5th Congress of the European Academy of Neurology

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Teaching Course 10

Clinical science in muscle disorders (Level 2)

Rigid Spine syndrome

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ean congress Oslo 2019

ean european academy of neurology

TEACHING COURSE 10:

« Clinical Science in Muscle Disorders » (Level 2)

« RIGID SPINE SYNDROME »

European Reference Networks

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UNIVERSITÉ CÔTE D'AZUR

ean european academy of neurology

Disclosures

Professor Sabrina Sacconi has

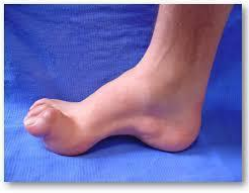
- served as a speaker for BioMarin, Sanofi/Genzyme, LFB, Biogen, Alnylam, Fulcrum
- received research/scientific grants from BioMarin, Sanofi/Genzyme, LFB, Grifols, Santhera, Biogen

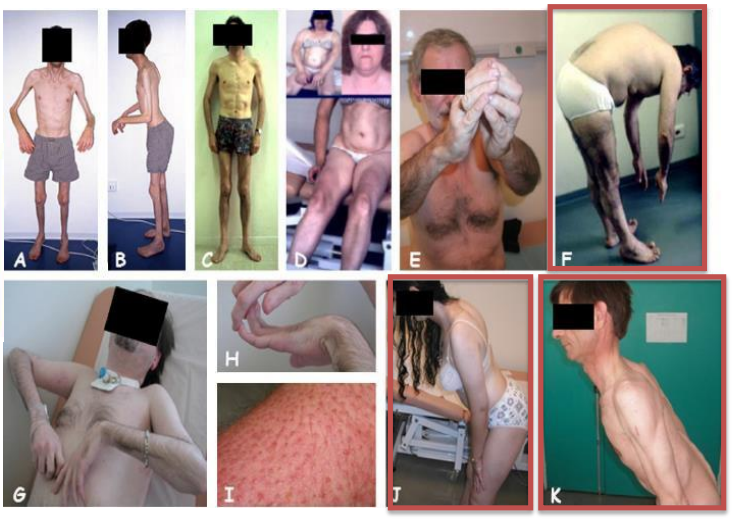
Contractures

- Stiffness or constriction in connective tissues of the body
- Muscle, joints (tendons, capsule) and skin
- They limit normal full range of motion of joints
- Most common cause: **inactivity** (scars and burn for skin), **ageing**
- Very common finding in NMD, (but also CNS* and OA** or RA***)
- In NMD, they are related to the extent and localization of muscular weakness and atrophy
- When they appear early in life, they may be associated with skeletal abnormalities (arthrogriposis, kyphosis, scoliosis *pes cavus*, *pectus carinatum*..)

*Central Nervous System; **OsteoArthritis, ***Rhumatoid Arthritis

Joint contractures

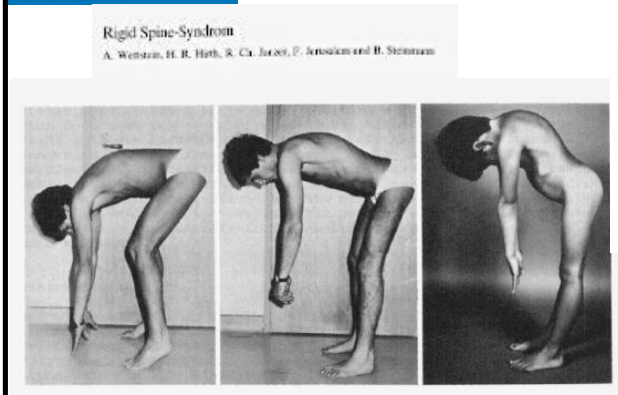




Rigid spine syndrome

B. Eymard et al., Revue Neurologique 169 (2013), 546-563

Rigid spine syndrome



Rigid Spine-Syndrom

A. Wettstein, H. R. Hatt, R. Ch. Israel, P. Jerusalem und B. Steinmann

Abb. 1. Von links nach rechts die Fälle 1, 2 und 3 beim Versuch zur maximalen Anteroflexion des Rumpfes und des Nackens. Bemerkenswert neben der Streckkontraktur der LWS und HWS ist die Achillessehnenverkürzung mit Spitzfußkontraktur bei Fall 1

Literatur

1. Dubowitz V (1973) Rigid spine syndrome: a muscle syndrome in search of a name. Proc roy Soc Med 66:219-220
2. Goebel HH, Lenard HG, Görke W, Kunze K (1977) Fibre type disproportion in the rigid spine syndrome. Neuropädiatrie 8:467-477
3. Goto I, Nagasaka S, Nagara H, Kuroiwa Y (1979) Rigid spine syndrome. J Neurol Neurosurg Psychiatry 42:276-279
4. Rowland LP, Fetell M, Olarte M, Hays A, Singh N, Wanat FE (1979) Emery-Dreifuss muscular dystrophy. Ann Neurol 5:111-117
5. Seay AR, Ziter FA, Petajan JH (1977) Rigid spine syndrome, a type I fiber myopathy. Arch Neurol 34:119-122

« Limitation of the flexion of cervical and dorso-lumbar spine caused by the shortening of the erector trunci muscles, without severe paresis »

Rigid spine and myopathies

- Congenital Muscular Dystrophies
- Congenital Myopathies
- Emery Dreyfuss Muscular Dystrophies
- Myofibrillar Myopathies
- Glycogenosis

Congenital Muscular Dystrophies & Congenital Myopathies

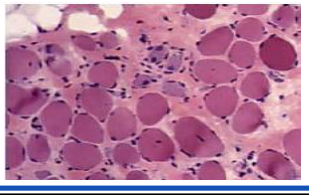
Early muscle weakness (generalized hypotonia)

