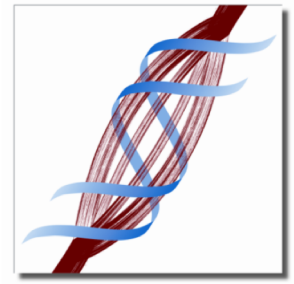


Introduction to *RYR1*-Related Diseases

A. Reghan Foley, MD, MD(Res)

Neuromuscular and Neurogenetic Disorders of Childhood Section

Neurogenetics Branch

National Institute of Neurological Disorders and Stroke, NIH

RYR-1 International Family Conference

July 14, 2018

National Institute of Neurological Disorders and Stroke

National Institutes of Health

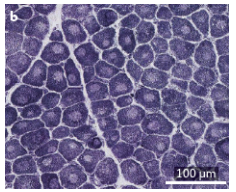
For ALL individuals with congenital myopathies around the world

who teach us everyday what <u>true</u> strength is

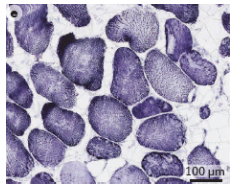
Congenital Myopathies

Beginning in the 1950s and 1960s muscle biopsy histochemical and ultrastructural techniques were used in recognizing congenital myopathy subtypes:

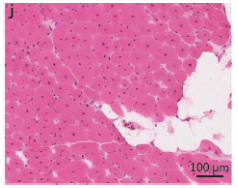
central core disease (CCD)[1]



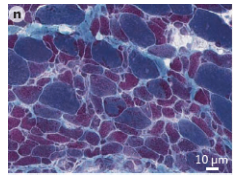
multi-minicore disease (MmD)[2]



centronuclear myopathy (CNM)[3]



nemaline myopathy[4]



[1]Magee et al. *Brain* 1956. [2]Engel et al. *Mayo Clin Proc.* 1971. [3]Sprio et al. *Arch Neurol.* 1966. [4]Shy et al. *Brain*. 1963.

Images from: Jungbluth et al. *Nat Rev Neurol.* 2018

RYR1 as the Causative Gene for Central Core Disease:

article

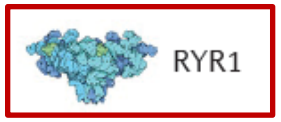
Mutations in the ryanodine receptor gene in central core disease and malignant hyperthermia

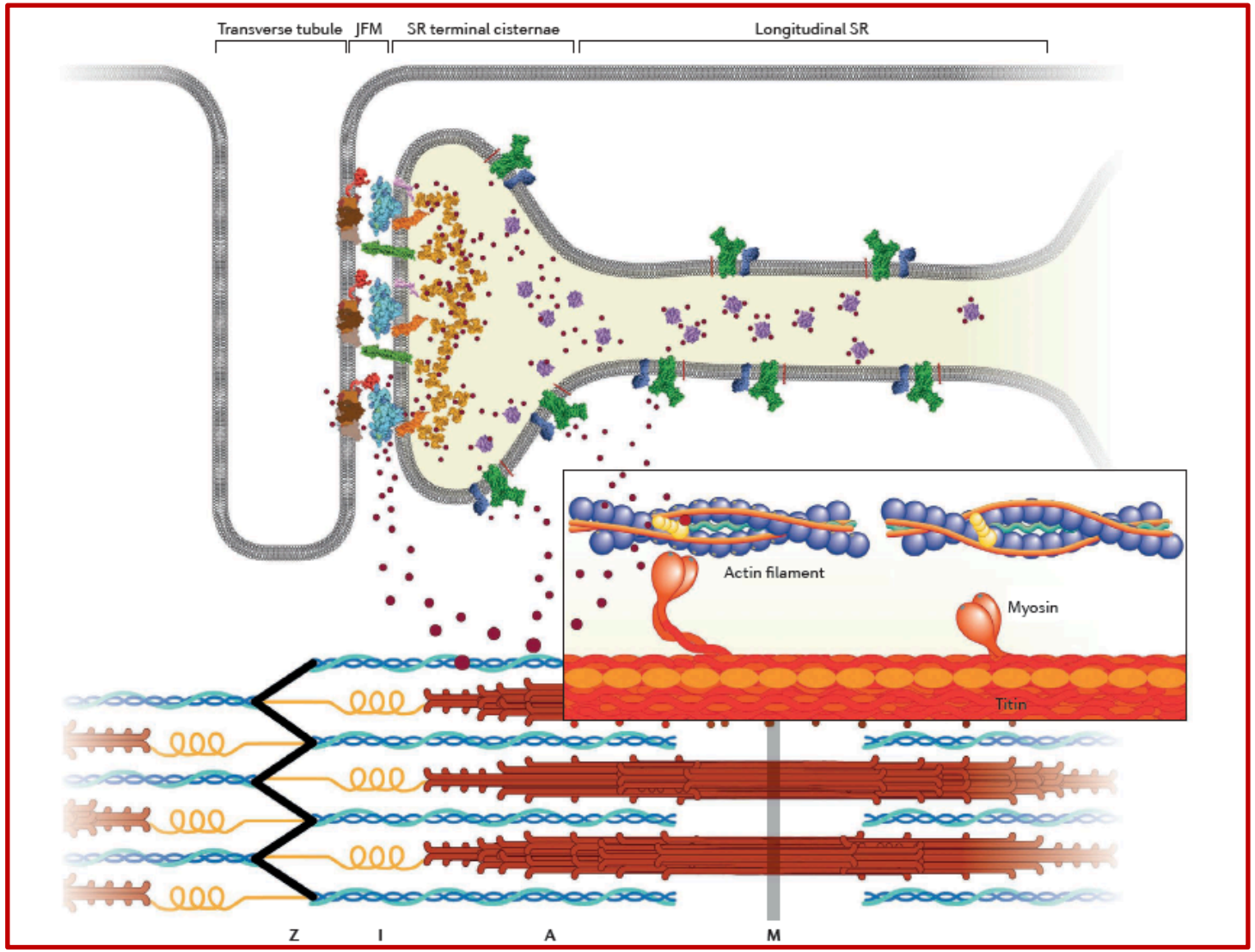
K. A. Quane[1], J.M.S. Healy[1], K. E. Keating[1], B. M. Manning[1], F. J. Couch[1], L. M. Palmucci[2], C. Doriguzzi[2], T. H. Fagerlund[3], K. Berg[4], H. Ording[5], D. Bendixen[5], W. Mortier[6], U. Linz[7], C. R. Muller[7] & T. V. McCarthy[1]

