



2ND SUMMIT  
**RARE**  
**DISEASES**  
C O P A C

**PEREGRINAJE  
DIAGNOSTICO DE LA  
ENFERMEDAD DE  
POMPE**

sanofi



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**RARE**  
**DISEASES**  
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*Conferencista:*

**Marcelo Rugiero**

- Jefe, Servicio de Neurología HIBA
- Sección de Enfermedades Neuromusculares
- Co- Autor de las guías de manejo y tratamiento de la enfermedad de Pompe en Argentina.

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## Declaración de Conflicto de Intereses:

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## 4 tipos de enfermedades musculares...

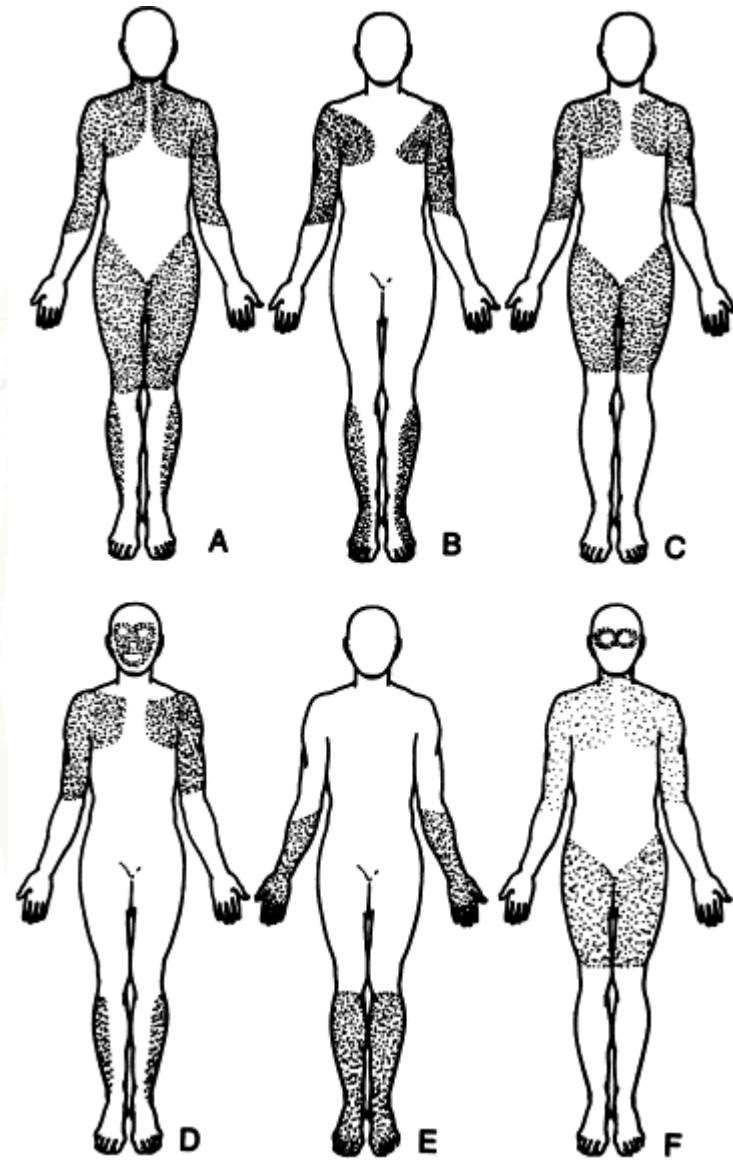
- Incurables e intratables con **manejo multidisciplinario**:  
distrofias musculares, miopatías congénitas, distrofia miotónica, algunas miopatías metabólicas
- Incurables con **tratamiento sintomático específico**: parálisis periódicas, miotonias no distroficas
- Incurables pero con **tratamiento específico de la enfermedad**: déficit de maltasa ácida (Pompe) y otras miopatías metabólicas
- Incurables pero que **responden potencialmente al tratamiento inmunosupresor**:  
miopatías inflamatorias

Hilton-Jones, Miositis-like síndrome, Curr Op Reum, 2014

## 4 tipos de enfermedades musculares...

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- Incurables pero con **tratamiento específico de la enfermedad**: déficit de maltasa ácida (Pompe) y otras miopatías metabólicas, **Distrofias Musculares, Fabry, FAP,AME**
- Incurables pero que **responden potencialmente al tratamiento inmunosupresor**:  
miopatías inflamatorias, **MG, LEMS, GBS, CIDP, NMM**

Hilton-Jones, Miositis-like síndrome, Curr Op Reum, 2014

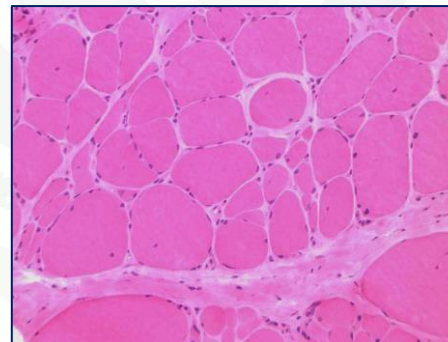
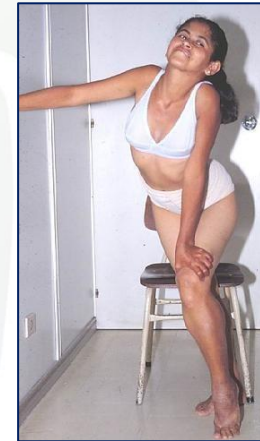


Distribution of predominant muscle weakness in different types of dystrophy: (A) Duchenne-type and Becker-type; (B) Emery–Dreifuss; (C) limb girdle; (D) facioscapulohumeral; (E) distal; (F) oculopharyngeal. (Reproduced by kind permission: Br Med J 1998;317:991-995)

## Distrofias musculares de cinturas

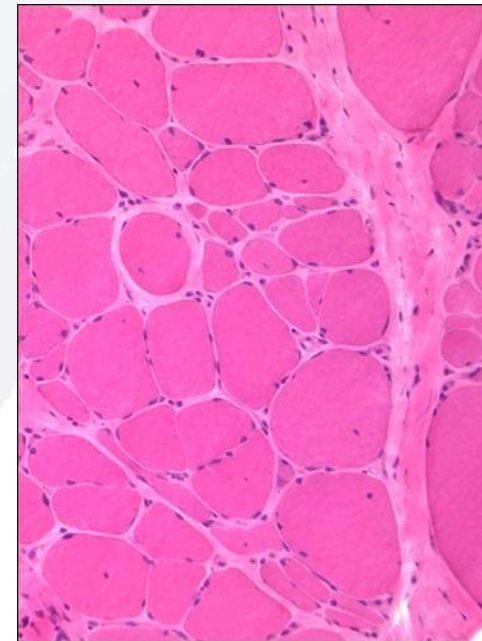
(Walton, 1950)

- Miopatías progresivas
- debilidad muscular cinturas escapular y pélvica
- Herencia autosómica
- Biopsia muscular con necrosis, regeneración y fibrosis
- Aumento variable de CPK

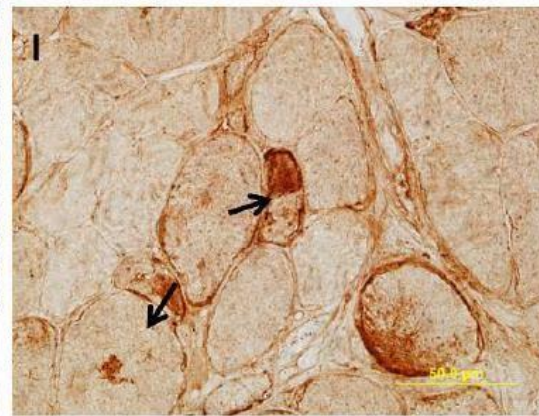
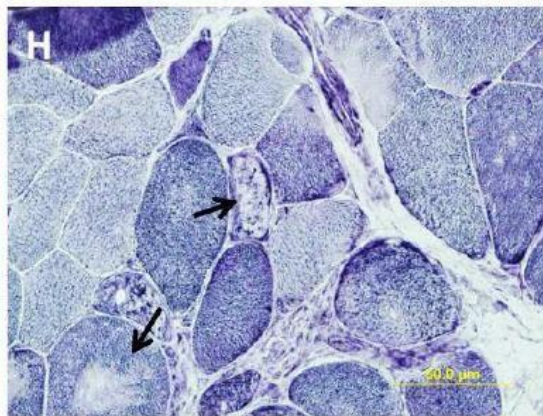
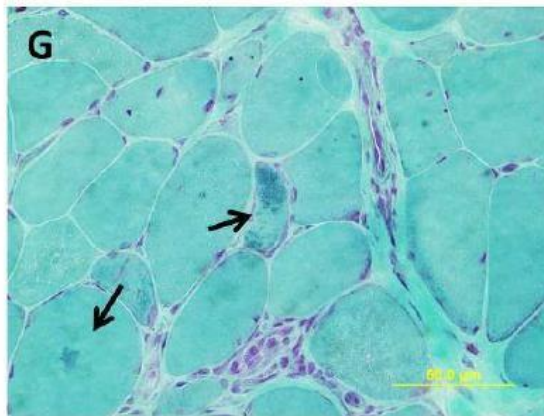
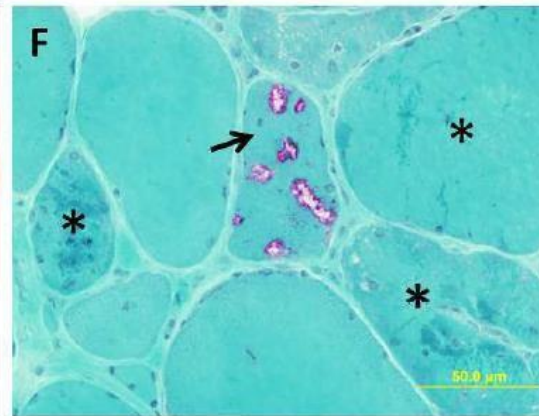
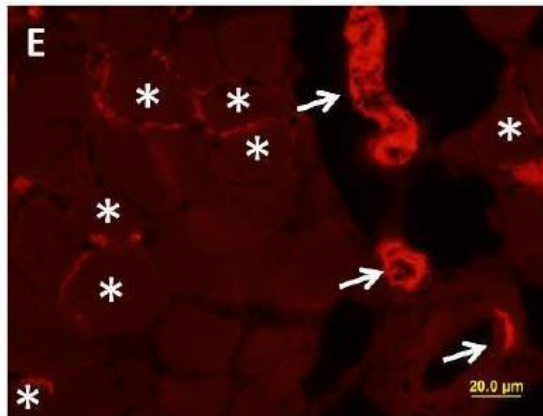
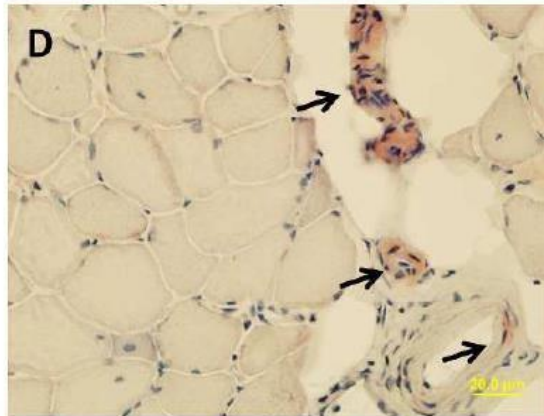
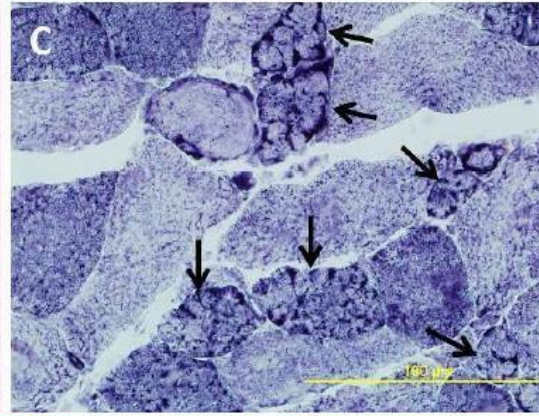
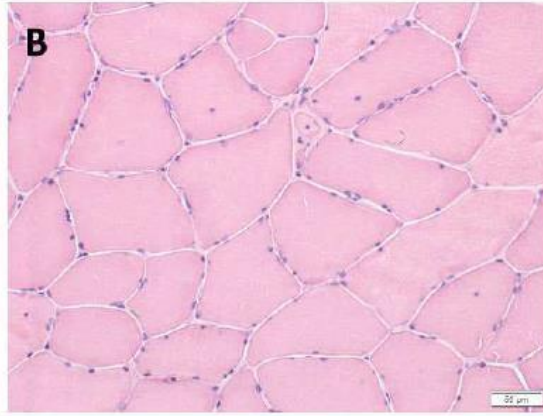
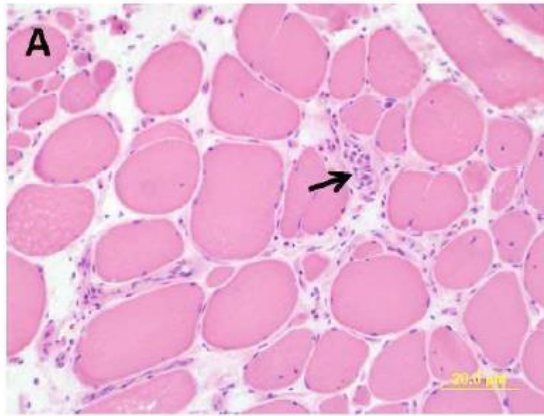


## LGMD: definición

- Grupo **heterogéneo** de enfermedades musculares **genéticamente** determinadas, que dan lugar a debilidad muscular predominante en **cintura escapular y pelviana**. Cursan con **elevación de la CK** sérica, y un **patrón distrófico** en la biopsia muscular





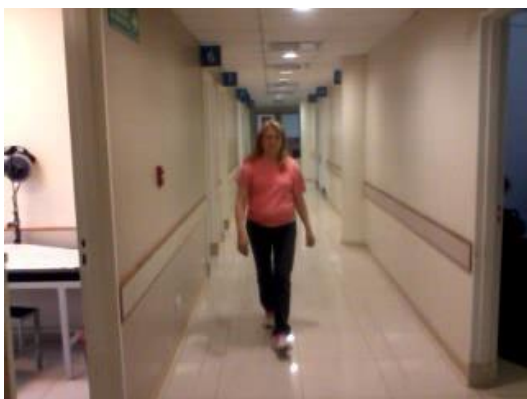


pero en la practica...

- algunas formas causan debilidad de predominio ***distal***.
- los niveles de ***CK*** sérica pueden ser ***normales***.
- en muchos casos ***no*** existe un ***patrón distrófico***.
- se ***confunden*** con ***miopatías inflamatorias***
- son enfermedades ***raras*** pero como grupo son las cuartas mas frecuentes con una prevalencia de 1.63/100.00

y además...

- su clasificación es engorrosa
- 34(o mas) LGMD recesivas y dominantes
- calpaina3 y desmina existen en forma AR y AD
- distintas fisiopatologías: superposición
- quedan fuera de las clasificación: DMD, BMD, ED, DOF, DM, FSH
- miofibrilares y distales?



Lipomatosis + miopatia mitocondrial



Miastenia gravis anti-MuSK



Enfermedad de Pompe



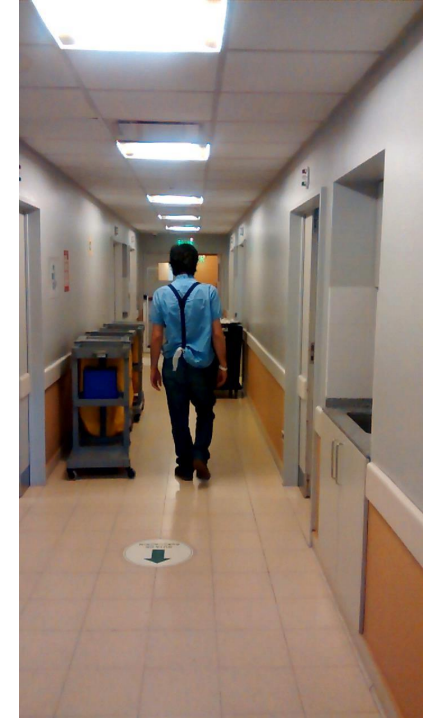
FSH



Miositis por Cuerpos de Inclusion

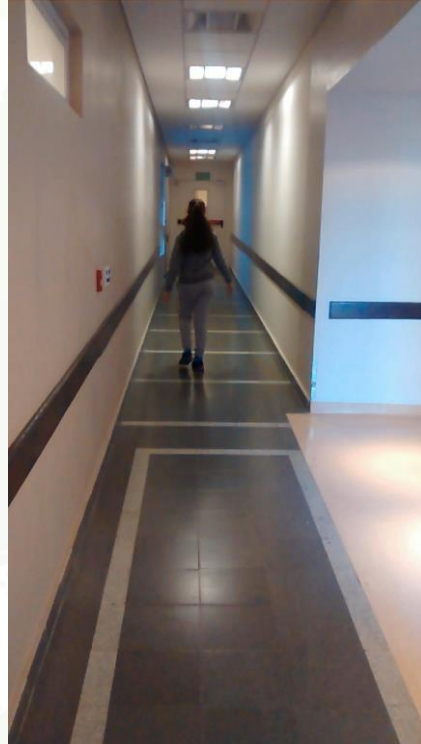


Miopatia Miofibrilar





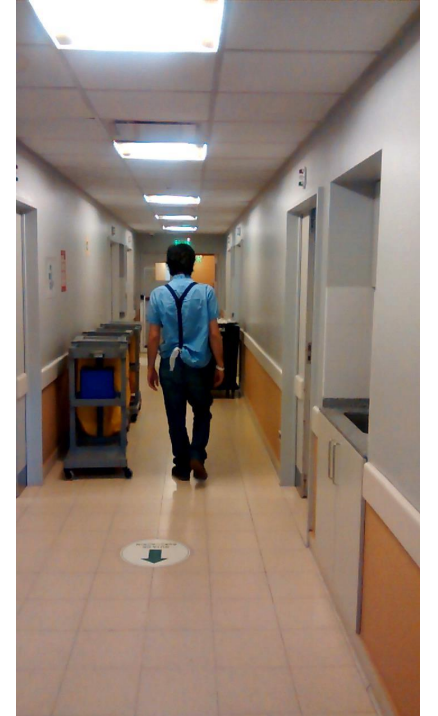
ELA



DM  
refractaria

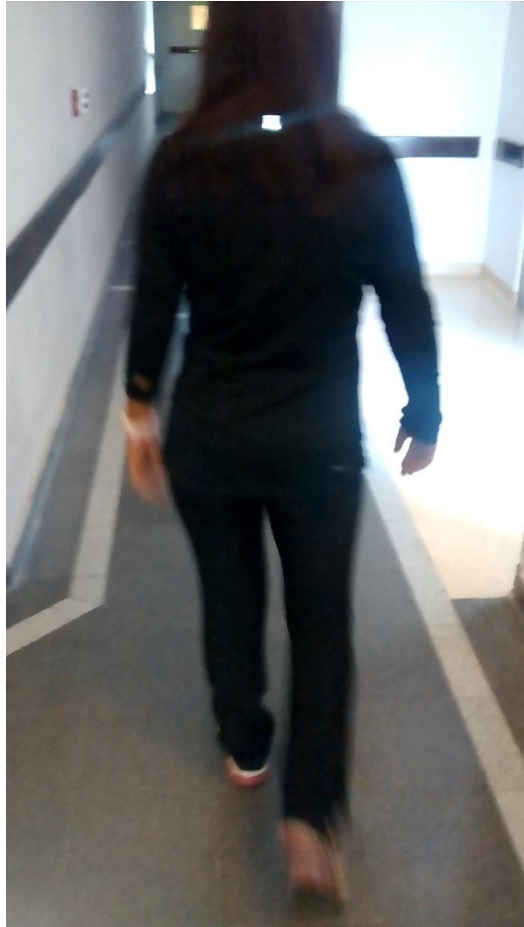


GBS



POMPE

# CIDP



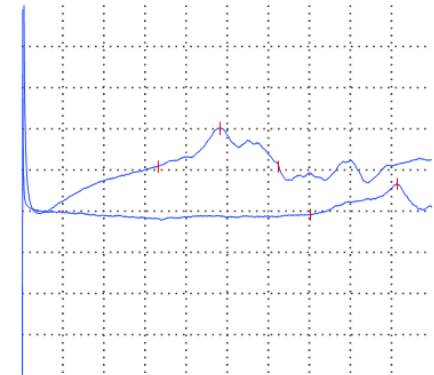
## Motor Nerve Conduction Studies

Izquierda Peroneus Motor			
	Lat	Amp	CV
	ms	mV	m/s
Ankle - EDB	16.6	0.47	
Bl. knee-Ankle	35.1	0.38	21.1

