Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Guido Primiano

Miopatie

Novità sull'argomento

Riunione Neurologi in Formazione
La richiesta di competenza neurologica nel prossimo futuro
Terza edizione, Roma 2019

Istituto di Neurologia
Fondazione Policlinico universitario A. Gemelli IRCCS/UCSC, Roma

Gemelli

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Novità in ambito <u>diagnostico</u>

European Reference Network
for rare or low prevalence complex diseases
Network Neuromuscular Diseases (ERN EURO-NMD)

EURO-NMD NEUROMUSCULAR PATHOLOGY WORKING GROUP

Recommended Standards for Muscle Biopsies; to be used by all partner laboratories

Routine stains for all new biopsies (frozen tissue)

Recommended extended methods – context dependent

- ***Muscular dystrophy, congenital and progressive myopathies***
- ***Immune mediated myopathies***
- ***Vacuolar and protein aggregate myopathies***
- ***Congenital myopathies***
- ***Mitochondrial myopathies***
- ***Toxic myopathies***
- ***Ion channel myopathies***
- ***Glycogenoses***
- ***High CK and exercise intolerance, cramps***
- ***Amyloid myopathy***
- ***Myopathies with affected neuromuscular junctions (NMJ)***

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Novità in ambito <u>diagnostico</u>

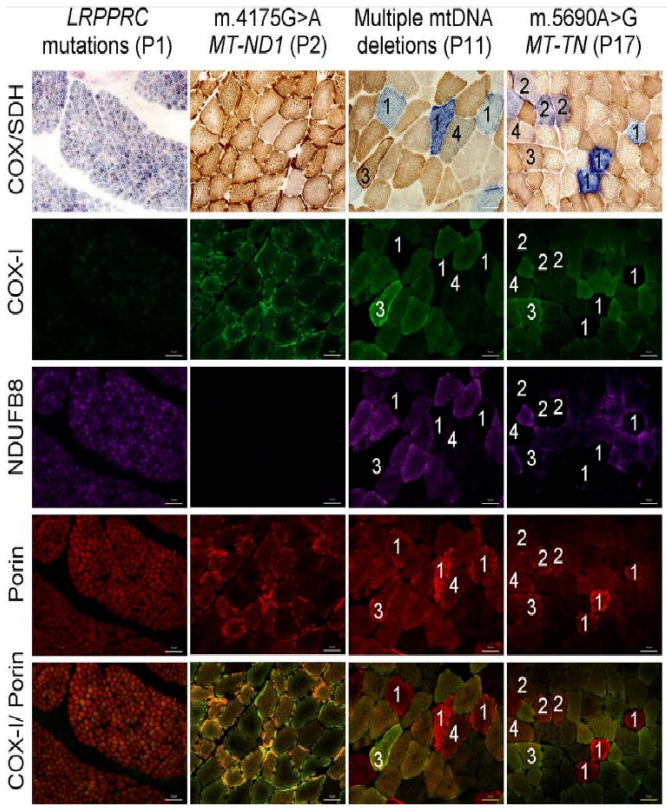
SCIENTIFIC REPORTS

OPEN

Received: 14 July 2015
Accepted: 04 September 2015
Published: 15 October 2015

A novel immunofluorescent assay to investigate oxidative phosphorylation deficiency in mitochondrial myopathy: understanding mechanisms and improving diagnosis

Mariana C. Rocha[1,2,*], John P. Grady[1,*], Anne Grünewald[3], Amy Vincent[1], Philip F. Dobson[1], Robert W. Taylor[1], Doug M. Turnbull[1,2] & Karolina A. Rygiel[1,2]



ELSEVIER

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Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 26 (2016) 691–701

NMD

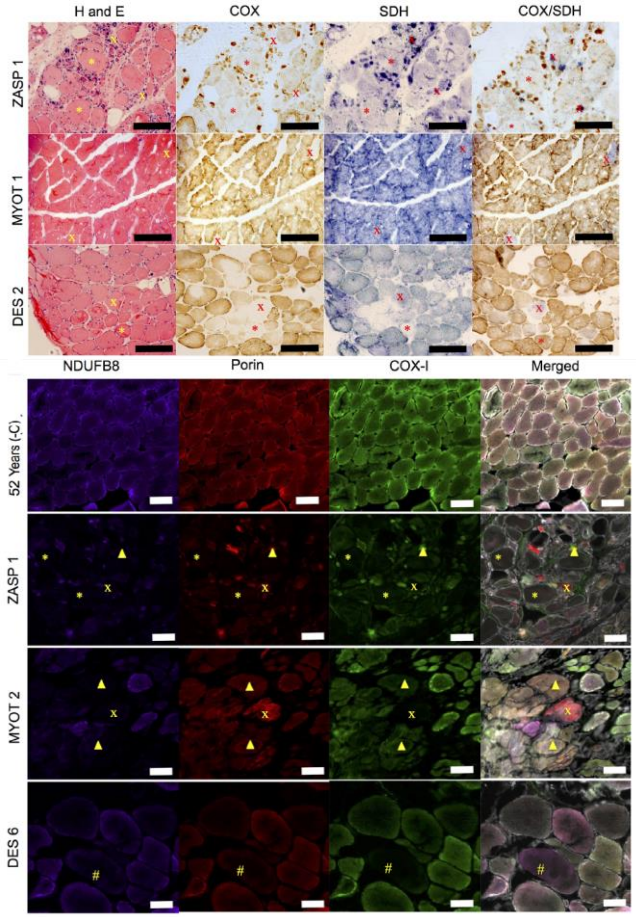
www.elsevier.com/locate/nmd

Mitochondrial dysfunction in myofibrillar myopathy

Amy E. Vincent [a], John P. Grady [a], Mariana C. Rocha [a], Charlotte L. Alston [a], Karolina A. Rygiel [a], Rita Barresi [b], Robert W. Taylor [a], Doug M. Turnbull [a,*]

