ICD-10 Codes for The Limb Girdle Muscular Dystrophies

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Limb Girdle Muscular Dystrophy

LIMB GIRDLE MUSCULAR DYSTROPHY

LGMD Awareness Day September 30th

www.LGMD-info.org

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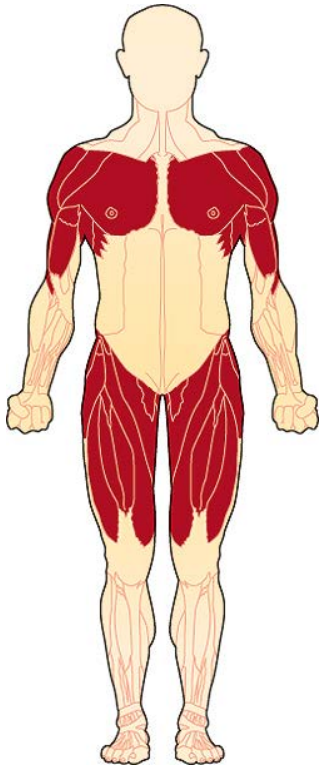
Current ICD-10 Codes for Muscular Dystrophies

- G71 Primary disorders of muscles
  - **G71.0 Muscular dystrophy**
  - G71.00 …… unspecified
  - G71.01 Duchenne or Becker muscular dystrophy
  - G71.02 Facioscapulohumeral muscular dystrophy
  - G71.09 Other specified muscular dystrophies
    - Benign scapuloperoneal muscular dystrophy with early contractures [Emery-Dreifuss]
    - Congenital muscular dystrophy NOS
    - Congenital muscular dystrophy with specific morphological abnormalities of the muscle fiber
    - Distal muscular dystrophy
    - Limb-girdle muscular dystrophy
    - Ocular muscular dystrophy
    - Oculopharyngeal muscular dystrophy
    - Scapuloperoneal muscular dystrophy

