Rare disease clinical trials
Power in numbers

Matthew P. Wicklund, MD

Correspondence to
Dr. Wicklund: mwicklund@hmc.psu.edu

Neural Genet
2016;2:e92; doi: 10.1212/NeurolGenet

The limb-girdle muscular dystrophies (LGMDs) encompass a collection of genetic muscle diseases with proximal-predominant weakness of the limbs. Thirty-two of these disorders are named via the common nomenclature, including 8 autosomal-dominant (LGMD1A-H) and 24 autosomal-recessive (LGMD2A-X) disorders. In addition, numerous other genetic muscle diseases, including Bethlem myopathy, dystrophinopathies, ryanodine receptor–associated myopathies, and many more, may clinically present with similar proximal-predominant weakness. Therefore, current genetic testing panels targeting neuromuscular weakness frequently encompass >75 genes. These disorders are quite rare, each with minimum prevalence estimates of 0.01–0.60 cases per 100,000 persons. LGMD2A (attributable to mutations in the gene for calpain-3) and LGMD2B (attributable to mutations in the gene for dysferlin) consistently are the 2 most prevalent LGMD subtypes in a variety of ethnic cohorts.

In this issue of Neurology® Genetics, Harris et al. describe baseline clinical and functional features in a large cohort of 193 patients participating in the international Clinical Outcome Study, a 3-year observational trial of dysferlinopathies. Criteria for inclusion required ≥2 pathogenic mutations in DYSF, the gene for dysferlin, or 1 pathogenic mutation plus evidence for significant quantitative deficiency of dysferlin protein. The investigators delineated 175 mutations, with no distinct hotspot along the gene, and 112 of these mutations were present in just 1 participant. Thus, many isolated, individual, unique mutations were selectively seen in a single person. On muscle immunohistochemistry or immunoblot, most patients had absent or diminished dysferlin expression. It is noteworthy, however, that dysferlin actually expressed normally in 3 patients with moderate to severe disease, reiterating the fact that protein-based assays may miss a portion of dysferlinopathy cases.

In this large, rare disease cohort, the clinical features reinforce findings in the literature. Harris et al. report onset at 3–60 years of age (median 19 years). Interestingly, 24% of patients serendipitously obtained their diagnosis after evaluation for hyperCKemia, whereas 13% were discovered after diagnosis in a family member. Dramatic improvement has occurred in the timeframe from symptom onset to diagnosis, reducing from 20.5 years in the 1970s to 3.1 years since the year 2000. Of the patients, 16% were misdiagnosed as polymyositis, and 25% received corticosteroid treatment, an ineffective treatment strategy in dysferlinopathies. Leg weakness was the common initial symptom and presented roughly equally in a proximal, distal, or proximodistal pattern. At all stages of disease, lower extremities were nearly uniformly more affected than upper extremities. And, in terms of pattern of weakness, hip extensors were statistically significantly weaker than hip flexors, while hip abductors were relatively spared, with hip adductors definitely weaker. Calf atrophy manifested in 71%; however, muscle hypertrophy actually occurred in 11%. Mean serum CK was 4,562 U/L (range, 209–23,124 U/L) with lower values seen over time. Similar to earlier publications of athletic prowess before disease onset, participation in sports was very common (80%), with 19% contending at regional or national levels.

One crucial reason to pursue a definitive, genetic diagnosis remains determination of the involvement of other organs in muscle diseases. In LGMDs, some subtypes have significant, early, or disproportionate cardiopulmonary dysfunction leading to greater morbidity and early mortality. LGMD1B (laminopathies), 2C-F (sarcoglycanopathies), and 2I (Fukutin-related protein and α-dystroglycanopathies) have significant risk of cardiac and/pulmonary dysfunction requiring pacemaker/defibrillator placement, management of congestive heart failure, and/or non-invasive ventilatory support. Conversely, LGMD2A (calpainopathies), 2B (dysferlinopathies), and 2L (anoctaminopathies) have been thought to be virtually without cardiopulmonary dysfunction. In this study, no patients had frank heart failure, only 6 patients had a forced vital capacity <50% (all with moderate to severe skeletal muscle weakness), and
only 4 patients used nocturnal noninvasive ventilation (all for the diagnosis of obstructive sleep apnea). This reemphasizes the paucity of clinically relevant cardiac and respiratory dysfunction in dysferlinopathies. Moreover, these data support published guideline recommendations that clinicians need not refer LGMD2A and LGMD2B patients for cardiopulmonary surveillance unless symptoms arise.7