Muscle biopsy

Congenital Muscular Dystrophies

Endomysial fibrosis

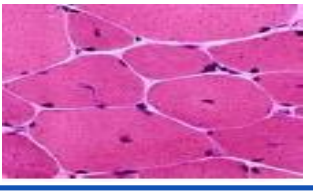
Fiber type variation ± necrosis and **regeneration**



Congenital Myopathies

No sign of dystrophy

Abnormalities of muscle fiber architecture



Congenital Muscular Dystrophies

Normal CK+ → **Elevated CK+++**

No CNS involvement → **CNS Involvement**

- Normal intelligence
- Normal Brain MRI

- Cognitive Impairment
- Abnormal CNS development +/- white matter abnormalities

Normal Merosin

- **COL6A1,A2, A3 (Ulrich) UCMD**
- **SEPN1 RSMD1**
- **LMNA (Drop head syndrome)**
- **L-CMD**

VARIOUS

- **CHKB** /Giant Mitochondria
- **ITGA9 α9 integrin**
- **ITGA7 α7 integrin**

Cerebellar syndromes

- **SIL-1 :** Marinesco-Sjögren
- **Nesprin-1** : adducted tumbs

Dystroglycanopathies (+/- mérosine)

- **MDC-1C**
- **FKRP**
- **FKTN**
- **Fukuyama / MEB**
- **POMGT1, FKRP, FKTN POMT1 POMT2 LARGE**
- **ADG**
- **Walker Warburg**
- **LARGE (MDC-1D)**
- **POMGT1 FKRP, FKTN POMT1 POMT2 LARGE**
- **ISPD**
- **CDG-Sd**
- **DPM2/DPM3 (O & N-glycosylation)**

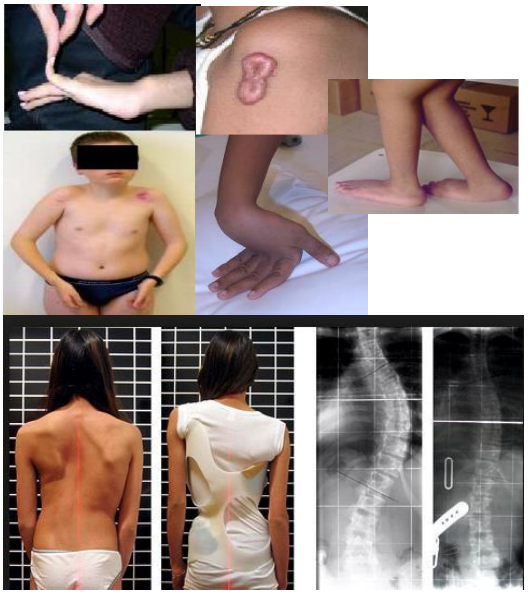
Merosin -

- *MDC1A*
- *LAMA2*

CMD,Ullrich type (COL6A1,COL6A2, COL6A3, AR) CMD

Scleroatonic Muscular Dystrophy

- Neonatal onset, severe progression
- Congenital hip luxation
- Torticollis
- Delayed motor milestones
- **Distal hyperlaxity**
- **Proximal contractures** (hip, **rigid spine**) >Distal contractures (fingers, wrist, elbow)
- **Proximal muscle weakness** followed by distal
- **Skin:** keloid scars, follicular hyperkeratosis
- protuberant calcaneus
- **Pied bot, clubfoot**
- **Respiratory insufficiency +++**
- **Scoliosis**

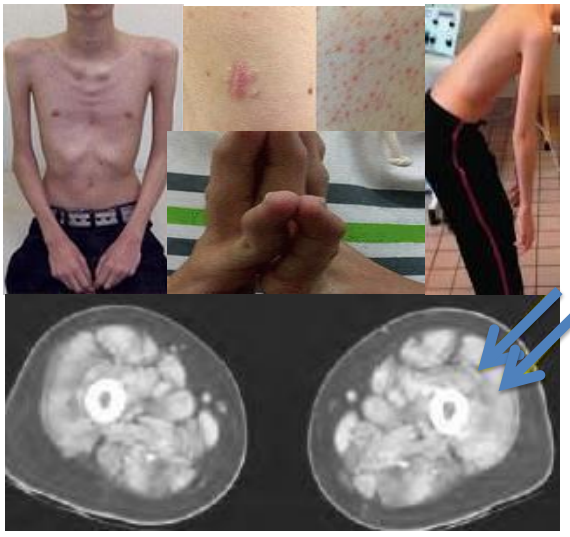


CMD Ullrich Type (COL6A1,COL6A2, COL6A3, AR)

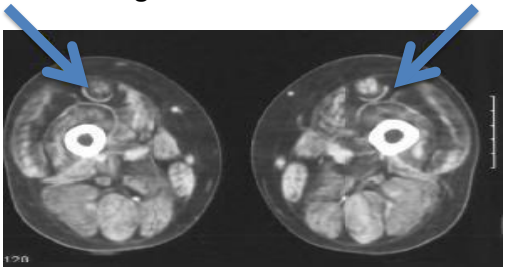
Clinical variability: related to the **age at onset**

Courtesy of T. Stojkovic

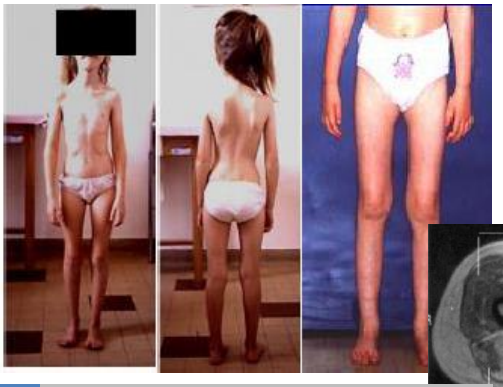
CMD, Bethlem type (COL6A1,COL6A2, COL6A3, AD)