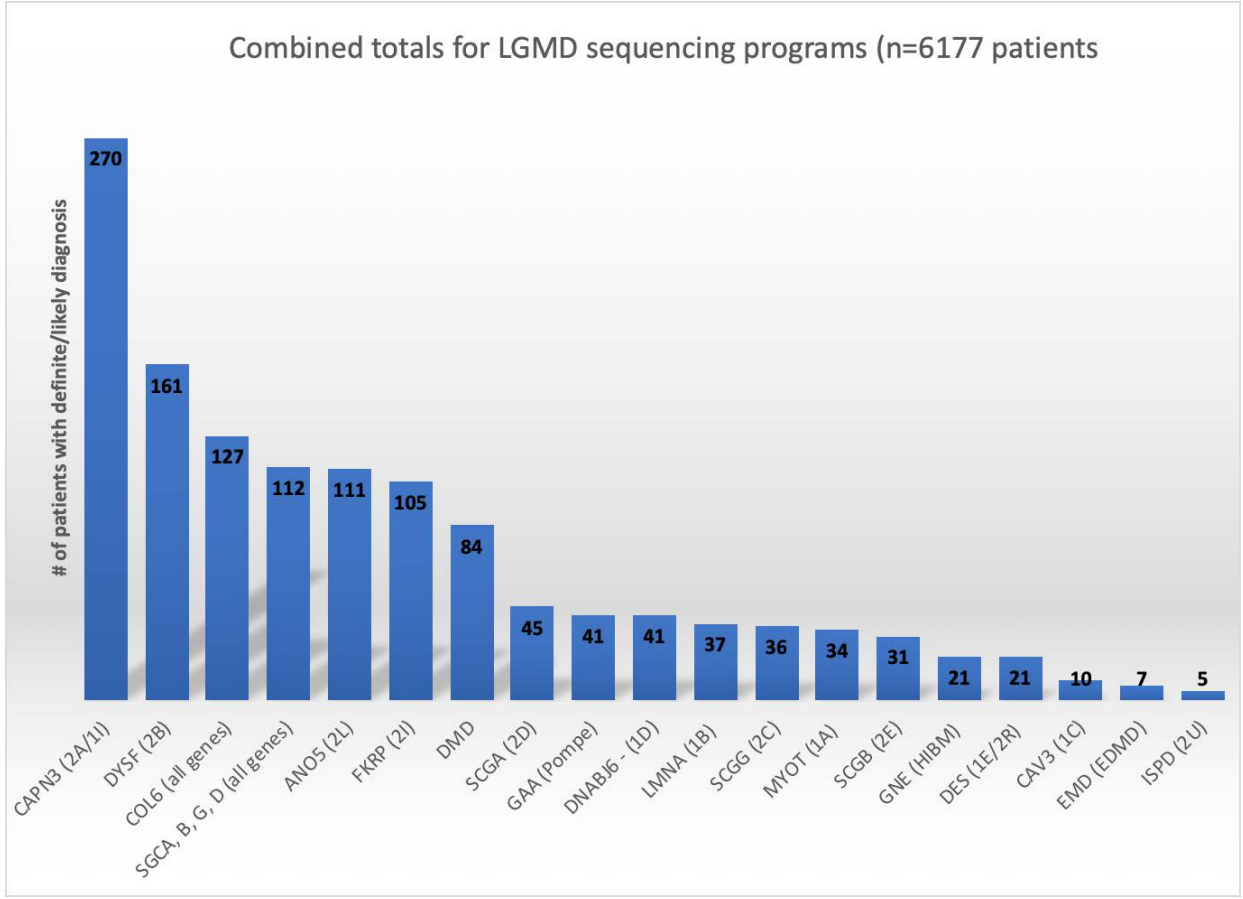


History of LGMD

- The term “LGMD” was first coined in 1954 by John Walton and FJ Nattrass to describe a class of muscular dystrophies that were distinct from other dystrophies such as DMD and myotonic dystrophy type 1
- LGMDs are a group of autosomally inherited neuromuscular dystrophies that are genetically diverse[1]
- All LGMDs manifest with progressive weakness in hip and shoulder girdle musculature[1]
- In total, 28 variants of LGMD have been identified[1]
- There is wide variation in the prevalence of LGMD subtypes, suggesting potential founder mutations[3]
- Each subtype represents a unique mutation and a compilation of symptoms
- There is significant heterogeneity between and within the varying subtypes

Epidemiology of LGMDs

- LGMDs are a group of autosomally inherited neuromuscular dystrophies that are genetically diverse
- All LGMDs manifest with progressive weakness in hip and shoulder girdle musculature
- In total, 28-34 variants of LGMD have been identified
- Approximate global prevalence of LGMDs as a group is 1.63 per 100,000
  - Prevalence estimates range from 0.56 to 5.75 per 100,000
- Prevalence of LGMD subtypes is variable between countries
- The most common form in American/European countries is LGMD2A



LGMD1 and LGMD2 classification

FEATURES	LGMD1	LGMD2
Inheritance	Autosomal dominant	Autosomal recessive
Population %	10% of total patients with LGMD	90% of total patients with LGMD
Subtypes	D1-D4 (4+)	R1-R24 (24+)
Typical age at onset	Adolescence to late adulthood*	Childhood to young adulthood
Limb weakness	Mild	Moderate to severe
CK levels	Normal to mildly elevated†	Mildly to highly elevated

- Subtypes are classified alphanumerically with assignation of D for dominant and R for recessive. A letter is added in order of discovery
  - e.g., LGMDD1, LGMDR1, LGMDR4

Clinical Features of LGMD

- Disease progression, as well as distribution and severity of muscle weakness/wasting, is variable among subtypes of LGMD
- Age of onset is also widely variable and depends upon subtype, and ranges between early childhood to adulthood
- General features of LGMDs include
  - Progressive weakness and wasting in limb musculature
  - Involvement of skeletal muscle
  - Variable age of onset from childhood to adulthood
  - Cardiac involvement (in some variants)
  - Incidence in both males and females (not X-linked)
  - Elevated CK levels (in some variants)
  - Exercise intolerance or rhabdomyolysis (in some variants)

