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Congenital Muscle Diseases: *Congenital Muscular Dystrophies and Structural Congenital Myopathies*

Edmar Zanoteli

Associate Professor
Department of Neurology
Medical School of the University of São Paulo, Brazil

(edmar.zanoteli@usp.br)

Faculty Disclosure

X	No, nothing to disclose
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Learning objectives

1. Recognize the clinical aspects of the most common forms of congenital muscle diseases

2. Recognize the most common subtypes of the congenital muscle diseases

3. Know the most important lab exams to diagnose

4. Know the key points for the treatment of these patients

Key messages

- Congenital muscle diseases are heterogeneous group of myopathies characterized by hypotonia, weakness and skeletal deformities noted in the first year of life, with a dystrophic aspect on muscle biopsy (congenital muscular dystrophies) or with structural changes on muscle biopsy (structural congenital myopathies).

- The most common forms of congenital muscular dystrophies are caused by deficiency of merosin, collagen 6 and selenoprotein and hypoglycosylation of alpha-dystroglycan. And the most common forms of structural congenital myopathies are nemaline, central-core/mini-core, centronuclear and congenital disproportion of fibers myopathies.

- Brain involvement occurs in only few subtypes, such as in the deficiency of merosin and alpha-dystroglycans

- Most of them develop a stable or slowly progressive course, but with important skeletal deformities and pulmonary involvement

- No specific therapy is available, and a multidisciplinary approach is needed, including physical therapy, cardiopulmonary evaluation , orthopedist and nutrition specialists

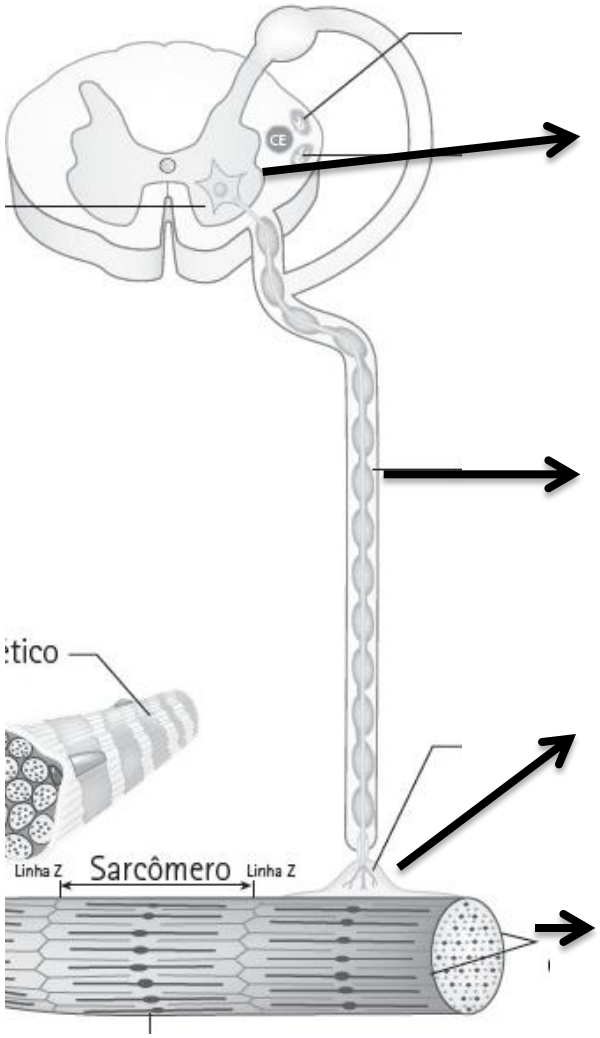
Common causes of hypotonia in children!

✓ **Central nervous system involvement** (hypoxic-ischemic injury, infections, cerebral dysgenesis)

✓ **Diseases of the motor unit** (spinal muscular atrophy, peripheral neuropathies, miastenia, myopathies)

✓ **Non-neurological conditions** (hypothyroidism, systemic illness, Down´s syndrome, Prader-Willi, Trisomy 21)

Common causes of motor unit involvement!



- Poliomyelitis (and pos-poliomyelitis)
- Spinal muscular atrophy

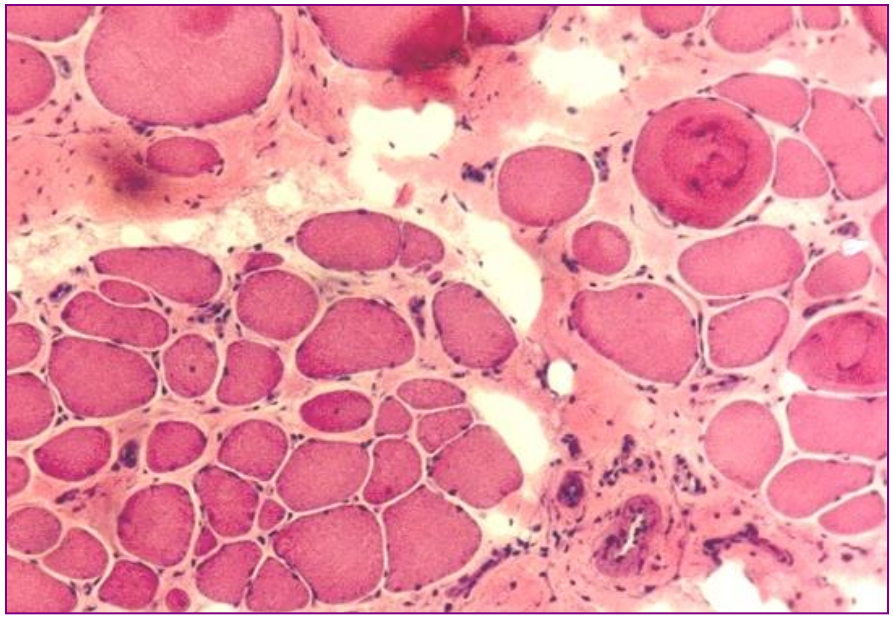
- Charcot-Marie-Tooth diseases
- Acquired peripheral neuropathies

- Myasthenia (transitional/acquired or congenital)

- Myopathies
  - Metabolic myopathies
  - Congenital muscle diseases (congenital muscular dystrophies and structural congenital myopathies)
  - Early onset muscular dystrophies
  - Congenital myotonic dystrophy

Defining congenital muscular dystrophies!

