U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Webb BD, Manoli I, Jabs EW. *STAC3* Disorder. 2019 Jun 20. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

STAC3 Disorder

Synonym: Native American Myopathy

Bryn D Webb, MD,[1] Irini Manoli, MD, PhD,[2] and Ethylin Wang Jabs, MD[1]

Created: June 20, 2019.

Summary

Clinical characteristics

STAC3 disorder is characterized by congenital myopathy, musculoskeletal involvement of the trunk and extremities, feeding difficulties, and delayed motor milestones. Most affected individuals have weakness with myopathic facies, scoliosis, kyphosis or kyphoscoliosis, and contractures. Other common findings are ptosis, abnormalities of the palate (including cleft palate), and short stature. Risk for malignant hyperthermia susceptibility and restrictive lung disease are increased. Intellect is typically normal. Originally described in individuals from the Lumbee Native American tribe (an admixture of Cheraw Indian, English, and African American ancestry) in the state of North Carolina and reported as Native American myopathy, *STAC3* disorder has now been identified in numerous other populations worldwide.

Diagnosis/testing

The diagnosis of *STAC3* disorder is established in a proband with suggestive clinical findings and biallelic pathogenic variants in *STAC3* identified by molecular genetic testing.

Management

Treatment of manifestations: At present, no treatment halts or reverses the manifestations of *STAC3* disorder. Treatment of musculoskeletal involvement is symptomatic and ideally provided by a multidisciplinary neuromuscular team to address the following:

- Occupational and physical therapy needs regarding range of motion and mobility
- Use of adaptive devices for mobility and activities of daily living
- Feeding difficulties
- Speech delays
- Scoliosis
- Respiratory insufficiency

Author Affiliations: 1 Icahn School of Medicine at Mount Sinai, New York, New York; Email: bryn.webb@mssm.edu; Email: ethylin.jabs@mssm.edu. 2 National Institutes of Health, Bethesda, Maryland; Email: manolii@mail.nih.gov.

Due to the medical comorbidities in *STAC3* disorder, decisions regarding type and timing of cleft palate surgery should be determined by a multidisciplinary craniofacial team. Depending on the structure of the managing craniofacial team, interventions for ptosis may be undertaken by an ophthalmologist as part of team care, or as an insertion intervention.

Surveillance: Routine monitoring of growth, musculoskeletal complications (e.g., scoliosis and/or joint contractures), speech development, swallowing function, respiratory function, and educational needs.

Agents/circumstances to avoid: Anesthetic agents with a high risk of triggering malignant hyperthermia.

Genetic counseling

STAC3 disorder is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Unless the reproductive partner of an affected individual also has *STAC3* disorder or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *STAC3.* Once the *STAC3* pathogenic variants have been identified in an affected family member, carrier testing of at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for *STAC3* disorder have not been established.

Suggestive Findings

STAC3 disorder (also known as Native American myopathy) **should be suspected** in individuals with the following clinical and laboratory findings.

Clinical findings

- **Congenital myopathy**
  - Congenital weakness
  - Myopathic facies, characterized by ptosis, inability to raise corners of mouth, and (in some individuals) hollowed-out cheeks from loss of facial musculature, which may cause an open-mouthed expressionless appearance with downturned corners of the mouth. Over time, the face often becomes long and narrow.
- **Musculoskeletal anomalies**
  - Congenital contractures ranging from talipes equinovarus (bilateral or unilateral) with or without other joint contractures to arthrogryposis (i.e., multiple contractures of the joints in more than one area of the body present at birth) [Hall 2010]
  - Scoliosis, kyphosis, or kyphoscoliosis
- **Palatal anomalies** including cleft palate
- **Micrognathia**
- **Characteristic facial features.** Myopathic facies, micrognathia, and palatal anomalies can be seen in a number of neuromuscular disorders of varying etiologies; the characteristics that best distinguish *STAC3* disorder from other conditions include low-set and/or posteriorly rotated ears, short and/or downslanting palpebral fissures, and telecanthus [Stamm et al 2008a] (see Figure 2: A-I).
- **Short stature**
- **Susceptibility to malignant hyperthermia**

Laboratory findings. Creatine kinase baseline levels are most often normal [Stewart et al 1988].

Establishing the Diagnosis

The diagnosis of *STAC3* disorder **is established** in a proband with clinical findings consistent with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *STAC3* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *STAC3* variants of uncertain significance (or of one known *STAC3* pathogenic variant and one *STAC3* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *STAC3* disorder is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of *STAC3* disorder has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of *STAC3* disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *STAC3* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications. Note: To date no large *STAC3* deletions or duplications have been identified in individuals reported with molecularly confirmed *STAC3* disorder.

