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**FAMILIES OF SPINAL MUSCULAR ATROPHY**

# ■ The Genetics of SMA

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*Balancing Life's Tough Times™*

# Introduction to Genetics

*Everything you've always wanted to know but were afraid to ask.*



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

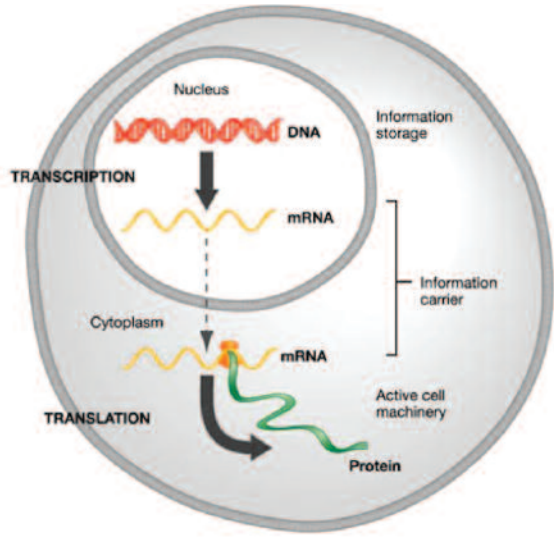
**Figure 2.** Humans have 23 pairs of chromosomes which contain our DNA. One of each pair of chromosomes is passed down from each parent. This figure shows a picture of the 23 pairs of chromosomes from a given individual. This is an example from a female with the 22 pairs of autosomal chromosomes and 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 DNA?** There are about 30,000 genes in the human genome that provide the blueprint for all the proteins that are required to maintain each cell in our body. The building blocks of this blueprint are molecules called deoxyribonucleic acid or DNA for short. There are four different DNA building blocks called nucleotides, adenine (A), thymine (T), cytosine (C) and guanine (G) and these nucleotide molecules are strung together much like beads on a string to form a necklace or DNA sequence (see Figure 1). It is the particular DNA sequence of these four nucleotides that distinguishes one gene from the other. The complete DNA sequence of the human genome is now publicly available. This sequence is the blueprint of life!

**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 ft. 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.).



**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 above, 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 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 can make a protein all the time, in all cells; another gene might make a protein in liver cells only in a 2-month-old fetus. All the information controlling when and where the gene is turned on is contained within the gene in regulatory sequences, called promoter and intronic sequences. The code that is the blueprint for the protein molecule is itself contained in regions called exons.

**How does the gene make protein?** First, the DNA sequence must be copied into a message. This message is a blueprint for protein. The building blocks of this blueprint, called messenger RNA or mRNA, are molecules called ribonucleic acid or RNA for short. 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 much smaller mRNA molecule. The next step in the process is to use the mRNA to make protein. The building block of proteins are amino acid molecules, there are 20 different amino acids. This process is outlined in Figure 3.

# Introduction to Genetics cont.

**What are mutations?** Any mistakes (mutations) in the DNA sequence will be copied into the mRNA 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 (in what cell types) and how much (quantity) 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, 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 removed, called a deletion, then the mutant mRNA will produce a protein with an internal chunk missing. Deletions of one or more exons of the dystrophin gene are a common cause of Duchenne muscular dystrophy, while deletions of the complete SMN1 gene are responsible for Spinal Muscular Atrophy.

# SMA Inheritance

## 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 SMN1 gene is sufficient for normal function. 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. Carriers do not have the disease since one normal gene is sufficient for proper functioning and compensates for the one faulty gene. It is estimated that about 1 in 40 people throughout the world (including the United States) are carriers of SMA.