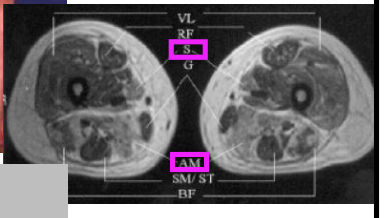


Age at onset : 1st and second decade
Skin abnormalities
No contractures except fingers
Proximal > distal deficiency
They don't loose the ability to walk
Respiratory insufficiency
Worsening at their 40ies



Selenoprotein 1-related myopathies (SEPN1)



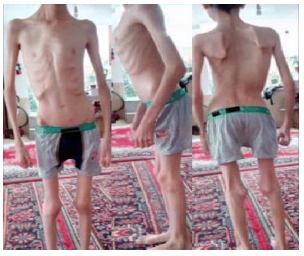


Early rigid spine and
Axial weakness >>Limb weakness
Respirator insufficiency
Scoliosis +++

No severe contractures
No skin involvement
No cardiac involvement

S = *sartorius*
AM= *adductor magnus*

Selenoprotein-related Myopathies (SEPN1)

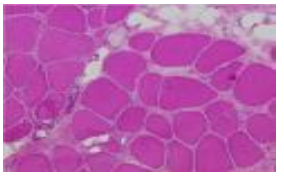


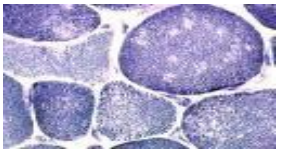
Congenital Muscular dystrophy associeted to rigid spine syndrome (RSMD1)

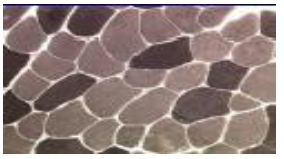
Multi-minicores Congenital myopathy (MmD)

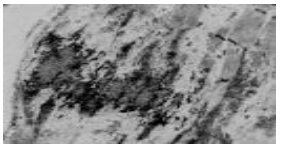
Fiber Type disproportion congenital dystrophy (FTCD)

Mallory Body Desmin-related myopathy (MB-DRM)



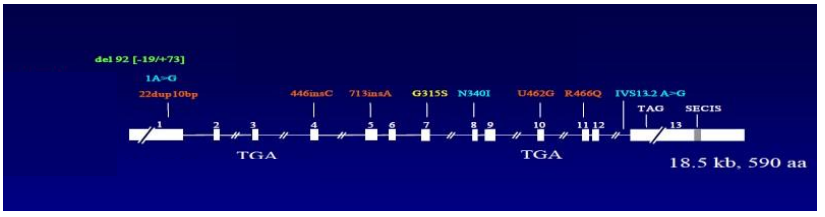






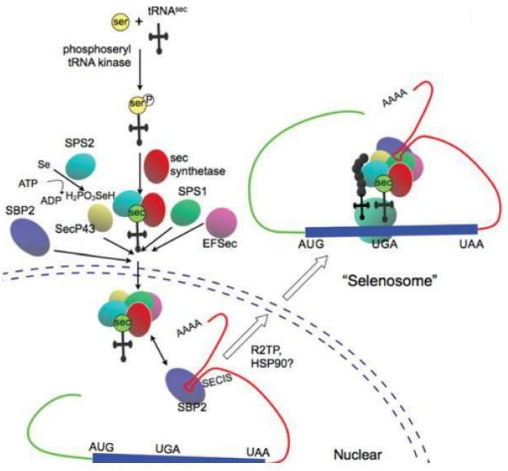
Seleprotein related myopathies (*SEPN1*, 1p36)

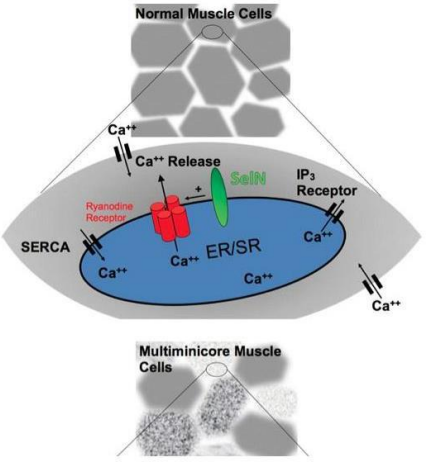
Genotype-Phenotype correlation



Rigid Spine Muscular dystrophy (RSMD1)
Moghadaszadeh et al, 2000
Multi-minicores Congenital myopathy
Ferrero et al, 2002
Mallory Body desmin related myopathy
Ferrero et al, 2004
Fiber type disproportion congenital dystrophy
Clarke et al 2006

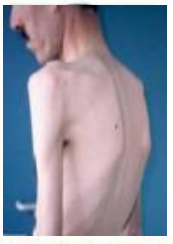
SEPN1 and *RYR1*

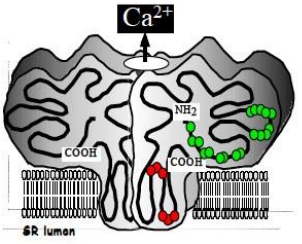




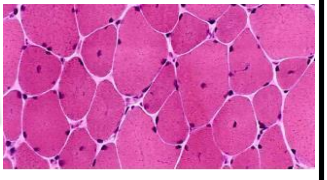
Bellinger et al, Biochem J 2009

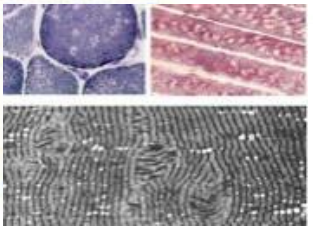
RYR1-related myopathies (AD, AR)



