Assessing the Future of Therapies in Development for LIMB GIRDLE MUSCULAR DYSTROPHY

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Assessing the Future of Therapies in Development for Limb Girdle Muscular Dystrophy

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PROGRAM OVERVIEW

This educational activity is designed for neurologists and associated health care practitioners (HCPs) including neuromuscular specialists, pediatric and developmental neurologists, pediatricians, geneticists, physical and occupational therapists, nurse practitioners and physicians' assistants, that are involved in the management of patients with limb girdle muscular dystrophy (LGMD). Specifically, the program will help HCPs assess the burden of LGMD to help justify the medical need for development of a viable therapy for patients whose only current alternative is supportive care. The program will introduce various investigational therapies for the treatment of LGMD and also help HCPs incorporate genetic testing as a routine procedure into the diagnostic process.

TARGET AUDIENCE

This activity is intended for general neurologists, particularly those that see older patients, pediatric and developmental neurologists, neuromuscular specialists, pediatricians, geneticists, genetic counsellors, physical and occupational therapists, nurse practitioners, and physician assistants involved in the management of patients with limb girdle muscular dystrophy (LGMD).

LEARNING OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Assess the burden of illness associated with LGMDs
- Incorporate genetic testing into the diagnostic process for LGMD
- Justify the medical need to develop a viable therapy for patients with LGMD, for whom supportive care is presently the only available option
- Evaluate the investigational therapies for the treatment of LGMD

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Aravindhan Veerapandiyan, MD	Consultant/Advisory Board	AMO Pharma, AveXis, Biogen, Edgewise Therapeutics, FibroGen, Novartis, Pfizer, PTC Therapeutics, Sarepta Therapeutics, UCB Pharma, Catalyst, Lupin, Entrada, Italfarmaco, and Scholar Rock
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NE-63L Assessing the Future of Therapies in Development for Limb Girdle Muscular Dystrophy

AGENDA

I. Brief Overview of LGMD

a. History
b. Pathophysiology/classification
c. New nomenclature

II. Relative Prevalence of LGMD

a. Physical, emotional, social, and economic burdens
b. Impact of burdens on caregivers, family, and healthcare systems

III. Diagnosing LGMD

a. Old paradigm for diagnosis
b. The rationale for genetic testing
c. Single gene, panel, and exome testing
d. Expanded genetic testing
e. New paradigm for diagnosis incorporating evidence-based recommendations for genetic testing into clinical practice

IV. The LGMD Treatment Landscape

a. Development of viable therapy for patients with LGMD
b. Symptomatic therapies and multidisciplinary team for management of symptoms of LGMD
c. Unique MOAs of investigational therapies for the treatment of various subtypes of LGMD
d. Ongoing studies of investigational therapies

V. Case Studies

VI. Conclusions

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Little Rock, AR

Disclosures

Dr Wicklund discloses the following

Relationship	Manufacturer
Consultant	Amicus Therapeutics, Lupin, ML Bio Solutions, Sarepta Therapeutics, Spark Therapeutics, UCB, Ultragenyx
Contracted Research	Avidity, Edgewise, Fulcrum, Harmony, ML Bio, Sarepta Therapeutics

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Relationship	Manufacturer
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Contracted Research	AMO Pharma, Capricor Therapeutics, Edgewise Therapeutics, FibroGen, Muscular Dystrophy Association, Novartis, Parent Project Muscular Dystrophy, Pfizer, RegenxBio, and Sarepta Therapeutics
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During the course of this lecture, Drs Wicklund and Veerapandiyan may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications.

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Learning Objectives

- Assess the burden of illness associated with limb girdle muscular dystrophy (LGMD)
- Incorporate genetic testing into the diagnostic process for LGMD
- Justify the medical need to develop a viable therapy for patients with LGMD, for whom supportive care is presently the only available option
- Evaluate the investigational therapies for the treatment of LGMD

Introduction to LGMD

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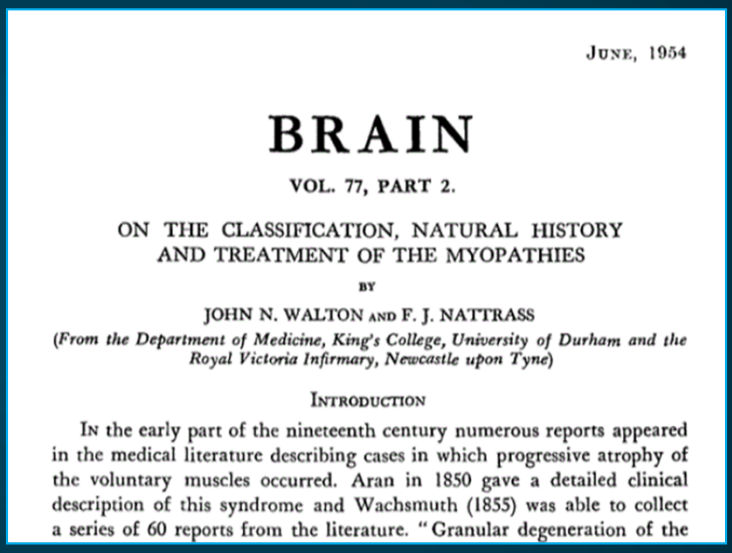
History

1954 – Lord John Walton and Frederick Nattrass

- Proposed LGMD as a distinct clinical entity
- Initially, they distinguished cases from the 3 most common muscular dystrophies



JUNE, 1954

BRAIN

VOL. 77, PART 2.

ON THE CLASSIFICATION, NATURAL HISTORY AND TREATMENT OF THE MYOPATHIES

BY

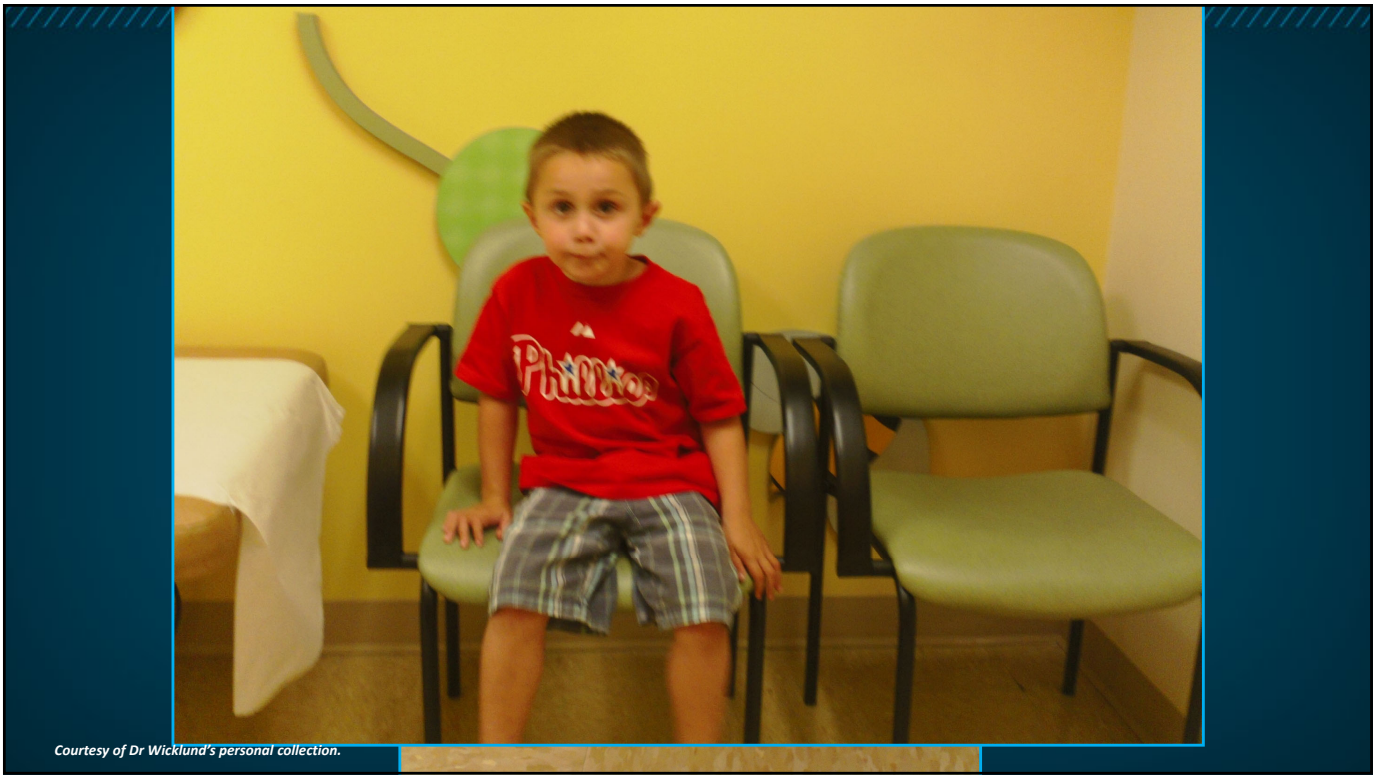
JOHN N. WALTON AND F. J. NATTRASS

(From the Department of Medicine, King's College, University of Durham and the Royal Victoria Infirmary, Newcastle upon Tyne)

