



# CURE SMA

CARE SERIES BOOKLET

A SOURCE OF INFORMATION AND SUPPORT FOR INDIVIDUALS LIVING WITH SPINAL MUSCULAR ATROPHY AND THEIR FAMILIES.

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## GENETICS OF SMA

**cure**  
**SMA.** Make today a  
breakthrough.

# SMA AND GENETICS

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

## **SMA is a genetic disease.**

“Genetic” means it is relating to the genes and is inherited. Genes are responsible for our traits and unique characteristics. In SMA, there is a mutation in a gene responsible for the survival motor neuron (SMN) protein, a protein that is critical to the function of the nerves that control normal muscle movements.

## **SMA is an autosomal recessive genetic disorder.**

“Autosomal recessive” refers to how the disease is inherited, or passed down, from the parents to the child. In SMA, the individual who is affected by SMA inherits two copies of a non-working gene—one copy from each parent.

## **SMA is a motor-neuron disease.**

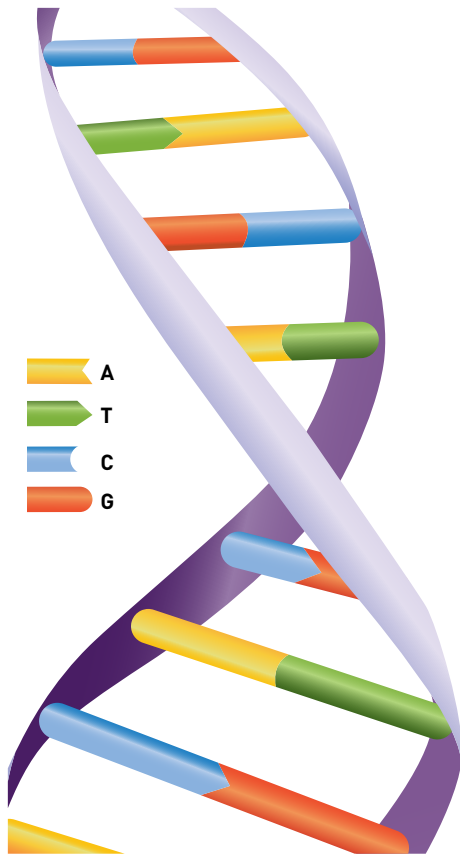
“Motor-neuron” refers to the type of nerve cell that sends messages to and from muscles responsible for movement and control of the head, neck, chest, abdomen, legs, and limbs. In SMA, the motor-neurons in the spinal cord do not have enough SMN protein. As a result, these motor-neurons do not function normally and may die, resulting in muscle weakness and atrophy (shrinkage).

## **SMA is a neuromuscular disease.**

A “neuromuscular disease” affects the neuromuscular system. This can include problems with the nerves that control muscles, the muscles, and the communication between the nerves and the muscles. Neuromuscular diseases can cause muscles to become weak and waste away.



# INTRODUCTION TO GENETICS



## What is DNA?

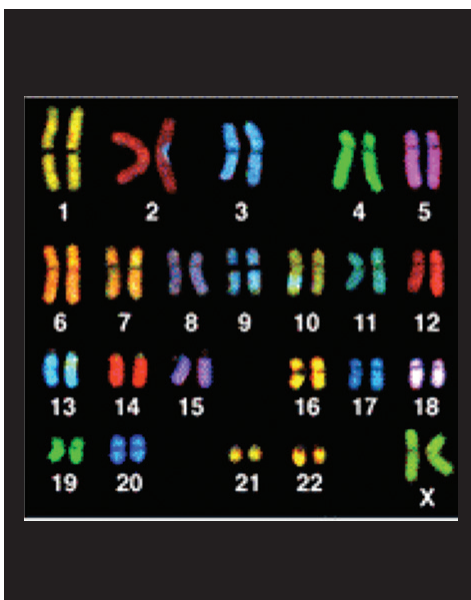
Deoxyribonucleic acid (DNA) is hereditary information in most living things, sometimes called the “building blocks of life.” It is comprised of four different nucleotides—adenine, thymine, cytosine, and guanine—that create long chains that twist together into a double helix (see Figure 1). These sequences of nucleotides make up genes, which provide instructions for the body to make proteins.

