



## Salih Myopathy

Synonym: Early-Onset Myopathy with Fatal Cardiomyopathy

Peter Hackman, PhD,<sup>1</sup> Marco Savarese, PhD,<sup>1</sup> Virginie Carmignac, PhD,<sup>2</sup> Bjarne Udd, MD, PhD,<sup>3</sup> and Mustafa A Salih, MB BS, MPCH, MD, Dr Med Sci, FRCPCH, FAAN<sup>4</sup>

Created: January 12, 2012; Updated: April 11, 2019.

## Summary

### Clinical characteristics

Salih myopathy is characterized by muscle weakness (manifest during the neonatal period or in early infancy) and delayed motor development; children acquire independent walking between ages 20 months and four years. In the first decade of life, global motor performance is stable or tends to improve. Moderate joint and neck contractures and spinal rigidity may manifest in the first decade but become more obvious in the second decade. Scoliosis develops after age 11 years. Cardiac dysfunction manifests between ages five and 16 years, progresses rapidly, and leads to death between ages eight and 20 years, usually from heart rhythm disturbances.

### Diagnosis/testing

The diagnosis is established in a proband by identification of biallelic pathogenic variants in the first three M-line-encoding exons (Mex1, Mex2, and Mex3) of *TTN*, the only gene in which pathogenic variants are known to cause Salih myopathy.

### Management

*Treatment of manifestations:* Care, best provided by a multidisciplinary team, includes stretching exercises and physical therapy; assistive mechanical devices for sitting and ambulation as needed; and appropriate technical support in educational settings. Treat heart failure and cardiac arrhythmia as soon as they are evident. Cardiac transplantation may be considered for progressive dilated cardiomyopathy and heart failure refractory to medical therapy.

**Author Affiliations:** 1 The Folkhälsan Institute of Genetics and the Department of Medical Genetics, Haartman Institute, University of Helsinki, Helsinki, Finland; Email: [peter.hackman@helsinki.fi](mailto:peter.hackman@helsinki.fi); Email: [marco.savarese@helsinki.fi](mailto:marco.savarese@helsinki.fi) 2 Equipe Génétique des Anomalies du Développement, IFR Santé-STIC, Université de Bourgogne, Dijon, France; Email: [virginie.carmignac@gmail.com](mailto:virginie.carmignac@gmail.com) 3 Tampere Neuromuscular Research Unit, The Folkhälsan Institute of Genetics and the Department of Medical Genetics, Haartman Institute, University of Helsinki, Helsinki, Finland; Email: [bjarne.udd@pshp.fi](mailto:bjarne.udd@pshp.fi) 4 Division of Pediatric Neurology, College of Medicine, King Saud University, Riyadh, Saudi Arabia; Email: [mustafa\\_salih05@yahoo.com](mailto:mustafa_salih05@yahoo.com).

*Prevention of secondary complications:* Annual influenza vaccine and other respiratory infection-related immunizations are advised. Aggressive treatment of lower-respiratory tract infections.

*Surveillance:* Electrocardiogram (EKG), 24-hour Holter EKG, and echocardiogram every six months beginning at age five years. Annual evaluation of respiratory function beginning at age 10 years. Clinical examination and x-ray as needed for orthopedic complications (e.g., foot deformity, joint contractures, spinal deformity).

*Agents/circumstances to avoid:* Ibuprofen in those with congestive heart failure.

## Genetic counseling

Salih myopathy is inherited in an autosomal recessive manner. The parents of an affected child are obligate heterozygotes (i.e., carriers of one pathogenic variant) and are asymptomatic. 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. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the pathogenic variants in the family have been identified.

## Diagnosis

### Suggestive Findings

Salih myopathy **should be suspected** in individuals with the following clinical, laboratory, electrophysiologic, imaging, and histopathology findings.

#### Clinical

- Muscle weakness manifesting during the neonatal period or in early infancy
- Delayed motor milestones but normal cognitive development
- Muscle weakness of limb-girdle distribution, myopathic face, variable degree of ptosis, and relative calf muscle hypertrophy
- Development of dilated cardiomyopathy between ages five and 16 years
- Major heart rhythm disturbances leading to sudden death before age 20 years

**Laboratory.** Serum creatine kinase (CK) is marginally to moderately increased (1.5-7x normal).

#### Electrophysiologic

- **Electrocardiography.** Left axis deviation (left anterior fascicular block) can be seen as early as age four years (Figure 1). With the onset of dilated cardiomyopathy, rhythm disturbances can include polymorphic premature ventricular complexes, bigeminy and trigeminy, couplets, triplets, atrioventricular heart block, atrioventricular nodal reentrant tachycardia, premature atrial complexes, premature ventricular complexes, and ventricular tachycardia.
- **Electromyography** shows myopathic features (low-amplitude polyphasic potentials of short duration).
- **Nerve conduction studies** are normal.

**Echocardiogram** reveals, at the onset of cardiomyopathy, reduced function of the left ventricle and dilatation and global hypokinesia without wall hypertrophy. Later, dilatation involves the left atrium and ventricle, subsequently affecting all chambers.

