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, are common to many neuromuscular disorders.[1] LGMW is present in 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 muscular dystrophy:

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]

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Testing Options for Limb Girdle Muscular Dystrophy

Some of the laboratories offering diagnostic testing for limb-girdle muscular dystrophy are listed below. There may be other testing appropriate for your patient, and this is not an endorsement of any specific laboratory. 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 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.

Laboratory	Limb Girdle Muscular Dystrophy Panel		Comprehensive Neuromuscular Panel	
	Panel Name (Test Code)	# of Genes	Panel Name (Test Code)	# of Genes
Blueprint Genetics	LGMD and Congenital Muscular Dystrophy Panel (NE0801)	56	Comprehensive Muscular Dystrophy / Myopathy Panel (NE0701)	161
GeneDx	Limb-Girdle Muscular Dystrophy Panel (890)	33	Neuromuscular Disorders Panel (889)	115
HNL Genomics	Limb girdle muscular dystrophy NGS panel (5217)	35		
Invitae	Limb-Girdle Muscular Dystrophy Panel (03304); Detect	38-40	Comprehensive Neuromuscular Disorders Panel (03280); Detect	(211-230)
Knight Diagnostic Laboratory	Limb-Girdle Muscular Dystrophy Panel	34	Comprehensive Neuromuscular Panel	79
Mayo Clinical Laboratories	Inherited Limb-Girdle Muscular Dystrophy and Congenital Myasthenic Syndrome Gene Panel (LGCMP)	65	Comprehensive Neuromuscular Gene Panel (MUPAN)	215
Prevention Genetics	Limb-Girdle Muscular Dystrophy NextGen Sequencing Panel (10401)	34	Comprehensive Neuromuscular Panel (10433)	142
Revvity Omics	Limb-Girdle Muscular Dystrophy Panel (D5218)	30	Comprehensive Neuromuscular Disorders Panel (D4035)	139
The Lantern Project	Focused Neuromuscular Disease Panel	66		

Laboratory (formal name)	Sample Requirements	Kits	Avg TAT	Billing	Contact
Blueprint Genetics	WB:: 1 mL EDTA (lavender) tube; Saliva	Blood	4 w	Inst, Self-Pay, Ins	P: 650-452-9340 Ext. 0 E: support.us@blueprintgenetics.com W: https://blueprintgenetics.com
GeneDx	WB: 2-5 mL EDTA (lavender) tube (preferred); Buccal swab	Blood; Buccal	4 w	Inst, Self-Pay, Ins	P: 301-519-2100 E: zebras@genedx.com W: www.genedx.com
HNL Genomics	WB: 3 mL EDTA (lavender) tuve; Saliva	No	2-4 w	Inst, Self-Pay, Ins	P: 484-244-2900 E: hnlgenomicsinquiries@hnl.com W: www.hnl.com
Invitae	WB: 3 mL EDTA (lavender) tube (preferred); Saliva; Buccal swab	Blood; Saliva; Buccal	10-21 d	Inst, Self-Pay, Ins, *no charge	P:800-436-3037 E: clinconsult@invitae.com W: www.invitae.com
Knight Diagnostic Laboratory	WB: 2-5 mL EDTA (lavender) or ACD (yellow) tube; Saliva	No	6 w	Inst, Self-Pay, Ins	P: 855-535-1522 E: KDLClientServices@ohsu.edu W: https://knightdxlabs.ohsu.edu/
Mayo Clinic Laboratories	WB: 3 mL EDTA (lavender) tube	No	28-42 d	Inst (ins possible in some cases, Inst acct required)	P: 800-533-1710 E: mcl@mayo.edu W: www.mayocliniclabs.com
Prevention Genetics	WB: 3-5 mL EDTA (lavender) or ACD (yellow) tube (preferred); DBS: 5 spots; Saliva	Blood; Saliva	18 d	Inst, Self-Pay, Ins	P: 715-387-0484 E: support@preventiongenetics.com W: www.preventiongenetics.com
Revvity Omics	WB: 5-10 mL EDTA (lavender) tube (preferred); DBS: 1 card; Saliva	Blood; DBS; Saliva	3-5 w	Inst; Self-Pay	P: 866-354-2910 E: genomics@revvity.com W: www.revvity.com
The Lantern Project	WB: 5-10 mL EDTA (lavender) tube (preferred); DBS: 1 card; Saliva	Blood; DBS; Saliva	3 w	No charge*	P: 866-354-2910 E: genomics@revvity.com W: www.lanternprojectdx.com

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.

***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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