***RYR1* mutations are the most frequent genetic cause of congenital myopathies**

RyR1 = ryanodine receptor type 1

a skeletal muscle sarcoplasmic reticulum calcium release channel





Jungbluth et al. *Nat Rev Neurol.* 2018

Mutations in *RYR1* can result in:

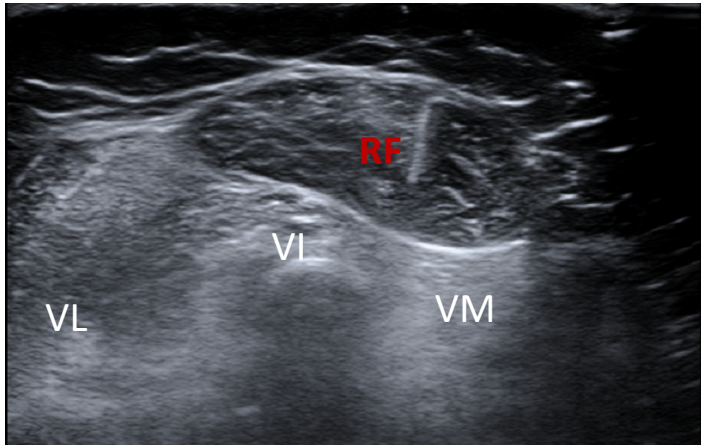
- Central core disease (CCD)
- Multiminicore disease(MmD)
- Centronuclear myopathy
- Congenital fiber-type disproportion
- Core-rod myopathy

Clinical course is typically either static or slowly progressive

RYR1-Related Myopathy Imaging: Muscle Ultrasound

Muscle Ultrasound:

- a non-invasive means of assessing muscle appearance
- can be performed at bedside
- relative sparing of the rectus femoris muscle is a pattern highly suggestive of *RYR1*-related myopathy



Quadriceps = 4 muscles:

1. **rectus femoris (RF)**
2. vastus lateralis (VL)
3. vastus intermedius (VI)
4. vastus medialis (VM)

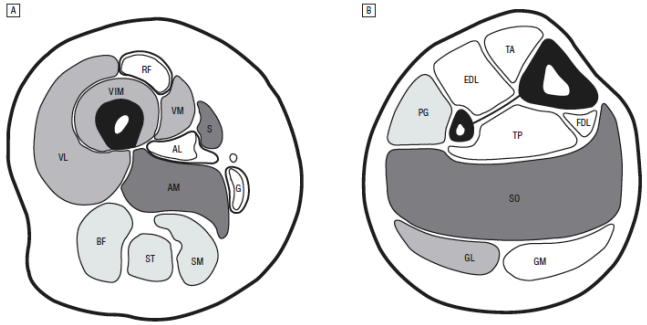
RYR1-Related Myopathy Imaging: Muscle MRI

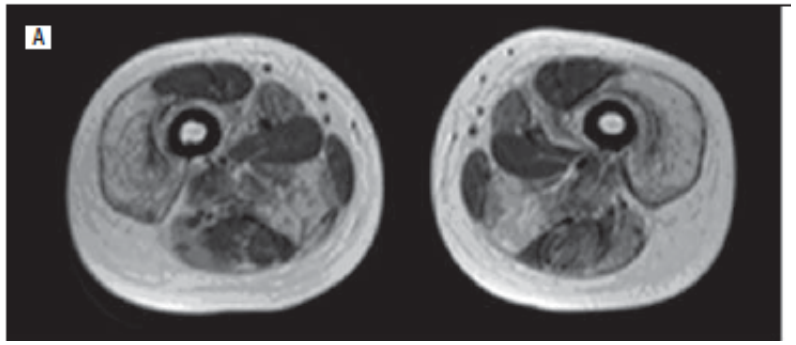
ORIGINAL CONTRIBUTION

Muscle Magnetic Resonance Imaging in Congenital Myopathies Due to Ryanodine Receptor Type 1 Gene Mutations

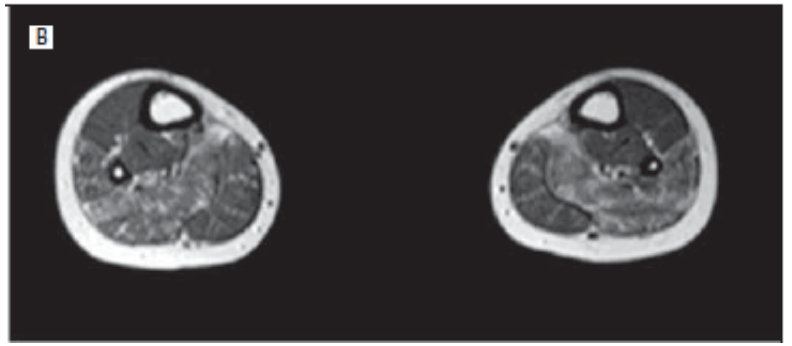
Andrea Klein, MD; Heinz Jungbluth, PhD; Emma Clement, MD, ChB; Suzanne Lillis, MSc, BSc; Stephen Abbs, PhD; Pinki Munot, MD; Marika Pane, MD, PhD; Elizabeth Wraige, MD; Ulrike Schara, MD; Volker Straub, MD, PhD; Eugenio Mercuri, PhD; Francesco Muntoni, MD

Arch Neurol. 2011;68(9):1171-1179





Upper leg: rectus femoris (RF), adductor longus (AL) and gracilis (G) are relatively spared – and may be hypertrophied



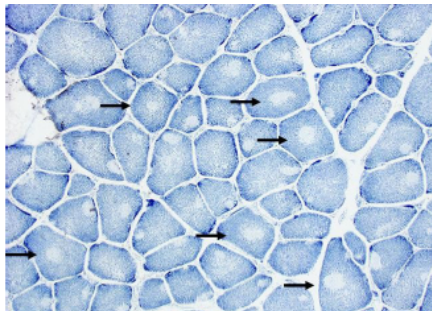
Lower leg: tibialis anterior (TA), extensor digitorum longus (EDL), tibialis posterior (TP) and gastrocnemius medialis (GM) are relatively spared

“Core” Myopathies

Named for the muscle histological appearance of focally reduced oxidative enzyme activity

Central Core Disease (CCD)

