Limb-Girdle Muscle Weakness

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]

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 40 000[5]

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]

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 subtypes[6]

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 subtypes[6]
- 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 diseases[6]
- 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 cases[2]
- Pulmonary function testing including spirometry and maximal inspiratory/expiratory force in the upright and supine positions may help narrow the differential diagnosis[2]

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:S7-S19. **7.** Pegoraro E, et al. **NCBI Bookshelf.** 2012;1-31.

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SANOFI GENZYME

Testing Options for Limb-Girdle Muscle Weakness

Some of the laboratories offering gene panels for limb-girdle muscle weakness are listed below. There may be other gene panels appropriate for your patient and this is not an endorsement of any one lab. Other testing options can be found at www.concertgenetics.com or www.ncbi.nlm.nih.gov/gtr. Consult each laboratory for a full range of options. Content is current at time of printing and tests may not be available in all states; please call laboratory to confirm test availability, sample shipping information, and all other logistics. Sanofi Genzyme does not review or control the content of non-Sanofi Genzyme websites. These listings do not constitute an endorsement by Sanofi Genzyme 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)			125 genes. Includes Pompe, LGMDs, hereditary myopathies, muscular dystrophies, collagen type VI-related disorders, maternally inherited mitochondrial genome.				
Centogene	Muscular Dystrophy Panel	WB: 1ml EDTA (lavender) tube; extracted DNA: 2 µg; DBS: 10 spots; saliva: Oragene; buccal swab	< 25 days	74 genes. Includes Pompe, LGMDs, hereditary neuropathies, myasthenic syndromes and muscular dystrophies	Buccal, DBS	Inst, Ins (prior auth), Self-Pay	Yes	**P:** 617-580-2102 **E:** customer.support-US@centogene.com **W:** www.centogene.com
EGL Genetics	LGMD Sequencing Panel (MM212)	WB: 2-10 ml EDTA (lavender) tube (volume varies with age)	6 wks	34 genes for LGMDs and Pompe	Blood, DBS, Saliva	Inst, Ins, Self-pay	No	**P:** 855-831-7447 **E:** eglcs@egl-eurofins.com **W:** www.egl-eurofins.com
	Expanded Neuromuscular Disorders Sequencing Panel (MM360)			78 genes. Includes LGMD genes plus overlapping muscular dystrophies, myopathies and myasthenic syndrome genes				
GeneDx	LGMD Panel (890)	WB: 2-5 ml EDTA (lavender) tube; buccal swabs	4 wks	30 genes for LGMDs and Pompe	Blood, Buccal, Oral rinse	Inst, Ins, Self-pay	Yes	**P:** 301-519-2100 **E:** genedx@genedx.com **W:** www.genedx.com
	Neuromuscular Disorders Panel (889)			99 genes. Includes above genes plus muscular dystrophies, myopathies, spinal muscular atrophies and myotonias				
Greenwood Genetics Center	Neuromuscular Disorders Sequencing Panel	WB: 5-7 ml EDTA (lavender); extracted DNA 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	Inst, Ins, Self-Pay	No	**P:** 800-473-9411 **E:** labgc@ggc.org **W:** www.ggc.org
Invitae Detect Muscular Dystrophy	LGMD Panel (03304)	WB: 3 ml EDTA (lavender) tube; Saliva/assisted saliva (per Oragene kit)	10-21 d	31-34 genes for LGMDs and Pompe	Blood, Saliva	No charge*	Yes	**P:** 800-436-3037 **E:** clinconsult@invitae.com **W:** www.invitae.com/en/detect-muscular-dystrophy
	Comprehensive Muscular Dystrophy Panel (03291)			56 genes. LGMDs, Pompe, and muscular dystrophies				
	Comprehensive Neuromuscular Disorders Panel (03280)			109-123 genes. LGMDs, Pompe, muscular dystrophies, myopathies, and congenital myasthenic syndromes				
The Lantern Project (performed at PerkinElmer)	Focused Neuromuscular Diseases Panel (SAN200)	WB: 3-5 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
PerkinElmer Genomics	Comprehensive Neuromuscular Disorders Panel (D4035)	WB: 3-5 ml EDTA (lavender) tube, DBS card: 5 circles, saliva: Oragene	3 wks	132 genes including LGMDs, Pompe and other inherited myopathies, dystrophies, myasthenic syndromes, and other neuromuscular disorders	Blood, DBS, Saliva	Inst, Ins, Self-pay	No	**P:** 866-354-2910 **E:** genomics@perkinelmer.com **W:** www.perkinelmergenomics.com
Prevention Genetics	LGMD Sequencing Panel (10401)	WB: 3-5 ml EDTA (lavender) or ACD (yellow) tube; DNA also accepted; saliva: Oragene/GeneFiX	18 d	34 genes for LGMDs and Pompe	Blood	Inst, Ins, Self-pay	No	**P:** 715-387-0484 **E:** clinicaldnatesting@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	LGMD Sequencing Panel (3106)	WB: 3-10 ml EDTA (lavender) tube; saliva (Oragene)	8 wks	31 genes for LGMDs and Pompe	No	Inst, Self-pay	No	**P:** 888-UC-GENES (824-3637) **E:** ucgslabs@genetics.uchicago.edu **W:** https://dnatesting.uchicago.edu
	Neuromuscular disorders sequencing panel (3118)			113 genes. Includes above genes plus DMD, other muscular dystrophies, myopathies, and myasthenic syndromes genes				

***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.

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