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 following diagram (Figure 4) shows the possible combinations of genes that could occur in any child of two SMA carriers. Each pregnancy has a

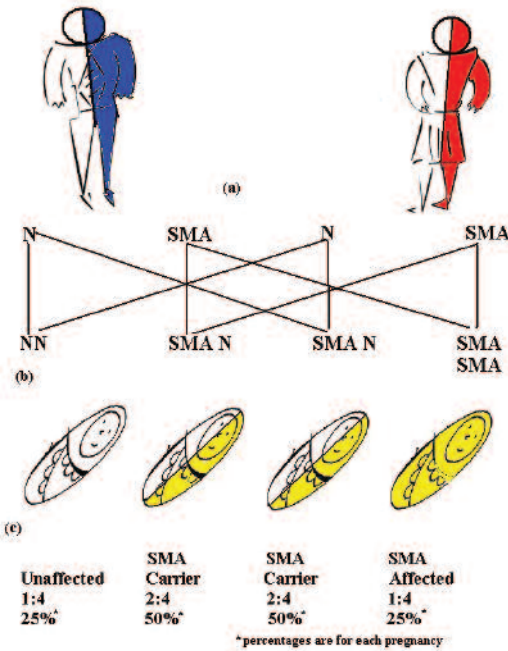
- 25% chance of producing a child who would be affected with SMA,
- 50% chance of producing a child who would be a SMA carrier, and a
- 25% chance of producing a child who would not have SMA and would not be a SMA carrier.

**What is 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 (sperm) and half from our biological mother (ovum). 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 either dominant or recessive. One can inherit two identical genes (homozygous) or one can inherit two genes that have differences (heterozygous).

**Autosomal dominant** inheritance refers to a trait that is passed on from a parent who expresses the trait to a child who will then also express the trait. The trait is expressed even if only one of the inherited genes has a mutation. Thus, the product of one gene is not sufficient for normal function.

# SMA Inheritance cont.



**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.

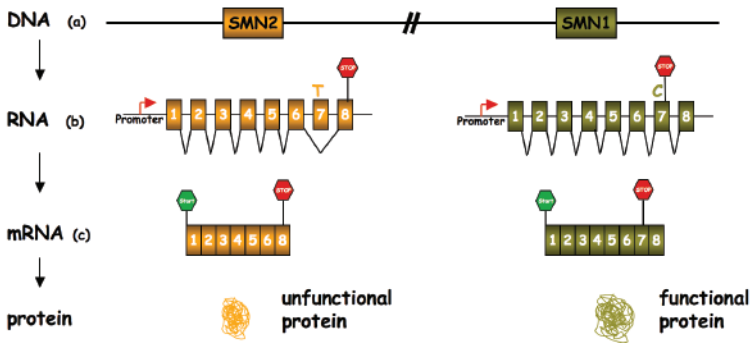
**Autosomal recessive** inheritance refers to a trait that is passed on from both parents who carry a mutated gene. Thus, the child must inherit two faulty (mutated) copies of the gene, one from each parent, to show the effects of having faulty genes. Because each parent typically only possesses one faulty copy of the gene, and two faulty copies are required to compromise cell function, parents do not show any signs of having (carrying) a mutated gene. SMA is an autosomal recessive disease. See Figure 4.

**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. The most well known X-linked recessive traits are hemophilia A and Duchenne muscular dystrophy (DMD).

## 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 (Paris, France) resulted in the identification of the SMA gene in 1995; this gene has been named SMN for "survival of motor neurons". Humans have two nearly identical copies of this gene that have been named SMN1 and SMN2. See figure 5a.

The major functional 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 throughout development.



**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. While 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 call 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.