Heterogeneous group of myopathies characterized by hypotonia and weakness noted in the first year of life, and with a dystrophic aspect on muscle biopsy without specific structural alterations of the muscle fibers



The incidence of all forms of congenital muscular dystrophies has been estimated at 1/21,500 with a prevalence of 1/125,000 (*Mostacciuolo ML, 1996*)

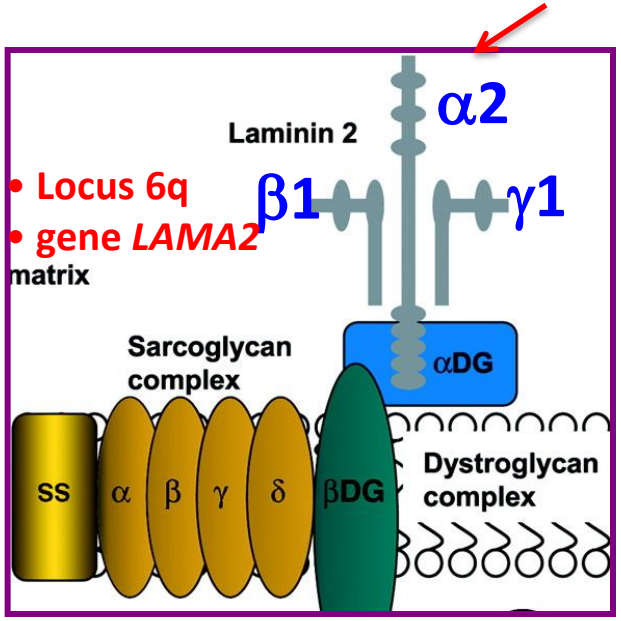
Defining congenital muscular dystrophies!
Classification

- Abnormalities of **extracellular matrix proteins** (LAMA2-merosin, COL6A1, COL6A2, COL6A3)
- Abnormalities of **α-dystroglycan glycosylation** (fukutin, POMGnT1, POMT1, POMT2, FKRP, LARGE)

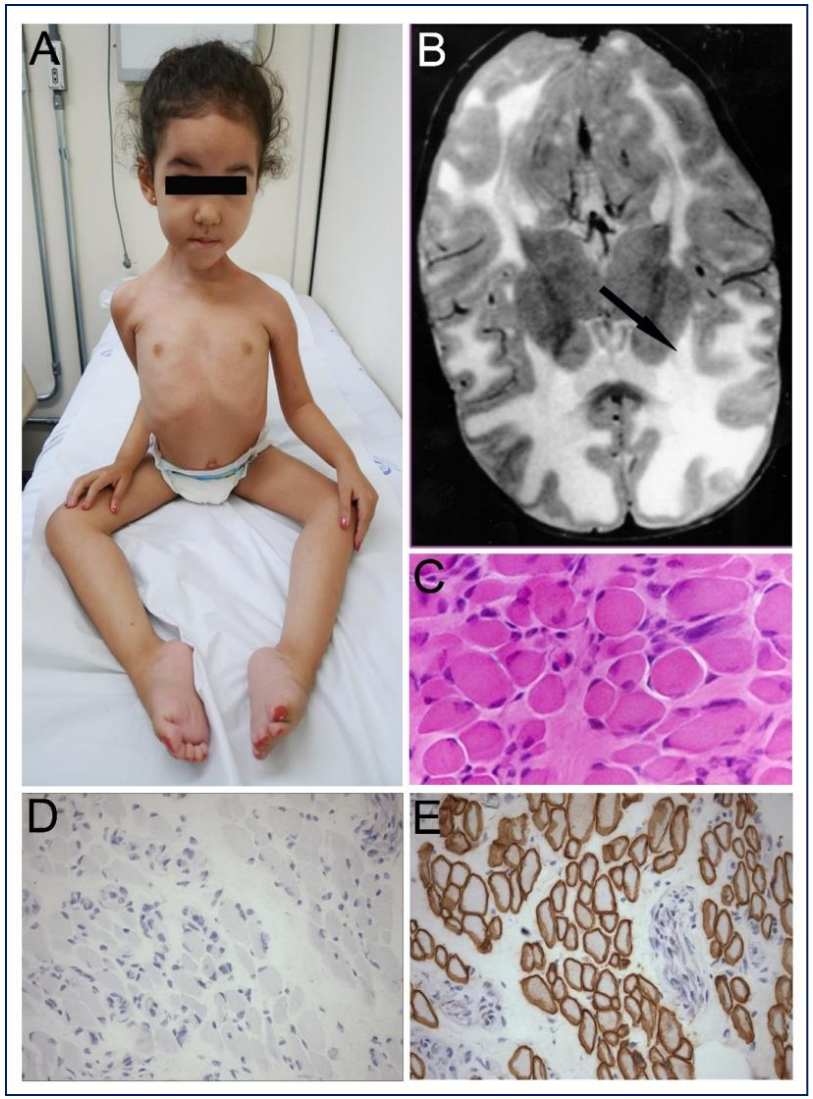
- Abnormalities of **nuclear proteins** (Lamin A/C)
- Abnormalities at the level of the **endoplasmic reticulum** (selenoprotein N*1*)