INTRODUCTION

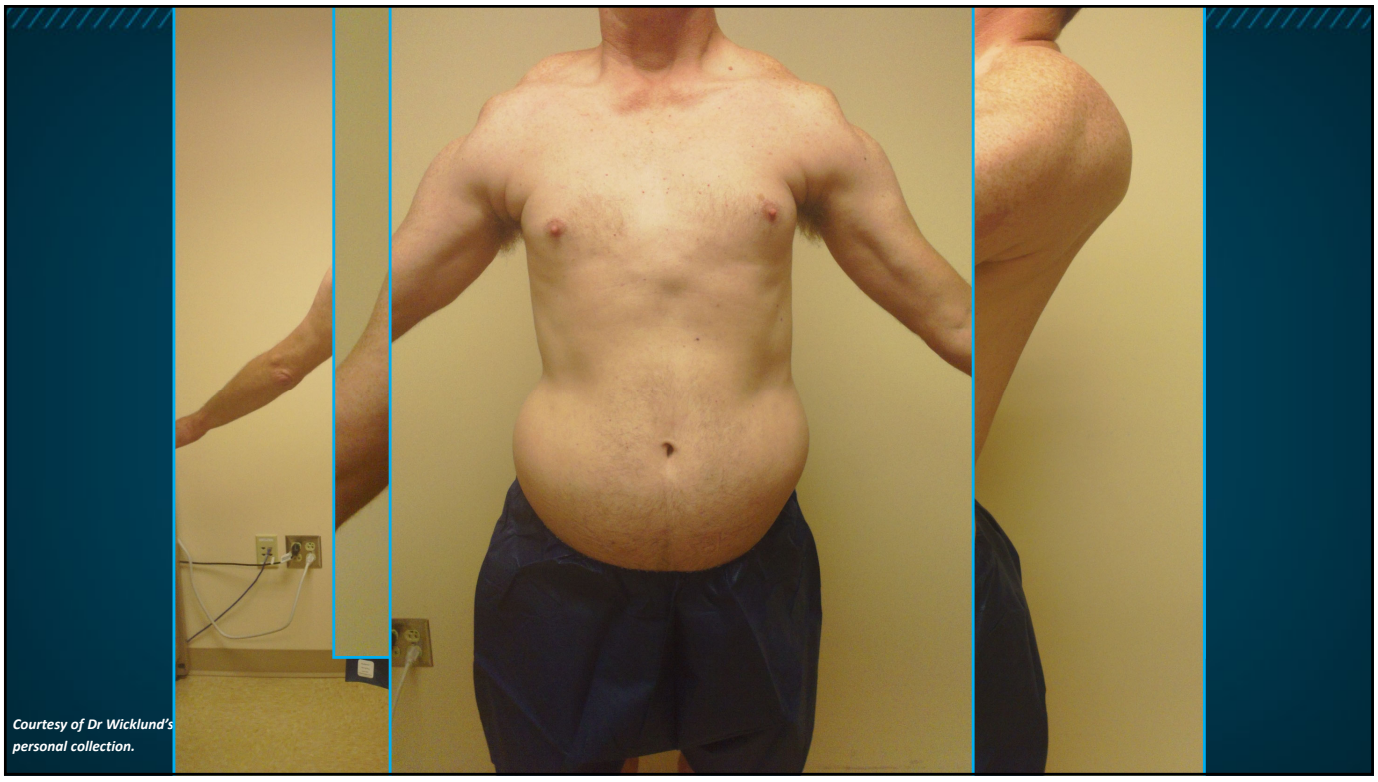
IN the early part of the nineteenth century numerous reports appeared in the medical literature describing cases in which progressive atrophy of the voluntary muscles occurred. Aran in 1850 gave a detailed clinical description of this syndrome and Wachsmuth (1855) was able to collect a series of 60 reports from the literature. "Granular degeneration of the

Walton JN, Nattrass FJ. *Brain*. 1954;77(2):169-231.



Courtesy of Dr Wicklund's personal collection.


Courtesy of Dr Wicklund's personal collection.

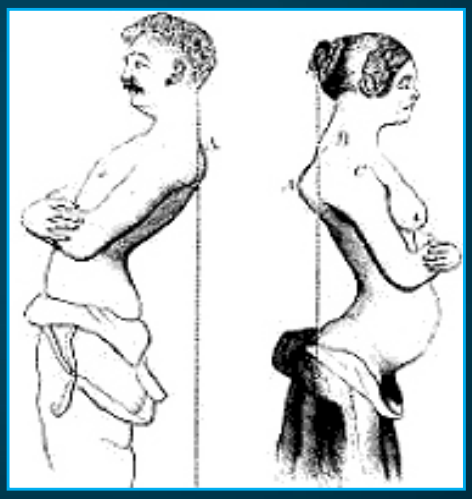

Courtesy of Dr Wicklund's personal collection.

Limb Girdle Muscle Weakness

"Post-natal onset of progressive weakness and muscle atrophy affecting proximal muscles of the lower and upper extremities."

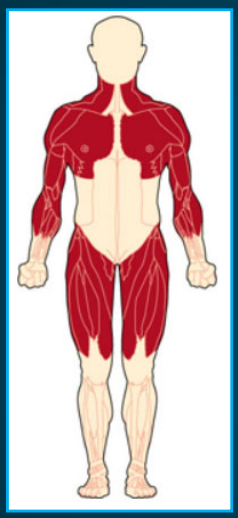
—Dr Wicklund

LGMD

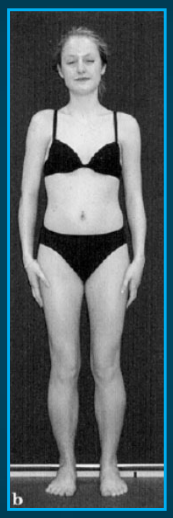


Neuromuscular. Muscular dystrophy syndromes, 2024 (https://neuromuscular.wustl.edu/musdist/lg.html). Accessed 5/14/2024. Quote by Dr. Wicklund.

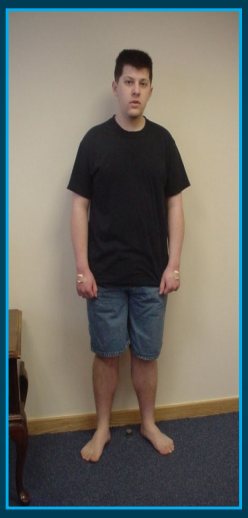
Limb Girdle Weakness



MDA. https://www.mda.org/disease/becker-muscular-dystrophy

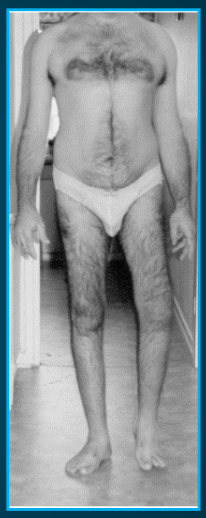


Mercuri E, et al. *Ann Neurol.* 2003;53:537-542.



Courtesy of Dr Wicklund's personal collection.

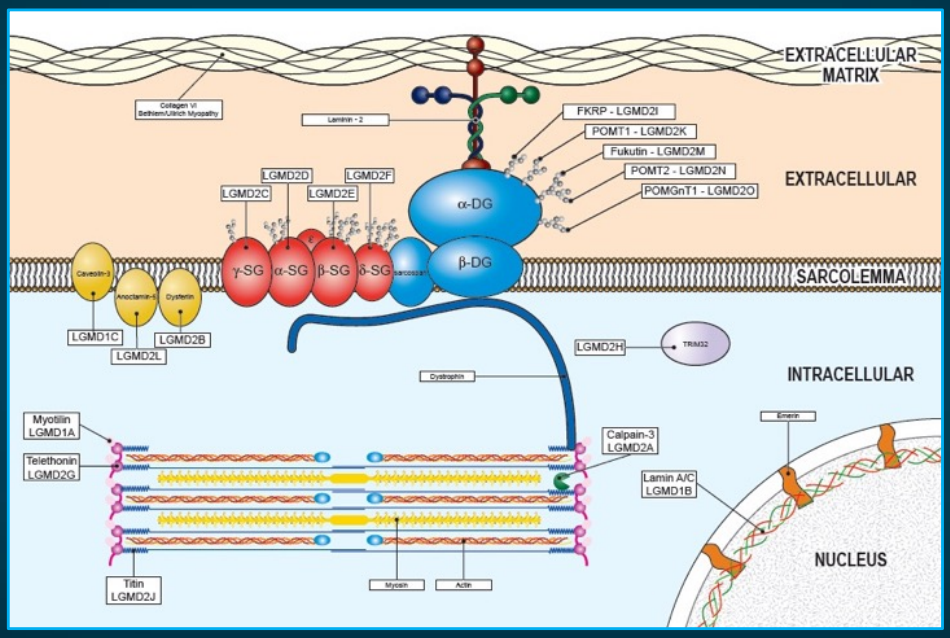
Fardeau M, et al. *Brain.* 1996;119:295-308.



Mahjneh I, et al. *Neuromuscul Disord.* 2001;11:20-26.

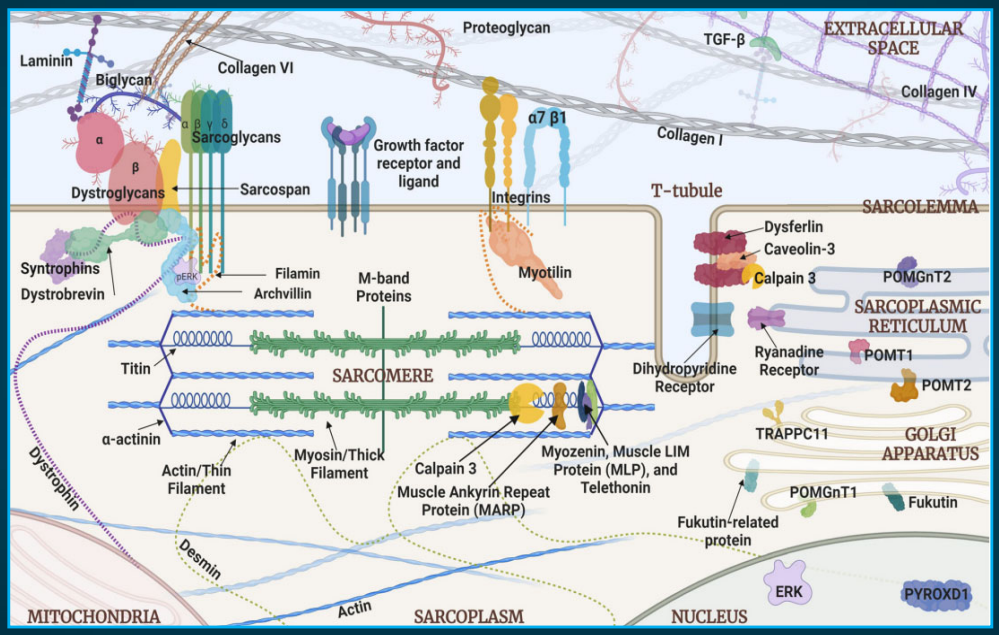
Muscular Dystrophy Association (MDA). Becker muscular dystrophy (https://www.mda.org/disease/becker-muscular-dystrophy). Accessed 5/14/2024.

