



The Genetics of Spinal Muscular Atrophy

SMA CARE SERIES



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Introduction

WHAT IS SPINAL MUSCULAR ATROPHY?

Spinal muscular atrophy (SMA) is often referred to by a number of terms, including “genetic disease”, “autosomal recessive genetic disorder”, “motor-neuron disease” or a “neuromuscular disease.”

SMA is a genetic disease

Genetic means relating to the genes. Genes are responsible for the vast majority of our traits and our unique characteristics. In SMA, there is a mutation in a gene responsible for a protein that supports normal muscle movement and control of the limbs, abdomen, head and neck, chest and breathing muscles.

SMA is an autosomal recessive genetic disorder

Autosomal recessive refers to how the disease is inherited or passed down from the parents to their child. In SMA, the child who is affected by SMA inherits two copies of a mutated gene, one copy from each parent. While not typically affected by SMA, each parent carries one copy of the mutated SMA gene.

SMA is a motor-neuron disease

Motor-neuron refers to the type of neuron (or nerve) that is affected in SMA. A neuron is a nerve cell that sends and receives messages to and from parts of the body. A motor-neuron is like a wire that sends messages to and from muscles responsible for movement and control in the head, neck, chest, abdomen, legs, and limbs.

In SMA, the motor-neurons in the spinal cord do not have enough of a certain protein, called SMN protein. As a result, these motor-neurons do not function normally and may die, resulting in muscle weakness and atrophy (shrinkage).

SMA is a neuromuscular disease

A neuromuscular disease (NMD) is a disease that affects the peripheral nervous system, which includes the motor-neuron cell body (located within the spinal cord), motor-neuron axons (projections from the cell body to muscles), neuromuscular junctions (the connection between the motor-neuron axons and muscles), or the muscles themselves. The central nervous system includes the brain and the spinal cord. The peripheral nervous system includes everything outside the brain and the spinal cord. The job of the peripheral nervous system is to send information to and from the central nervous system to regulate muscle activity.

Introduction to Genetics

WHAT IS DNA?

Basic science research looks at the fundamental building blocks of life, including molecules, proteins, cells and genes. Often referred to as “lab” or “bench” research, basic science research is carried out in a laboratory by researchers using microscopes and petri dishes. Other types of research, like translational research (see next section) or clinical research, are based on the findings and clues offered by basic science research.

Basic science research plays a critical role in the discovery and testing of chemical or biological materials that have the potential to become drugs and therapies to treat SMA; and the identification of existing drugs with potential to treat SMA. Testing at this stage is conducted on proteins, cells, and in living animals, but not in humans.

Critical questions in SMA biology, including what is going wrong in the body to cause SMA, are answered by basic science research. It gives researchers many seed ideas or clues that lead to more advanced research.



Figure 1. This figure shows the structure of the DNA double helix. It is comprised of four different types of building blocks called nucleotides. These are designated A, T, C, and G. Note that nucleotide adenine (A) in a DNA molecule always pairs with the nucleotide thymine (T), while cytosine (C) always pairs with guanine (G). This schema was taken from www.biotechnologyonline.gov.au/biotec/dnalook/cfm

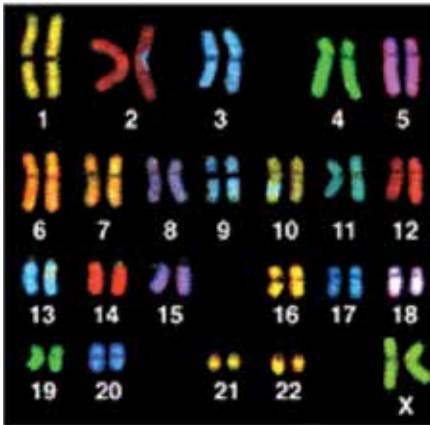


Figure 2. Humans have 23 pairs of chromosomes which contain our DNA. One of each pair of chromosomes is passed down from each parent. This figure shows a picture of the 23 pairs of chromosomes from a given individual. This is an example from a female with the 22 pairs of autosomal chromosomes and one pair of X chromosomes. A male would have one X and one Y chromosome. This schema was taken from <http://www.genome.gov> National Human Genome Research Institute of NIH.

WHAT IS A CHROMOSOME?