  Note: Targeted analysis for the *STAC3* pathogenic variant c.851G>C can be performed first in individuals of Lumbee Native American ancestry [Horstick et al 2013].

- **A congenital myopathy multigene panel** that includes *STAC3* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of *STAC3* disorder, some panels for congenital myopathy may not include this gene. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of *STAC3* disorder is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. Note: To date no large *STAC3* deletions or duplications have been identified in individuals reported with molecularly confirmed *STAC3* disorder.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *STAC3* Disorder

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
STAC3	Sequence analysis [3]	All pathogenic variants reported to date [4]
	Gene-targeted deletion/duplication analysis [5]	To date no deletions/duplications have been identified.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Horstick et al [2013], Grzybowski et al [2017], Telegrafi et al [2017]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Clinical Characteristics

Clinical Description

STAC3 disorder is characterized by congenital myopathy and musculoskeletal involvement of the trunk and extremities. Most children have weakness with myopathic facies, progressive kyphoscoliosis, and contractures. Other common findings are palatal anomalies (including cleft palate) and short stature. Risks for malignant hyperthermia susceptibility and restrictive lung disease are increased. Intellect is typically normal.

Prior to knowledge of its genetic cause, *STAC3* disorder was initially reported as Native American myopathy in an infant from the Lumbee tribe whose findings at birth included arthrogryposis with talipes equinovarus, cleft palate, and micrognathia; at age three months she developed malignant hyperthermia during halothane anesthesia for gastrostomy tube placement due to poor feeding [Bailey & Bloch 1987]. Subsequently 20 additional individuals of Lumbee descent with a clinical diagnosis of Native American myopathy were reported, six by Stewart et al [1988] and 14 by Stamm et al [2008a]. Additional variable findings included ptosis, congenital joint contractures, and scoliosis.

Following the identification of biallelic pathogenic variants in *STAC3* in five individuals with Native American myopathy from five families of Lumbee descent by Horstick et al [2013], *STAC3* disorder has been confirmed molecularly in another 23 individuals from 15 families of various ancestry: African (5 families), Middle Eastern (4), Puerto Rican (1), Turkish (1), Afro-Caribbean (1), Comoro Islands (1), South American (1), and mixed African and Afro-Caribbean (1) [Grzybowski et al 2017, Telegrafi et al 2017, Zaharieva et al 2018].

The findings of all individuals reported to date with molecularly confirmed *STAC3* disorder and clinically diagnosed Native American myopathy are summarized in Table 2 and discussed in more detail in the text that follows the table.

Table 2. Clinical Findings in Individuals with *STAC3* Disorder

Finding		Lumbee [1] (n=21)	Non-Lumbee [2] (n=23)	Total (n=44)
Congenital myopathy	Hypotonia	21/21	20/20 (3 not recorded)	41/41
	Myopathic facies	21/21	23/23	44/44
	Ptosis	14/16 (5 not recorded)	19/23	33/39
	Poor feeding	11/17 (4 not recorded)	18/23	29/40
Musculo-skeletal	Congenital contractures	17/20 (1 not recorded)	18/23	35/43
	Scoliosis, kyphosis, or kyphoscoliosis	15/16 (5 not recorded)	16/23	31/39
Short stature		6/6 (not recorded [3])	13/23	19/29
Palate anomalies (cleft palate, high-arched palate, or bifid uvula)		21/21 (16 w/cleft palate)	15/23 (9 w/cleft palate)	36/44 total (25/44 w/ cleft palate)
Malignant hyperthermia		7/21	12/23	19/44
Respiratory impairment		5/6 (not recorded [4])	11/23	16/29
Cryptorchidism		6/8 males	7/13 males	13/21 males

1. Bailey & Bloch [1987] (n=1), Stewart et al [1988] (n=6), Stamm et al [2008a] (n=14). The five individuals of Lumbee descent with molecularly confirmed *STAC3* disorder reported in Horstick et al [2013] were previously described in Stamm et al [2008a].
2. Grzybowski et al [2017] (n=1), Telegrafi et al [2017] (n=4), Zaharieva et al [2018] (n=18). All of these cases were molecularly confirmed.
3. 6/6 patients in Stewart et at [1988] had short stature; 2/2 adults in Stamm et al [2008a] had short stature (not included in tally); information was incomplete on all other individuals in Bailey & Bloch [1987] and Stamm et al [2008a].
4. At least two individuals in Stamm et al [2008a] had respiratory findings (not included in tally); information was incomplete on additional individuals.