Izquierda Peroneus

Ankle-EDB  
0.5mV/D 5ms/D

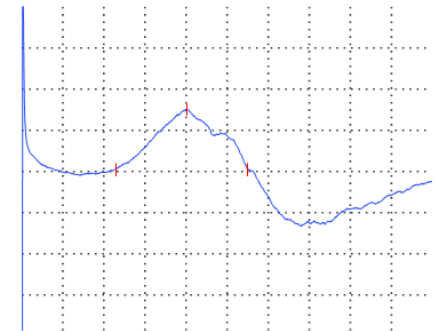
Bl. knee-EDB  
0.5mV/D 5ms/D



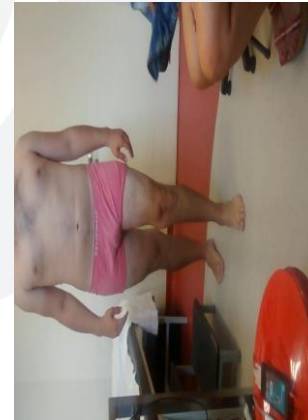
Derecha Peroneus Motor			
	Lat	Amp	CV
	ms	mV	m/s
Ankle - EDB	11.5	0.73	

Derecha Peroneus

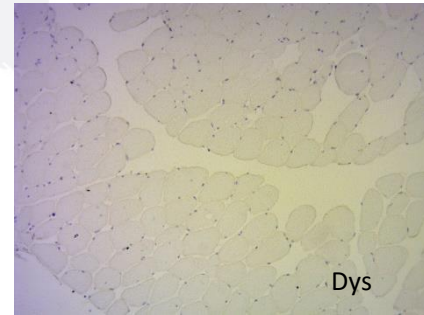
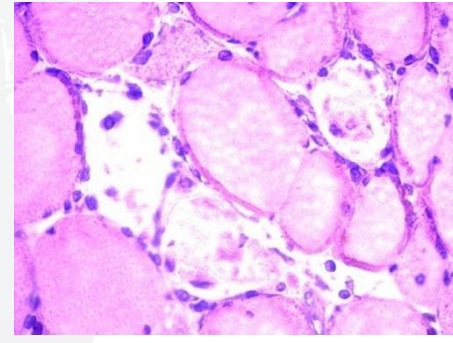
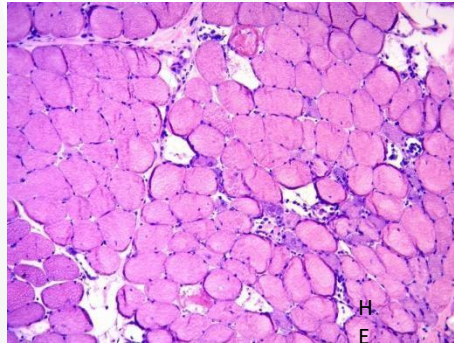
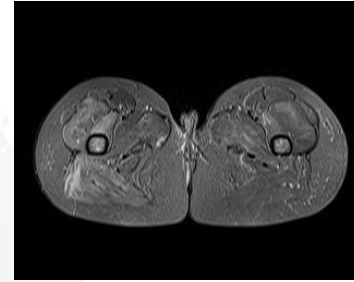
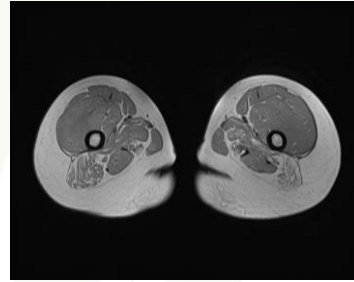
Ankle-EDB  
0.5mV/D 5ms/D



# Nuevos patrones: Miopatías Distales







# Miopatías en el anciano



FSH



FSH



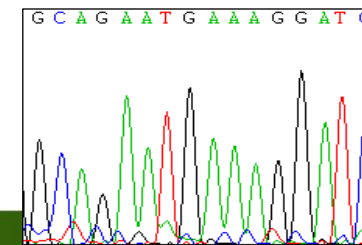
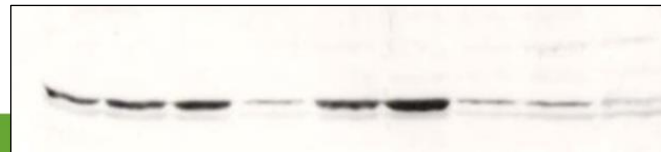
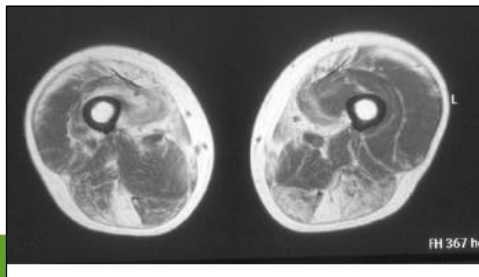
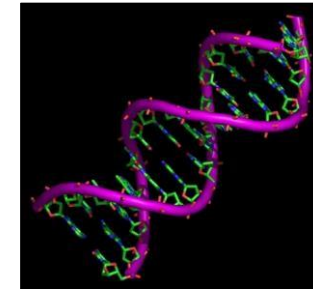
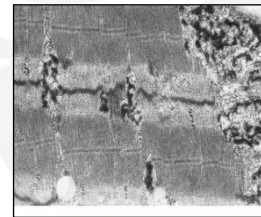
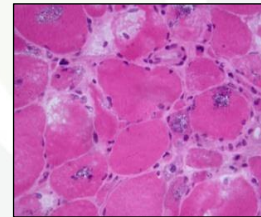
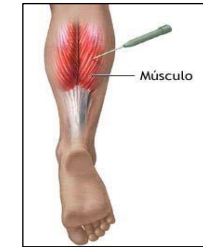
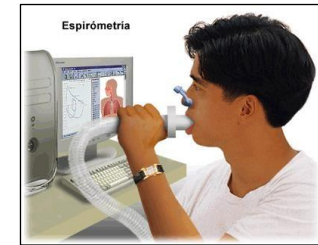
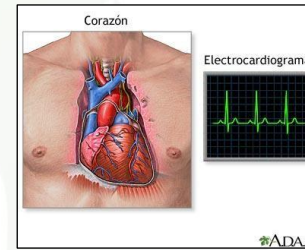
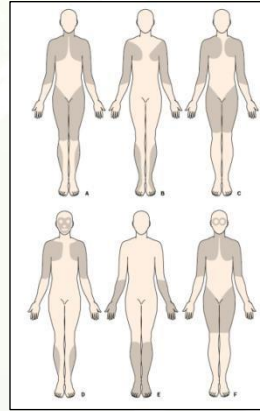
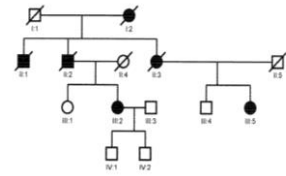
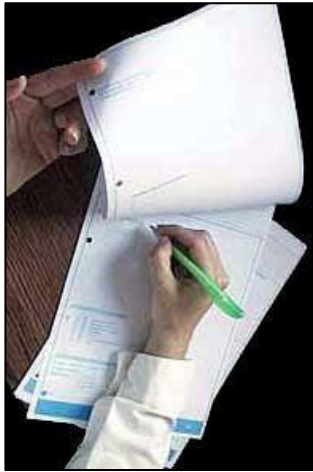
IBM

## Diagnostico de enfermedades neuromusculares en la era moderna

- **Semiologia: Reconocimiento del fenotipo clinico**
- Laboratorio/Metodo de screening: ↑ CPK
- Uso de electrodiagnostico: raramente
- Ocasionalmente: Biopsia muscular
- **Estudios geneticos moleculares**



# Herramientas Diagnosticas



# The Role of Muscle Imaging in the Diagnosis and Assessment of Children with Genetic Muscle Disease

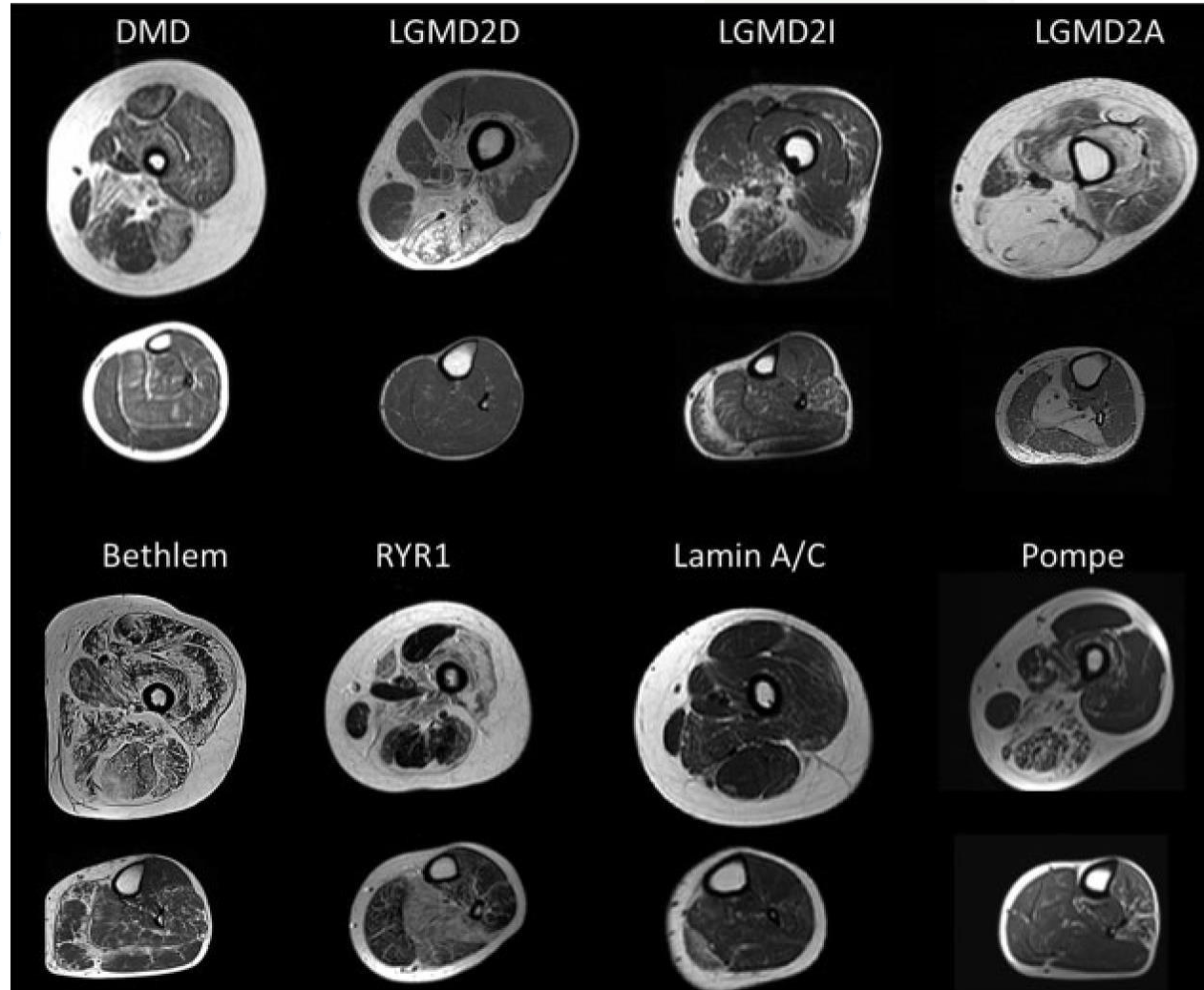
Jodi Warman Chardon<sup>1,2,3</sup> Volker Straub<sup>3</sup>

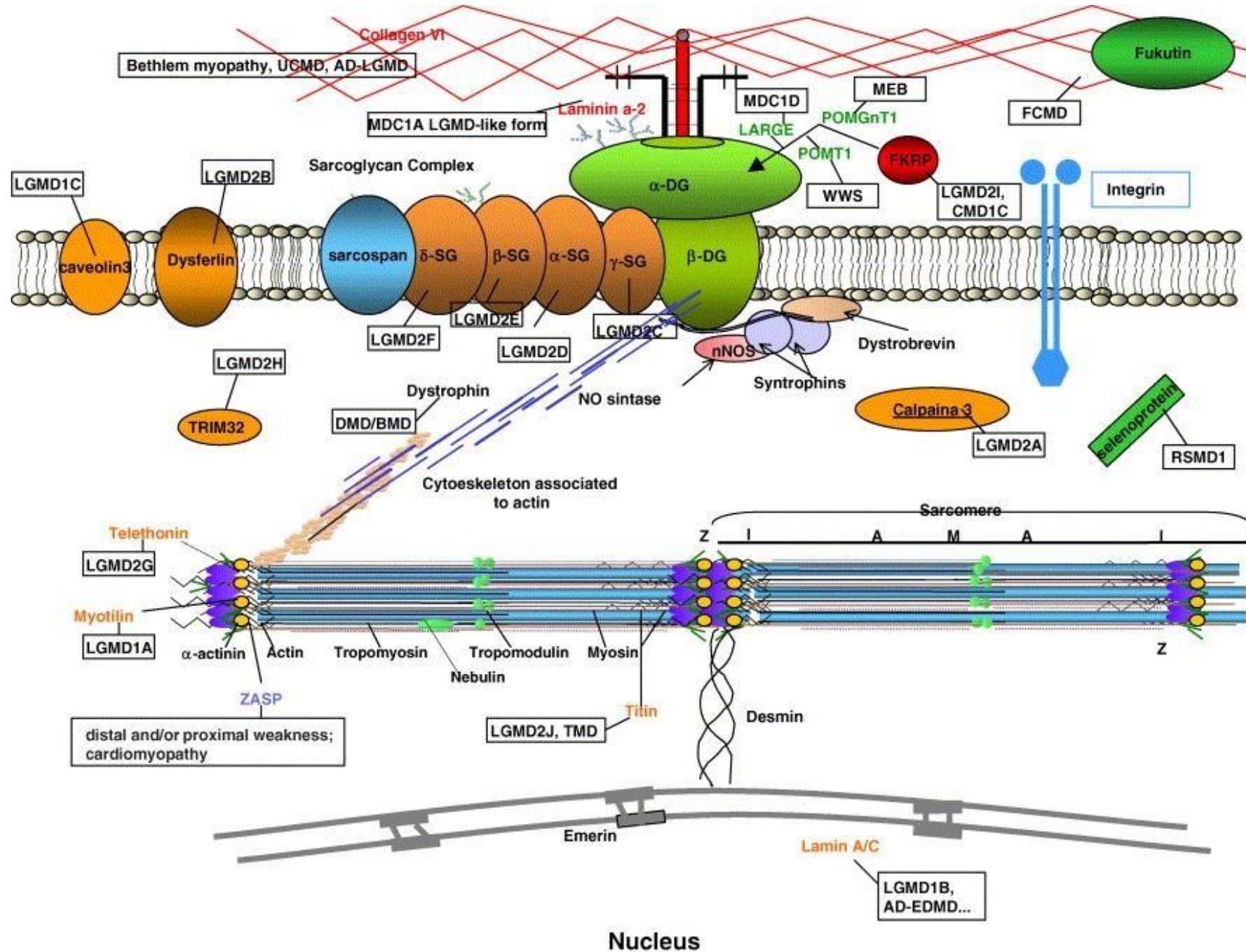
<sup>1</sup>Department of Genetics, Children's Hospital of Eastern Ontario/Research Institute, Ottawa, Ontario, Canada

<sup>2</sup>Division of Neurology, The Ottawa Hospital/Research Institute, Ottawa, Canada

<sup>3</sup>The John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom

Neuropediatrics





## CLINICAL PHENOTYPE

Severe early onset dystrophy  
DMD-like



**$\alpha$ -sarcoglycan**  
376ins8bp  
699del4bp



**dystrophin**  
del ex12-44

BMD-like



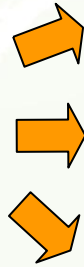
**dystrophin**  
del ex48-49



**FKRP**  
C826A

# CLINICAL PHENOTYPE IN $\alpha$ -SARCOGLYCANOPATHIES

LGMD2D ( $\alpha$ -SG)