Congenital Muscular Dystrophies

Deficiency of **Merosin**

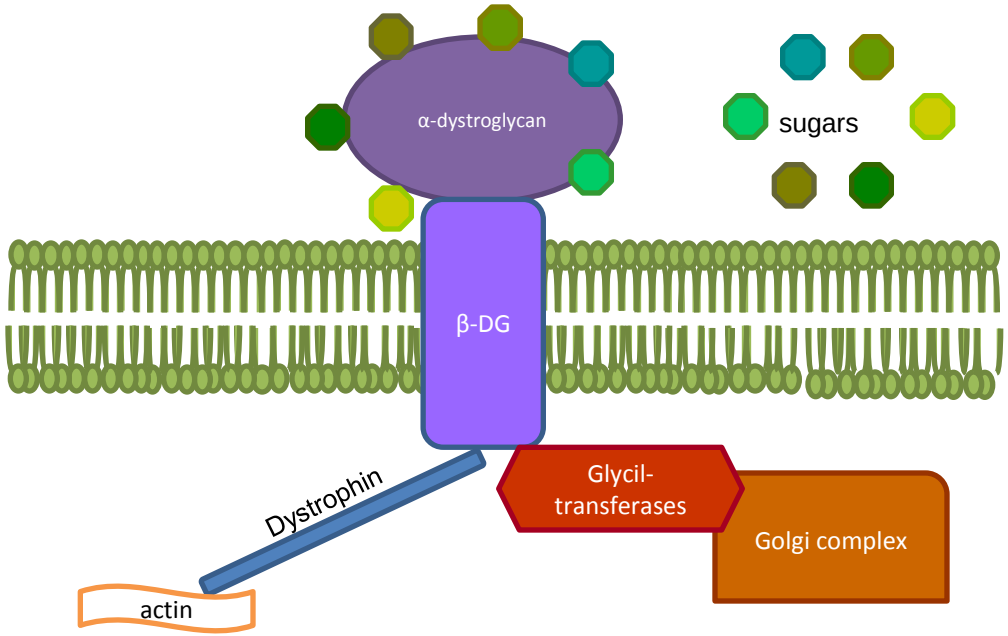


- 40-50% of the CMD
- Increase of CK (>5X)
- CNS - white matter changes
- Normal cognition



Hypoglycosylation of **α-dystroglycan**

- Post-translational modification of O-mannosylglycans on α-dystroglycan is required for its binding to laminin, agrin and perlecan on the extracellular matrix (ECM)
- Hypoglycosylation of α-dystroglycan due to glycosyltransferases deficiency reduce its binding to ECM components weakening the sarcolemma
- At least 15 glycosyltransferases were identified causing hypoglycosylation of α-dystroglycan



- **POMT1 and POMT2**: Initial link between mannose and alpha-DG (mannosylation)
- **POMGnT1**: Add residues of GlcNAc (transference of N-acetylglucosamine) to alpha-DG
- **Fukutin and fukutin related protein (FKRP)**: Synthesis of tetrasaccharides ?

Spectrum of the involvement of α-dystroglycanophaties

Central nervous system

Supratentorial

- Agyria
- Encephalocele
- Pachygyria
- Lissencephaly
- Abnormalities of white matter
- Hydrocephalus

Infratentorial

- Cerebellar hypoplasia
- Cerebellar cysts
- Pons and brainstem dysplasia

Eye

- Myopia
- Microphthalmia
- Retina defects
- Defects of anterior chamber

Skeletal muscle

- Mild to severe weakness and hypotonia
- Increase of CK
- Reduction of merosin stain on muscle biopsy
- Hypoglycosylated ADG in the muscle biopsy

Collagen 6 deficiency

Ullrich

Intermediate forms

Bethlem

- Distal joint hyperlaxity
- Proximal joint retractions
- Severe motor involvement

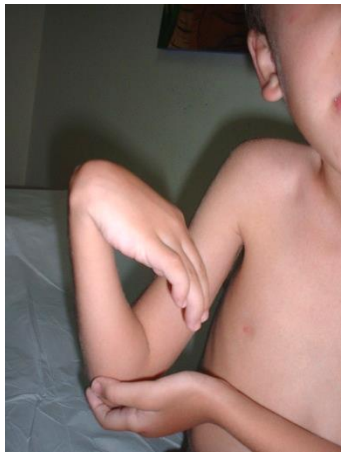
Normal CK

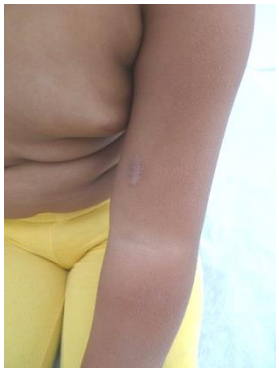
- Fingers retraction
- **Mild motor involvement**

Recessive inheritance

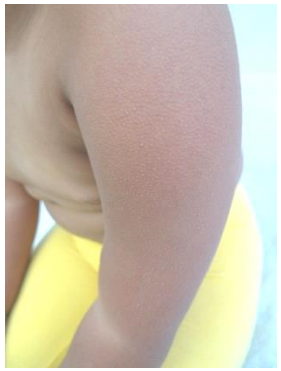
- Normal cognition
- **Respiratory involvement**
- No cardiac involvement

Dominant inheritance

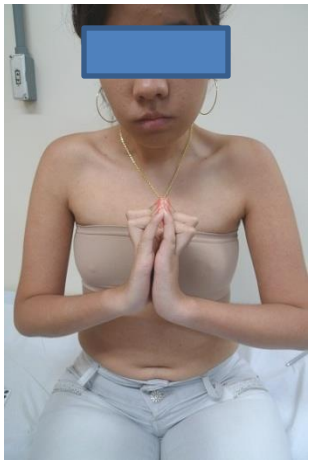




keloid



Follicular hyperkeratosis



Congenital Muscular Dystrophies

Rigid spine – Selenoprotein deficiency

- **Severe respiratory insufficiency**
- Mild to moderate limb and walking involvement

***SEPN1* (1p) gene**

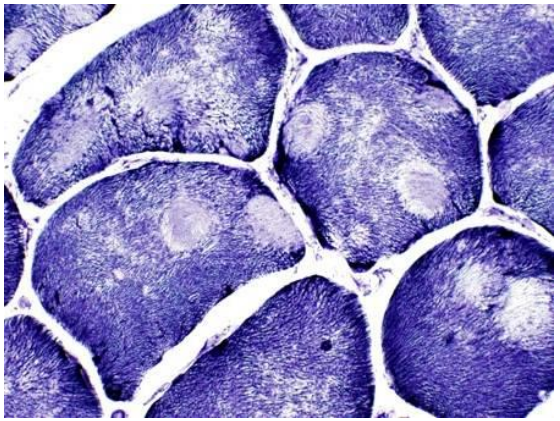
- Glycoprotein localized at ER and cell membrane
- Protection against oxidative stress