Congenital myopathy. The congenital myopathy is slowly progressive with myopathic facies. Deep tendon reflexes in the upper and lower extremities are often decreased or absent. Strength is often decreased in facial, axial, and proximal limb muscles, and may be decreased in distal limb muscles. Examination of older affected individuals may reveal muscle wasting.

Motor delays are most often present by infancy or very early childhood. The maximum motor ability in 15 individuals old enough for evaluation was walking (11), short walk (2), running (1), and sitting independently (1) [Zaharieva et al 2018]. Some affected individuals may be wheelchair bound by adolescence.

Feeding problems. Poor feeding may be due to a combination of structural differences (e.g., cleft palate or high-arched palate, micrognathia) and functional differences (e.g., weak suck, impaired coordination of feeding, abnormal tongue movements, respiratory insufficiency). Descending aspiration may also contribute to feeding and respiratory difficulties. Children with micrognathia and cleft palate may be at increased risk for respiratory issues during feeding (see Management).

Ptosis refers to downward placement (i.e., drooping) of the upper eyelids. In children, ptosis that obstructs the pupil may result in vision impairment or amblyopia. Ptosis may also cause loss of peripheral vision and blurred vision. To maximize vision individuals with ptosis may assume a posture with head tilted backwards and chin pointed upwards.

Musculoskeletal. Congenital contractures can involve the fingers (camptodactyly), hands, wrists, elbows, hips, knees, or feet/ankles (talipes equinovarus). The severity and functional disability range from mild to severe and depend on the joint involved.

Joint laxity has been seen in individuals with or without contractures.

Spinal involvement, including scoliosis, kyphosis, or kyphoscoliosis, is often present by early childhood and is often progressive.

Short stature. Adult height is commonly below the third percentile. Birth length is most often normal.

Speech impairments. Speech development is typically abnormal and dysarthria is common. Factors that can contribute to speech issues in children with *STAC3* disorder include the following (see also Management):

- Abnormal palatal formation, including cleft palate
- Abnormal tongue movement
- Compensatory misarticulation
- Velopharyngeal insufficiency
- Neurologic factors
- Atypical resonance
- Respiratory insufficiency
- Apraxia

Malignant hyperthermia (MH). All individuals with a reported history of MH survived. Of the cases in which details were provided, most individuals were treated by discontinuing the anesthetic and surgery, and administering dantrolene [Bailey & Bloch 1987, Stamm et al 2008a].

Although MH has been reported in a significant number of individuals, the true frequency of MH susceptibility is likely higher as not all reported individuals had prior surgery or had been exposed to an MH-provoking anesthetic.

Respiratory impairment. Respiratory insufficiency may present in early childhood, late childhood, or adulthood [Stamm et al 2008a, Telegrafi et al 2017, Zaharieva et al 2018].

Other. The majority of affected individuals have normal intelligence; mild intellectual disability is rare [Stewart et al 1988, Stamm et al 2008a].

Conductive hearing loss is common.

Facial hemangiomas may also be present.

Life expectancy. Thirty-six percent of individuals affected with *STAC3* disorder died by age 18 years [Horstick et al 2013]. In a study of 14 affected individuals, three died during the first year of life, one from severe pulmonary hypoplasia and one from apnea secondary to enterococcal pneumonia [Stamm et al 2008a].

Muscle findings. Muscle biopsy reveals variable findings:

- **Light microscopy.** Small type I and II fibers in some individuals and fiber-type disproportion in others. Increased numbers of central nuclei may be seen.
- **Electron microscopy.** An increase in lipid droplets and/or subsarcolemmal mitochondrial accumulations

Electromyogram revealed normal results in some individuals and evidence of myopathy in others [Stewart et al 1988, Stamm et al 2008a].

Genotype-Phenotype Correlations

To date no genotype-phenotype correlations are known.

Prevalence

STAC3 disorder was originally identified in individuals of the Lumbee Native American tribe, which is recognized by the state of North Carolina and has approximately 60,000 enrolled members. The ancestry of Lumbee Native Americans is a mixture of Cheraw Indian, English, and African American [Stamm et al 2008b]. A founder pathogenic variant has been identified in this population (see Molecular Genetics). It is estimated that one in 5,000 Lumbee Native Americans has *STAC3* disorder.

