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## Facts About Spinal Muscular Atrophy

### What is Spinal Muscular Atrophy?

*Spinal muscular atrophy (SMA)* is a genetic disease affecting the part of the nervous system that controls voluntary muscle movement.

Most of the nerve cells that control muscles are located in the spinal cord, which accounts for the word *spinal* in the name of the disease. SMA is *muscular*, because its primary effect is on muscles, which don't receive signals from these nerve cells. *Atrophy* is the medical term for wasting or shrinkage, which is what generally happens to muscles when they're not active.

SMA involves the loss of nerve cells called *motor neurons* in the spinal cord and is classified as a *motor neuron disease*.

There's a great deal of variation in the scope and severity of SMA in different people.

### What causes SMA?

Most cases of SMA are caused by a deficiency of a motor neuron protein called *SMN*, for *survival of motor neurons*. This protein, as its name implies, seems to be necessary for normal motor neuron function. Recent evidence suggests that a lack of SMN might also directly affect muscle cells.

There are other forms of SMA not related to the SMN protein.

### What are the forms of SMA?

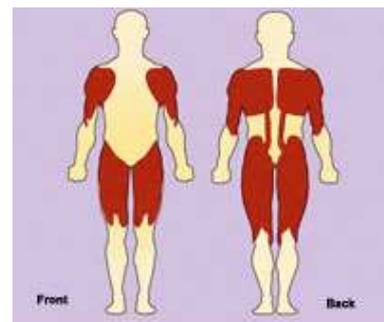
#### *SMN-Related SMA*

SMN-related SMA is usually broken down into three categories. Type 1 is the most severe with the earliest age of onset, and type 3 is the least severe, with the latest age of onset. Some doctors add a type 4 for moderate or mild SMA that begins in adulthood.

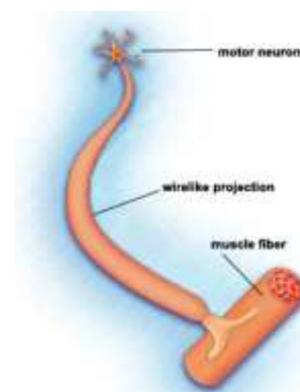
All these types are related to genetic mistakes (the scientific term is mutations) on chromosome 5 that affect the amount of SMN protein that can be produced. In general, a higher level of SMN protein lessens the severity of SMA. See "Does It Run in the Family?" for more about how these mutations lead to SMA.

#### *Non-SMN SMA*

There are also forms of SMA that aren't related to SMN and don't stem from chromosome 5 mutations. For more about these disorders, see "What Happens to People With Other Forms of SMA?"



The muscles closer to the center of the body (proximal muscles) are usually more affected in spinal muscular atrophy than are the muscles farther from the center (distal muscles).



Muscle-controlling nerve cells (motor neurons) are located mostly in the spinal cord. Long, wire-like projections connect the motor neurons to muscles in the limbs and trunk. Normally, signals from the neurons to the muscles cause muscles to contract. In SMA, motor neurons are lost, and muscles can't function.



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### *Spinal-Bulbar Muscular Atrophy*

A type of SMA that's usually called SBMA, for spinal-bulbar muscular atrophy, stems from a gene defect on the X chromosome. This type of SMA, also known as Kennedy's disease, is quite different from the chromosome 5 type. See SBMA for more information.

## **What happens to someone with SMN-Related SMA?**

The severity of SMN-related SMA is roughly correlated with how early symptoms begin, which in turn is roughly correlated with how much SMN protein there is in the motor neurons. The later the symptoms begin and the more SMN protein there is, the milder the course of the disease is likely to be.

Most doctors, however, now consider SMN-related SMA to be a continuum of severity and prefer not to make rigid predictions about life expectancy or weakness based strictly on age of onset. Recent research has supported this flexibility.

### *Type 1 SMA (Werdnig-Hoffmann Disease)*

Children with SMA who are very weak in the early months of life and have breathing, sucking and swallowing difficulties in infancy aren't likely to have a good prognosis. In the past, it was said that such children weren't likely to survive more than two years. Today, this is still often true.

However, increasingly, modern technology is being used to ensure that children have the best quality of life possible. Non-invasive mechanical ventilation (using a face mask rather than by inserting a tube into the wind pipe) and feeding tubes can assist natural breathing and eating functions.

Mental and emotional development and sensation are entirely normal in SMA.