Figure 1 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.dnaloook/cfm](http://www.biotechnologyonline.gov.au/biotec.dnaloook/cfm)

## What is a Chromosome?

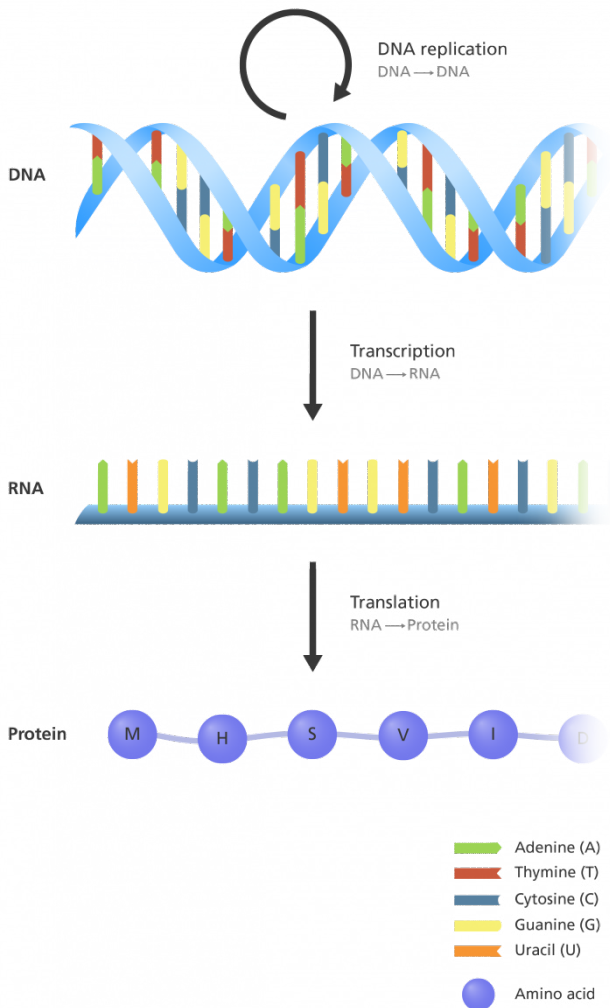
The complete human genome contains 3 billion DNA molecules. If we were to stretch out this DNA, it would measure 6 feet. For all this material to be present in the nucleus of each cell, DNA wraps itself around a protein, which is then packaged into very compact structures, called chromosomes. Each human cell contains 46 chromosomes, or 23 pairs—one chromosome of each pair inherited from the father and the other inherited from the mother (see Figure 2).

Figure 2 shows an example of 23 pairs of chromosomes from a female with 22 pairs of autosomal chromosomes and one pair of X chromosomes.



## What is a Gene?

A gene is a DNA sequence that contains information to produce a specific protein at a specific time and in specific cells. Genes are made of introns and exons. Exons are the parts of genes which are spliced together and code for proteins. Each gene codes for a protein that will have its own tasks in cells. One gene might make a protein all the time, in all cells, while another gene might make a protein in specific cells for a short period of time. When genes are turned on, their DNA is copied into messenger ribonucleic acid (mRNA). mRNA provides the instructions for the needed amino acids. Amino acids join to make proteins. The specific sequence of amino acids is what differentiates proteins from one another.



## What are Mutations?

Any mistakes in the DNA sequence will be copied into RNA when the gene is turned on and affects the production of the final protein product. These mistakes are called mutations. There are many different types of mutations.

- The promoter (i.e., engine of the gene) begins the process of the gene making proteins, dictating where, when, and how much RNA is made. If one gene has a mutation in the promoter, then too much or too little RNA will be made. In turn, too much or too little protein 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. These types of single nucleotide changes are called point mutations.
- If small chunks of DNA are completely absent, called a deletion, then the mutated RNA will produce a protein with an internal chunk missing.