Intense axial weakness

Limitation of spinal movements

Scoliosis

Normal CK level



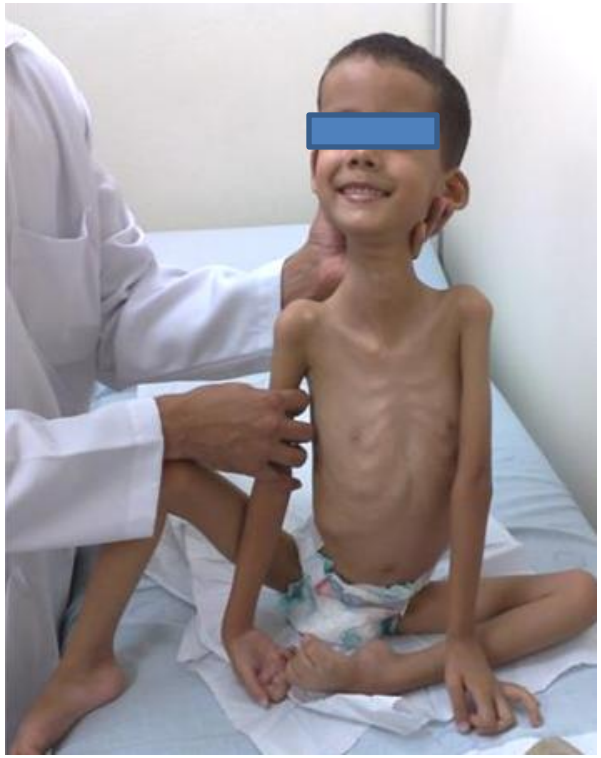
Mini-cores

Congenital Muscular Dystrophies

Other forms

- Lamin A/C (nuclear protein)
- Nesprin 1 (nuclear protein)
- *CHKB* (mitochondrial CMD)
- *ITGA7* (integrin α7)
- *ITGA9* (integrin α9)

Dropped head phenotype



(Mercure & Muntoni, 2012)

Key points for the diagnosis of CMD subtypes

Merosin

- Not acquisition of walking
- Increased CK
- White matter changes on brain MRI, but normal cognition

α-DG

- Mild to severe weakness and hypotonia
- CNS abnormalities
- Cognitive alterations and epilepsy
- Increased CK

Collagen 6

- Distal joint hyperlaxity
- Keloids and follicular hyperkeratosis
- Normal CK

SEPN1

- Rigid spine
- Early respiratory insufficiency
- Normal CK

Structural congenital myopathies!

What are they?

- Heterogeneous group of myopathies that typically present in childhood with weakness and hypotonia

  Symptoms usually present at birth but can present at any age

  Normal or mild increase of serum CK level

- Historically defined and classified by characteristic features on muscle biopsy: 4 predominant subtypes

  Core myopathies (central core disease and multi/minicore myopathy)

  Centronuclear myopathies

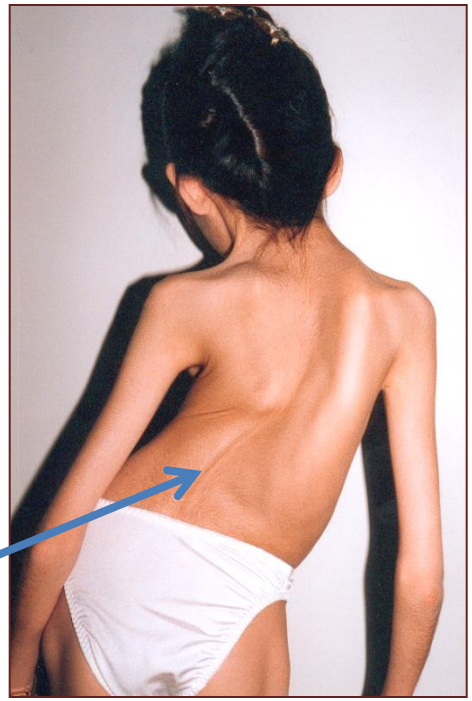
  Nemaline myopathies

  Congenital Fiber Type Disproportion

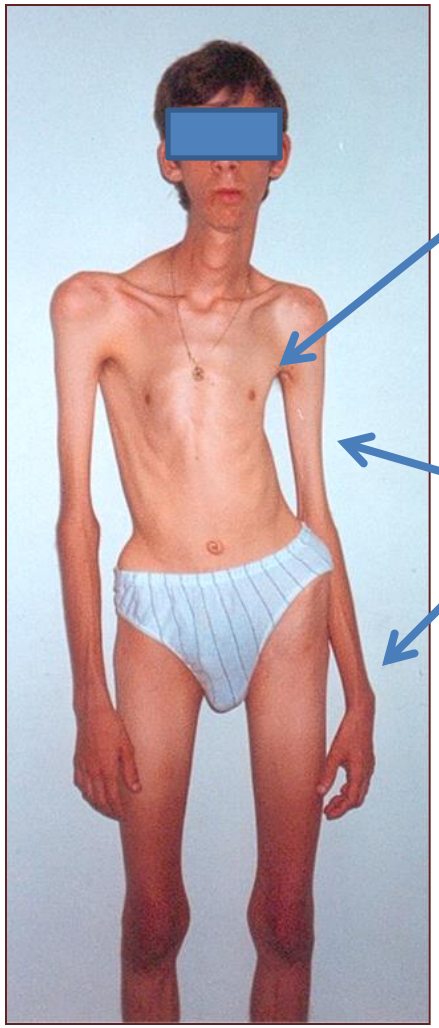
- Current standards for diagnosis include clinical, histopathological, imaging and genetic considerations

