



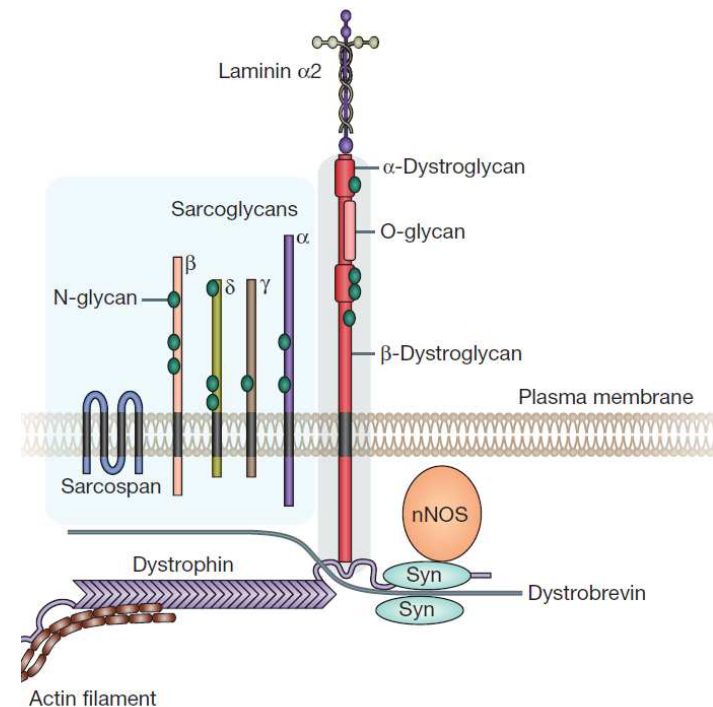
Hospital Universitario
12 de Octubre



DISTROGLICANOPATÍAS

Ana Camacho

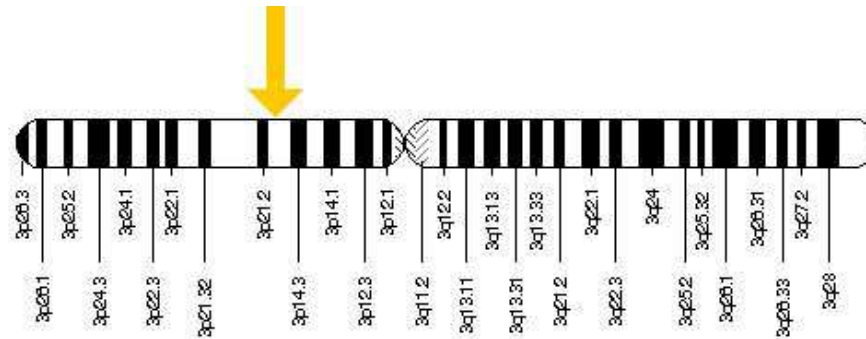
Sección de Neurología Infantil



OBJETIVOS

- Concepto
- Clasificación (siglas)
- Epidemiología
- Claves diagnósticas
- Fenotipos
- Genes
- Tratamiento