[a] Wellcome Trust Centre for Mitochondrial Research, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK
[b] Rare Diseases Advisory Group Service for Neuromuscular Diseases, Muscle Immunoanalysis Unit, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, NE2 4AZ, UK

Received 6 April 2016; received in revised form 5 August 2016; accepted 9 August 2016



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Novità in ambito nosologico

Old name	Gene	Proposed new nomenclature	Reason for exclusion
LGMD 1A	*Myot*	Myofibrillar myopathy	Distal weakness
LGMD 1B	*LMNA*	Emery–Dreifuss muscular dystrophy (EDMD)	High risk of cardiac arrhythmias; EDMD phenotype
LGMD 1C	*CAV3*	Rippling muscle disease	Main clinical features rippling muscle disease and myalgia
LGMD 1D	*DNAJB6*	LGMD D1 DNAJB6-related	
LGMD 1E	*DES*	Myofibrillar myopathy	Primarily false linkage; distal weakness and cardiomyopathy
LGMD 1F	*TNP03*	LGMD D2 TNP03-related	
LGMD 1G	*HNRNPDL*	LGMD D3 HNRNPDL-related	
LGMD 1H	?	Not confirmed	False linkage
LGMD 1I	*CAPN*	LGMD D4 calpain3-related	
LGMD 2A	*CAPN*	LGMD R1 calpain3-related	
LGMD 2B	*DYSF*	LGMD R2 dysferlin-related	
LGMD 2C	*SGCG*	LGMD R5 γ-sarcoglycan-related[a]	
LGMD 2D	*SGCA*	LGMD R3 α-sarcoglycan-related	
LGMD 2E	*SGCB*	LGMD R4 β-sarcoglycan-related	
LGMD 2F	*SGCD*	LGMD R6 δ-sarcoglycan-related	
LGMD 2G	*TCAP*	LGMD R7 telethonin-related	
LGMD 2H	*TRIM32*	LGMD R8 TRIM 32-related	
LGMD 2I	*FKRP*	LGMD R9 FKRP-related	
LGMD 2J	*TTN*	LGMD R10 titin-related	
LGMD 2K	*POMT1*	LGMD R11 POMT1-related	
LGMD 2L	*ANO5*	LGMD R12 anoctamin5-related	
LGMD 2M	*FKTN*	LGMD R13 Fukutin-related	
LGMD 2N	*POMT2*	LGMD R14 POMT2-related	
LGMD 2O	*POMGnT1*	LGMD R15 POMGnT1-related	
LGMD 2P	*DAG1*	LGMD R16 α-dystroglycan-related	
LGMD 2Q	*PLEC*	LGMD R17 plectin-related	
LGMD 2R	*DES*	myofibrillar myopathy	Distal weakness
LGMD 2S	*TRAPPC11*	LGMD R18 TRAPPC11-related	
LGMD 2T	*GMPPB*	LGMD R19 GMPPB-related	
LGMD 2U	*ISPD*	LGMD R20 ISPD-related	
LGMD 2V	*GAA*	Pompe disease	Known disease entity, histological changes
LGMD 2W	*PINCH2*	PINCH-2 related myopathy	Reported in one family
LGMD 2X	*BVES*	BVES related myopathy	Reported in one family
LGMD 2Y	*TOR1AIP1*	TOR1AIP1 related myopathy	Reported in one family
LGMD 2Z	*POGLUT1*	LGMD R21 POGLUT1-related	
Bethlem myopathy recessive	*COL6A1, COL6A2, COL6A3*	LGMD R22 collagen 6-related	
Bethlem myopathy dominant	*COL6A1, COL6A2, COL6A3*	LGMD D5 collagen 6-related	
Laminin α2-related muscular dystrophy	*LAMA2*	LGMD R23 laminin α2-related	
POMGNT2-related muscular dystrophy	*POMGNT2*	LGMD R24 POMGNT2-related	

Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 28 (2018) 702–710
www.elsevier.com/locate/nmd

Workshop report

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

Volker Straub[a,*], Alexander Murphy[a], Bjarne Udd[b,c,d], on behalf of the LGMD workshop study group

"*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.*"

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Novità in ambito nosologico

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Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 27 (2017) 1126–1137

NMD
www.elsevier.com/locate/nmd

Workshop report

International Workshop:
Outcome measures and clinical trial readiness in primary mitochondrial myopathies in children and adults. Consensus recommendations.
16–18 November 2016, Rome, Italy

Michelangelo Mancuso [a,*], Robert McFarland [b], Thomas Klopstock [c], Michio Hirano [d] on behalf of the consortium on Trial Readiness in Mitochondrial Myopathies [1]

Definition	Consensus	
	Percentuage of sum 4 + 5	Mean score
DEFINITION OF PRIMARY MITOCHONDRIAL MYOPATHIES		
PMM are genetically defined disorders leading to defects of oxidative phosphorylation affecting predominantly, but not exclusively, skeletal muscle. Secondary involvement of mitochondria, frequently observed in multiple neuromuscular diseases (i.e. inclusion body myositis, Duchenne muscular dystrophy, Kennedy disease) are not considered PMM.	100%	4.88

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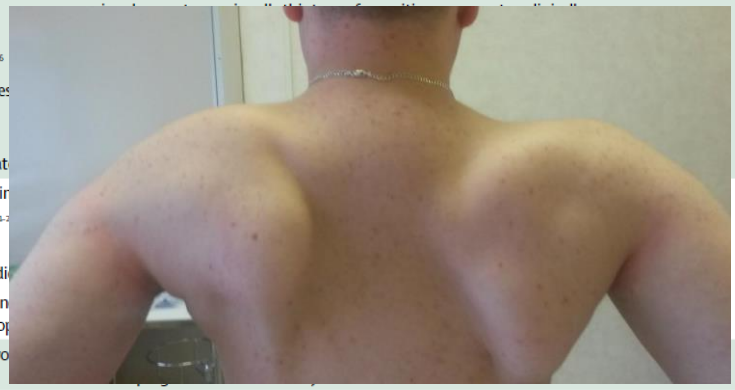
Lancet Neurol 2018; 17: 816–28