Treatment trials in rare diseases pose significant challenges. They require large, multicenter, collaborative efforts to identify, recruit, and retain sizable pools of patients for statistically meaningful results in studies with adequate power. Yet, understandably, most trial participants prefer not to go untreated. This creates an honest conundrum for clinical trial design. If rare disease populations could be well defined, those populations could theoretically be used to chart disease trajectories as historical control groups. However, this concept has not been generally accepted. So, of late, trials disproportionately divide cohorts into treated:untreated ratios of 2:1 or 3:1. As we move through to the era of genetic therapies,8 impeccable descriptions of disease manifestations and progression in large populations, as in the Clinical Outcome Study for Dysferlinopathy, will prove imperative for successful trial design, accomplishment, and analysis.

In rare diseases, the power in numbers will be the big deal propelling us forward! The efforts of Harris et al. reflect a noble step in that direction.

STUDY FUNDING
No targeted funding reported.

DISCLOSURE
M. Wickland has received funding for travel and speaker honoraria from CHI St Luke’s Health, Muscular Dystrophy Association, Mount Nittany Medical Center, Nationwide Children’s Research Institute, Georgia Regents University, University of California–Irvine, Athena Diagnostics, Jain Foundation, the American Academy of Neurology, Children’s Hospital of Philadelphia, Vanderbilt University; has served on speaker’s bureaus for Sanofi-Genzyme; has received research support from Eli Lilly, Sarepta, Sanofi-Genzyme, NIH, and National Institute of Neurological Disorders and Stroke. Go to Neurology.org/ng for full disclosure forms.

REFERENCES
1. Nigro V, Savarese M. Genetic basis of limb-girdle muscular dystrophies: the 2014 update. Acta Myologica 2014;33:1–12.
2. Gordon ES, Hoffman EP. The ABC’s of limb-girdle muscular dystrophy: α-sarcoglycanopathy, Bethlem myopathy, calpainopathy and more. Curr Opin Neurol 2001;14:567–573.
3. Norwood FLM, Harling C, Chinnery PF, Eagle M, Bushby K, Straub V. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. Brain 2009;132:3175–3186.
4. Harris E, Bladen CL, Mayhew A, et al. The Clinical Outcome Study for dysferlinopathy: an international multicenter study. Neurol Genet 2016;2:e89. doi: 10.1212/NXG.0000000000000089.
5. Nilsson MI, Laureano ML, Saeed M, Tarnopolsky MA. Dysferlin aggregation in limb-girdle muscular dystrophy type 2B/Myoshi myopathy necessitates mutational screen for diagnosis. Muscle Nerve 2013;47:740–747.
6. Walter MC, Reilich P, Thiele S, et al. Treatment of dysferlinopathy with deflazacort: a double-blind, placebo-controlled clinical trial. Orphanet J Rare Dis 2013;8:26.
7. Narayanaswami P, Weiss M, Selcen D, et al. Evidence-based guideline summary: diagnosis and treatment of limb-girdle and distal dystrophies: report of the guideline development subcommittee of the American Academy of Neurology and the practice issues review panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology 2014;83:1453–1463.
8. Sondergaard PC, Griffin DA, Pozsgai ER, et al. AAV. dysferlin overlap vectors restore function in dysferlinopathy animal models. Ann Clin Transl Neurol 2015;2:256–270.
## Rare disease clinical trials: Power in numbers

Matthew P. Wicklund  
*Neurol Genet* 2016;2;  
DOI 10.1212/NXG.0000000000000092

This information is current as of August 4, 2016

| Updated Information & Services | including high resolution figures, can be found at:  
| References | http://ng.neurology.org/content/2/4/e92.full.html#ref-list-1  
| Citations | This article has been cited by 1 HighWire-hosted articles:  
| Permissions & Licensing | Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:  
| Reprints | Information about ordering reprints can be found online:  

*Neurol Genet* is an official journal of the American Academy of Neurology. Published since April 2015, it is an open-access, online-only, continuous publication journal. Copyright © 2016 American Academy of Neurology. All rights reserved. Online ISSN: 2376-7839.