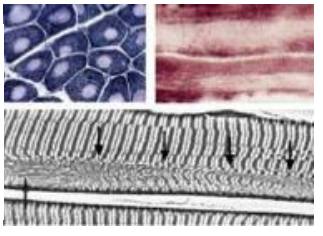


Centronuclear





Multiminicore

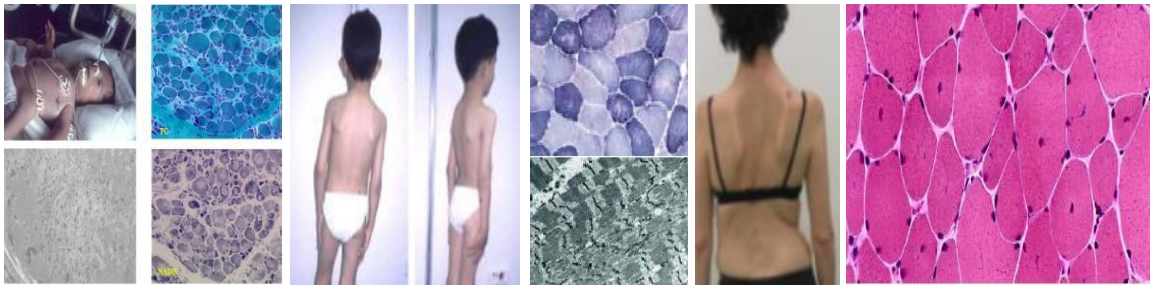


Central Core

Malignant Hyperthermia
HyperCKemia
& rhabdomyolysis

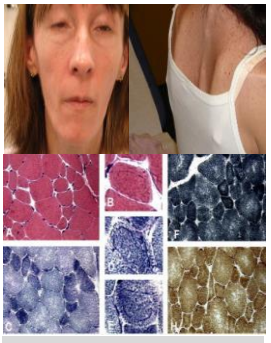
Romero et al, Neuromuscular Dis 2003

RYR1-related myopathies
(AUT DOM, AUT REC)



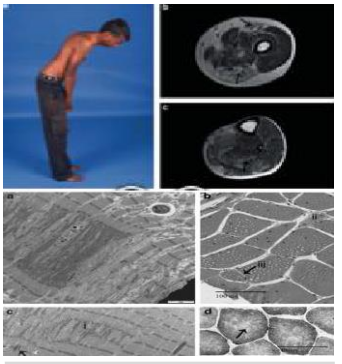
Variability in age at onset, disease progression, symptoms, histopathological findings.
Rigid spine and paraspinal muscle involvement in 10 to 15% of patients.
Malignant hyperthermia, ptosis and ophtalmoplegia may be associated

Other congenital myopathies with rigid spine



DNMN2, Centronuclear, AD
Sacconi et al, Eur J of Hum Gen 2009

BIN1, centronuclear, AD
Cabrera-Serrano et al, Neurology 2018



ACTA1, AR
Nemaline myopathy,
O'Grady et al, Eur J Hum Gen, 2015

Emery-Dreyfuss Muscular Dystrophy

Prevalence: 1:400.000

1) Joint contractures of the Achilles, elbow and posterior neck tendons;

2) Slowly progressive **muscle weakness and atrophy** (initially and generally with a **humeroperoneal** or **scapuloperoneal** distribution but later becoming more diffuse).

3) Cardiac involvement: conduction defects, rhythm disturbances and dilated cardiomyopathy. They may lead to sudden death.

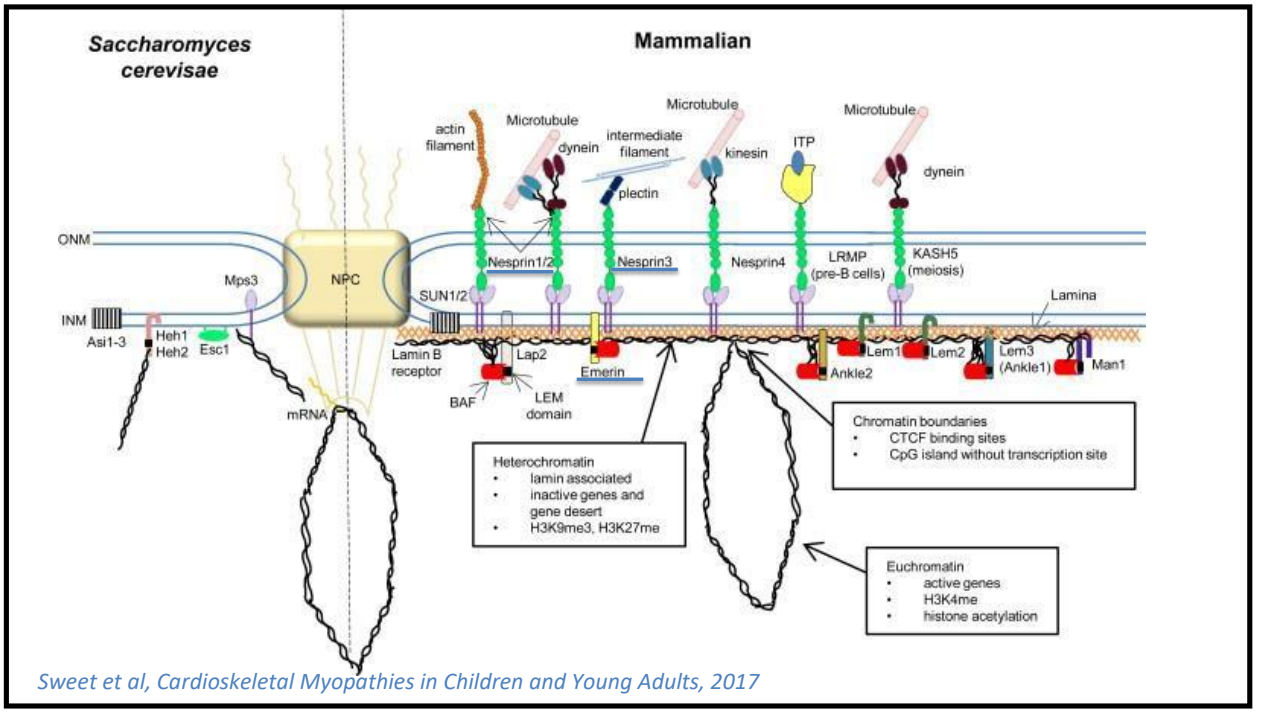
Emery AE. Emery-Dreifuss syndrome. J Med Genet 1989