**Skeletal muscle biopsy.** The following findings help distinguish Salih myopathy from congenital muscular dystrophy (CMD) and other congenital myopathies. Muscle biopsy sections should be examined for histology, histochemistry, immunohistochemistry, and electron microscopy:

- Histology of skeletal muscle reveals a pattern compatible with congenital myopathy (Figure 2): mild variation in fiber size, abundant centrally located nuclei, no increase in connective tissue before age six years, and mild endomysial fibrosis after age six years.  
Oxidative stains reveal multiple small lesions of reduced or absent oxidative activity with poorly defined boundaries.  
Myofibrillar ATPase staining shows remarkable type 1 fiber predominance (>90%). In one individual, massive muscle fiber loss was seen in a second biopsy taken at age ten years [Carmignac et al 2007].
- **Immunohistochemistry** of skeletal muscle shows normal expression of dystrophin, laminin  $\alpha 2$  chain (merosin), integrin  $\alpha 7$ ,  $\alpha$ - and  $\beta$ -dystroglycan, desmin, emerin, and the sarcoglycans  $\alpha$  (adhalin),  $\beta$ ,  $\gamma$ , and  $\delta$ .
- **Electron microscopy** of skeletal muscle (Figure 3) highlights the "minicore-like" lesions seen on histology and reveals multiple foci of sarcomere disruption and mitochondria depletion.

## Establishing the Diagnosis

The diagnosis of Salih myopathy **is established** in a proband by identification of biallelic pathogenic variants in M-line-encoding exons Mex1, Mex2, and Mex3\* of *TTN* on molecular genetic testing (see Table 1).

\*Note: The last six exons of *TTN* (359 to 364 in the LRG [NG\_011618.3] numbering that numbers the exons sequentially along the chromosome; C-terminal domain) encode the part of titin that spans the sarcomere M-line; these exons are called Mex1-Mex6 for "M-line-encoding exons 1 through 6." For mapping of these exons to other transcripts, see Molecular Genetics.

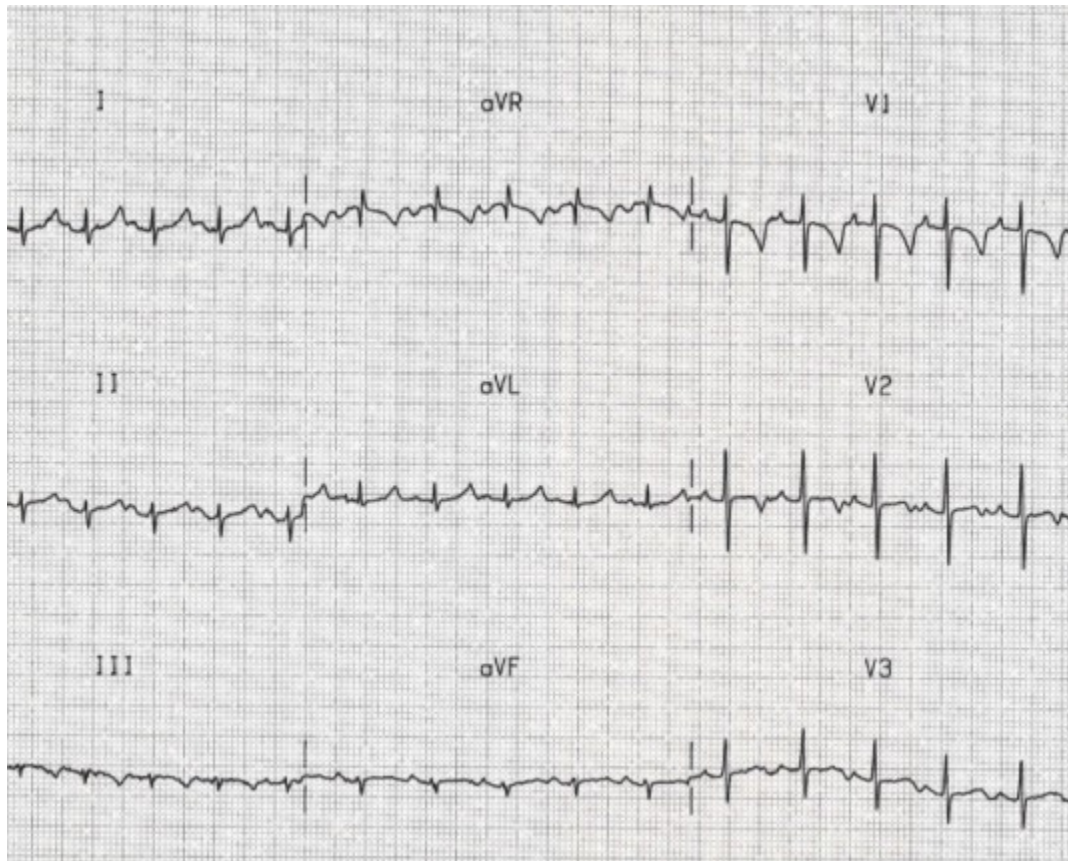
Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Salih myopathy 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 with a phenotype indistinguishable from many other inherited disorders with myopathy and/or cardiomyopathy are more likely to be diagnosed using genomic testing (see Option 2).