Figure 3 shows how DNA directs the production of protein. The image was taken from yourgenome.org.

# 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. A person inherits half of their chromosomes from the biological father (from sperm) and half from the biological mother (from egg). 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.

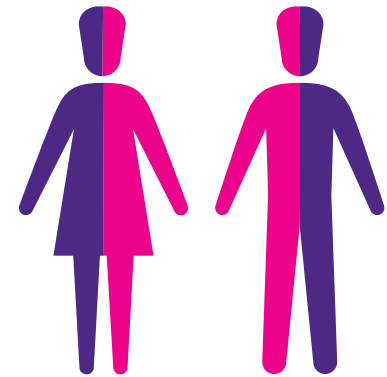
- **Autosomal dominant** inheritance refers to a trait that is passed from one or both parents that have the trait on to a child. Autosomal means that the gene is located on one of the non-sex chromosomes (not X or Y chromosome). Dominant means that a single copy of the trait or disease-associated mutation is enough to cause the trait or disease. This trait is dominant over other traits.
- **Autosomal recessive** inheritance refers to a trait passed on from both parents who carry a mutated gene and do not demonstrate the trait. Two copies of the mutation are needed to cause the trait or disease. Typically, each parent who does not have the trait or disease each carry one mutated copy of the gene. Two faulty copies together will present the trait or disease in the child (see Figure 4).

## How is SMA Inherited?

SMA is an autosomal recessive genetic disorder caused by mutations in the SMN1 (survival motor neuron) gene that is found on chromosome 5. To be affected by SMA, an individual inherits two faulty SMN1 genes, one from each parent. This is often referred to as 5q-SMA referring to the gene location on chromosome 5, the long arm q.

Parents of an affected individual may have SMA (2 faulty SMN1 genes), or they may have only one non-functioning SMN1 gene, and therefore they do not express the trait and do not have SMA. People who have one non-functioning SMN1 gene are described as carriers. It is estimated that about 1 in 50 people throughout the world are carriers of SMA. SMA affects all races and all genders.

WHEN TWO CARRIERS OF THE SMA MUTATION HAVE A CHILD



THERE ARE THREE POSSIBILITIES

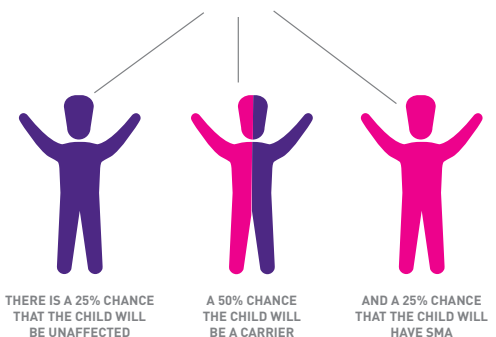


Figure 4 shows SMA recessive inheritance between 2 people who are carriers of SMA. Each has one functioning SMN1 gene and one faulty SMN1 gene. For each pregnancy there is a 25% chance of having a child with SMA, 50% chance of having a child who is a carrier of SMA and a 25% chance of having a child who is not affected and not a carrier. Having a child with SMA can also occur between a carrier of SMA and a person living with SMA, or between 2 people living with SMA.

## What is the Genetic Basis of SMA?

SMA is an autosomal recessive disorder, meaning individuals with this disease typically have inherited a non-functioning SMN1 gene from each of their parents. Most mutations responsible for SMA are either mutations or deletions (see Figure 5).

- A deletion involves partial or complete removal of the SMN1 gene (see Figure 5a).
- In a gene conversion, the SMN1 gene is “converted” into an SMN2-like gene because the “C” nucleotide in exon 7 is changed into a “T” nucleotide (see Figure 5b).
- The remaining mutations that cause SMA are point mutations that affect only a few nucleotides of the SMN1 gene (see Figure 5c).