The complete human genome contains 3 Billion DNA molecules and if we were to stretch out this DNA it would measure 5.7 feet. Hard to imagine that all this material is present in the nucleus of each cell! For this to happen, DNA wraps itself around protein which is then packaged into very compact structures we call chromosomes. Each human cell contains 46 chromosomes or 23 pairs of chromosomes (one chromosome of each pair is inherited from our father and the other is inherited from our mother; see Figure 2.).

WHAT IS A GENE?

A gene is a specific DNA sequence that contains all of the information to produce a given protein at a specific time and in specific cells. Each gene codes for a particular protein that will have its own responsibilities in cells. One gene might make a protein all the time, in all cells; another gene might make a protein in liver cells for a short period of time. The engine of a gene is called a promoter and it contains most of the information controlling when and where the gene is turned on. The code that is the blueprint for the protein molecule is contained in regions called exons.

HOW DOES THE GENE MAKE PROTEIN?

First, the DNA sequence must be copied into a message. This message is the blueprint for protein. The building blocks of this blueprint, called messenger RNA or mRNA, are molecules called ribonucleic acid. The blueprint for protein is included in exons, and exons are separated by DNA sequences called introns. Once the DNA sequence has been copied into RNA, the introns must be removed and the exons brought together by a process called mRNA splicing. Imagine a pair of scissors that cut the RNA at the beginning and end of each exon, removes the intron, followed by a needle and thread that sews the exons together to form a smaller mRNA molecule. The next step in the process is to use the mRNA to make protein. The building blocks of proteins are amino acid molecules. There are 20 different amino acids. It is the particular sequence of amino acids that distinguishes one protein from another. This whole process is outlined in Figure 3.

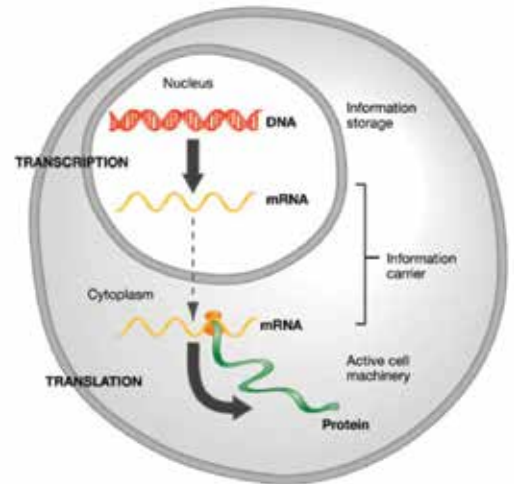


Figure 3. What genes do: DNA to mRNA to protein. Genes are comprised of DNA that is made into messages called mRNA during cellular processes called transcription and RNA splicing. As shown to the left, this occurs in the area of the cell called the nucleus. mRNA messages contain the blueprint from which specific proteins are produced, for example the SMN protein relevant in SMA. The process of producing protein from the mRNA template is called translation and occurs in the part of the cell called the cytoplasm. This schema was taken from <http://fig.cox.miami.edu>

WHAT ARE MUTATIONS?

Any mistakes in the DNA sequence will be copied into the RNA transcript and will affect the production of the final protein product. There are many different types of mutations and some examples follow:

- The engine of a gene is called a “promoter”. The promoter drives the production of RNA transcripts, it dictates where, when, and how much RNA is made. Basically, it controls whether a gene is turned on or off. If one has a mutation in the promoter, then too much or too little RNA will be made.
- If a single nucleotide in the DNA is changed, then a different amino acid will be incorporated into the protein. This could alter the folding and the function of the protein itself. These types of single nucleotide changes are called point mutations.
- If small chunks of DNA are completely absent, called a deletion, then the mutant mRNA will produce a protein with an internal chunk missing. Deletions of the *SMN1* gene are responsible for SMA.

SMA Inheritance

WHAT IS INHERITANCE?

In this context, we are talking about passing on genetic material from one generation to the next. This genetic material is packaged into chromosomes and we inherit half of our chromosomes from our biological father (from sperm) and half from our biological mother (from egg). The fertilized egg that will give rise to all the cells in our body throughout our lifetime contains 22 pairs of autosomes; named chromosomes 1 through 22, and 2 sex chromosomes (see Figure 2). We have two X chromosomes if we are female and one X and one Y chromosome if we are male.