Classification and management of adult inflammatory myopathies

Albert Selva-O'Callaghan, Iago Pinal-Fernandez, Ernesto Trallero-Araguás, José César Milisenda, Josep Maria Grau-Junyent, Andrew L Mammen

	Clinical features	Type of organ involvement and severity		
		Muscle	Lung	Skin
Dermatomyositis				
Anti-Mi2 autoantibodies[12]	Mild-to-moderate muscle involvement with classical skin rash	Moderate	None	Moderate
Anti-NXP2 autoantibodies[13,14]	Mild-to-moderate muscle involvement with myalgia, classical skin rash, calcinosis, distal extensor weakness and oedema, and dysphagia; increased risk of cancer	Moderate	None	Moderate
Anti-TIF1 autoantibodies[14,15]	Strong association with cancer; mild muscle involvement with marked skin	Mild	None	Moderate
Anti-SAE autoantibodies[16]			None	Moderate
Anti-MDA5 autoantibodies			Severe	Severe
Antibody-negative dermat			Unknown	Moderate
Immune-mediated necrotisin				
Anti-SRP autoantibodies[23-2			Mild	None
Anti-HMGCR autoantibodi			None	None
Antibody-negative immun mediated necrotising myop			Unknown	None
Sporadic inclusion-body myo			None	None
Overlap myositis				
Antisynthetase syndrome				
Anti-Jo1 autoantibodies[28,29]	Mild-to-moderate muscle involvement with progressive lung involvement and possible mild dermatomyositis skin rash (~50% of patients); other characteristic cutaneous features (eg, mechanic's hands and Raynaud syndrome)	Moderate	Moderate	Mild
Anti-PL7 autoantibodies[28]	Symptoms are similar to those of anti-Jo1 autoantibody-positive myositis with more severe lung involvement	Moderate	Severe	Mild
Anti-PL12 autoantibodies[28]	Severe lung involvement with mild muscle weakness	Mild	Severe	Mild
Anti-Pm/Scl autoantibodies[30]	Mild myositis and scleroderma features with muscle weakness, interstitial lung disease, and skin involvement	Mild	Mild	Mild
Anti-Ku autoantibodies[31]	Mild muscle involvement and interstitial lung disease	Mild	Mild	Mild
Anti-U1RNP autoantibodies[32]	Myositis, scleroderma, and systemic lupus erythematosus features; glomerulonephritis and pulmonary hypertension are possible	Mild	Mild	Mild
Polymyositis	Diagnosis of exclusion; heterogeneous clinical features	Unknown	Unknown	Unknown



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Novità in ambito clinico

LGMD

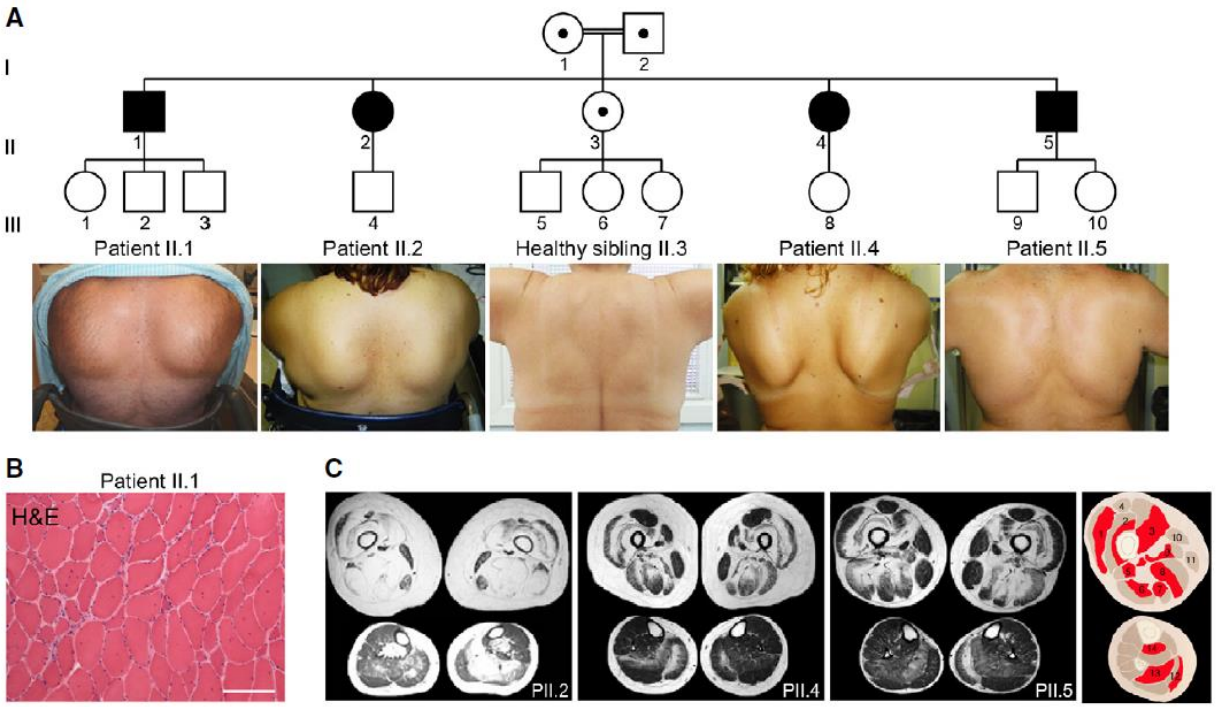
Published online: October 10, 2016

Research Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

A *POGLUT1* mutation causes a muscular dystrophy with reduced Notch signaling and satellite cell loss