Genetic Basis of LGMD

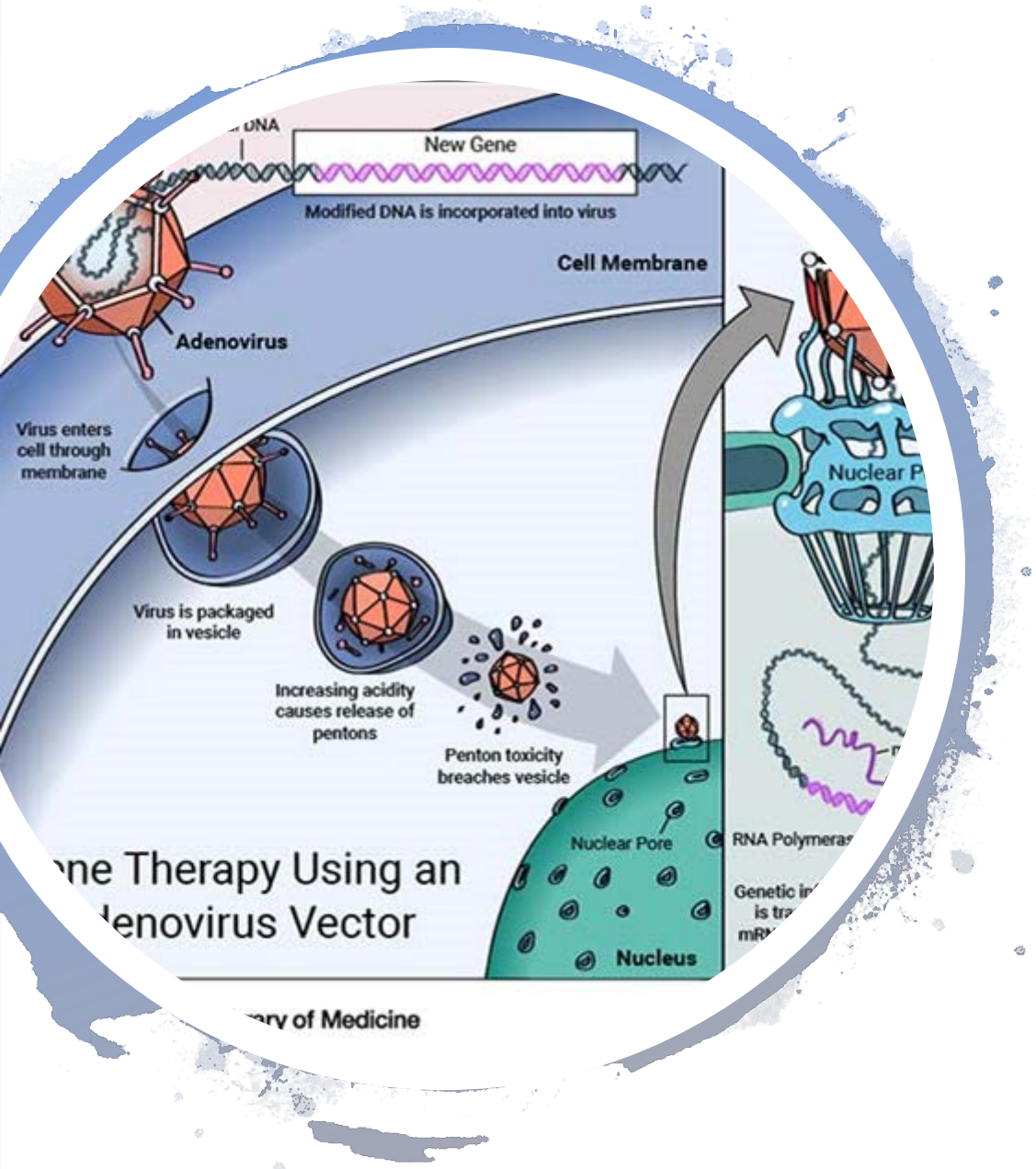
•At least twenty-eight genetically distinct variants of LGMD have been identified based on their causative genes or identified genetic loci.

- Incidence of LGMD has been observed in both males and females (not X-linked)
- Two major classes of LGMD based upon mode of inheritance, autosomal dominant (LGMDD or LGMD1) or autosomal recessive (LGMDR or LGMD2)
  - Generally, LGMDR/2 variants are more common
- Letters were subsequently added to the nomenclature, designating the order in which the variants were discovered (eg, LGMD2A/R1)