A genetic trait can be dominant or recessive.

Autosomal dominant inheritance refers to a trait that is passed from a parent who shows the trait on to a child who will then also show the trait. The trait is expressed even if only one of the inherited genes has a mutation.

Autosomal recessive inheritance refers to a trait that is passed on from both parents who carry a mutated gene. Thus, the child must inherit two faulty (mutated) copies of the gene, one from each parent, to show the effects of having faulty genes. Because each parent typically only possesses one faulty copy of the gene, and two faulty copies are required to have the disease, parents do not show any symptoms of having (carrying) one mutated gene.

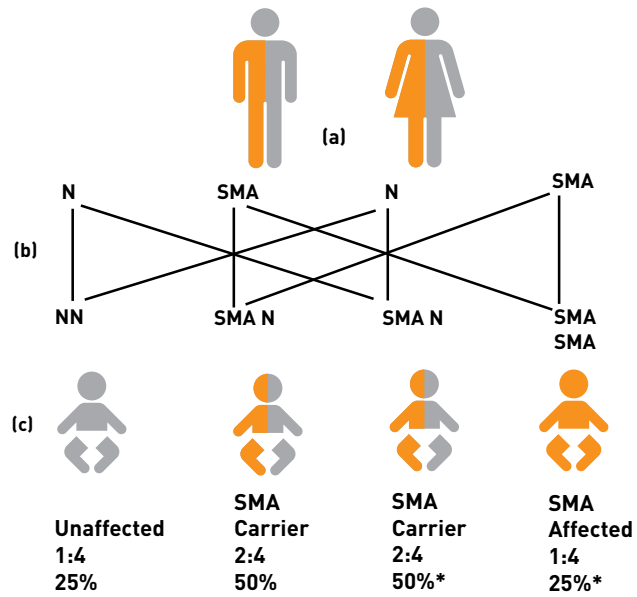
SMA is an autosomal recessive disease. See Figure 4 (next page).

HOW IS SMA INHERITED?

5q-SMA is an autosomal recessive genetic disorder. It is caused by mutations in the *SMN1* (*survival motor neuron*) gene that is found on chromosome 5 (hence the name 5q). To develop SMA, an individual must inherit two faulty *SMN1* genes, one from each parent.

Because the parents of an affected child typically have only one faulty *SMN1* gene each, the parents do not express the trait and do not have SMA. Thus, the product of one normal *SMN1* gene is sufficient for normal function and compensates for the one faulty gene. This person is described as a carrier. Each parent of a child with SMA is almost always a carrier. In about 2% of cases they are not. It is estimated that about 1 in 40 people throughout the world are carriers of SMA.

Figure 4. Inheritance of SMA. SMA is an autosomal recessive genetic disorder, which means an affected individual must have two defective copies of the disease causing gene. One copy of the defective gene is inherited from each parent. This scenario is illustrated here. N designates a normal *SMN1* gene and SMA a faulty *SMN1* gene. (a) Parents of an affected individual are typically carriers of one defective copy of the disease causing gene and are unaffected by the disease. (b) Chromosomes carrying the *SMN* gene are passed down to offspring from one generation to the next to produce affected (SMA SMA), unaffected SMA carriers (SMA N or N SMA), or unaffected non-carrier individuals (NN). In a family where both parents are carriers (SMA N), there is a 25% chance that each of their children will have two defective copies of the *SMN1* gene and have SMA, a 50% chance each of their children will be carriers and not have the disease, and a 25% chance that each of their children will have two normal *SMN1* genes and not have the disease.



*percentages are for each pregnancy.

Having a child affected by SMA occurs in a pregnancy between two SMA carriers or between a SMA carrier and a person living with SMA. Two carrier parents can produce children who would be affected, carriers, or non-carriers. The diagram above (Figure 4) shows the possible combinations of genes that could occur in any child of two SMA carriers. Each pregnancy has a:

- 25% chance of producing a child who would be affected with SMA,
- 50% chance of producing a child who would be a SMA carrier, and a
- 25% chance of producing a child who would not have SMA and would not be a SMA carrier.

WHAT IS X-LINKED INHERITANCE?

