work

Genes are sets of instructions that control the way your body is made, what it looks like, and how it works.

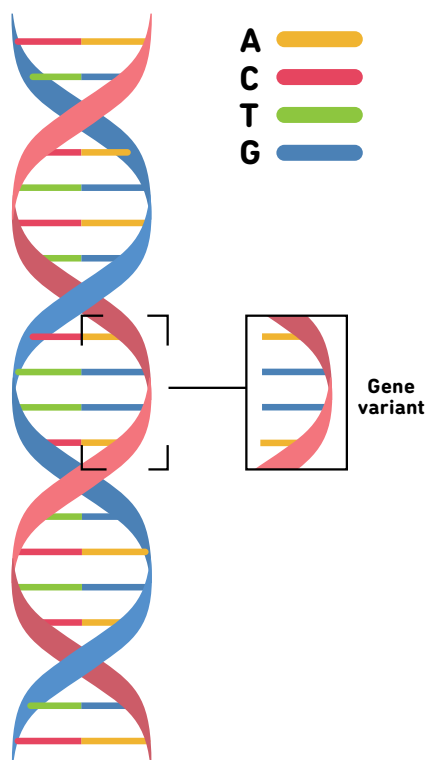
- ▶ Your body is made of cells.
- ▶ Cells contain two copies of each chromosome.
- ▶ **Chromosomes** carry groups of genes.
- ▶ Genes are sections of **DNA** coded with instructions.
- ▶ Each gene carries specific instructions telling cells how to grow or work.



Genetic disorders

The building blocks of DNA are amino acids (represented by the letters A, C, T, G) that are linked together in specific sequences. These patterns are important.

Imagine you're reading instructions to build a robot, and a typo in one step changes how you connect two components. Your robot probably would not work properly. This is similar to a variant in a gene carrying instructions for the muscles or nerves to work. Without the correct instructions, that part of the body does not work as well as it should.



Identifying genes

There has been huge progress in identifying genes that cause neuromuscular conditions when they have a variant. Identifying the root cause of a disease is important because it helps researchers understand the mechanism behind the disease and gives them a potential target at which to aim treatments and cures.

Researchers tend to identify the genes linked to the most common genetic conditions first. There are many rare types of neuromuscular diseases for which the gene causing the disease has not been found, but it may be discovered in the future.



Words in blue are defined in the Glossary on **page 6**.

Genetic testing

Using **genetic testing** to confirm a specific diagnosis is critical to providing high-quality care to individuals and families living with neuromuscular disease.

Genetic testing can:

- ▶ Help establish a diagnosis
- ▶ Shorten the diagnostic odyssey by ruling out other diseases or confirming a suspected diagnosis
- ▶ Alleviate the need for invasive and painful procedures, such as muscle biopsy
- ▶ Mitigate costs by preventing unnecessary procedures and treatments
- ▶ Improve the psychological impact on individuals and family members by confirming a diagnosis
- ▶ Assist with family planning
- ▶ Guide the testing of relatives
- ▶ Allow an individual to participate in research studies for their condition
- ▶ Help with disease management by:
 - Providing a prognosis for disease severity and/or progression
 - Identifying eligibility for treatments
 - Guiding treatment plans



If you have symptoms, genetic testing can provide the exact cause of your condition. There can be many different causes and treatments for the same symptoms, so having a genetically confirmed diagnosis helps your doctors provide better care.

If you have previously had a genetic test, you might consider getting retested if:

- ▶ Your previous genetic test was negative or did not provide an answer. There may be additional genes discovered or new tests available since the last time you were tested.
- ▶ You were tested through a research study. You may want to have the result confirmed in a laboratory approved by the **Clinical Laboratory Improvement Amendments (CLIA)**, which has stricter standards than a research laboratory.
- ▶ You're considering a gene-targeted therapy. Ask your doctor or genetic counselor if you should be retested before starting a new therapy.

Some people decide genetic testing is unlikely to provide them with helpful information or change the treatment of their condition. Some people feel it would be too stressful to know the results. It is important to hear all the information about genetic testing and talk through concerns with a professional, such as a genetic counselor, so you can be sure you are making a fully informed decision in line with your values and goals.

MDA's Resource Center may be able to help you find resources for genetic testing. Call us at **833-ASK-MDA1**.