Most common genes and nomenclature associated with LGMD		
Gene	**Old nomenclature**	**Proposed nomenclature**
CAPN3	LGMD2A/LGMD1I	LGMD D4 calpain3-related
DSYF	LGMD2B	LGMD R2 dysferlin-related
SGCA	LGMD2D	LGMD R3 alpha-sarcoglycan related
SGCB	LGMD2E	LGMD R4 beta-sarcoglycan related
SGCG	LGMD2C	LGMD R5 gamma-sarcoglycan related
SGCD	LGMD2F	LGMD R6 delta sarcoglycan related
FKRP	LGMD2I	LGMD R9 FKRP-related
ANO5	LGMD2L	LGMD R12 anoctamin5-related
DNAJB6	LGMD1D	LGMD D1 DNAJB6-related
TNP03	LGMD1F	LGMD D2 TNP03-related

Diagnosis of LGMD

- The course of LGMD is progressive, and severity of symptoms and age of onset vary among subtypes
  - Some cases of LGMD are mild, whereas others are severe
- Patients may present with progressive weakness and wasting of the hip or shoulder girdle
- Serum CK may be elevated
- Muscle biopsy may show muscle fiber degeneration/regeneration
- Some LGMD variants may be diagnosed through biochemical testing (eg, immunoblotting) to confirm the absence of a specific protein
- Genetic testing is often required to identify mutations