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Novità in ambito clinico

Miopatie congenite

OXFORD

Human Molecular Genetics, 2018, Vol. 27, No. 24 4263–4272

doi: 10.1093/hmg/ddy320
Advance Access Publication Date: 12 September 2018
General Article

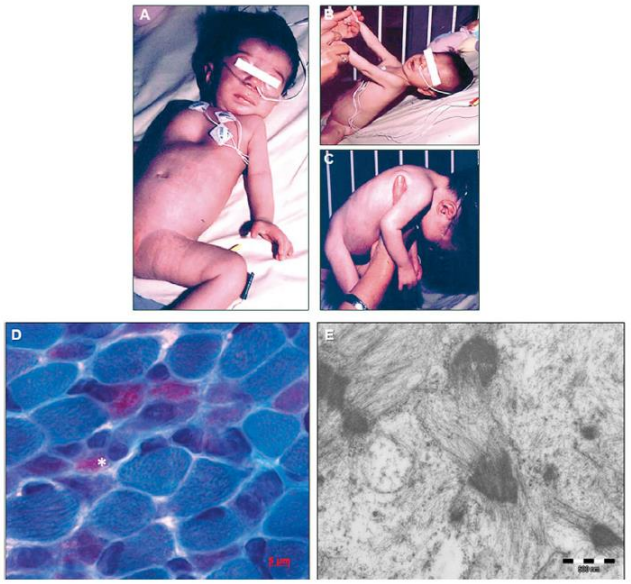
GENERAL ARTICLE

Bi-allelic mutations in *MYL1* cause a severe congenital myopathy

Journal of Neuromuscular Diseases 2 (2015) 219–227
DOI 10.3233/JND-150085
IOS Press

Research Report

A Premature Stop Codon in *MYO18B* is Associated with Severe Nemaline Myopathy with Cardiomyopathy



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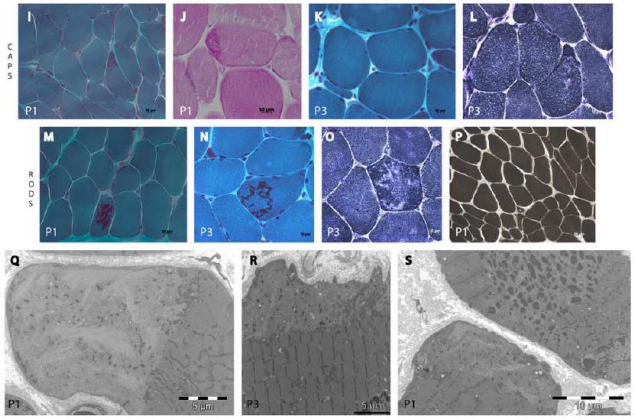
Novità in ambito clinico

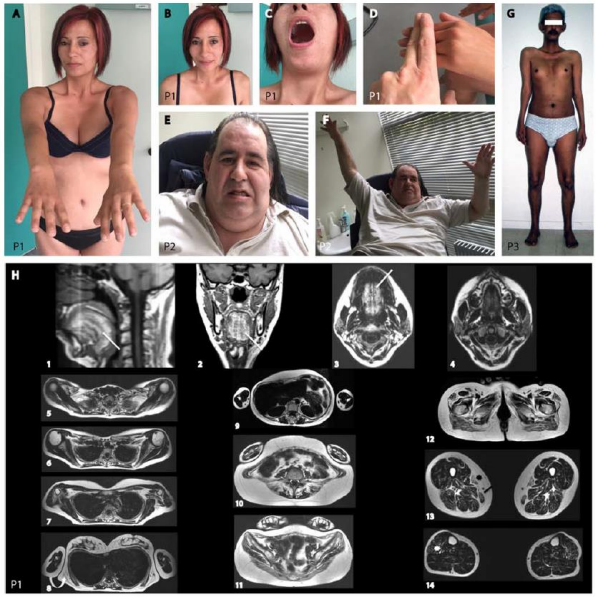
Miopatie congenite

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society

Brief Communication | Full Access

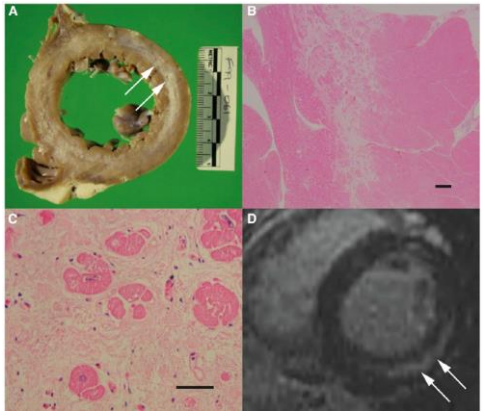
Recessive *MYPN* mutations cause cap myopathy with occasional nemaline rods





The American Journal of Human Genetics *99*, 1–9, September 1, 2016 1

Sudden Cardiac Death due to Deficiency of the Mitochondrial Inorganic Pyrophosphatase PPA2



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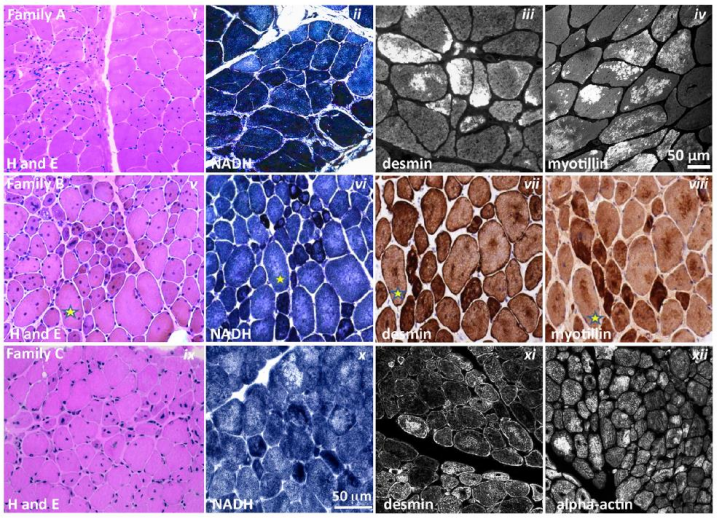
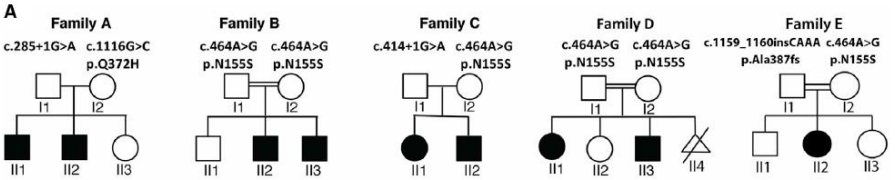
Novità in ambito clinico