As most of the sex-linked genes are found on the X chromosome, sex-linked inheritance is generally X-linked. Again, a trait can be either dominant or recessive. If the trait is dominant, both females and males will express the trait and a mutation in only one X-linked gene is necessary. If recessive, usually only males will express this trait as they have a single X chromosome.

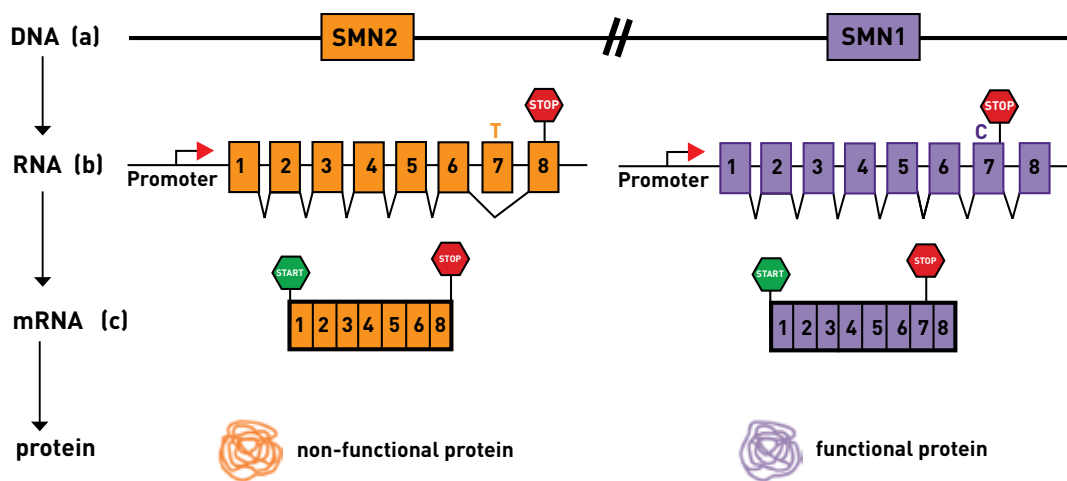


Figure 5. Schematic of a portion of chromosome 5 that contains the two SMN genes. The major difference between the two SMN gene copies is the C (*SMN1*) to T (*SMN2*) nucleotide change in exon 7 in their DNA. Because of this difference, *SMN2* mostly makes mRNA message that excludes exon 7 and produces a smaller, unstable SMN protein. *SMN1* makes mRNA message that includes exon 7 and makes functioning full-length SMN protein. This process is explained below. (a) The *SMN1* and *SMN2* gene organization on chromosome 5. (b) The SMN genes are turned on by their respective promoters (areas of DNA that turn genes on) in a process called transcription. Transcription results in a preliminary RNA that contains an intermediate blueprint for protein production. (c) The preliminary RNA message is processed in an event called RNA splicing to become a useful blue print for protein production. RNA splicing removes chunks of RNA called introns from the preliminary message, which are not part of the protein blueprint. The remaining blueprint regions are called exons. Notice exon 7 is missing from the *SMN2* mRNA, due to defective RNA splicing. (d) The final mRNA message that results from the splicing process is used as the template for protein production in a process called translation.

WHAT IS THE GENETIC BASIS OF 5Q SMA?

Genetic linkage studies of families with a history of SMA allowed researchers to localize the region containing the gene responsible for SMA to the long arm of chromosome 5 in 1992. Worldwide efforts, and especially the work by Dr. Judith Melki's research team, resulted in the identification of the SMA gene in 1995; this gene has been named SMN for the "survival motor neuron" gene. Humans have two nearly identical copies of this gene that have been named *SMN1* and *SMN2* (see Figure 5a).

The major difference between *SMN1* and *SMN2* is found in exon 7. There is a single nucleotide difference at the beginning of exon 7 (C for *SMN1* and T for *SMN2*, see Figure 5b) which is important for SMN RNA splicing. Thus the *SMN1* mRNA includes exon 7 whereas the *SMN2* mRNA generally excludes exon 7 (see Figure 5c).

The presence of exon 7 is critical for the production of fully functional and stable SMN protein. Because the mRNA from the *SMN2* gene excludes exon 7, protein made from the *SMN2* gene lacks a chunk of the normal protein. Thus, the *SMN2* gene alone cannot provide sufficient amounts of fully functional (full-length exon 7-containing) SMN protein that is necessary to maintain survival of motor neurons.