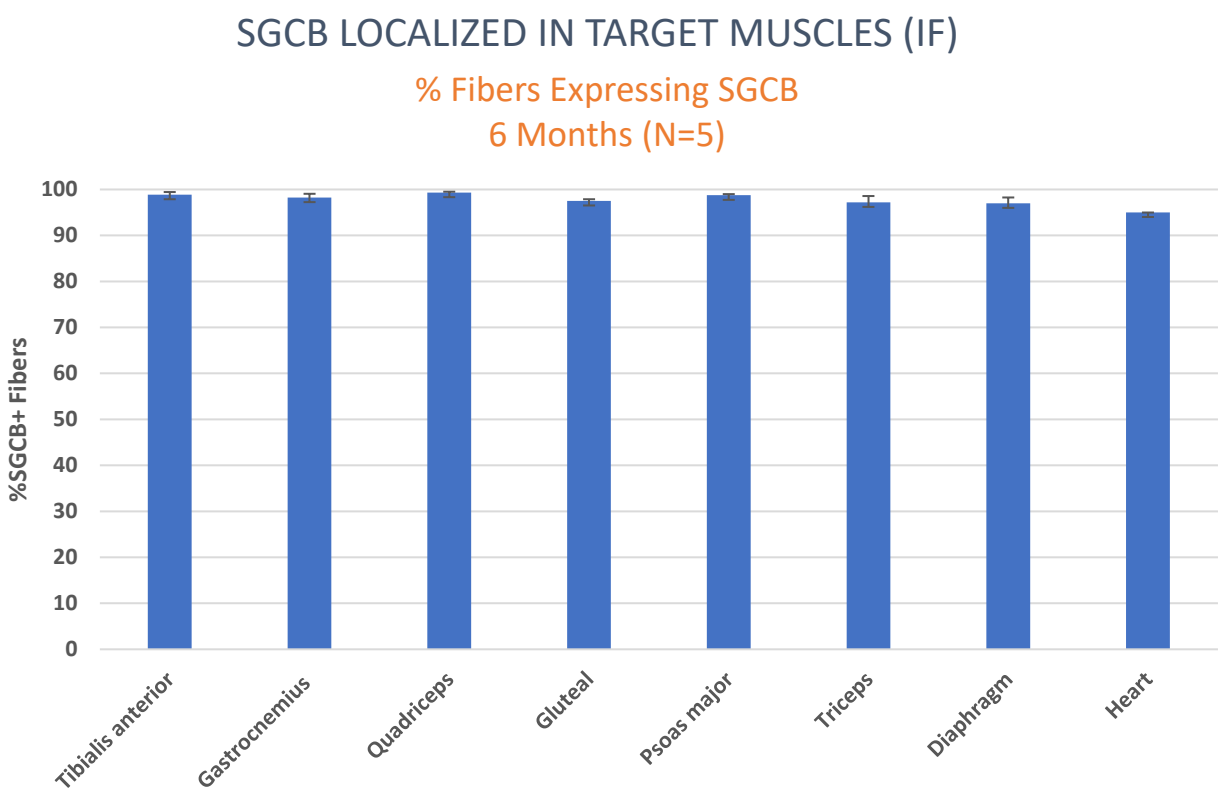


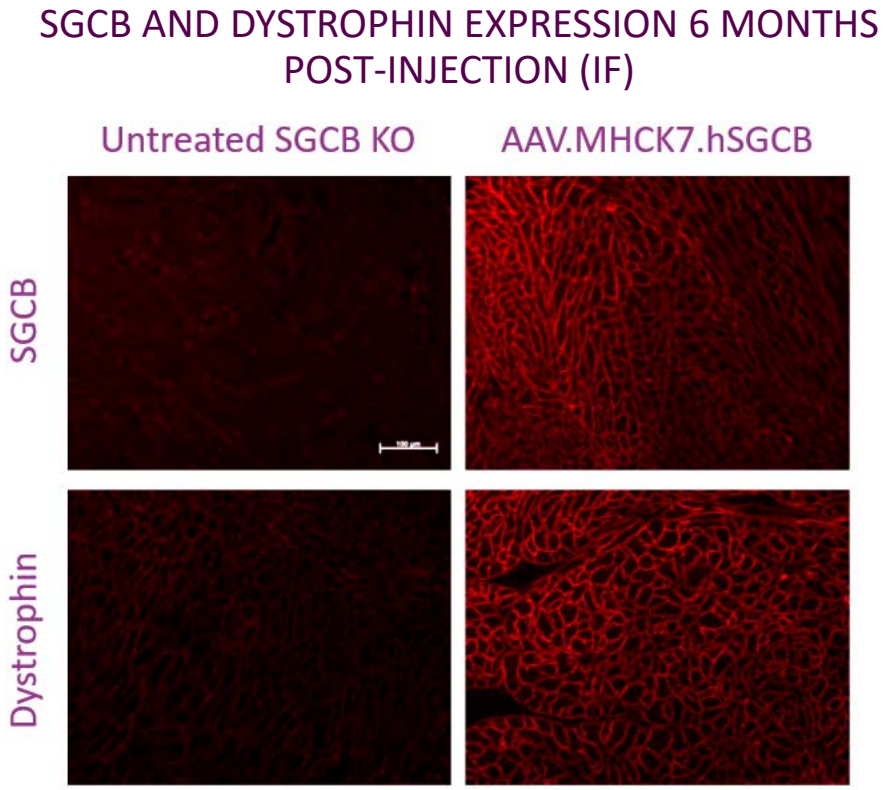
Therapeutic development in LGMD

- Gene therapy has promise for many recessive forms of LGMD
- Purpose is to use a modified viral vector to deliver human DNA
- Why?
  - Viruses are good at penetrating cells
  - Can package any DNA/RNA

Transduction and Localization of AAVrh74.MHCK7.hSGCB Led to Restoration of DAPC Proteins in *LGMD2E-/-* Mice

SGCB and Dystrophin Expression 6 Months After IV Treatment ($1x10^{12}$ vg total dose)