Subcellular Localization of the Limb Girdle Muscular Dystrophies



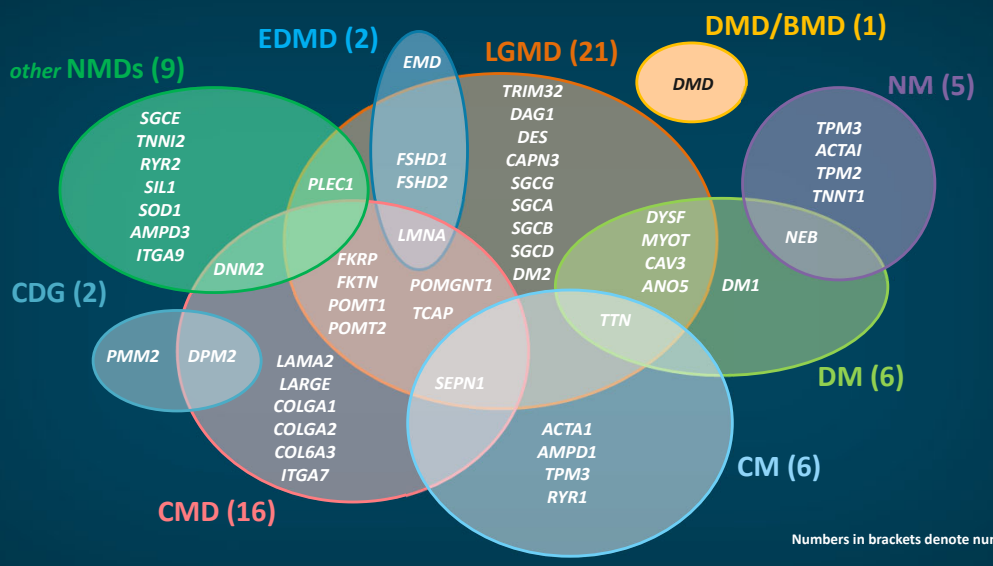
Wicklund M. *Continuum.* 2019;25:1599-1618.

Proteins Associated With Limb Girdle Muscular Dystrophy



Barton ER, et al. *Skelet Muscle.* 2020;10:22.

LGMD and Other Muscular Dystrophies



Numbers in brackets denote number of genes.

Multiple, overlapping phenotypes associated with numerous gene loci

CDG = congenital disorders of glycosylation; CM = congenital myopathy; CMD = congenital muscular dystrophy; DM = myotonic dystrophy; DMD/BMD = Duchenne muscular dystrophy/Becker muscular dystrophy; EDMD = Emery-Dreifuss muscular dystrophy; NM = nemaline myopathy; NMD = neuromuscular disorders.

Liewluck T, Milone M. *Muscle Nerve*. 2018;58(2):167-177. Neuromuscular. Muscular dystrophy syndromes, 2024 (https://neuromuscular.wustl.edu/musdist/lg.html). Accessed 5/14/2024.

Limb Girdle Weakness

- 26+ autosomal recessive LGMDs
- 10+ autosomal dominant LGMDs
- 20+ distal myopathies (1A, 1E, 2B, 2L)
- 7+ EDMD (1B)
- 13+ myofibrillar myopathies (1A, 1E)
- 7+ metabolic myopathies
- 3 dystrophinopathies (Duchenne, Becker, and carriers)
- 1 lysosomal storage disease

300+ genes in total

Benarroch L, et al. *Neuromuscular Disord*. 2023;33(1):76-117.

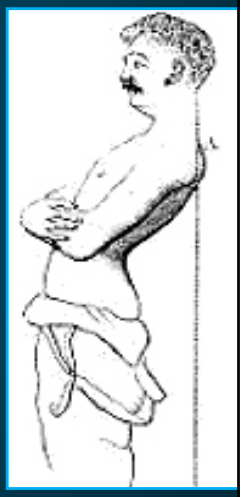
2018 ENMC LGMD Definition

1. Genetically inherited condition
2. Primarily affects skeletal muscle
3. Leads to progressive, predominantly proximal muscle weakness at presentation
4. Caused by loss of muscle fibers

Criteria to be classified as a LGMD subtype

1. Be described in at least 2 unrelated families
2. Individuals must achieve independent walking
3. Elevated serum creatine kinase (CK) levels
4. Degenerative changes on muscle imaging
5. A dystrophic pattern on muscle biopsy

LGMD



ENMC = European Neuromuscular Center.

Straub V, et al. *Neuromuscular Disord*. 2018;28(8):702-710.

How Do We Talk About the LGMDs?

OLD

- LGMDs subdivided into autosomal dominant and autosomal recessive
  - LGMD1 = dominant
  - LGMD2 = recessive
- Each LGMD received a letter designation delineating the order in which the chromosomal locus was discovered
  - LGMD2A = calpainopathy—first discovered
  - LGMD2B = dysferlinopathy—second discovered
  - LGMD2Z = POGLUT1—26th discovered

NEW

- Named as follows
  - LGMD
    - R for recessive or D for dominant
      - Order of gene discovery
        - » Affected protein
- Some former subtypes were removed (eg, LGMD1A-C,E)
- Proposed
  - LGMD2A -> LGMD R1-calpain3-related
  - Bethlem -> LGMD D5-collagen 6-related

Straub V, et al. *Neuromuscular Disord*. 2018;28(8):702-710.

Some Common LGMD Subtypes: Old and New Nomenclature

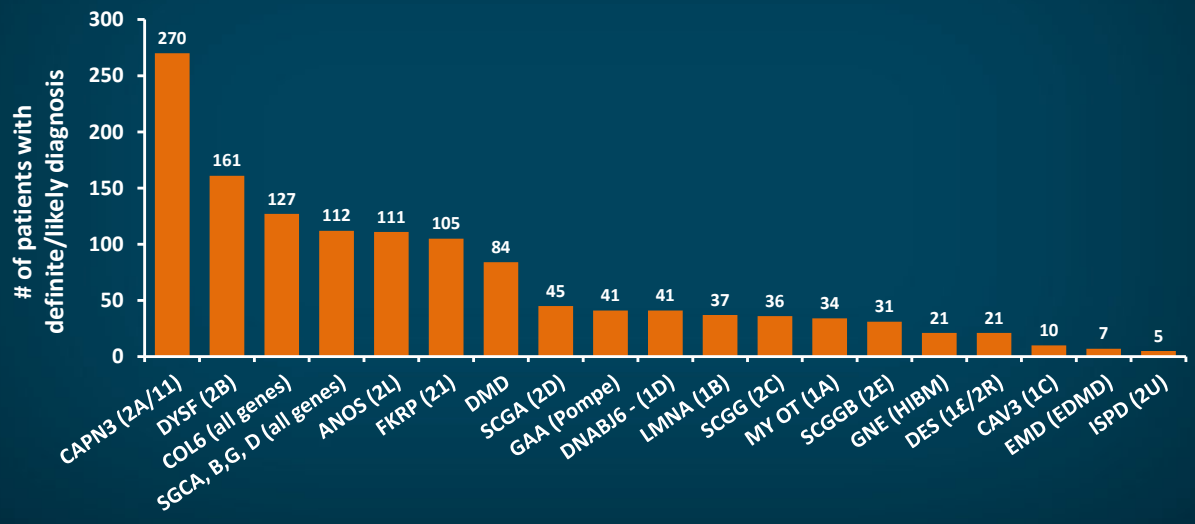
OLD SUBTYPE	NEW SUBTYPE	GENE	GENE PRODUCT
LGMD1B		LMNA	Lamin A/C
LGMD1D	LGMDD1	DNAJB6	Molecular chaperone protein
	LGMDD5	COL6A1/2/3	Collagen VI
LGMD2A	LGMDR1	CAPN3	Calpain-3
LGMD1I	LGMDD4	CAPN3	Calpain-3
LGMD2B	LGMDR2	DYSF	Dysferlin
LGMD2C	LGMDR5	SGCG	g-sarcoglycan
LGMD2D	LGMDR3	SGCA	a-sarcoglycan
LGMD2E	LGMDR4	SGCB	b-sarcoglycan
LGMD2F	LGMDR6	SGCD	d-sarcoglycan
LGMD2L	LGMDR12	ANO5	Anoctamin 5
LGMD2V		GAA	A-1, 4-glucosidaseGE

Barton ER, et al. *Skelet Muscle*. 2020;10:22.

LGMD Relative Prevalence

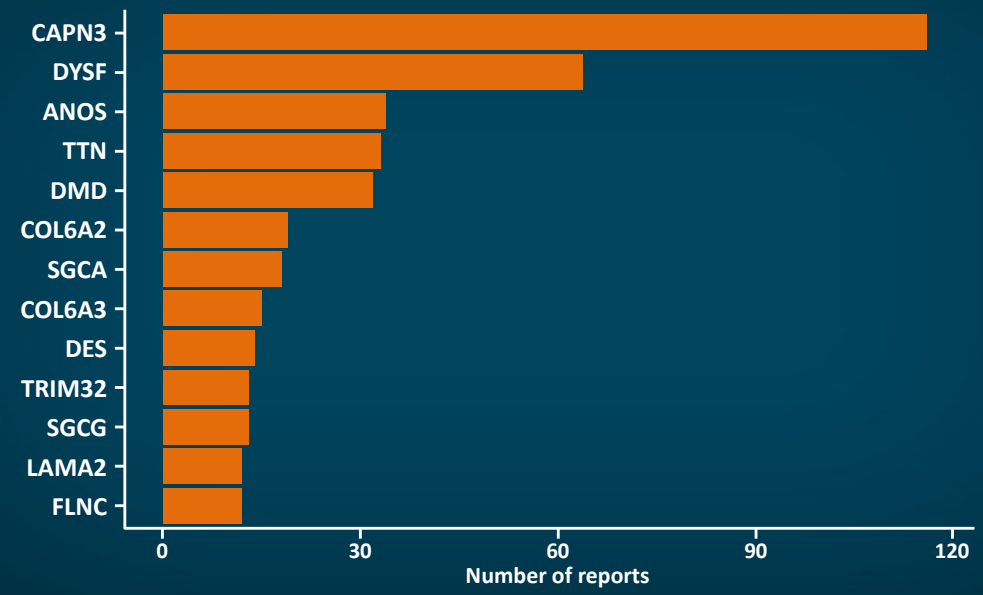
USA

Relative prevalence in ~4600 patients from LGMD sequencing programs



Nallamilli BRR, et al. *Ann Clin Transl Neurol.* 2018;5(12):1574-1587. Pooled data presented by Dr Wicklund, unpublished.

