

ALEX

Gene therapy R&D
Sarepta

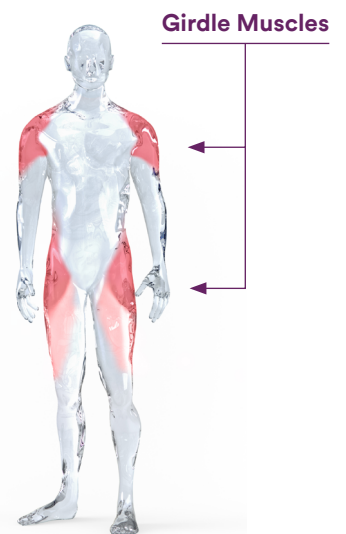
Limb-girdle muscular dystrophy



What it is:

Limb-girdle muscular dystrophy (LGMD) is a term used to identify 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 more than 30 subtypes of LGMD, each caused by a unique gene mutation with its own distinct symptoms, progression, morbidity and disease management approaches.²

- LGMD is caused by a broad range of mutations in the genes that encode for specific proteins that control muscle function, regulation 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 generally worsen over time. Significant disabilities include changes in posture and gait, abnormal appearance of the shoulders, back and arms, and overgrown calf muscles (hypertrophy).²
- Cardiac and respiratory involvement is common, patients may experience weakening of the heart muscle (cardiomyopathy) and severe breathing difficulties, and may require a ventilator for breathing support.¹ In some subtypes of the disease severe cardiac complications can be fatal in some cases and may precede muscle weakness.²



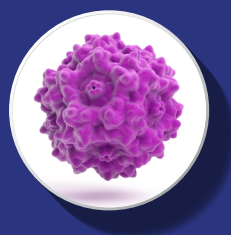
LGMD diagnosis and current disease management^{5,6}

- Establishing a definitive diagnosis of a specific LGMD subtype is challenging because of both the overlap between subtypes and the variability among 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 tests are an important part of confirming a diagnosis and genome sequencing may help identify the specific mutation subtype.
- Treatments currently available for LGMD are directed at symptom management for individual patient needs, and aim to manage the progression of symptoms, improve quality of life and prolong survival.

Types of LGMD

- Each subtype of LGMD represents a unique genetic mutation, and there is wide variation in the prevalence of LGMD subtypes.²
- Subtypes of LGMD are classified based on whether they are inherited through a dominant (LGMD1 or LGMDD) or recessive (LGMD2 or LGMDR) gene.^{2,7}
- 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 some dominant subtypes (instead of numeral 1) and the letter “R” (instead of numeral 2) is used for some recessive subtypes, plus a number (instead of a letter) for the order of discovery.⁷

FEATURES	LGMD1 (LGMD1) ^{3,8,9}	LGMD2 (LGMD2) ^{3,8,9}
Inheritance	Autosomal dominant, one copy of the mutated gene in each cell is sufficient to cause the disorder	Autosomal recessive, both copies of the gene (one from each parent) in each cell have mutations
Population %	10% of total patients with LGMD	90% of total patients with LGMD
Subtypes	~8	~26
Typical age at onset	Adolescence to late adulthood*	Childhood to young adulthood
Limb weakness	Mild	Moderate to severe



Sarepta's gene therapy pipeline for LGMD

- 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.⁹

PROGRAM (SUBTYPE)	VECTOR	PROMOTER	TRANSGENE	DISCOVERY	PRE-CLINICAL	CLINICAL
SRP-9003 (LGMD2E) <i>LGMDR4</i>	AAVrh74	MHCK7	β-sarcoglycan	[Progress bar: ~80%]		
SRP-9004 (LGMD2D) <i>LGMDR3</i>	AAVrh74	tMCK	α-sarcoglycan	[Progress bar: ~80%]		
SRP-9005 (LGMD2C) <i>LGMDR5</i>	AAVrh74	MHCK7	γ-sarcoglycan	[Progress bar: ~60%]		
SRP-6004 (LGMD2B) <i>LGMDR2</i>	AAVrh74	MHCK7	dysferlin	[Progress bar: ~80%]		
SRP-9006 (LGMD2L) <i>LGMDR12</i>	AAVrh74	tMCK	anoctamin-5	[Progress bar: ~60%]		
Calpain-3 (LGMD2A) <i>LGMDR1</i> <i>Nationwide Children's</i>	AAVrh74	tMCK	calpain-3	[Progress bar: ~60%]		

As of February 2020

Footnotes and References

*Except for Emery-Dreifuss muscular dystrophy (LGMD1B), rippling muscle disease (LGMD1C), and LGMD1 DNAJB6-related (LGMD1D), which may present with childhood onset.

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