gen DAG1



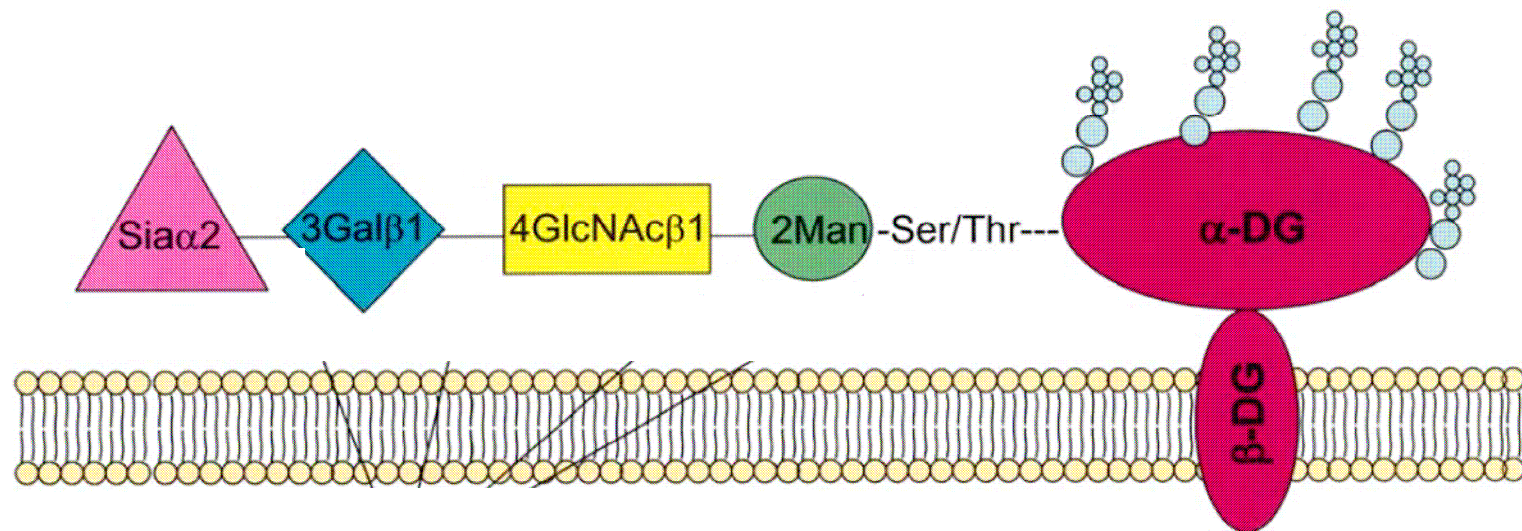
distroglicano

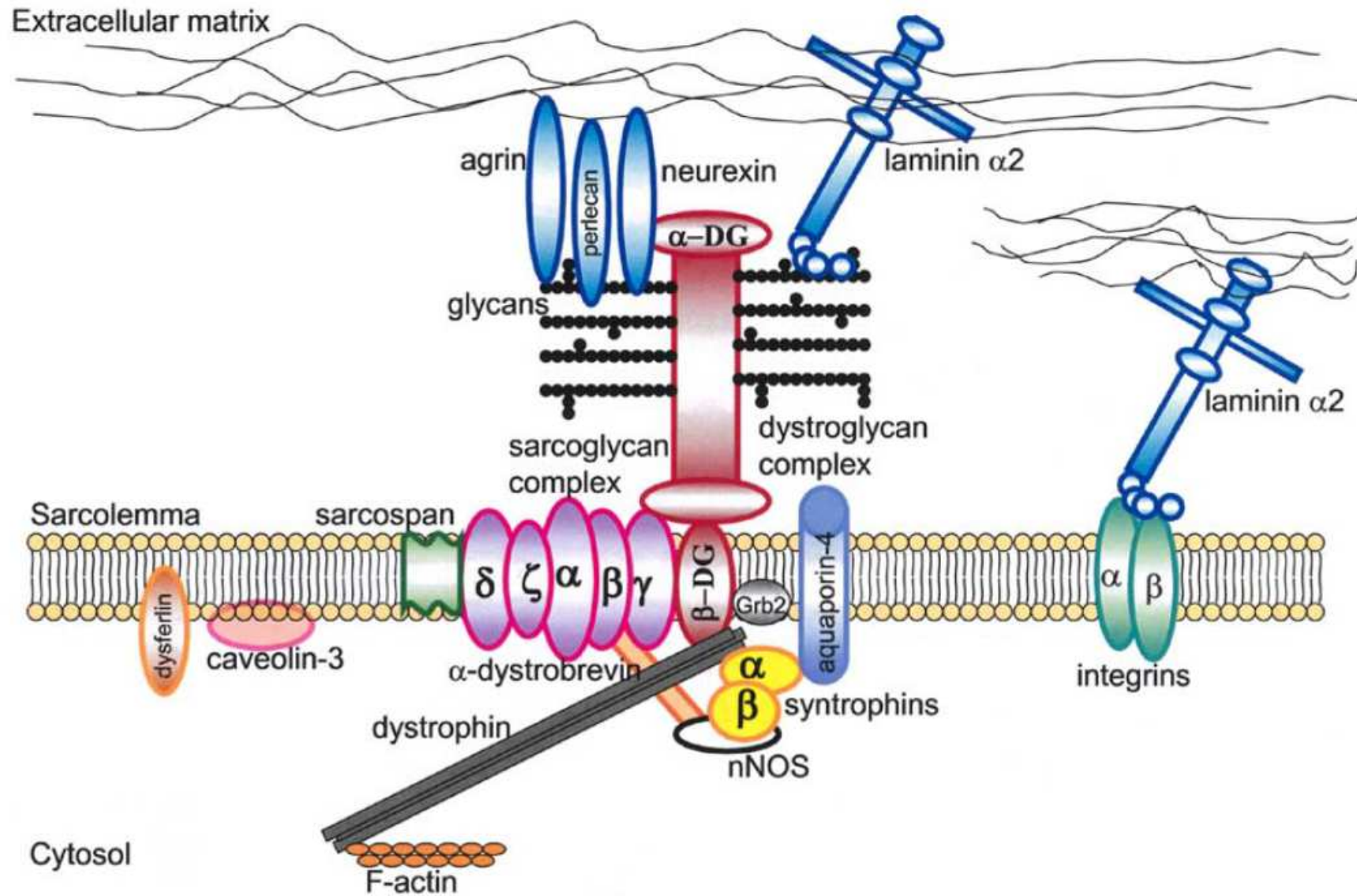
β -distroglicano

α -distroglicano

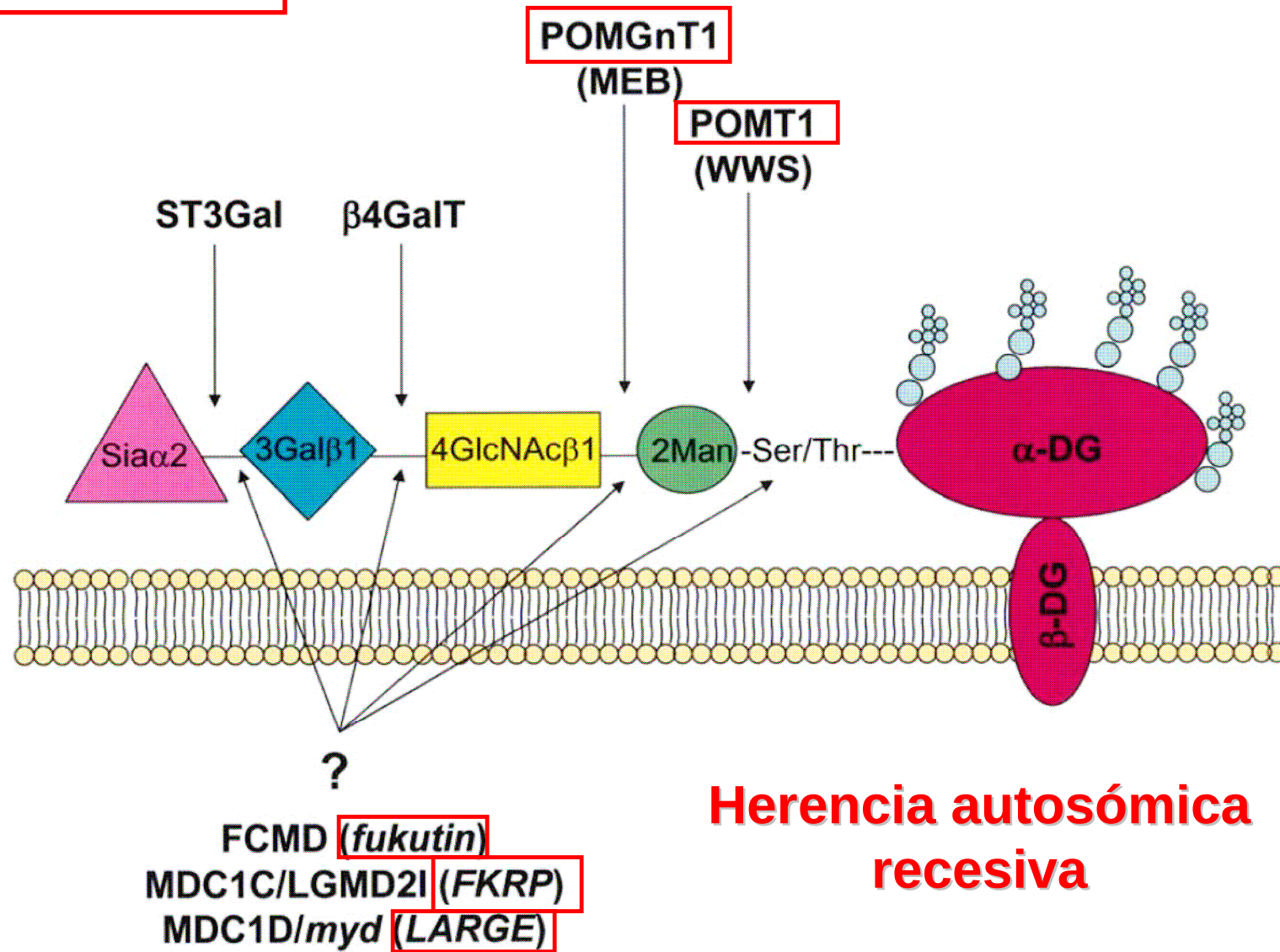
120-180kD

O-glicosilación



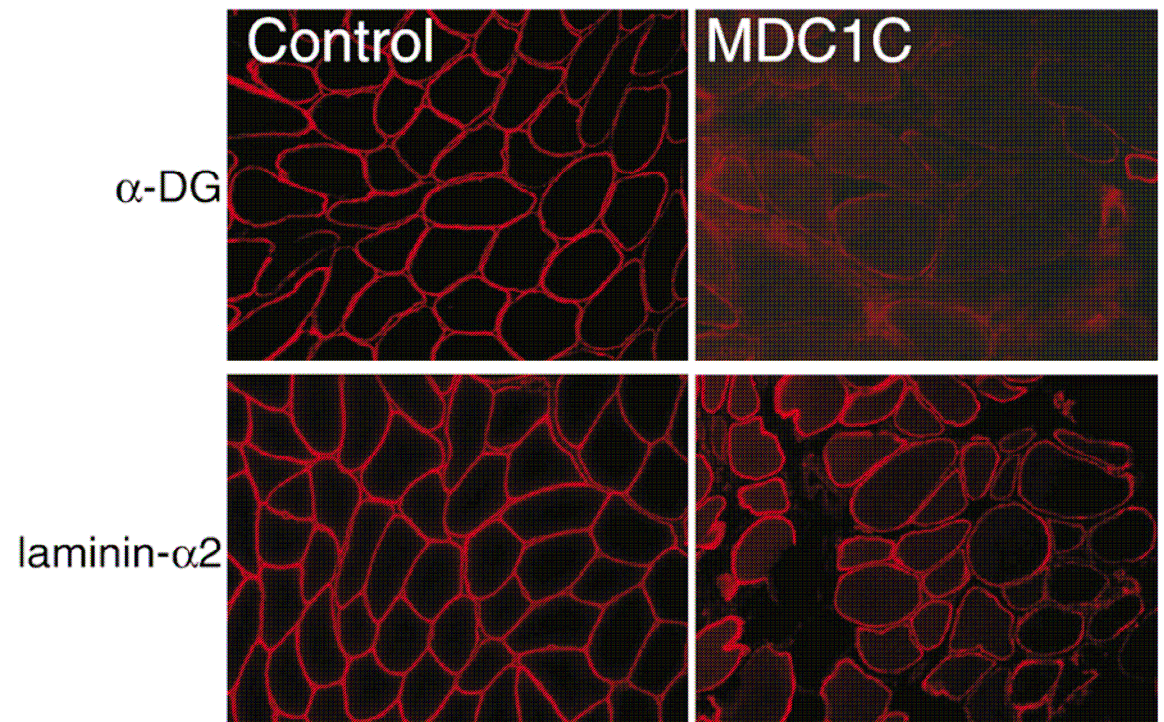
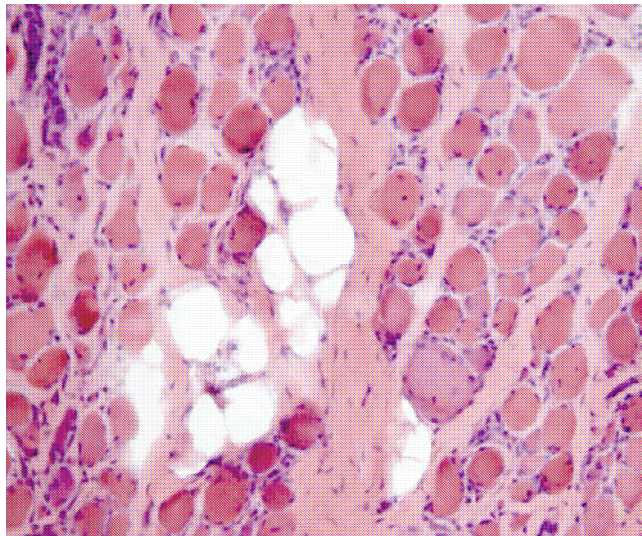


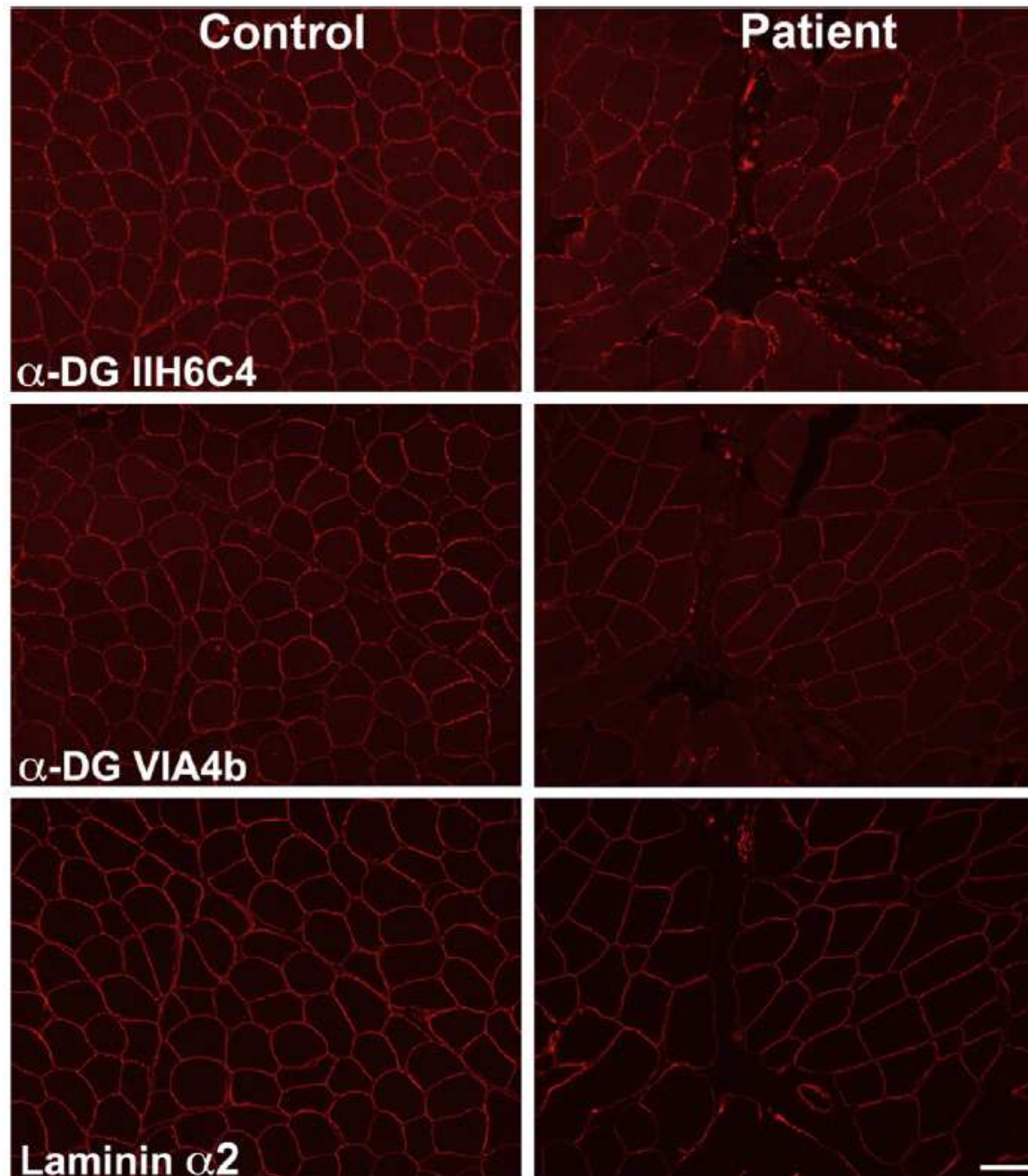
O-glicosilación



Dystroglicanopatías: biopsia muscular

- HE: patrón distrófico
- IHQ: depleción de alfa-DG glicosilado (y laminina $\alpha 2$)
 - IIH6
 - V1A4
- WB





