

STAC3 Disorder

Subjects: **Genetics & Heredity**

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STAC3 disorder (formerly known as Native American myopathy) is a condition that primarily affects skeletal muscles, which are muscles that the body uses for movement.

genetic conditions

1. Introduction

People with STAC3 disorder have muscle weakness (myopathy) and poor muscle tone (hypotonia) throughout the body that typically begins at birth.

Muscle weakness underlies many of the characteristic features of STAC3 disorder. Affected individuals may have feeding and swallowing difficulties in infancy. They usually have delayed development of motor skills such as sitting, crawling, standing, and walking. Many have facial features described as "myopathic facies", which include drooping eyelids (ptosis), sunken cheeks, and a mouth often held in an open position and with the corners turned downward. Other distinctive facial features in people with STAC3 disorder can include a small lower jaw (micrognathia), an opening in the roof of the mouth (cleft palate), low-set ears that slant backward, eye openings that are shorter than average or that point downward (short or downslanting palpebral fissures), or an increased distance between the inner corners of the eyes (ocular telecanthus).

Individuals with STAC3 disorder may also be born with joint deformities that restrict movement (contractures) or develop an abnormal side-to-side or back-to-front curvature of the spine (scoliosis or kyphosis, often called kyphoscoliosis when they occur together). Affected individuals tend to be shorter than their peers and others in their family.

People with STAC3 disorder also have an increased risk of developing a severe reaction to certain drugs used during surgery and other invasive procedures. This reaction is called malignant hyperthermia. Malignant hyperthermia occurs in response to some anesthetic drugs, which are used to block the sensation of pain, either given alone or in combination with a particular type of muscle relaxant. If given these drugs, people at risk of malignant hyperthermia may experience muscle rigidity, breakdown of muscle fibers (rhabdomyolysis), a high fever (hyperthermia), increased acid levels in the blood and other tissues (acidosis), and a rapid heart rate. The complications of malignant hyperthermia can be life-threatening unless the drugs are stopped and the symptoms are treated promptly.

2. Frequency

STAC3 disorder was first found in individuals from the Lumbee Native American Tribe in North Carolina. The condition affects an estimated 1 in 5,000 people in this population. STAC3 disorder has since been found in other populations worldwide, though its prevalence is not known.

3. Causes

STAC3 disorder is caused by mutations in the *STAC3* gene. This gene provides instructions for making a protein that plays a role in the tensing (contraction) of skeletal muscles. Muscle contractions are triggered by changes in the concentration of certain charged atoms (ions) in muscle cells. The STAC3 protein aids in the process that triggers the release of calcium ions within muscle cells to start (initiate) muscle contraction.

The STAC3 protein interacts with two structures in muscle cells that are critical for calcium ion flow, dihydropyridine receptor (DHPR) and ryanodine receptor 1 (RYR1). However, STAC3's role in this formation is unclear. RYR1 forms a channel (the RYR1 channel) through which calcium ions can flow. In response to certain signals, DHPR turns on (activates) the RYR1 channel, and the activated RYR1 channel releases calcium ions stored in structures inside muscle cells. The resulting increase in the calcium ion concentration within muscle cells stimulates muscles to contract, allowing the body to move.

STAC3 gene mutations reduce the amount or impair the function of the STAC3 protein. Although the mechanism is unclear, studies show that a shortage of functioning STAC3 protein prevents the release of stored calcium ions by RYR1 channels. A disruption in calcium ion release prevents muscles from contracting normally, leading to the muscle weakness characteristic of STAC3 disorder.

It is unclear how these *STAC3* gene mutations lead to malignant hyperthermia in susceptible individuals. Mutations in other genes related to malignant hyperthermia activate the RYR1 channel improperly in response to certain drugs. As a result, large amounts of calcium ions are released from storage within muscle cells, causing skeletal muscles to contract abnormally. An increase in calcium ion concentration also activates processes that generate heat (leading to hyperthermia) and produce excess acid (leading to acidosis). It is unknown if *STAC3* gene mutations have a similar effect on RYR1 channel activity.

3.1.The Gene Associated with STAC3 disorder

- STAC3

4. Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. 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.

5. Other Names for This Condition

- myopathy, congenital, Bailey-Bloch
- myopathy, congenital, with myopathic facies, scoliosis, and malignant hyperthermia
- NAM
- Native American myopathy

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