# SMN1 Mutations

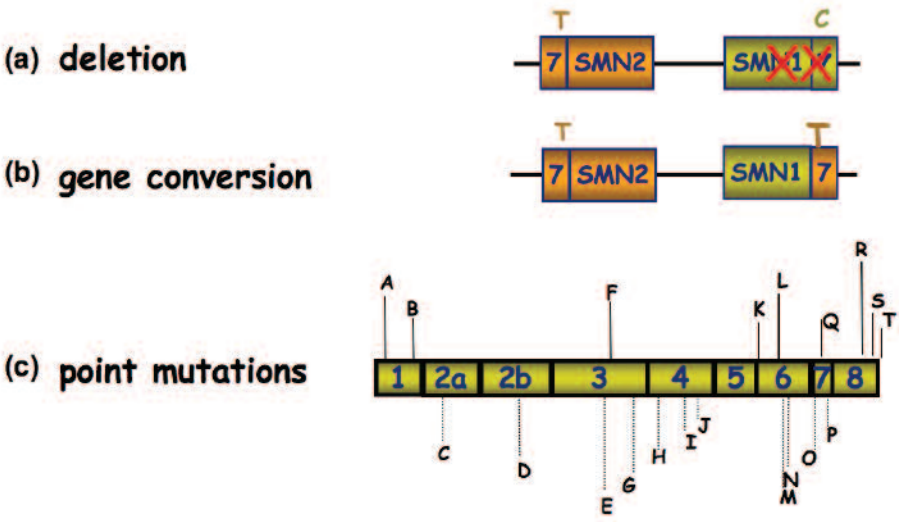
As 5q-SMA is an autosomal recessive disorder, individuals with this disease typically have inherited a faulty (mutant) SMN1 gene from each of their parents. The majority of mutations responsible for 5q-SMA are either deletions or gene conversions. See Figure 6.

- A deletion involves partial or complete removal of the SMN1 gene (Figure 6a) For example, type I SMA patients are generally missing both SMN1 genes and have 1 or 2 SMN2 genes.
- 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). This SMN1-converted gene now produces mostly mRNA transcripts missing exon 7. The majority of type III SMA patients have 1 or 2 SMN1-converted genes. Therefore, they have no functional SMN1 genes and 3 or 4 SMN2 genes.

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. See Figure 6c.

Because deletions/gene conversion mutations are very frequent and point mutations are very rare, about 96% of SMA patients are homozygous for deletion/gene conversion mutations: they have deletion/gene conversion mutations on both their chromosome 5s. Some rare SMA patients (about 4%) are compound heterozygotes: they have a deletion/gene conversion mutation on one of their chromosomes 5 and a point mutation on the other chromosome 5. The SMN gene composition in SMA patients, carriers and non-carriers is based on data reviewed in Ogino and Wilson (Ogino S and Wilson RB (2004) *Expert Rev Mol Diagn* 4(1):15-29.)



**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, and 96% of 5q-SMA patients have these two types of mutation, which 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 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 4% 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.

# Appropriate Genetic Testing

**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 these tools and knowledge are 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 or your relatives are carriers. If you or a relative is indeed a carrier, there is a risk of having a child with this disorder.
- **Prenatal testing:** to determine if your unborn baby has inherited this genetic disorder.

**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 (CVS) or amniotic fluid cells. DNA prepared from CVS or amniotic fluid cells can be used to detect the change in DNA (mutation) that causes 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 your baby 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:** Molecular analysis of SMA, using DNA prepared from a blood sample or fetal cells is now possible. 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 spouse or partner of a known SMA carrier.

**SMN diagnostic test:** Because both copies of SMN1 exon 7 are missing in most SMA individuals, 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 25 (4%) 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:** 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 1 copy of SMN1 are 5q-SMA carriers. Because most chromosome 5's have 1 SMN1 gene (about 96%) we can be certain that an individual with just one copy of SMN1 is indeed a 5q-SMA carrier.

**How certain are we that individuals with 2 copies of SMN1 are not carriers?** In the general population, about 2 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, there is about a 2 to 3% chance that this person has 2 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 and is passed on to offspring, but the same mutation is not present in the blood cells of the parent used to detect the SMN1 mutation

- A parent with a “de novo” mutation would have 2 copies of SMN1 (non-carrier), but still be at risk of having a child with SMA.