INSURANCE CONSIDERATIONS

If a genetic test confirms you have a genetic condition, it could affect your health and life insurance coverage. The effect depends on the specific condition, your age, whether you have symptoms of the condition or if it is just in your family, your employment or future employment, and many other factors.

In general, if you have symptoms and already have a clinical diagnosis, genetic testing is unlikely to have an impact on obtaining these types of insurance. But if it is in your family and you do not yet have symptoms, a positive result could affect your eligibility for or the cost of that insurance.



Genetic counseling

Anyone considering genetic testing should see a genetic counselor, particularly if you do not yet have symptoms.

A genetic counselor will take a detailed family history, provide information about potential conditions, talk about the chances the test will be positive or negative, and make sure you are aware of any other possible results. A genetic counselor also will address the pros and cons of testing, including psychological concerns.

When test results are in, the genetic counselor can help interpret the results, address any implications for you and your family, and help you communicate the results to your family members.

If your doctor refers you to a genetic counselor, most insurance companies will cover the visit. Additionally, some labs and sponsored genetic testing programs include genetic counseling at no cost. You also may choose to pay out of pocket to see a genetic counselor in person or via telehealth. It is important to make sure you see a certified genetic counselor.

Family genetic testing

A genetic test can tell you who else in your family is at risk for the same condition. Talk with your genetic counselor about who in your family should be tested based on the type of disease and who else is showing symptoms.

Sometimes, your doctor or genetic counselor can tell which inheritance pattern your condition has by looking at who has the condition in the family. If you are the first person in your family to be diagnosed with a genetic condition, a genetic diagnosis is needed to confirm the inheritance pattern.

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If someone in the family has received a confirmed diagnosis from genetic testing, it is likely that other family members with the same condition have the same genetic cause. Genetic testing may not be needed if the diagnosis is already established in the family.

However, there may be other reasons for genetic testing, such as establishing eligibility for treatments or research studies. A genetic counselor can help make sure you are aware of all the information that pertains to your situation.

Family genetic testing is a personal decision. Everyone should respect one another's wishes about whether they want to be tested or not. It is important that family members are informed and knowledgeable about the

condition and options for genetic testing, but each person is allowed to make their own decision regarding testing.

Family planning options include testing that can be done before or during pregnancy.

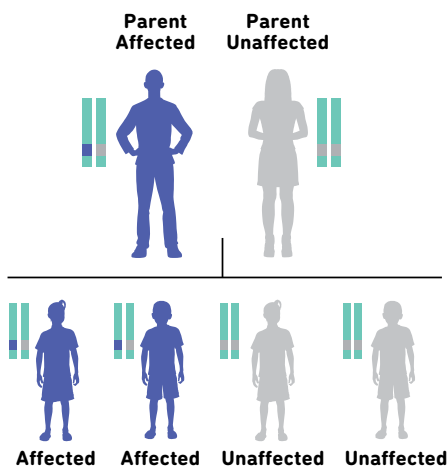
Testing performed during a pregnancy can be done as early as 10 weeks via **chorionic villus sampling (CVS)** and later via **amniocentesis**. These tests can detect a genetic condition early in the pregnancy.

Alternatively, **preimplantation genetic diagnosis (PGD)** can be done prior to a pregnancy using the same technology involved with in vitro fertilization. By genetically testing embryos for the condition before implantation, parents can screen embryos for the condition.

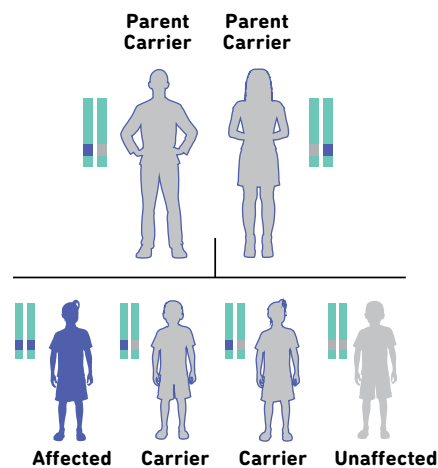
COMMON INHERITANCE PATTERNS

- ▶ **Autosomal dominant** — A child is affected if they inherit the gene variant from one parent.
- ▶ **Autosomal recessive** — A child is affected if they inherit gene variants from both parents. If they inherit one gene variant, they are a carrier.
- ▶ **X-linked recessive** — The gene variant is on the X chromosome. Because boys have only one X chromosome, they will be affected if they inherit the gene variant from their mother. Girls who inherit the gene variant will be carriers.