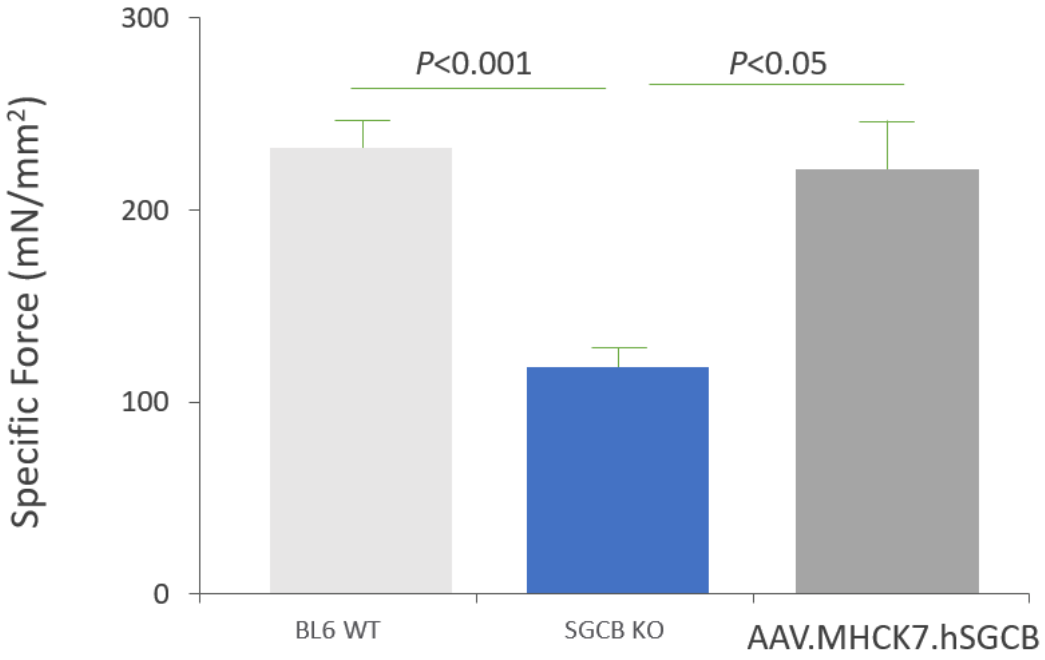


Pozsgai ER, et al., 2017

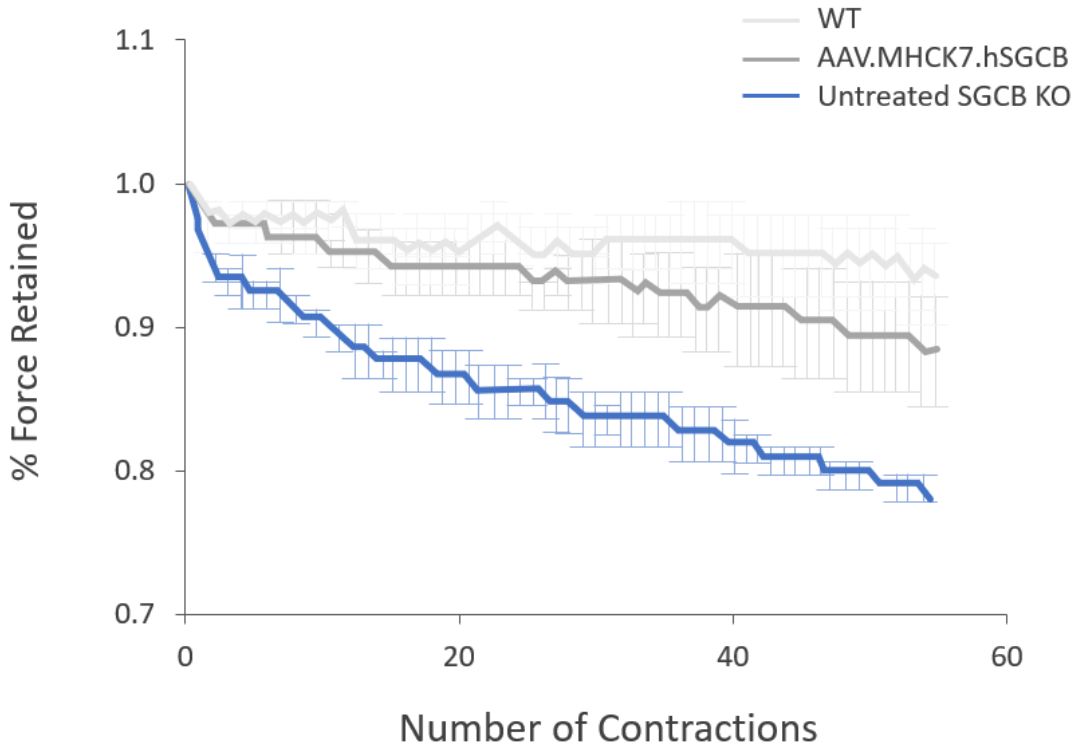
Systemic Delivery Improved Diaphragm Function 6 Months Post-Injection

SGCB Expression Following Systemic Delivery of the Construct Restored Diaphragm Function in Mice

SPECIFIC FORCE



FATIGUE



Pozsgai ER, et al. 2017

Ongoing phase I clinical trial in LGMD R4

- In initial cohort:
  - Reported CK reduction at 270 days
  - Improvement in functional measures
  - Improved SGC-beta expression