Alfa-distroglicano se localiza en:

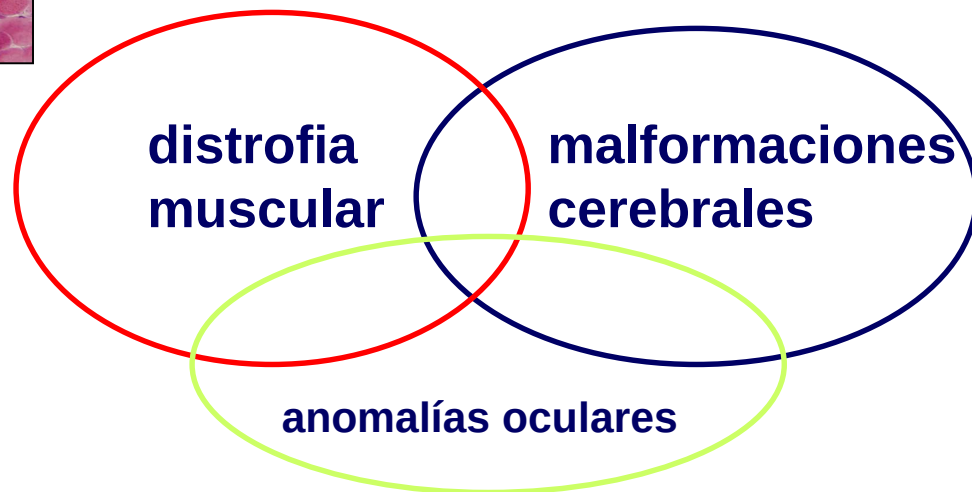
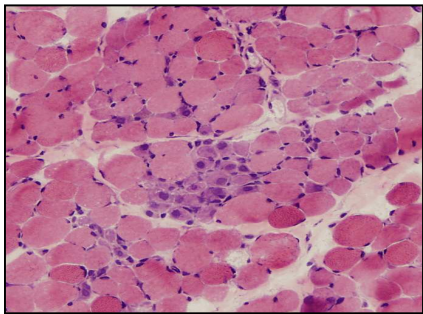
- Músculo
- Cerebro
- Retina
- Cóclea
- Célula de Schwann
- Epitelio

Morfogénesis

Transducción de señales

Sinaptogénesis

Distroglicanopatías



- retraso mental
- epilepsia
- espasticidad

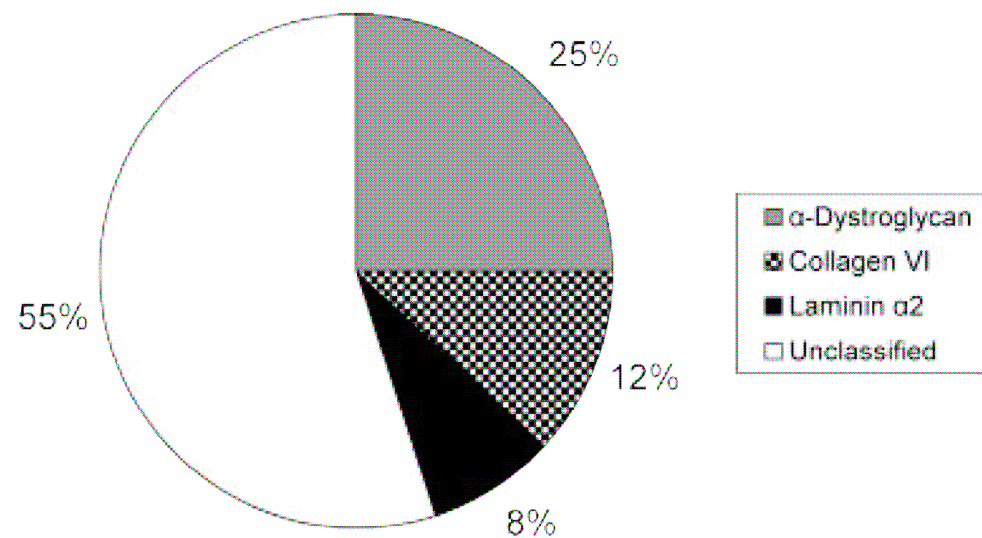


Frecuencia: CMD

Australia

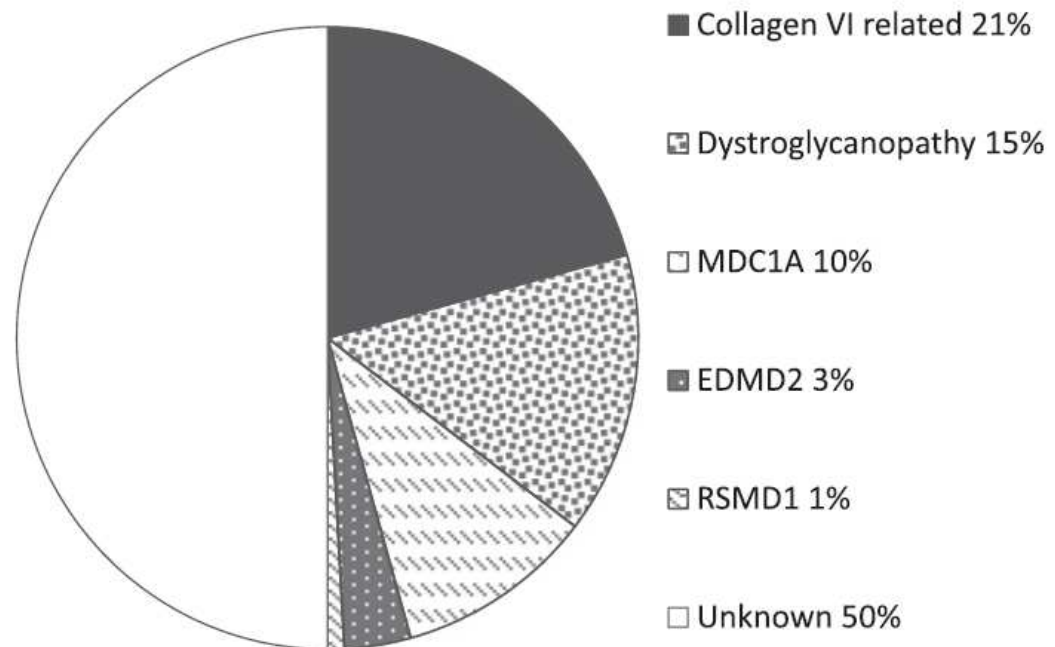
Figure 1

Classification of patients with congenital muscular dystrophy (CMD)



Frecuencia: CMD

Reino Unido



Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population



LGMD2A-calpaína 26.5%

LGMD2I-FKRP 19.1%

Sarcoglicanos 11.7%

LGMD1C 1.3%

▪

▪

▪

No clasificado 27.9%

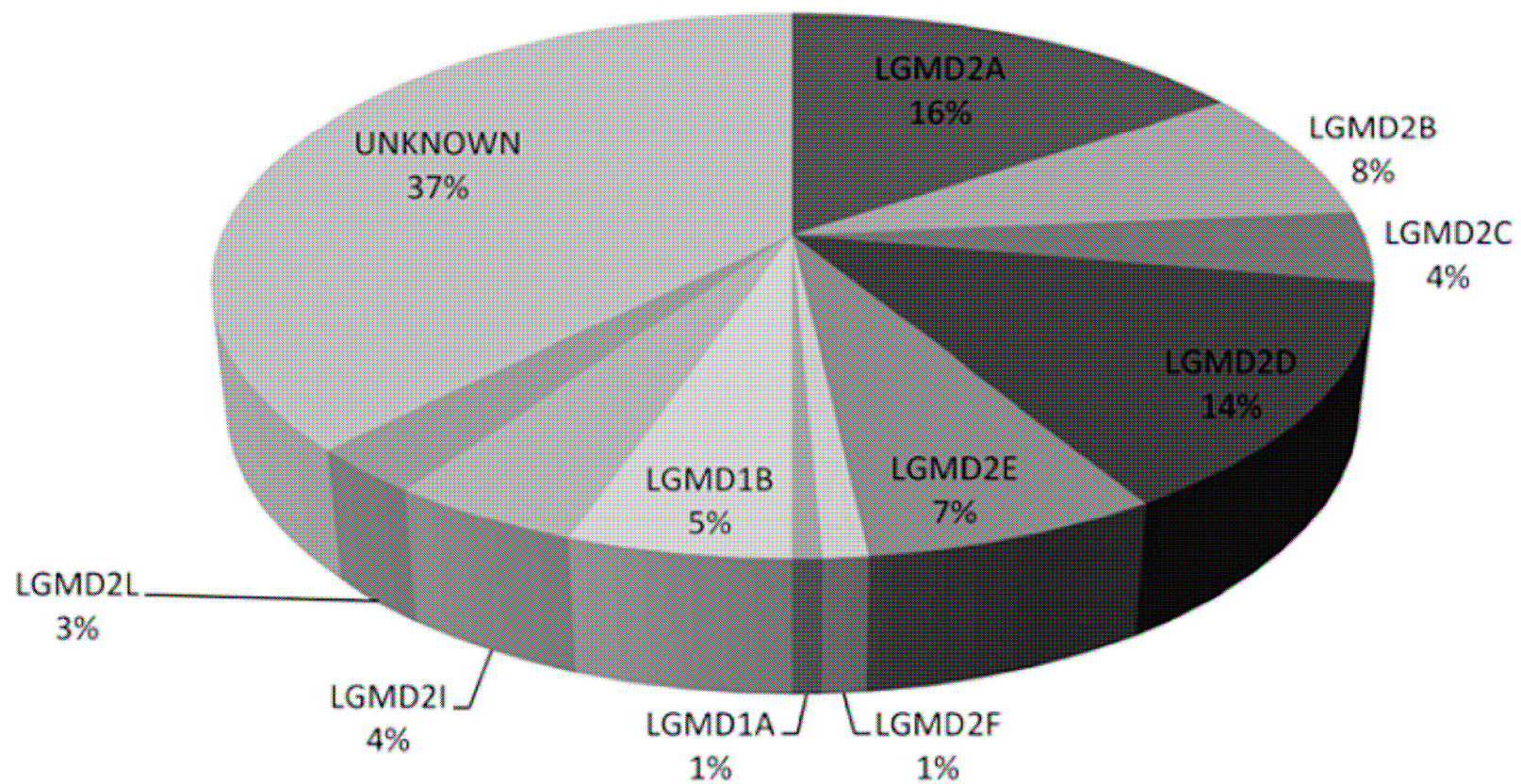


Figure 5. Frequency of various types of limb-girdle muscular dystrophy in the North American population. LGMD, limb-girdle muscular dystrophy.