SMN1 Mutations

As SMA is an autosomal recessive disorder, individuals with this disease typically have inherited a faulty (mutant) *SMN1* gene from each of their parents. The majority of mutations responsible for 5q-SMA are either deletions or gene conversions. See Figure 6.

- A deletion involves partial or complete removal of the *SMN1* gene (Figure 6a).
- In a gene conversion, the *SMN1* gene is “converted” into an *SMN2*-like gene because the “C” in exon 7 is changed into a “T” (Figure 6b).

In both cases, deletion and gene conversion, SMA patients are missing *SMN1* exon 7, referred to as homozygous absence of *SMN1* exon 7. Therefore, SMA patients make insufficient amounts of full-length (exon 7 containing) SMN protein.

The remaining mutations that cause SMA are point mutations that affect only a few nucleotides of the *SMN1* gene. These point mutations result in the production of non-functional or unstable SMN protein. (Figure 6c).

Because deletions and gene conversion mutations are very frequent and point mutations are very rare, about 95% of SMA patients are homozygous for deletion/gene conversion mutations: they have deletion/gene conversion mutations on both their chromosome 5's. Some rare SMA patients (about 5%) are compound heterozygotes: they have a deletion/gene conversion mutation on one of their chromosome 5's and a point mutation on the other chromosome 5.

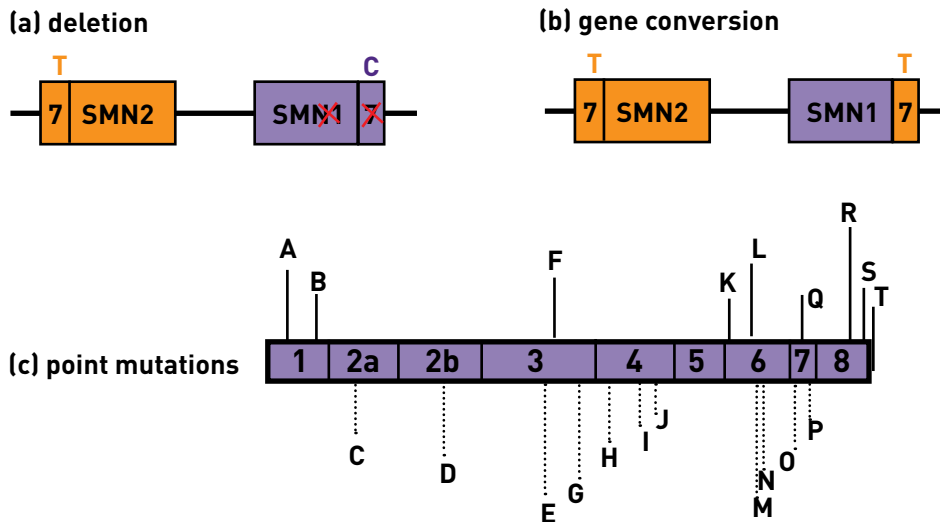


Figure 6. This figure illustrates the three types of *SMN1* mutations: deletions, gene conversion of *SMN1* to *SMN2*, and single nucleotide point mutations. (a) Xs indicate a deletion. A deletion removes part or all of the *SMN1* gene. (b) In the case of gene conversion, the *SMN1* gene has been converted to an *SMN2*-like gene (indicated by the nucleotide change to T). These two types of mutations (deletions and gene conversion events) are the most frequent types found in *SMN1*. About 95% of 5q-SMA patients have these two types of mutation, and these mutations are easily detected by the current diagnostic test for SMA as they both result in the loss of *SMN1* exon 7. (c) Point mutations can also be found in the *SMN1* gene, but at a much lower frequency than the other two types of mutations. Shown here are the locations of point mutations that have been found in the *SMN1* gene. They are labeled A through T. About 5% of 5q-SMA patients have a deletion or gene conversion mutation on one chromosome and a point mutation on the other chromosome. An individual with this combination of mutations (point mutation with either a deletion or conversion mutation) will not be diagnosed as having SMA using the SMA diagnostic test as only one copy of the *SMN1* gene is gone. Rather, this person will look like a carrier using the quantitative carrier test, even though they are symptomatic for SMA.

Genetic Testing

WHAT IS DNA TESTING?