### *Type 2 SMA (Intermediate SMA)*

A diagnosis of type 2 SMA allows parents and children to plan for a future, even if life span may be shorter than normal. This type of SMA begins in childhood but generally after infancy. Some sources say the onset has to be between 6 and 18 months to be type 2. Others say that any child who has been able to sit without support after being placed in a sitting position can be classified as type 2.

The muscles closer to the center of the body (proximal muscles) are usually more affected, or at least affected much sooner, than the muscles farther away from the center in SMA type 2. For example, the muscles of the thighs are weaker than the muscles of the lower legs and feet.

Also, legs tend to weaken before arms. Hands may get weak eventually, but they usually stay strongest the longest, and, even if they do weaken, they usually remain strong enough for typing on a computer keyboard and other basic functions of modern life.

Children with type 2 SMA benefit greatly from physical therapy and assistive technology of all kinds. Aids to walking and standing, such as lightweight braces (*orthoses*) and standing frames, allow for more mobility today than in the past.



*Many children with SMA can benefit greatly from physical therapy and assistive technology.*



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Many children can handle a power wheelchair or other type of powered vehicle very early, even at age 3 or so, depending on the child's maturity and general outlook. Many professionals have observed that children with SMA seem unusually intelligent, and a small body of research supports this observation.

The most serious danger in type 2 SMA comes from the weakness of muscles necessary for breathing. Careful attention to respiratory function is needed throughout life, with prompt attention to infections. Your doctor can help you with details of maintaining respiratory health, including clearance of secretions and perhaps assisted ventilation (not necessarily around the clock).

Another major problem in type 2 SMA is spinal curvature, usually a side-to-side type of curvature called *scoliosis*. Scoliosis occurs because of weakness of the muscles that normally support the spine, which is a flexible column. Scoliosis can be very uncomfortable, interfere with position and mobility, and damage a child's (or adult's) body image. Some studies have shown that spinal curvatures, if they're severe, can interfere with breathing.

Many children with SMA start to show a scoliosis curve early in life. Surgeons generally like to wait until growth is complete or nearly so before surgically straightening and fusing the spine. They also take into account the child's lung function and how fast the curve is likely to progress.

At this time, life expectancy in childhood-onset SMA varies. Survival is often into middle age or beyond.

#### ***Type 3 SMA (Kugelberg-Welander Disease or Mild SMA)***

Some sources describe type 3 SMA as a type of SMA that begins any time after 18 months of age, while others prefer to describe it as SMA that begins after the child has started walking or has taken at least five independent steps.

Many people with this type of SMA walk until their 30s or 40s, although some stop walking in adolescence.

Careful attention to respiratory function and potential spinal curvature remain important. Adaptive equipment, such as power wheelchairs, tools for using a computer, etc., are usually essential in type 3 SMA. Some people need only a cane and perhaps a portable seat, with a wheelchair for going longer distances, as in airports and malls.

People with this milder type of SMA can survive long into adulthood.

#### ***Type 4 SMA (Adult-Onset SMA)***

This is a still milder type of SMA on the continuum. By definition, it begins in adulthood. Some physicians lump types 3 and 4 or types 2 and 3 together.



*Scoliosis (spinal curvature) is a common problem in SMA and should be corrected.*



*People with SMA type 3 often retain some ability to walk well into adulthood.*



## What happens to people with other forms of SMA?

Other types of SMA, not related to the SMN deficiency, vary greatly in severity and in the muscles most affected. Some forms of SMA, like the SMN-related type, affect mostly the proximal muscles, while others affect mostly the *distal* muscles, those farther away from the body's center, at least at the beginning. The hands and feet are typically affected early in the disease.

Sometimes, in adults with a disorder of uncertain origin that affects only the motor neurons in the spinal cord and lower part of the brain, the condition is referred to as *progressive muscular atrophy*. This condition sometimes progresses to involve motor neurons in the upper part of the brain, and it's then referred to as *amyotrophic lateral sclerosis (ALS)* or *motor neurone disease (MND)*. It doesn't always become ALS/MND.

Special aspects of SBMA are discussed below.

While all known forms of SMA are apparently genetic, they result from defects in different genes and have different inheritance patterns and implications for family planning.

If you or your child has been told the diagnosis is SMA but it's not the SMN-related type, you'll need to talk with your doctor and perhaps a genetic counsellor to find out more about the genetics and prognosis for the particular SMA involved.

