Updates in Limb-Girdle Muscular Dystrophy (LGMD)

A Resource for Clinicians

Background

- LGMD is a term for a heterogenous group of diseases characterized by pelvic and shoulder girdle muscle weakness.[1,2]
- This document captures highlights from an MDA webinar with LGMD experts.
- View the CE-accredited companion webinar here.

Overview

Description

- Classified based on new nomenclature as of 2018[3]
  - LGMD dominant (**LGMDD**)
  - LGMD recessive (**LGMDR**)
- Shows genetic heterogeneity[4]
  - Mutations in different genes cause similar phenotype (both *SGCG* and *SGCA* pathogenic variants are similar phenotypically)
- Shows genetic pleiotropy[4,5]
  - Different mutations in same gene cause different phenotypes (*DYSF* pathogenic variants can cause limb-girdle and distal myopathy phenotypes)

Epidemiology

- LGMD worldwide prevalence is 0.8-6.9 cases per 100,000[3,5]
- ~2800-24,150 affected patients in the United States
- Affects both sexes equally[3]

Onset and Prognosis

- Age of onset varies by subtype (from childhood to young adult or later)[3]
- Severe forms of LGMD cause ambulatory loss[3]
- Other subtypes lead to limited mobility[3]
- Impacts patients' quality of life and caregivers' burden[3]

SGCA, α-sarcoglycan; SGCG, γ-sarcoglycan.
1. Liu W, et al. *Genet Med*. 2019;21(11):2512-2520. 2. Bouchard C, Tremblay JP. *J Clin Med*. 2023;12(14):4769. 3. Georganopoulou DG, et al. *Protein J*. 2021;40(4):466-488. 4. Angelini C. *Acta Myol*. 2020;39(4):207-217. 5. Johnson NE, Statland JM. *Continuum (Minneap Minn)*. 2022;28(6):1698-1714.

LGMD: Clinical Manifestations

Muscle weakness[1]

Affects limb-girdle muscles first (shoulders and hips)
- Difficulties in raising arms/objects above head
- Difficulties in climbing/descending stairs, running, carrying groceries, getting off floor (Gower's maneuver)
- Difficulty with sports in youth

Progresses slowly; face is spared until very late
- Proximal muscle weakness
- Posterior compartment of thigh and leg > anterior

Additional symptoms in certain subtypes of LGMDs:
- Difficulties in standing on toes (dysferlin, anoctamin 5)[2]
- Scapular winging (eg, sarcoglycanopathies)
- Calf hypertrophy

Cognition[1]

- Usually **not affected**

Respiratory weakness[1,3]

- More common **in recessive forms of LGMD** and **after wheelchair dependency**
- Weak cough, difficulty taking deep breaths, orthopnea
- Diaphragm weakness is more common in sarcoglycanopathies (R3-R6)

Cardiomyopathies[1]

Occurs **only in some subtypes of LGMDs**
- Sarcoglycanopathies (R3-R6)
- FKRP (R9)
- Telethonin (R7)

Pain[3]

- **Imbalance** due to joint weakness
- **Low back pain** occurs commonly, mostly due to extensor weakness
- Pain occurs **secondary to immobility**

FKRP, fukutin-related protein; LGMD, limb-girdle muscular dystrophy.
1. Georganopoulou DG, et al. *Protein J*. 2021;40(4):466-488. 2. Soontrapa P, et al. *Genes (Basel)*. 2022;13(10):1736. 3. Narayanaswami P, et al. *Neurology*. 2014;83(16):1453-1463.

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LGMD: Diagnosis

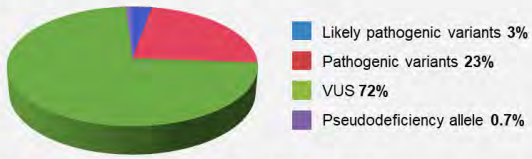
Laboratory and clinical examinations

- **Measure CK levels**[1,2]
  - Elevated in all LGMDs
  - Higher values may be indicative of recessive disease
- **Muscle biopsy**[1,3,4,5]
  - Immunofluorescence staining
  - Some LGMDs have distinguishing features
- **Electromyography**[5]
  - Most useful in excluding nerve diseases with proximal muscle weakness

Genetic testing to confirm LGMD subtype[4,6]

- Panel tests have improved accuracy of diagnosis[5,6]
- Panels may be free or sponsored[6]
- They include ~230 genes[2]
- Are easily collected[5]

72% of patients diagnosed with clinical LGMDs have VUS[7]
(large LGMD US cohort of 4656 patients)



From Nallamilli BRR, et al. *Ann Clin Transl Neurol*. 2018;5(12):1574-1587.