Emery-Dreyfuss Muscular Dystrophy

LINC:
- **EDMD1**: *STA*/Emerine; Xq28; Recessive (UMD-*EMD Database)*
- **EDMD2**: *LMNA*/Lamine A/C; 1q21.2; Dominant
- **EDMD3**: *LMNA*/Lamine A/C; 1q21.2; Recessive
- EDMD4: *SYNE1/*Nesprine1; 6q25; Dominant
- EDMD5: *SYNE2/*Nesprine2; 14q23; Dominant

Non LINC:
- **EDMD6**: *FHL1*; Xq26.3; Semi-Dominant
- EDMD7: *TMEM43*; 3p25; Dominant

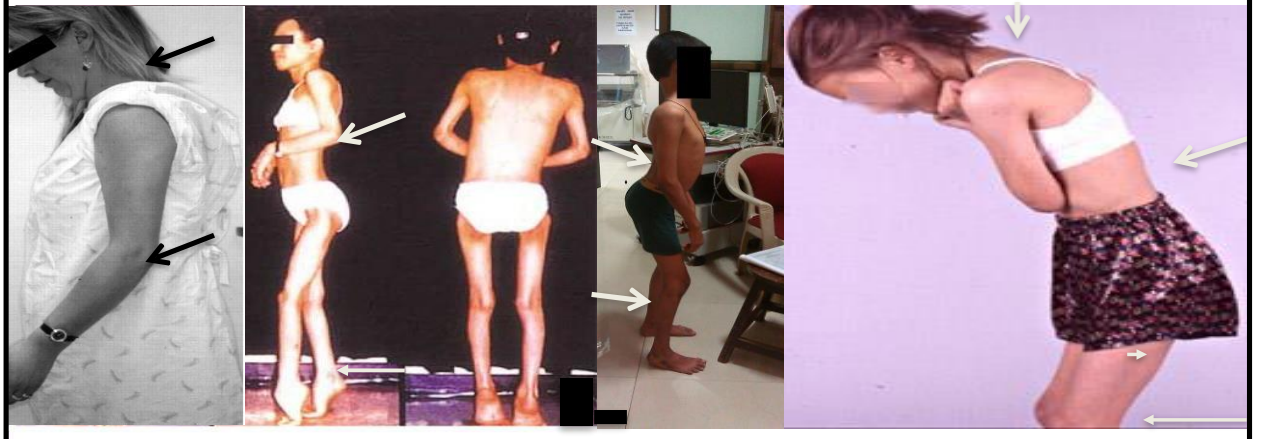
45% of the patients: causative gene remains to be identified



Sweet et al, Cardioskeletal Myopathies in Children and Young Adults, 2017

Emery-Dreyfuss Muscular Dystrophy

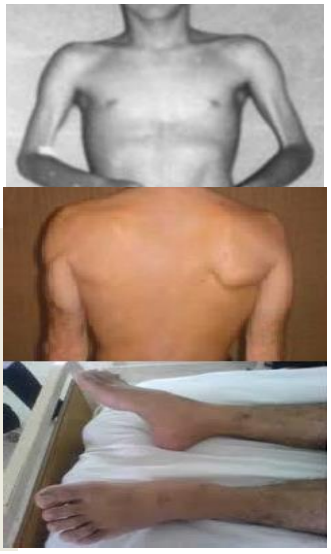
1. Joint contractures



Contractures starts very early in life and limit the autonomy of the patients

Emery-Dreyfuss Muscular Dystrophy

2. Muscular weakness



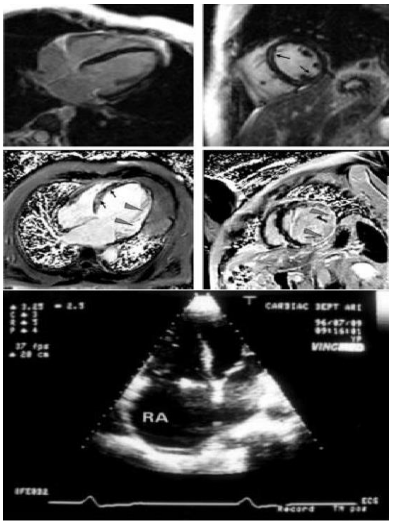
HUMERAL weakness:
Predominant in the higher part of biceps and triceps with relative sparing of deltoid in early stages of the disease.

SCAPULAR weakness:
Simmetric scapular winging

PERONEAL weakness:
Antero-medial compartement (**Laminopathies AD, AR**), posterior compartment +/- calf pseudohypertrophy (**Emerinopathie liée à X**)

Emery-Dreyfuss Muscular Dystrophy

3. Cardiac Involvement



Dilated>Hypertrophic cardiomyopathy with reduction of systolic function.

A-V conduction bloc: sinus bradycardia, I, II, III degree AVB

Rhythm disturbances:
Atrial: AES, fibrillation or flutter
Ventricular: VESV, ventricular tachycardia

Less frequently :