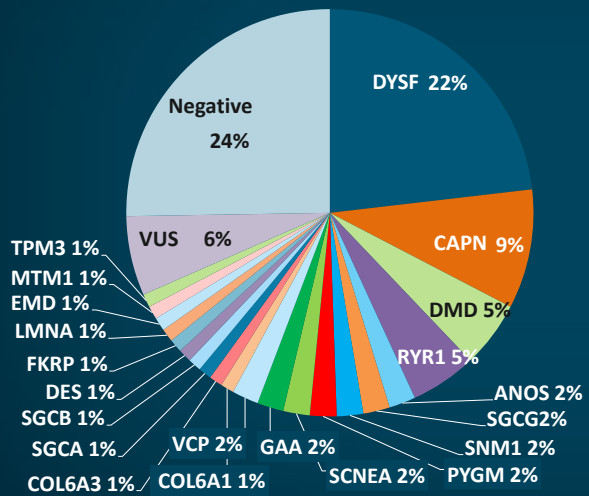
MYO-SEQ Data From Europe: 1001 Patients



Töpf A, et al. *Genet Med.* 2020;22:1478-1488.

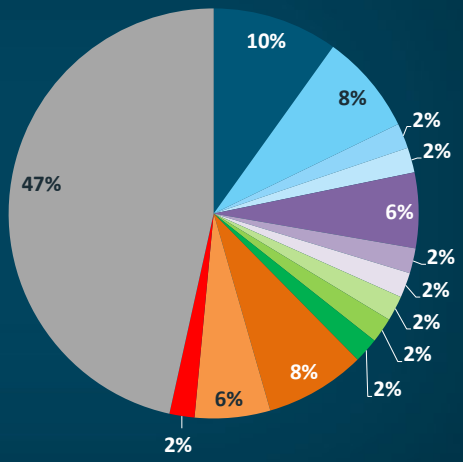
South America

Chile



DYSF > CAPN3 > DMD > RYR1 (SMN1…)

Brazil

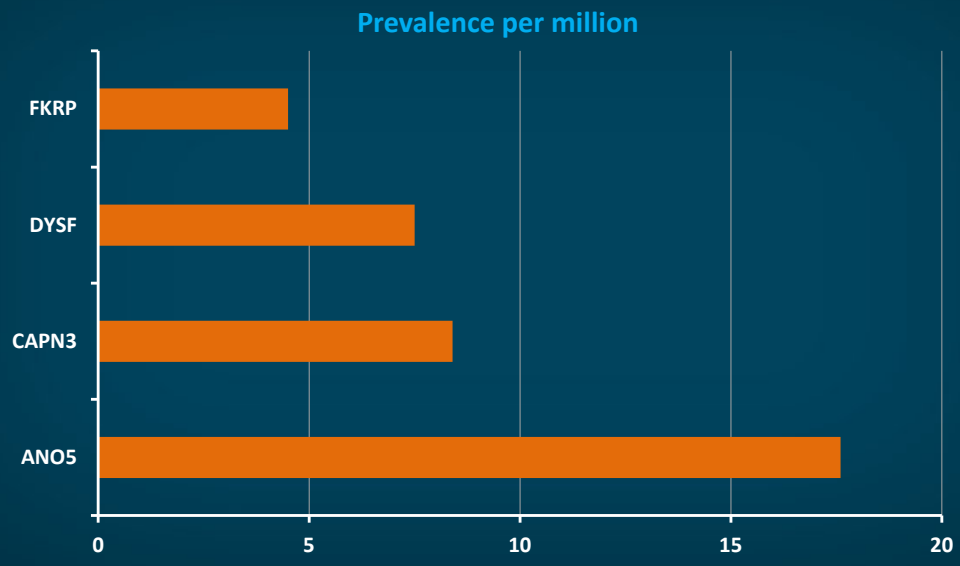


N = 51

CAPN3 > DYSF > RYR1 > COL6A > EMD

Cerino M, et al. *Genes.* 2022;13:1076. Winckler PB, et al. *Neurol Sci.* 2022;43:4473-4481.

Prevalence From Genetic Databases



ANO5 = anoctamin 5; CAPN3 = calpain 3; DYSF = dysferlin; FKRP = fukutin-related protein.

Liu W, et al. *Genet Med.* 2019;21(11):2512-2520.

Minimum Prevalence Estimates of LGMD Occurrence

- 2.27 per 100,000 in the north of England (2009 data)
- 1.44 per 100,000 in the Netherlands

- ~1 to 3 per 100,000 in USA
  - ~10,000 = total number of persons with LGMD in the USA

Norwood FL, et al. *Brain.* 2009;132(pt 11):3175–3186. Bardakov SN, et al. *Mol Genet Genomic Med*. 2023;11(10):e2236. Doody A, et al. *BMC Neurol*. 2024;24:96.

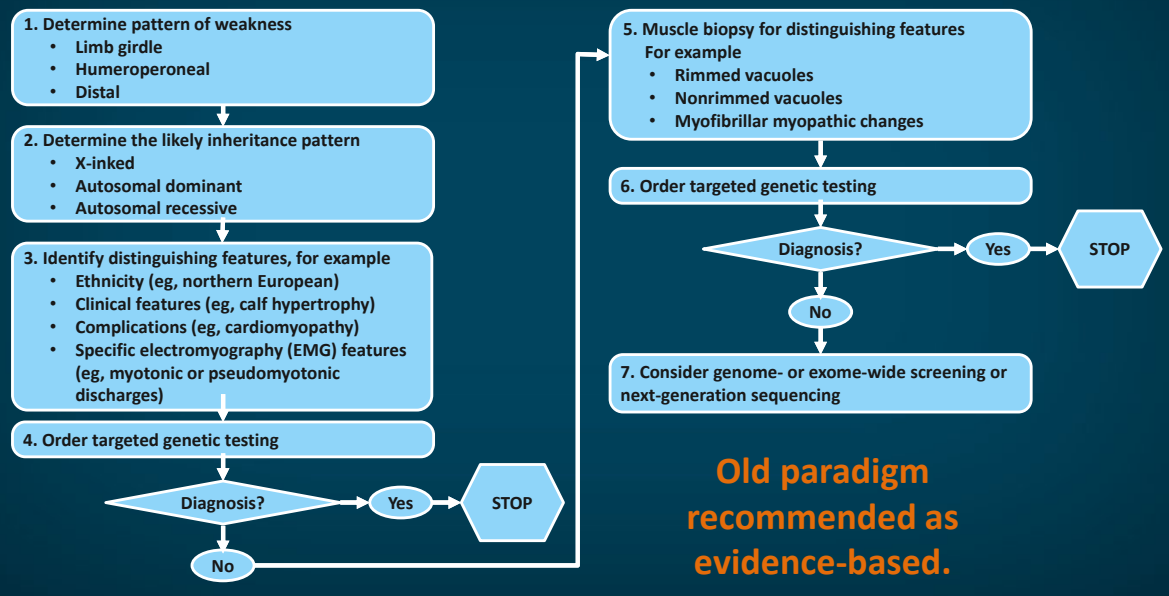
Animation 1

Depiction of LGMD pathophysiology

Recommendations Related to Diagnosis

Diagnosis

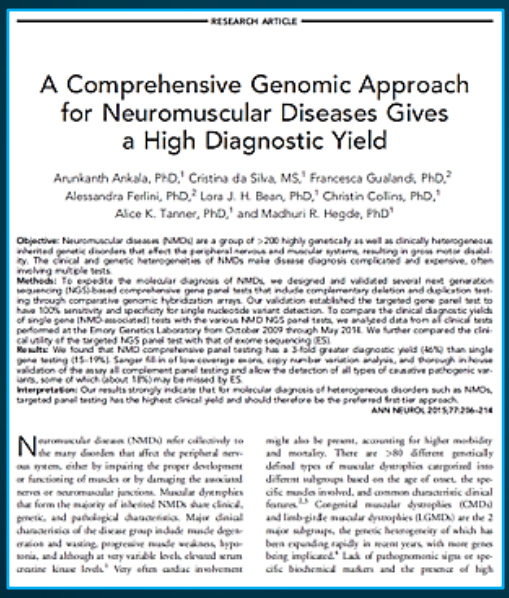
Conceptual approach to a patient with a suspected limb girdle muscular dystrophy



Old paradigm recommended as evidence-based.

Narayanaswami P, et al. *Neurology*. 2014;83(16):1453-1463.