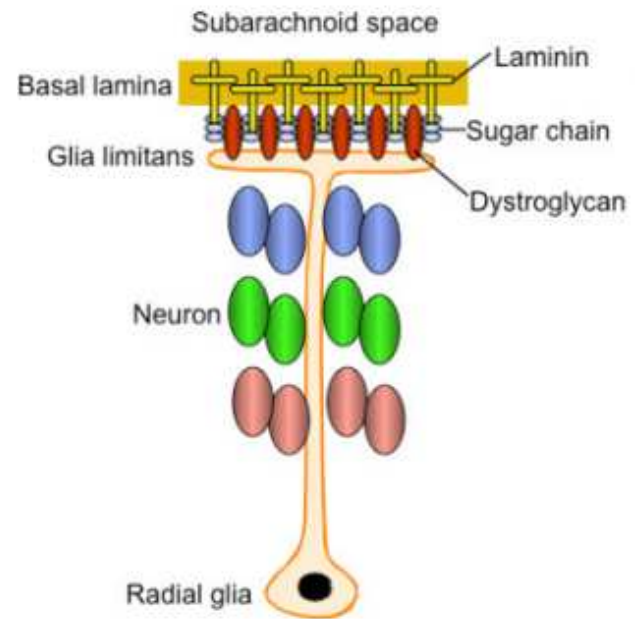
Distroglicanopatías: MÚSCULO

	Distrofia muscular congénita	Distrofia de cinturas
Función motora	raramente se adquiere la marcha	marcha adquirida; curso variable
Debilidad	proximal>distal	proximal>distal
Cardiopatía	no frecuente	++
Afectación respiratoria	+	+(+)
Curso	lentamente progresivo	progresivo
CK	↑↑↑	↑↑↑

Distroglicanopatías: CEREBRO

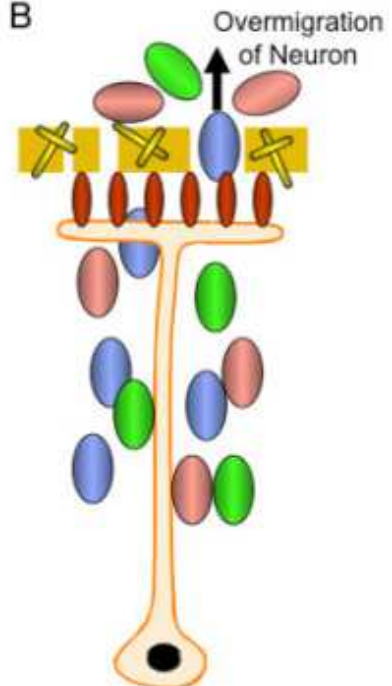
- Lisencefalia tipo cobblestone
- Paquigiria/polimicrogiria (anterior>posterior)
- Doble córtex
- Hidrocefalia
- Encefalocele posterior
- Hipoplasia de tronco con tectum prominente
- Hipoplasia cerebelosa
- Quistes cerebelosos
- Alteración de señal de sustancia blanca

A



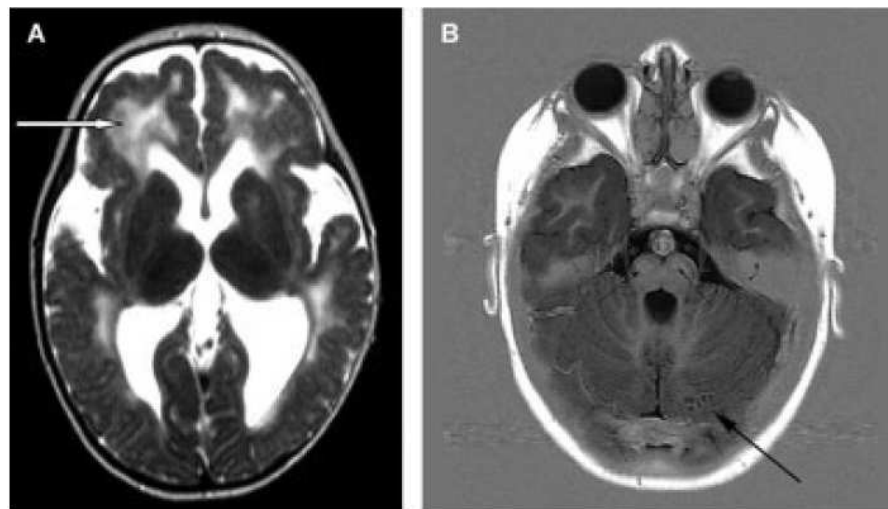
normal

B

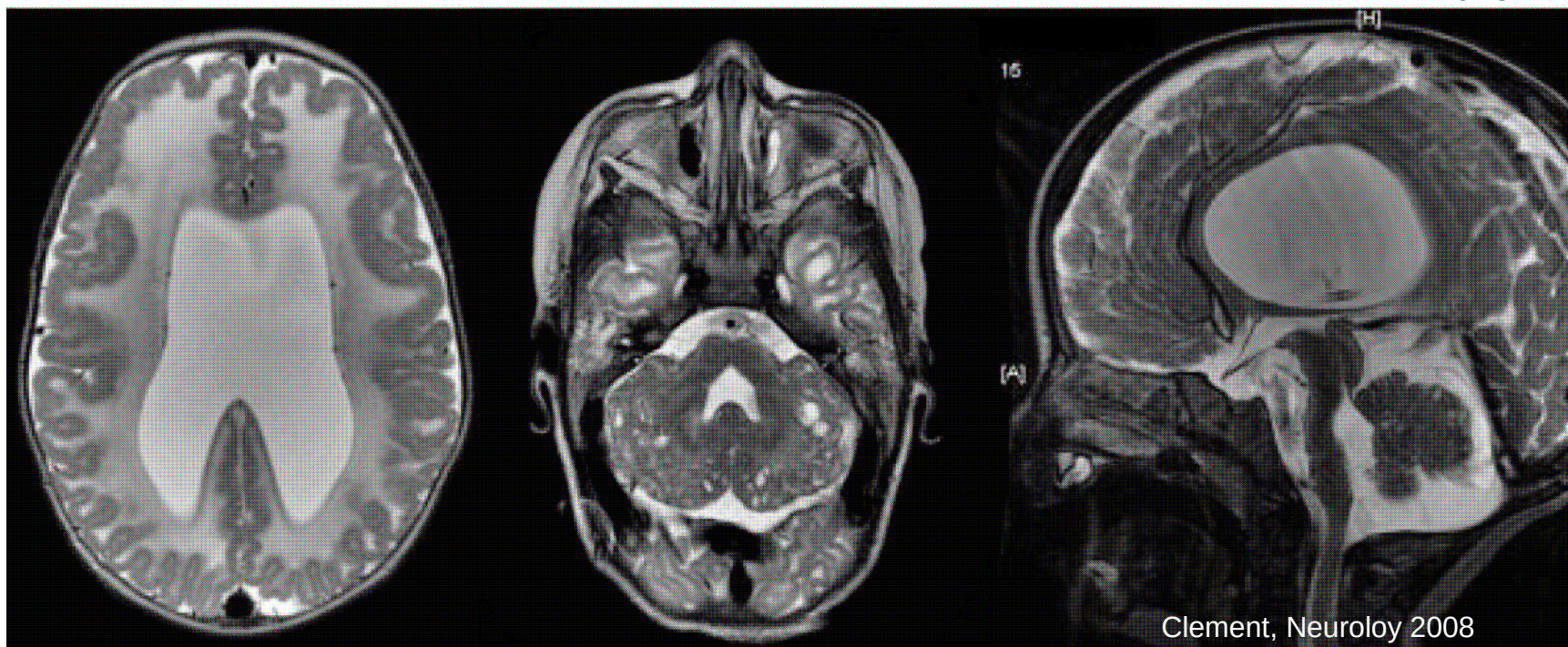
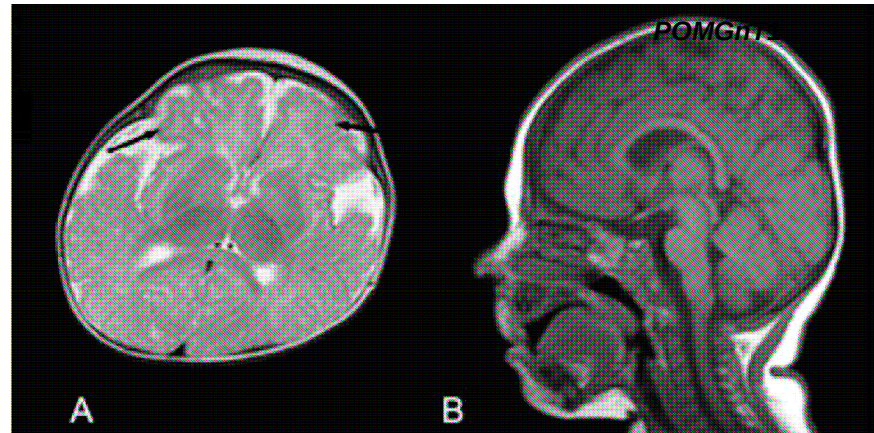


lissencephaly
cobblestone

POMGnT1



POMT1



Distroglicanopatías: OJO

- Microftalmia
- Miopía
- Cataratas
- Glaucoma
- Persistencia del vítro primario
- Desprendimiento de retina
- Atrofia óptica