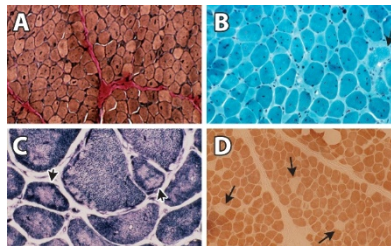
### Option 1

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

- **Single-gene testing.** Sequence analysis of *TTN* 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 of select exons (Mex1, Mex2, Mex3) first. If only one or no pathogenic variant is found, perform *TTN* sequence analysis of the remaining exons and deletion/duplication analysis.  
Note: If biallelic *TTN* pathogenic variants are not identified with the above testing, RNA sequencing to identify variants that alter splicing and/or expression and western blot analysis can be considered; however, such testing may not be available on a clinical basis [Savarese et al 2018a].
- **A multigene panel** that includes *TTN* 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



**Figure 1.** Electrocardiogram at age four years showing left axis deviation (left anterior fascicular block)

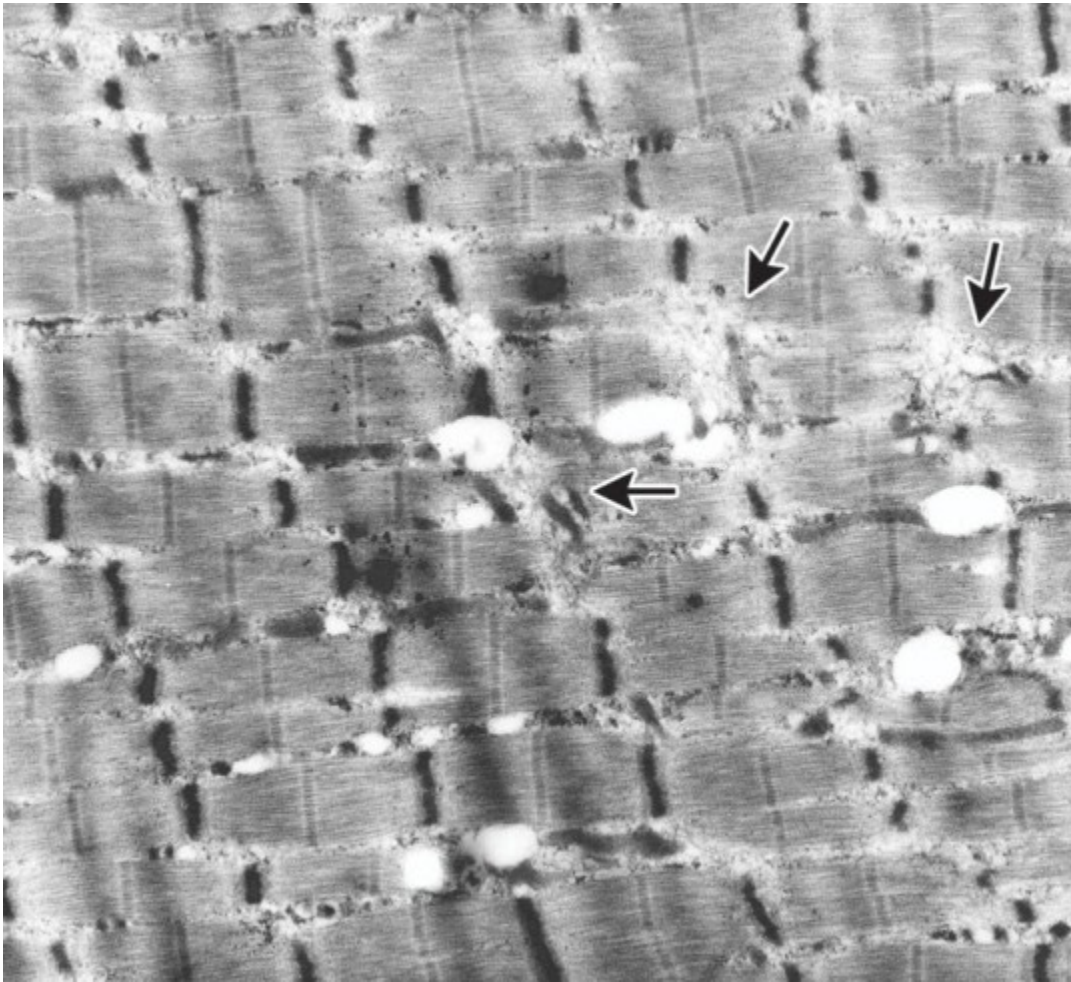


**Figure 2.** Skeletal muscle histology of two children with Salih myopathy taken at age four years (A and D) and 14 years (B and C).

A and D. The early biopsy shows (A) increased fiber size variability, abundant centrally located nuclei (CNLs) but no endomyseal fibrosis or necrosis (Van Gieson's stain; original magnification x250). (D) Type 1 fibers (dark) predominate and type 2 fibers (pale, arrows) are scanty (myofibrillar ATPase [4.3]; original magnification x250).

B and C. At age 14 years there is also a remarkable number of CNLs (B), associated with endomyseal fibrosis and few necrotic fibers (arrow) (GT; original magnification x250). (C) Oxidative staining reveals the minicore-like lesions (arrowheads; original magnification x250).

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 Salih myopathy, some panels for myopathy and/or cardiomyopathy 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.



**Figure 3.** Longitudinal electron microscopy section of skeletal muscle taken at age ten years reveals focal disruptions of sarcomeric structures (arrows), Z-disk abnormalities including focal loss of dark Z-disk material, and early dissolution of I-band filaments (original magnification x6000).

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

## Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by myopathy, **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.