Single Gene vs Panel vs Exome



RESEARCH ARTICLE

A Comprehensive Genomic Approach for Neuromuscular Diseases Gives a High Diagnostic Yield

Arunkanth Arikala, PhD,[1] Cristina da Silva, MS,[1] Francesca Gualandi, PhD,[2] Alessandra Ferlini, PhD,[2] Lora J. H. Bean, PhD,[1] Christin Collins, PhD,[1] Alice K. Tanner, PhD,[1] and Madhuri R. Hegde, PhD[1]

Objective: Neuromuscular diseases (NMDs) are a group of >200 highly genetically as well as clinically heterogeneous inherited genetic disorders that affect the peripheral nervous and muscular systems, resulting in gross motor disability. The clinical and genetic heterogeneities of NMDs make disease diagnosis complicated and expensive, often involving multiple tests.
Methods: To expedite the molecular diagnosis of NMDs, we designed and validated several next generation sequencing (NGS)-based comprehensive gene panel tests that include complementary deletion and duplication testing through comparative genomic hybridization arrays. Our validation established the targeted gene panel test to have 100% sensitivity and specificity for single nucleotide variant detection. To compare the clinical diagnostic yields of single gene (NMD-associated) tests with the various NMD NGS panel tests, we analyzed data from all clinical tests performed at the Emory Genetics Laboratory from October 2009 through May 2014. We further compared the clinical utility of the targeted NGS panel test with that of exome sequencing (ES).
Results: We found that NMD comprehensive panel testing has a 2-fold greater diagnostic yield (46%) than single gene testing (15–19%). Sanger fill-in of low-coverage exons, copy number variation analysis, and thorough in-house validation of the assay all complement panel testing and allow the detection of all types of causative pathogenic variants, some of which (about 18%) may be missed by ES.
Interpretation: Our results strongly indicate that for molecular diagnosis of heterogeneous disorders such as NMDs, targeted panel testing has the highest clinical yield and should therefore be the preferred first-tier approach.

ANN NEUROL 2015;77:206–214

Neuromuscular diseases (NMDs) refer collectively to the many disorders that affect the peripheral nervous system, either by impairing the proper development or functioning of muscles or by damaging the associated nerves or neuromuscular junctions. Muscular dystrophies that form the majority of inherited NMDs share clinical, genetic, and pathological characteristics. Major clinical characteristics of the disease group include muscle degeneration and wasting, progressive muscle weakness, hypotonia, and although at very variable levels, elevated serum creatine kinase levels.[1] Very often cardiac involvement might also be present, accounting for higher morbidity and mortality. There are >80 different genetically defined types of muscular dystrophies categorized into different subgroups based on the age of onset, the specific muscles involved, and common characteristic clinical features.[2,3] Congenital muscular dystrophies (CMDs) and limb-girdle muscular dystrophies (LGMDs) are the 2 major subgroups, the genetic heterogeneity of which has been expanding rapidly in recent years, with more genes being implicated.[4] Lack of pathognomonic signs or specific biochemical markers and the presence of high

Diagnostic yields

- Single gene = 15% to 19%
- Panel = 46%
- Exome = ~37%

- Genome = ~60% to 80%???

Ankala A, et al. *Ann Neurol*. 2015;77(2):206-214.

Expanded Genetic Testing

Past

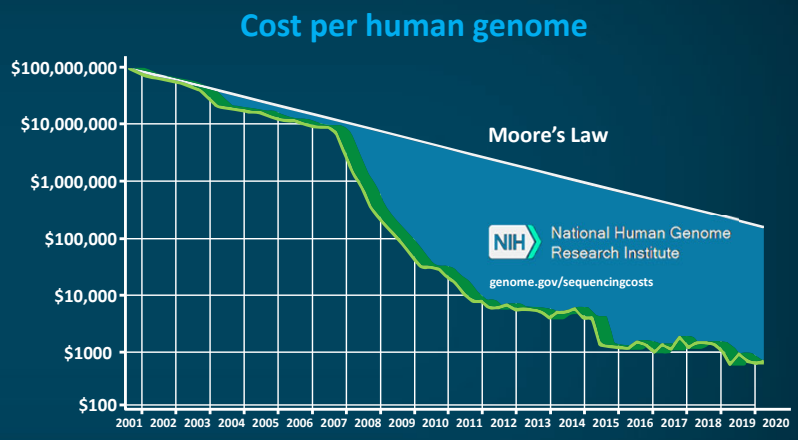
- Numerator testing
- Tautological understanding of disease

Future

- Denominator testing
- More understanding of the full breadth and intricacies of disorders

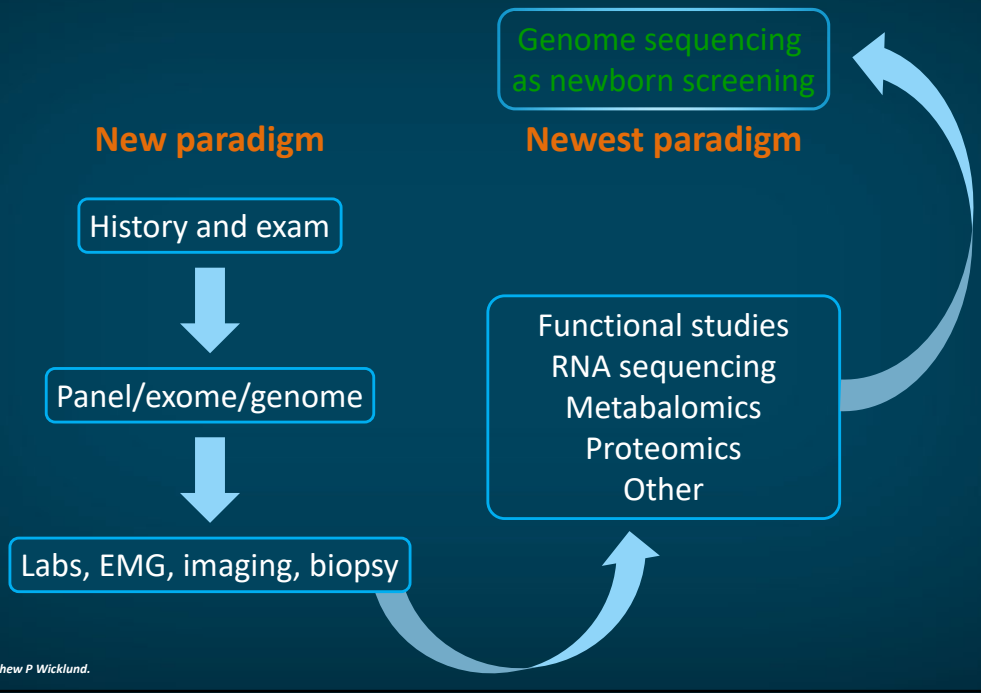
Genome Cost Dropping Precipitously

- 1993 to 2003: First genome, ~$1 to $3 billion
- 2007: ~$8 million
- Current genome: ~$450 to run
  - ~$1000 total
- Illumina technology
  - $100, 1-hour genome



National Institutes of Health (NIH) National Human Genome Research Institute. The cost of sequencing a human genome (https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost). Accessed 5/14/2024.

Diagnosis

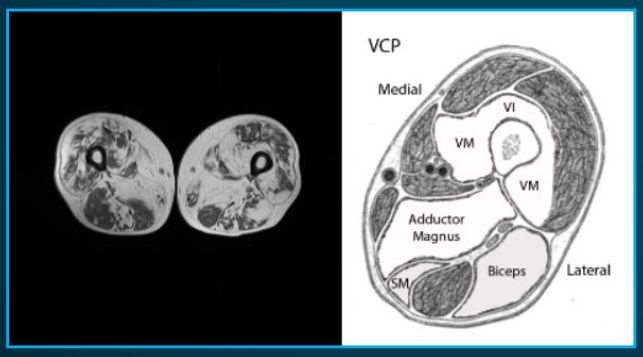


Flowchart courtesy of Dr Mathew P Wicklund.

What If Genetic Testing Is Negative or Equivocal?

Consider acquired disorder

- HMGCR Ab+ myositis
- Anti-SRP myopathy



Further genetics

- Test for repeat sequence disorders
  - DM2, FSHD, OPMD, others
- Genome sequencing
- Consider multigenic modes of inheritance
- Variant resolution/confirmation
  - Evaluate other family members
  - RNA sequencing, proteomics, other
  - Ancillary testing (eg, bone specific alkaline phosphatase and magnetic resonance imaging [MRI] in VCP)

VCP = valosin containing protein.

Neuromuscular. MRI patterns of neuromuscular disease involvement, 2023 (https://neuromuscular.wustl.edu/pathol/diagrams/musclemri.htm). Accessed 5/30/2024.

Case Studies

Case Study 1

- 28-year-old Asian American male with chief complaint: Persistently elevated CK levels
- At 24 to 26 years of age: 6' 5", 305 lb pro-football defensive lineman
- 27 years of age: Lost his "explosiveness" of the line; noted muscle soreness
- Sought evaluation of elevated "liver function tests (LFTs)" but CK = 8,423 U/L
  - Hospitalized for "rhabdomyolysis" > intravenous (IV) fluid hydration
  - Placed on prednisone for "polymyositis"
- Recurrent hospitalizations for CK = 1400 to 3200 U/L
- At 28 years of age: Transferred for further evaluation

Case Study 1

Past medical history (PMH)

- Exceptional athlete in high school and college
- No significant issues

Family history

- No history of muscle disease

Medication history

- Previously used a number of supplements including creatine, inhalers, anabolic steroids, and human growth hormone (HGH)
- Used marijuana during downtime and amphetamines during game time

…Other diagnoses

- Low testosterone levels

Case Study 1

Examination – age 28 years

- Heart and lungs: Normal
- Neurological exam: Normal
- Strength: Phenomenal!

Lab test results

- **CK level = 865 – 2137 U/L** on multiple blood draws (depending on steroid dose)
- **Testosterone = 107** (normal limits [NL] = 250–900)

Normal/negative

- Thyroid-stimulating hormone (TSH), antistreptolysin O (ASO), antinuclear antibodies (ANA), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), carnitine (total, free and esters)
- Hepatitis panel, alpha-1 antitrypsin, ceruloplasmin, gamma-glutamyl transferase (GGT), myositis antibody (Ab) panel

Echocardiogram: Normal

Case Study 1: Question 1

What is in the differential?

a) Acquired inflammatory myopathy
b) HMGCoA reductase Ab necrotizing myopathy
c) Muscular dystrophy
d) Myopathy due to substance abuse
e) Other

HMGCoA = β-hydroxy β-methylglutaryl-coenzyme A.