DMD-like (23%) rapid course; missense mutations; absent protein

LGMD (59%) variable course; missense mutations; reduced protein

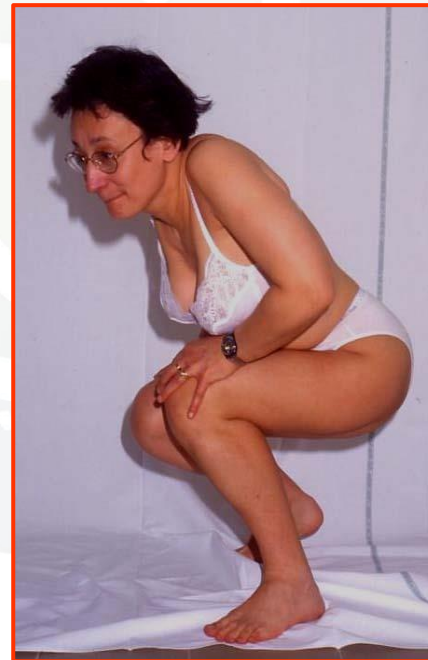
High CK (18%) missense mutations; reduced protein



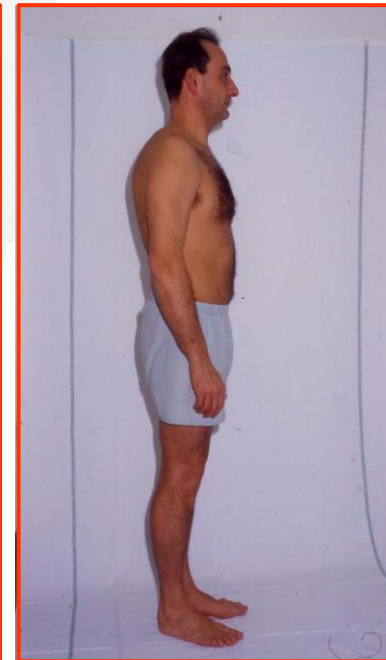
DMD-like



LGMD

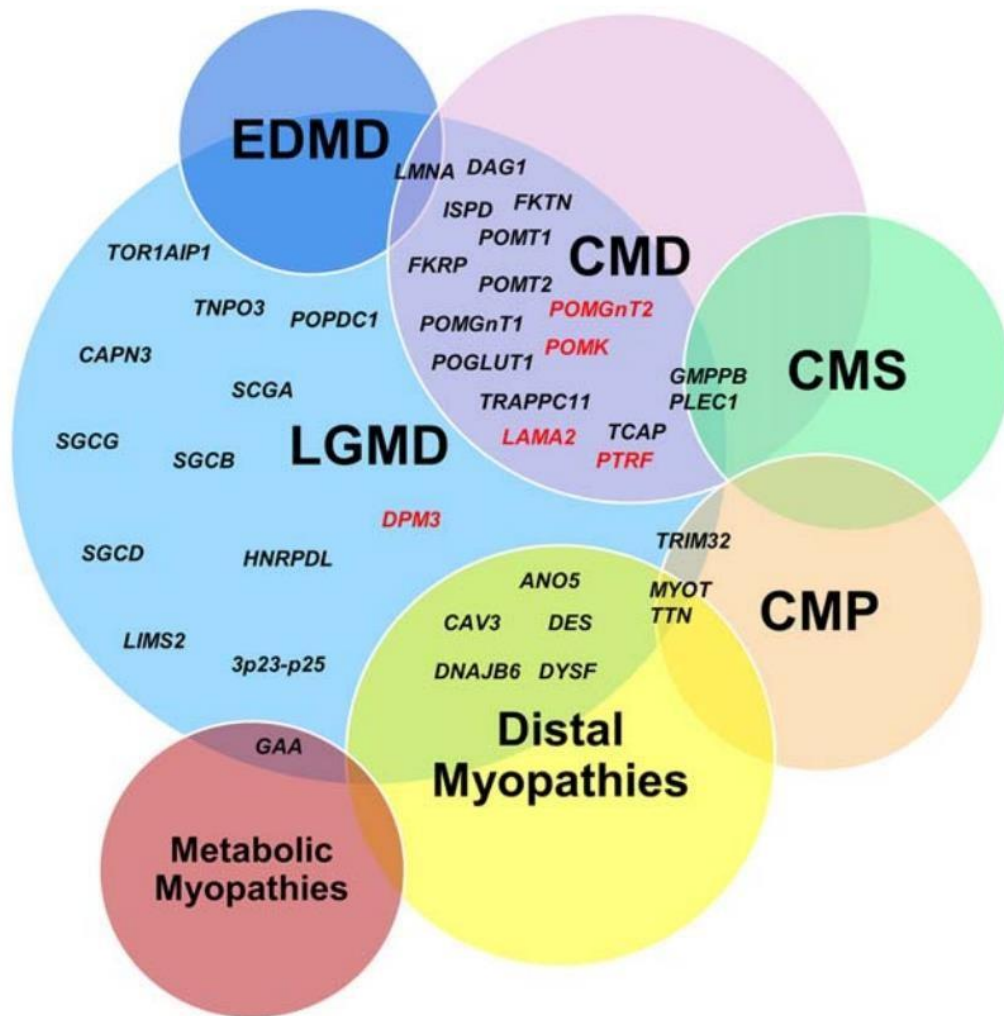


LGMD



High CK





**FIGURE 2.** Overlapping phenotypes between LGMD-causing genes and genes responsible for congenital muscular dystrophies (CMD), congenital myopathies (CMP), congenital myasthenic syndromes (CMS), distal myopathies, Emery–Dreifuss muscular dystrophies (EDMD), and metabolic myopathies. Red highlights CMD-causing genes that were also reported with the LGMD phenotype, but have not yet been classified as LGMD.

INVITED REVIEW

## UNTANGLING THE COMPLEXITY OF LIMB-GIRDLE MUSCULAR DYSTROPHIES

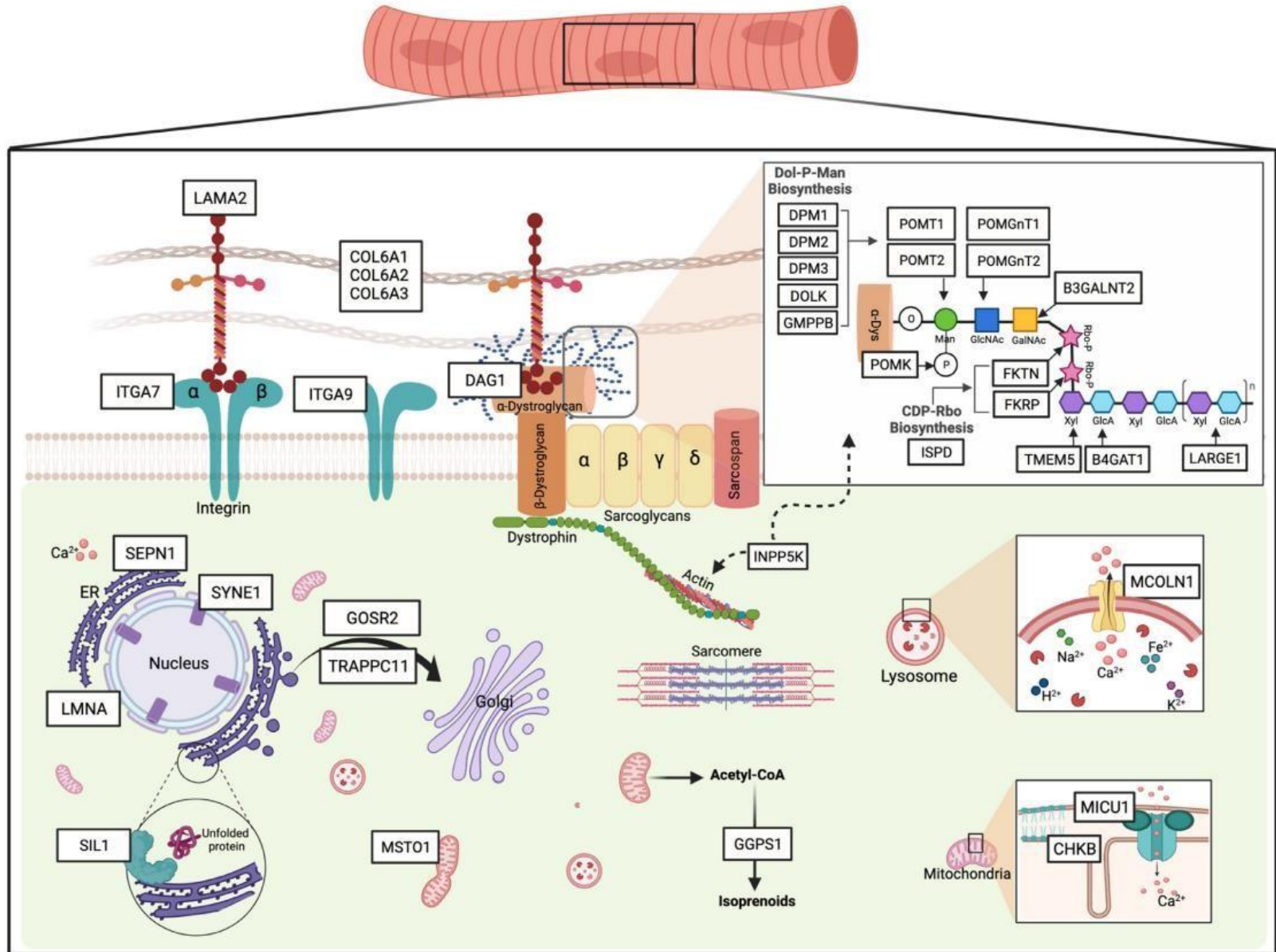
TEERIN LIEWLUCK, MD , and MARGHERITA MILONE, MD, PhD 

Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota, 55905, USA

Accepted 16 January 2018

# Distrofias Musculares Congénitas

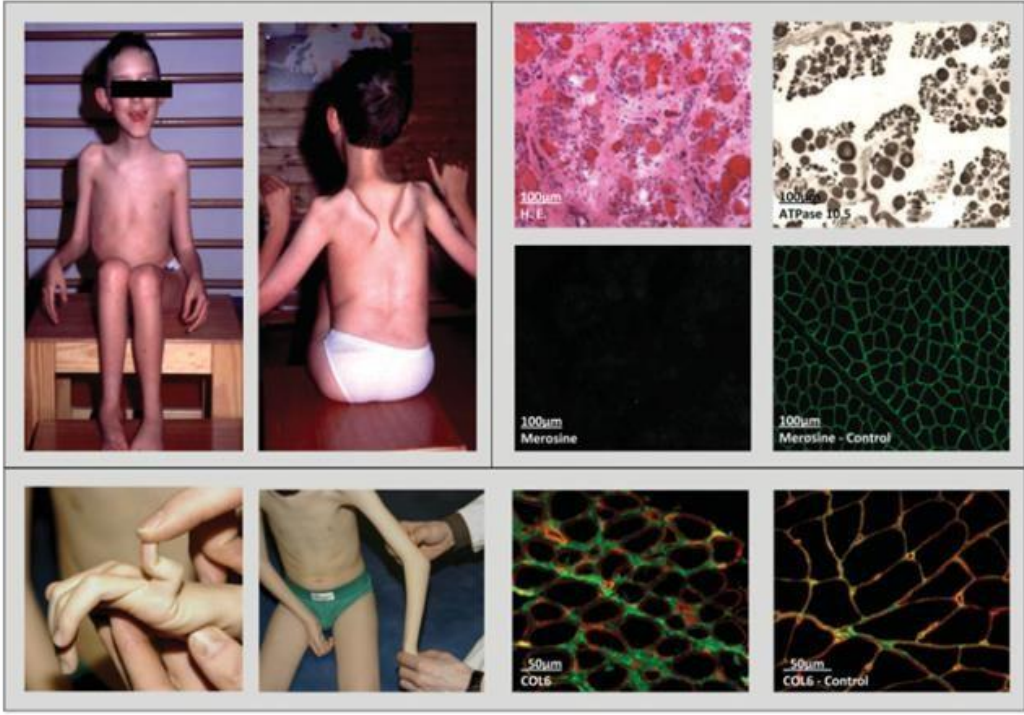
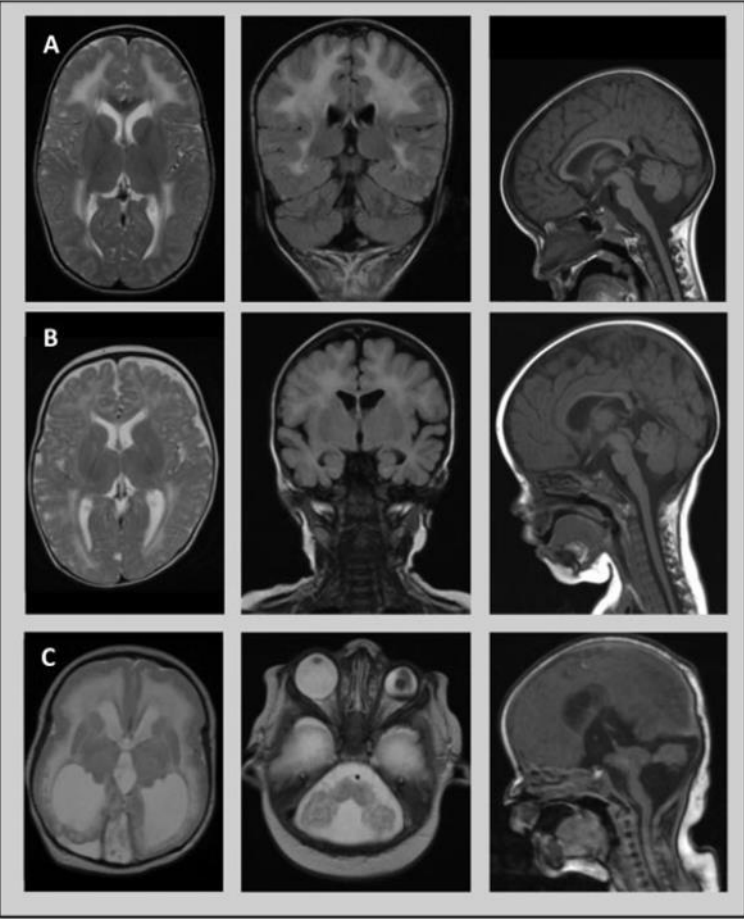
- Grupo de enfermedades hereditarias que provocan debilidad muscular que ocurren durante el desarrollo, con retraso de la adquisición motora y hallazgos patológicos distróficos.
- 0.6-0.9/100.000, mayoría autosómica recesiva
- 35 genes asociados a DMC
- Amplio espectro fenotípico
- Compromiso cardíaco/respiratorio, SNC, estructuras oculares
- COL6-RD (12–19%), distroglicanopatías (DGP; 12–25%), laminin-alpha 2 related dystrophies (LAMA2-RD; 10–37%), y selenoprotein N related myopathy (SEPN1-RM; 11.65%), Fukuyama CMD (FCMD) es la más frecuente en Japón
- CMD mimics: RYR1 y ACTA 1, glucogenopatías, mitocondriopatías



# Distrofias Musculares Congénitas

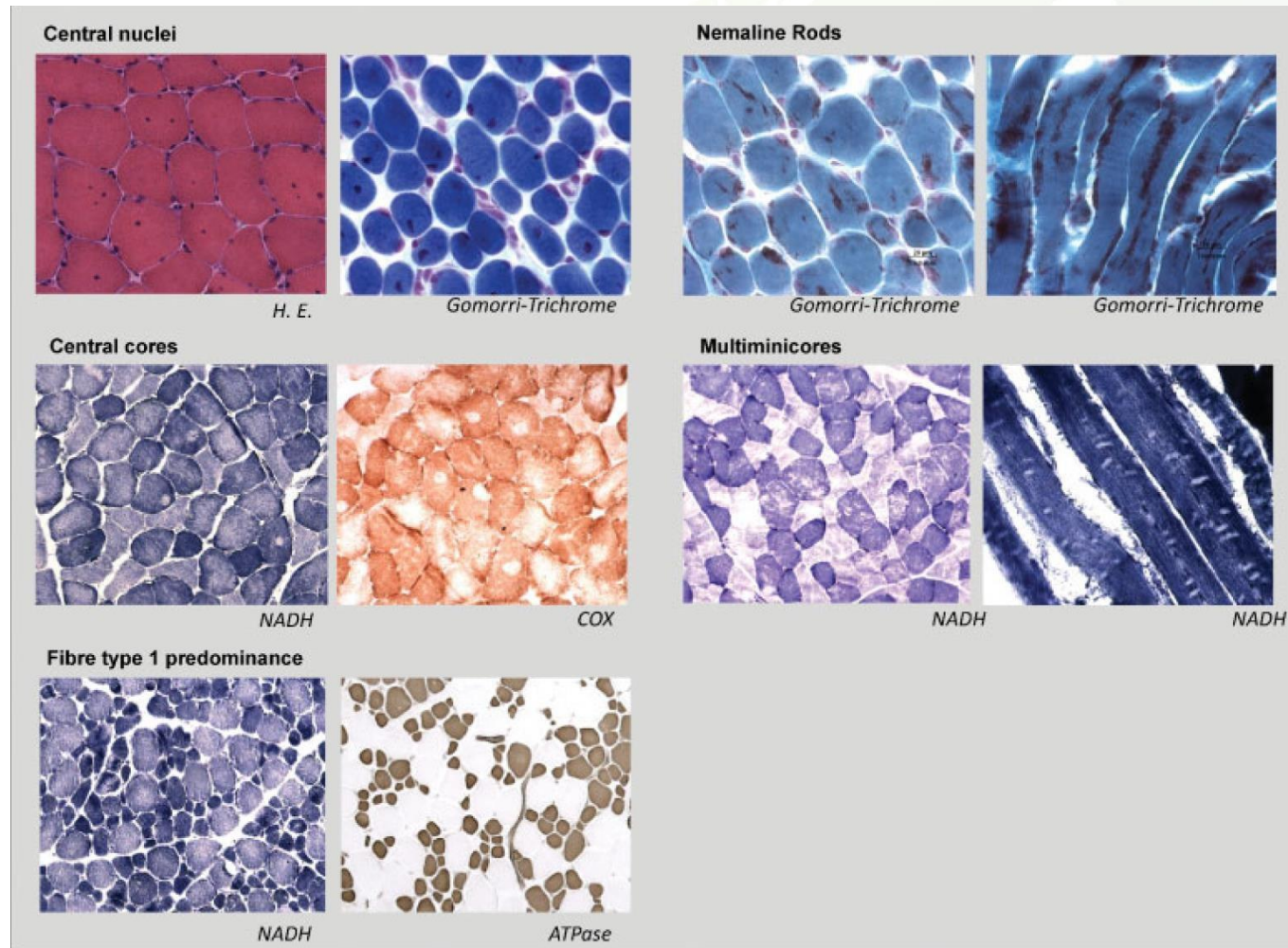
**Table 1** Overview of the

Phenotype	Gene	Inh		
<b>Collagen VI and integrin related</b>				
Ullrich CMD Intermediate phenotypes Bethlem myopathy	COL 6A1 COL 6A2 COL 6A3	AD, AR		
Integrin $\alpha 7$ deficiency	ITGA7	AR		
<b>Laminin <math>\alpha 2</math> related dystrophy</b>				
Merosin-deficient CMD	LAMA2	AR		
<b>LMNA-related dystrophy</b>				
LMNA-CMD "Dropped-head syndrome"	LMNA	AD		
<b>SELENON-related myopathy</b>				
Rigid spine syndrome Multiminicore myopathy	SELENON1 (SEPN1)	AR		
<b><math>\alpha</math>-Dystroglycan-related dystro</b>				
Walker-Warburg syndrome	POMT1	AR		
	POMT2			
	POMGn1			
	LARGE		22q12	Acetylglucosaminyltransferase-like-protein
	FKTN	9q31	Fukutin	
	FKRP	19q13	Fukutin-related protein	
	ISPD	7p21	Isoprenoid synthase domain containing protein	
	B4GAT1	11q13	Beta-1,3-acetylgalactosaminyl-transferase 2 1	AR



**Fig. 2** LAMA2- and COL6-related congenital muscular dystrophy (CMD). *Above left*: photographs of an 8-year-old boy with LAMA2-related CMD with severe scoliosis, contractures of knees and elbows, and facial involvement. *Above right*: Histological findings in a 6-month-old girl with LAMA2-related CMD, showing dystrophic changes in hematoxylin and eosin staining, mild fiber type 1 predominance in ATPase staining, and negative result in immunohistochemical staining of laminin 211 (merosin). *Below left*: photographs of a boy with Ullrich CMD with identified mutation in COL6 showing proximal hyperlaxity of distal joints and proximal contractures. *Below right*: costaining for collagen (Coll) IV (red) and Coll VI (green) shows mislocalization of Coll VI.