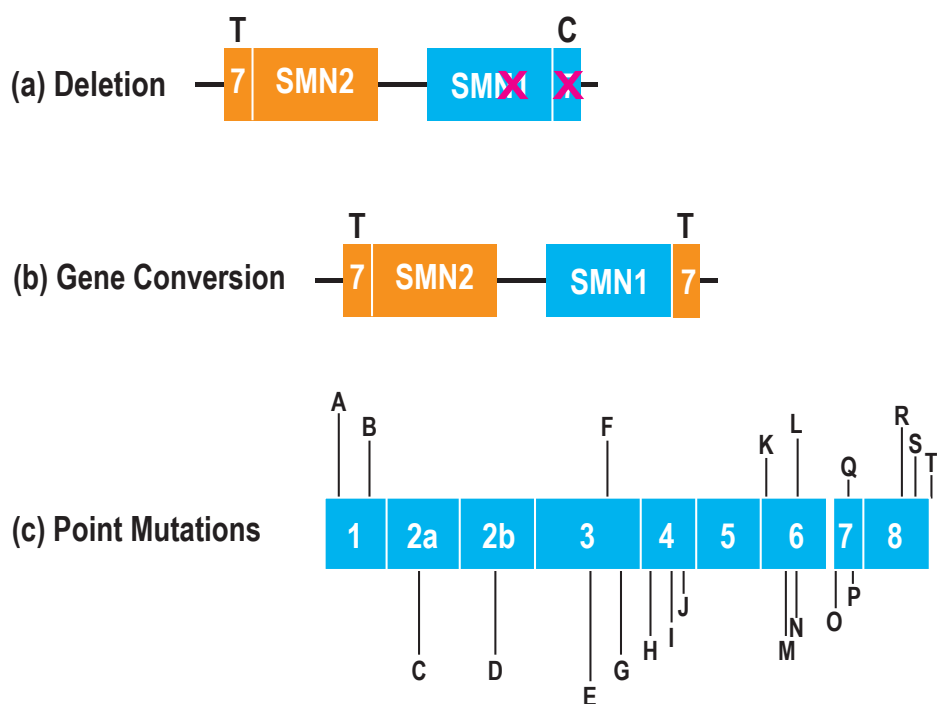


Figure 5 illustrates the three types of SMN1 mutations: (a) Xs indicate a deletion. A deletion removes part or all of the SMN1 gene. (b) In the case of gene conversion, the SMN1 gene has been converted to an SMN2-like gene (indicated by the nucleotide change from C to T). (c) Point mutations can be found 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 labeled A through T.

*Figure courtesy of Dr. Louise Simard, PhD, University of Manitoba*

In cases of deletion and gene conversion, individuals with SMA are missing part of the SMN1 gene, exon 7. DNA is made up of introns and exons. During the process of making a protein, introns are removed and exons are spliced together and code for the resulting protein. When exon 7 is missing from both chromosomes, this is referred to as “homozygous absence of SMN1 exon 7.” Therefore, individuals with SMA make insufficient amounts of full-length SMN protein.

These two types of mutations (deletions and gene conversion events) are the most frequent types found in SMN1. About 95% of people with 5q-SMA 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.

About 5% of people with 5q-SMA 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 will not be diagnosed as having SMA using the SMA diagnostic test as the diagnostic test does not detect point mutations and the result will show one copy of SMN1. This person will require further genetic testing with SMN1 gene sequence testing (see Genetic Testing).

## What about SMN2?

Next to the SMN1 gene, there is a nearly identical gene, SMN2. Like SMN1, SMN2 produces functional SMN protein but only 10-15% of the time. 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, although there are exceptions. Individuals with SMA have at least one copy of the SMN2 gene. The SMN2 gene can be viewed as a back-up to the lost SMN1 gene function in people with SMA.