Structural Congenital Myopathies
clinical aspects

Atrofia muscular global



Fraqueza paravertebral



Deformidades caixa torácica

Fraqueza apendicular difusa

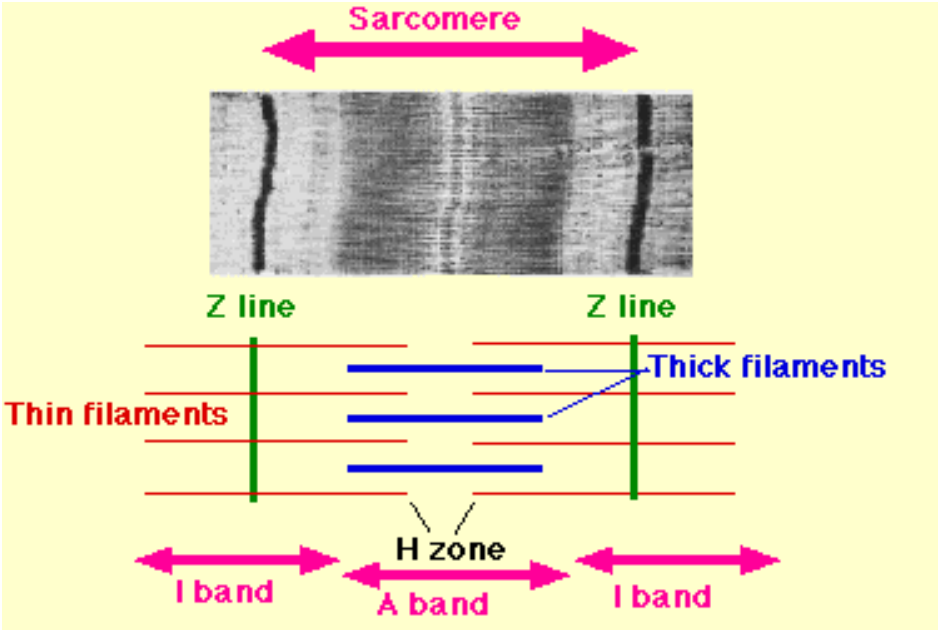
Stable or slowly progressive course

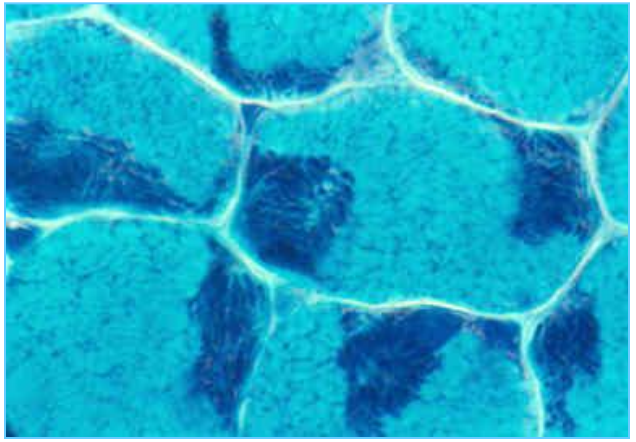
Craniofacial involvement

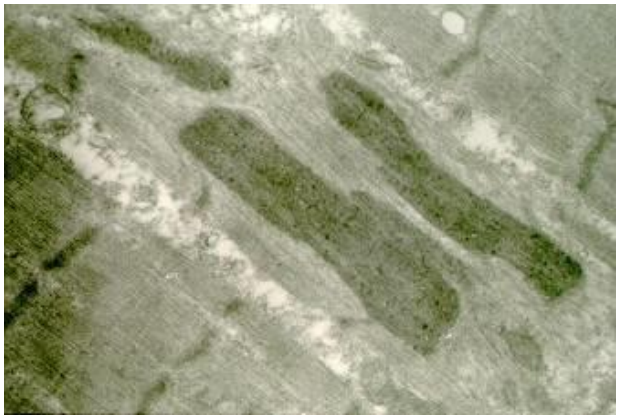
Nemaline Myopathy

"Rods" are formed at Z line of sarcomere

Thin filaments disease



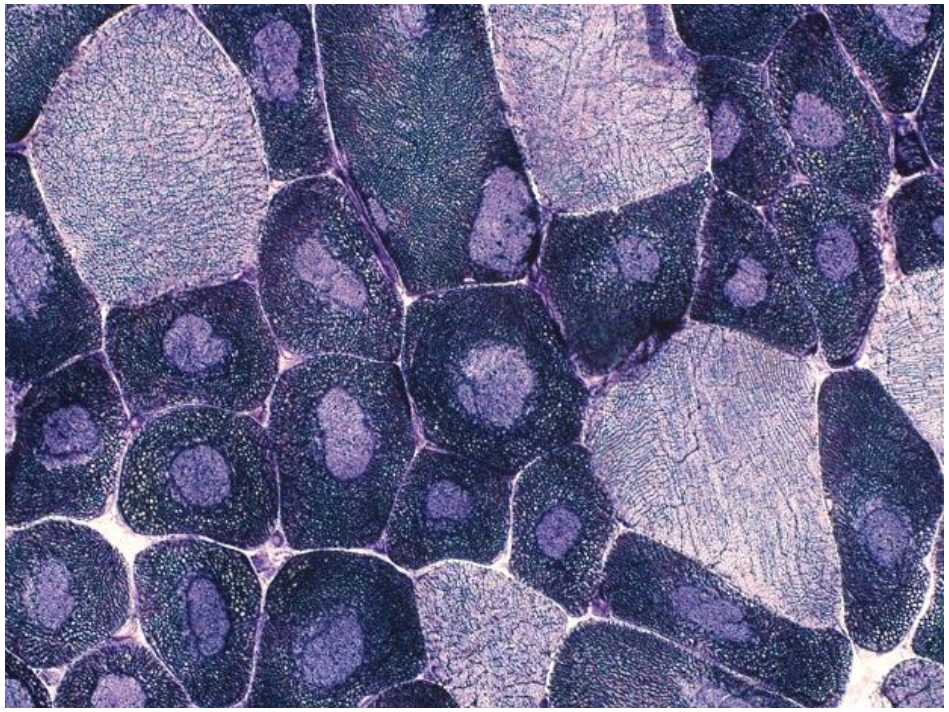




Nebulin, α-actin, tropomyosins and troponins interact with one another during muscle contraction

Central-Core Myopathy

RYR1 gene (ryanodine receptor)