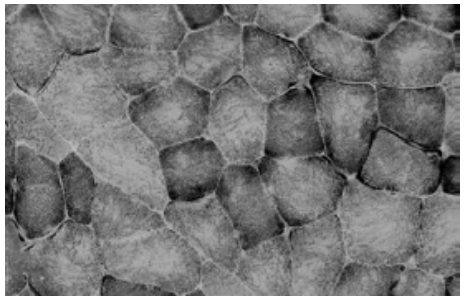
- centrally located cores
- well demarcated cores



Jungbluth. *Orphanet J Rare Dis*. 2007

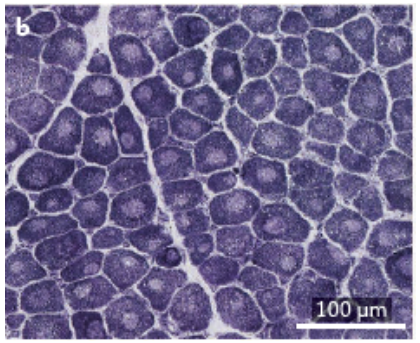
Multiminicore Disease (MmD)

- multiple cores
- less well-defined cores



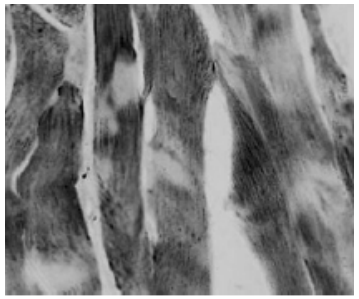
Jungbluth et al. *Semin Pediatr Neurol*. 2011

Central Core Myopathy: *Clinical Picture*



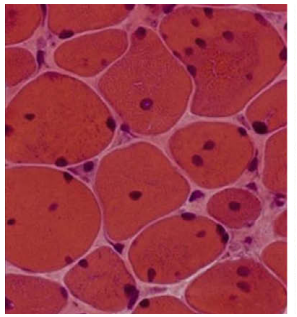
- Hypotonia, congenital hip dislocation and scoliosis are common
- Extraocular muscle involvement, respiratory involvement, facial weakness and bulbar weakness are often mild
- Most patients achieve independent ambulation

Multiminicore Myopathy
Clinical Picture



- Can be caused by autosomal recessive mutations in *RYR1* (or *SEPN1*)
- External ophthalmoplegia (in *RYR1*-related Multiminicore Myopathy) and prominent axial and proximal muscle weakness are common
- Severe cases with antenatal onset and arthrogryposis and respiratory insufficiency can occur

RYR1-Related Centronuclear Myopathy

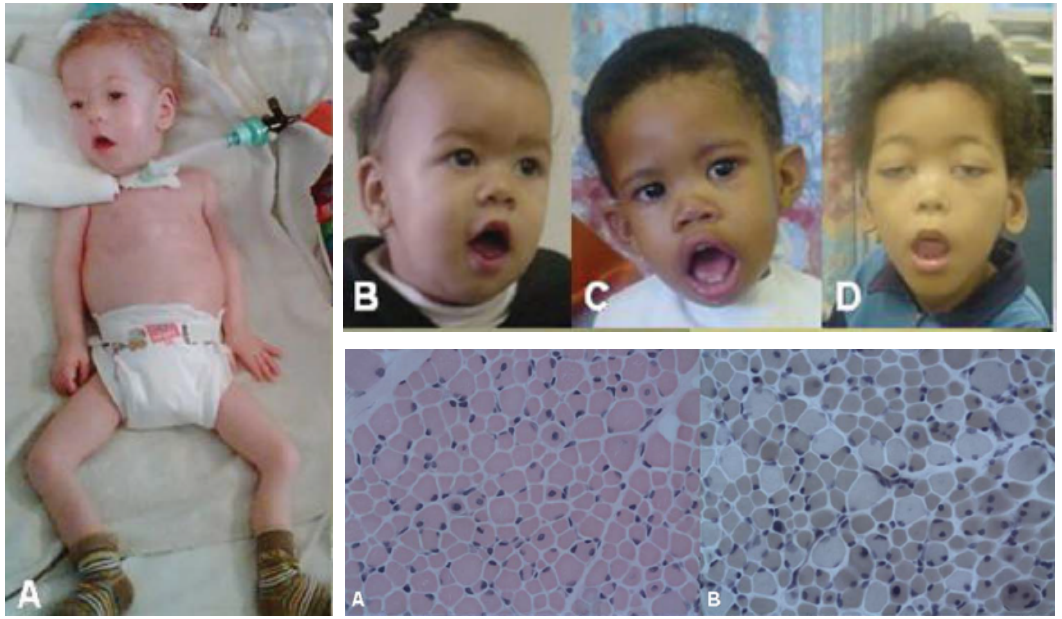


ORIGINAL ARTICLE

RYR1 Mutations Are a Common Cause of Congenital Myopathies with Central Nuclei

J.M. Wilmshurst, MD,[1] S. Lillis, BSc,[2] H. Zhou, PhD,[3] K. Pillay, MBChB,[4] H. Henderson, PhD,[5] W. Kress, PhD,[6] C.R. Müller, PhD,[6] A. Ndondo, MBBS,[1] V. Cloke, BSc,[2] T. Cullup, BSc,[2] E. Bertini, MD,[7] C. Boennemann, PhD,[8] V. Straub, PhD,[9] R. Quinlivan, MD,[10] J.J. Dowling, PhD,[11] S. Al-Sarraj, MD,[12] S. Treves, PhD,[13] S. Abbs, PhD,[2] A.Y. Manzur, MBBS,[3] C.A. Sewry, PhD,[3,10] F. Muntoni, MD,[3] and H. Jungbluth, MD, PhD[14,15]

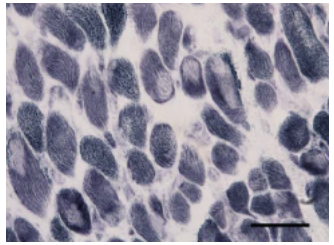
ANN NEUROL 2010;68:717–726



Clinical features:

- Congenital symptoms
- Extraocular muscle weakness
- Bulbar weakness
- Proximal muscle weakness