What If the CK Is Very High (>10,000 U/L)?

- HMGCR Ab+ or SRP Ab+ necrotizing myositis

- LGMD2A – calpain
- LGMD2B – dysferlin
- LGMD2C-F – sarcoglycans
- LGMD2I – FKRP
- LGMD2L – anoctamin 5

- Dystrophinopathy (Duchenne/Becker)

SRP = signal recognition peptide.

Case Study 1: Question 2

What would you do for diagnosis (choose all that apply)?

a) Further endocrinologic evaluation
b) Urine drug screen
c) Nerve conduction study/electromyography (NCS/EMG)
d) Muscle MRI
e) Muscle biopsy
f) Genetic testing

Case Study 1

Examination – age 28 years
- Heart and lungs: Normal
- Neurological exam: Normal
- Strength: Phenomenal!

Examination – age 29 years
- Heart and lungs: Normal
- Strength: Slight hamstring weakness
- Difficulty standing on toes

Examination – age 30 years
- Heart and lungs: Normal
- Strength: Mild lower extremity (LE) weakness
- "Diamond on quadriceps sign"

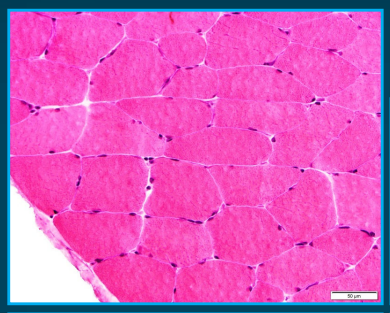
Lab test results
- **CK level = 865 – 2137 U/L** on multiple blood draws (depending on steroid dose)
- Testosterone = 107 (NL = 250–900)

Normal/negative
- TSH, ASO, ANA, RF, ESR, carnitine (total, free and esters)
- Hepatitis panel, alpha-1 antitrypsin, ceruloplasmin, GGT, myositis Ab panel

Echocardiogram: Normal

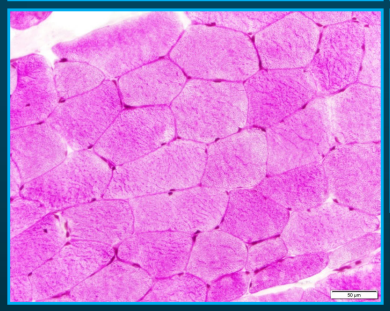
Muscle Biopsy

Hematoxylin and eosin (H&E): NL morphology without inflammation



Dysferlin: Control

Periodic acid schiff (PAS): NL (also oil red O [ORO] staining, myophosphorylase, phosphofructokinase [PFK], and [MAD])



Dysferlin: Patient

Diagnosis: Dysferlinopathy

Genetic testing

Genetic testing confirmed

- Heterozygous pathogenic variants in dysferlin
  - ***DYSF* – c.4794G>A (splice site)**
  - ***DYSF* – c.6197C>T (p.Ala2066Val)**

Clinical course

- Starting to have difficulty traversing stairs
- Cannot walk on toes
- Proud father of a 14-month-old son
- Successfully navigating substance abuse abstinence therapy

Harris E, et al. Neurol Genet 2016;2:e89. doi: 10.1212

Dysferlinopathy

- Onset – mean 18 to 32 years (range 0–73 years)
- Second most prevalent LGMD
- Most have
  - Some ***distal***, calf weakness
  - Calf atrophy common (inability to stand on toes)
- No scapular winging, dysphagia, dysarthria, contractures
- P wave morphology abnormalities in ~50%
  - But no increase in arrhythmias or cardiomyopathy
- Respiratory – rarely symptomatic
  - Mean forced vital capacity (FVC) = 88% predicted (30% patients <80% predicted)
  - FVC decreased by 2% predicted over 3 years
  - Only 7/188 required nocturnal noninvasive ventilation (NIV) (6 with obstructive sleep apnea [OSA])

Moore U, et al. *Muscle Nerve*. 2022;65-531-540.

Case Study 2

Case Study 2

Disease course

54-year-old Caucasian woman

- Noted fatigue in middle and high school
- As a teen, compared to peers
  - Somewhat slower running
  - Could not jump very high
- In her 20s running slowed further
- In her 30s noted
  - Difficulty ascending stairs
  - Using arms over her head
  - Mild foot drop, bilaterally

Current state

By her 50s

- Unable to ride a bike
- Unable to hike
- Unable to play golf
- Unable to walk any significant distance (no more big box stores)
- Falling perhaps once a month
- Unable to arise from the floor

Family history

- No similar disorder

Case Study 2

Examination

- No tongue hypertrophy
- Lateral calf hypertrophy
- NL CN
- Symmetric weakness
  - Proximal upper extremity (UE) = 4/4, 4+/5
  - Distal UE = 5/5
  - HF = 4-/5, HE/HAB/HAD = 2/5
  - KE = 5/5, KF = 4+/5
  - ADF = 3/5, APF = 5/5
- Camptocormic with trouble standing erectly

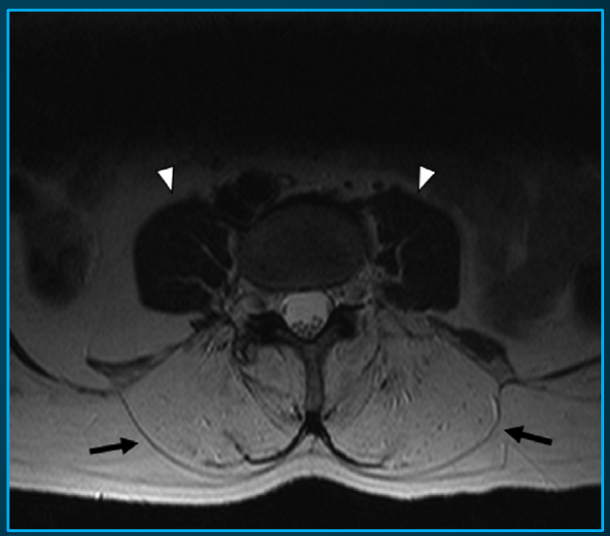
Early evaluations

- CK = 900 to 2700 U/L
- EMG in her 30s "consistent with a myopathy"
- Muscle biopsy in her 30s
  - "Myopathic changes and mildly dystrophic pattern"

Case Study 2

Current evaluations

- MRI brain: NL
- Muscle ultrasound
  - Generalized myopathy without distinct pattern
- MRI L spine
  - Complete fatty replacement of paraspinous muscles
  - Relative preservation of iliopsoas muscles
- Pulmonary function tests (PFTs)
  - FVC = 74% predicted upright
  - FVC = 56% predicted supine
- Transthoracic echocardiogram (TTE): NL



Bockhorst J, Wicklund M. *Neurol Clin.* 2020;38:493-504.

Case Study 2: Question 1

What is your differential diagnosis?

a) Metabolic myopathy
b) Muscular dystrophy
c) Channelopathy
d) Myasthenia gravis
e) Lambert-Eaton myasthenic syndrome
f) Congenital myasthenic syndrome

Case Study 2: Question 2

What further testing would you do?

a) Further lab tests
b) NCS/EMG
c) Muscle biopsy
d) Genetic testing
e) NCS/EMG and muscle biopsy
f) NCS/EMG and genetic testing
g) Mitochondrial testing and muscle biopsy

What Did We Do?

Further electrodiagnostic testing

NCS/EMG with repetitive stimulation

- Normal nerve conduction study (NCS)
- EMG with low amplitude, short duration motor units
- Repetitive stimulation
  - Spinal accessory nerve compound muscle action potential (CMAP) to trapezius muscle
    - 23% decrement in amp and area

Further laboratory testing

Lab test results

- Acetylcholine receptor antibody titer: Negative
- MuSK antibody titer: Negative
- Anti-titin Ab: Negative
- Anti-LRP Ab: Negative
- Anti-agrin Ab: Negative
- Voltage-gated calcium channel (VGCC) Ab: Negative

Case Study 2

Diagnosis – genetic testing

- *GMPPB*
  - c.79G>C (p.Asp27His) – PATHOGENIC
  - c.1099G>A (p.Gly367Arg) – PATHOGENIC
- GDP mannose pyrophosphorylase B
  - 1 of >18 genes associated with glycosylation of alpha-dystroglycan
- *GMPPB*-related disease
  - CMD with brain and eye involvement
  - Congenital myasthenic syndrome
  - LGMD R19/2T (milder phenotype).

Treatment

- Pyridostigmine*
- Salbutamol* or albuterol*

Discuss

Benefits/risks and safety/efficacy of proposed treatments

Other disorders with both myopathic changes on muscle biopsy along with evidence for abnormal neuromuscular transmission

- Myopathies
  - ***BIN1, DES, DNM2, MTM1, PLEC***
- Congenital myasthenic syndromes
  - ***DOK7, ALG2, ALG14, COL13A1, DPAGT1, GFPT1***

* Not FDA-approved for treatment of LGMD.

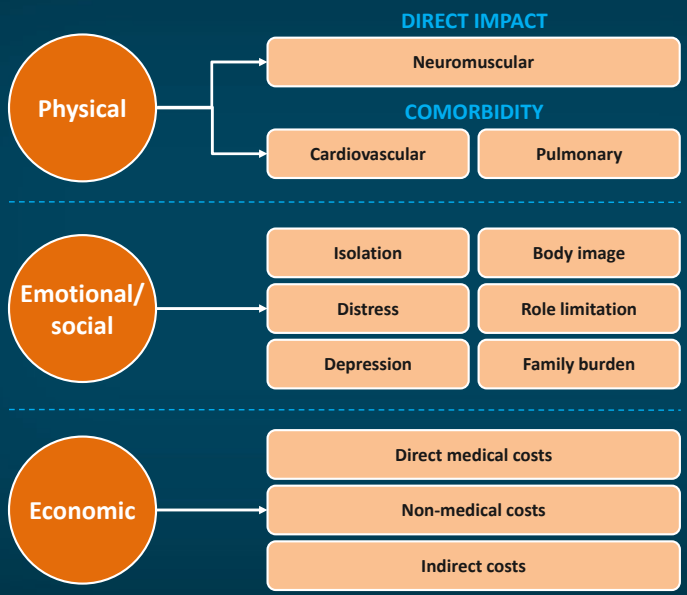
Do not forget to assess the neuromuscular junction in patients with weakness.