# Miopatías Congénitas



- Rods(Miopatía Nemalínica)
- Nucleos Centrales(M. Centronuclear)
- Cores (Core-minicore)

**Table 1.** Dominantly (LGMD1) and recessively inherited (LGMD2) types of LGMDs with the corresponding affected gene and protein

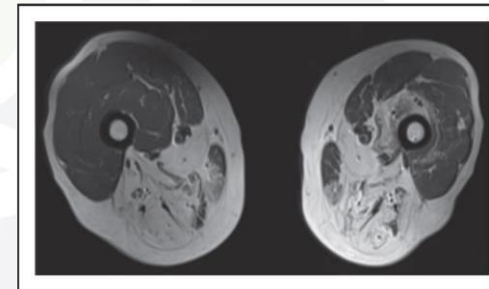
Disorder	Gene	Protein
LGMD1A	MYOT	Myotilin
LGMD1B	LMNA	Lamin A/C
LGMD1C	CAV3	Caveolin 3
LGMD1D	DNAJB6	Hsp40
LGMD1E	DES	Desmin
LGMD1F	TNPO3	Transportin 3
LGMD1G	HNRPDL	Heterogeneous nuclear ribonucleoprotein D-like protein
LGMD1H	3p23-p25	?
LGMD1I	CAPN3	Calpain 3
LGMD2A	CAPN3	Calpain 3
LGMD2B	DYSF	Dysferlin
LGMD2C	SGCG	$\gamma$ -Sarcoglycan
LGMD2D	SGCA	$\alpha$ -Sarcoglycan
LGMD2E	SGCB	$\beta$ -Sarcoglycan
LGMD2F	SGCD	$\delta$ -Sarcoglycan
LGMD2G	TCAP	Telethonin
LGMD2H	TRIM32	Tripartite motif containing 32
LGMD2I	FKRP	Fukutin-related protein
LGMD2J	TTN	Titin
LGMD2K	POMT1	Protein-O-mannosyl transferase 1
LGMD2L	ANO5	Anoctamin 5
LGMD2M	FKTN	Fukutin
LGMD2N	POMT2	Protein-O-mannosyl transferase 2
LGMD2O	POMGNT1	Prot. O-linked mannose $\beta$ -1,2-N-acetylglucosaminyl trans.
LGMD2P	DAG1	Dystroglycan
LGMD2Q	PLEC1	Plectin
LGMD2R	DES	Desmin
LGMD2S	TRAPPC11	Transport protein particle complex 11
LGMD2T	GMPPB	GDP-mannose pyrophosphorylase B
LGMD2U	ISPD	Isoprenoid synthase domain containing
LGMD2V	GAA	$\alpha$ -1,4-glucosidase
LGMD2W	LIMS2	Lim and senescent cell antigen-like domains 2
LGMD2X	BVES	Blood vessel endothelial substance

LGMDs, limb girdle muscular dystrophies.

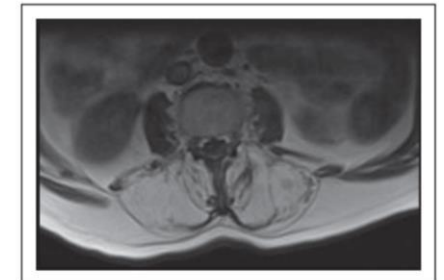
**Table 2.** The different types of LGMDs associated particular symptoms and signs

Symptom/sign	LGMDs affected
Myoglobinuria	LGMD2 C-E, I, L
Cardiomyopathy	LGMD1 A, B, D, E LGMD2 B, C, (D), F, G, I, M, N, R, T, U,
Heart arrhythmias	LGMD1B, LGMD2R
Asymmetric muscle involvement	LGMD2 A, L LGMD1A, I
Prominent distal muscle involvement	LGMD1 A-G, I LGMD2 A, B, G, J, L,
Rippling muscle	LGMD1C

LGMDs, limb girdle muscular dystrophies.



LGMD2A



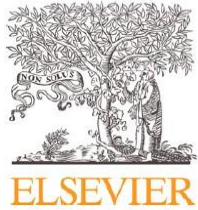
LGMD1A



Limb girdle muscular dystrophies: classification, clinical spectrum and emerging therapies

John Vissing

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Neuromuscular Disorders 000 (2018) 1–9



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Workshop report

229th ENMC international workshop:  
Limb girdle muscular dystrophies –  
Nomenclature and reformed classification  
Naarden, the Netherlands, 17–19 March 2017

Volker Straub<sup>a,\*</sup>, Alexander Murphy<sup>a</sup>, Bjarne Udd<sup>b,c,d</sup>, on behalf of the LGMD workshop study group

<sup>a</sup>*The John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Central Parkway, Newcastle upon Tyne, United Kingdom*

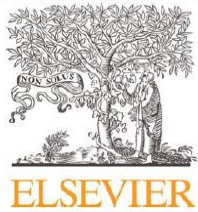
<sup>b</sup>*Department of Neurology, Neuromuscular Research Center, Tampere University and University Hospital, Neurology, Tampere, Finland*

<sup>c</sup>*The Department of Medical Genetics, Folkhälsan Institute of Genetics, University of Helsinki, Helsinki, Finland*

<sup>d</sup>*Department of Neurology, Vaasa Central Hospital, Vaasa, Finland*

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*“Limb girdle muscular dystrophy is a genetically inherited condition that primarily affects skeletal muscle leading to progressive, predominantly proximal muscle weakness at presentation caused by a loss of muscle fibres. To be considered a form of limb girdle muscular dystrophy the condition must be described in at least two unrelated families with affected individuals achieving independent walking, must have an elevated serum creatine kinase activity, must demonstrate degenerative changes on muscle imaging over the course of the disease, and have dystrophic changes on muscle histology, ultimately leading to end-stage pathology for the most affected muscles.”*

Volker St

<sup>a</sup>The John Walto

<sup>b</sup>Dep

<sup>c</sup>The Department of Medical Genetics, Folkhälsan Institute of Genetics, University of Helsinki, Helsinki, Finland

<sup>d</sup>Department of Neurology, Vaasa Central Hospital, Vaasa, Finland

Received 25 March 2018

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) workshop study

itals NHS Foundation Trust,

Tampere, Finland



Comparison of the previous LGMD nomenclature to the proposed classification system after the definition has been applied to the current list of LGMD. Conditions which are no longer considered LGMDs are highlighted in grey with a reason for their exclusion given.

Old name	Gene	Proposed new nomenclature	Reason for exclusion
LGMD 1A	<i>Myot</i>	Myofibrillar myopathy	Distal weakness
LGMD 1B	<i>LMNA</i>	Emery–Dreifuss muscular dystrophy (EDMD)	High risk of cardiac arrhythmias; EDMD phenotype
LGMD 1C	<i>CAV3</i>	Rippling muscle disease	Main clinical features rippling muscle disease and myalgia
LGMD 1D	<i>DNAJB6</i>	LGMD D1 DNAJB6-related	
LGMD 1E	<i>DES</i>	Myofibrillar myopathy	Primarily false linkage; distal weakness and cardiomyopathy
LGMD 1F	<i>TNP03</i>	LGMD D2 TNP03-related	
LGMD 1G	<i>HNRNPDL</i>	LGMD D3 HNRNPDL-related	
LGMD 1H	?	Not confirmed	False linkage
LGMD 1I	<i>CAPN</i>	LGMD D4 calpain3-related	

LGMD 2A	<i>CAPN</i>	LGMD R1 calpain3-related	
LGMD 2B	<i>DYSF</i>	LGMD R2 dysferlin-related	
LGMD 2C	<i>SGCG</i>	LGMD R5 $\gamma$ -sarcoglycan-related <sup>a</sup>	
LGMD 2D	<i>SGCA</i>	LGMD R3 $\alpha$ -sarcoglycan-related	
LGMD 2E	<i>SGCB</i>	LGMD R4 $\beta$ -sarcoglycan-related	
LGMD 2F	<i>SGCD</i>	LGMD R6 $\delta$ -sarcoglycan-related	
LGMD 2G	<i>TCAP</i>	LGMD R7 telethonin-related	
LGMD 2H	<i>TRIM32</i>	LGMD R8 TRIM 32-related	
LGMD 2I	<i>FKRP</i>	LGMD R9 FKRP-related	
LGMD 2J	<i>TTN</i>	LGMD R10 titin-related	
LGMD 2K	<i>POMT1</i>	LGMD R11 POMT1-related	
LGMD 2L	<i>ANO5</i>	LGMD R12 anoctamin5-related	
LGMD 2M	<i>FKN</i>	LGMD R13 Fukutin-related	
LGMD 2N	<i>POMT2</i>	LGMD R14 POMT2-related	
LGMD 2O	<i>POMGnT1</i>	LGMD R15 POMGnT1-related	
LGMD 2P	<i>DAG1</i>	LGMD R16 $\alpha$ -dystroglycan-related	
LGMD 2Q	<i>PLEC</i>	LGMD R17 plectin-related	
LGMD 2R	<i>DES</i>	myofibrillar myopathy	Distal weakness
LGMD 2S	<i>TRAPPC11</i>	LGMD R18 TRAPPC11-related	
LGMD 2T	<i>GMPPB</i>	LGMD R19 GMPPB-related	
LGMD 2U	<i>ISPD</i>	LGMD R20 ISPD-related	
LGMD 2V	<i>GAA</i>	Pompe disease	Known disease entity, histological changes
LGMD 2W	<i>PINCH2</i>	PINCH-2 related myopathy	Reported in one family
LGMD 2X	<i>BVES</i>	BVES related myopathy	Reported in one family
LGMD 2Y	<i>TOR1AIP1</i>	TOR1AIP1 related myopathy	Reported in one family
LGMD 2Z	<i>POGLUT1</i>	LGMD R21 POGLUT1-related	
Bethlem myopathy recessive	<i>COL6A1, COL6A2, COL6A3</i>	LGMD R22 collagen 6-related	
Bethlem myopathy dominant	<i>COL6A1, COL6A2, COL6A3</i>	LGMD D5 collagen 6-related	
Laminin $\alpha$ 2-related muscular dystrophy	<i>LAMA2</i>	LGMD R23 laminin $\alpha$ 2-related	
POMGNT2-related muscular dystrophy	<i>POMGNT2</i>	LGMD R24 POMGNT2-related	

<sup>a</sup> Sarcoglycan-related LGMDs rationalised based on order of gene discovery.

# Algunas claves diferenciales

Laminopatía (LGMD 1B)	<p>Debilidad cintura pelviana</p> <p>Trastornos ritmo cardíaco/miocardopatía</p> <p>Retracciones articulares</p>
Caveolinopatía (LGMD 1C)	<p>Mialgias</p> <p>Fenómeno de <i>rippling</i></p>
Calpainopatía (LGMD 2A)	<p>Afectación adductores, grupo posterior muslo y pierna</p> <p>Preservación abductores</p> <p>Escápula alata precoz</p>
Disferlinopatía (LGMD 2B)	<p>Inicio rápido</p> <p>CK exageradamente alta</p> <p>Afectación gemelos precoz, no escápula alata</p> <p>Infiltrado inflamatorio en la biopsia muscular</p>
Sarcoglicanopatías (LGMD 2C-2F)	<p>Inicio 6-8 años</p> <p>Fenotipo parecido a DMD/BMD con mayor afectación escapular</p>
Teletoninopatía (LGMD 2G)	<p>Fenotipo LGMD con afectación selectiva tibial anterior</p>
LGMD 2I (FKRM)	<p>Fenotipo DMD/BMD like</p> <p>Escápula alata. Hipertrofia gemelar, macroglosia</p> <p>Insuficiencia respiratoria precoz</p> <p>Miocardopatía dilatada</p>
LGMD 2L(ANO5)	<p>Atrofia asimétrica de cuádriceps</p> <p>CK muy alta</p>

## Calpainopatía (LGMD2A)



Tabla 1: Variantes identificadas en el paciente.

Gen y transcripción	Ubicación	Variante	Genotipo	Clasificación	Enfermedad	Herencia
<i>CAPN3</i> NM_000070	chr15:42695066 GRCh37/Hg19	exón 13 c.1611C>A; p. (Tyr537*)	Heterocigótico	Patogénica	Distrofia Muscular del anillo óseo tipo 2A OMIM:114240	Recesiva autosómica
<i>CAPN3</i> NM_000070	chr15:42701579 GRCh37/Hg19	Exón-intrón 17 c.1992+1G>T; p.(?)	Heterocigótico	Patogénica	Distrofia Muscular del anillo óseo tipo 2A OMIM:114240	Recesiva autosómica

## Emery-Dreifuss phenotype



no facial weakness

rigid spine

humeral wasting

marked elbow contractures +++

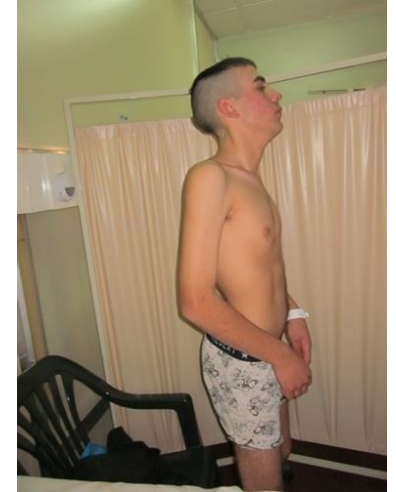
peroneal wasting

Achilles tendon contractures



# LGMD 1 B (LAMINOPATÍA)

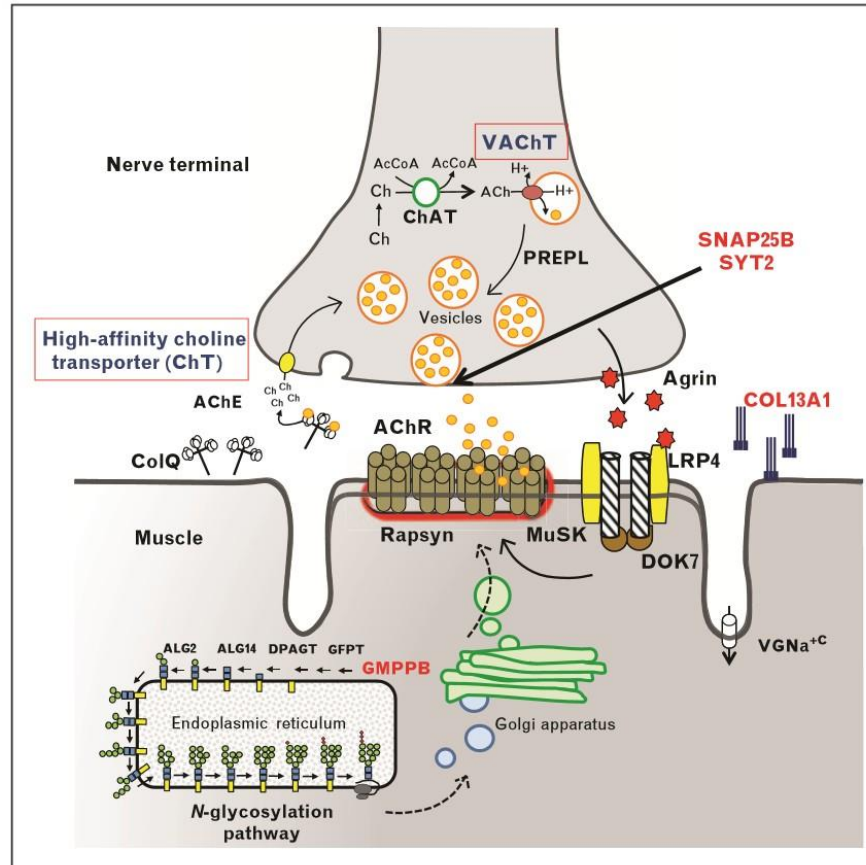
- AD
- *LMNA*, 1q11-21, lamina A/C, proteína membrana nuclear
- Otros fenotipos:
  - Distrofia muscular de Emery Dreifuss, forma dominante
  - Miocardiopatía con trastornos de la conducción
  - Lipodistrofia parcial familiar
  - AR-CMT2A
  - Displasia mandíbuloacral
  - Síndromes de envejecimiento prematuro
  - Distrofia muscular congénita