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 Salih Myopathy

Gene <sup>1</sup>	Method	Proportion of Pathogenic Variants <sup>2</sup> Detectable by Method
TTN	Sequence analysis <sup>3</sup>	~100% <sup>4</sup>
	Gene-targeted deletion/duplication analysis <sup>5</sup>	Unknown, none reported

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic 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. To date, biallelic pathogenic variants reported to cause Salih myopathy are small frameshifts in M-line-encoding exons of *TTN* (NM\_001256850.1:exons 358-360, termed Mex1 - Mex3) in consanguineous families of Moroccan and Sudanese origin [Carmignac et al 2007] (see Molecular Genetics).

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

Salih myopathy is characterized by muscle weakness manifest during the neonatal period or in early infancy, and delayed motor development. Children acquire independent walking between ages 20 months and four years. In the first decade of life, global motor performance is stable or tends to improve. During this period skeletal muscle involvement mainly manifests as difficulty in running, climbing stairs, and rising from a sitting position. Those who survive childhood remain ambulant, with or without support, and maintain normal cognitive function.

**Musculoskeletal.** Moderate joint and neck contractures and spinal rigidity may appear in the first decade but become more obvious in the second decade. Respiratory function tests show a moderate restrictive pattern. Scoliosis develops after age 11 years.

**Cardiac dysfunction** manifests between ages five and 16 years and progresses rapidly, leading to death between ages eight and 20 years. Heart rhythm disturbances are the major cause of sudden death and their frequency and severity suggest primary involvement of the conduction system.

**Electrocardiography (EKG)** is very helpful in signaling the occurrence of cardiac involvement. Left axis deviation (left anterior fascicular block) can be seen as early as age four years (Figure 1). With the onset of dilated cardiomyopathy (between ages 5 and 16 years), major rhythm disturbances become evident on EKG and Holter monitoring, including polymorphic premature ventricular complexes, bigeminism and trigeminism, couplets, triplets, atrioventricular heart block, atrioventricular nodal reentrant tachycardia, premature atrial complexes, premature ventricular complexes, and ventricular tachycardia.

**Echocardiogram** reveals, at the onset of cardiomyopathy, reduced function of the left ventricle and dilatation and global hypokinesia without wall hypertrophy. Later, dilatation involves the left atrium and ventricle, subsequently affecting all chambers and leading to congestive heart failure.

**Radionuclide angiography** using MUGA (*multi-gated acquisition*) scan reveals the deteriorating ventricular function with reduction of the left ventricular ejection fraction followed by reduction of the right ventricle ejection fraction.

**Heart muscle biopsies** (taken from 2 individuals) showed increased interstitial fibrosis compatible with dilated cardiomyopathy [Carmignac et al 2007]. Oxidative staining was normal without focal oxidative defects or significant disarray of the cardiomyocyte structure, in contrast to the classic observation in hypertrophic cardiomyopathy.

**Heterozygotes.** In contrast to individuals with heterozygous pathogenic variants in *TTN* associated with [Udd distal myopathy](#), the heterozygous parents of individuals with Salih myopathy remain asymptomatic with no cardiac or muscle disorder (Figure 4).

## Genotype-Phenotype Correlations

No genotype-phenotype correlations are known.

## Nomenclature

Salih myopathy was initially referred to as Salih congenital muscular dystrophy [Salih et al 1998, Subahi 2001]. Subsequently, it was renamed Salih myopathy [Fukuzawa et al 2008, Pernigo et al 2010].

## Prevalence

Salih myopathy is thought to be rare. It has been described in consanguineous families of Arab descent originating from Sudan and Morocco. The actual prevalence is unknown.

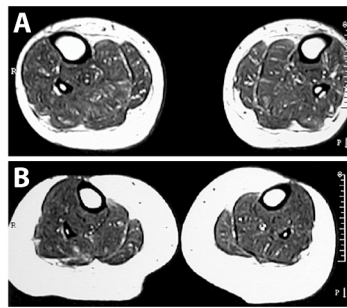
## Genetically Related (Allelic) Disorders

**Limb-girdle muscular dystrophy type 2J (LGMD2J)**, which is allelic to Salih myopathy and is caused by mutation of the C terminus of *TTN*, has a later onset (childhood or later) than Salih myopathy.

Other phenotypes known to be associated with *TTN* include the following autosomal dominant disorders:

- [Hypertrophic cardiomyopathy \(HCM\)](#)
- [Dilated cardiomyopathy \(DCM\)](#)
- [Udd distal myopathy](#)
- [Hereditary myopathy with early respiratory failure \(HMERF\)](#)
- [Arrhythmogenic right ventricular cardiomyopathy](#)

For comprehensive reviews of *TTN*-related disorders, see Savarese et al [2016] and Hackman et al [2017].



**Figure 4.** Mid-calf muscle MRI of parents of a proband at age (A) 55 years and (B) 44 years were normal and showed no fatty degeneration of the anterior tibial muscles.