	Distrofia muscular congénita	Distrofia de cinturas
Función motora	raramente se adquiere la marcha	marcha adquirida; curso variable
Debilidad	m. superiores> inferiores	proximal>distal
Cardiopatía	no frecuente	++
Afectación respiratoria	+	+(+)
Curso	lentamente progresivo	progresivo
CK	↑↑↑	↑↑↑
Otros signos	malformaciones cerebrales frecuentes; posibles anomalías oculares	algún caso con retraso mental

Fenotipos



PERGAMON

Neuromuscular Disorders 14 (2004) 635–649



www.elsevier.com/locate/nmd

Review

The congenital muscular dystrophies in 2004: a century of exciting progress

Francesco Muntoni^{a,*}, Thomas Voit^b

^a*Department of Paediatrics and Neonatal, Dubowitz Neuromuscular Unit, Imperial College School of Medicine, Hammersmith Hospital Campus,
Du Cane Road, London W12 0NN, UK*

^b*Department of Pediatrics and Pediatric Neurology, University Hospital Essen, Hufelandstrasse 55, D-45122 Essen, Germany*

Received 18 April 2004; received in revised form 7 June 2004; accepted 8 June 2004

Fenotipos

Distrofia
muscular
congénita
(CMD)



Distrofia de
cinturas
(LGMD2)

Walker-
Warburg
(WWS)

POMT1
(*POMT2*)

Fukuyama
(FCMD)

FKTN

Músculo-ojo-cerebro
(MEB)

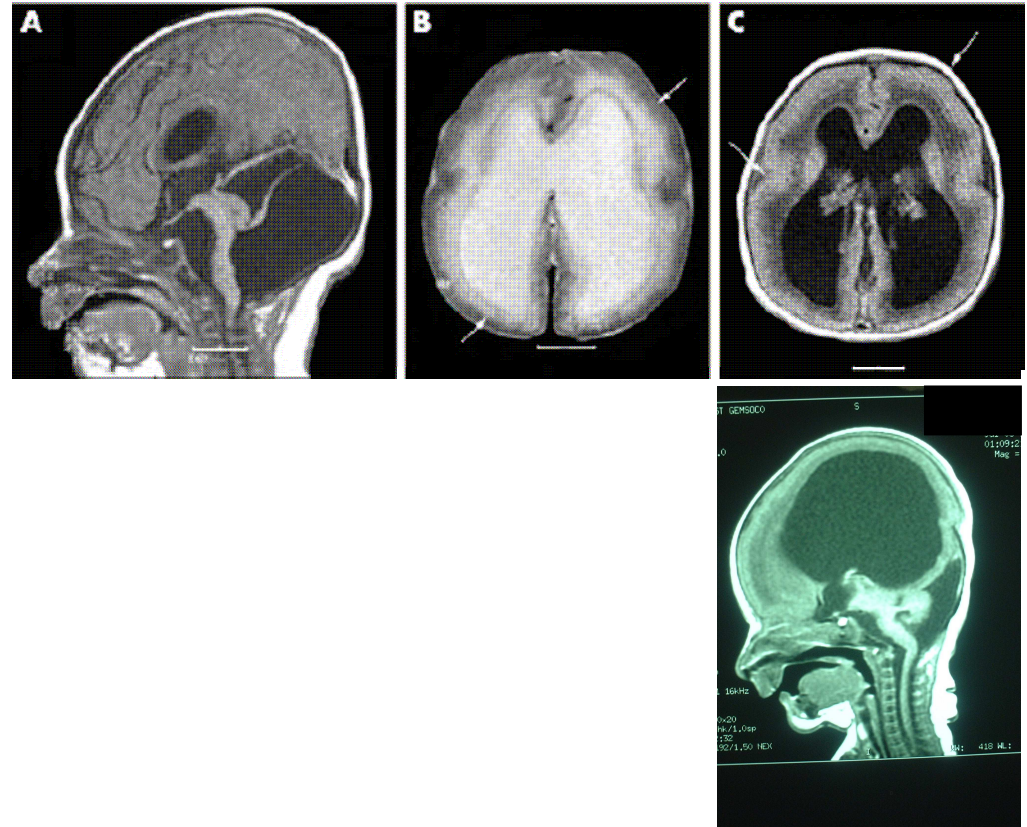
POMGnT



Walker-Warburg (WWS)

- 1942
- Gen **POMT1** (*fukutina* y *FKRP*)
- Fenotipo más grave
 - Lisencefalia, encefalocele, hidrocefalia
 - Malformación retiniana
 - Muerte precoz

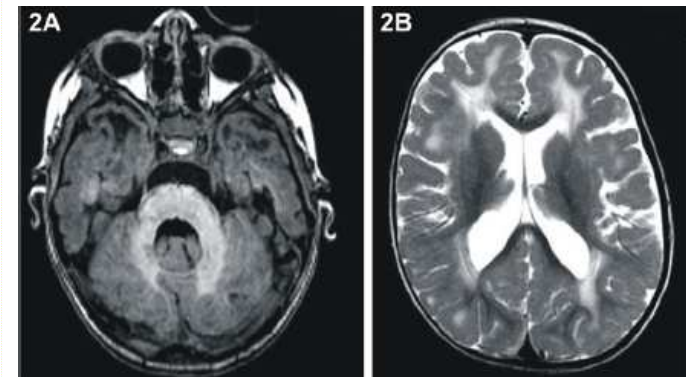
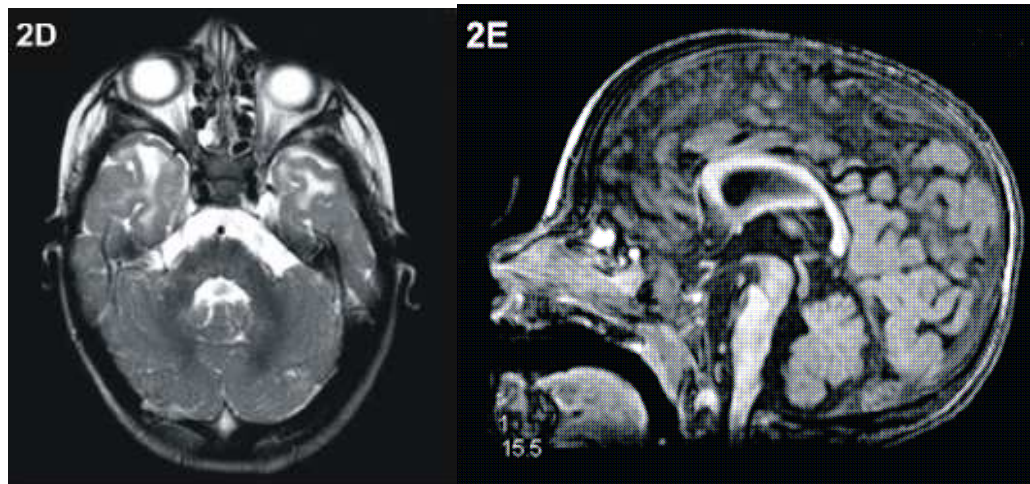
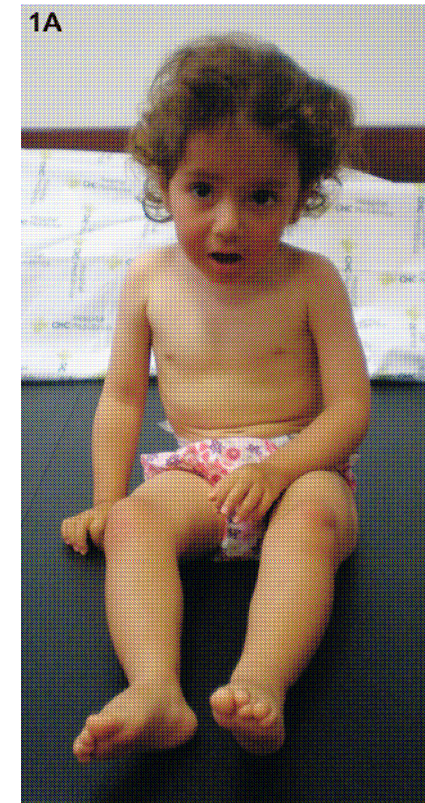
Beltrán Valero de Bernabé, J Med Genet 2004



Fukuyama

Costa, Neuromusc Disord 2013

- 1970
 - Japón 1:10.000 hab
 - Gen **FKTN** → fukutina
 - Mutación fundacional: inserción de 3kB en la región no codificante 3' de FKTN
 - Afectación motora grave
 - Retraso mental
 - Afectación ocular 50%
- +/- hipertrofia focal
+/- cardiopatía

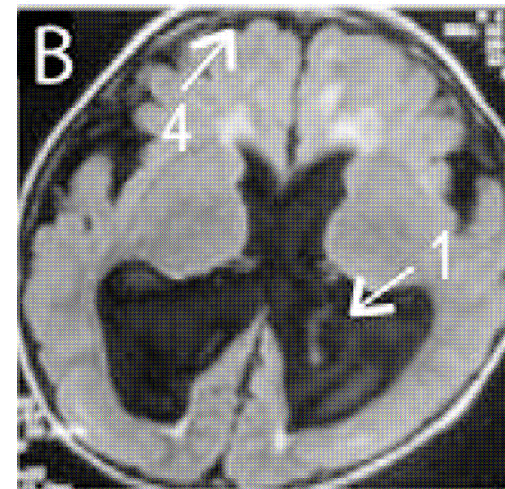
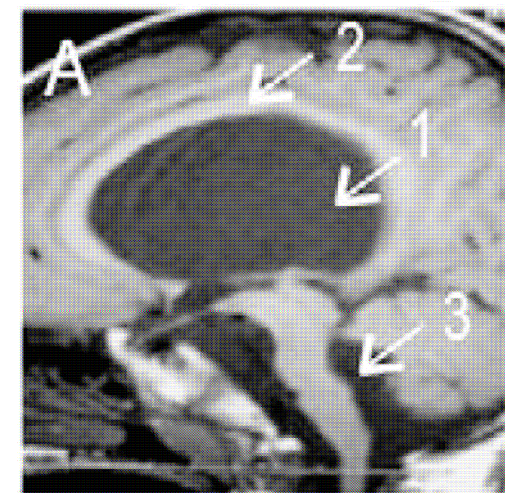