# Congenital myasthenic syndromes: recent advances

David Beeson

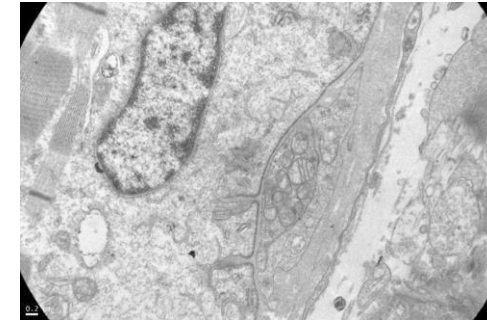
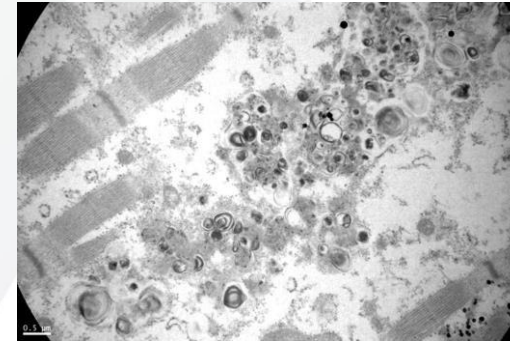
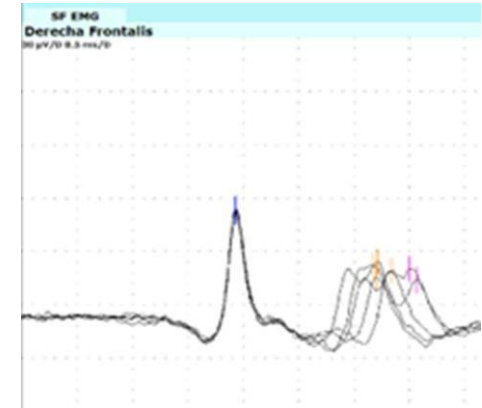
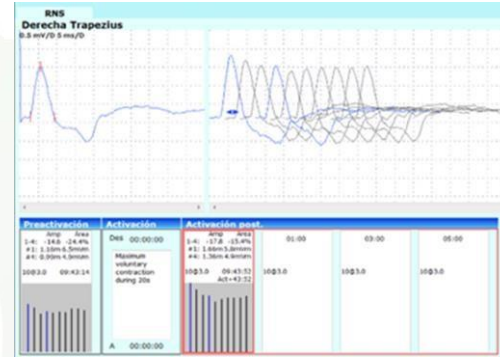
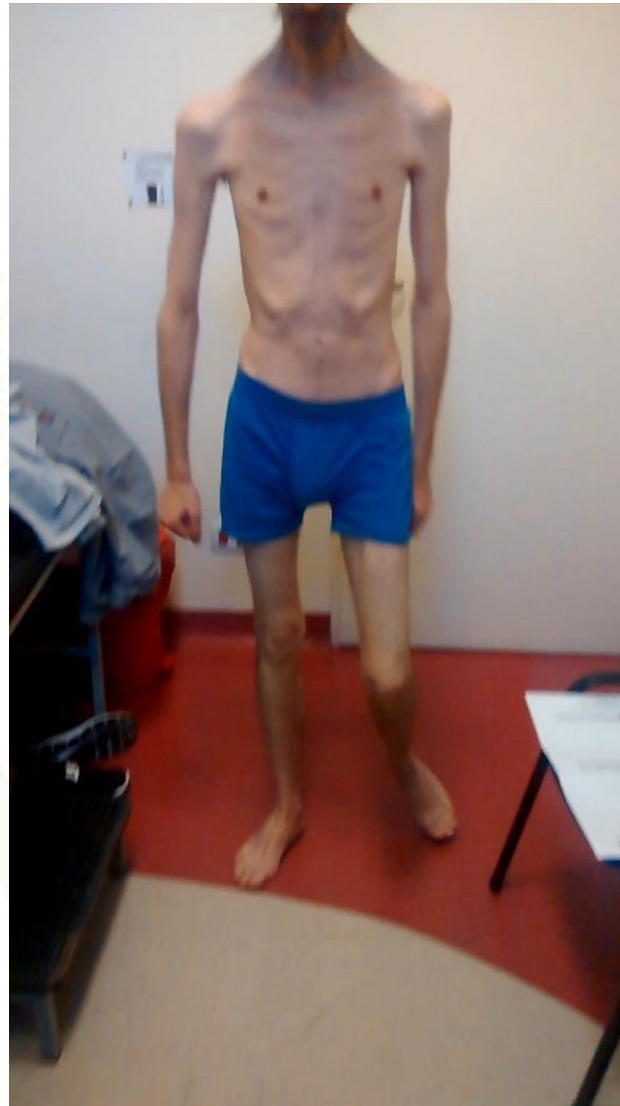


**Table 1.** Congenital myasthenic syndromes subtypes and associated genes

Congenital myasthenic syndrome	Gene
Ubiquitously expressed proteins	
N-glycosylation pathway	
GFPT1	GFPT1
DPAGT1	DPAGT1
°ALG2	ALG2
°ALG14	ALG14
GMPPB	GMPPB
Propyl-oligopeptidase	
°PREPL	PREPL
Proteins with defined function at the neuromuscular junction	
Presynaptic	
Choline acetyltransferase	CHAT
°Synaptotagmin	SYT2
°SNAP25B	SNAP25B
Synaptic	
Endplate AChE deficiency	COLQ
°Laminin β2 deficiency	LAMB2
Agrin	AGRN
°Collagen 13A1	COL13A1
Postsynaptic	
Primary acetylcholine receptor deficiency	CHRNA1, CHRNB1, CHRND, CHRNE
Escobar syndrome	CHRNA1, CHRNB1, CHRND, CHRNE
Rapsyn	RAPSN
DOK7	DOK7
Slow-channel syndrome	CHRNA1, CHRNB1, CHRND, CHRNE
Fast-channel syndrome	CHRNA1, CHRNB1, CHRND, CHRNE
°Low-conductance syndrome	CHRNE
°MuSK	MUSK
°Plectin deficiency	PLEC1
°Na-channel myasthenia	SCN4A
°LRP4	LRP4

Source: Updated from Rodrigues-Cruz, Palace, Beeson Curr Opin Neurol 2014. AChE, acetylcholinesterase.







# Muscle involvement in limb-girdle muscular dystrophy with GMPPB deficiency (LGMD2T)

OPEN

## ABSTRACT

**Objective:** In this study, muscle involvement assessed by MRI and levels of GMPPB and glycosylation of  $\alpha$ -dystroglycan expression in muscle were examined in patients with limb-girdle muscular dystrophy (LGMD) type 2T.

**Methods:** Six new patients with genetically verified mutations in *GMPPB* were studied. T1-weighted magnetic resonance images were obtained in 4 participants. Muscle strength and potential involvement of extramuscular organs were examined. Glycosylation of  $\alpha$ -dystroglycan in muscle was studied, and GMPPB and  $\alpha$ -dystroglycan expression was analyzed by Western blotting. Prevalence of LGMD2T was calculated from the total LGMD population in Denmark. *GMPPB* was sequenced in all unclassified cases.

**Results:** Two patients carried 3 new mutations in *GMPPB*. The other 4 patients carried previously described pathogenic mutations in *GMPPB*. MRI showed that the paraspinal muscles were the most affected, followed by involvement of hamstrings. Our results showed a loss of glycosylation of  $\alpha$ -dystroglycan as well as secondary loss of merosin expression on Western blotting. The prevalence of LGMD2T in the Danish cohort of patients with LGMD is 1.5%.

**Conclusions:** The new findings of this study are (1) the consistent finding of a preferential affection of paraspinal and hamstring muscles in LGMD2T, (2) 3 new mutations in *GMPPB*, (3) variable loss of glycosylation tested with I1H6 and VIA4 antibodies, and (4) a prevalence of LGMD2T of 1.5% in a well-characterized Danish LGMD cohort. *Neuro Genet* 2016;2:e112; doi: 10.1212/NXG.000000000000112

Table Baseline characteristics of 6 patients with LGMD2T

	Case 1	Case 2	Case 3	Case 4	Case 5 <sup>a</sup>	Case 6
<b>Mutation</b>	c.859C>T (p.Arg287Trp), c.79G>C (p.Asp27His)	c.859C>T (p.Arg287Trp), c.79G>C (p.Asp27His)	c.464G>A (p.Arg155His), c.1039_1043dup (p.Ile349Serfs <sup>3</sup> )	c.79G>C (p.Asp27His), c.760G>A (p.Val254Met)	c.859C>T (p.Arg287Trp), c.79G>C (p.Asp27His)	c.902C>G (p.Ser301Cys), c.1069G>A (p.Val357Ile)
<b>Sex/age, y</b>	Male/51	Female/44	Female/32	Female/33	Male/53	Male/59
<b>Disease onset, y</b>	15	30	12	18	5	25
<b>Presenting symptoms</b>	Difficulties running	Difficulties climbing stairs	Difficulties running	Exercise intolerance with fatigue	Walked at 5 years old	Difficulties walking and running
<b>Age at MRI, y</b>	51	44	27	28	ND	ND
<b>Origin</b>	CA, DK	CA, DK	CA, Fr	CA, Fr	CA, DK	CA, Fr
<b>MMSE</b>	30/30	30/30	30/30	27/30	ND	28/30
<b>FVC, %</b>	59	66	76	95	61	43
<b>ECG</b>	Normal	Normal	Normal	Normal	Normal	Normal
<b>Cardiac echo</b>	Normal	Normal	Normal	Normal	Normal	Ejection fraction 48%
<b>10-m walk test, s</b>	13	11	6	14	7	Cannot walk
<b>Walking aids</b>	Wheelchair, but ambulant	Scooter	None	Wheelchair, but ambulant	None	Wheelchair
<b>FSS</b>	48/63	61/63	35/63	58/63	ND	43/63
<b>EMG</b>	Myopathic	ND	Myopathic	Myopathic	ND	ND
<b>Decrement,<sup>b</sup> %</b>	26-29	ND	11-13	10-23	ND	13
<b>CK, U/L</b>	2,390	1,520	1,604	1,200	1,327	619

Abbreviations: CK = creatine kinase; CA = Caucasian; DK = Danish; Fr = French; FSS = Fatigue Severity Scale; FVC = forced vital capacity; MMSE = Mini-Mental State Examination; ND = not done.

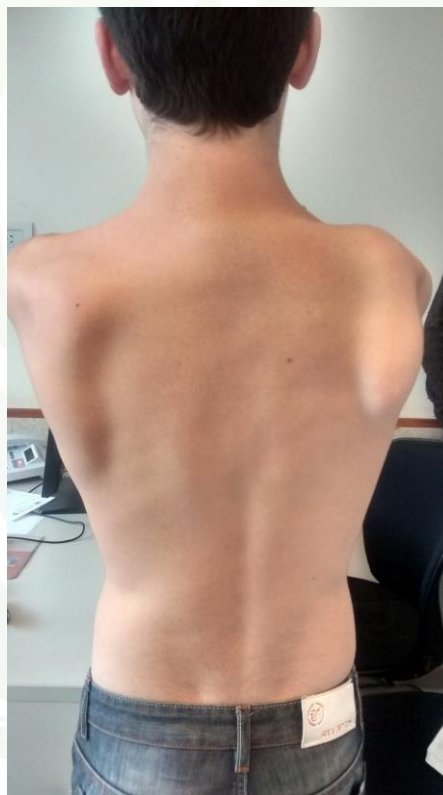
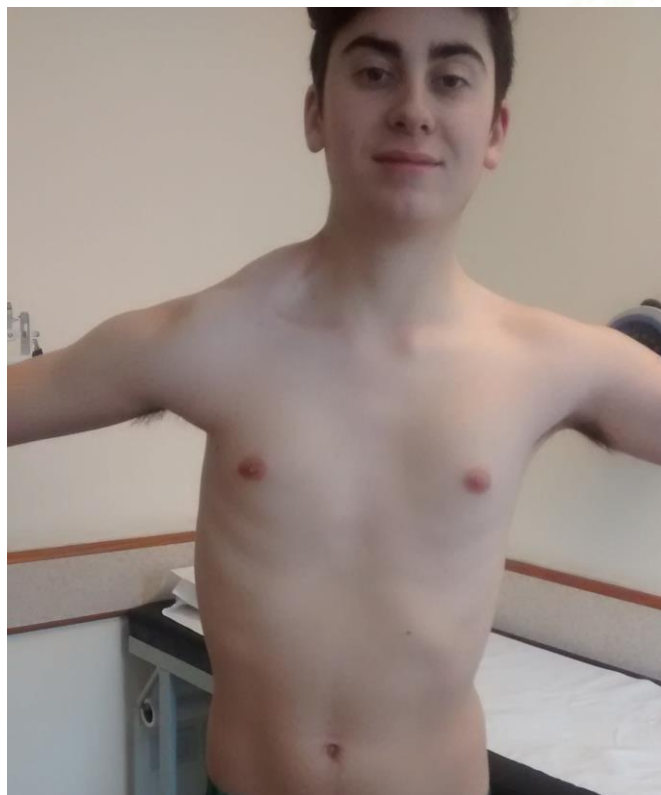
<sup>a</sup>Data obtained at the latest visit 12 years ago, at age 41 years. This patient is the brother of case 1 and has intellectual disability due to prolonged oxygen deficiency at birth and could not cooperate to perform MRI.

<sup>b</sup>Analyses of decrement, using 3-Hz stimulation frequency, were obtained in different muscles (recording electrode on trapezius muscle, anconeus muscle, and the tibialis anterior muscle, respectively).

S.T. Oestergaard, BSc  
T. Stojkovic, PhD  
J.R. Dahlqvist, MD  
C. Bouchet-Seraphin, PhD  
J. Nectoux, PhD  
F. Leturcq, PharmD  
M. Cossée, PhD  
G. Solé, MD  
C. Thomsen, DMSc  
T.O. Krag, PhD  
J. Vissing, DMSc

Correspondence to  
Sofie T. Oestergaard:  
sofie.thuroe.oestergaard.02  
@regionh.dk

# FSHD



# Distrofia Miotónica tipo 2

**Table I.** Etiology of DM1 and DM2.

	<b>DM1</b>	<b>DM2</b>
Chromosomal locus	19q 13.3	3q 21.3
Gene	DMPK	ZNF9/CNBP
Inheritance	Autosomal dominant	Autosomal dominant
Mechanism	CTG repeat expansion	CCTG repeat expansion
Normal repeat size	< 37	< 27
Pathologic repeat size	> 50	> 75?
Expanded repeat range	50-4000	75-5000 -> 11000
Anticipation	Yes	----

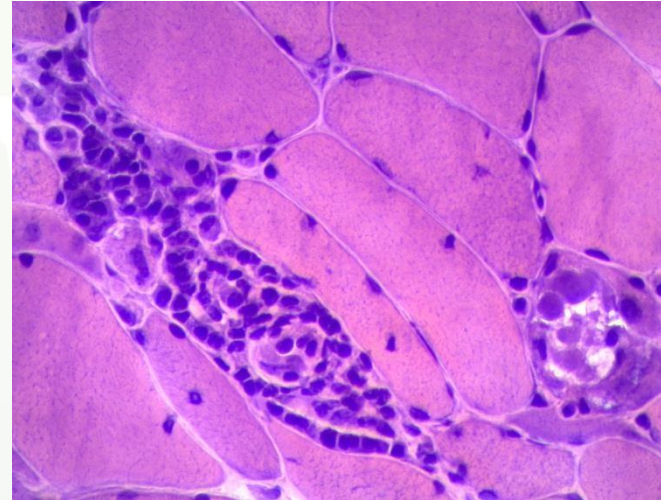
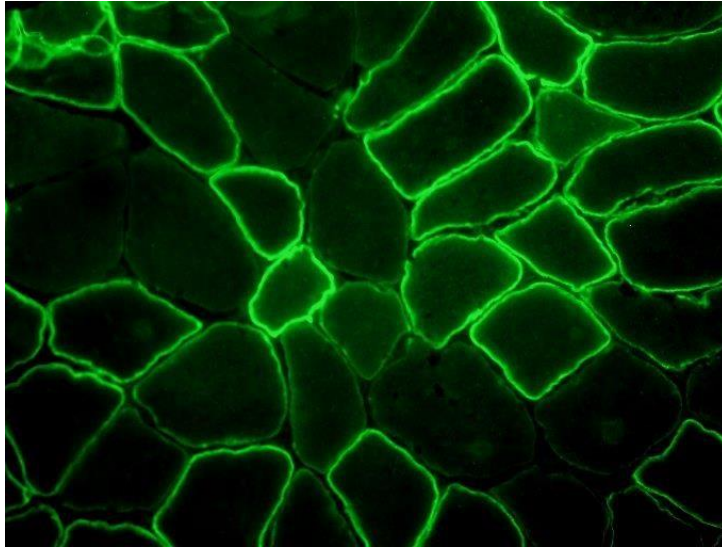
**Table II.** Multisystemic aspects of adult onset DM2.