Severe Neonatal Presentation of *RYR1*-Related Myopathy

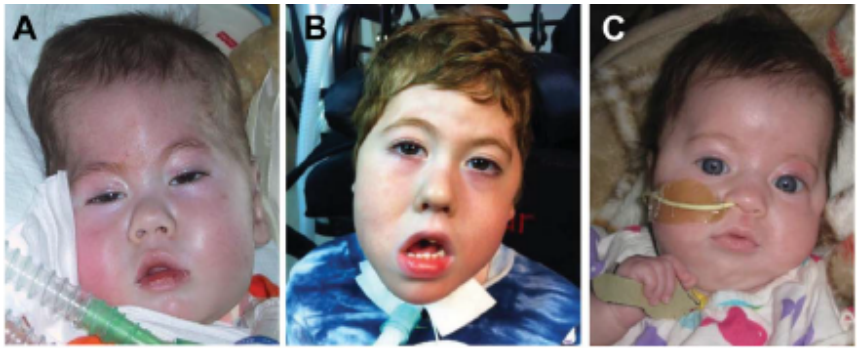


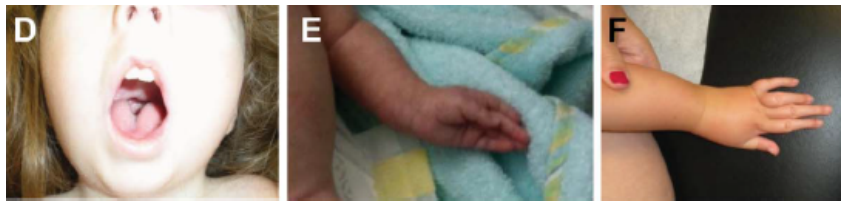
Diana Xerxes Bharucha-Goebel, MD
Mariarita Santi, MD
Līvija Medne, MS, CGC
Kristin Zukosky, BA
Jahannaz Dastgir, DO
Perry B. Shieh, MD, PhD
Thomas Winder, PhD
Gihan Tennekoon, MD
Richard S. Finkel, MD
James J. Dowling, MD, PhD
Nicole Monnier, PhD
Carsten G. Bönnemann, MD

Severe congenital *RYR1*-associated myopathy

The expanding clinicopathologic and genetic spectrum

Neurology® 2013;80:1584–1589





Clinical features:

- Myopathic face
- Respiratory involvement
- Poor feeding
- Ophthalmoplegia
- Hypotonia
- Arthroygryposis

RYR1-Related Congenital Fiber-Type Disproportion (CFTD)

HUMAN MUTATION Mutation in Brief 31: E1544-E1550 (2010) Online

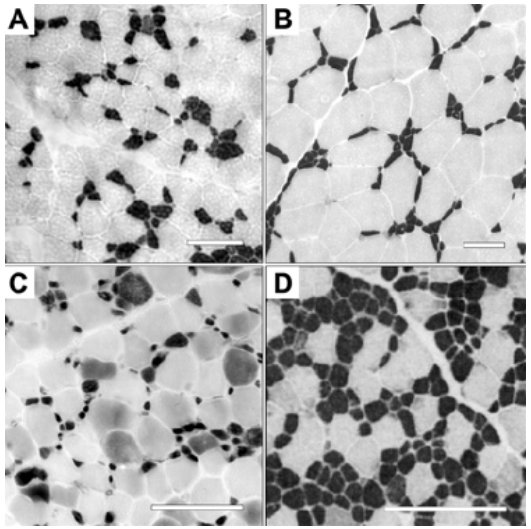
MUTATION IN BRIEF

HUMAN MUTATION

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

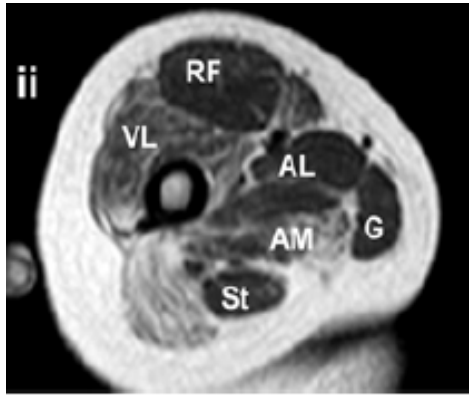
Recessive Mutations in *RYR1* Are a Common Cause of Congenital Fiber Type Disproportion

Nigel F. Clarke[1,2], Leigh B. Waddell[1,2], Sandra T. Cooper[1,2], Margaret Perry[2,3], Robert L.L. Smith[4], Andrew J. Kornberg[5], Francesco Muntoni[6], Suzanne Lillis[7], Volker Straub[8], Kate Bushby[8], Michela Guglieri[8], Mary D. King[9], Michael A. Farrell[10], Isabelle Marty[11], Joel Lunardi[11], Nicole Monnier[11], and Kathryn N. North[1,2]



"congenital fiber-type disproportion"

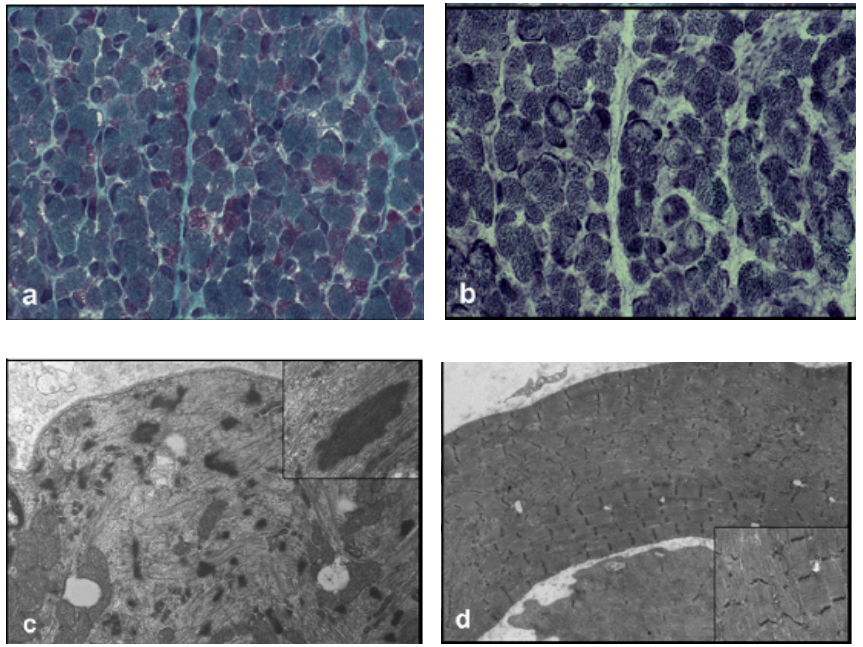
- a muscle pathology descriptive term
- type 1 fiber hypotrophy compared to type 2 fibers
- not specific for *RYR1*-related myopathy