## Differential Diagnosis

**Table 2.** Early-Onset Muscle Disorders to Consider in the Differential Diagnosis of Salih Myopathy

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping w/Salih myopathy	Distinguishing from Salih myopathy
Spinal muscular atrophy (SMA)	<i>SMN1</i>	AR	<ul style="list-style-type: none"> <li>• Early-onset muscle weakness (age 6-12 mos) (SMA II)</li> <li>• Weakness → frequent falling &amp; difficulty walking up &amp; down stairs (SMA III)</li> <li>• Normal intelligence</li> </ul>	<ul style="list-style-type: none"> <li>• Onset age: &gt;12 mos (SMA III)</li> <li>• Frequent finger trembling</li> <li>• Sparing of facial muscles</li> <li>• Serum CK: normal</li> <li>• EKG: frequent background tremors but no cardiac involvement</li> <li>• EMG: neurogenic features (polyphasic waves, positive sharp waves &amp; fibrillations) (versus myopathic EMG features seen in Salih myopathy)</li> <li>• Skeletal muscle histology: group atrophy of type 1 &amp; type 2 muscle fibers (vs type 1 fiber predominance seen in Salih myopathy)</li> </ul>
Duchenne muscular dystrophy	<i>DMD</i>	XL	<ul style="list-style-type: none"> <li>• Usually manifests in early childhood w/delayed milestones</li> <li>• Subclinical or clinical cardiac involvement presents in majority of affected individuals</li> </ul>	<ul style="list-style-type: none"> <li>• Serum CK: ↑ (&gt;10-300x normal)</li> <li>• EKG: characteristic pattern</li> <li>• Skeletal muscle histology: established dystrophic morphology early in childhood</li> <li>• Immunohistochemical staining of skeletal muscle: negative for dystrophin</li> </ul>



Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping w/Salih myopathy	Distinguishing from Salih myopathy
Sarcoglycanopathies <sup>1</sup>	SGCA SGCB SGCG SGCD	AR	<ul style="list-style-type: none"> <li>Onset age: 3-15 yrs</li> <li>In some, delayed walking &amp; frequent falling</li> <li>Cardiomyopathy</li> <li>EKG: left anterior fascicular block</li> </ul>	<ul style="list-style-type: none"> <li>Serum CK: ↑ (10-70x normal)</li> <li>EKG: tall R wave in V1 &amp; V2 (vs Salih myopathy, in which deep S waves are seen in the right precordial leads assoc w/↓ R/S ratio; see Figure 1.)</li> <li>Echocardiogram: left ventricular dysfunction associated w/regional wall motion abnormalities (e.g., inferior wall &amp; posterior septum hypokinesia) (vs Salih myopathy, in which the contractile dysfunction &amp; dilatation, initially restricted to the left ventricle, subsequently affects all chambers)</li> <li>Skeletal muscle histology: dystrophic early in disease course</li> <li>Immunohistochemical staining of skeletal muscle: negative staining for ≥1 of the sarcoglycans α (adhalin), β, γ, &amp; δ</li> </ul>
Muscular dystrophy-dystroglycanopathy (limb-girdle), type C5 (previously LGMD2I; OMIM 607155)	FKRP	AR	<ul style="list-style-type: none"> <li>Onset age: &lt;1 yr</li> <li>In some, infantile cardiomyopathy</li> <li>Muscle weakness &amp; calf muscle hypertrophy</li> <li>Skeletal muscle histology: in some, mild myopathic features (but significantly ↓ signal w/α-dystroglycan on immunostaining)</li> </ul>	<ul style="list-style-type: none"> <li>Absence of ptosis</li> <li>Serum CK: elevated</li> <li>EKG: dysmorphic notched P-waves, complete or incomplete right BBB or incomplete left BBB, &amp; Q waves in lateral leads</li> </ul>
LGMD2J	TTN	AR	See Genetically Related Disorders.	See Genetically Related Disorders.
Fukuyama CMD	FKRP	AR	<ul style="list-style-type: none"> <li>Muscle weakness typically begins at birth or in early infancy.</li> <li>Children present w/delay or arrest of gross motor development.</li> <li>Dilated cardiomyopathy</li> </ul>	<ul style="list-style-type: none"> <li>Intellectual disability</li> <li>Epilepsy</li> <li>Variable eye malformations</li> <li>Brain MRI: central nervous system malformations</li> </ul>
LAMA2-related muscular dystrophy	LAMA2	AR	<ul style="list-style-type: none"> <li>Congenital hypotonia</li> <li>Delayed or arrested motor milestones</li> <li>Progressive diffuse joint contractures</li> <li>Spinal rigidity</li> <li>Normal cognitive abilities in majority of affected individuals</li> <li>~1/3 of individuals develop left ventricular dysfunction</li> <li>Myopathic facies</li> <li>± calf muscle hypertrophy</li> </ul>	<ul style="list-style-type: none"> <li>Brain MRI: diffuse white matter signal abnormalities</li> <li>Immunohistochemical staining of skeletal muscle: total or partial merosin deficiency</li> </ul>

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping w/Salih myopathy	Distinguishing from Salih myopathy
LMNA-related CMD (OMIM 613205)	LMNA	AD	<ul style="list-style-type: none"> <li>• Infantile hypotonia &amp; weakness of axial-cervical muscles</li> <li>• Dilated cardiomyopathy</li> </ul>	<ul style="list-style-type: none"> <li>• Facial weakness</li> <li>• Ptosis</li> <li>• Muscle pseudohypertrophy</li> </ul>
Classic multiminicore disease (OMIM 606210, 180901)	RYR1 SELENON	AR (AD)	<ul style="list-style-type: none"> <li>• Neonatal hypotonia &amp; early-onset delayed motor development</li> <li>• Weakness of trunk &amp; neck flexors &gt; pelvic &amp; shoulder girdle muscles</li> <li>• Individuals usually ambulatory</li> <li>• Facial muscle weakness ranging from absent to severe</li> <li>• Serum CK: may be slightly ↑.</li> <li>• Similar skeletal muscle histology</li> </ul>	<ul style="list-style-type: none"> <li>• Major respiratory involvement requiring respiratory support</li> <li>• Cardiac involvement (right ventricular failure, cardiomyopathy) secondary to respiratory impairment</li> </ul>