See Clinical Description for other populations in which *STAC3* disorder has been observed.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *STAC3*.

Differential Diagnosis

Table 3. Disorders with Facial Weakness and Hypotonia to Consider in the Differential Diagnosis of *STAC3* Disorder

DiffDx Disorder	Gene(s)	MOI	Additional Clinical Features of DiffDx Disorder	
			Overlapping w/*STAC3* Disorder	Distinguishing from *STAC3* Disorder
Central core disease (OMIM 117000)	*RYR1*	AD AR	• Respiratory insufficiency • Contractures • Arthrogryposis • Susceptibility to MH	• External ophthalmoplegia may be present. • Serum CK may be ↑ in King-Denborough syndrome.
RYR1-related congenital fiber-type disproportion		AR		
RYR1-related multiminicore disease		AR		
RYR1-related King-Denborough syndrome [1] (See Malignant Hyperthermia Susceptibility.)		AD		
Carey Fineman Ziter syndrome [2] (OMIM 254940)	*MYMK*	AR	• Upturned/broad nasal tip • Micro/retrognathia • Generalized muscle hypoplasia • Delayed motor milestones • Normal cognition	No susceptibility to MH documented to date

Table 3. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Additional Clinical Features of DiffDx Disorder	
			Overlapping w/*STAC3* Disorder	Distinguishing from *STAC3* Disorder
Moebius syndrome [3] (OMIM 157900)	Unknown etiology in most cases [4] *PLXND1* *REV3L* [5]	Unknown in most cases; AD in small # of persons [4]	• Cleft palate • Talipes equinovarus • Short stature • Scoliosis • Joint contractures	• Impairment in ocular abduction is obligatory. • Variably present: ◦ Cranial nerve abnormalities ◦ Hearing loss ◦ Poland anomaly ◦ Limb reduction defects ◦ DD, ASD

AD = autosomal dominant; AR = autosomal recessive; ASD = autism spectrum disorder; DD = developmental delay; DiffDx = differential diagnosis; MH = malignant hyperthermia; MOI = mode of inheritance; XL = X-linked

1. King & Denborough [1973], D'Arcy et al [2008], Dowling et al [2011]

2. Carey et al [1982], Di Gioia et al [2017], Telegrafi et al [2017], Alrohaif et al [2018], Hedberg-Oldfors et al [2018]

3. Moebius syndrome was defined by the Moebius Syndrome Foundation Research Conference with the minimum criteria of congenital, nonprogressive facial weakness with limited abduction of one or both eyes [Miller 2007].

4. Both genetic and environmental etiologies have been proposed. Additionally, prenatal exposure to misoprostol and other agents has been known to cause a Moebius syndrome phenotype.

5. Heterozygous *de novo* pathogenic variants in *PLXND1* and *REV3L* have been described in a small number of individuals with congenital facial weakness associated with a variety of additional findings that overlap the Moebius syndrome spectrum [Tomas-Roca et al 2015].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *STAC3* disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *STAC3* Disorder

System/Concern	Evaluation	Comment
Constitutional	Measure height, weight, head circumference.	Assess for evidence of failure to thrive.
Neuromuscular	Refer to pediatric or adult neurologist.	Assess severity of muscle weakness.
	Refer to neuromuscular clinic incl physical medicine & rehab / PT / OT eval.	Assess need for PT &/or OT & adaptive equipment.
Musculoskeletal	Orthopedic / physical medicine & rehab / PT / OT eval in multidisciplinary neuromuscular clinic	Assess for kyphoscoliosis, talipes deformities, & joint contractures.
Ptosis	Refer to pediatric or adult ophthalmologist; may be part of craniofacial team.	Assess extraocular movements, visual acuity, & visual field.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Feeding issues	Refer to speech therapist, OT, nutritionist, or multidisciplinary craniofacial team.	Evals may incl: • Physical exam • Clinical feeding eval using different types of nipples • Video fluoroscopic swallow study • Lab eval (e.g., total carbon dioxide level) • Chest x-ray • Upper GI series
Palatal anomalies incl cleft palate	Refer to multidisciplinary craniofacial team.	Team will assess effect of palatal anomalies on feeding, speech development, & need for surgical interventions.
Respiratory	Refer to pulmonologist.	• Polysomnography needed to evaluate for central &/or obstructive sleep apnea as well as hypoxia • Spirometry + measurement of maximal inspiratory & expiratory pressures & cough peak flow • For older children & adults, pulmonary function tests may be helpful. • If concern for ascending or descending microaspiration, evaluate for chronic lung disease. • Evaluate severely affected infants for pulmonary hypoplasia.
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	Review natural history of disorder, MOI, recurrence risk, & prognosis.
	Obtain surgical history.	Evaluate for evidence of MH.