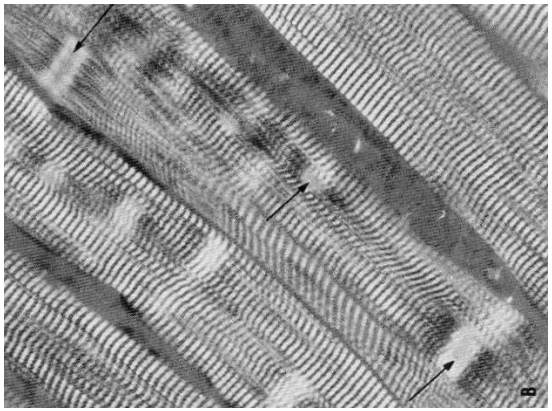


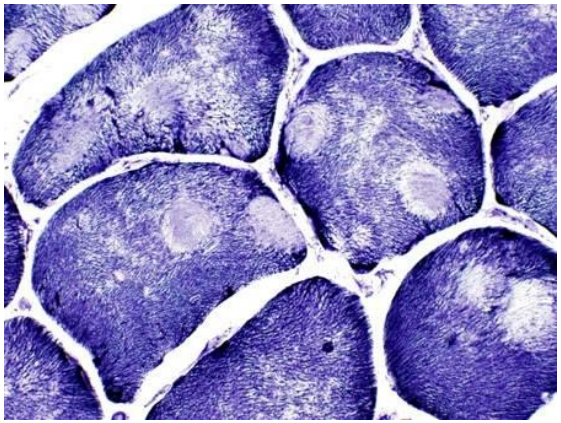
- Areas devoid of oxidative activity located on the central part of the fibers, detected by NADH and SDH stains

- **Structured**: normal myofibrils
- **Non-structured**: disorganized myofibrils

- Usually the muscle tissue is non dystrophic

Mini/multi-cores Myopathy





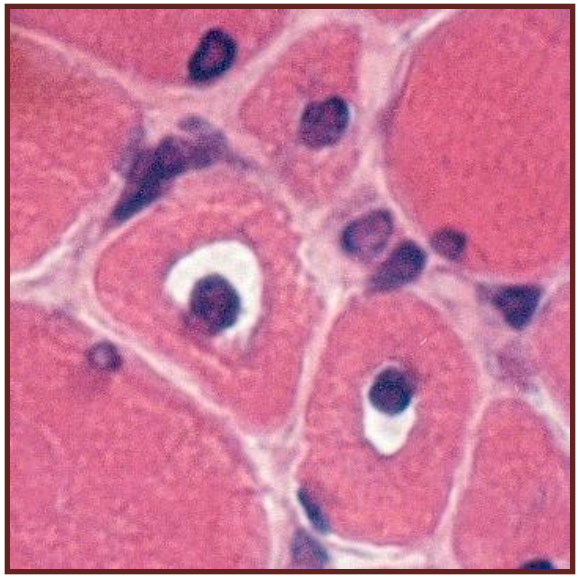
Multiple areas devoid of oxidative activity into de fibers (mini-cores)

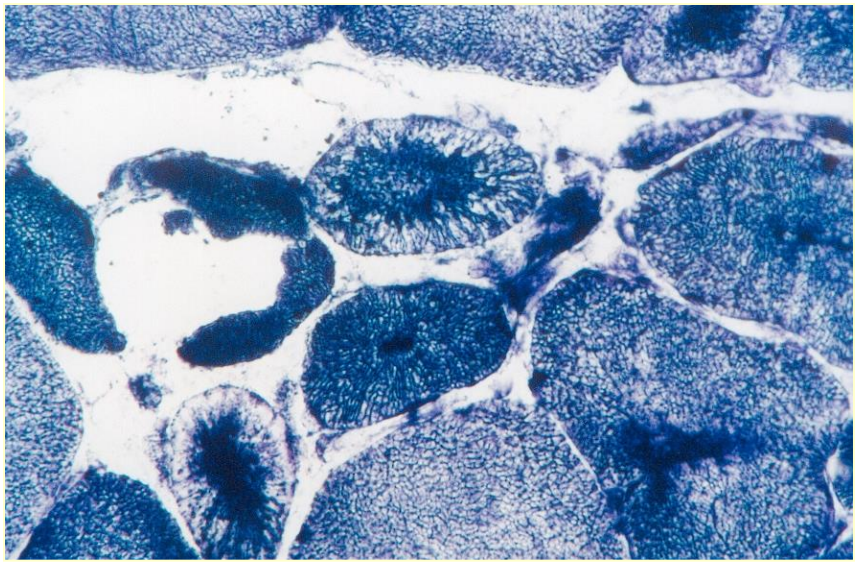
- ***RYR1***
- **Selenoprotein N,1**
- **Titin**
- **Megf10 (expression in satellite cells)**

- Childhood onset
- Clinical variability
- General weakness and hypotonia
- Craniofacial involvement
- Stable course

Centronuclear myopathy

Delay of maturation of muscle fibers?





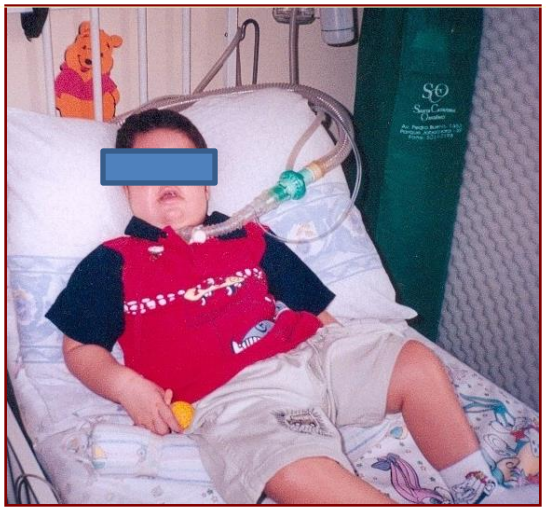
- Spiro (1966)
- Myotubos: fetal period
- Abnormal persistence of myotubular aspect

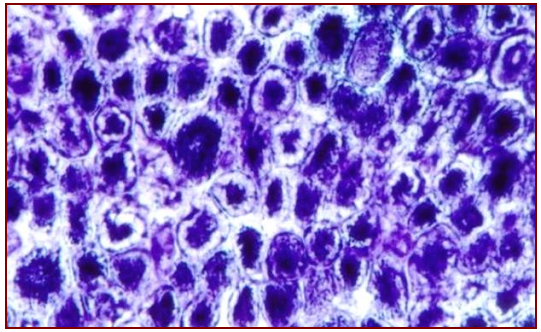
Increase of the oxidative activities on the central parts and on the subsarcolemmal region of the fibers

