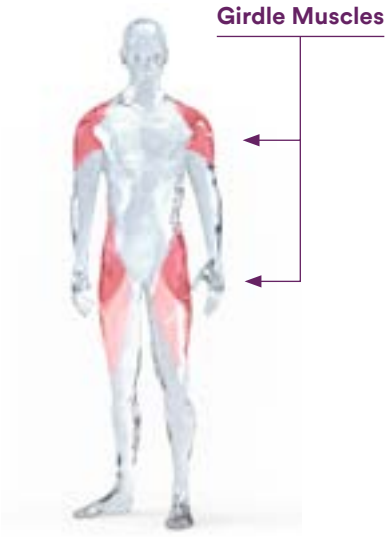

# Limb-girdle muscular dystrophies

SAREPTA THERAPEUTICS

## What it is:

The limb-girdle muscular dystrophies are a group of inherited neuromuscular diseases that cause progressive weakness and wasting in “girdle muscles” — those in the pelvic area and shoulders — and eventually the upper arms and thighs.[1] There are approximately 30 subtypes of LGMD, each caused by a mutation(s) (pathogenic variant) in a unique gene, with varying severity and age of onset of symptoms.[2]

- LGMDs are caused by a mutation(s) (pathogenic variant) in the genes that encode specific proteins that control muscle function, maintenance and repair. These genetic diseases may appear at any age in both males and females.[1-4]
- Approximate global prevalence of all LGMDs is 1.63 per 100,000 people.[3]
- Initial symptoms may be mild but they generally worsen over time.[2] Patients typically experience symmetrical weakness in the limb-girdle muscles,[5] resulting in a “waddling” gait and frequent falls, in addition to difficulty with climbing stairs, standing from a sitting position, raising arms over the head, and lifting objects.[6,7]
- Signs of LGMDs include changes in posture and gait, abnormal appearance of the shoulders, back and arms, and overgrown calf muscles (hypertrophy).[2]
- Cardiac and respiratory involvement occurs in some forms of LGMD. Some patients may experience weakening of the heart muscle (cardiomyopathy) and breathing difficulties, and some may require a ventilator for breathing support.[1]



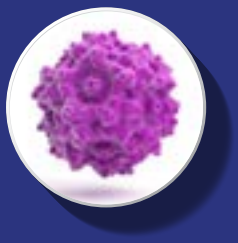

## LGMD diagnosis and current disease management[5,9]

- Establishing a definitive (genetic) diagnosis of a specific LGMD subtype is challenging due to the overlap between LGMD subtypes, with other non-LGMD conditions, and the variability in symptoms and age of onset.
- For children, the path to diagnosis typically depends on when symptoms are noticeable enough to be brought to a physician. Older patients may not consult a health care provider for years, as symptoms may first be attributed to fatigue or aging.
- Genetic testing is a critical step to confirming an LGMD diagnosis and identifying the specific LGMD subtype.
- There are currently no approved treatments for any LGMD. Disease management is limited to supportive care and aims to manage the progression of symptoms, improve quality of life, and prolong survival.

## Subtypes of LGMD

- Each subtype of LGMD is linked to a specific gene and there is wide variation in the prevalence of each subtype.
- Subtypes of LGMD are classified based on whether they are inherited through an autosomal dominant (LGMD1 or LGMDD) or recessive (LGMD2 or LGMDR) pattern.[2,9]
- In 2017, a new subtype classification system was introduced to better account for the increasing number of newly identified subtypes. The letter "D" is used for dominant subtypes (instead of numeral 1) and the letter "R" is used for recessive subtypes (instead of numeral 2), plus a number (instead of a letter) for the order of discovery.[9]

| FEATURES | LGMDD (LGMD1)[3,9,10,11] | LGMDR (LGMD2)[3,9,10,11] |
|---|---|---|
| Inheritance | Autosomal dominant, one copy of the mutated gene is sufficient to cause the disorder | Autosomal recessive, both copies of the gene (one from each parent) have mutations |
| Population % | 10% of total patients with LGMD | 90% of total patients with LGMD |
| Subtypes | ~5 | ~25 |
| Typical age at onset | Adolescence to late adulthood* | Childhood to young adulthood |
| Symptom severity | Mild | Moderate to severe |



## Sarepta's gene therapy pipeline for LGMDs

- The three essential elements of gene therapy development are: a vector, promoter and transgene.
- The goal of investigational gene therapies is to transfer a copy of the missing or non-functional gene to the target cell and ultimately express the protein of interest.
- Sarepta is focusing current R&D efforts on subtypes that represent a large portion of the known LGMD population. Sarepta's current gene therapy pipeline offers the potential to address six LGMD subtypes, which together represent more than 70% of all known LGMDs.[11]

| **PROGRAM** (SUBTYPE) | VECTOR | PROMOTER | TRANSGENE | DISCOVERY | PRE-CLINICAL | CLINICAL |
|---|---|---|---|---|---|---|
| **SRP-9003** (LGMD2E/R4) | AAVrh74 | MHCK7 | β-Sarcoglycan | | | |
| **SRP-9004** (LGMD2D/R3) | AAVrh74 | tMCK | α-Sarcoglycan | | | |
| **SRP-9005** (LGMD2C/R5) | AAVrh74 | MHCK7 | γ-Sarcoglycan | | | |
| **SRP-6004** (LGMD2B/R2) | AAVrh74 | MHCK7 | Dysferlin | | | |
| **SRP-9006** (LGMD2L/R12) | AAVrh74 | tMCK | Anoctamin-5 | | | |
| **Calpain-3** (LGMD2A/R1) | AAVrh74 | tMCK | Calpain-3 | | | |

As of July 2024

### Footnotes and References

*Except for LGMDD1 DNAJB6-related (LGMD1D), which may present with childhood onset.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