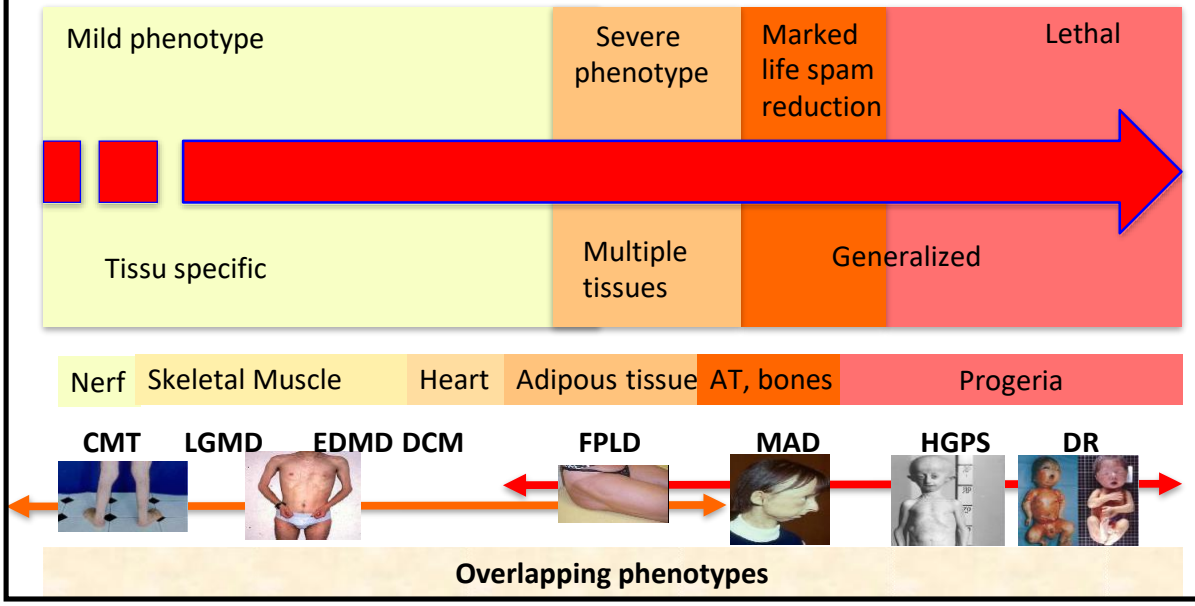
Right ventricular Cardiopathy
Left ventricular aneurism
Reduced Left ventricular compaction

Emery-Dreyfuss Muscular Dystrophy

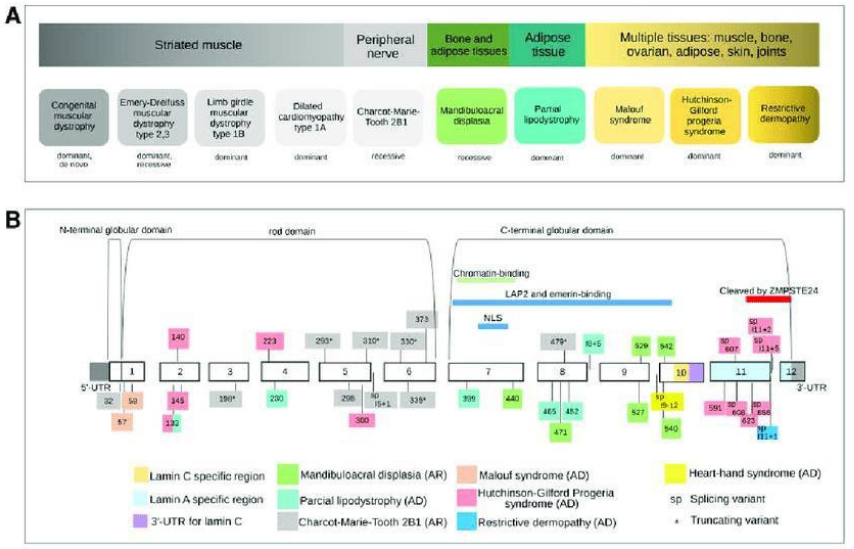
Emerinopathies vs Laminopathies

	EMERINOPATHIES (X^{rec})	LAMINOPATHIES (AD, AR)
CONTRACTURES	**Frequently the first sign**	Later in disease course
MUSCULAR WEAKNESS	Humeroperoneal predominant un antero-lateral compartment LGMD phenotype rare Wheelchair-bunded very rare	Humero-peroneal but also scapulo-peroneal Early calf involvement some patients associated with hypertrophy LGMD Phentype more frequent **More severe**
CARDIAC INVOLVEMENT	++ All cardiac involvement are possible	**+++++** **Cardiac involvement may be the only symptom**
RESPIRATORY INVOLVEMENT	Rare	Rare, but can be present in the most severe cases