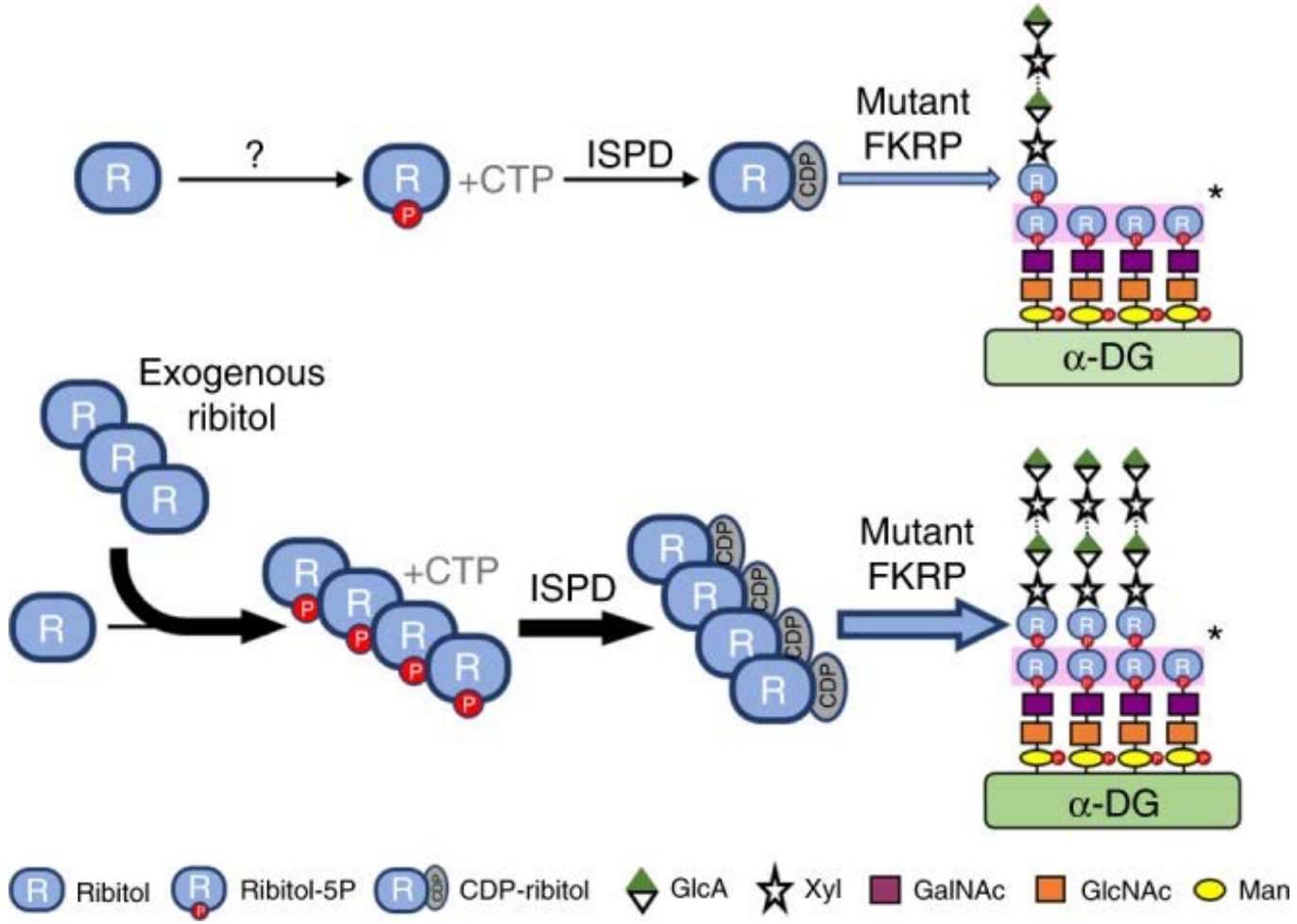
Current gene replacement therapy programs in development

- Clinical
  - SGC-B (LGMD2E)
  - SGC-a (LGMD2D)
  - DYSF (LGMD2B)
- Preclinical
  - SGC-g (LGMD2C)
  - ANO5 (LGMD2L)
  - CAPN3 (LGMD2A)
  - FKRP (LGMD2I)