RYR1-Related Core-Rod Myopathy

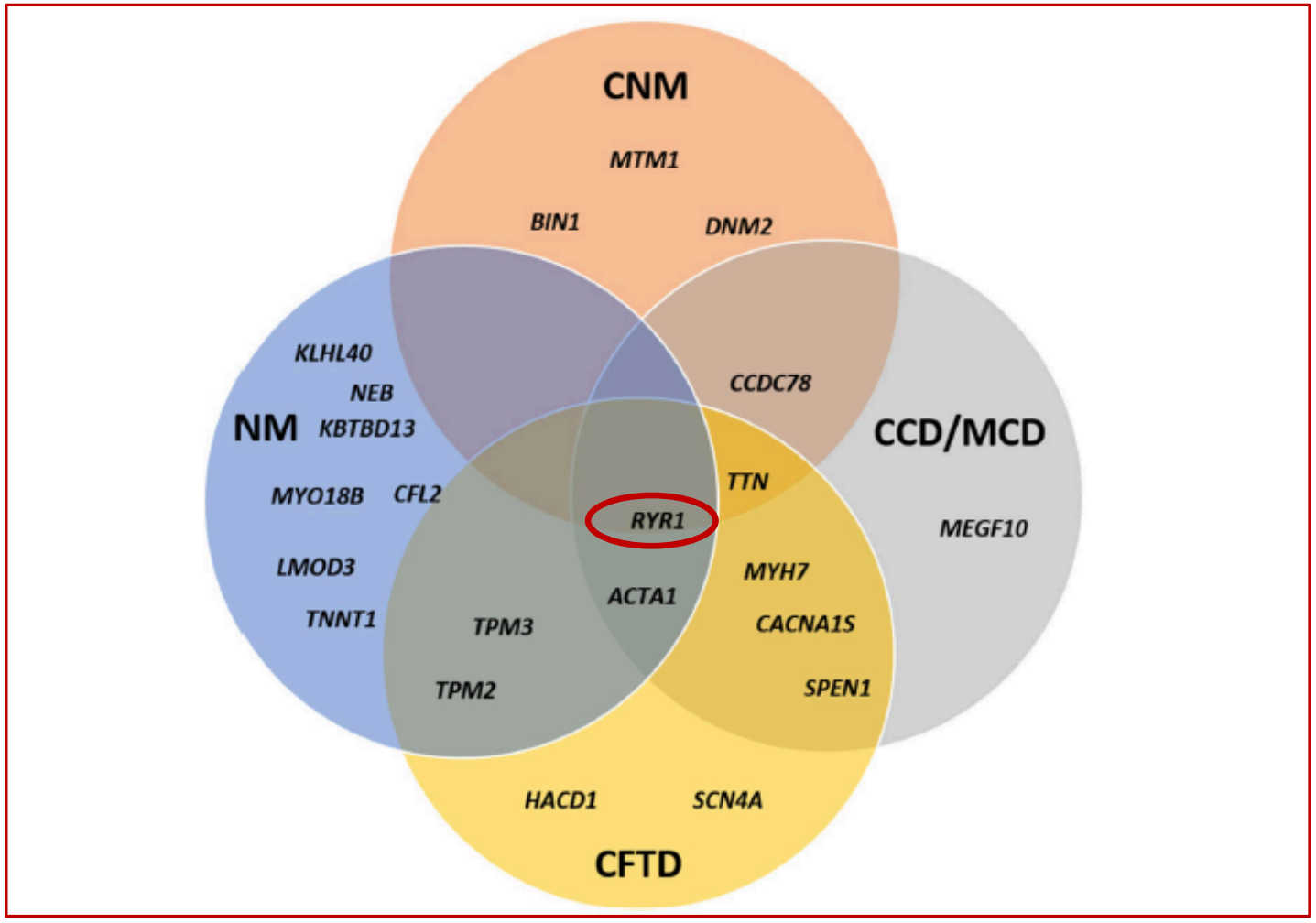
"core-rod myopathy"

- a muscle pathology finding of both cores and rods
- not specific for *RYR1*-related myopathy
- has been reported in association with a severe form of neonatal *RYR1*-related myopathy



Hernandez-Lain et al. *Eur J Med Genet.* 2011

Congenital myopathy genes



Gonorazky, Bönnemann and Dowling. *Hand Clin Neurol*. 2018

Late-onset axial myopathy due to dominant *RYR1* mutations

Neuromuscular Disorders 19 (2009) 344–347

Contents lists available at ScienceDirect

Neuromuscular Disorders

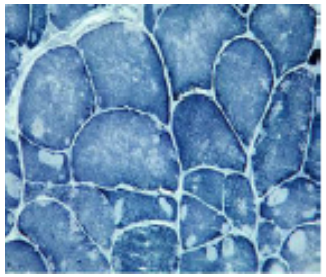
journal homepage: www.elsevier.com/locate/nmd

Case report

Late-onset axial myopathy with cores due to a novel heterozygous dominant mutation in the skeletal muscle ryanodine receptor (*RYR1*) gene

Heinz Jungbluth [a,b,*], Suzanne Lillis [c], Haiyan Zhou [d], Stephen Abbs [c], Caroline Sewry [e], Michael Swash [f], Francesco Muntoni [d]

[a] Clinical Neuroscience Division, King's College, London, UK
[b] Department of Paediatric Neurology Neuromuscular Service, Evelina Children's Hospital, St. Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, UK
[c] DNA Laboratory, GSTS Pathology, Guy's Hospital, London, UK
[d] Dubowitz Neuromuscular Centre, Institute of Child Health, London, UK
[e] Centre for Inherited Neuromuscular Disorders, RJAH, Robert Jones & Agnes Hunt Orthopaedic Hospital, Oswestry, UK
[f] Department of Neurology, Royal London Hospital, London, UK

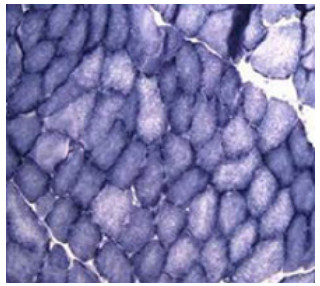


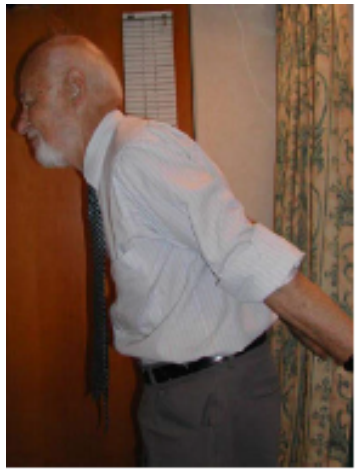
J Neurol (2013) 260:1504–1510
DOI 10.1007/s00415-012-6817-7