Laminopathies : clinical spectrum

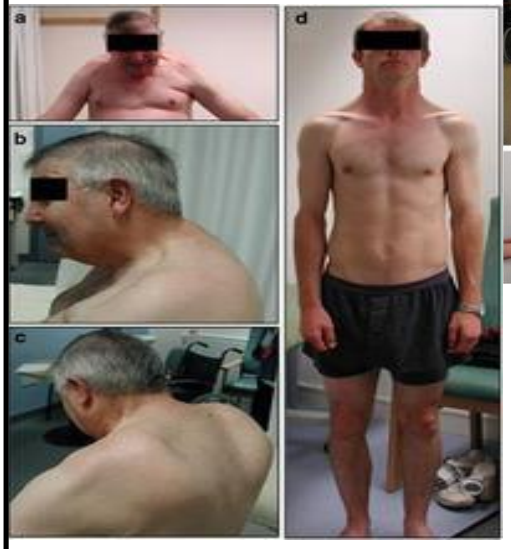


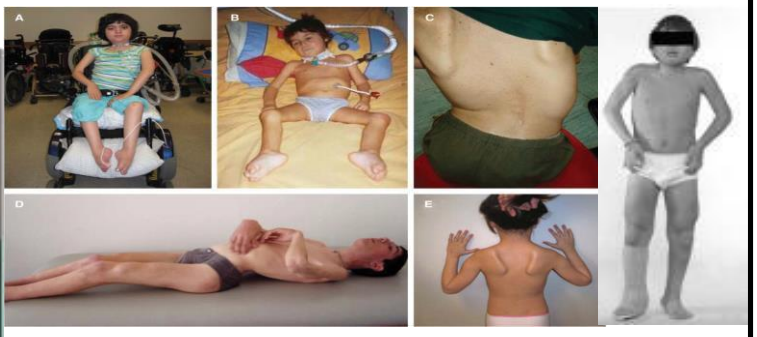
Laminopathies : genotype/phenotype



Roca et al, Int J Mol Scie, 2018

FHL1-related myopathies

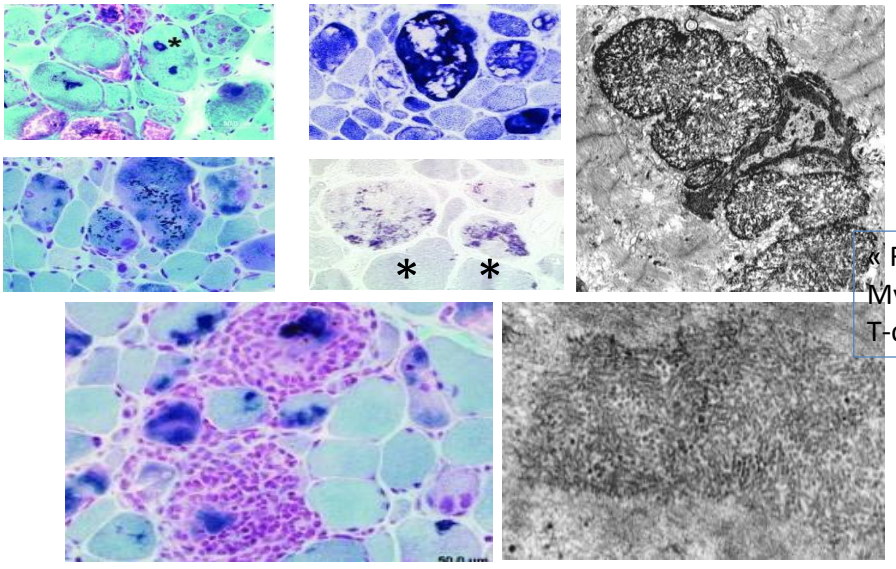




- **Scapulo-axial and peroneal associated with Muscular hypertrophy** *Windpassinger et al 2008*
- **Rigid spine syndrome** *Shalaby et al 2008*
- **Emery-Dreyfuss Muscular dystrophy** *Gueneau et al 2008*
- **Isolated cardiomyopathy** *Friedrich et al 2012*

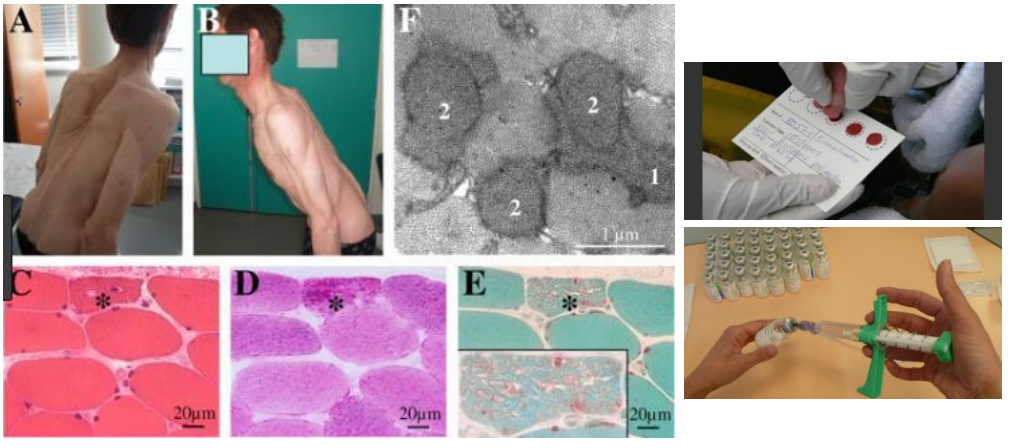
FHL1-related myopathies

Muscle biopsy



« Reducing bodies »
Myofibrillar accumulation
T-cell inflammation

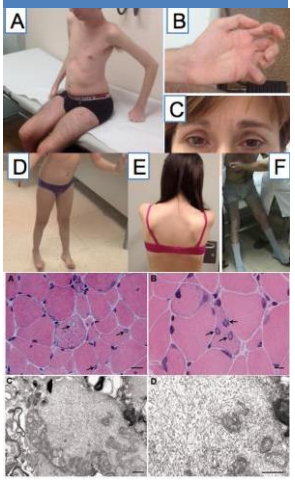
Glycogenosis : Pompe Disease



Laforêt et al, Neuromuscular Dis 2010

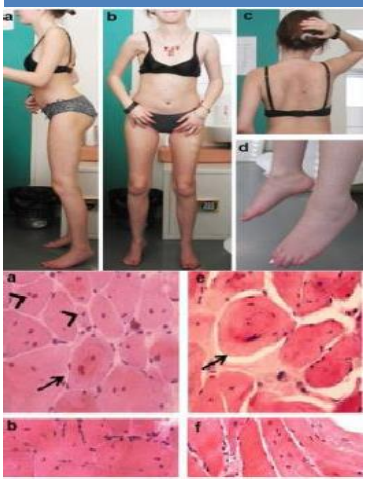
…. other genes associated with rigid spine