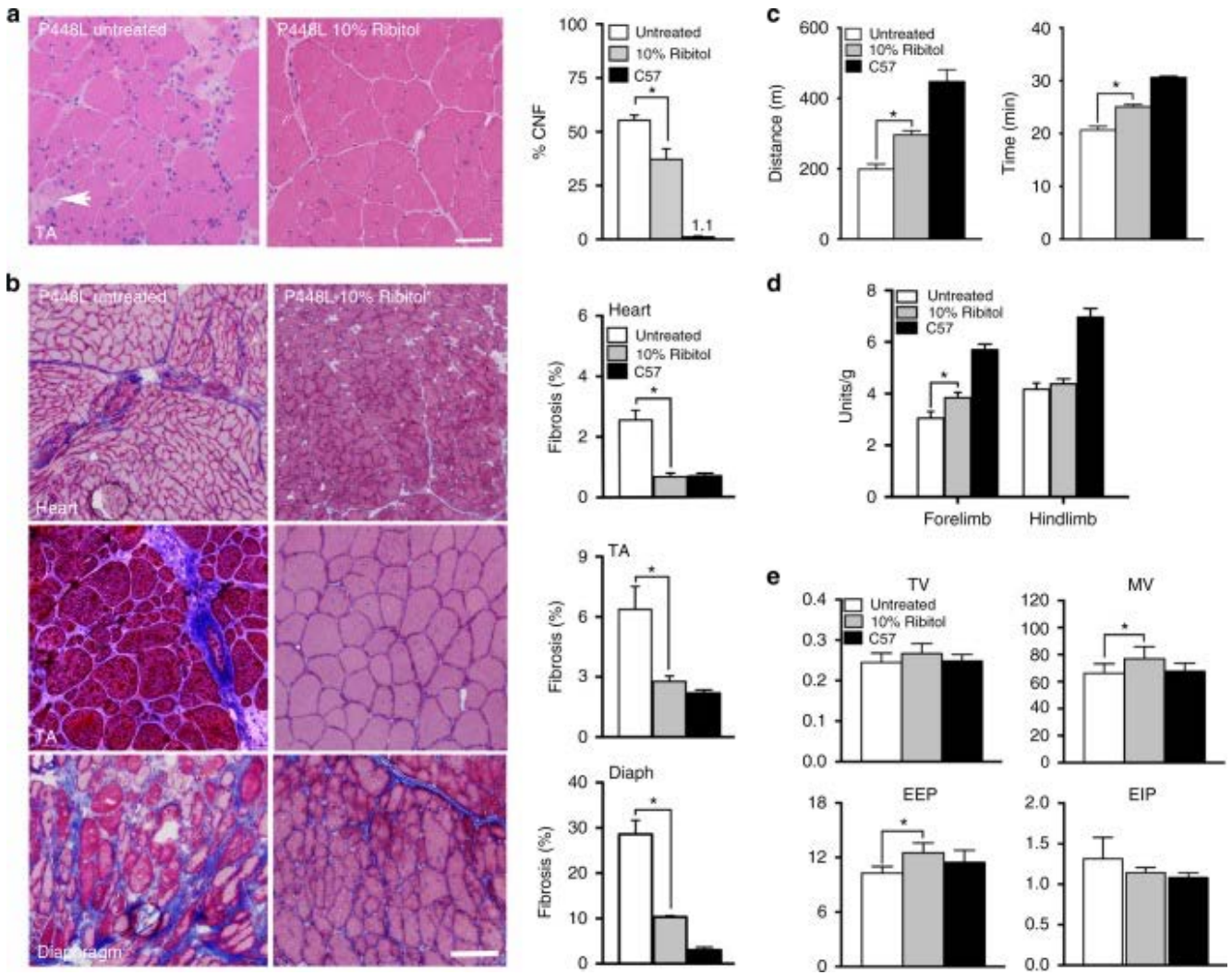
Source: Sarepta.com; askbio.com

Small molecule potential for LGMD2i/R9

- Ribitol is a natural pentose alcohol
- Evidence suggests that ribitol can improve expression of alpha-DG in P448L mice



Treatment with Ribitol improves strength



Cataldi, et al, 2018

Summary

- The LGMDs are related disorders, but have distinct features in subtypes
- There is a difference in progression, clinical phenotype and inheritance between LGMD1 and LGMD2
- LGMD2A, LGMD2B, LGMD2I, and LGMD2L are the most common
- A number of forms of LGMD have clinical trials nearing human phases