Enf. músculo-ojo-cerebro (MEB)

- 1977
- Santavuori, Finlandia 1:50.000
- Gen ***POMGnT1***
 - Afectación motora grave
 - Retraso mental
 - Ojos: miopía, glaucoma



Yis et al, Pediatr Neurol 2014



Raducu et al, J Child Neurol 2014

Fenotipos

Distrofia muscular congénita (MDC)



Distrofia de cinturas (LGMD2)

Walker-Warburg (WWS)

POMT1
POMT2

Fukuyama (FCMD)

FKTN

Músculo-ojo-cerebro (MEB)

POMGnT

MDC1D

LARGE

MDC1C

FKRP

FKRP



LGMD 2I

- Frecuente en norte de Europa (C826A)
- Gen ***FKRP***
 - Becker-like
 - Hipertrofia muscular:
 - pantorrillas
 - lengua
 - Afectación cardíaca
 - Afectación respiratoria (diafragma)

Inteligencia y RMN craneal normal

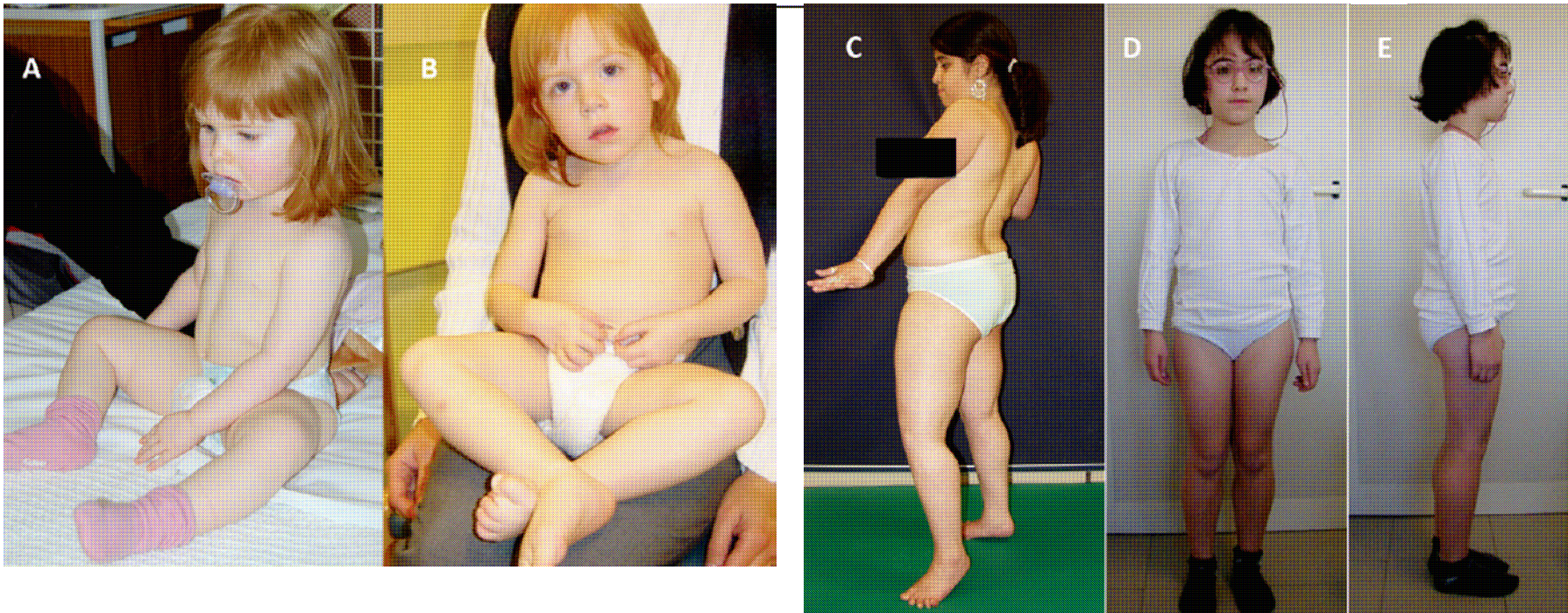


Complejidad genética

- Se han descrito más genes

ISPD gene mutations are a common cause of congenital and limb-girdle muscular dystrophies

Sebahattin Cirak,¹ Aileen Reghan Foley,¹ Ralf Herrmann,² Tobias Willer,^{3,4,5,6} Shu Yau,⁷ Elizabeth Stevens,¹ Silvia Torelli,¹ Lina Brodd,⁷ Alisa Kamynina,¹ Petr Vondracek,⁸ Helen Roper,⁹ Cheryl Longman,¹⁰ Rudolf Korinthenberg,¹¹ Gianni Marrosu,¹² Peter Nürnberg,¹³ UK10K Consortium,* Daniel E. Michele,¹⁴ Vincent Plagnol,¹⁵ Matt Hurles,¹⁶ Steven A. Moore,¹⁷ Caroline A. Sewry,^{1,18} Kevin P. Campbell,^{3,4,5,6} Thomas Voit¹⁹ and Francesco Muntoni¹



“Distrofia muscular + afectación estructural cerebelosa”

Complejidad genética

- Se han descrito más genes
- No hay clara correlación genotipo-fenotipo

The 2014 version of the gene table of monogenic neuromuscular disorders (nuclear genome)

Jean-Claude Kaplan^{a,*}, Dalil Hamroun^b

^a Institut Cochin, Université Paris Descartes, 27 Rue du Faubourg Saint Jacques, 75014 Paris, France

^b Centre Hospitalo-Universitaire de Montpellier, Hôpital Arnaud de Villeneuve, 34000 Montpellier, France

OMIM phenotypic classifications assigned in 2010: Muscular dystrophy-dystroglycanopathy (MDDG)		
A- congenital with brain and eye abnormalities	B- congenital with / without mental retardation	C- limb-girdle

LGMD2: autosómico recesivo

Subtipo	Proteína	Locus
2A	CAPN3 (Calpaina-3)	15q15.1
2B	DYSF (Disferlina)	2p13
2C	SGCG (γ -Sarcoglicano)	13q12
2D	SGCA (α -Sarcoglicano)	17q21
2E	SGCB (β -Sarcoglicano)	4q12
2F	SGCD (δ -Sarcoglicano)	5q33
2G	TCAP	17q12
2H	TRIM32	9q31
2I	FKRP	19q13.3
2J	TTN	2q24
2K	POMT1	9q34
2L	ANO5	11p13
2M	Fukutina	9q31
2N	POMT2	14q24
2O	POMGnT1	1p34
2Q	PLEC	8q24
2R	DESM	2q35
2S	TRAPPC11	4q35.1
2T (MDDGC14)	GMPPB	3p21.31
	DAG1	3p21
	DPM3	1q22
	ISPD	7p21.22

2013 →

2013 →

Deficiency of Dol-P-Man Synthase Subunit DPM3 Bridges the Congenital Disorders of Glycosylation with the Dystroglycanopathies

N-glicosilación

Dirk J. Lefeber,^{1,15,*} Johannes Schönberger,^{6,15} Eva Morava,² Mailys Guillard,¹ Karin M. Huyben,¹ Kiek Verrijp,³ Olga Grafakou,⁷ Athanasios Evangeliou,⁸ Frank W. Preijers,⁴ Panagiota Manta,⁹ Jef Yildiz,¹ Stephanie Grünewald,¹⁰ Martha Spilioti,¹¹ Christa van den Elzen,⁵ Dominique Klein,¹² Daniel Hess,¹² Hisashi Ashida,¹³ Jan Hofsteenge,¹² Yusuke Maeda,¹⁴ Lambert van den Heuvel,¹ Martin Lammens,³ Ludwig Lehle,⁶ and Ron A. Wevers¹

The American Journal of Human Genetics 85, 76–86, July 10, 2009

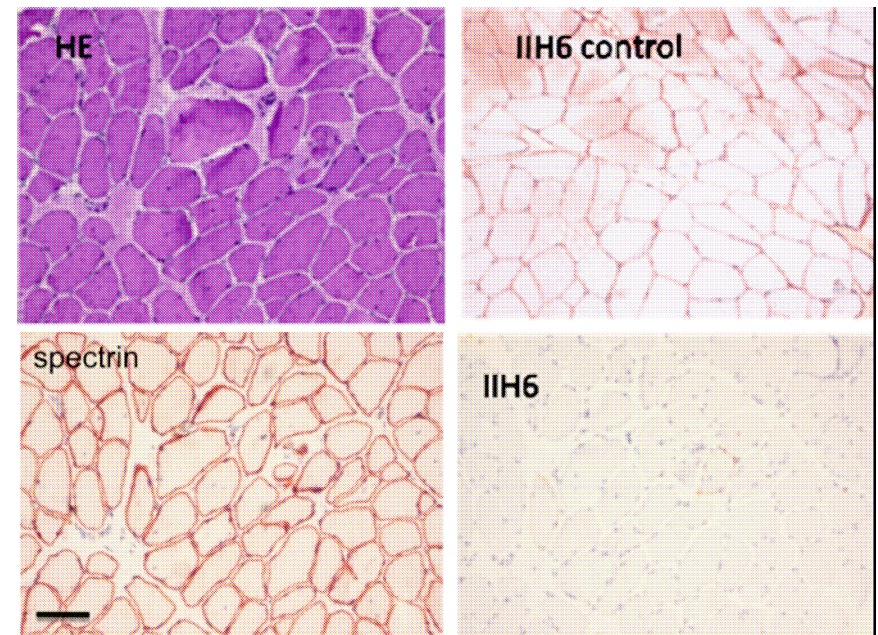
Mujer

- 11 años: debilidad leve
- 20 años: miocardiopatía dilatada
- 21 años: ictus
- 27 años: CI normal (RMN craneal N)

Bx muscular: distrofia muscular moderada

CPK: 1.500-3.000U/l

CDT: patrón anormal CDG tipo I



A Dystroglycan Mutation Associated with Limb-Girdle Muscular Dystrophy

DAG1

Yuji Hara, Ph.D., Burcu Balci-Hayta, Ph.D., Takako Yoshida-Moriguchi, Ph.D.,
Motoi Kanagawa, Ph.D., Daniel Beltrán-Valero de Bernabé, Ph.D.,
Hülya Gündeşli, M.S., Tobias Willer, Ph.D., Jakob S. Satz, Ph.D.,
Robert W. Crawford, B.S., Steven J. Burden, Ph.D., Stefan Kunz, Ph.D.,
Michael B.A. Oldstone, M.D., Ph.D., Alessio Accardi, Ph.D., Beril Talim, M.D.,
Francesco Muntoni, M.D., Haluk Topaloğlu, M.D., Pervin Dinçer, Ph.D.,
and Kevin P. Campbell, Ph.D.

