Spinal Muscular Atrophy (SMA) is an inherited genetic condition that mainly affects muscle movement. It is characterized by progressive weakness and wasting of muscles due to a loss of motor neurons involved in muscle movement control. Motor neurons are needed to transmit signals from the brain and spinal cord to the muscles, which tells the muscles when to contract, which allows the body to move.

People with SMA have muscle weakness that typically worsens with increasing age. Muscles that are closer to the center of the body (proximal) are typically more affected than muscles that are further away from the center of the body (distal). In additional to muscle weakness and wasting of muscles, people with SMA can also experience poor weight gain and growth failure, restrictive lung disease, scoliosis, joint contractures, and sleep difficulties. SMA is not thought to impact the brain directly, so generally people with SMA have normal intelligence and cognitive functioning.

There are many types of SMA, broken down by the age of onset as well as the severity of the muscle weakness.

SMA Type 0: The rarest and most severe form of SMA that is evident before birth. Pregnancies that are affected with SMA type 0 generally appear to show less fetal movement, often resulting in joint deformities (contractures) at birth. Some infants may also have congenital (from birth) heart defects. Affected infants have severe muscle weakness and low muscle tone (hypotonia), especially the muscles in the respiratory system. Because of this, most infants with SMA type 0 do not survive past infancy due to respiratory failure.

SMA Type 1: The most common form of SMA, and babies with SMA type 1 can typically be identified at birth or shortly thereafter. Affected infants are unable to control head movements or sit independently. They may also experience swallowing difficulty. Weakness of the respiratory muscles often leads to respiratory failure. Most infants and children with SMA type 1 do not survive past early childhood.

SMA Type 2: Muscle weakness develops in children with SMA type 2 between 6 to 12 months. Affected children can typically sit unassisted but may required help getting into the seated position. Their weakness, however, is progressive and becomes worse later in childhood. They are unable to stand or walk unaided, and can often also have scoliosis, tremors of the fingers, and weakness of the respiratory muscles that can be fatal. The lifespan of these affected individuals varies but many are able to live into their twenties or thirties.

SMA Type 3: Develops after 12 months of age, with onset after affected children have

started standing and walking independently. Muscle weakness predominantly affects the lower extremities before progressing to the upper limbs. Difficulty walking or climbing stairs is common, however some affected individuals retain the ability to walk into adulthood. Scoliosis and finger tremors are also common, with less respiratory involvement than types 1 or 2. Life expectancy is normal or near-normal.

SMA Type 4: This adult-onset form is typically diagnosed in the third decade of life, presenting with gradual muscle weakness affecting the legs and hips before progressing to the shoulders and arms. Mobility is often affected, with a 'waddling gait' being fairly common, and affected individuals may eventually require the use of a wheelchair or other assistance. Finger trembling and muscle twitches may also occur. Life expectancy is normal.

In the past, individuals were classified into these different subtypes based on their physical presentation. With our increasing understanding of the genetics behind SMA, we are finding that there may be an even wider spectrum of how severely someone with SMA is affected. Combining someone's physical presentation with their genetics can sometimes make it difficult to classify a patient clearly into a sub-type.

Causes

We have over 20,000 different genes in the body. These genes are like instruction manuals for how to build a protein, and each protein has an important function that helps to keep our body working how it should. The *SMN1* gene makes a protein called the survival motor neuron (SMN) protein. The SMN protein is found throughout the body, but is the most concentrated in the spinal cord, and it works to keep special nerve cells (called motor neurons) working. These motor neurons are responsible for carrying signals from the brain and the spinal cord to our muscles that tell them to contract, which allows the body to move.

If someone has a harmful change (called a pathogenic variant) in **both** of their *SMN1* genes (the one they got from their mom **and** the one they got from their dad), then their body is not going to make enough of the SMN protein. If the body does not have enough SMN protein, then the motor neurons cannot transmit the signals from the brain and spinal cord to the muscles in the body as easily. Without signals to tell the muscles to contract, the muscles can become weaker and waste away. This is what leads to the symptoms we associate with SMA.

In addition to the *SMN1* gene, the number of *SMN2* genes that someone has can be helpful to try to predict the severity of the condition. Like the *SMN1* gene, the *SMN2* gene is responsible for making SMN proteins. However, the amount of SMN proteins made by the

SMN2 gene is relatively small compared to the *SMN1* gene. While we all have two copies of the *SMN1* gene, the number of *SMN2* genes that people have varies, ranging from one to eight copies. Having multiple copies of the *SMN2* gene and the SMN proteins that they make can help to make up for the lack of SMN proteins caused by the non-working *SMN1* genes. This is believed to be associated with less severe symptoms of SMA, but the exact relationship between the number of *SMN2* genes and the severity of the SMA symptoms is not fully understood yet.

SMA is inherited in an autosomal recessive pattern. This means an individual who has SMA has inherited two non-working copies of the *SMN1* gene; the one they inherited from their mom is not working **and** the one they inherited from their dad is not working. In the case of autosomal recessive conditions, if you inherit one working *SMN1* gene from a parent and one non-working *SMN1* gene from a parent, you are called a 'carrier' for SMA. Carriers do not have SMA, and typically do not have signs or features of SMA.

It is estimated that approximately 1 in 8000 to 1 in 10,000 people have spinal muscular atrophy. About half of these will have SMA type 1.

Medical Management for SMA

Management of SMA should include an assessment of the patient's nutritional state, their respiratory function, and an evaluation of their bones. If nutrition is a concern, placement of a gastrostomy tube (G-tube) may be recommended. Consultation with a pulmonologist familiar with SMA is also recommended, especially if issues with respiratory function become a problem. Children with SMA should have an evaluation that looks at their muscles and bones to see if they are having any difficulties that may be improved with additional therapies or services, such as a wheelchair or orthotic inserts.

Research on SMA has focused on increasing the body's production of SMN proteins, since the absence of this is what causes SMA. In 2017, the U.S. Food and Drug Administration (FDA) approved a treatment called antisense therapy for SMA, which basically changes someone's *SMN2* genes so that they can produce more of the SMN protein. Because this therapy is designed to treat SMA by going directly to the cause of it, this medication could potentially be effective at slowing or stopping the symptoms of SMA.

Click here to learn more about scheduling a genetic counseling appointment for pregnancy-related questions.

Click here to learn more about scheduling a genetic counseling appointment for infertility or preconception questions.

Click here to learn more about scheduling a genetic counseling appointment for questions about pediatric or adult genetic conditions.

Additional Resources

Spinal Muscular Atrophy Foundation

GeneReviews

Genetics Home Reference