<b>Brain</b>	<ul style="list-style-type: none"> <li>• Similar visual-spatial executive function deficits to those present in DM1</li> </ul>
<b>Heart</b>	<ul style="list-style-type: none"> <li>• Significant disturbances in conduction much less common than in DM1</li> </ul>
<b>Respiratory</b>	<ul style="list-style-type: none"> <li>• Obstructive sleep apnea</li> </ul>
<b>Anesthesia</b>	<ul style="list-style-type: none"> <li>• Limited information is available to determine if there is a significant and increased risk of general anesthesia. Recommended careful monitoring in postoperative period until more information is published</li> </ul>
<b>Hypersomnia and fatigue</b>	<ul style="list-style-type: none"> <li>• Excessive daytime sleepiness is not as prominent in DM1</li> <li>• Obstructive sleep apnea</li> <li>• CNS and muscle related fatigue</li> </ul>
<b>Endocrine</b>	<ul style="list-style-type: none"> <li>• Gonadal insufficiency</li> <li>• Low testosterone</li> <li>• Erectile dysfunction</li> <li>• Insulin resistance</li> <li>• Hyperlipidemia</li> <li>• Hypothyroidism</li> </ul>
<b>Pregnancy</b>	<ul style="list-style-type: none"> <li>• Limited information is available to determine if there is significant risk of complication during pregnancy and delivery</li> <li>• Weakness and stiffness may worsen during pregnancy and improve following delivery</li> </ul>
<b>Muscle pain</b>	<ul style="list-style-type: none"> <li>• Often a major symptoms, especially in the arms and upper lower back</li> <li>• Fluctuates in duration, location and intensity</li> <li>• Can worsen with exercise and cold temperature</li> <li>• Aches and stiffness</li> </ul>



# Rippling





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Short communication

### Immune-mediated rippling muscle disease and myasthenia gravis

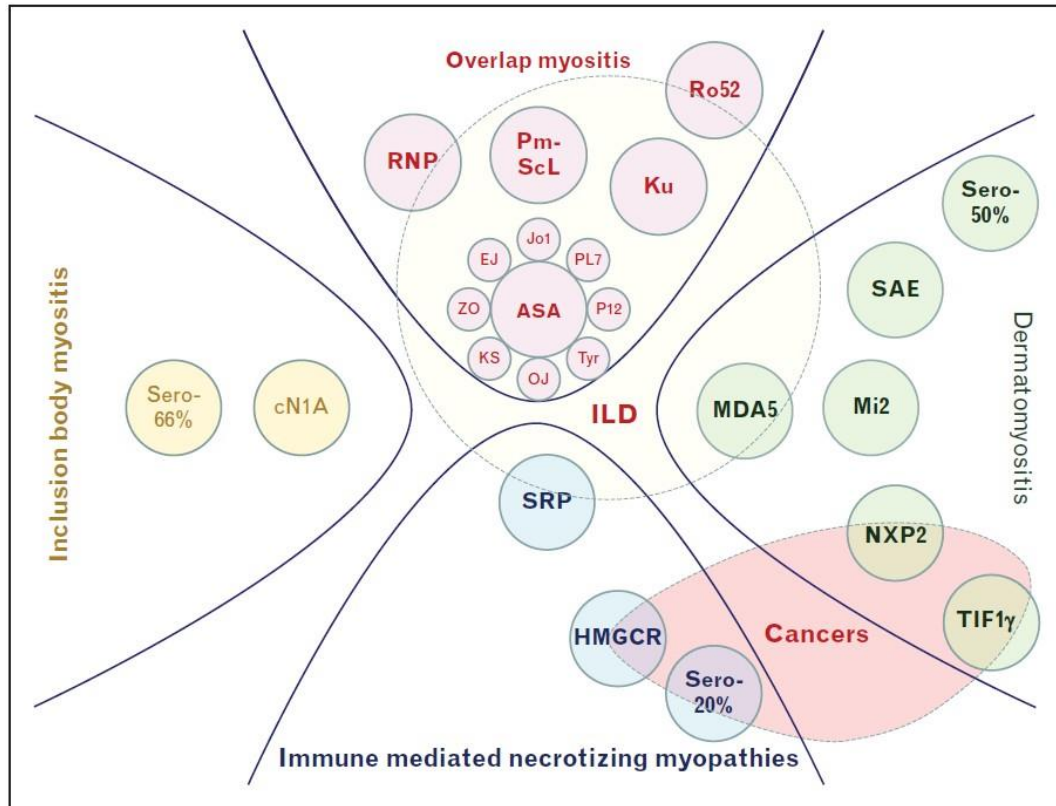
Mariela Bettini<sup>a,\*</sup>, Hernan Gonorazky<sup>a</sup>, Marcelo Chaves<sup>a</sup>, Ernesto Fulgenzi<sup>b</sup>, Alejandra Figueredo<sup>c</sup>,  
Silvia Christiansen<sup>a</sup>, Edgardo Cristiano<sup>a</sup>, Enrico S. Bertini<sup>d</sup>, Marcelo Rugiero<sup>a</sup>

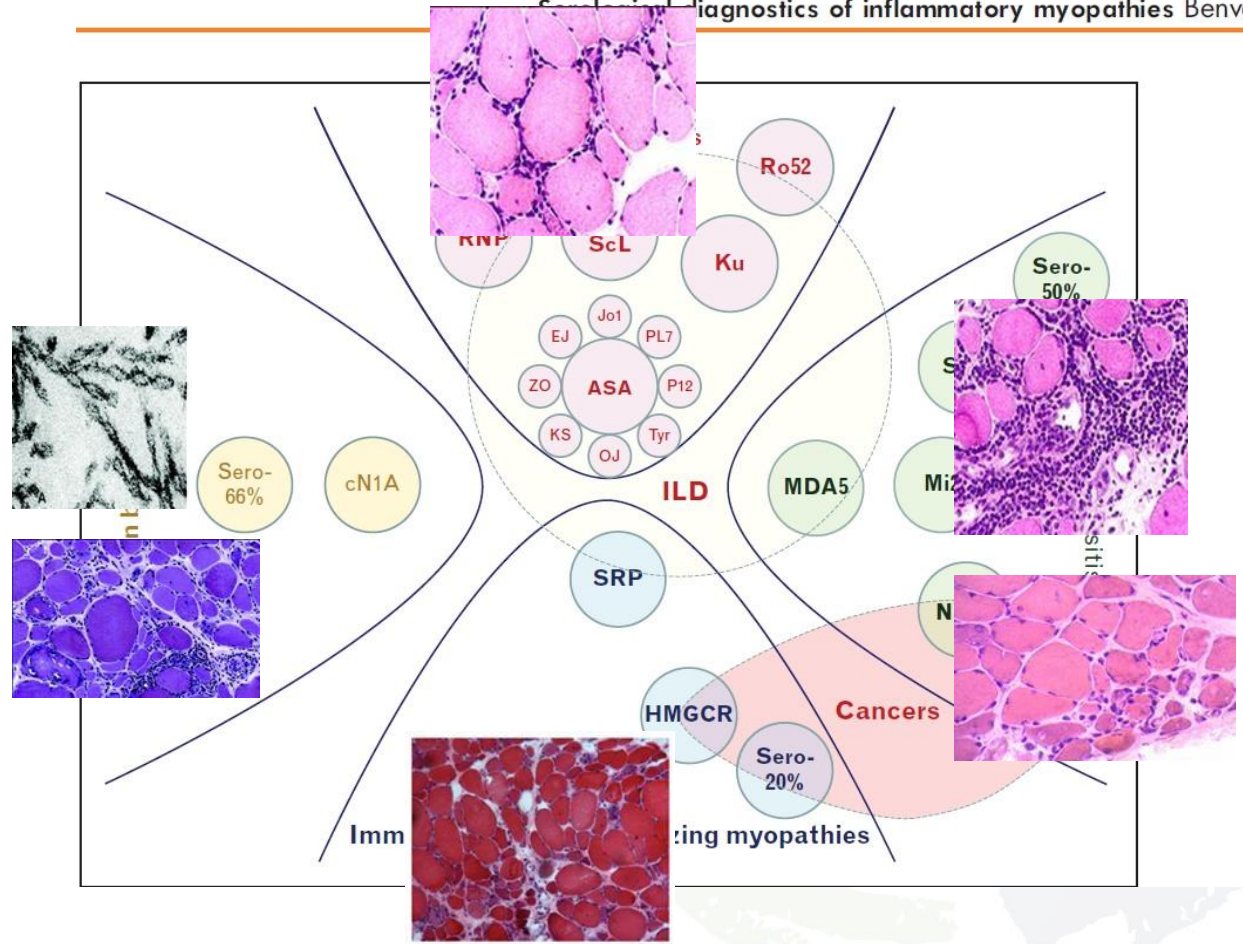
<sup>a</sup> Neuromuscular Diseases Section, Neurology Department, Italian Hospital of Buenos Aires, Argentina

<sup>b</sup> Neurology Department, Cesar Milstein Care Unit, Buenos Aires, Argentina

<sup>c</sup> Neurology Department, San Roque Hospital, La Plata, Argentina

<sup>d</sup> Unit of Neuromuscular and Neurodegenerative Disorder, Bambino Gesù Children's Hospital, Rome, Italy





Review

# Anti-HMGCR Myopathy

Payam Mohassel<sup>a</sup> and Andrew L. Mammen<sup>b,\*</sup>

<sup>a</sup>National Institutes of Health, NINDS, Bethesda, MD, USA

<sup>b</sup>National Institutes of Health, NIAMS, Bethesda, MD, USA

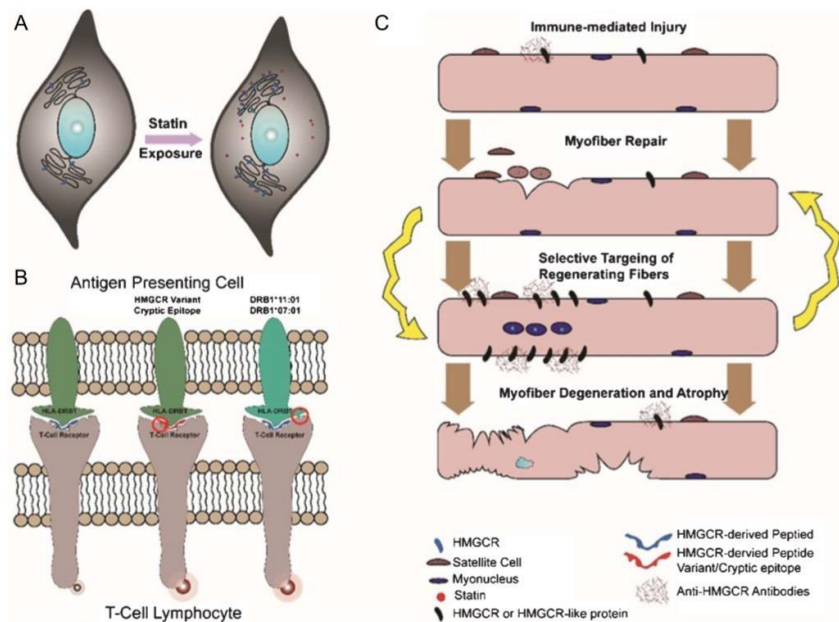
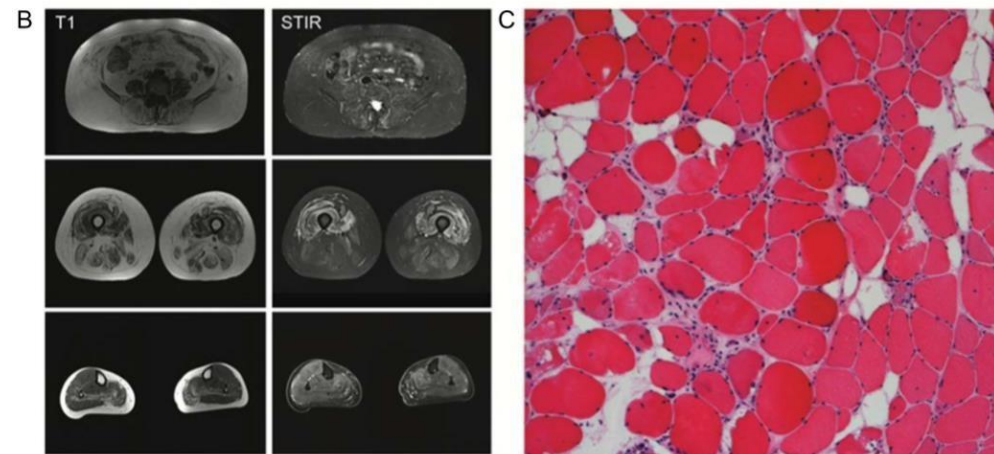


Fig. 2. Schematic of postulated pathomechanisms of anti-HMGCR myopathy. (A) Statin exposure results in overexpression of HMGCR in multiple tissues and cell types. (B) Processing of HMGCR by antigen-presenting cells under different scenarios. Variants in HMGCR or cryptic epitopes unmasked by drugs (e.g. statins) and/or polymorphisms in the HLA molecule may increase T-cell receptor activation and initiate autoimmunity. (C) Immune-mediated injury to the muscle is directed against HMGCR or other antigens recognized by anti-HMGCR antibody. Attempts at myofiber repair results in increased HMGCR (or its mimic) expression and sustained autoimmunity with ultimate atrophy and degeneration of myofibers.



A

Typical Clinical Features of anti-HMGCR Myopathy	
Pattern of Weakness	Progressive, proximal weakness, especially posterior thigh, medial thigh, and gluteal compartments
Creatine Kinase	Usually >1,000-10,000 Units/L
Electromyography	Myopathic, usually with spontaneous activity in the form of fibrillations and sharp waves
Muscle Biopsy	Necrotizing myopathy; Increased MHC-1 or MAC staining
Muscle Imaging	T1 hyperintensity especially in posterior thigh; STIR signal is increased and may be asymmetric
Risk Factors	Statin drugs or supplements; HLA-DRB1*11:01 and 07:01 alleles





# Anti-HMGCR Antibody–Related Necrotizing Autoimmune Myopathy Mimicking Muscular Dystrophy

Céline Tard<sup>1,2</sup> Vincent Tiffreau<sup>1,3</sup> Emmanuelle Jaillette<sup>1,4</sup> Fabienne Jouen<sup>5</sup> Isabelle Nelson<sup>6</sup>  
 Gisèle Bonne<sup>6</sup> Rabah Ben Yaou<sup>6</sup> Norma Romero<sup>6</sup> Louis Vallée<sup>1,7</sup> Patrick Vermersch<sup>1,2</sup>  
 Sylvie Nguyen<sup>1,7</sup> Claude-Alain Muraige<sup>1,8</sup> Jean-Marie Cuisset<sup>1,7</sup>

## ANTI-3-HYDROXY-3-METHYLGLUTARYL-COENZYME A REDUCTASE NECROTIZING MYOPATHY MASQUERADING AS A MUSCULAR DYSTROPHY IN A CHILD

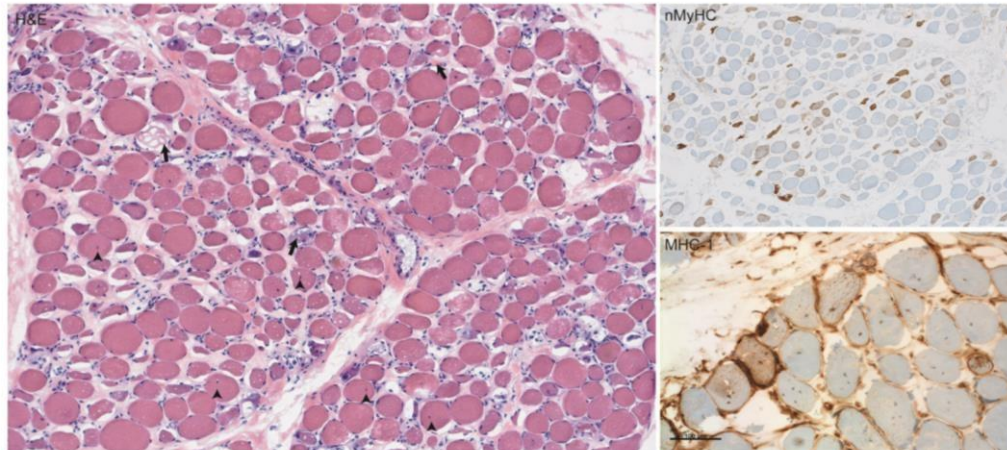
PAYAM MOHASSEL, MD,<sup>1</sup> A. REGHAN FOLEY, MD,<sup>1</sup> SANDRA DONKervoort, MS,<sup>1</sup> PIERRE R. FEQUIERE, MD,<sup>2</sup>  
 KATHERINE PAK, MD,<sup>3</sup> CARSTEN G. BÖNNEMANN, MD,<sup>1</sup> and ANDREW L. MAMMEN, MD, PhD<sup>3</sup>

<sup>1</sup>National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA

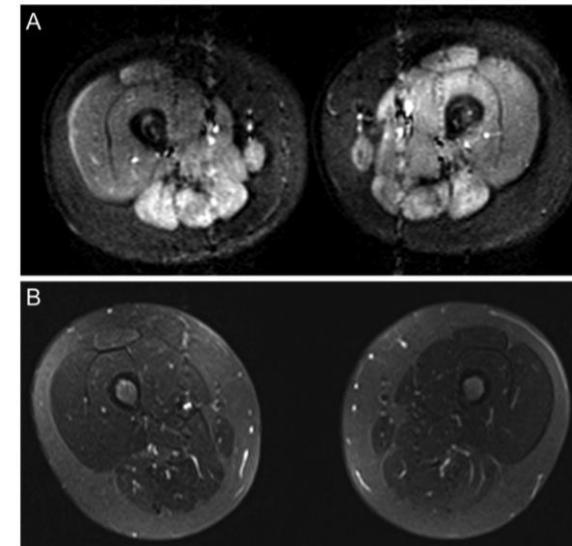
<sup>2</sup>Department of Pediatrics, Division of Pediatric Neurology, University of Alabama at Birmingham, Birmingham, Alabama, USA

<sup>3</sup>Muscle Disease Unit, Laboratory of Muscle Stem Cells and Gene Regulation, National Institute of Arthritis, Musculoskeletal and Skin Diseases, National Institutes of Health, Building 50, Room 1146, Bethesda, Maryland 20892, USA

Accepted 6 January 2017



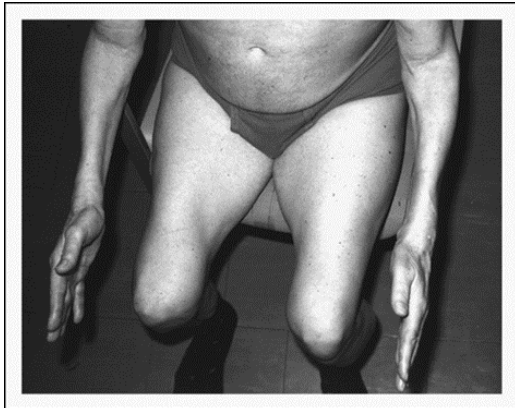
**FIGURE 1.** Biopsy of right quadriceps muscle. In spite of handling artifact, hematoxylin and eosin (H&E) stain highlights several degenerating fibers (short black arrows), internally placed nuclei (arrowheads), fiber size variability, and increased endomysial and perimysial fibrosis. Neonatal myosin heavy chain (nMyHC) immunostain highlights many regenerating myofibers. A few scattered non-necrotic myofibers appear to have increased sarcoplasmic and cytoplasmic major histocompatibility 1 (MHC-1) immunostaining.