DNA is the genetic material found in each cell of the body. Diagnosis and carrier testing is most often done with a small blood sample which is used to prepare DNA. If you do not have the disease, this DNA can be used to determine if you carry the mutation for the genetic disorder in your family. Prenatal diagnosis is generally carried out using a chorionic villus sample or amniotic fluid cells.

WHY DO DNA TESTING?

DNA testing is relevant when a family member has been diagnosed with a genetic disorder and when the gene and the mutations responsible for the genetic disorder have been identified. When this knowledge is available, DNA testing can be done for the following purposes:

- **Diagnosis:** to determine if you have the specific genetic disorder.
- **Carrier testing:** to determine if you are a carrier of a genetic disorder.
- **Prenatal testing:** to determine if your unborn baby has inherited a genetic disorder.

WHAT IS THE DIFFERENCE BETWEEN AMNIOCENTESIS AND CHORIONIC VILLUS SAMPLING?

Amniocentesis is the most common type of prenatal test. This test is usually performed after the 14th week of pregnancy. A very fine needle is inserted into the woman's abdomen and amniotic fluid surrounding the fetus is extracted. This fluid contains fetal cells that are used to prepare DNA and then examined for genetic disorders such as SMA. The risk associated with amniocentesis is that 1 in 200 women may miscarry.

Chorionic Villus Sampling (CVS) is usually performed as early as the 10th-12th week of pregnancy. A catheter inserted through the vagina or a very thin needle inserted through the abdomen is used to extract samples of the fingerlike structures that form the placenta (the chorionic villi). Once extracted, these cells are used to prepare DNA and then determine if a fetus has a genetic disorder such as SMA. The risk associated with CVS is that 1 in 100 women may miscarry.

DNA TESTING FOR 5Q SMA.

There are two types of SMN tests:

- One SMN test is used for the DIAGNOSIS of SMA individuals showing muscular atrophy caused by degeneration of motor neurons.
- The second SMN test is used to determine CARRIER STATUS, that is, the possibility of passing on a *SMN1* gene mutation to an offspring. This test is offered to individuals with a family history of SMA or to a partner of a known SMA carrier.

SMN DIAGNOSTIC TEST.

Because both copies of *SMN1* exon 7 are missing in most SMA individuals either through deletion or conversion, a simple DNA test can be done to detect the presence or absence of *SMN1*. *SMN1* will be present when DNA is prepared from individuals with 1 or 2 normal *SMN1* genes. *SMN1* will be absent when DNA is prepared from individuals with 5q-SMA.

Because about 95% of SMA patients possess DNA changes that can be detected with this test, namely homozygous deletion/gene conversion mutations, the SMN diagnostic test is said to have about 95% sensitivity. This means that the current SMA diagnostic test can detect 95% of SMA patients who have 5q-SMA. The SMN diagnostic test is not informative for non-5q-SMA.

About 1 in 20 (5%) patients with 5q-SMA have rare point mutations that are not detected by the SMN tests described here. Most of these SMA individuals have one *SMN1* gene in which *SMN1* exon 7 is missing and a second *SMN1* gene with a rare point mutation. One must identify *SMN1* mutations in both genes in order to confirm that such an individual has 5q-SMA.

QUANTITATIVE SMN CARRIER TEST.

Carrier screening is a type of genetic testing. It is an optional laboratory test that uses a small sample of blood. The results will inform the individual if he or she carries or has one copy of the mutated or deleted gene and identifies the risk of giving birth to a child with the disease. Carrier screening can be provided to individuals, couples, or population groups considered at risk for certain disorders.

- 1 in 50 people in the general population are SMA carriers
- 1 in 10,000 babies in the U.S. is born with SMA.

The SMN diagnostic test is not sensitive enough to determine if an individual has one or two copies of *SMN1*, it can only detect whether *SMN1* is present or absent. Therefore, the SMN diagnostic test cannot distinguish between unaffected individuals and SMA carriers.

A quantitative PCR test is used to determine carrier status. While this test is much more complex and takes more time to complete, it is very sensitive.

- Individuals with one copy of *SMN1* are 5q-SMA carriers. We can be certain that an individual with just one copy of *SMN1* is indeed a 5q-SMA carrier because most chromosome 5's have only one *SMN1* gene (about 95%).