ORIGINAL COMMUNICATION

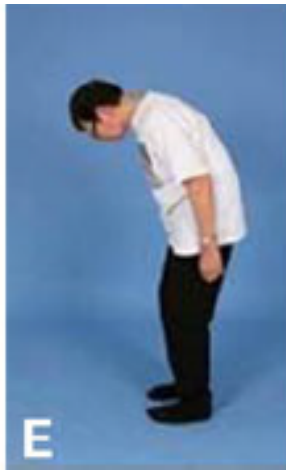
A novel late-onset axial myopathy associated with mutations in the skeletal muscle ryanodine receptor (*RYR1*) gene

Sissel Løseth · Nicol C. Voermans · Torberg Torbergsen · Sue Lillis · Christoffer Jonsrud · Sigurd Lindal · Erik-Jan Kamsteeg · Martin Lammens · Marcus Broman · Gabriele Dekomien · Paul Maddison · Francesco Muntoni · Caroline Sewry · Aleksandar Radunovic · Marianne de Visser · Volker Straub · Baziel van Engelen · Heinz Jungbluth





- 77-year-old with 5-10 years of progressive trunk extension weakness
- dominant mutation in *RYR1*



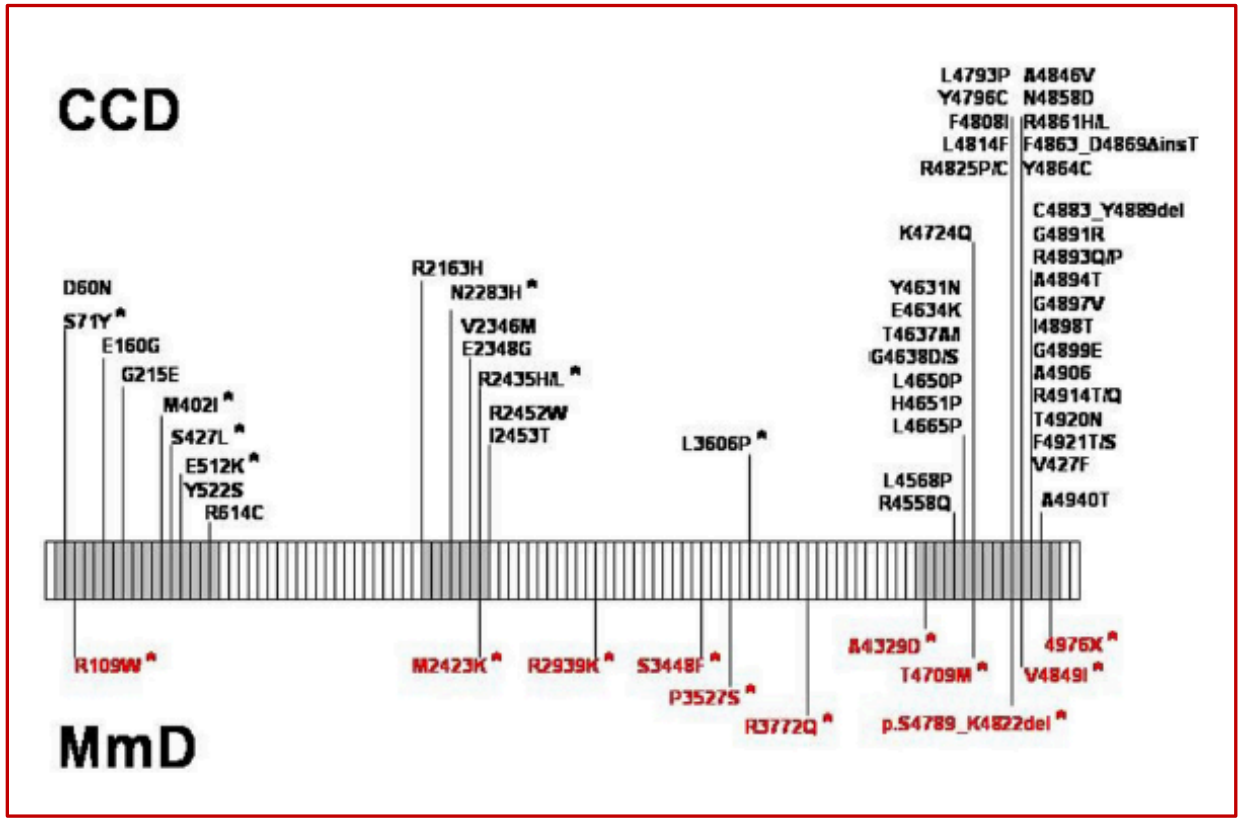
- Onset in 60s of progressive trunk extension weakness
- dominant mutation in *RYR1*

RYR1-Related Myopathies:
WIDE Phenotypic (Clinical) Spectrum

- **Severe neonatal form**
  - With respiratory involvement
  - With poor feeding
  - With arthrogryposis
- **Congenital myopathy**
  - With restricted extraocular movements
  - With hypotonia
  - With scoliosis
- **Congenital myopathy**
  - With clear proximal weakness during childhood and predominantly limb girdle weakness in adulthood
- **Late-onset axial myopathy**
  - Late adult onset weakness of trunk extension

RYR1 genetics

With the increased availability of next generation sequencing, the clinical spectrum associated with RYR1 mutations will likely continue to expand



Jungbluth. *Orphanet J of Rare Dis*. 2007

Paroxysmal "Episodes": related to abnormal functioning of the *RYR1*-encoded calcium release channel

Malignant Hyperthermia Susceptibility (MHS):

"a pharmacogenetic disorder of skeletal muscle that presents as a hypermetabolic response to potent volatile anesthetic gases such as halothane, sevoflurane, desfurane, isoflurane and the depolarizing muscle relaxant succinylcholine, and rarely, in humans, to stressors such as vigorous exercise and heat"

Signs: hyperthermia, tachycardia, tachypnea, increased carbon dioxide production, increased oxygen consumption, acidosis, hyperkalemia, muscle rigidity and rhabdomyolysis