Centronuclear myopathy

Myotubular

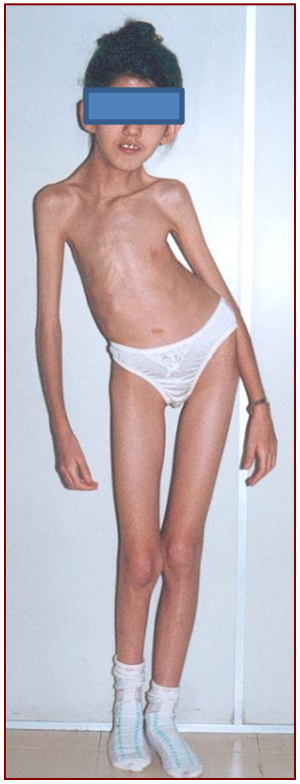
Neonatal severe form





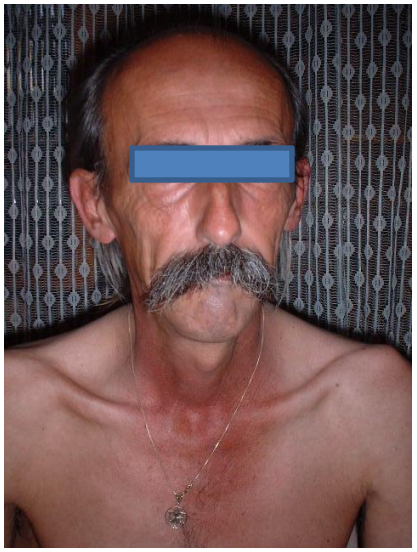
- Xq28 - *MTM1* gene
- Severe neonatal involvement

Childhood onset form



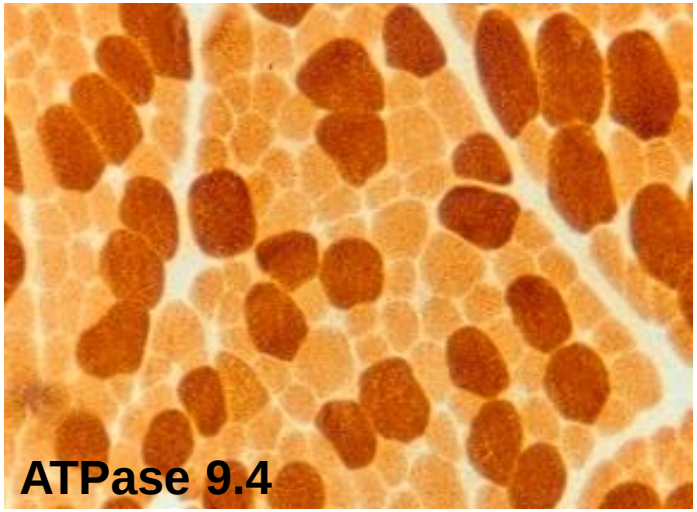
- Anphiphysin-1 (BIN1) 2q
- RYR1 gene
- Autosomal recessive

Adult onset form



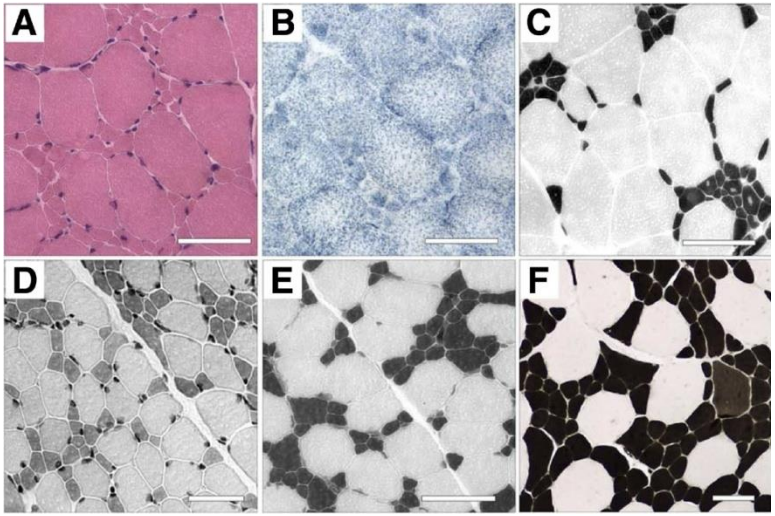
- Dynamin 2 gene
- Autosomal dominant
- Mild clinical form

Congenital Disproportion of Fibers



Type 1 fibers lesser than 12% of type 2 fibers

Genes involved
α-actin *(ACTA1)*
Tropomyosin 3 *(TPM3)*
Tropomyosin 2 (*TPM2*)
Ryanodine receptor gene (*RYR1*)



Clarke, 2011

Different degrees of fiber type disproportion can be seem in other types of neuromuscular and CNS diseases