GI = gastrointestinal; MH = malignant hyperthermia; MOI = mode of inheritance; OT = occupational therapist/therapy; PT = physical therapist/therapy

Treatment of Manifestations

At present, no treatment halts or reverses the manifestations of *STAC3* disorder; treatment involves reducing symptoms and preventing secondary complications (see Table 5).

Table 5. Treatment of Manifestations in Individuals with *STAC3* Disorder

Manifestation/ Concern	Treatment	Considerations/Other
Hypotonia/ Myopathy	OT & PT	Consider use of adaptive devices to improve mobility.
Contractures	Consider: • PT to improve range of motion; • Stretching, night splints, or serial casts.	Avoid periods of prolonged immobilization (e.g., following surgery).
Talipes equinovarus	Per recommendations of treating orthopedist	Serial casting, splinting, & surgical intervention may be required.
Scoliosis	Per recommendations of treating orthopedist	Often initial bracing is followed by progressive scoliosis requiring surgery.
Ptosis	Surgical repair, such as levator resection or frontalis sling surgeries	Uncorrected ptosis may lead to ↓ visual acuity & ↓ visual fields - most commonly visual field loss.
Poor weight gain / Weight-faltering	Assessment of caloric intake; high-calorie foods/ formulas &/or supplementation via nasogastric or enteral feeding may be necessary.	

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Poor feeding	Per recommendations of speech therapist/OT, nutritionist, or multidisciplinary craniofacial team	May incl specialized bottles, nasogastric or enteral feeding tube, [1] feeding therapy
Cleft palate	Specialized cleft bottles; timing & type of surgical repair determined by craniofacial team [1]	If micrognathia also present, may be evaluated for Pierre Robin sequence
Speech issues	Assessment by speech-language pathologist as part of multidisciplinary craniofacial team [2]	Interventions depend on etiology of speech issues & may include speech therapy, surgery, &/or use of assistive communication devices.
Respiratory insufficiency	• Invasive or noninvasive ventilatory support, mechanical cough assist (in exsufflator) • As per recommendations of pulmonary & craniofacial team	• Aggressive treatment & prevention of lower respiratory tract infections (influenza & PCV-23 vaccines) • May incl need for noninvasive or invasive positive pressure ventilation (e.g., CPAP, BiPAP via mask, tracheostomy w/ventilation); assessment for ascending or descending microaspiration w/appropriate interventions

OT = occupational therapy; PT = physical therapy

1. Enteral feeding tubes may be needed if there is concern for aspiration or if the affected individual is unable to take in adequate calories for growth. Some children with more significant respiratory issues may require surgical feeding tubes and/or procedures to protect their lungs from microaspiration.

2. Due to the complexity of speech evaluation in children with myopathic facies, structural differences with or without cleft palate, a speech-language pathologist on a multidisciplinary craniofacial team will be needed to determine the contributing factors in most children.

Surveillance

Table 6. Recommended Surveillance for Individuals with *STAC3* Disorder

System/Concern	Evaluation	Recommended Frequency
Growth	PCP should monitor growth incl weight, height, & head circumference.	At each visit
Neuromuscular	Multidisciplinary neuromuscular clinic monitoring of: • Respiratory status, speech development, swallowing function • Musculoskeletal complications (e.g., scoliosis &/or joint contractures)	• Infants age <12 mos: every 3-4 mos • Older children & adults: every 6-12 mos
Cleft palate	Multidisciplinary craniofacial team: • Equipment & techniques for feeding infants w/cleft palate • Surgical repair timing & type of procedure determined by team • Anesthesiologist should be aware of risk of MH. • Audiologic eval as part of craniofacial team as needed	• Infants: visit frequency determined by feeding & respiratory issues • Children: varies depending on comorbidities; at least annually
Feeding	Multidisciplinary craniofacial team in conjunction w/PCP: • Measure growth parameters. • Evaluate nutritional status & safety of oral intake. • Consider clinical feeding eval &/or video fluoroscopic swallow study.	At each visit

Table 6. continued from previous page.