## Appropriate Genetic Testing cont.

Because of the existence of 2 SMN1 genes on one chromosome and de novo SMN1 mutations, the sensitivity of the quantitative SMN1 carrier test is not 100%. The quantitative SMN1 carrier test can detect about 95% of carriers in the general population.

**Do I have to have a DNA test or bank my DNA?** 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 professional health care worker (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 human SMN2 gene varies in the human 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.

SMN2 copy number has also been shown to modify SMA disease severity in mice. Data generated in the Burghes laboratory at the Ohio State University indicates that adding copies of the human SMN2 gene to SMA mice reduces their SMA symptoms. For example, SMA mice no longer show any signs of SMA when 8 copies of the SMN2 gene are present. Therefore, a higher number of SMN2 gene copies is broadly associated with less severe SMA symptoms.

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. Remember, 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 therapeutic 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. FSMA is funding a project at deCODE Genetics to find drugs to do this.
- The second is to correct the defective splicing of the SMN2 RNA. FSMA is funding a project at Paratek Pharmaceuticals to find drugs to do this.
- The third is to find drugs that stabilize the protein produced by the SMN2 gene. This strategy is currently being assessed by PTC Pharmaceuticals and the SMA Project funded by NINDS.

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 hydroxy urea) have been approved by the FDA for use in other human diseases and are being actively assessed in clinical trials for SMA at this time. 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

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 neuropathy, distal with vocal cord paralysis	DHMNVP, type VII, HMN VII, HMN7, Harper-Young myopathy	Autosomal Dominant
Arthrogryposis Multiplex Congenita, neurogenic type	AMCN	Autosomal Recessive
SMA, Distal, Type V	DSMAV, HMNV, dHMNV	Autosomal Dominant
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**

A number of additional inherited motor neuron diseases occur in children that are caused by mutations in genes other than the SMN1 gene. These are referred to as non-5q-SMAs, meaning that the genes causing these other forms of SMA are not located in the SMN region of chromosome 5. Similar to 5q-SMA, children 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-SMAs 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-SMAs is presented in Table 1.

# DNA Testing for Non-5q SMA

As mentioned previously, there are 3 billion DNA molecules in the human genome. Each time a cell divides, this DNA must be copied and errors can occur. Therefore, the genome sequence is not identical from one individual to another. If DNA changes affect the function of a gene, these changes are mutations and mutations can result in genetic disorders. If DNA changes do not affect the function of a gene, these changes are DNA variants (also called DNA polymorphisms).

For 5q-SMA, DNA variants were first used to link SMA to chromosome 5. Second, this information was used to physically identify the SMN gene. Third, mutations that affect the function of the SMN1 gene were then identified in SMA patients.

The faulty gene has been identified for a number of non-5q-SMAs and direct mutation analysis is now possible for family members. However, there are still a number of non-5q-SMAs where the gene and mutations responsible for muscle atrophy have not yet been identified. Nonetheless, genetic linkage studies can be used to confirm the diagnosis of a specific form of non-5q-SMA and determine carrier status for family members. On going research should lead to the identification of the mutations responsible for these disorders.

If you or a family member has been diagnosed with non-5q-SMA and would like more information, FSMA has an additional packet on the genetics on non-5q-SMA.

This educational brochure was produced thanks to the generosity of  
The Angel Baby Foundation.

# 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, 96% of patients have SMN1 gene deletions or SMN1 gene conversions. Only about 4% 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 point mutations. This means that this test can diagnose 96% of 5q-SMA cases, but not the 4% of patients with point mutations in the SMN1 gene.
- 8.** 95% of SMA cases can be detected prenatally using either amniocentesis or a chronic villus sample (CVS).
- 9.** Carrier testing can detect 97% of individuals carrying one copy of the SMN1 gene (SMA carriers). 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. Indeed, about 4 to 5% of SMA patients have non-5q-SMA. 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. DNA diagnostic tests are available for a subset of non-5q-SMA-like diseases, but not all of them at this time.



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