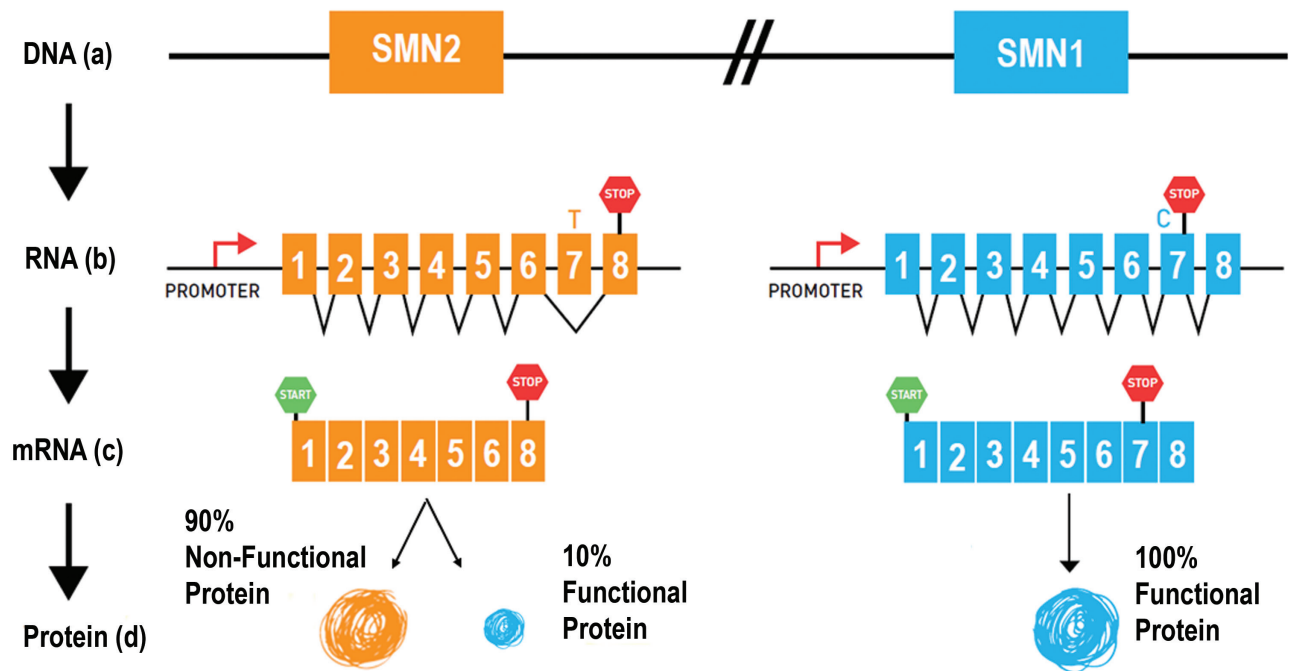


Figure 6 shows (a) a schematic of a portion of chromosome 5 that contains the two SMN genes. (b) The major difference between the two SMN genes is the C (SMN1) to T (SMN2) nucleotide change in exon 7. The SMN genes are turned on by their respective promoters (areas of DNA that turn genes on) in a process called transcription. (c) Transcription results in a preliminary RNA that contains an intermediate blueprint for protein production. The preliminary RNA undergoes RNA splicing to remove chunks of RNA called introns 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. In contrast, SMN1 makes mRNA that includes exon 7. (d) Translation is the process of making protein from the final mRNA message. SMN1 mRNA is complete and produces fully functional protein. However, SMN2 mRNA is missing exon 7 and as a result the majority of protein produced is smaller and non-functional. A very small amount of functional protein is produced from SMN2.

*Figure modified and provided courtesy of Louise Simard, PhD, University of Manitoba*

# GENETIC TESTING



## What to Expect from Genetic Testing for SMA

Genetic testing is a voluntary process where a sample of DNA is collected and tested. This may include buccal (mouth cheek) swab, saliva, blood, or prenatal specimens. Testing may confirm a diagnosis or carrier status of SMA.

