

Limb-Girdle Muscle Weakness



Incidence

- Estimated prevalence ranging from 2.4-7.3 per 100 000 (Becker) to 0.07 per 100 000 (LGMD2D, E) to 0.43 per 100 000 (LGMD2I)²
- Pompe disease has an estimated incidence of 1 in 40 000⁵



Inheritance

- Most subtypes of LGMW are autosomal recessive (LGMD2A-Q, Pompe)⁴
- Several rare subtypes are autosomal dominant (LGMD1A-E)⁴
- A few myopathies are X-linked (Becker, EDMD-X1, -X2)⁴

Overview

Limb-girdle muscle weakness (LGMW) is a term describing the weakness pattern encompassing a group of diseases associated with weakness and wasting of predominantly proximal muscles of the pelvic and shoulder girdles. Diagnosis is challenging as many symptoms, like progressive muscle weakness in the shoulders, pelvis, and lower limbs, as well as elevations in creatine kinase, can overlap.¹ LGMW encompasses a heterogeneous group of disorders (limb-girdle muscular dystrophies (LGMDs), and other myopathies) that vary in severity and age of onset and can be classified into 2 main groups, depending on the inheritance pattern: LGMD1 is autosomal dominant, and LGMD2 is inherited in an autosomal recessive pattern.² There are very few pathognomonic features of LGMDs that clearly distinguish one from the other, or even from other diseases characterized by muscle weakness.

Late Onset Pompe Disease (LOPD) shares considerable phenotypic overlap with the LGMDs, presenting with progressive proximal weakness (particularly pelvic girdle), scapular winging, feeding/swallowing difficulties and respiratory insufficiency. Pompe is an autosomal recessive disorder, caused by mutations in the *GAA* gene and should be considered in the differential diagnosis of LGMDs.^{3,4}

Diagnosis

When a diagnosis of LGMD is suspected, ruling out other diseases, such as Pompe disease, can shorten the diagnostic delay.^{2,4}

The following evaluations may support a diagnosis of limb-girdle muscle weakness:



Clinical Findings

- A medical history to determine age of onset and a family history, along with a physical examination can distinguish patterns of weakness specific to certain LGMD subtypes⁶



Laboratory Testing

- Serum creatine kinase levels are typically elevated secondary to muscle degeneration/regeneration^{6,7}
- Next-generation sequencing (NGS) allows for the rapid sequencing of multiple genes in parallel and can more easily determine LGMD subtypes⁶
- Muscle biopsy^{3,6,7}: Morphology, immunostaining/immunoblotting and biochemical testing may be helpful or diagnostic, though many providers are electing to use NGS testing panels before more invasive testing



Other

- Electrophysiology and MRIs may be useful in the differential diagnosis and to rule out other neuromuscular diseases⁶
- Electromyography (EMG) findings suggestive of LGMW include myotonic or pseudomyotonic discharges. EMG in LGMD may show short-duration, small-amplitude motor units with early recruitment in weak muscles; findings may be subtle in mild cases²
- Pulmonary function testing including spirometry and maximal inspiratory/expiratory force in the upright and supine positions may help narrow the differential diagnosis²

References: 1. Barba-Romero MA, et al. *Rev Neurol*. 2012;54:497-507 2. Narayanaswami P, et al. *Neurology*. 2014;83:1453-1463. 3. American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM). 2014. American Academy of Neurology. <https://www.aan.com/Guidelines/home/GetGuidelineContent/672>. Accessed March 22, 2020. 4. American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM). *Muscle Nerve*. 2009;40:149-160. 5. Martiniuk F et al. *Am J Med Genet*. 1998;79:69-72. 6. Murphy AP, et al. *J Neuromusc Dis*. 2015;2:57-519. 7. Pegoraro E, et al. **NCBI Bookshelf**. 2012;1-31.

Testing Options for Limb-Girdle Muscle Weakness

Some of the laboratories offering diagnostic testing for limb-girdle muscular dystrophy are listed below. There may be other diagnostic testing appropriate for your patient, and this is not an endorsement of any specific lab. Other testing options can be found at www.concertgenetics.com or www.ncbi.nlm.nih.gov/fti. Consult each laboratory for a full range of options. Content is current at time of publication, and tests may not be available in all states; please call laboratory to confirm test availability, sample shipping information, and all other logistics. Sanofi does not review or control the content of non-Sanofi websites. This listing does not constitute an endorsement by Sanofi of information provided by any other organizations.