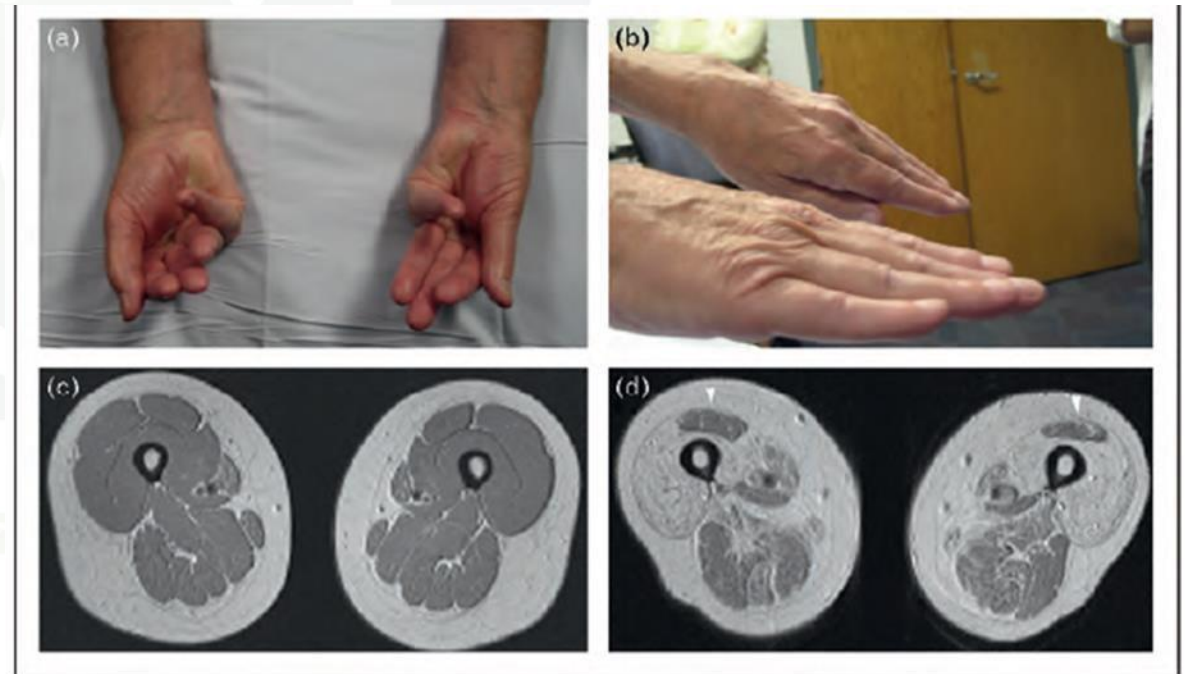
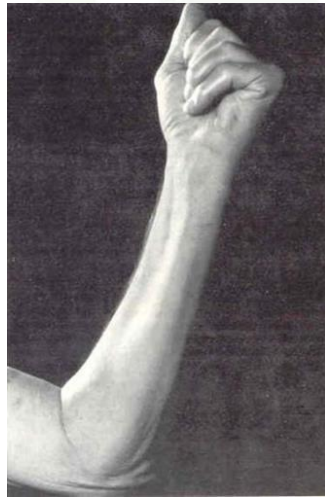
**FIGURE 2.** Muscle MRI images before (A) and after (B) immunotherapy with intravenous immunoglobulins. Note significant reduction in STIR signal in response to therapy.

# Miositis por Cuerpos de Inclusión: clínica

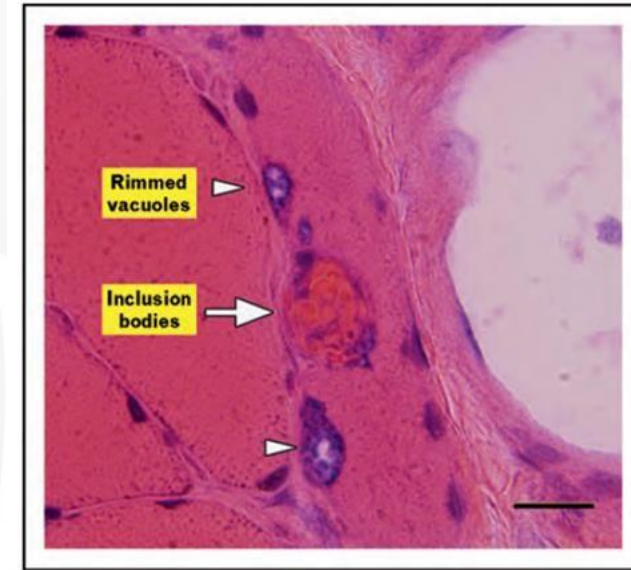
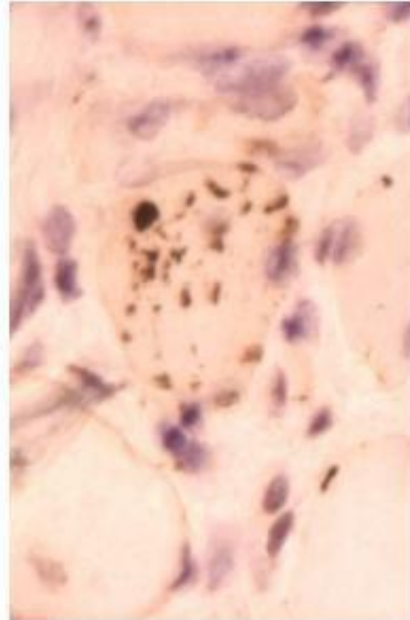
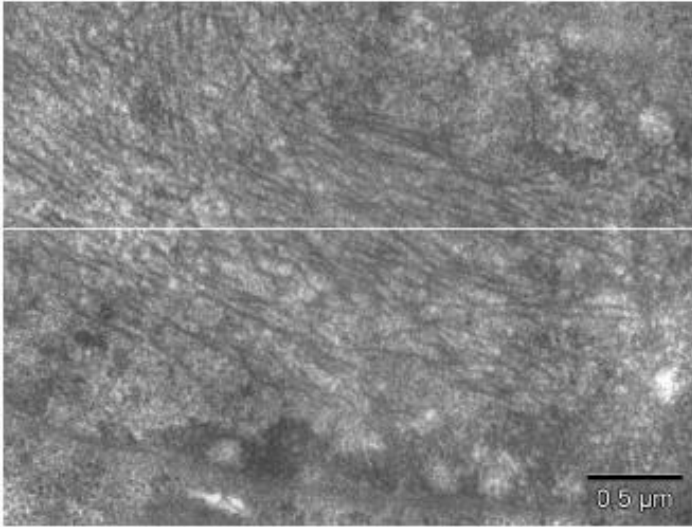
- Miopatía adquirida más frecuente en pacientes mayores de 50 años
- Músculos proximales y **distales** (tibial anterior, cuádriceps, flexores de muñeca y dedos, dorsiflexores del pie)
- Más “heterogéneo”
- **Pobre o nula respuesta al tratamiento inmunosupresor**



Shown is atrophy of quadriceps and flexor digitorum profundus muscles in a patient with sporadic inclusion body myositis.

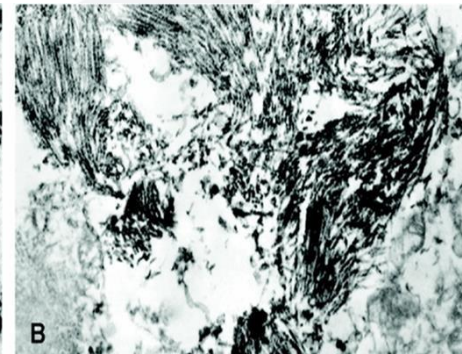
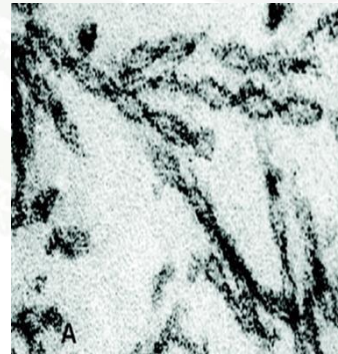
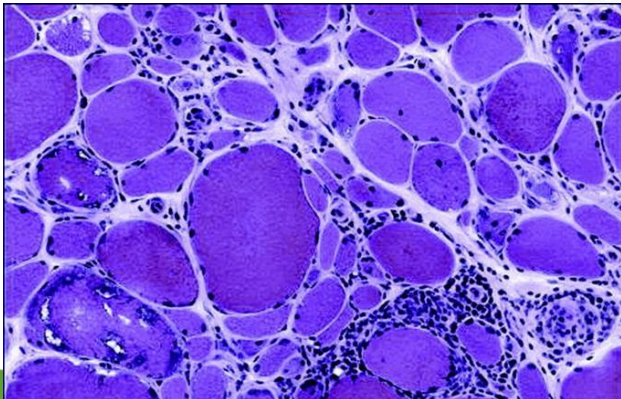


# Vacuolas Rimmed: inclusiones confirman el diagnostico



**FIGURE 2.** Rimmed vacuoles and inclusion bodies in an inclusion body myositis myofiber. On hematoxylin and eosin staining, rimmed vacuoles are lined with granular basophilic material. [Copyright S.A.G., courtesy of the Inclusion Body Myositis Foundation, Inc. (<http://www.ibmfoundation.org/ibm-picture-gallery/rimmed-vacuoles/>)].

Composition of inclusions = Alzheimer deposits (proteins :  $\beta$ -amyloïde,  $\beta$ -amyloïde precursor, phosphorylated tau, preseniline-1, etc)



# MIOPATÍA NEMALÍNICA ESPORÁDICA DE INICIO TARDÍO: REPORTE DE UN CASO.

<sup>1</sup>Azcona CL, <sup>1</sup>Leccini L, <sup>1</sup>Bettini M, <sup>1</sup>Sosa P; <sup>3</sup>Taratuto AL, <sup>2</sup>Christiansen S, <sup>1</sup>Rugiero M

<sup>1</sup>Servicio de Neurología. <sup>2</sup>Servicio de Anatomía Patológica. Hospital Italiano de Buenos Aires. <sup>3</sup>Laboratorio de Neuropatología y Patología Neuromuscular.

## INTRODUCCIÓN:

La miopatía nemalínica esporádica de inicio tardío (SLONM por sus siglas en inglés), es una enfermedad rara, adquirida, que afecta adultos, de curso frecuentemente subagudo.

Compromete principalmente a los músculos proximales de los miembros, pudiendo también involucrar músculos axiales, faciales, respiratorios y bulbares.

Suele asociarse a gammopatías monoclonales como así también a infección por VIH.

La anatomía patológica del músculo se distingue por la presencia de cuerpos nemalínicos, con escasa o nula inflamación.

Múltiples esquemas terapéuticos han sido descritos en distintos reportes o series de casos, no existiendo estudios controlados. Se destacan el empleo de inmunoglobulina intravenosa (IGIV), quimioterapia y trasplante autólogo de células madre en el caso de asociación a componente monoclonal y esteroides en contexto de VIH.

Nuestro objetivo es describir un caso de SLONM, no asociado a gammopatía monoclonal ni VIH, en quién se indicó tratamiento inmunomodulador.

**MATERIALES Y MÉTODOS:** reporte de un caso.

## RESULTADOS:

### Caso clínico

Mujer de 59 años, sin antecedentes personales o familiares de relevancia, quien consultó por un cuadro de debilidad de cinturas progresivo, menor a 1 año de evolución, asociado a mialgias cervicobraquiales e importante astenia.

Al examen físico se evidenció debilidad facial, axial y de cinturas escapular y pélvica simétrica. Hipotrofia de los grupos musculares más comprometidos. Signo de Gowers positivo y marcha basculante. Resto de examen neurológico sin hallazgos destacables. Fig.1 y 2.

Estudios complementarios:

\*CPK 420 U/L. \* Resonancia muscular de pelvis, muslos y ambas piernas: atrofia de músculos para-espinales, glúteos, semimembranosos y del sóleo izquierdo. \*Espirometría con patrón restrictivo moderado. \*Ecocardiograma transtorácico sin alteraciones.

\*Biopsia del músculo bíceps braquial: se evidenciaron con microscopía óptica, acúmulos intermiofibrilares en el Tricrómico de Gomori, confirmándose la presencia de cuerpos nemalínicos con microscopía electrónica. Fig.3 y 4.

**Se interpretó el cuadro como SLONM.**

Se descartó la presencia de gammopatía monoclonal e infección por VIH.

Se decidió indicar tratamiento con IGIV 2g/kg, mensual.

Recibió inicialmente 2 ciclos, siendo interrumpido el tratamiento el contexto de la pandemia por SARS-CoV-2 y reiniciado recientemente.

Se observa al momento una discreta mejoría, sobre todo en algunas pruebas funcionales.

## CONCLUSIÓN

Se reporta un caso de SLONM, no asociado a gammopatía monoclonal ni VIH. Se destaca la importancia del reconocimiento temprano de esta entidad, teniendo en cuenta su potencial susceptibilidad a un tratamiento inmunomodulador.



Fig. 1. Debilidad facial

Fig. 2. Debilidad cintura escapular



Fig. 3. Tricrómico de Gomori 40x. Acúmulos intermiofibrilares.

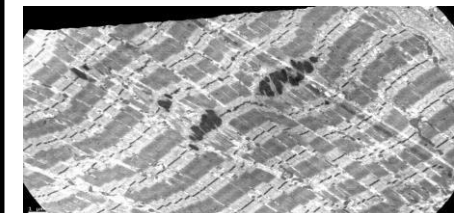


Fig. 4. ME. Cuerpos nemalínicos.

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- Nemaline myopathies: a current view. C. Sewry et al. J Muscle Res Cell Motil. 2019; 40(2): 111–126..

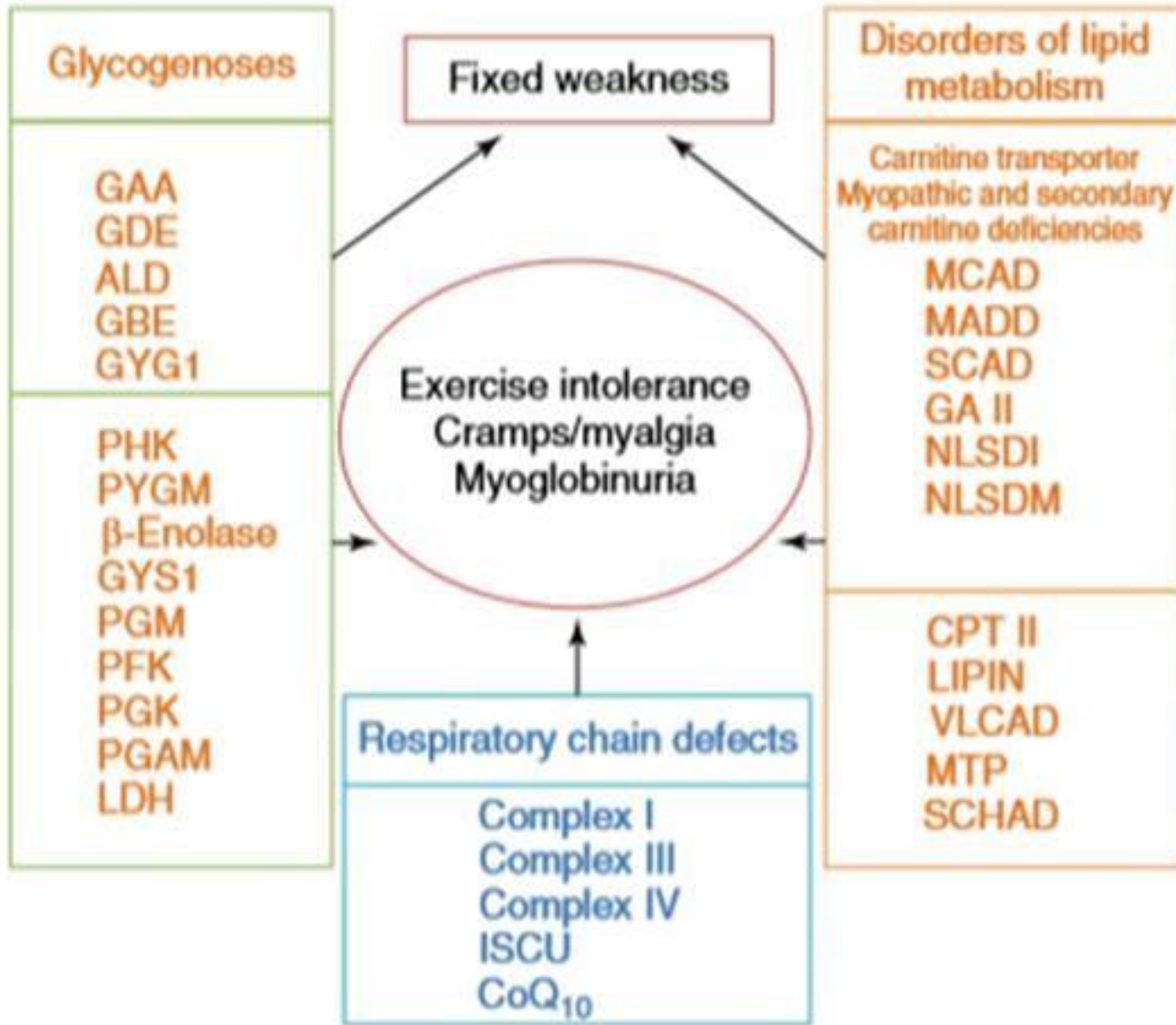
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HIV, rods, and the muscles—a discussion about HIV-associated nemaline rod myopathy. Madonia P, Wilson J, Bican O, Willis M, Bass P. J Neurol Sci. 2019; 401: 320–323.