AD = autosomal dominant; AR = autosomal recessive; BBB = bundle branch block; CMD = congenital muscular dystrophy; EMG = electromyography; LGMD = limb-girdle muscular dystrophy; MOI = mode of inheritance; XL = X linked

I. Nigro & Savarese [2014]

## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Salih myopathy, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis of Salih Myopathy

System/Concern	Evaluation	Comment
<b>CNS</b>	Neurologic exam	
<b>Cardiac</b>	In persons age ≥5 yrs: <ul style="list-style-type: none"> <li>• Referral to a cardiologist</li> <li>• EKG</li> <li>• 24-hr Holter EKG</li> <li>• Echocardiogram</li> </ul>	Evaluate for cardiomyopathy &/or arrhythmia.
<b>Pulmonary</b>	<ul style="list-style-type: none"> <li>• Respiratory rate assessment</li> <li>• Pulmonary function testing</li> </ul>	Evaluate for restrictive lung disease.
<b>Musculoskeletal</b>	PT & OT eval	Assess strength & joint mobility.
	Spinal x-rays for persons age ≥10 yrs	Evaluate for presence of scoliosis.
<b>Other</b>	Consultation w/clinical geneticist &/or genetic counselor	

EKG = electrocardiogram; OT = occupational therapy; PT = physical therapy

## Treatment of Manifestations

Treatment involves prompt management of disease manifestations using a multidisciplinary approach that includes specialists in pediatric neurology, physiotherapy, occupational therapy, orthopedics, cardiology, and pulmonology.

Stretching exercises and physical therapy help prevent contractures and promote mobility. Assistive mechanical devices including orthotics, canes, and walkers can be used as needed.

Individuals with Salih myopathy have normal cognition: technical support should be provided in the school environment. Stimulation and emotional support can improve school performance and sense of social involvement.

Parents and/or caregivers should be made aware of the symptoms of heart failure, arrhythmia (including presyncope and syncope), and thromboembolic disease, and of the need to urgently seek medical care when any of these symptoms appear.

Training of caregivers in cardiopulmonary resuscitation may be suggested once the symptoms of cardiomyopathy start.

Adequate posture should be maintained when lying prone and sitting. Garchois brace (made of plexidur, a rigid but light and heat-deformable material) is used to reduce the degree of deformity and slow the progression of scoliosis [Wang et al 2010].

Cardiac transplantation should be considered for progressive dilated cardiomyopathy and heart failure refractory to medical therapy.

## Prevention of Secondary Complications

Annual influenza vaccine and other respiratory infection-related immunizations are advised.

Lower respiratory tract infections should be treated aggressively when they occur.

## Surveillance

**Table 4.** Recommended Surveillance for Individuals with Salih Myopathy

System/Concern	Evaluation	Frequency
<b>Cardiac</b>	<ul style="list-style-type: none"> <li>EKG</li> <li>24-hr Holter EKG</li> <li>Echocardiogram</li> </ul>	Every 6 mos starting at age 5 yrs
<b>Pulmonary</b>	Respiratory function, using pulmonary function testing or spirometry	Annually starting at age 10 yrs
<b>Musculoskeletal</b>	Clinical exam & x-rays as needed for orthopedic complications (e.g., foot deformity, joint contractures, spinal deformity)	As needed

## Agents/Circumstances to Avoid

Ibuprofen (Brufen®):

- Give with care in those with evidence of cardiomyopathy. A patient who had reduced left ventricular ejection fraction developed edema following its administration [Subahi & Salih, unpublished observation].
- Avoid in those with congestive heart failure.

## Evaluation of Relatives at Risk

Early diagnosis of at-risk sibs by clinical examination and/or molecular genetic testing is important in order to monitor motor development and cardiac function so that treatment can be instituted promptly.

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

## Pregnancy Management

If a fetus is diagnosed prenatally with Salih myopathy, special considerations are needed at and following delivery since muscle weakness may manifest during the neonatal period.

## Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://clinicaltrialsregister.eu) 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

Salih myopathy 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 Salih myopathy-related *TTN* pathogenic variant.
- Heterozygotes (carriers) are asymptomatic. Note: In contrast to individuals with heterozygous pathogenic variants in *TTN* associated with Udd distal myopathy, the parents of individuals with Salih myopathy remain asymptomatic with no cardiac or muscle disorder (Figure 4).

### 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.

**Offspring of a proband.** Individuals with Salih myopathy are not known to have reproduced.

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

## Carrier Detection

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

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

### 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 carriers or are at risk of being carriers.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *TTN* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for Salih myopathy are possible.