Lab	Test name (Test Code)	Sample Requirements	Avg TAT	Test Details	Kits	Billing	Mobile Blood Draw	Contact
Blueprint Genetics	LGMD and Congenital Muscular Dystrophy Panel (NE0801)	WB: 1ml EDTA (lavender) tube; extracted DNA: 2 µg; saliva: Oragene	4 wks	56 genes including Pompe, LGMDs, and congenital muscular dystrophies	Blood, Saliva	Inst, Ins, Self-pay	No	P: 650-452-9340 E: support-us@blueprintgenetics.com W: www.blueprintgenetics.com
	Comprehensive Muscular Dystrophy/Myopathy Panel (NE0701)			161 genes. Includes Pompe, LGMDs, congenital muscular dystrophies, Emery-Dreifuss muscular dystrophy, dystrophinopathies, collagen type IV-related disorders, Nemaline myopathies.				
GeneDx	LGMD Panel (890)	WB: 2-5 ml EDTA (lavender) tube; buccal swabs	4 wks	33 genes for LGMDs and Pompe	Blood, Buccal, Oral rinse	Inst, Ins, Self-pay	No	P: 301-519-2100 E: zebras@genedx.com W: www.genedx.com
	Neuromuscular Disorders Panel (889)			115 genes. Includes above genes plus muscular dystrophies, myopathies, spinal muscular atrophies and myotonias				
Greenwood Genetics Center	Neuromuscular Disorders Sequencing Panel	WB: 5-6 ml EDTA (lavender) tube; extracted DNA and saliva also accepted	8-10 wks	144 genes. Includes Pompe, LGMDs, nuclear-encoded mitochondrial genes, select storage disorders, hereditary neuropathies, myasthenic syndromes and muscular dystrophies	Blood, Saliva	Inst, Ins, Self-Pay	No	P: 800-473-9411 E: labgc@ggc.org W: www.ggc.org
	LGMD Panel (03304)			38-40 genes for LGMDs and Pompe				
Invitae Detect Muscular Dystrophy	Comprehensive Muscular Dystrophy Panel (03291)	WB: 3 ml EDTA (lavender) tube; Saliva/assisted saliva (per Oragene kit); buccal swab; 2 ORAcollect Dx	10-21 d	53-60 genes. LGMDs, Pompe, and muscular dystrophies	Blood, Saliva, Buccal	No charge*	Yes	P: 800-436-3037 E: clinconsult@invitae.com W: www.invitae.com/en/detect-muscular-dystrophy
	Comprehensive Neuromuscular Disorders Panel (03280)	OCD-100		211-230 genes. LGMDs, Pompe, muscular dystrophies, myopathies, and congenital myasthenic syndromes				
The Lantern Project (performed at PerkinElmer)	Focused Neuromuscular Diseases Panel (SAN200)	WB: 5-10 ml EDTA (lavender) tube, DBS card: 5 circles, saliva: Oragene	3 wks	66 genes including LGMDs, Pompe and other inherited myopathies, dystrophies and myasthenic syndromes	Blood, DBS, Saliva	No charge*	Yes	P: 866-354-2910 E: genomics@perkinelmer.com W: www.lanternprojectdx.com
	Comprehensive Neuromuscular Disorders Panel (D4035)			133 genes including LGMDs, Pompe and other inherited myopathies, dystrophies, myasthenic syndromes, and other neuromuscular disorders				
PerkinElmer Genomics	Comprehensive Muscular Dystrophy Panel (D4032)	WB: 5-10 ml EDTA (lavender) tube, DBS card: 5 circles, saliva: Oragene	3-5 wks	56 genes for Pompe, LGMDs, and other muscular dystrophies	Blood, DBS, Saliva	Inst, Ins, Self-pay	No	P: 866-354-2910 E: genomics@perkinelmer.com W: www.perkinelmergenomics.com
	Limb-Girdle Muscular Dystrophy Panel (D5218)			30 genes for Pompe and LGMDs				
Prevention Genetics	LGMD Sequencing Panel (10401)	WB: 3-5 mL EDTA (lavender) or ACD (yellow) tube; DNA: 5-10 g; Saliva: Oragene/GenetiX; Buccal: OCCD-100	18 d	34 genes for LGMDs and Pompe	Blood	Inst, Ins, Self-pay	No	P: 715-387-0484 E: support@preventiongenetics.com W: www.preventiongenetics.com
	Comprehensive Neuromuscular Sequencing Panel (10433)			142 genes. Includes all above genes in addition to genes for other neuromuscular disorders				
University of Chicago, Genetic Services Laboratory	Neuromuscular disorders sequencing panel (3118)	WB: 3-10 ml EDTA (lavender) tube; saliva (Oragene)	6 wks	138 genes. Includes above genes plus DMD, other muscular dystrophies, myopathies, and myasthenic syndromes genes	No	Inst, Ins, Self-pay	No	P: 888-UC-GENES (824-3637) E: ucslabs@genetics.uchicago.edu W: https://dnatesting.uchicago.edu

****Testing is performed at no charge; local charges may apply for sample collection, processing, or shipping.**

avg TAT = average turnaround time; d = days; DBS = dried blood spot; Ins = insurance; Inst = institution; WB = whole blood; wks = weeks.