Mujer

N Engl J Med 2011;364:939-46.

-3 años: debilidad en MMII

-Hipertrofia gemelar, contracturas aquíleas e hiperlordosis

-16 años: camina 20 m

-CI 50

CPK: 4.133 U/l

RMN craneal normal

Complejidad genética

- Se han descrito más genes
- No hay clara correlación genotipo-fenotipo
- Genes implicados en la N-glicosilación
- Gen DAG1 (dystroglycanopathy primaria)
- Pacientes sin diagnóstico (50%)

Complejidad genética

O-glicosilación

POMT1

POMT2

POMGnT1

FKRP

FKTN

LARGE

ISPD

GTDC2

B3GALNT2

B3GNT1

TMEM5

GMPPB

SGK196

34-53%

N-glicosilación

DPM1

DPM2

DPM3

DOLK

Distroglicanopatía primaria

DAG1

Distroglicanopatías: Cómo orientar el diagnóstico genético

¿Panel de secuenciación masiva?

Molecular diagnosis of congenital muscular dystrophies with defective glycosylation of alpha-dystroglycan using next-generation sequencing technology

Byung Chan Lim^{a,1}, Seungbok Lee^{b,c,1}, Jong-Yeon Shin^b, Hee Hwang^a, Ki Joong Kim^a,
Yong Seung Hwang^a, Jeong-Sun Seo^{b,c,d,f}, Jong-Il Kim^{b,c,e,f,*}, Jong Hee Chae^{a,*}

N=4 sin mutación en *fukutin*

NGS: *POMT1*, *POMT2*, *POMGnT1*, *FKRP*, *FKTN*, *LARGE*

2/4 *POMGnT1*

Problemas de cobertura → Sanger

Distroglicanopatías: Cómo orientar el diagnóstico genético

¿Biopsia muscular?

RESEARCH ARTICLE

A Comparative Study of α -Dystroglycan Glycosylation in Dystroglycanopathies Suggests that the Hypoglycosylation of α -Dystroglycan Does Not Consistently Correlate with Clinical Severity

Cecilia Jimenez-Mallebrera¹; Silvia Torelli¹; Lucy Feng¹; Jihee Kim¹; Caroline Godfrey¹; Emma Clement¹; Rachael Mein²; Stephen Abbs²; Susan C. Brown^{1,7}; Kevin P. Campbell³; Stephan Kröger⁴; Beril Talim⁵; Haluk Topaloglu¹⁰; Ros Quinlivan⁶; Helen Roper⁸; Anne M. Childs⁹; Maria Kinali¹; Caroline A. Sewry^{1,6}; Francesco Muntoni¹

¹ Dubowitz Neuromuscular Centre, Institute of Child Health and Great Ormond Street Hospital for Children, UCL, London, UK.

² DNA Laboratory, Genetics Centre, Guy's Hospital, London, UK.

³ Howard Hughes Medical Institute, Department of Molecular Physiology and Biophysics, Internal Medicine and Neurology, University of Iowa Carver College of Medicine, Iowa City, Ia.

⁴ Physiological Institute, Ludwig-Maximilians-University, Munich, Germany.

⁵ Department of Paediatric Pathology, Hacettepe Children's Hospital, Ankara, Turkey.

⁶ Wolfson Centre for Inherited Neuromuscular Diseases, Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, UK.

⁷ Division of Neurosciences, Imperial College London, London, UK.

⁸ Department of Paediatrics, Birmingham Heartlands Hospital, Birmingham, UK.

⁹ Department of Paediatric Neurosciences, Leeds General Infirmary, Leeds, UK.

¹⁰ Child Neurology Unit, Department of Pediatrics, Hacettepe University, Ankara, Turkey.

N=24

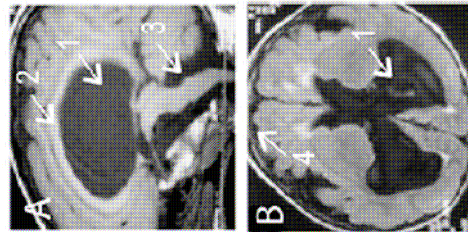
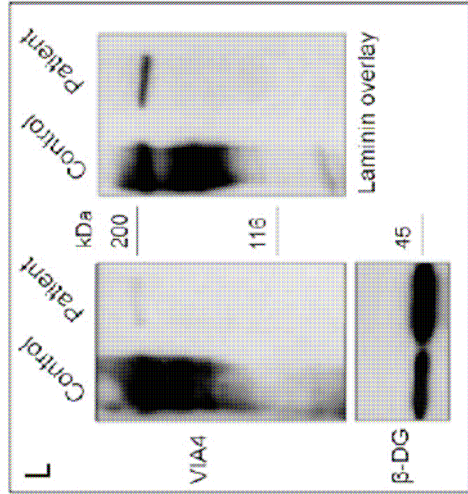
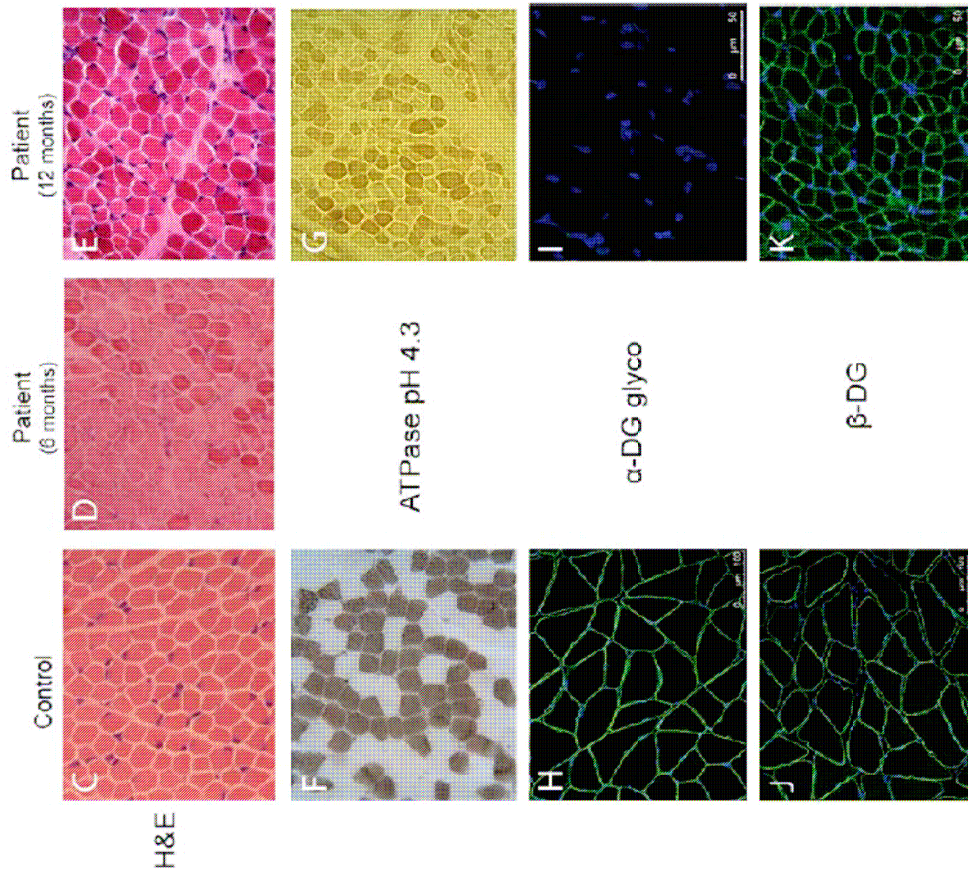
Buena correlación: *POMT1*, *POMT2*, *POMGnT1*

No correlación *FKRP*, *FKTN*

Clinical Features and Molecular Characterization of a Patient With Muscle-Eye-Brain Disease: A Novel Mutation in the *POMGNT1* Gene

Madalina Raducu, PhD¹, Rocío P. Cotarelo, PhD¹, Rogelio Simón, MD², Ana Camacho, MD², Marcos Rubio-Fernández, MS¹, Aurelio Hernández-Lain, MD³, and Jesús Cruces, PhD¹