Bockhorst J, Wicklund M. *Neurol Clin.* 2020;38:493-504.

Rationale for Development of Viable Therapy for LGMD

Aravindhan Veerapandiyan, MD
Associate Professor of Pediatrics
University of Arkansas for Medical Sciences
Director, Comprehensive Neuromuscular Program
Co-Director, Muscular Dystrophy Association Pediatric Care Center
Arkansas Children's Hospital
Little Rock, AR

Burden of LGMD



Georganopoulou DG, et al. *Protein J.* 2021;40(4):466-488.

Development of Viable Therapy for Patients With LGMD

- Viable therapy may
  - Improve the quality of life for these patients
  - Improve their functional status
  - Improve psychological status
- Treatment may facilitate patients' involvement, engagement, and productivity in society
- Treatment may decrease the need of healthcare and social resources in the future for these patients
- Slow down, stop, or perhaps reverse disease progression

Georganopoulou DG, et al. *Protein J.* 2021;40(4):466-488.

Genetic Resolution and Assessments Solving Phenotypes in LGMD (GRASP-LGMD)

Aims

1. Accelerate clinical trial readiness through natural history trials
2. Gene discovery through exome and genome sequencing
3. Variant resolution for those of undetermined significance (50%–70%)
4. Discovery of modifying factors
   - Genetic
   - Posttranslational
   - Environmental

Participating institutions

- Virginia Commonwealth
- California, Irvine
- Colorado
- Kansas
- Washington University, St. Louis
- Iowa
- Nationwide Children's Hospital
- Atrium Health – North Carolina
- Kennedy Krieger
- Florida
- Newcastle
- Copenhagen
- Yale
- UT Health San Antonio

Platform serving as a catalyst for therapeutic transformation

Doody A, et al. *BMC Neurol.* 2024;24:96.

Symptomatic Management for LGMD

Aims to alleviate symptoms, improve quality of life, and maintain functional abilities

- Physical therapy
- Occupational therapy
- Respiratory support
- Cardiac monitoring and therapeutics
- Pain management
- Nutritional support
- Psychosocial support
- Regular monitoring and follow-up

Georganopoulou DG, et al. *Protein J.* 2021;40(4):466-488.

Investigational Compounds

Investigational Molecular and Gene Therapies for LGMD

Technique	Description
Small molecules	Act on DNA regulation or on downstream pathways
Exon skipping	Using antisense oligonucleotides to skip the mutated exon and produce a truncated functional protein
Gene transfer	Delivery of a gene to the cell with local or systemic injection of a vector, eg, an AAV
RNA inhibitor	An interfering RNA knocks down the mRNA of the mutant allele
Gene editing	Recognizing a specific DNA or RNA sequence and modifying it
Stem cell transplantation	Systemic or local injection of stem cells

Straub V, et al. *Neuromuscular Disord*. 2018;28(8):702-710.

Animation 2

Depiction of various approaches to the development of therapies for patients with LGMD

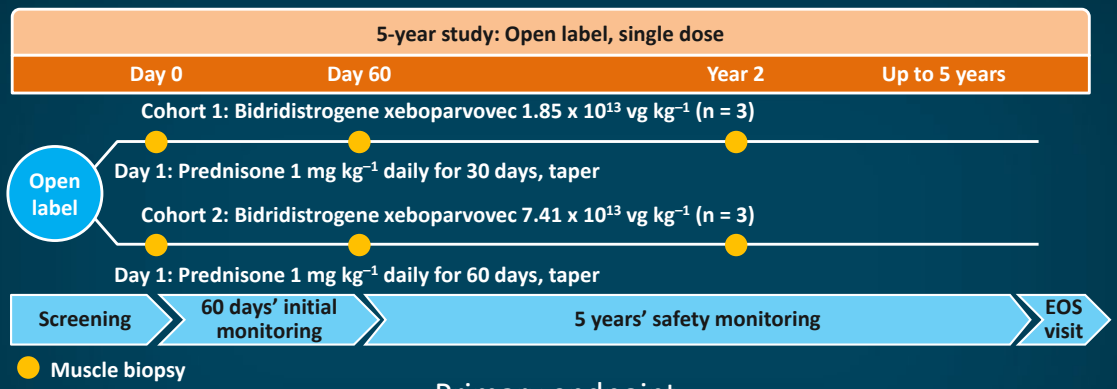
Gene Therapy – Investigational Drugs*

Clinical trial	Stage of study	LGMD type	Name of molecule; target
—	Preclinical	2A/R1	SRP-9010, GNT008; Calpain-3
NCT05906251	Phase 1/2	2B/R2	SRP-6004; Dysferlin
NCT06246513	Phase 3	2E/R4	SRP-9003 (Bidrisdistrogene xeboparvovec); ß-sarcoglycan
NCT05973630	Preclinical/Phase 1	2C/R5	ATA-200, SRP-9005, GNT007; γ-sarcoglycan
NCT05230459/NCT05224505	Phase 1/2	2I/R9	LION-101,AB-1003/ATA-100, GNT006; FKRP
NCT01976091	Phase 1/2	2D/R3	SRP-9004 (Patidistrogene bexoparvovec), α-sarcoglycan
—	Preclinical	2L/R12	SRP-5006; Anoctamin 5
NCT05588401	Phase 1/2 GenPHSats-bASKet trial	LGMD	GenPhSats (gene edited primary human satellite cell derived muscle stem cells)

Genethon. Limb girdle muscular dystrophies (https://www.genethon.com/our-pipeline/limb-girdle-muscular-dystrophies/). Sarepta. Our pipeline, 2021 (https://www.sarepta.com/sites/sarepta-corporate/files/2021-04/Pipeline%202021%20040621.pdf). URLs accessed 5/23/2024.

* Not FDA-approved for LGMD.

Gene Therapy With Bidridistrogene Xeboparvovec: Phase 1/2 Open-Label Trial*



Primary endpoint

Evaluation of safety of bidridistrogene xeboparvovec

Secondary endpoint

Change in quantity of SGCB protein in skeletal muscle from baseline to Day 60 as assessed by immunoblot and immunofluorescence staining

EOS = end of study; SGCB = β-sarcoglycan.

Mendell JR, et al. *Nat Med.* 2024;30:199-204.

* Not FDA-approved for LGMD.

Gene Therapy With Bidridistrogene Xeboparvovec: Phase 1/2 Open-Label Trial*

Primary outcome of treatment-related, treatment-emergent adverse events at 2 years

System organ class preferred term	Cohort 1 (dose, 1.85 x 10^{13} vgkg^{-1})[a] (n = 3)	Cohort 2 (dose, 7.41 x 10^{13} vgkg^{-1})[b] (n = 3)	Total (n = 6)
Subjects with any treatment-related, treatment-emergent adverse event	2 (66.7%)	3 (100.0%)	5 (83.3%)
Gastrointestinal disorders	1 (33.3%)	3 (100.0%)	4 (66.7%)
Abdominal pain	0	2 (66.7%)	2 (33.3%)
Abdominal pain, upper	1 (33.3%)	1 (33.3%)	2 (33.3%)
Nausea	0	2 (66.7%)	2 (33.3%)
Vomiting	1 (33.3%)	3 (100.0%)	4 (66.7%)
General disorders and administration site conditions	0	1 (33.3%)	1 (16.7%)
Pyrexia	0	1 (33.3%)	1 (16.7%)
Hepatobiliary disorders	1 (33.3%)	0	1 (16.7%)
Hepatitis	1 (33.3%)	0	1 (16.7%)
Hyperbilirubinemia	1 (33.3%)	0	1 (16.7%)
Investigations	2 (66.7%)	3 (100.0%)	5 *83.7%)
Gamma-glutamyl transferase (GGT) increased	2 (66.7%)	1 (33.3%)	3 (50.0%)
Neutrophil count decreased	0	1 (33.3%)	1 (16.7%)
White blood cell count decreased	0	2 (66.7%)	2 (33.3%)
Metabolism and nutrition disorders	1 (33.3%)	1 (33.3%)	2 (33.3%)
Decreased appetite	1 (33.3%)	0	1 (16.7%)
Dehydration	0	1 (33.3%)[c]	1 (16.7%)
Nervous system disorders	1 (33.3%)	0	1 (16.7%)
Dizziness	1 (33.3%)	0	1 (16.7%)

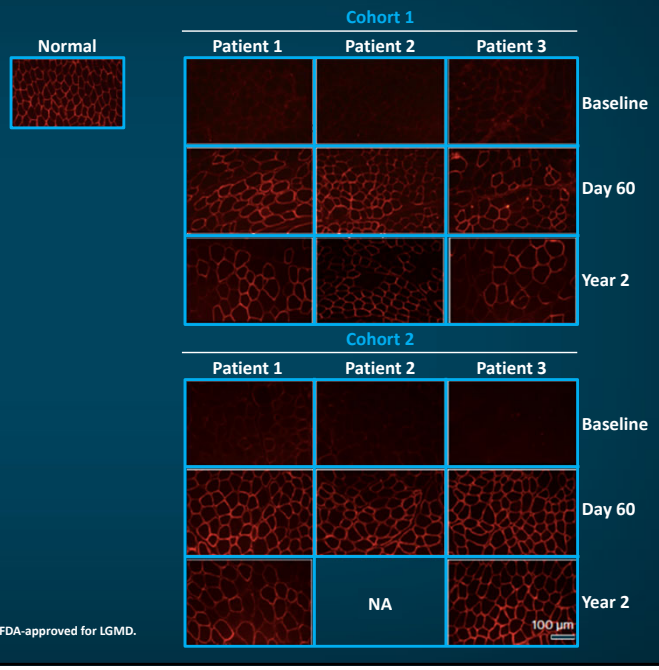
[a]1.85 Å~ 1013 vg kg–1 (linear standard qPCR). [b]7.41 Å~ 1013 vg kg–1 (linear standard qPCR). [c]SAE = serious adverse event.