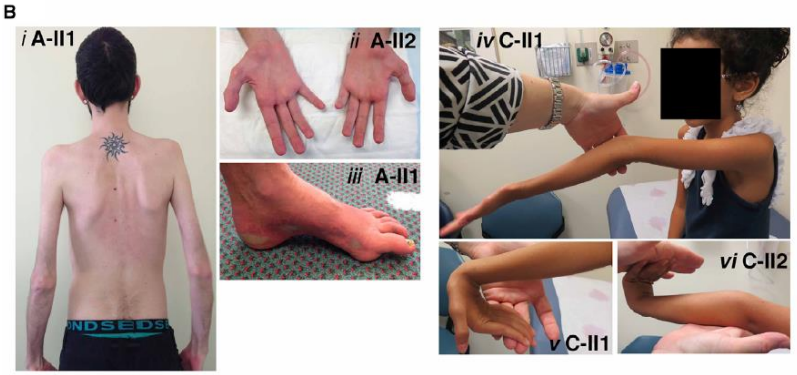
Miopatie congenite e canalopatie muscolari

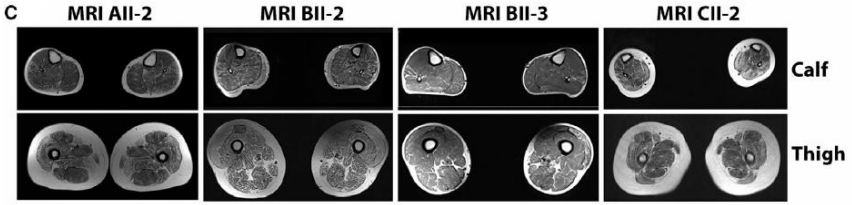
The American Journal of Human Genetics *99*, 1–20, November 3, 2016 1

Variants in the Oxidoreductase PYROXD1 Cause Early-Onset Myopathy with Internalized Nuclei and Myofibrillar Disorganization









Lancet 2018; 391: 1483–92

Dysfunction of NaV1.4, a skeletal muscle voltage-gated sodium channel, in sudden infant death syndrome: a case-control study

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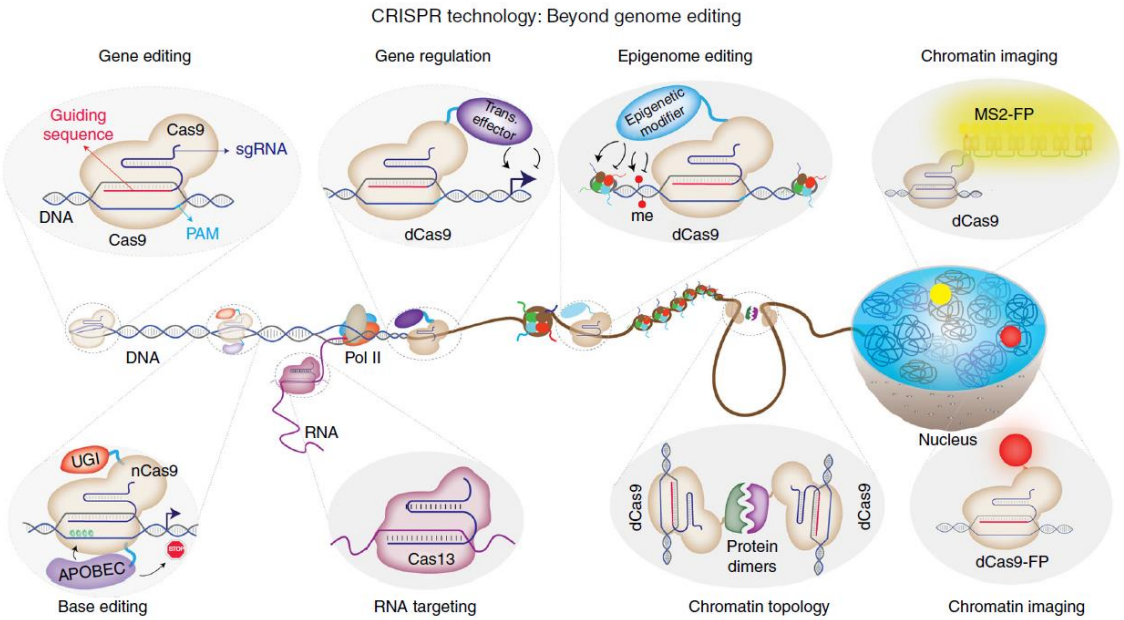
Novità in ambito terapeutico