System/Concern	Evaluation	Recommended Frequency
Respiratory	Pulmonologist: • Assessment of pulmonary status & pulmonary function testing • Polysomnography • Evaluate for signs of ascending or descending aspiration.	Clinical eval at least annually but likely more often during infancy or when any signs of respiratory insufficiency, aspiration, &/or sleep apnea develop
Speech	Multidisciplinary craniofacial team: • Speech assessment by speech-language pathologist familiar w/ cleft palate & neuromuscular contributors to speech issues • Consider speech therapy, surgical interventions, & augmentative communication devices.	At least annually

Wang et al [2012]
MH = malignant hyperthermia; PCP = primary care physician

Agents/Circumstances to Avoid

Persons with *STAC3* disorder are at increased risk for malignant hyperthermia (MH) crises when exposed to certain agents used with general anesthesia – most commonly volatile anesthetic gases (including halothane, isoflurane, and sevoflurane) and depolarizing muscle relaxants (e.g., succinylcholine and decamethonium). It is imperative that persons with *STAC3* disorder discuss their diagnosis with anesthesiologists and treating physicians prior to surgical procedures to ensure that appropriate anesthetics are chosen to reduce the risk of MH.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

STAC3 disorder is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *STAC3* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless the reproductive partner of an affected individual also has *STAC3* disorder or is a carrier, offspring will be obligate heterozygotes (carriers) for a pathogenic variant in *STAC3*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *STAC3* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *STAC3* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *STAC3* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Malignant Hyperthermia Association of the United States (MHAUS)**
  11 East State Street
  PO Box 1069
  Sherburne NY 13460
  Phone: 800-644-9737 (Toll-free Emergency Hotline); 607-674-7901; 315-464-7079
  Fax: 607-674-7910
  Email: info@mhaus.org
  www.mhaus.org

- **Muscular Dystrophy Association (MDA) - USA**
  Phone: 833-275-6321
  www.mda.org
- **Muscular Dystrophy UK**
  United Kingdom
  Phone: 0800 652 6352
  www.musculardystrophyuk.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. STAC3 Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
STAC3	12q13.3	SH3 and cysteine-rich domain-containing protein 3	STAC3	STAC3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for STAC3 Disorder (View All in OMIM)

255995	CONGENITAL MYOPATHY 13; CMYP13
615521	SH3 AND CYSTEINE-RICH DOMAINS 3; STAC3

Gene structure. *STAC3* spans more than 7 kb and encodes for at least three alternatively spliced transcripts. The longest transcript variant (NM_145064.2) has 12 exons and is composed of 1,668 base pairs.

See Table A, **Gene** for a detailed summary of the gene, transcripts, and protein isoforms.

Pathogenic variants. Molecularly confirmed *STAC3* disorder has been reported for 28 individuals from 20 families. To date, a total of five pathogenic variants have been identified.

Horstick et al [2013] identified homozygous c.851G>C missense variants in five affected individuals from five Lumbee Native American families.

Grzybowski et al [2017] identified compound heterozygous pathogenic *STAC3* variants in one individual of Turkish ancestry that included a nonsense change (c.862A>T) and a splice donor site variant c.432+4A>T.

Telegrafi et al [2017] reported two affected sisters of Qatari ancestry who were homozygous for the c.851G>C pathogenic variant. Two affected sibs of Puerto Rican ancestry were compound heterozygous for the c.851G>C and c.763_766delCTCT *STAC3* variants.

Zaharieva et al [2018] reported 18 additional individuals from 12 families; of these, 17 from 11 families were homozygous for the c.851G>C missense variant (5 families of African descent, 3 of Middle Eastern descent, 1 of Afro-Caribbean descent, 1 of Comoro Islands descent, and 1 of South American descent). An additional individual of mixed African and Afro-Caribbean descent was a compound heterozygote for the variants c.851G>C and c.997-1G>T.

Table 7. *STAC3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.851G>C	p.Trp284Ser	NM_145064.2 NP_659501.1
c.862A>T	p.Lys288Ter	
c.432+4A>T		NM_145064.2
c.763_766delCTCT	p.Leu255Ilefster58	NM_145064.2 NP_659501.1
c.997-1G>T		NM_145064.2

Variants listed in the table have been provided by the authors.*GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *STAC3* encodes SH3 and cysteine-rich domain-containing protein 3 (STAC3), which is composed of 364 amino acids (NP_659501.1) and has a calculated molecular mass of approximately 41.41 kd.

STAC3 contains an N-terminal cysteine-rich domain and two SH3 domains.

STAC3 is a component of the excitation-contraction coupling machinery of muscles and biochemically associates with dihydropyridine receptor (DHPR) and ryanodine receptor 1 (RYR1) at triadic complexes, which are required for normal calcium release from the sarcoplasmic reticulum in skeletal muscle that leads to muscle contraction.