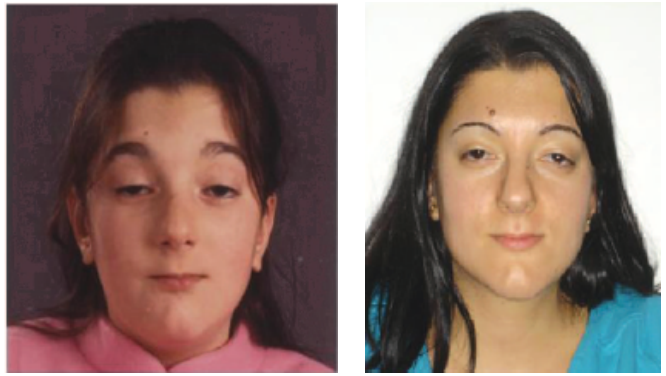
Rosenberg et al. *Orphanet J Rare Dis*. 2007

King-Denborough Syndrome: may be a form of *RYR1*-related myopathy

KING-DENBOROUGH SYNDROME CAUSED BY A NOVEL MUTATION IN THE RYANODINE RECEPTOR GENE

Neurology 71 September 2, 2008

C.E. D'Arcy, BMSc (Hons)
A. Bjorksten, PhD
E.M. Yiu, MBBS, FRACP
A. Bankier, MBBS (Hons), FRACP
R. Gillies, MBBS (Hons), FANZCA
C.A. McLean, MBBS, MD, BSc, FRCPA
L.K. Shield, MBBS, FRACP
M.M. Ryan, MBBS, MMed,



Characteristic features:
- ptosis
- prominent philtrum
- low set ears
- webbed neck
- short stature
- spinal rigidity
- scoliosis

- Tendency toward anesthesia-induced malignant hyperthermia (MH)
- Proximal weakness
- Characteristic features

RYR1-Related Exertional Myalgia and Rhabdomyolysis (EMR)

Available online at www.sciencedirect.com
SciVerse ScienceDirect
Neuromuscular Disorders 23 (2013) 540–548
www.elsevier.com/locate/nmd

Mutations in *RYR1* are a common cause of exertional myalgia and rhabdomyolysis

N. Dlamini [a,1], N.C. Voermans [b,1], S. Lillis [c], K. Stewart [c], E.-J. Kamsteeg [d], G. Drost [b], R. Quinlivan [e], M. Snoeck [f], F. Norwood [g], A. Radunovic [h], V. Straub [i], M. Roberts [j], A.F.J.E. Vrancken [k], W.L. van der Pol [k], R.I.F.M. de Coo [l], A.Y. Manzur [m], S. Yau [c], S. Abbs [c], A. King [n], M. Lammens [o], P.M. Hopkins [p], S. Mohammed [q], S. Treves [r], F. Muntoni [m], E. Wraige [a], M.R. Davis [s], B. van Engelen [b,1], H. Jungbluth [a,t,u,*,1]

Despite the same RYR1 mutation (p.Gly2434Arg):

Mother: recurrent rhabdomyolysis; limb-girdle weakness (5th decade)
Daughter: recurrent rhabdomyolysis
Son: baseline hyperCKemia (high CK), muscle hypertrophy

All 3 family members have ptosis (surgically corrected in mother)

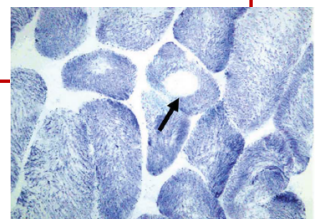
Paroxysmal “Episodes” related to Channel Function

Atypical periodic paralysis and myalgia

A novel *RYR1* phenotype

Emma Matthews, MRCP, Christoph Neuwirth, MD, Fatima Jaffer, MRCP, Renata S. Scalco, MD, Doreen Fialho, MRCP, Matt Parton, FRCP, Dipa Raja Rayan, MRCP, Karen Suetterlin, MRCP, Richa Sud, PhD, Roland Spiegel, MD, Rachel Mein, BSc, Henry Houlden, FRCP, Andrew Schaefer, MRCP, Estelle Healy, FRCPath, Jacqueline Palace, FRCP, Ros Quinlivan, FRCP, Susan Treves, PhD, Janice L. Holton, FRCPath, Heinz Jungbluth, PhD,* and Michael G. Hanna, FRCP*

Neurology® 2018;90:e412-e418. doi:10.1212/WNL.0000000000004894



Neuromuscular Disorders 20 (2010) 166–173

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Multi-minicore disease and atypical periodic paralysis associated with novel mutations in the skeletal muscle ryanodine receptor *(RYR1)* gene

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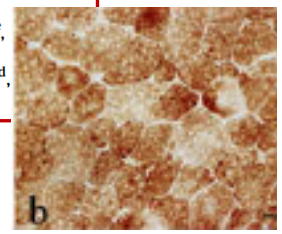
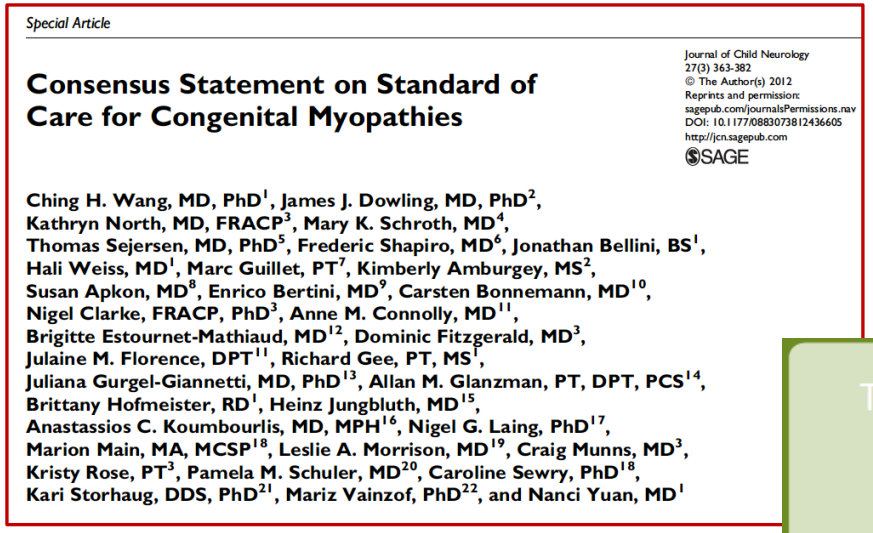


- some patients with history of proximal weakness
- episodes are later-onset (late teenage years – 30s)
- episodes of sudden, severe myalgias followed by severe weakness lasting for several hours
- episodic cramps and myalgias also common