## 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](#).*

- **Muscular Dystrophy Association (MDA) - USA**

**Phone:** 833-275-6321

[www.mda.org](http://www.mda.org)

- **Muscular Dystrophy Canada**

Canada

**Phone:** 800-567-2873

**Email:** [info@muscle.ca](mailto:info@muscle.ca)

[www.muscle.ca](http://www.muscle.ca)

- **Muscular Dystrophy UK**

United Kingdom

**Phone:** 0800 652 6352

[www.muscardystrophyuk.org](http://www.muscardystrophyuk.org)

- **Congenital Muscle Disease International Registry (CMDIR)**

*The CMDIR is a global partnership of patient advocacy organizations, researchers, and clinicians, all working toward the same goal: to find treatments for congenital muscle disease.*

CMDIR/Cure CMD

[www.cmdir.org](http://www.cmdir.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.** Salih Myopathy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<i>TTN</i>	2q31.2	Titin	<a href="#">TTN homepage - Leiden Muscular Dystrophy pages</a>	TTN	TTN

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 Salih Myopathy ([View All in OMIM](#))

188840	TITIN; TTN
611705	CONGENITAL MYOPATHY 5 WITH CARDIOMYOPATHY; CMYP5

## Molecular Pathogenesis

To date, biallelic pathogenic variants reported to cause Salih myopathy are small frameshift deletions in *TTN* exons Mex1 and Mex3 in consanguineous families of Moroccan and Sudanese origin [Carmignac et al 2007]. Carriers of these frameshift variants (i.e., heterozygotes) are asymptomatic, presumably as a result of nonsense-mediated decay (NMD) of the mutated mRNA. Since homozygotes survive, the NMD cannot be complete. Some titin protein that lacks the last C-terminal domains is produced. Whether the total decrease of titin protein or the loss of C terminus is more important for the phenotype is not known.

**Gene structure.** The longest *TTN* transcript, NM\_001267550.1, has 363 exons with a coding capacity of 113,414 bp. *TTN* has a large number of alternative splicing variants, which can result in confusion in exon and nucleotide numbering in the literature [Bang et al 2001, Guo et al 2010, Savarese et al 2018b]. Transcript variant (N2A) [NM\\_133378.4](#) is a long transcript with 312 exons that encodes the isoform N2A, the predominant titin isoform in skeletal muscle. For a detailed summary of gene and protein information, see Table A, **Gene**.

The Mex1 – Mex6 domain exons correspond to the following exons:

- LRG\_391 (NG\_011618.3): exons 359-364
- NM\_133378.4: exons 307-312
- NM\_001267550.1: exons 358-363
- NM\_001256850.1: exons 307-312

**Pathogenic variants.** To date, the biallelic variants reported to cause Salih myopathy are small frameshift deletions in *TTN* exons Mex1 and Mex3 in two consanguineous families of Moroccan and Sudanese origin [Carmignac et al 2007] (Table 2).

**Table 5.** Selected *TTN* Pathogenic Variants

DNA Nucleotide Change (Alias <sup>1</sup> )	Predicted Protein Change (Alias <sup>1</sup> )	Reference Sequences
c.105528_105535del (c.97824_97831del) <sup>2</sup> (g.289385_289392delACCAAGTG) <sup>3</sup>	p.Gln35176HisfsTer9 (p.Gln32608HisfsTer9) <sup>2</sup> (Q33535HRfsTer7) <sup>3</sup>	NM_001267550.1 NP_001254479.2
c.106571delA (c.98867delA) <sup>2</sup> (g.289390_289397delA or 291297delA) <sup>3</sup>	p.Lys35524ArgfsTer22 (p.Lys32956ArgfsTer22) <sup>2</sup> (Lys33883ArgfsTer20) <sup>3</sup>	

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](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions
2. Reference sequence: [NM\\_133378.4](#) ([NP\\_596869.4](#))
3. Reference sequence: [AJ277892.2](#)

**Normal gene product.** Titin is the biggest single polypeptide in humans, found in numerous isoforms of varying size. The entire coding region predicts a protein of 38,138 amino acids (4,200 kd). Titin is expressed as several different isoforms, caused by alternative splicing, in different skeletal muscles and in cardiac muscle [Bang et al 2001, Guo et al 2010].

Titin functions as a template in sarcomere assembly and for maintenance of sarcomere integrity. The titin protein is the third myofilament in the sarcomere along with myosin and actin filaments. Titin spans more than one half the length of a sarcomere in heart and skeletal muscle. Structurally different parts of the protein perform distinct functions (mechanical, developmental, and regulatory) [Carmignac et al 2007]. Titin binds and interacts with a large number of other sarcomeric proteins.

**Abnormal gene product.** The predicted truncated titin proteins resulting from the frameshift variants in Mex1, Mex2, and Mex3 are incorporated into ultrastructurally normal sarcomeres in homozygous affected individuals [Carmignac et al 2007]. Therefore, absence of the last five (Mex2-Mex6) exons is compatible with life but causes this severe congenital disorder. Asymptomatic heterozygous carriers of these titin deletions presumably have sufficient full-length titin to result in normal sarcomere function.

## Chapter Notes

### Acknowledgments

The authors would like to thank Loida M Sese for secretarial work, and Sayed Taha and Vir Salvador for medical illustration.