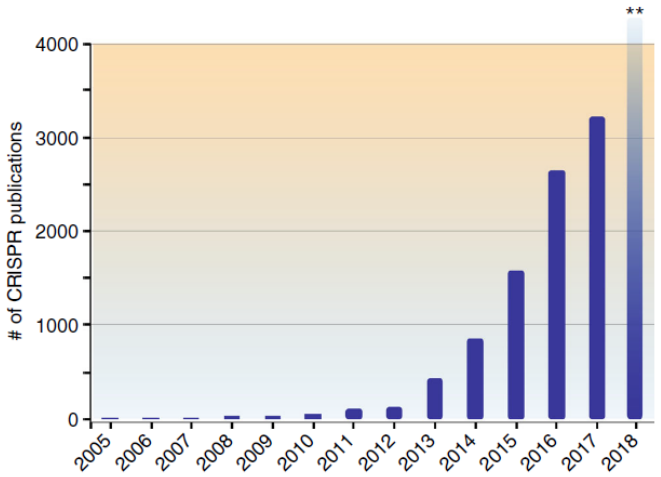
nature COMMUNICATIONS

REVIEW ARTICLE

DOI: 10.1038/s41467-018-04252-2 OPEN

The CRISPR tool kit for genome editing and beyond





ARTICLE

The American Journal of Human Genetics 98, 90–101, January 7, 2016

Spell Checking Nature: Versatility of CRISPR/Cas9 for Developing Treatments for Inherited Disorders

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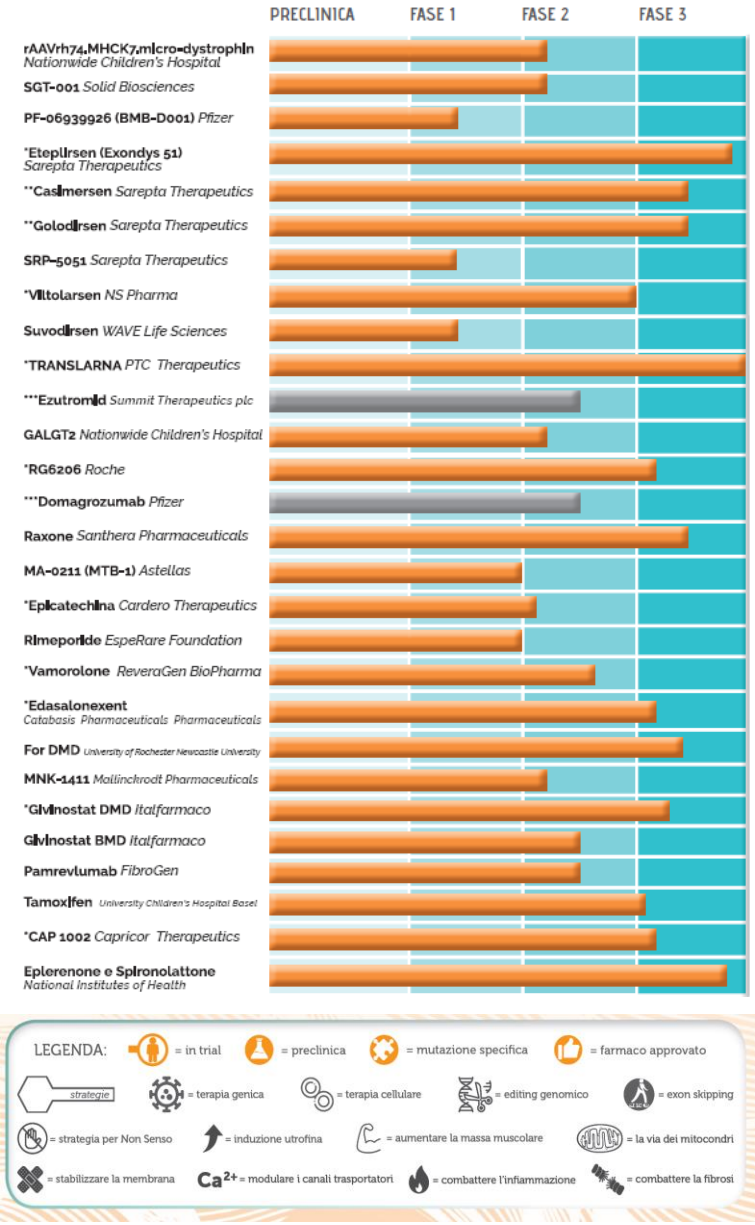
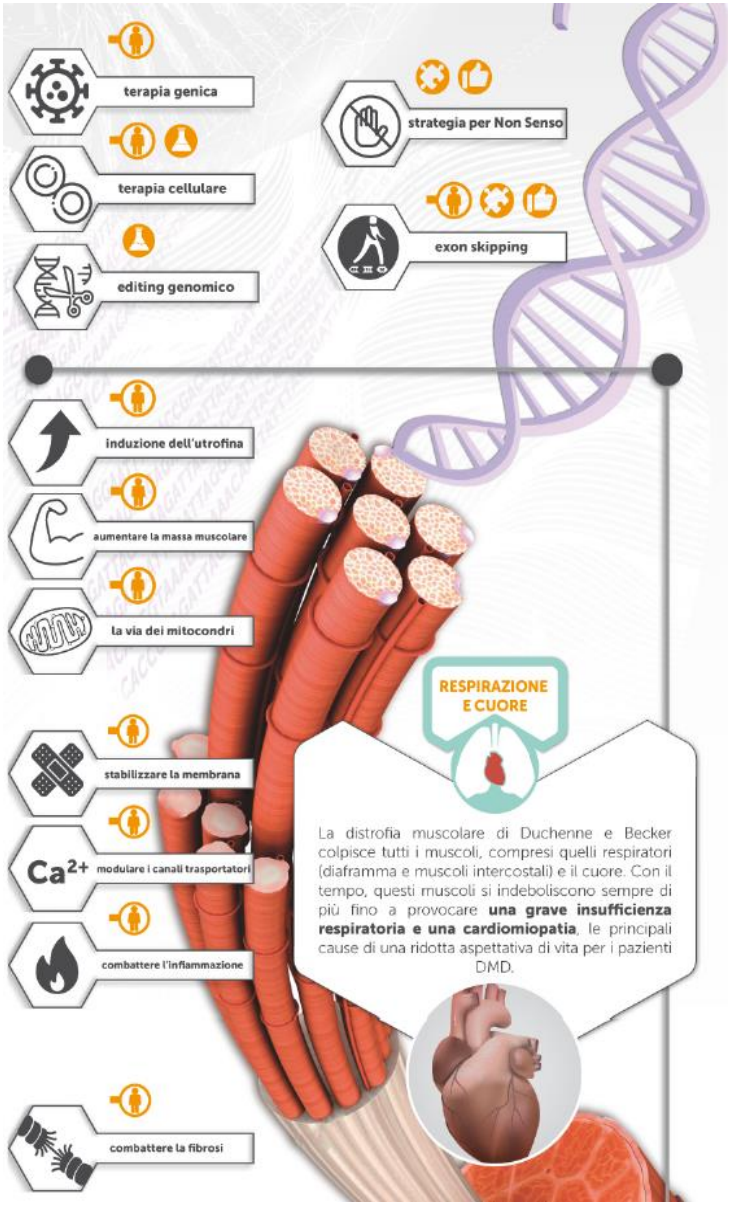
Novità in ambito terapeutico





