SMN1 and Spinal Muscular Atrophy

Description

Spinal muscular atrophy is a genetic disorder that affects the control of muscle movement. It is caused by a loss of specialized nerve cells called motor neurons in the spinal cord and the part of the brain that is connected to the spinal cord (the brainstem). The loss of motor neurons leads to weakness and wasting (atrophy) of muscles used for activities such as crawling, walking, sitting up, and controlling head movement. In severe cases of spinal muscular atrophy, the muscles used for breathing and swallowing are affected. **There are many types of spinal muscular atrophy distinguished by the pattern of features, severity of muscle weakness, and age when the muscle problems begin.**

Type I Spinal Muscular Atrophy

Type I spinal muscular atrophy also called Werdnig-Hoffman disease is a severe form of the disorder that is evident at birth or within the first few months of life. Affected infants are developmentally delayed, most are unable to support their head or sit unassisted. Children with this type have breathing and swallowing problems that may lead to choking or gagging.

Type II Spinal Muscular Atrophy

Type II spinal muscular atrophy is characterized by **muscle weakness that develops in children between ages 6 and 12 months.** Children with type II can sit without support, although they may need help getting to a seated position. Individuals with this type of spinal muscular atrophy cannot stand or walk unaided.

Type III Spinal Muscular Atrophy

Type III spinal muscular atrophy also called Kugelberg-Welander disease or juvenile type **has milder features that typically develop between early childhood and adolescence.** Individuals with type III spinal muscular atrophy can stand and walk unaided, but walking and climbing stairs may become increasingly difficult. Many affected individuals will require wheelchair assistance later in life.

Type IV Spinal Muscular Atrophy

The signs and symptoms of type IV spinal muscular atrophy **often occur after age 30. Affected individuals usually experience mild to moderate muscle weakness, tremor, twitching, or mild breathing problems.** Typically, only muscles close to the center of the body (proximal muscles), such as the upper arms and legs, are affected in type IV spinal muscular atrophy.

X-Linked Spinal Muscular Atrophy

The features of X-linked spinal muscular atrophy appear in infancy and include severe muscle weakness and difficulty breathing. Children with this type often have joint deformities (contractures) that impair movement. In severe cases, affected infants are born with broken bones. Poor muscle tone before birth may contribute to the contractures and broken bones seen in these children.

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Spinal Muscular Atrophy Dominant (SMA-LED)

Spinal muscular atrophy, lower extremity, dominant (SMA-LED) **is characterized by leg muscle weakness that is most severe in the thigh muscles (quadriceps). This weakness begins in infancy or early childhood and progresses slowly.** Affected individuals often have a waddling or unsteady walk and have difficulty rising from a seated position and climbing stairs.

Adult-Onset Spinal Muscular Atrophy

An adult-onset form of spinal muscular atrophy that **begins in early to mid-adulthood affects the proximal muscles** and is characterized by muscle cramping of the limbs and abdomen, weakness in the leg muscles, involuntary muscle contractions, tremors, and a protrusion of the abdomen thought to be related to muscle weakness. Some affected individuals experience difficulty swallowing and problems with bladder and bowel function.

Frequency - How Often Does Spinal Muscular Atrophy Occur?

Spinal muscular atrophy occurs in approximately 1 in 6,000 to 10,000 newborns in the United States. SMA occurs in people of every race and ancestry, but is more common in the Caucasian (White) population, with a carrier frequency of 1 in 35.

Normal Function of the SMN1 Gene And Genetic Changes

Mutations in the SMN1, UBA1, DYNC1H1, and VAPB genes cause spinal muscular atrophy. Extra copies of the SMN2 gene modify the severity of spinal muscular atrophy.

The SMN1 and SMN2 genes provide instructions for making a protein called the survival motor neuron (SMN) protein. The SMN protein is important for the maintenance of specialized nerve cells called motor neurons. Motor neurons are located in the spinal cord and the brainstem; they control muscle movement. **Most functional SMN protein is produced from the SMN1 gene, with a small amount produced from the SMN2 gene. Several different versions of the SMN protein are produced from the SMN2 gene, but only one version is full size and functional.**

Mutations in the SMN1 gene cause spinal muscular atrophy types I, II, III, and IV. SMN1 gene mutations lead to a shortage of the SMN protein. Without SMN protein, motor neurons die, and nerve impulses are not passed between the brain and muscles. As a result, some muscles cannot perform their normal functions, leading to weakness and impaired movement.

Some people with type II, III, or IV spinal muscular atrophy have three or more copies of the SMN2 gene in each cell. Having multiple copies of the SMN2 gene can modify the course of spinal muscular atrophy. The additional SMN proteins produced from the extra copies of the SMN2 gene can help replace some of the SMN protein that is lost due to mutations in the SMN1 gene. In general, symptoms are less severe and begin later in life as the number of copies of the SMN2 gene increases.