## How is SMA treated?

The biggest potential problems in SMA, especially the chromosome 5 type, are, in approximate order of importance:

1. respiratory muscle weakness
2. swallowing muscle weakness
3. back muscle weakness with progressive spinal curvature
3. abnormal reactions to muscle-relaxing medications

These problems can be, and need to be, treated or prevented.

### 1. Respiratory Muscle Weakness

In the more severe forms of SMN-related SMA, and in some other forms of SMA, respiratory muscle weakness is an enormous problem. It's the usual cause of death in types 1 and 2 SMA. When the respiratory muscles weaken, air doesn't move into and out of the lungs very well, with subsequent adverse effects on general health. Signs of weakening respiratory muscles are headaches, difficulty sleeping at night, excess sleepiness during the day, poor concentration, chest infections and, eventually, possible heart damage and respiratory failure.

In type 1 SMA, the muscles between the ribs are very weak, while the diaphragm muscle stays fairly strong. This leads to children who appear to be breathing by moving their bellies rather than their chests and to a pear-shaped body in these infants.



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Parents of newborns with type 1 SMA may face the question of whether to prolong the lives of their children, who weren't expected to survive more than two years. In recent years, the availability of more portable, less invasive ventilation devices has given parents more choices to maximize the quality of life of their children.

For children and adults with SMA who are less severely affected, various types of ventilatory assistance can help. Many physicians advise starting out with non-invasive ventilation, which generally means air (usually room air, not enriched with oxygen) delivered under pressure through a mask or mouthpiece.

This kind of system comes in many forms and can be used as many hours of the day and/or night as necessary. It can easily be removed for eating, drinking, talking or, when possible, breathing normally without it.

For severely affected children and adults, ventilatory assistance delivered through a tracheostomy — a surgical hole in the trachea, or windpipe — can be considered.

## 2. Swallowing Muscle Weakness

Weakness of the muscles of the mouth and throat cause problems in swallowing, especially in the more severe forms of SMA. Babies with type 1 SMA usually have trouble swallowing and sucking and, in the past, this in itself often brought an end to their lives. Sucking weakness led to dehydration and poor nutrition, while swallowing weakness led either to obstruction of the airway by inhaled food or liquids or to respiratory infections from them. The medical term for this kind of inhalation is aspiration.

Nowadays, babies who can't swallow can be fed with alternative methods, such as a *gastrostomy tube*. Modern systems are often constructed so that the tube can be detached from a "button" on the abdomen when it's not in use. Liquid food, readily available in stores, is put into the tube either with a syringe or via a feeding pump. Some people grind up their own food.

Some gastrostomy tube users also eat and drink through the mouth, in addition to using the tube. If the main problem is weakness of the chewing muscles, making eating laborious and time-consuming, then it's fine to eat for pleasure and extra nutrition and use the gastrostomy tube for basic calories. If, on the other hand, the main reason for the tube is constant inhaling of food and liquid, then it's probably not safe to eat and drink through the mouth.

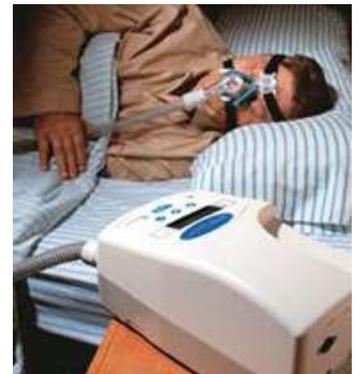
In *SBMA*, swallowing and chewing muscle weakness pose a choking hazard. A swallowing specialist should be consulted to determine the safest ways of swallowing and altering food consistency. A feeding tube can be considered in cases of extreme weakness.

## 3. Back Muscle Weakness

Weakness of the muscles of the back that normally support the flexible, growing spine is a major problem in childhood-onset SMA. If it's not corrected, the child may develop scoliosis — a side-to-side curvature of the spine — or *kyphosis*, a forward curvature of the spine, or both. Some may even end up with "pretzel" types of curvatures that make it impossible to sit or lie down with comfort.



*Noninvasive ventilation can be delivered through a mask or mouthpiece. (Photo on right courtesy of Respironics)*



*Because SMA affects the swallowing muscles, this baby is fed through a gastrostomy tube.*



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Many physicians believe that severe spinal curvatures also compromise respiratory function, since the curved spine may compress a lung. In severe SMA, it's hard to say how much respiratory decline would have occurred even without the curvature, so its contribution is uncertain.