How certain are we that individuals with two copies of *SMN1* are not carriers? In the general population about two to 3% of chromosome 5's have two copies of the *SMN1* gene instead of one.

- Even if the carrier test shows that a person has two copies of *SMN1*, some individuals have two copies of *SMN1* on just one chromosome and no copies of *SMN1* on the second chromosome. This person will be a carrier but this will not be detected by the current carrier tests. This occurs about 2 to 3% of the time.

We also know that brand new mutations are detected in about 2% of families with SMA. A brand new or “de novo” mutation is a mutation that occurs in the egg or sperm, but the same mutation is not present in the parents.

- A parent with a “de novo” mutation in egg or sperm would have two copies of *SMN1* (non-carrier) in their blood cells, but still be at risk of having a child with SMA by passing a “de novo” mutation in their egg or sperm cells.

Because of the existence of two *SMN1* genes on one chromosome, *SMN1* point mutations and de novo *SMN1* mutations, the sensitivity of the quantitative *SMN1* carrier test is not 100%. The quantitative *SMN1* carrier test can detect about 90% of carriers in the general population.

DO I HAVE TO HAVE A DNA TEST?

The decision whether or not to have a DNA test or to bank DNA is a personal one. The family members who would most benefit from DNA testing will depend upon the inheritance pattern of the genetic disorder. A health care professional (physician, genetic counselor, etc.) can help you assess if you would indeed benefit from DNA testing. By seeking this information, you can make a decision that is right for you and/or your family.

WHY BANK DNA?

If a DNA test for the genetic disorder in your family is not currently available, you can store your DNA (called banking) for when a DNA test becomes available at a future date. This is particularly relevant for non-5q-SMA cases. DNA will be prepared from blood and can be stored for many years.

The SMN2 Gene As A Disease Modifier

The number of copies of the *SMN2* gene varies in the population. The number of *SMN2* gene copies a person possesses has been shown to modify SMA disease severity: the severity of SMA in people living with the disease broadly correlates with the number of *SMN2* gene copies. More copies = less severe. Every person living with SMA has at least one copy of the *SMN2* gene, since some amount of SMN protein is required for every type of cell in the human body to survive.

The observed correlation between *SMN2* gene copy number and SMA severity has led to the idea that increasing the amount of SMN produced from the *SMN2* gene is an ideal target for drug intervention. Each and every SMA patient possesses at least one *SMN2* gene. Therefore, the *SMN2* gene can be viewed as a back-up to the lost *SMN1* gene in SMA patients. The goal is to increase the amount of SMN protein made by the *SMN2* gene, and this can be achieved in several ways:

- The first is by turning up the *SMN2* “promoter” to produce more *SMN2* mRNA and then SMN protein.
- The second is to correct the defective splicing of the *SMN2* mRNA.
- The third is to find drugs that stabilize the protein produced by the *SMN2* gene.

A series of compounds such as sodium butyrate, 4-phenylbutyrate, valproate, hydroxyurea, aminogangliosides, and aclarubicin have already been reported to increase SMN protein levels from the *SMN2* gene in cellular models of SMA. Several of these (valproate, phenyl butyrate and hydroxyurea) have been approved by the FDA for use in other human diseases and are being actively assessed in clinical trials for SMA. Hopefully, the unique genetic situation in SMA, in which a back-up gene (*SMN2*) is present, will lead us to beneficial drug treatments for this disease.

Non-5q Forms of SMA

A number of additional inherited motor neuron diseases occur that are caused by mutations in genes other than the *SMN1* gene. These are referred to as non-5q- SMA diseases, meaning that the genes causing these other forms of SMA are not located in the SMN region of chromosome 5. Similar to 5q-SMA, people with non- 5q-SMA also have early muscle weakness but with a number of features that differ from 5q-SMA. These features can include distal rather than proximal weakness, early contractures, diaphragmatic paralysis with early respiratory failure, and cerebellar degeneration. A subset of non-5q-SMA diseases can be diagnosed with DNA diagnostic tests, but for some this is still not possible as the affected genes have not yet been identified. A list of some non-5q-SMA diseases is presented in Table 1