CK, creatine kinase; LGMD, limb-girdle muscular dystrophy; VUS, variants of uncertain significance.
1. Bushby K. *Pract Neurol*. 2009;9(6):314-323. 2. Ng KWP, et al. *Front Neurol*. 2022;13:997551. 3. Moore SA, et al. *J Neuropathol Exp Neurol*. 2006;65(10):995-1003. 4. Narayanaswami P, et al. *Neurology*. 2014;83(16):1453-1463. 5. Georganopoulou DG, et al. *Protein J*. 2021;40(4):466-488. 6. Johnson NE, et al. *Continuum (Minneap Minn)*. 2022;28(6):1698-1714. 7. Nallamilli BRR, et al. *Ann Clin Transl Neurol*. 2018;5(12):1574-1587.

Genetic Testing and VUS

1. Identify VUS and verify the number of VUS matches the inheritance pattern (dominant or recessive)
   - If it does not match, consider alternate diagnoses. Variant may not be able to be assessed as pathogenic

- If dominant→1 variant
- If recessive→2 variants

2. Verify the report demonstrates low population frequency and predicted pathogenic outcome
   - If this is not demonstrated, consider alternate diagnoses. Variant may not be able to be assessed as pathogenic

Or if in silico algorithms predict an indeterminate effect

3. Test family for variant
   - If VUS does not match family pattern of disease, consider alternate diagnoses. Variant may not be able to be assessed as pathogenic
   - If VUS matches family pattern of disease, variant may be pathogenic

In case of a pathogenic variant:
- If recessive→must be in trans
- If dominant→*de novo* or affected parent (reduced penetrance)?

4. Confirm protein loss in muscle biopsy
   - If there is no protein loss in the biopsy, consider alternate diagnoses. Variant may not be able to be assessed as pathogenic, and it may be a potential candidate for research studies
   - If protein loss is observed, variant may be pathogenic

VUS, variants of uncertain significance.
Johnson NE, et al. *Continuum (Minneap Minn)*. 2022;28(6):1698-1714.

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LGMD: New Classification

New nomenclature (2018) and characteristics[1,2]

Dominant - LGMDD

- ~10% of all LGMD
- 5 subtypes
- **Age of onset:** adolescence to late adulthood
- Mild limb weakness
- Normal to mildly elevated CK levels (~1000 U/L)
- Slow progression

Recessive - LGMDR

- ~90% of all LGMD
- 24 subtypes
- **Age of onset:** childhood to young adulthood
- Moderate to severe limb weakness
- Mild to highly elevated CK levels (between 1000 and 30,000 U/L)
- Fast progression (often requires mobility aides)

Primary distinction from the previous nomenclature[1-3]

- Presence of limb-girdle pattern of weakness is required
- Becker, desminopathies, and *LMNA* gene variants have been excluded from the LGMDs category
- Pathology must be dystrophic
  - Myofibrillar myopathy and metabolic diseases have been removed
- Gene is added to the name

CK, creatine kinase; LGMD, limb-girdle muscular dystrophy.
1. Georganopoulou DG, et al. *Protein J*. 2021;40(4):466-488. 2. Johnson NE, Statland JM. *Continuum (Minneap Minn)*. 2022;28(6):1698-1714. 3. Angelini C. *Acta Myol*. 2020;39(4):207-217.

New Classification Examples

Gene	New Name	Old Name
CAPN3	LGMDR1 calpain3-related	LGMD2A
DYSF	LGMDR2 dysferlin-related	LGMD2B
SGCA	LGMDR3 α-sarcoglycan-related	LGMD2D
SGCB	LGMDR4 β-sarcoglycan-related	LGMD2E
SGCG	LGMDR5 γ-sarcoglycan-related	LGMD2C
SGCD	LGMDR6 δ-sarcoglycan-related	LGMD2F
TCAP	LGMDR7 telethonin-related	LGMD2G
TRIM32	LGMDR8 TRIM32-related	LGMD2H
FKRP	LGMDR9 FKRP-related	LGMD2I
TTN	LGMDR10 titin-related	LGMD2J
POMT1	LGMDR11 POMT1-related	LGMD2K
ANO5	LGMDR12 anoctamin5-related	LGMD2L
FKTN	LGMDR13 fukutin-related	LGMD2M
POMT2	LGMDR14 POMT2-related	LGMD2N
POMGnT1	LGMDR15 POMGnT1-related	LGMD2O

Gene	New Name	Old Name
DAG1	LGMDR16 α-dystroglycan-related	LGMD2P
PLEC	LGMDR17 plectin-related	LGMD2Q
TRAPPC11	LGMDR18 TRAPPC11-related	LGMD2S
GMPPB	LGMDR19 GMPPB-related	LGMD2T
ISPD	LGMDR20 ISPD-related	LGMD2U
POGLUT1	LGMDR21 POGLUT1-related	LGMD2Z
COL6A1, 2, 3	LGMDR22 collagen 6-related	Bethlem myopathy
LAMA2	LGMDR23 laminin α 2-related	Merosin
POMGNT2	LGMDR24 POMGNT2-related	POMGNT2-related muscular dystrophy

Gene	New Name	Old Name
DNAJB6	LGMDD1 DNAJB6-related	LGMDD1D
TNP03	LGMDD2 TNP03-related	LGMD1F
HNRNPDL	LGMDD3 HNRNPDL-related	LGMD1G
CAPN3	LGMDD4 calpain3-related	LGMD1I
COL6A1, 2, 3	LGMDD5 collagen 6-related	Bethlem myopathy

LGMD, limb-girdle muscular dystrophy.
Straub V, et al. *Neuromuscul Disord*. 2018;28(8):702-710.