The permanent solution to spinal curvature is almost always spine-straightening surgery (spinal fusion), which can be done if the child's respiratory status is good enough to withstand the surgery. Doctors generally like to wait until maximum spinal growth has been achieved, so a simpler surgical technique can be used. On the other hand, they often can't wait until growth is complete, because respiratory status may be deteriorating at the same time. The timing of back surgery is tricky. Here again, the team at your Neuromuscular clinic can help you decide.

#### 4. Anaesthesia Concerns

A child or adult with SMA who must undergo surgery (for example, to correct scoliosis) needs to take special precautions. The surgical team, particularly the anaesthetist, must thoroughly understand SMA.

Sometimes, especially in the early stages of SMA, the muscle cells that aren't receiving nerve signals develop certain abnormalities as they try to "reach out" to nerves. These abnormalities can lead to dangerous reactions to muscle-relaxing drugs often used during surgery. Doctors can get around this problem if they're aware of it, by using different drugs.



*People with SMA must take special precautions when undergoing anesthesia.*

### What about diet?

Many people wonder whether feeding their child or themselves in a special way will affect the course of SMA. So far, there's little evidence to suggest that any particular type of diet is useful in SMA.

It seems to make sense to many parents that a high-protein diet or some sort of special nutritional formula will help their child's muscles get stronger. While it's certainly true that children with SMA need good nutrition, there's no evidence that any particular type of diet is necessary. Some children may do better with small, frequent feedings than with three large meals a day.

Some children and many adults with SMA become overweight, probably because they can't exercise effectively and are taking in too many calories for their level of activity. With the guidance of a physician or nutritionist, it should be possible to keep weight under control, which is important for health, appearance and the backs of caregivers who must often help with lifting and transferring every day.

Some physicians recommend over-the-counter supplements, including creatine and/or coenzyme Q10, to meet nutritional needs. Creatine is being studied in SMA.

Your doctor and a dietitian can help you with nutritional issues for yourself or your child.



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## What kind of exercise is best?

Most physicians advise people with SMA and parents of children with SMA that doing as much physical activity as is comfortable without going to extremes is a good idea, for general physical and psychological health and well-being.

It's important to protect joints from stiffness or injury, preserve range of motion (flexibility in the joints), maintain circulation and, especially for children, allow enough mobility for exploration of the environment.

Exercising in a warm pool may be particularly beneficial. A person with SMA shouldn't swim alone, and appropriate safety precautions should be provided.

Some physical therapy experts have raised questions about whether it's wise to put too much demand on a gradually decreasing number of motor neurons, which have to do the work that would normally be done by many more such cells. Research is needed to determine whether this theoretical issue should actually be considered in designing an exercise plan. Some experts believe it's impossible to overdo it, while others believe exercising to exhaustion can "burn out" remaining motor neurons before their time. It seems sensible to exercise with discretion and stop before reaching the point of exhaustion.

*Physical therapy and occupational therapy* programs can help both children and adults learn the best ways to use the muscle function they have and to come up with the most effective ways to accomplish activities of daily living. You can obtain a referral to a physical or occupational therapist through your Neuromuscular clinic.

Today, an array of assistive technology products can help even very young children explore the world despite having very weak muscles. Stenders, walkers, various kinds of powered and manual wheeled vehicles, and braces (the medical term is orthoses) can help with standing and moving around. Therapists can also help teachers and parents find the best physical solutions for the school environment.

Some families have even designed and built their own vehicles with special capabilities, such as adjustable heights that allow children to explore things at floor level or sit at tables and desks.

Special aids for writing, painting, using a computer or telephone, and electronically controlling the environment (for example, temperature, lighting, television and so forth) are helpful to adults and children with SMA-related weakness.

## How is SMA diagnosed?

The first steps in diagnosis of a neuromuscular disease are usually a physical examination and family history, with some tests to distinguish SMA from similar conditions (such as muscular dystrophy).

The doctor may order a simple blood test for an enzyme called creatine kinase (CK). This enzyme leaks out of muscles that are deteriorating. It's a non-specific test, since CK levels are elevated in many neuromuscular diseases, but it's often useful anyway. High blood CK levels aren't harmful; they're just an indicator of muscle damage.



*Physical therapy is an important part of preserving joint flexibility in SMA.*



*Adults with SMA are often able to drive with specialized hand controls.*



*Occupational therapy can help people with SMA learn to write, use a computer and do other daily tasks.*



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The doctor will probably recommend genetic testing if SMA is suspected, since this is the least invasive and most accurate way to diagnose SMN-related SMA or SBMA.