DMD e BMD

Duchenne Parent Project onlus

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Novità in ambito terapeutico

DMD

Neurological Sciences (2018) 39:1837–1845
https://doi.org/10.1007/s10072-018-3555-3

REVIEW ARTICLE

Clinical management of Duchenne muscular dystrophy: the state of the art

Sonia Messina[1,2,3] · Gian Luca Vita[2]

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Developing standardized corticosteroid treatment for Duchenne muscular dystrophy☆

- 0.75 mg/kg/day prednisone
- 0.75 mg/kg/day prednisone 10 days on/10 days off
- 0.9 mg/kg/day deflazacort

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Novità in ambito terapeutico

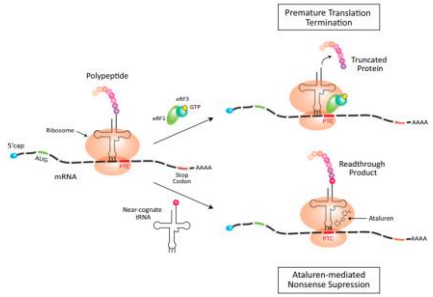
DMD

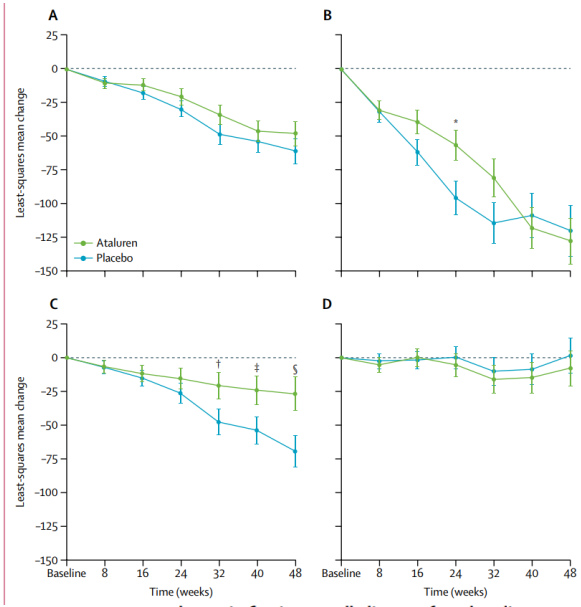
THE LANCET
Volume 390, Issue 10101, 23–29 September 2017, Pages 1489-1498

Articles

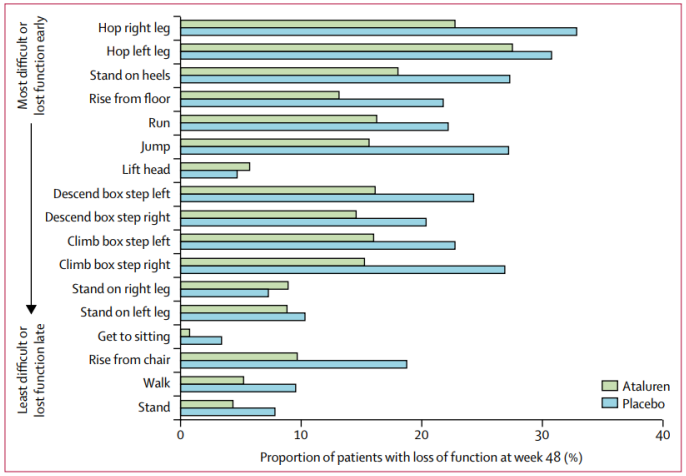
Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

PNAS





Least-squares mean change in 6-minute walk distance from baseline to week 48



Proportion of patients who lost the ability to perform each individual item in the North Star

NCT03179631
(Fase 3)

NCT02819557
(Fase 2, ≥2 to <5 anni)

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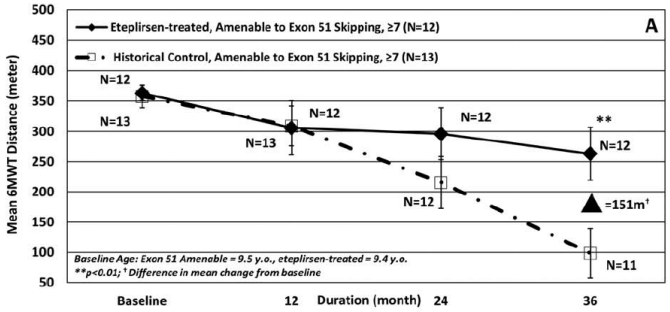
Novità in ambito terapeutico

DMD
Exon skipping

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
Research Article | Open Access

Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy



→ **PROMOVI (NCT02255552 Fase 3)**

Golodirsen → **Skipping dell'esone 53 (8% pazienti DMD patients)**

Casimersen → **Skipping dell'esone 45 (8% pazienti DMD patients**

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Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 26 (2016) 643–649
NMD
www.elsevier.com/locate/nmd