Name	Alternative titles/symbols	Mode of inheritance
Spinal and Bulbar Muscular atrophy	SBMA, SMAX1, X-linked 1, Kennedy Disease	X-linked recessive
Arthrogryposis Multiplex Congenita	AMC, SMAX2, X-linked 2	X-linked recessive
Spinal Muscular Atrophy, distal, X-linked	SMAX3, DSMAX, X-linked 3	X-linked recessive
Motor neuronopathy, distal with vocal cord paralysis	DHMNVP, type VII, HMN VII, HMN7 Harper-Young myopathy	Autosomal Dominant
Arthrogryposis Multiplex Congenita, neurogenetic type	AMCN	Autosomal Recessive
SMA, Distal, Type V	DSMAV, HMNV, dHMNV	Autosomal Dominant
SMA with respiratory distress 1	SMARD1, type VI, HMV VI	Autosomal Recessive
SMA, congenital, scapuloperoneal amyotrophy	SPSMA	Autosomal Dominant
SMA, proximal, adult	Finkle type	Autosomal Dominant

Table 1. Non-5q-SMAs

For More Information

Cure SMA website: www.cureSMA.org

The American College of Medical Genetics
www.acmg.net

The American College of Obstetricians and Gynecologists
www.acog.org

National Society of Genetic Counselors
www.nsgc.org

Genetics & IVF Institute
www.givf.com/

About Cure SMA

Cure SMA is dedicated to the treatment and cure of spinal muscular atrophy (SMA)—a disease that takes away a person’s ability to walk, eat, or breathe. It is the number one genetic cause of death for infants.

Since 1984, we’ve directed and invested in comprehensive research that has shaped the scientific community’s understanding of SMA. We are currently on the verge of breakthroughs in treatment that will strengthen our children’s bodies, extend life, and lead to a cure.

We have deep expertise in every aspect of SMA—from the day-to-day realities to the nuances of care options—and until we have a cure, we’ll do everything we can to support children and families affected by the disease.

Learn more about how you can help us reach a treatment and cure at www.cureSMA.org.



Cure SMA

925 Busse Road
Elk Grove Village, IL 60007



Phone: 1.800.886.1762
Fax: 847.367.7623



E-mail: info@curesma.org



We’re on the Web!
www.cureSMA.org

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Fast Facts

1. SMA is an autosomal recessive disease caused by mutations in both copies of the *SMN1* gene located on chromosome 5. This is called 5q-SMA.
2. People who have one defective copy of the *SMN1* gene are called carriers, and they do not have SMA.
3. More than 98% of the time, both parents of a child with SMA are carriers. In rare cases, mutations in the *SMN1* gene can occur during egg or sperm production. In this situation, only one parent will be a carrier of the defective *SMN1* gene.
4. When both parents are carriers, with each pregnancy they have a 25% chance of producing a child who would be affected with SMA; a 50% chance of producing a child who would be a SMA carrier; and a 25% chance of producing a child who would not have SMA and would not be a SMA carrier.
5. SMA results from very low amounts of functional SMN protein. Three different classes of mutations can cause SMA: deletions of the *SMN1* gene, conversions of the *SMN1* gene to a *SMN2*-like gene, and rare point mutations within the *SMN1* gene.
6. Of the three classes of mutations responsible for 5q-SMA, about 95% of patients have *SMN1* gene deletions or *SMN1* gene conversions. Only about 5% of patients have point mutations in the *SMN1* gene.
7. The current DNA diagnostic test for SMA is capable of detecting *SMN1* gene deletions and *SMN1* gene conversions, but not the point mutations. This means that this test can diagnose about 95% of SMA cases, but not the 5% of patients with point mutations in the *SMN1* gene.
8. 95% of SMA cases can be detected prenatally using either amniocentesis or a chorionic villus sample (CVS).
9. Carrier testing can detect 97% of individuals carrying one copy of the *SMN1* gene. This test cannot detect the 3% of carriers who have TWO copies of *SMN1* on one chromosome and ZERO copies of *SMN1* on the second chromosome.
10. Other types of SMA exist, which are not caused by a defect in the *SMN1* gene. These diseases are also characterized by childhood muscle weakness and motor neuron loss; however, they have unique characteristics not shared with 5q-SMA. They are caused by mutations in genes other than *SMN1*, which are located on chromosomes other than chromosome 5.



925 Busse Road, Elk Grove Village, IL 60007
1.800.886.1762 • Fax 847.367.7623
www.cureSMA.org • info@curesma.org