Genetic testing requires only a blood sample. However, it has implications for the whole family that must be considered (see "Does It Run in the Family?").

Genetic tests are readily available for SMN-related SMA and SBMA, while genetic tests for the rarer forms of SMA are generally available only as part of a research study. However, such tests are improving and expanding rapidly, as knowledge and technology improve. In the near future, highly detailed genetic tests for SMN-related SMA will likely be used to predict the course of the disease with greater accuracy than is now possible.

It's a good idea to talk with a genetic counsellor when someone in the family is found to have a genetic disease or when testing is undertaken. You could do this through their neuromuscular clinic or the MDA can help you find one.

The age distribution and symptoms of SBMA and adult-onset SMA overlap with those of another motor neuron disease, ALS, so the two are sometimes confused early in the diagnostic workup. It's very much worth knowing which disorder affects you or your family members, since ALS is a much more severe and rapidly progressive condition than are SBMA or adult-onset SMA.

In rare cases, doctors want the person suspected of having SMA to have a muscle biopsy, which involves taking a small sample of muscle tissue, usually from the thigh, and looking at it under a microscope.

Other tests that may be requested are those that measure nerve conduction velocity — the speed with which signals travel along nerves — and the electrical activity in muscle. The latter is called an electromyogram, or EMG. Nerve conduction velocity tests involve sensations that feel like mild electric shocks, and EMGs require that short needles be inserted in the muscles.

## What is Spinal-Bulbar Muscular Atrophy?

Spinal-bulbar muscular atrophy, or SBMA, is sometimes called Kennedy's disease, after William Kennedy, the physician who originally described the disease in 1968. It's also sometimes called *bulbospinal muscular atrophy*.

This disease is a variant of spinal muscular atrophy. The adjective *bulbar* refers to a bulblike structure in the lower part of the brain that contains nerve cells controlling muscles in the face, mouth and throat.

SBMA also involves weakness and atrophy of the arm and leg muscles, particularly those nearest the center of the body. Twitching or cramping of muscles can also occur.

## What Happens to Someone With SBMA?

SBMA mostly affects men and usually begins between the ages of 30 and 50, although symptoms have begun in boys as young as 15 or men as old as 60. In those few women who have the disease, the symptoms are usually mild.



*A physical exam is a key part of diagnosing SMA.*



*A nerve conduction velocity test may be part of the diagnostic process in SMA.*



*SBMA usually affects men between ages 30 and 50.*



SBMA is different from other forms of late-onset SMA. In contrast to most forms of SMA that begin in adulthood, the bulbar muscle involvement in SBMA can be significant, affecting speech, chewing and swallowing. The swallowing muscle weakness can lead to choking on food or liquids or inhaling them into the lungs. This kind of inhalation can lead to obstruction of airways or infection.

Weakness in the throat muscles can also make breathing during sleep difficult. Ventilation aids, which push air in under pressure, can help with this.

Facial muscle weakness can occur, making it hard to smile or convey emotion through facial expressions.

SBMA is *like* other forms of adult-onset SMA in that it causes weakness of the limbs. This weakness is often first noticed as trouble with stairs or difficulty walking long distances, such as through malls or parking lots. It progresses very slowly, over decades. As time goes by, a cane may be sufficient help for short distances, while a scooter or wheelchair may be needed for longer ones.

One aspect of SBMA that doesn't apply to any other form of SMA is that men with the disease can develop enlarged breasts (*gynecomastia*) and may have reduced fertility and atrophy (shrinkage) of the testicles. These symptoms, which became important clues to the cause of the disease, are related to the way the body's cells fail to process male hormones, known as *androgens*.

The usual form of SBMA is inherited in an *X-linked pattern* (see "Does It Run in the Family?").

## What is the underlying cause of SBMA?

The genetic flaw in X-chromosome SBMA is an expanded section of DNA called a *trinucleotide* repeat in a gene that carries instructions for a protein known as the *androgen* receptor.

The normal function of the androgen receptor is to help cells process androgens (male hormones). When the androgen receptor has extra DNA, it's longer than it's supposed to be and may be sticky. The flawed androgen receptor can't transport male hormones in the right way, and it may "gum up the works" of motor neurons in other ways that keep them from performing their usual functions.

## Can women develop SBMA?

Because SBMA is an X-linked disease, it usually affects men. However, in some cases, women can have the disease, although it's almost always a very mild case.