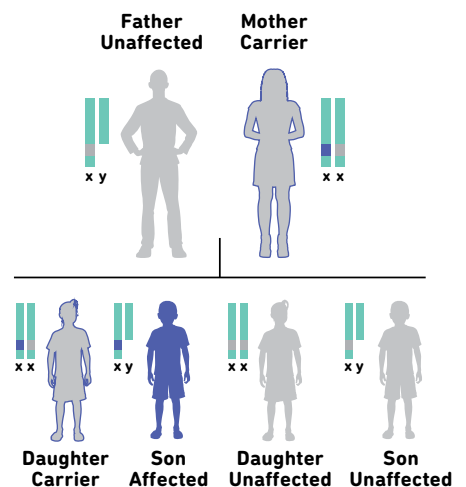
Autosomal Dominant



Autosomal Recessive



X-linked Recessive



Gene-targeted therapies

After an individual receives a diagnosis from a genetic test, a neurologist may be able to direct them to **gene-targeted therapies** that can keep symptoms from worsening or prevent them from occurring at all.

Conventional medications for neuromuscular diseases are mainly used to help manage symptoms or try to slow down their progression, but these medicines will not eliminate symptoms or stop them from progressing. Gene-targeted therapies hold great promise because they seek to fix the underlying cause of a genetic disorder.

There are different types of gene-targeted therapies being studied and developed. Some work by introducing a working copy of a gene with a variant into target cells. Others, such as **antisense oligonucleotides (ASOs)**, block the gene variant from being used. Someday, we may be able to cut a flawed section of DNA out of a gene and replace it using a gene editing tool (**CRISPR-Cas9**).

Currently, targeted therapies that replace or alter the expression of genes or enzymes are available for several neuromuscular conditions: Pompe disease, spinal muscular atrophy (SMA), Duchenne muscular dystrophy (DMD), and TTR amyloidosis. Clinical trials are ongoing for therapies to treat certain genetic types of many different neuromuscular conditions, including muscular dystrophies, congenital myopathies, hereditary neuropathies, and amyotrophic lateral sclerosis (ALS).

This resource was developed with the expertise and knowledge of Tiffany Grider, MS, LGC, from the University of Iowa Hospitals and Clinics.

GLOSSARY

Amniocentesis: A procedure in which amniotic fluid, which surrounds and protects a baby during pregnancy, is removed from the uterus for testing or treatment.

Antisense oligonucleotides (ASOs): Small, synthetic pieces of DNA that are used to stop the function in the cell of specific genes that may contain pathogenic variants.

Chorionic villus sampling (CVS): A prenatal test that involves taking a sample of tissue from the placenta to test for genetic problems.

Chromosomes: A structure of DNA and protein found within cells that carries genes. In humans, each cell normally contains 23 pairs of chromosomes, for a total of 46.

Clinical Laboratory Improvement Amendments (CLIA): Regulations established in 1988 that set federal standards for all U.S. facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease. CLIA requires clinical laboratories to be certified by the Center for Medicare and Medicaid Services (CMS) before they can accept human samples for diagnostic testing.

CRISPR-Cas9: A technology that enables editing of the genetic material in cells by removing, adding, or altering sections of the DNA sequence.

DNA: This stands for deoxyribonucleic acid. It is the biologic material in living organisms that provides instructions for how organisms are made, what they look like, and how their bodies work. The building blocks of DNA — abbreviated A, T, C, and G — are linked together in specific sequences to encode genes.

Preimplantation genetic diagnosis (PGD): A procedure used prior to implantation to identify genetic defects within embryos.

Variant: A copy of a gene with a difference in its DNA sequence. Gene variants can be pathogenic (disease-causing) or benign (not causing disease).

To learn more about neuromuscular disease, genetic testing, and gene-targeted therapies, visit mda.org or contact the MDA National Resource Center at 833-ASK-MDA1 (275-6321).



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