## Miopatías Metabólicas: definiciones

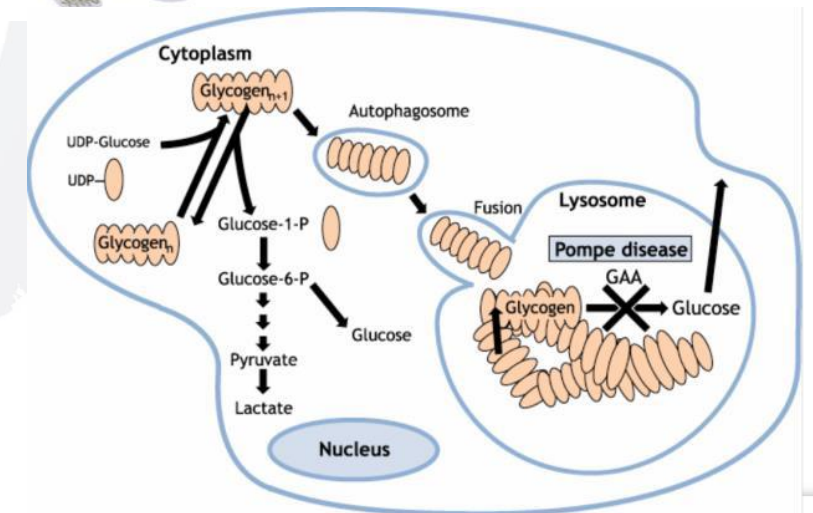
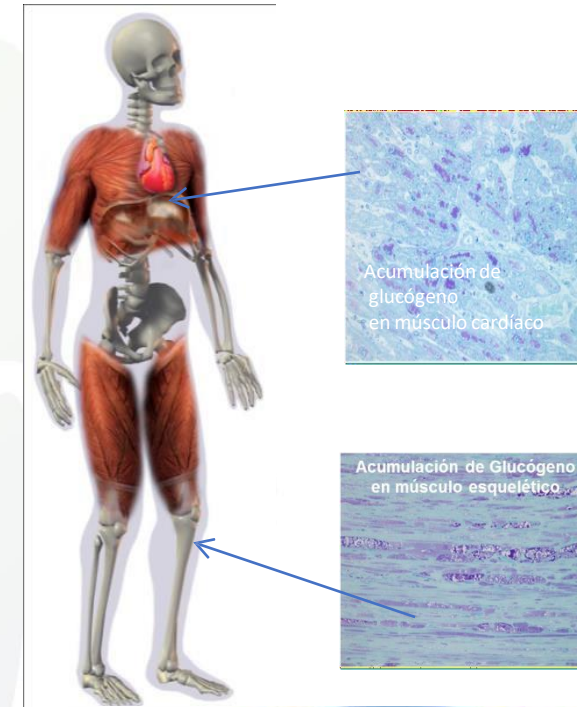
- Formas “agudas”(recurrente): Intolerancia al ejercicio, contracturas, mialgias, hiperCKemia, mioglobinuria y rabdomiolisis
- Formas “crónicas”(progresiva): debilidad de cinturas y axial, compromiso de otros órganos (hígado, corazón, SNC, SNP)
- Factores precipitantes: fiebre, stress, infecciones, ayuno, drogas



# Enfermedad de Pompe

## Hallazgos Clínicos

	Infantil	Comienzo Tardío
<b>Cardiaco</b>	<ul style="list-style-type: none"> <li>cardiomegalia</li> <li>cardiomiopatía</li> <li>insuficiencia cardíaca</li> </ul>	<ul style="list-style-type: none"> <li>datos escasos</li> <li>Síndrome de WPW</li> </ul>
<b>Musculoesquelético</b>	<ul style="list-style-type: none"> <li>debilidad muscular progresiva</li> <li>deambulación tardía</li> </ul>	<ul style="list-style-type: none"> <li>debilidad muscular progresiva (tronco y MMII)</li> <li>trastornos en la marcha</li> <li>mialgias</li> <li>dificultad para escaleras</li> <li>Caidas frecuentes</li> <li>Winging</li> <li>Intolerancia al ejercicio</li> </ul>
<b>Pulmonar</b>	<ul style="list-style-type: none"> <li>Infecciones respiratorias frecuentes</li> <li>Insuficiencia respiratoria</li> </ul>	<ul style="list-style-type: none"> <li>fallo/insuficiencia respiratoria</li> <li>ortopnea</li> <li>Apnea de sueño</li> <li>infecciones respiratorias</li> </ul>
<b>Gastrointestinal</b>	<ul style="list-style-type: none"> <li>Dificultad para tragar</li> <li>Organomegalia (hepatomegalia, esplenomegalia, macroglosia)</li> </ul>	<ul style="list-style-type: none"> <li>puede requerir SNG</li> <li>Colon Irritable</li> <li>perdida de peso</li> </ul>
<b>otro</b>		<ul style="list-style-type: none"> <li>somnolencia diurna</li> <li>cefaleas matinales</li> <li>aneurismas cerebrales</li> </ul>
<b>prevalencia</b>	1/138.000	1/57.000



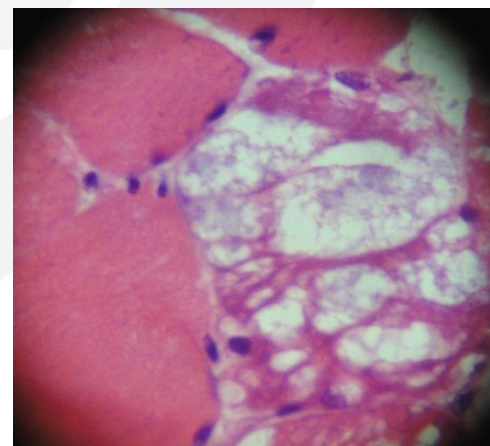
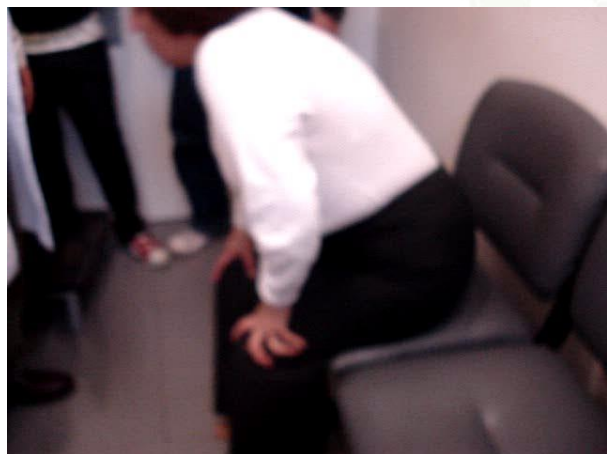
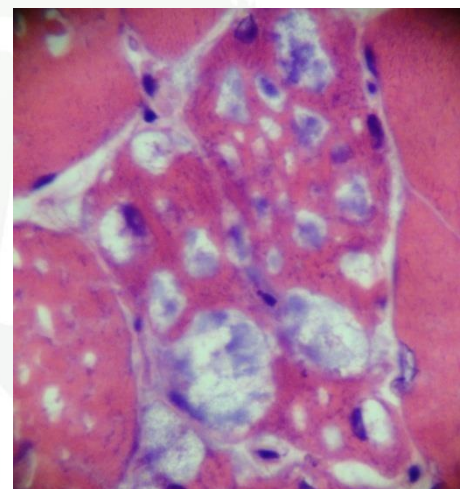
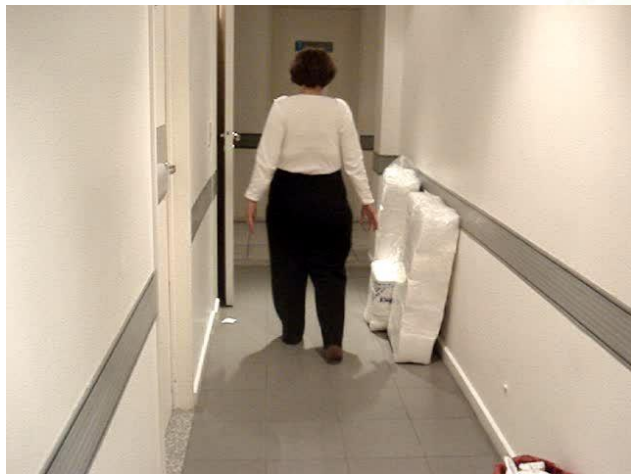
# CASO 1

- 48, masculino
- sin antecedentes
- debilidad progresiva, disnea de 4 años de evolución
- cinturas escapular y pelviana (3-4/5 MRC), facial, cuello
- CK: 500U/ml
- EMG: miopatico, descargas miotonicas escasa
- Espirometría : restricción severa
- Biopsia
- Test de gota seca





## CASO 2

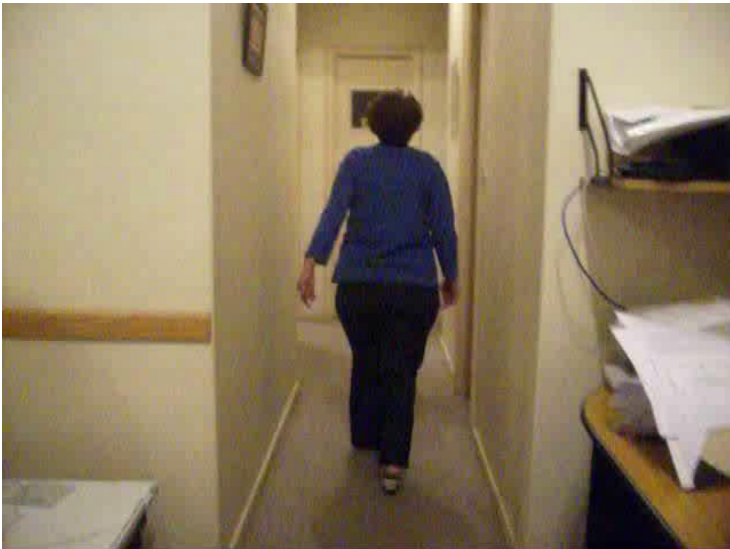




Pre TRE



5 años TRE



Post-TRE



## CASO 3



# CASO 4





Barrios C<sup>1</sup>, Rugiero M<sup>1</sup>, Stefani C<sup>1</sup>, Christiansen S<sup>2</sup>, Cristiano E<sup>1</sup>.  
1 Sección de Enfermedades Neuromusculares, Servicio de Neurología de Adultos  
2 Servicio de Anatomía Patológica. Hospital Italiano de Buenos Aires

## Introducción y Objetivo

La enfermedad de Pompe, también llamada enfermedad de depósito de glucógeno tipo II o déficit de maltasa ácida es una enfermedad autosómica recesiva causada por el déficit de la enzima  $\alpha$ -1,4-glucosidasa (GAA). Esta deficiencia causa acumulación del glucógeno intralisosomal en diferentes órganos.

La forma clásica es la infantil con hipotonía y cardiomiopatía en el lactante. Existe una forma menos frecuente en el paciente adulto que causa una miopatía progresiva de las cinturas escapular y pelviana y fallo respiratorio.

Presentamos el caso de un paciente que fue derivado a la Unidad de Terapia Intensiva (UTI) de nuestro Hospital en el contexto de enfermedad neuromuscular con compromiso respiratorio.

## Caso Clínico

Paciente de 44 años de edad, de sexo masculino, con antecedente de debilidad progresiva de cinturas escapular y pelviana de cuatro años de evolución y comienzo asimétrico. Ingresó a la UTI por cuadro de insuficiencia respiratoria de 4 meses de evolución en ARM y posterior traqueotomía.

Recibió en su lugar de origen tratamiento inmunomodulante por sospecha de enfermedad de etiología autoinmune sin respuesta.

Paciente alerta, sin afectación de pares craneales, que presentaba atrofia severa y debilidad de la mayoría de los grupos musculares, arreflexia generalizada y sin trastornos sensitivos.

Datos de Laboratorio: CPK: 65.0 UI, aldolasa: 13.5

EMG: patrón mixto proximal, pérdida importante de unidades motoras, denervación distal en mmii. No se observó actividad espontánea en músculos proximales.

Biopsia de músculo deltoides: fibras anguladas denervadas (NADH y estearasa Fig.1 y 2), vacuolas de tipo "rimmed" (Tricromo Gomori Fig.3 y 4) e incremento de los depósitos glucogénicos PAS+ (Fig. 5)

Test de Gota Seca: déficit de alfa-glucosidasa

Como intercurencias presento: Peritonitis de origen apendicular (AP: tumor neuroendocrino), infección por *Strongiloides Stercoralis* tratada con ivermectina y Colitis Pseudomembranosa que requirió colectomía total luego de la cual presento disfunción orgánica múltiple y deceso.

## Conclusión

• La enfermedad de Pompe (EP) es una enfermedad subdiagnosticada y potencialmente tratable por la aparición de las terapias de reemplazo enzimático.

• Presentamos el caso de un paciente con un EP severa con un cuadro de difícil interpretación clínica, CK normal y hallazgos anatomopatológicos neurogenéticos.

• La EP no solo debe ser considerada entre los diagnósticos diferenciales de las miopatías del adulto sino también entre aquellos pacientes con insuficiencia respiratoria de causa desconocida en la Unidad de Cuidados Intensivos.

• Destacamos la utilidad del Test de gota seca como herramienta diagnóstica.

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4. Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease Pellegrini N, Laforet P, Orlikowski D, et al. *Eur Respir J*. 2005;26(6):1024-1031.
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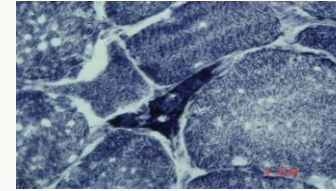


Figura 1

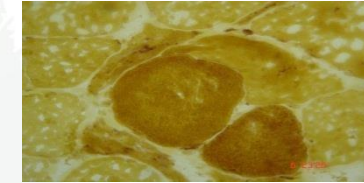


Figura 2



Figura 3



Figura 4

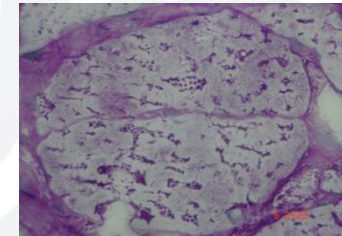
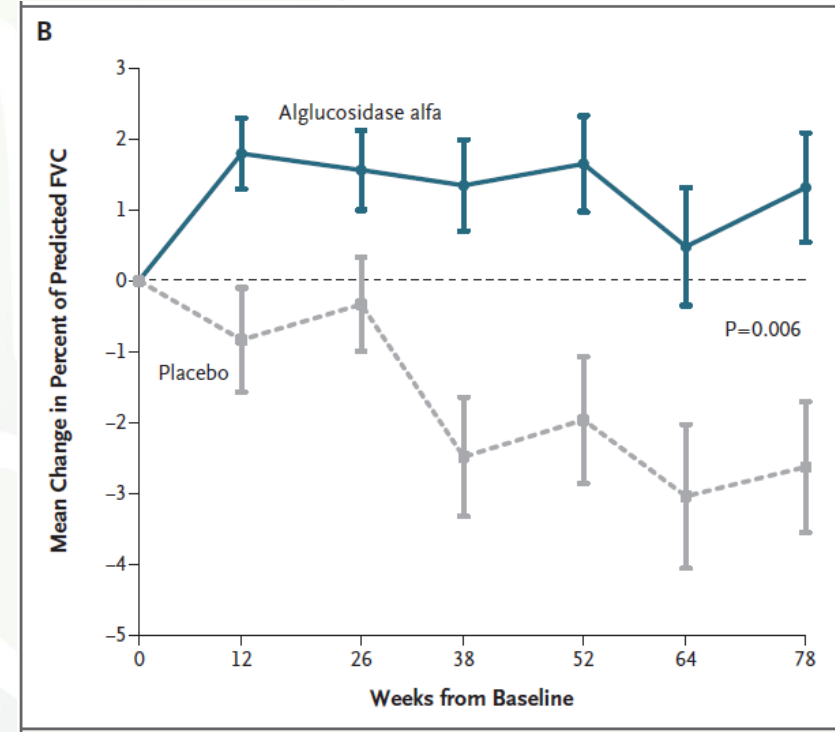
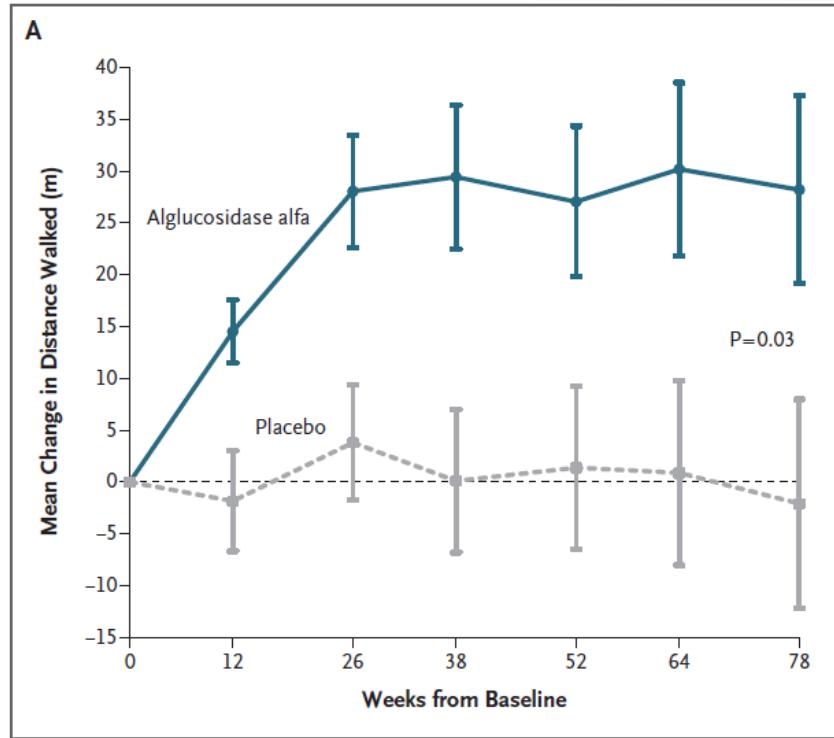


Figura 5

ORIGINAL ARTICLE

## A Randomized Study of Alglucosidase Alfa in Late-Onset Pompe's Disease

Ans T. van der Ploeg, M.D., Ph.D., Paula R. Clemens, M.D., Deyanira Corzo, M.D.,  
Diana M. Escolar, M.D., Julaine Florence, P.T., D.P.T.,  
Geert Jan Groeneveld, M.D., Ph.D., Serge Herson, M.D., Priya S. Kishnani, M.D.,  
Pascal Laforet, M.D., Stephen L. Lake, Sc.D., Dale J. Lange, M.D.,  
Robert T. Leshner, M.D., Jill E. Mayhew, P.T., Claire Morgan, M.D., M.P.H.,  
Kenkichi Nozaki, M.D., Ph.D., Dorothy J. Park, M.D., Alan Pestronk, M.D.,  
Barry Rosenbloom, M.D., Alison Skrinar, M.P.H., Carine I. van Capelle, M.D.,  
Nadine A. van der Beek, M.D., Melissa Wasserstein, M.D.,  
and Sasa A. Zivkovic, M.D., Ph.D.



**Figure 1.** Changes from Baseline in Distance Walked and in Forced Vital Capacity, According to Study Group.



cintura pelviana:  
gluteos  
isquiotibiales

Musculos axiales  
abdominales  
paravertebrales

escoliosis  
espina rigida



lengua

COMPROMISO  
RESPIRATORIO

Sintomas precoces:  
fatiga  
intolerancia al ejercicio

Hallazgos "raros:"

Ptoxis

Mialgias

Facial

Dolor lumbar

Aneurisma

Hipoacusia

Espina Rigida

## Conclusión

- el diagnóstico de las LGMD, entre ellas la Enfermedad de Pompe, es **difícil** y es difícil determinar **si el peregrino es el paciente o el médico tratante**
- desarrollo de **nuevas terapias** : diferenciar de entidades tratables inmunomediadas o no de las No tratables
- trabajo **multidisciplinario** tanto para el diagnóstico como para el tratamiento
- uso racional de los **métodos diagnósticos** disponibles en su medio
- requiere **conocimiento** de las enfermedades neuromusculares: **programas educativos**

Servicio de Neurología

Sección de Enfermedades  
Neuromusculares

Dr. Marcelo Rugiero

Dra. Mariela Bettini

Dr. Omar Gerardi

Dra. Carolina Azcona

Dra. Lucila Lecchini

Anatomía Patológica: Dra. Silvia Christiansen

Imágenes\_: Dr. Alejandro Rassumoff

Neumonología: Dr. Hernán Benito

Dr. Rodrigo Castro

ORL/deglucion\_: Dr. Federico Sala

Kinesiología : Lic. Mayra Reinoso

Lic. Nicolás Roux

Laboratorio: Dra. Patricia Sorroche





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