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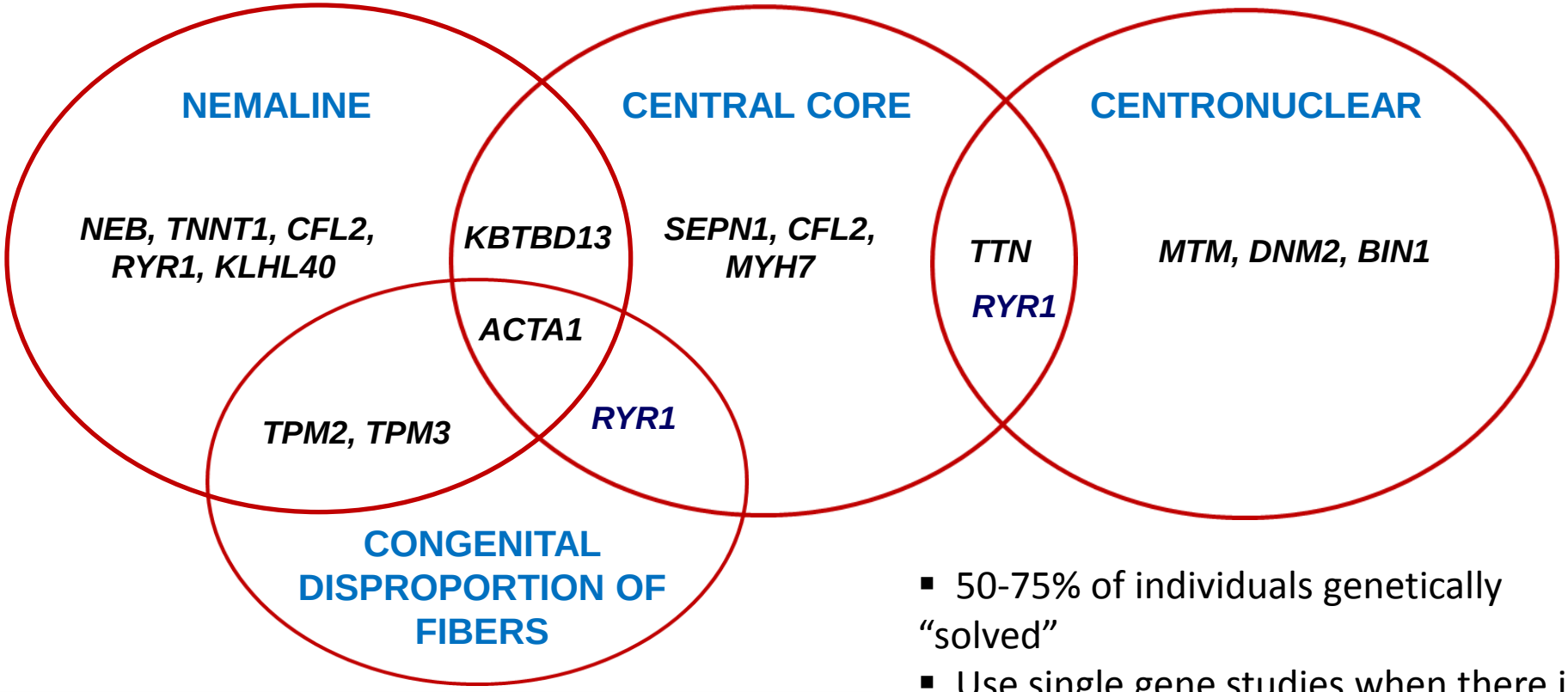
Diagnosis of exclusion !

Structural Congenital Myopathies

Genetics

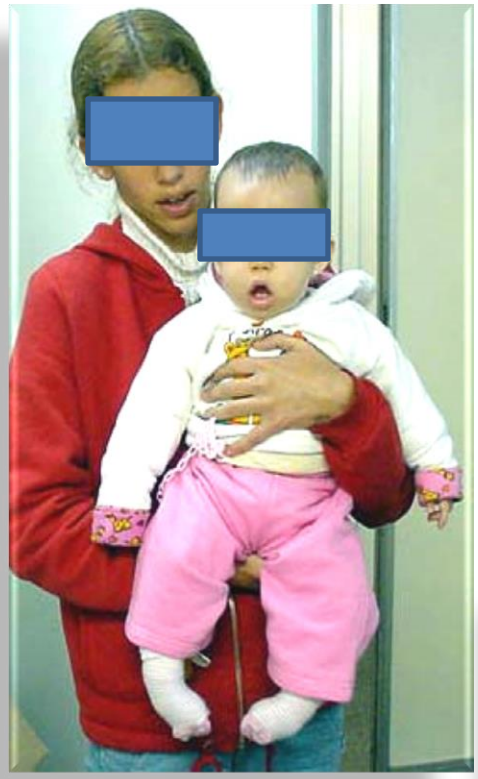


- Many genetic causes for each subtype
- Individual genes associated with several subtypes
- Use of combination of clinical, biopsy and MRI to help organize

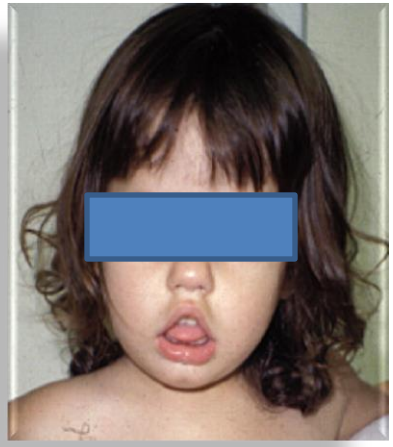
- 50-75% of individuals genetically "solved"
- Use single gene studies when there is high degree of suspicion
- Use panels in situations where several causes possible
- Consider whole exome sequencing when panel is negative

Congenital Muscle Diseases

Congenital myotonic dystrophy (Steinert)



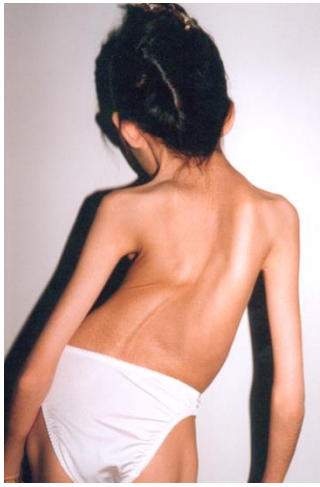
- Woman with Steinert´s diseases: risk of 80%
- Severe neonatal involvement: sucking and respiratory problems, facial involvement, skeletal deformities
- Stable course on childhood: facial involvement, cognitive impairment



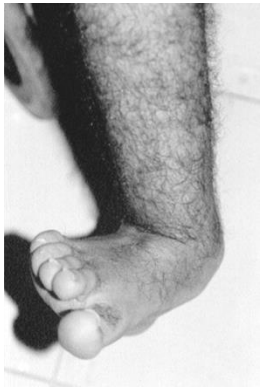
Congenital Muscle Diseases

Treatment

- No specific treatment is available
- **Symptomatic treatment**
- Genetic counseling
- Rehabilitation



Scoliosis



Contractures

- **Skeletal deformities**
- **Nutrition**
- **Pulmonary insufficiency**

Congenital Muscle Diseases

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