### There are different types of genetic testing related to SMA:

- **Diagnostic:** Confirms if you have SMA.
- **Familial:** Confirms if you have the specific mutation identified in your family.
- **Carrier:** Confirms whether you are a carrier of SMA.
- **Prenatal:** Determines if your unborn baby has inherited SMA.



A main benefit of genetic testing is early confirmation of a suspected diagnosis of SMA. It is important to pursue additional testing if SMA is suspected and initial diagnostic tests are negative. For example, someone with symptoms of SMA and a diagnostic gene test that shows one copy of SMN1 should have further testing that typically includes SMN1 gene sequencing. Approximately 5% of people with SMA have point mutations that are not identified by typical SMA genetic testing. Early diagnosis enables early treatment, which results in better outcomes.

Although confirmatory genetic testing provides a diagnosis, the tests may not determine when symptoms will appear or the severity of SMA. Speaking to a genetic counselor is important, as they can help in understanding the benefits, risks, and limitations of genetic testing. Find a genetic counselor through the National Society of Genetic Counselors at [www.nsgc.org/page/find-a-genetic-counselor](http://www.nsgc.org/page/find-a-genetic-counselor).



## SMA Carrier Test

As previously mentioned, it is estimated that 1 in 50 people are carriers for SMA. 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 because two SMN1 genes are on one chromosome, carrier status will not be detected by current carrier tests. This occurs about 2 to 3% of the time.

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. In that case, brand new mutations are detected in about 2% of families with SMA.

The sensitivity of the deletion SMN1 carrier test is not 100%, because the following situations cannot be detected: the existence of two SMN1 genes on one chromosome, SMN1 point mutations, and de novo SMN1 mutations. The deletion SMN1 carrier test can detect about 95% of carriers in the general population.

If one or both parents test negative for carrier screening, this greatly reduces (but does not eliminate) the risk of having a pregnancy affected with SMA.





## Preconception and Prenatal Options for Known Carrier Couples

Prenatal genetic testing options, such as chorionic villus sampling (CVS) and amniocentesis, are available to determine if a pregnancy is at risk for being affected with SMA. For more information, consult your healthcare provider.

Preconception genetic testing, such as preimplantation genetic diagnosis (PGD), is a reproductive option that has allowed couples who are both carriers the opportunity to pursue pregnancies selecting for known non-affected embryos. This method involves in vitro fertilization (IVF) of the couple's egg and sperm cells, with subsequent single-cell embryo biopsies. The single cell, removed from the early embryo, undergoes genetic testing for SMA. Embryos found to be unaffected with SMA are used for implantation.

Notifying your healthcare provider early in any future pregnancies will allow for earlier referral to a prenatal genetic counseling center for more information about your testing options.

**Amniocentesis** is the most common type of prenatal test. This test is usually performed between 15 and 20 weeks of pregnancy. A very fine needle is inserted into the woman's abdomen and a small amount of amniotic fluid surrounding the fetus is removed. This fluid contains fetal cells that are used to obtain DNA to test for genetic disorders such as SMA.

**Chorionic Villus Sampling (CVS)** is usually performed as early as the 10th-13th week of pregnancy. A catheter inserted through the cervix 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.

# CURE SMA

Cure SMA is a non-profit organization and the largest worldwide network of families, clinicians, and research scientists working together to advance SMA research, support affected individuals/caregivers, and educate the public and professional communities about SMA.

Cure SMA is a resource for unbiased support. We are here to help all individuals living with SMA and their loved ones, and do not advocate any specific choices or decisions. Individuals and caregivers make different choices regarding what is best for their situation, consistent with their personal beliefs. Parents and other important family members should be able to discuss their feelings about these topics, and to ask questions of their SMA care team. Such decisions should not be made lightly, and all options should be considered and weighed carefully. All choices related to SMA are highly personal and should reflect personal values, as well as what is best for each individual and their caregivers.



**Remember that your healthcare team and Cure SMA are here to support you. To continue learning, please see other available Care Series booklets:**

- Breathing Basics
- Caring Choices
- Musculoskeletal System
- Nutrition Basics
- Understanding SMA



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