The second X chromosome that females have is usually enough to protect them from most aspects of the disease. However, females (who also produce and use androgens, although less so than males) carrying the androgen receptor gene defect on one X chromosome (*carriers* of SBMA) can have muscle cramps and twitches, particularly as they get into their 60s or 70s. The hormonal differences between men and women may also contribute to the less severe course in women.



## Does it run in the family?

When people learn that a family member has a genetic disorder, they often wonder how this could be the case if it doesn't "run in the family."

The chromosome 5 (SMN gene) type of SMA (the most common type) follows an inheritance pattern known as *autosomal recessive*, which often takes families by surprise. Diseases that are *recessive require* two gene flaws — usually one from each parent, but occasionally one from one parent and one that occurs as a fetus is being formed — before the disease shows itself. People who have only one gene mistake (mutation) for a recessive disease are said to be carriers and usually show no symptoms. Often, a family has no idea that some members are carriers until a child is born with a recessive disorder.

The *autosomes* are the numbered chromosomes, that is, all the chromosomes except the X and the Y, which determine gender.

If both parents are carriers of SMN-related SMA, the risk of each pregnancy producing a child with the disease is 25 percent. This risk doesn't change no matter how many children in the family have been affected previously. The "dice are rolled again" with each new conception.

Genetic testing for chromosome 5 SMA is widely available for those suspected of having the disease, including unborn babies. However, carrier testing for SMA is more difficult and not as widely available.

Genetic testing is expanding and changing rapidly, but its implications can be complex. It's best to talk with a genetic counsellor (through your neuromuscular clinic) before embarking on testing.

In contrast to chromosome 5 (SMN-related) SMA, the gene mutation causing most cases of spinal-bulbar muscular atrophy (SBMA) is on the X chromosome, leading to an X-linked inheritance pattern.

Females have two X chromosomes, and males have an X and a Y chromosome. Females who have a gene mutation on one X chromosome are usually considered 'carriers' of an X-linked disease (although sometimes they can have a mild form of the disease). Males, in contrast, have no second X to protect them from the full effects of a gene mutation on the X chromosome and show the full effects of such a mutation.

Males who inherit an X-linked gene mutation generally have the disease. Each son of a woman who carries an X-linked disease has a 50 percent chance of inheriting the gene mutation and developing the disease. Each daughter has a 50 percent chance of inheriting the gene mutation and being a carrier herself.

Genetic testing via a blood test is available for SBMA.

For more on genetics and genetic testing, see the MDA publication "Genetics and Neuromuscular Diseases."



*In this family, two of the six children have SMA because they each inherited a flawed gene from each parent. The other children may be SMA carriers, able to pass a flawed gene to their*



## Search for treatments and cures

The research picture has brightened considerably for chromosome 5-linked SMA in the last decade.

There are some special circumstances that pertain to the genetics of SMN-related, chromosome 5 SMA, and these have provided researchers with some special opportunities for intervention.

Since 1995, scientists have known that the main gene that determines whether someone develops SMA is a gene for the SMN protein. The SMN gene comes in two slightly different versions, called *SMN1* (also known as *SMN-T*) and *SMN2* (also known as *SMN-C*).

The protein molecules made from the *SMN1* gene's instructions are longer than most of those made from the *SMN2* gene. These longer ("full-length") SMN protein molecules appear to be necessary for the proper survival and function of the motor neurons.

The *SMN2* gene can provide a certain amount of full-length SMN protein, but not enough. Fortunately, many people have multiple copies of the *SMN2* gene on one or both of their chromosome 5s. These "extra" *SMN2* genes can lessen the impact of a flaw in both *SMN1* genes. In general, the more *SMN2* genes a person has, the milder the course of his or her chromosome 5 SMA is likely to be.

Many research strategies to treat SMA are based on increasing production of full-length SMN from the *SMN2* gene.

Other approaches include less specific methods of helping motor neurons to survive in adverse circumstances.

Drugs that are based on *neurotrophic factors* (natural body chemicals that have a positive effect on nerve cells) and *anabolic* (tissue-building) chemicals are under consideration.

Also being studied is *creatine*, a substance that may help muscle or nerve cells produce energy more readily.

In SBMA, research has focused largely on strategies to block the formation of abnormal clumps found inside cells in this condition; ways to interfere with some of the actions of male hormones; and methods to influence how genetic instructions are "read" by cells. (See "What Is Spinal-Bulbar Muscular Atrophy?" for more on SBMA.)