→ **BMD, Fase 2 (26 pazienti)**

Histological effects of givinostat in boys with Duchenne muscular dystrophy

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Novità in ambito terapeutico

Malattie mitocondriali

BJP British Journal of Pharmacology

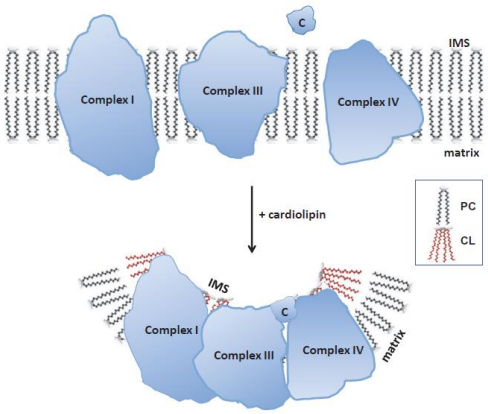
Themed Issue: Mitochondrial Pharmacology: Energy, Injury & Beyond

RESEARCH PAPER

Targeting mitochondrial cardiolipin and the cytochrome c/cardiolipin complex to promote electron transport and optimize mitochondrial ATP synthesis

A V Birk[1]*, W M Chao[1]*, C Bracken[2,3], J D Warren[2,4] and H H Szeto[1]

BJP H H Szeto



Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy

Amel Karaa, MD, Richard Haas, MD, Amy Goldstein, MD, Jerry Vockley, MD, PhD, W. Douglas Weaver, MD, and Bruce H. Cohen, MD

Correspondence
Dr. Karaa
akaraa@mgh.harvard.edu

Neurology® 2018;90:e1212-e1221. doi:10.1212/WNL.0000000000005255

→ **140 pazienti arruolati**

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Novità in ambito terapeutico

LOPD

JID: NMD [m5+;February 12, 2019;19:55]

Available online at www.sciencedirect.com

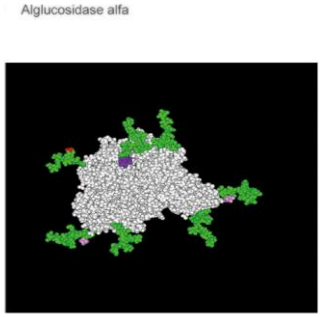
ScienceDirect

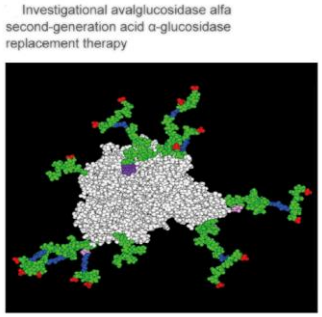
Neuromuscular Disorders xxx (xxxx) xxx

www.elsevier.com/locate/nmd

Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naïve and alglucosidase alfa-treated patients with late-onset Pompe disease: A phase 1, open-label, multicenter, multinational, ascending dose study

COMET (Fase 3): 84 pazienti arruolati





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Miopatie infiammatorie

NATURE REVIEWS | RHEUMATOLOGY VOLUME 14 | MAY 2018 | 279

Treatment in myositis

Chester V. Oddis and Rohit Aggarwal*

Table 1 | **Summary of biologic agents used in the treatment of myositis: selected trials**

Biologic agent	Therapeutic target	Study population	Study design	Primary end points	Results	Refs
Rituximab	B cells	Adult polymyositis and dermatomyositis and JDM ($n = 200$)	Randomized, double-blind and placebo-phase	IMACS DOI	Primary end point was not met, but 83% of study participants met the DOI	39
		Anti-SRP-positive individuals ($n = 8$)	Open-label	MMT and creatine kinase decline	Six of eight patients showed improvements	38
Infliximab	TNF	Adult polymyositis and dermatomyositis ($n = 12$)	Randomized, double-blind, placebo-controlled and crossover	≥15% MMT improvement	<33% response rate	50
Etanercept	TNF	Adult dermatomyositis ($n = 16$)	Randomized, double-blind and placebo-controlled	Adverse events; time from randomization to treatment failure; prednisone wean	Five of 11 etanercept-treated patients were weaned off prednisone; no adverse events	43
Tocilizumab	IL-6	Adult polymyositis, dermatomyositis and IMNM ($n = 40$)	Randomized, double-blind and placebo-controlled	Myositis Total Improvement Score	Study in progress	58
Abatacept[a]	T cells	Adult polymyositis and dermatomyositis ($n = 20$)	Randomized, open-label and 'delayed-start'	IMACS DOI	Treatment resulted in lower disease activity in nearly 50% of patients	63
Anakinra	IL-1 receptor	Adult polymyositis, dermatomyositis and IBM ($n = 15$)	Open-label	IMACS DOI and functional index	Seven of the 15 patients responded to treatment	64

DOI, definition of improvement; IBM, inclusion body myositis; IMACS, International Myositis Assessment and Clinical Studies; IMNM, immune-mediated necrotizing myopathy; JDM, juvenile dermatomyositis; MMT, manual muscle testing; SRP, signal recognition particle. [a]Larger, international study in progress[65].

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The Official Journal of the American Academy of Neurology

Neurology. 2014 Dec 9; 83(24): 2239–2246.
doi: 10.1212/WNL.0000000000001070
PMCID: PMC4277670
PMID: 25381300

Treatment of sporadic inclusion body myositis with bimagrumab

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Risultati promettenti nello studio di fase 2, non confermati nello studio di fase 3 (RESILIENT), in attesa di valutazione degli outcomes secondari

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Canalopatie

doi:10.1093/brain/awx192 BRAIN 2017: 140; 2295–2305 | 2295

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CLINICAL TRIAL

The antimyotonic effect of lamotrigine in non-dystrophic myotonias: a double-blind randomized study

Grete Andersen,[1] Gitte Hedermann,[1] Nanna Witting,[1] Morten Duno,[2] Henning Andersen[3] and John Vissing[1]