Journal of Child Neurology
2014, Vol. 29(2) 289-294

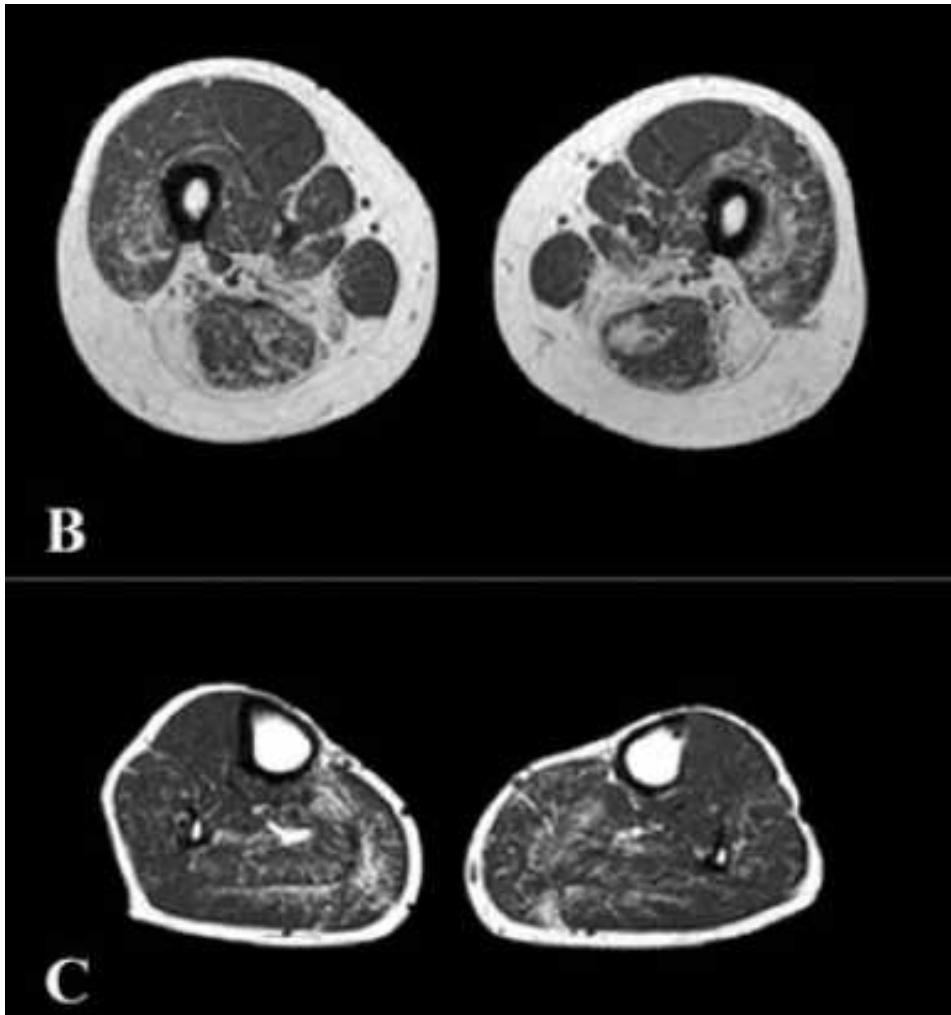


Distroglicanopatías: Cómo orientar el diagnóstico genético

¿RMN muscular?

LGMD 2I: FKRP

RMN



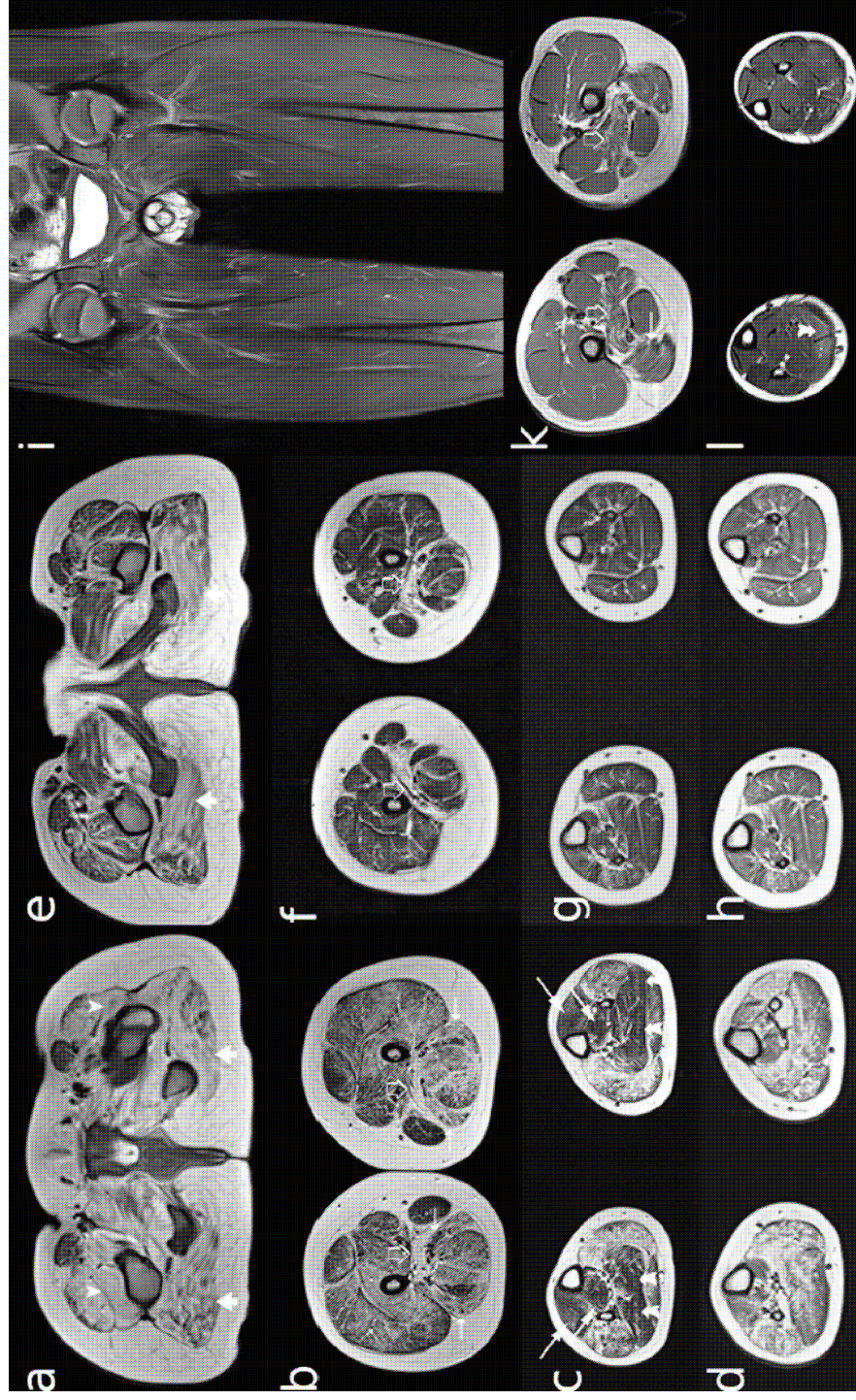
compartimento
posterior
adductor
bíceps femoral

(gemelo interno
sóleo)

Case report

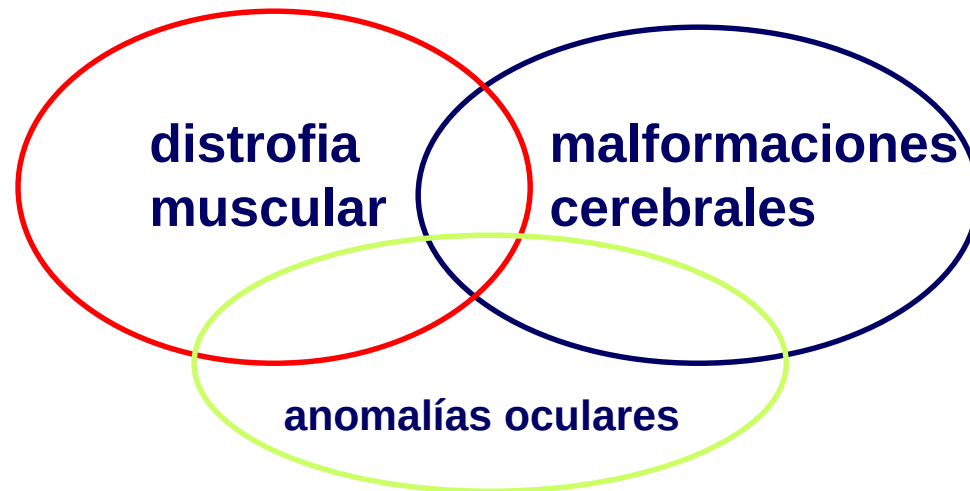
Skeletal muscle MRI of the lower limbs in congenital muscular dystrophy patients with novel *POMT1* and *POMT2* mutations

Patricia Hafner^{a,b,1}, Ulrike Bonati^{a,b,*}, Arne Fischmann^c, Jacques Schneider^d,
Stephan Frank^e, Deborah J. Morris-Rosendahl^f, Anamaria Dumea^g, Karl Heinemann^g,
Dirk Fischer^{a,b,*}



Distroglicanopatías: Cómo orientar el diagnóstico genético

Fenotipo



Orientación genética por fenotipo

Table II

Phenotypes associated with mutations in the causative dystroglycanopathy genes

	Dystroglycanopathy core phenotypic categories proposed by Godfrey et al 2007						
	Congenital muscular dystrophy (CMD)					Limb girdle muscular dystrophy (LGMD)	
	WWS/ WWS-like	MEB/ FCMD-like	CMD CRB	CMD MR	CMD no MR	LGMD MR	LGMD no MR
<i>POMT1</i>	(LGMD2K)						
<i>POMT2</i>						(LGMD2N)	
<i>POMGNT1</i>							†
<i>FKTN</i>							(LGMD2M)
<i>FKRP</i>	(MDC1C)						(LGMD2I)
<i>LARGE</i>	(MDC1D)						
<i>DPM2</i>	- - - - - *						
<i>DPM3</i>	- - - - - **						

Godfrey et al, Curr Opin Genet Dev 2011

Orientación genética por fenotipo

- En función de la geografía/etnia:
 - MEB + Finlandia: **POMGnT1** (mut. fundacional)
 - WWS + Ashkenazi: **FKTN** (mut. fundacional)
 - MEB-like + Japón: **FKTN** (mut. fundacional retrotransposón)

Orientación genética por fenotipo

- WWS: ***POMT1, POMT2***
- MEB-like + quistes cerebelosos +/- macrocefalia: ***POMGnT1, FKRP, FKTN, LARGE***
- CMD + hipoplasia cerebelosa pura: ***ISPD***
- CMD/LGMD + inteligencia normal, +/- cardiomiopatía: ***FKRP, FKTN*** (no mutación japonesa), ***ISDP***
- CMD+ retraso mental+microcefalia y RM normal: ***POMT1***
POMT2

TRATAMIENTO

- Fisioterapia
- Cirugía ortopédica
- Cardiología
- Neumología
- ¿Corticoides?
 - LGMD2I-FKRP *Darin, Eur J Paediatr Neurol 2007*
- Futuro: sobreexpresión de LARGE (LARGE^{myd})

Barresi, Nat Med 2004

Reflexiones finales

- Grupo de enfermedades en expansión
- Nuevos fenotipos
- Nuevos genes
- Nuevas clasificaciones