Optimizing Care in *RYR1*-Related Myopathies



Special Article

Consensus Statement on Standard of Care for Congenital Myopathies

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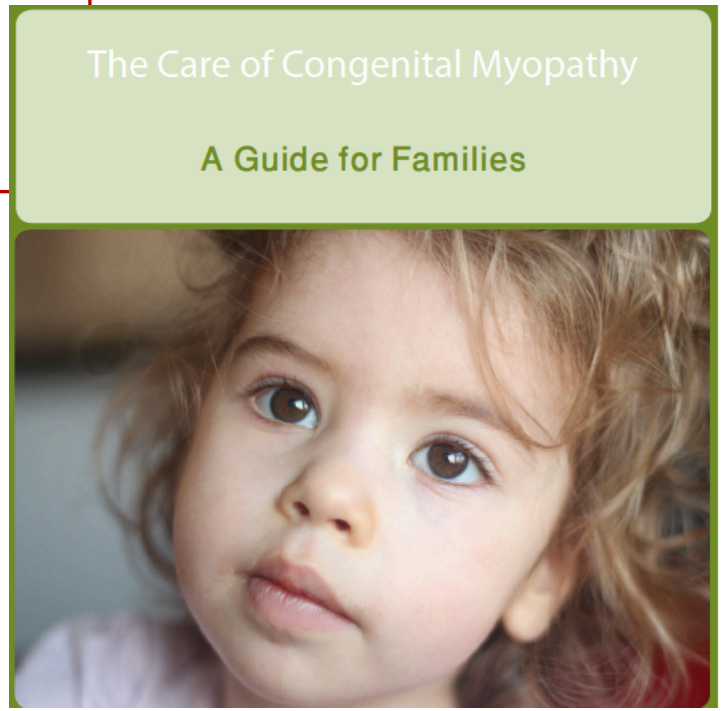
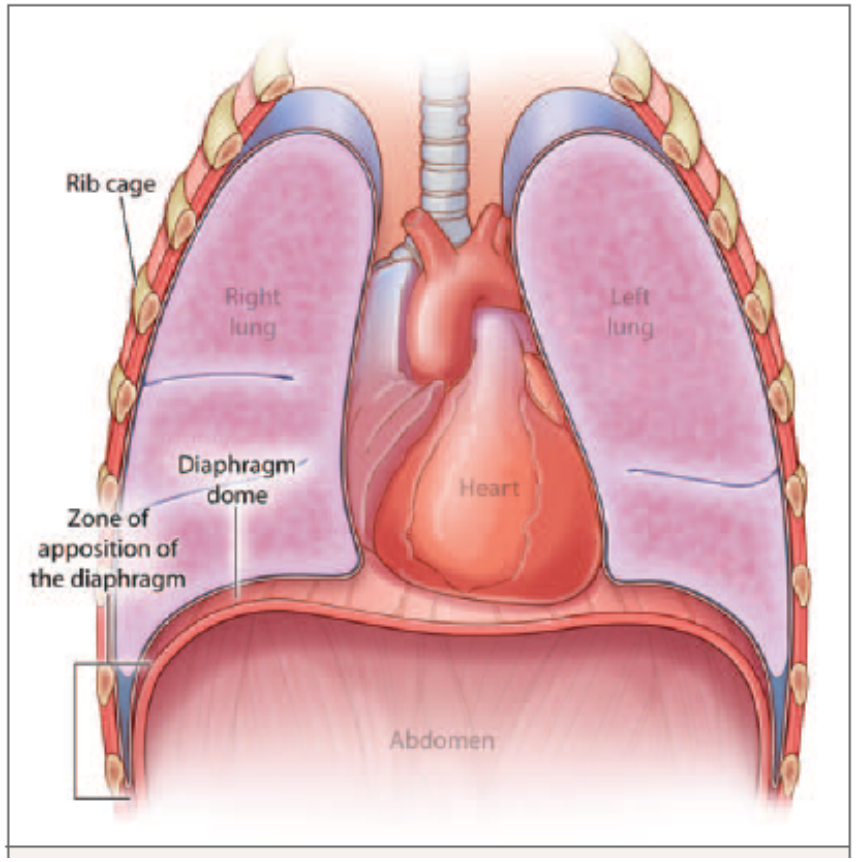


www.curecmd.org/care-guidelines

- Respiratory
- Nutrition
- Spine surveillance
- Physical therapy

Instead of "Reactive" Respiratory Care, "Proactive" Respiratory Care



McCool et al. Dysfunction of the Diaphragm. *NEJM*. 2012

"Restrictive" lung pattern

= most common pattern in congenital myopathies

There is restricted lung expansion due to weakness of the intercostal muscles, weakness of the diaphragm and decreased compliance of the chest wall: **"extrinsic" causes of "restrictive" lung disease**

Sleep Study or "Polysomnogram"

- The gold standard for assessing for nocturnal / sleep hypoventilation
- Carbon dioxide (CO_2) should be monitored throughout the sleep study
- In sleep hypoventilation, CO_2 increases in deep sleep
- BiPAP: Bilevel Positive Airway Pressure

  = the recommended form of non-invasive ventilation (NIV) for congenital muscle disease

"BiPAP is your Buddy"

Cough Assist Machine
= Insufflator / Exsufflator

- Alternates positive and negative airway pressure
- Stimulates cough (and thus helps to expectorate phlegm)
- Increased use during and immediately following respiratory infections is essential to help clear mucous: so-called “airway clearance”
- Daily use of the Cough Assist Machine (on the “Insufflation” mode) helps to promote chest wall and lung compliance

Progressing Toward Clinical Trials in the *RYR1*-Related Myopathies:

- **Optimize care**
- **Comprehensive natural history studies**
- **Patient registry**

"We tend to assume that the medical staff will always know what is best. I think if we enter every situation realizing that each of us has useful knowledge and experience with CM, it helps to remind us that we (parents and those affected) can contribute in helpful ways and even educate others. We are all on the same team." - a mother of a child with CM

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Patient Organizations and Research on Rare Diseases

Julie R. Ingelfinger, M.D., and Jeffrey M. Drazen, M.D.

LAM is not the only medical condition in which patient groups have sponsored both clinical and basic research, have located patients to participate in trials, and have enlisted the help of expert clinicians and investigators. Other examples are cystic fibrosis, Huntington's disease, Waldenström's macroglobulinemia, oxalosis and primary hyperoxaluria, cystinosis, autosomal recessive polycystic kidney disease, and Duchenne's muscular dystrophy, to name just a few. In each case, patients have formed groups to drive research aimed at understanding and treating their particular illness. The key to success for such groups has been to support basic research that is held to the highest scientific standards.

(2011)