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MDT and Management of Patients With LGMDs

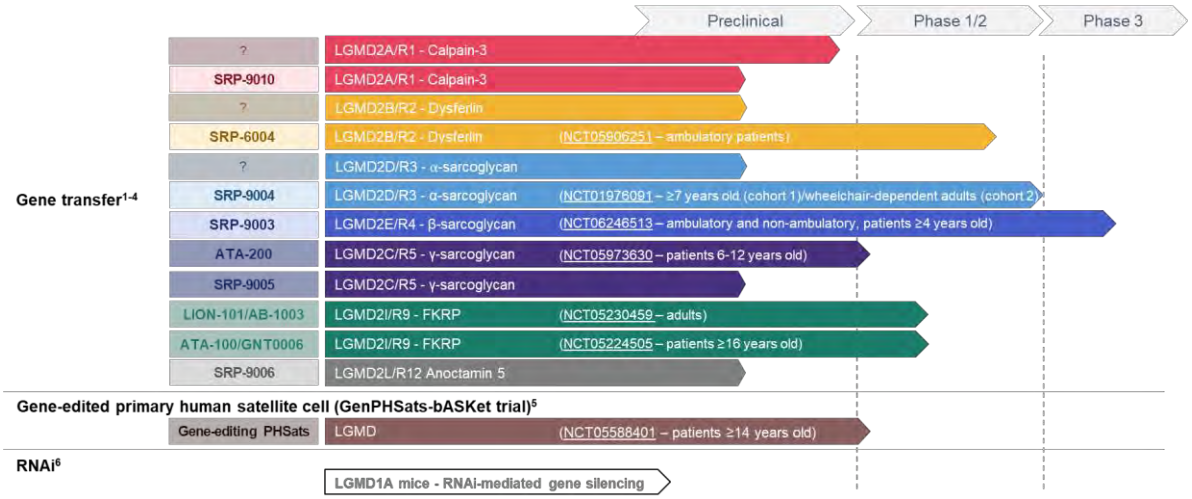
There is no disease-modifying therapy available currently for any LGMD

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

Physical therapy and rehabilitation[1,2]	Provide assistive devices like 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 (pre-implantation 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

LGMD Gene Therapies in Pipeline



LGMD, limb-girdle muscular dystrophy; PHSats, primary human satellite cells; RNAi, RNA interference.
1. Limb-girdle muscular dystrophy type 2I/R9. AskBio website. https://www.askbio.com/limb-girdle-muscular-dystrophy-type-2i-r9-clinical-trial/. 2. Our pipeline. Atamyo Therapeutics website. https://atamyo.com/science-technology/pipeline/. 3. Building an industry-leading genetic medicine pipeline. Sarepta Therapeutics, Inc. website. https://www.sarepta.com/products-pipeline/pipeline. 4. Limb-girdle muscular dystrophy | gene therapy. ClinicalTrials.gov website. https://www.clinicaltrials.gov/search?cond=Limb%20Girdle%20Muscular%20Dystrophy&intr=gene%20therapy&page=1. 5. Three therapeutic platforms target different muscle diseases. MyoPax website. https://myopax.com/pipeline/. 6. Liu J, et al. *Mol Ther Nucleic Acids*. 2014;3(4):e160.

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LGMD: Key Resources

Register your patient in a disease-specific national database

- JAIN FOUNDATION (LGMD2B/R2 | DYSFERLINOPATHY | MIYOSHI) — https://www.jain-foundation.org/
- MDA Muscular Dystrophy Association — https://www.mda.org/
- GLOBAL FKRP REGISTRY — https://www.fkrp-registry.org/
- Coalition to Cure Calpain 3 (Overcoming Weakness with Strength) — https://www.curecalpain3.org/
- LGMD2D Foundation — https://lgmd2d.org/

LGMD, limb-girdle muscular dystrophy.

Resources to Help With VUS Analysis

Websites

- OMIM® An Online Catalog of Human Genes and Genetic Disorders — https://www.omim.org/
- ClinVar — https://www.ncbi.nlm.nih.gov/clinvar/
- gnomAD Genome Aggregation Database — https://gnomad.broadinstitute.org/

Book

- GeneReviews — https://www.ncbi.nlm.nih.gov/

Useful Information

- Wait for second family to be discovered
- Partner with clinician scientists for further testing
  - Advanced/specific computer modeling
  - RNA sequencing on muscle

VUS, variants of uncertain significance.

Access companion CE-accredited MDA webinar here

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