Abnormal gene product. *STAC3* disorder results from biallelic loss-of-function pathogenic variants.

- The c.851G>C missense variant identified in Lumbee Native American families leads to decreases in the quantity, organization, stability, and voltage sensitivity of Ca^{2+} channels [Horstick et al 2013].
- cDNA studies confirmed two aberrant transcription products for the c.432+4A>T splicing variant in lymphocytes, including skipping of exon 4 and activation of a new splice site in intron 4 [Grzybowski et al 2017].
- For the c.997-1G>T variant, cDNA studies confirmed activation of a cryptic acceptor site within exon 12 leading to deletion of 12 nucleotides from mature *STAC3* RNA [Zaharieva et al 2018].

Chapter Notes

Author Notes

Bryn Webb is a clinical geneticist, clinical molecular geneticist, and pediatrician specializing in genetic studies of rare congenital anomalies. She is co-director of the Cleft and Craniofacial Program at the Icahn School of Medicine at Mount Sinai. Webb Laboratory

Irini Manoli is a clinical and biochemical geneticist and pediatrician with a focus on clinical and translational research in rare genetic syndromes and inborn errors of metabolism. She works at the National Human Genome Research Institute of the National Institutes of Health.

Ethylin Wang Jabs is a medical geneticist with a clinical focus in dysmorphology and a clinical, translational, and basic research interest in developmental genetics, in particular craniofacial disorders. Ethylin Wang Jabs Laboratory

Revision History

- 20 June 2019 (bp) Review posted live

- 13 August 2018 (bw) Original submission

References

Literature Cited

Alrohaif H, Töpf A, Evangelista T, Lek M, McArthur D, Lochmüller H. Whole-exome sequencing identifies mutations in MYMK in a mild form of Carey-Fineman-Ziter syndrome. Neurol Genet. 2018;4:e226. PubMed PMID: 29560417.

Bailey AG, Bloch EC. Malignant hyperthermia in a three-month-old American Indian infant. Anesth Analg. 1987;66:1043–5. PubMed PMID: 3631569.

Carey JC, Fineman RM, Ziter FA. The Robin sequence as a consequence of malformation, dysplasia, and neuromuscular syndromes. J Pediatr. 1982;101:858–64. PubMed PMID: 7131178.

D'Arcy CE, Bjorksten A, Yiu EM, Bankier A, Gillies R, McLean CA, Shield LK, Ryan MM. King-Denborough syndrome caused by a novel mutation in the ryanodine receptor gene. Neurology. 2008;71:776–7. PubMed PMID: 18765655.

Di Gioia SA, Connors S, Matsunami N, Cannavino J, Rose MF, Gilette NM, Artoni P, de Macena Sobreira NL, Chan WM, Webb BD, Robson CD, Cheng L, Van Ryzin C, Ramirez-Martinez A, Mohassel P, Leppert M, Scholand MB, Grunseich C, Ferreira CR, Hartman T, Hayes IM, Morgan T, Markie DM, Fagiolini M, Swift A, Chines PS, Speck-Martins CE, Collins FS, Jabs EW, Bönnemann CG, Olson EN, Carey JC, Robertson SP, Manoli I, Engle EC, et al. A defect in myoblast fusion underlies Carey-Fineman-Ziter syndrome. Nat Commun. 2017;8:16077. PubMed PMID: 28681861.

Dowling JJ, Lillis S, Amburgey K, Zhou H, Al-Sarraj S, Buk SJ, Wraige E, Chow G, Abbs S, Leber S, Lachlan K, Baralle D, Taylor A, Sewry C, Muntoni F, Jungbluth H. King-Denborough syndrome with and without mutations in the skeletal muscle ryanodine receptor (RYR1) gene. Neuromuscul Disord. 2011;21:420–7. PubMed PMID: 21514828.

Grzybowski M, Schänzer A, Pepler A, Heller C, Neubauer BA, Hahn A. Novel STAC3 mutations in the first non-Amerindian patient with Native American myopathy. Neuropediatrics. 2017;48:451–5. PubMed PMID: 28411587.

Hall J. Athrogryposis. In: Cassidy SB, Allanson, JE, eds. *Management of Genetic Syndromes*. 3rd ed. Hoboken, NJ: Wiley; 2010: 81-96.

Hedberg-Oldfors C, Lindberg C, Oldfors A. Carey-Fineman-Ziter syndrome with mutations in the myomaker gene and muscle fiber hypertrophy. Neurol Genet. 2018;4:e254. PubMed PMID: 30065953.