TPN03



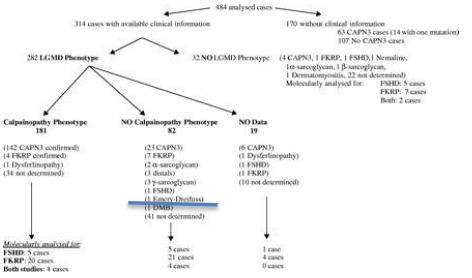
Mélia et al, Brain 2013

TTN, AR



Chauveau et al, Hum Mol Gen 2014

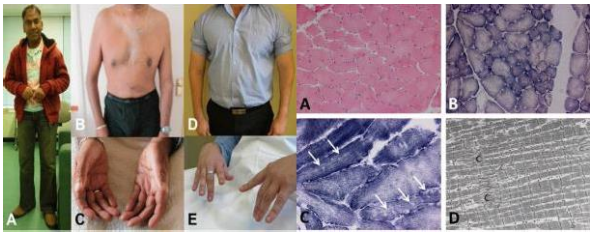
CAPN3, AR



Saenz et al, Brain2005

…. other genes associated with rigid spine

MYH7



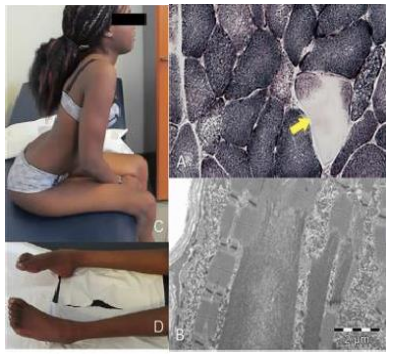
Cullup et al, Neuromusuclar disorder, 2012

Neuromuscul Disord. 2016 Oct;26(10):681-687. doi: 10.1016/j.nmd.2016.07.005. Epub 2016 Jul 25.

A novel neuromuscular form of glycogen storage disease type IV with arthrogryposis, spinal stiffness and rare polyglucosan bodies in muscle.

Malfatti E[1], Barnerias C[2], Hedberg-Oldfors C[3], Gitiaux C[4], Benezit A[2], Oldfors A[3], Carlier RY[5], Quijano-Roy S[6], Romero NB[7]

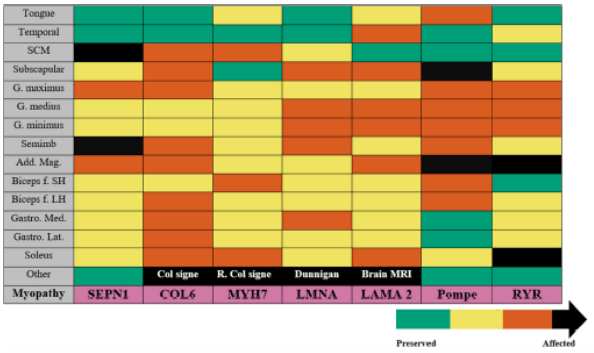
BAG3



Noury et al, Muscle and Nerve, 2017

Muscle MRI in diagnosis of rigid spine associated myopathies

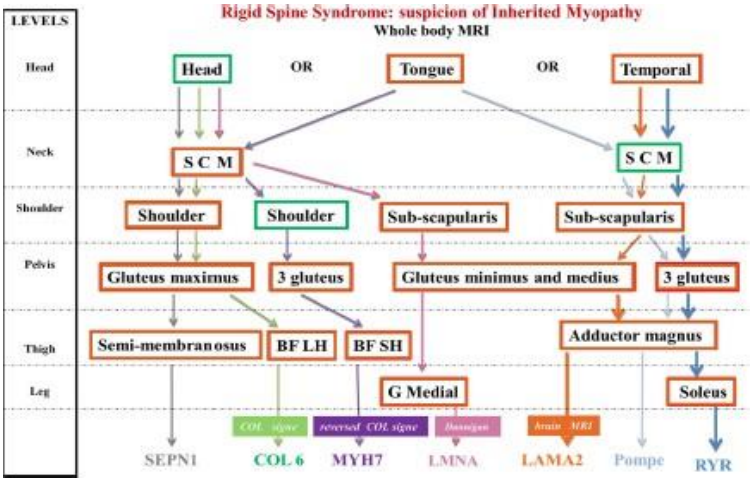
76 patients with genetically confirmed inherited myopathy were included.
They were affected by Pompe disease or harbored mutations in RYR1, collagen VI, *LMNA*, *SEPN1*, *LAMA2* and *MYH7* genes.



Novel decision algorithm based on muscle fat replacement graded on mWB-MRI : 94.3% accuracy

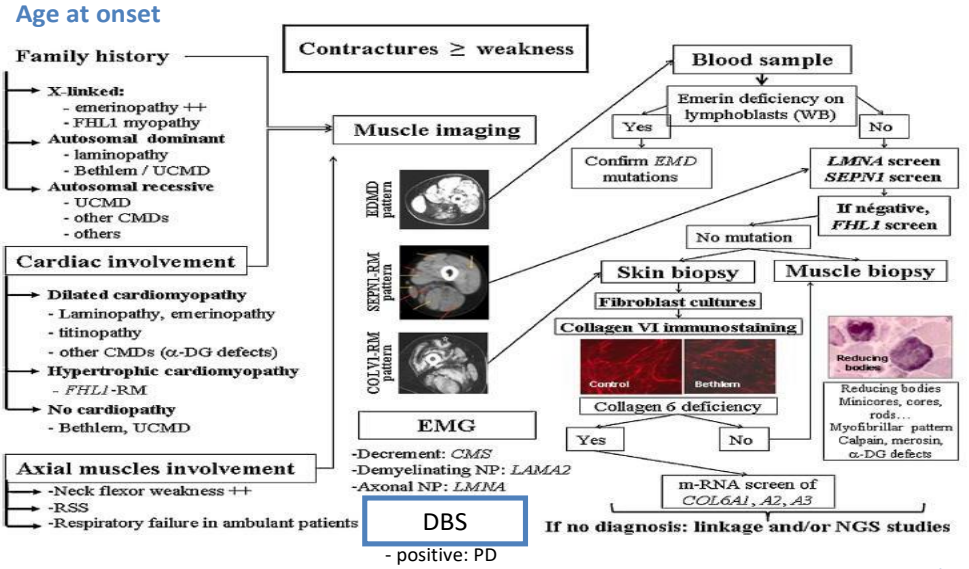
Tordjmann et al, Europ Radiol, 2018

Muscle MRI in diagnosis of rigid spine associated myopathies



Tordjmann et al, Europ Radiol, 2018

Diagnostic work-flow



B. Eymard et al., Revue Neurologique 169 (2013), 546-563

Tusen takk