Mutations in the UBA1 gene cause X-linked spinal muscular atrophy. The UBA1 gene provides instructions for making the ubiquitin-activating enzyme E1. This enzyme is involved in a process that targets proteins to be broken down

(degraded) within cells. UBA1 gene mutations lead to reduced or absent levels of functional enzyme, which disrupts the process of protein degradation. A buildup of proteins in the cell can cause it to die; motor neurons are particularly susceptible to damage from protein buildup.

The DYNC1H1 gene provides instructions for making a protein that is part of a group (complex) of proteins called dynein. This complex is found in the fluid inside cells (cytoplasm), where it is part of a network that moves proteins and other materials. **In neurons, dynein moves cellular materials away from the junctions between neurons (synapses) to the center of the cell. This process helps transmit chemical messages from one neuron to another. DYNC1H1 gene mutations that cause SMA-LED disrupt the function of the dynein complex.** As a result, the movement of proteins, cellular structures, and other materials within cells are impaired. A decrease in chemical messaging between neurons that control muscle movement is thought to contribute to the muscle weakness experienced by people with SMA-LED. It is unclear why this condition affects only the lower extremities.

The adult-onset form of spinal muscular atrophy is caused by a mutation in the VAPB gene. The VAPB gene provides instructions for making a protein that is found in cells throughout the body. Researchers suggest that this protein may play a role in preventing the buildup of unfolded or misfolded proteins within cells. It is unclear how a VAPB gene mutation leads to the loss of motor neurons. An impaired VAPB protein might cause misfolded and unfolded proteins to accumulate and impair the normal function of motor neurons.

Other types of spinal muscular atrophy that primarily affect the lower legs and feet and the lower arms and hands are caused by the dysfunction of neurons in the spinal cord. When spinal muscular atrophy shows this pattern of signs and symptoms, it is also known as distal hereditary motor neuropathy. The various types of this condition are caused by mutations in other genes.

Pattern of Inheritance - How Is Spinal Muscular Atrophy Inherited?

Types I, II, III, and IV spinal muscular atrophy are inherited in an autosomal recessive pattern. This type of inheritance requires the presence of two copies of a pathogenic variant in the gene for a person to have the genetic disease. Both parents must be carriers of a pathogenic variant in the gene in order to be at risk of having an affected child. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. The child must inherit a pathogenic variant from each carrier parent in order to be affected. There is a 1 in 4 chance that a baby will inherit two mutated copies of the gene and be affected when both parents are carriers. In about 98% of SMA cases, both parents of an affected child are pathogenic variant carriers while about 2% of affected children have a new pathogenic variant in one copy of the SMN1 gene. In this situation, the pathogenic variant will only be detected in one parent.

Extra copies of the SMN2 gene are due to a random error when making new copies of DNA (replication) in an egg or sperm cell or just after fertilization.

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SMA-LED and the late-onset form of spinal muscular atrophy caused by VAPB gene mutations are inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

X-linked spinal muscular atrophy is inherited in an X-linked pattern. The UBA1 gene is located on the X chromosome, which is one of the two sex chromosomes. Males have only one X chromosome therefore one altered copy of the gene in each cell is sufficient to cause the condition. Females have two X chromosomes therefore a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, males are affected by X-linked disorders much more frequently than females. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

What Does It Mean To Be A Carrier?

There are generally no signs or symptoms associated with being a carrier for SMA. Carriers are at an increased risk of having a child with SMA. Testing of reproductive partners is recommended for SMA carriers. Typically a person who is not a carrier of SMA will have two copies of the SMN1 gene, one on each chromosome. Some carriers will have both of their copies of the SMN1 gene on the same chromosome and a deletion on the other chromosome and will go undetected with our current level of testing. This, however, is a rare occurrence.

Carrier Rates

Ethnicity	Detection Rate	Carrier Frequency
African/African American	71%	1 in 72
Ashkenazi Jewish	90%	1 in 67
East Asian	93%	1 in 59
General Population	91%	1 in 54
Hispanic	90%	1 in 68
Northern European Caucasian	95%	1 in 47
South Asian	90%	1 in 52
Southeast Asian	93%	1 in 59

Clinician References

OMIM [SMN1: 600354] (http://www.ncbi.nlm.nih.gov/omim)

Gene Reviews: Spinal Muscular Atrophy (SMA) (http://www.ncbi.nlm.nih.gov/books/NBK1116/)

Patient and Family Resources

Genetics Home Reference: Spinal muscular atrophy (SMA) (http://ghr.nlm.nih.gov/)

Genetic Alliance: Spinal muscular atrophy (http://www.diseaseinfosearch.org/)