### Author History

Virginie Carmignac, PhD (2012-present)

Peter Hackman, PhD (2012-present)

Mustafa Salih, MB BS, MPCH, MD, Dr Med Sci, FRCPCH, FAAN (2012-present)

Marco Savarese, PhD (2019-present)

Tiina Suominen, MSc; University of Helsinki (2012-2019)

Bjarne Udd, MD, PhD (2012-present)

## Revision History

- 11 April 2019 (sw) Comprehensive update posted live
- 12 January 2012 (me) Review posted live
- 28 October 2011 (mas) Original submission

## References

### Literature Cited

- Bang ML, Centner T, Fornoff F, Geach AJ, Gotthardt M, McNabb M, Witt CC, Labeit D, Gregorio CC, Granzier H, Labeit S. The complete gene sequence of titin, expression of an unusual approximately 700-kDa titin isoform, and its interaction with obscurin identify a novel Z-line to I-band linking system. *Circ Res*. 2001;89:1065–72. PubMed PMID: 11717165.
- Carmignac V, Salih MAM, Quijano-Roy S, Marchand S, Marchand S, Al Rayess MM, Mukhtar MM, Ja U, Labeit S, Guicheney P, Leturcq F, Gautel M, Fardau M, Campbell KP, Richard I, Estournet B, Ferreiro A. C-terminal titin deletions cause a novel early-onset myopathy with fatal cardiomyopathy. *Ann Neurol*. 2007;61:340–51. PubMed PMID: 17444505.
- Fukuzawa A, Lange S, Holt M, Vichola A, Carmignac V, Ferreiro A, Udd B, Gautel M. Interchains with titin and myomesin target obscuring and obscuring-like 1 to the M-band-implication for hereditary myopathies. *J Cell Sci*. 2008;121:1841–51. PubMed PMID: 18477606.
- Guo W, Bharmal SJ, Esbona K, Greaser ML. Titin diversity--alternative splicing gone wild. *J Biomed Biotechnol*. 2010;2010:753675. PubMed PMID: 20339475.
- Hackman P, Udd B, Bönnemann CG, Ferreiro A, et al. 219th ENMC International Workshop Titinopathies International database of titin mutations and phenotypes, Heemskerk, The Netherlands, 29 April-1 May 2016. *Neuromuscul Disord*. 2017;27:396–407. PubMed PMID: 28214268.
- Nigro V, Savarese M. Genetic basis of limb-girdle muscular dystrophies: the 2014 update. *Acta Myol*. 2014;33:1–12. PubMed PMID: 24843229.
- Pernigo S, Fukuzawa A, Bertz M, Holt M, Reif M, Steiner RA, Gautel M. Structural insight into M-band assembly and mechanics from the titin-obscurin-like-1 complex. *Proc Natl Acad Sci USA*. 2010;107:2908–13. PubMed PMID: 20133654.
- Salih MA, Al Rayess M, Cutshall S, Urtizberca JA, Al-Turaiki MH, Ozo CO, Straub V, Akbar M, Abid M, Andeejani A, Campell KP. A novel form of familial congenital muscular dystrophy in two adolescents. *Neuropediatrics*. 1998;29:289–93. PubMed PMID: 10029346.
- Savarese M, Jonson PH, Huovinen S, Paulin L, Auvinen P, Udd B, Hackman P. The complexity of titin splicing pattern in human adult skeletal muscles. *Skelet Muscle*. 2018a;8:11. PubMed PMID: 29598826.
- Savarese M, Maggi L, Vihola A, Jonson PH, Tasca G, Ruggiero L, Bello L, Magri F, Giugliano T, Torella A, Evilä A, Di Fruscio G, Vanakker O, Gibertini S, Vercelli L, Ruggieri A, Antozzi C, Luque H, Janssens S, Pasanisi MB, Fiorillo C, Raimondi M, Ergoli M, Politano L, Bruno C, Rubegni A, Pane M, Santorelli FM, Minetti C, Angelini C, De Bleecker J, Moggio M, Mongini T, Comi GP, Santoro L, Mercuri E, Pegoraro E, Mora M, Hackman P, Udd B, Nigro V. Interpreting genetic variants in titin in patients with muscle disorders. *JAMA Neurol*. 2018b;75:557–65. PubMed PMID: 29435569.
- Savarese M, Sarparanta J, Vihola A, Udd B, Hackman P. Increasing role of titin mutations in neuromuscular disorders. *J Neuromuscul Dis*. 2016;3:293–308. PubMed PMID: 27854229.
- Subahi SA. Distinguishing cardiac features of a novel form of congenital muscular dystrophy (Salih cmd). *Pediatr Cardiol*. 2001;22:297–301. PubMed PMID: 11455396.



Wang CH, Bonnemann CG, Rutkowski A, Sejersen T, Bellini J, Battista V, Florence JM, Schara U, Schuler PM, Wahbi K, Aloysius A, Bash RO, Bérout C, Bertini E, Bushby K, Cohn RD, Connolly AM, Deconinck N, Desguerre I, Eagle M, Estournet-Mathiaud B, Ferreiro A, Fujak A, Goemans N, Iannaccone ST, Jouinot P, Main M, Melacini P, Mueller-Felber W, Muntoni F, Nelson LL, Rahbek J, Quijano-Roy S, Sewry C, Storhaug K, Simonds A, Tseng B, Vajsar J, Vianello A, Zeller R. Consensus statement on standard of care for congenital muscular dystrophies. *J Child Neurol.* 2010;25:1559–81. PubMed PMID: 21078917.

## License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (<http://www.genereviews.org/>) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the [GeneReviews® Copyright Notice and Usage Disclaimer](#). No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the [GeneReviews® Copyright Notice and Usage Disclaimer](#).

For questions regarding permissions or whether a specified use is allowed, contact: [admasst@uw.edu](mailto:admasst@uw.edu).