Horstick EJ, Linsley JW, Dowling JJ, Hauser MA, McDonald KK, Ashley-Koch A, Saint-Amant L, Satish A, Cui WW, Zhou W, Sprague SM, Stamm DS, Powell CM, Speer MC, Franzini-Armstrong C, Hirata H, Kuwada JY. Stac3 is a component of the excitation-contraction coupling machinery and mutated in Native American myopathy. Nat Commun. 2013;4:1952. PubMed PMID: 23736855.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

King JO, Denborough MA. Anesthetic-induced malignant hyperpyrexia in children. J Pediatr. 1973;83:37–40. PubMed PMID: 4149045.

Miller G. Neurological disorders. The mystery of the missing smile. Science. 2007;316:826–7. PubMed PMID: 17495152.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint

consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Stamm DS, Aylsworth AS, Stajich JM, Kahler SG, Thorne LB, Speer MC, Powell CM. Native American myopathy: congenital myopathy with cleft palate, skeletal anomalies, and susceptibility to malignant hyperthermia. Am J Med Genet A. 2008a;146A:1832–41. PubMed PMID: 18553514.

Stamm DS, Powell CM, Stajich JM, Zismann VL, Stephan DA, Chesnut B, Aylsworth AS, Kahler SG, Deak KL, Gilbert JR, Speer MC. Novel congenital myopathy locus identified in Native American Indians at 12q13.13-14.1. Neurology. 2008b;71:1764–9. PubMed PMID: 18843099.

Stewart CR, Kahler SG, Gilchrist JM. Congenital myopathy with cleft palate and increased susceptibility to malignant hyperthermia: King syndrome? Pediatr Neurol. 1988;4:371–4. PubMed PMID: 3245876.

Telegrafi A, Webb BD, Robbins SM, Speck-Martins CE, FitzPatrick D, Fleming L, Redett R, Dufke A, Houge G, van Harssel JJT, Verloes A, Robles A, Manoli I, Engle EC, Jabs EW, Valle D, Carey J, Hoover-Fong JE, Sobreira NLM, et al. Identification of STAC3 variants in non-Native American families with overlapping features of Carey-Fineman-Ziter syndrome and Moebius syndrome. Am J Med Genet A. 2017;173:2763–71. PubMed PMID: 28777491.

Tomas-Roca L, Tsaalbi-Shtylik A, Jansen JG, Singh MK, Epstein JA, Altunoglu U, Verzijl H, Soria L, van Beusekom E, Roscioli T, Iqbal Z, Gilissen C, Hoischen A, de Brouwer AP, Erasmus C, Schubert D, Brunner H, Pérez Aytés A, Marin F, Aroca P, Kayserili H, Carta A, de Wind N, Padberg GW, van Bokhoven H. De novo mutations in PLXND1 and REV3L cause Möbius syndrome. Nat Commun. 2015;6:7199. PubMed PMID: 26068067.

Wang CH, Dowling JJ, North K, Schroth MK, Sejersen T, Shapiro F, Bellini J, Weiss H, Guillet M, Amburgey K, Apkon S, Bertini E, Bonnemann C, Clarke N, Connolly AM, Estournet-Mathiaud B, Fitzgerald D, Florence JM, Gee R, Gurgel-Giannetti J, Glanzman AM, Hofmeister B, Jungbluth H, Koumbourlis AC, Laing NG, Main M, Morrison LA, Munns C, Rose K, Schuler PM, Sewry C, Storhaug K, Vainzof M, Yuan N. Consensus statement on standard of care for congenital myopathies. J Child Neurol. 2012;27:363–82. PubMed PMID: 22431881.

Zaharieva IT, Sarkozy A, Munot P, Manzur A, O'Grady G, Rendu J, Malfatti E, Amthor H, Servais L, Urtizberea JA, Neto OA, Zanoteli E, Donkervoort S, Taylor J, Dixon J, Poke G, Foley AR, Holmes C, Williams G, Holder M, Yum S, Medne L, Quijano-Roy S, Romero NB, Fauré J, Feng L, Bastaki L, Davis MR, Phadke R, Sewry CA, Bönnemann CG, Jungbluth H, Bachmann C, Treves S, Muntoni F. STAC3 variants cause a congenital myopathy with distinctive dysmorphic features and malignant hyperthermia susceptibility. Hum Mutat. 2018;39:1980–94. PubMed PMID: 30168660.

License