Mendell JR, et al. *Nat Med*. 2024;30:199-204.

* Not FDA-approved for LGMD.

Gene Therapy With Bidridistrogene Xeboparvovec: Phase 1/2 Open-Label Trial*

- Secondary and exploratory outcomes of SGCB and sarcoglycan complex expression—immunofluorescence images of biopsied muscle sections stained for SGCB from each patient pretreatment and posttreatment (Day 60 and Year 2) compared with normal muscle
- Study of long-term effects ongoing to study potential or waning of effects over time
- Phase 3 trial (EMERGENE) currently underway



NA = not applicable.

Mendell JR, et al. *Nat Med*. 2024;30:199-204.

* Not FDA-approved for LGMD.

Other Investigational Targets: Antimyostatin*

- Blockage of myostatin has been shown to have positive effects in muscle, physiology, and muscle function in animal models of LGMD R3
- In January 2019 Pfizer completed a phase 1/2 trial (NCT02841267) in ambulatory patients with LGMD R9 treated with PF-06252616
- No clinical data in R9 patients have been published or reported

Georganopoulou DG, et al. *Protein J*. 2021;40(4):466-488.

* Not FDA-approved for LGMD.

Other Investigational Targets*

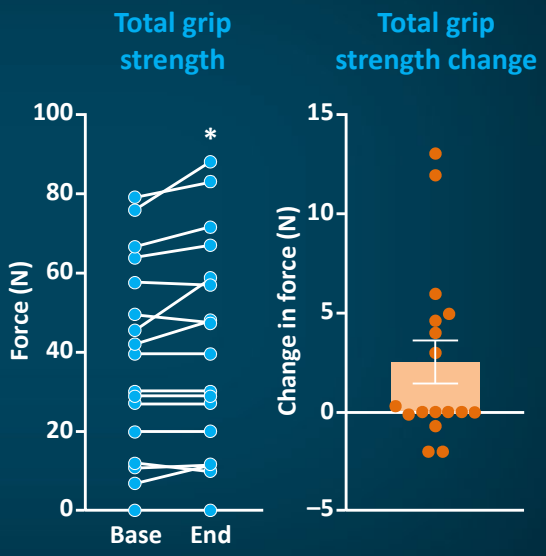
- Steroids: Mixed success in patients with LGMD
  - Vamorolone: Dissociative steroid with potent anti-inflammatory activity via NF-kB inhibition
  - Deflazacort (NCT00527228; trial ongoing)
- Coenzyme Q10 and lisinopril

Georganopoulou DG, et al. *Protein J*. 2021;40(4):466-488. NCT00527228 (https://clinicaltrials.gov/study/NCT00527228). Accessed 5/30/2024.

* Not FDA-approved for LGMD.

Weekly Steroids in Muscular Dystrophy (WSiMD) Open-Label Pilot Study

- Open-label 24-week trial
- Primary objective to assess safety and efficacy of once-weekly prednisone* in LGMD and BMD
- Prednisone administered once weekly at 0.75 to 1 mg/kg in 19 patients with LGMD
- Prednisone found to be safe and well-tolerated
- Functional measures suggest trends in improved muscle performance
- Whole body DEXA scanning suggests a possible increase in lean mass and reduction in adiposity



BMD = Becker muscular dystrophy; DEXA = dual-energy X-ray absorptiometry.

Zelikovich AS, et al. *J Neuromuscul Dis*. 2022;9(2):275-287.

* Not FDA-approved for LGMD.

Other Investigational Target*

- Resolaris (ATYR1940): First-in-class intravenous (IV) histidyl tRNA synthetase therapy—thought to act as an immune system modulator interacting with T cells to halt their activation and reduce the inflammatory response
- The phase 1/2 open-label extension trial (NCT02836418) was completed and showed that many participants maintained or increased their MMT/INQoL scores
- Granted fast-track and orphan drug designations for the treatment of LGMD by the US FDA

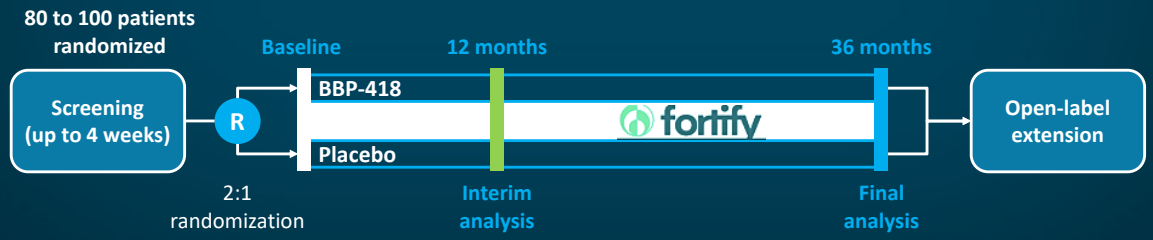
INQoL = individualized neuromuscular quality of life; MMT = manual muscle testing.

Muscular Dystrophy News Today. Resolaris (ATYR1940), 11/6/2019 (https://musculardystrophynews.com/resolaris-atyr1940/). Accessed 5/23/2024.

* Not FDA-approved for LGMD.

Other Investigational Targets: Ribitol*

- BBP-418 (Ribitol): Small molecule FKRP gene modulator and dystroglycan modulator
- Phase 2 study results (n = 14) suggest BBP-418 impacts disease at molecular level, with encouraging safety and clinical activity.
- FORTIFY study: Ribitol efficacy and safety profile in patients with LGMD2I/R9
- Primary efficacy endpoint: Change from baseline in NSAD at 36 months
- Safety endpoints: Frequency and severity of TEAEs and treatment-emergent SAEs, physical exams including vital signs, chemistry and hematology lab analyses, 12-lead ECG, including QTc intervals



ECG = electrocardiogram; NSAD = North Star Assessment for Dysferlinopathy; SAEs = serious adverse events; TEAE = treatment-emergent adverse events.

Reddy DB, et al. 2024 Muscular Dystrophy Association (MDA) Clinical & Scientific Conference; Poster T370.

* Not FDA-approved for LGMD.

Other Investigational Targets*

- Intrathecal autologous bone marrow mononuclear cell therapy
- TXA-127: Peptide and angiotensin II receptor modulator
- Rimeporide: Small molecule sodium hydrogen exchanger 1 inhibitor
- Small molecule corrector
  - EDG-5506 (sevasemten) is an orally administered skeletal myosin inhibitor in clinical trial for patients with LGMD

* Not FDA-approved for LGMD.

BioSpace. News release 2/13/2024 (https://www.biospace.com/article/releases/edgewise-receives-u-s-fda-fast-track-designation-for-edg-5506-for-the-treatment-of-duchenne-muscular-dystrophy-duchenne-/#:~:text=About%20Edgewise%20Therapeutics&text= EDG%2D5506%20is%20an%20orally%20administered%20skeletal%20myosin%20inhibitor%20in,as%20well%20as%20McArdle%20Disease). Accessed 5/23/2024.

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Case Study

Case Study

- An 8-year-old boy presents to the pediatric neurology clinic with a history of difficulty walking and frequent falls over the past year
- Always been slower in achieving motor milestones compared to his peers, but his family has became increasingly concerned when he started having trouble keeping up with his classmates in physical activities
- Born full term, no complications
- Motor delays as described
- No relevant family history

Case Study

General

- Alert and cooperative
- Age-appropriate behavior

Musculoskeletal examination

- Gower's sign positive (uses hands to push off when rising from the floor)
- Waddling gait with proximal muscle weakness noted in the hips and shoulders
- Mild calf hypertrophy
- Normal sensation and reflexes

Cardiovascular and respiratory examination

- Within normal limits

Case Study: Question 1

What is in the differential?

A. Duchenne muscular dystrophy (DMD)
B. LGMD
C. Other muscular dystrophies/myopathies
D. Acquired muscle problems
E. All of the above

Case Study: Question 2

What further testing would you recommend (choose all that apply)?

A. Blood work including creatinine kinase
B. Genetic testing
C. Nerve conduction study/electromyography (NCS/EMG)
D. Muscle magnetic resonance imaging (MRI)

Case Study

- **Blood work**
  - CK 15,000 units/l
- **Genetic testing**
  - SGCB gene: Heterozygous pathogenic variants
    - C.31 C>T (P.Gln11stop) exon 1
    - C.341 C>T (P.Ser114Phe) exon 3

Discussion: What are your next steps?

SGCB = b-sarcoglycan.

MDT and Management of Patients With LGMDs

There is no disease-modifying therapy available currently for any LGMD.

An MDT approach is recommended for management of LGMDs.[1,2]

Physical therapy and rehabilitation[1,2]	Provide assistive devices such as ankle-foot orthosis, walkers, and wheelchairs
Cardiac surveillance[1,2]	Periodic ECGs, ECHOs, Holters, and cMRIs for specific subtypes
Pulmonary surveillance[1]	Serial PFTs for some subtypes of LGMDs and depend on rate of progression
Sleep support[1]	Check for obstructive sleep apnea/nocturnal hypercapnia Use of bilevel ventilation: Nocturnal and progressively daytime
Genetic counseling[2]	Educate patients on risk of recurrence Support patients with family planning (preimplantation genetic diagnosis)

CMRI = cardiac magnetic resonance imaging; ECG = echocardiogram; ECHO = echocardiogram; LGMD = limb-girdle muscular dystrophy; MDT = multidisciplinary team; PFT = pulmonary function test.

1. Narayanaswami P, et al. *Neurology*. 2014:83(16):1453-1463. 2. Georganopoulou DG, et al. *Protein J*. 2021.40(4):466-488.

Thank you!

NE-63L
Assessing the Future of Therapies in Development for Limb Girdle Muscular Dystrophy

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