GRASP-LGMD (Genetic Resolution and Assessments Solving Phenotypes) in LGMD Consortium

Jeffrey Statland, MD on Behalf of the GRASP-LGMD Investigators
Associate Professor of Neurology, University of Kansas Medical Center
GRASP LGMD is a Group Effort

- Nicholas Johnson (VCU) – overall lead
- Jeff Statland (KU) and Nick Johnson – lead on clinical outcome assessment
- Chris Weihl (Wash U) and Monkol Lek (Yale) – lead on genetic resolution and gene discovery
- Matthew Wicklund (U of CO) – advocacy outreach and education
- All the site PIs (Tahseen Mozaffar - UCI!)
- All the PMs and coordinators
- Advocacy partners
Disclosures

• Grant support: FSH Society, NINDS, MDA, Friends of FSH Research
• Consultant/Advisory Board: Acceleron Pharma, Fulcrum Therapeutics, Sarepta, and Strongbridge
Background LGMD

- Group of heterogenous muscular dystrophies which share a common phenotype: shoulder and pelvic girdle weakness
- Originally coined to distinguish from x-linked muscular dystrophy (DMD) and myotonic dystrophy
- Can affect men and women
- Age of onset from childhood to adulthood
- Prevalence taken together worldwide
  - 3/100,000 or ~10,000 in the US
- In general slowly progressive
  - Morbidity: ambulation or maintain a job
  - Some: cardiac and respiratory complications

## LGMD Genetics: What’s in a name

<table>
<thead>
<tr>
<th>Features</th>
<th>LGMD1</th>
<th>LGMD2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>Autosomal dominant</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>Subtypes</td>
<td>1A–1H</td>
<td>2A–2Z</td>
</tr>
<tr>
<td>Typical age at onset</td>
<td>Adolescent to late adulthood except LGMD1B–1D may present with childhood onset</td>
<td>Childhood to young adulthood</td>
</tr>
<tr>
<td>Limb weakness</td>
<td>Mild</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Creatine kinase (CK) levels</td>
<td>Normal to mildly elevated except for LGMD1C that typically have significantly elevated CK levels</td>
<td>Mildly to highly elevated</td>
</tr>
<tr>
<td>Exercise intolerance or rhabdomyolysis</td>
<td>1C</td>
<td>2A, 2B–2E, 2I, 2L, and 2T</td>
</tr>
</tbody>
</table>

~90% LGMD

>30 LGMD

LGMD Mutations

- Many in structural muscle proteins (dystrophin-associated glycoprotein complex)
  - Genes like sacroglycans role in protecting against damage during contractions
  - Genes like anoctamin 5, dysferlin role in membrane repair

Image from MDA website
Allelic Disorders

• Some overlap between LGMD and other myopathies

LGMD Genetics: what’s in a name?

• More recent ENMC workshop on naming
• Only included disorders in > 2 families
• Primary limb-girdle presentation
• Left out:
  • Type 1A-C: Myot, LMNA, CAV3
  • Type 2: GAA, DES
• Changed nomenclature
  • D=dominant, R=recessive
  • Number according to order gene discovered

<table>
<thead>
<tr>
<th>Gene</th>
<th>Old nomenclature</th>
<th>Proposed nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPN</td>
<td>LGMD2A</td>
<td>LGMDR1 calpain3-related</td>
</tr>
<tr>
<td>DSYF</td>
<td>LGMD2B</td>
<td>LGMDR2 dysferlin-related</td>
</tr>
<tr>
<td>SGCA</td>
<td>LGMD2D</td>
<td>LGMDR3 α-sarcoglycan-related</td>
</tr>
<tr>
<td>SGCB</td>
<td>LGMD2E</td>
<td>LGMDR4 β-sarcoglycan-related</td>
</tr>
<tr>
<td>SGCG</td>
<td>LGMD2C</td>
<td>LGMDR5 γ-sarcoglycan-related</td>
</tr>
<tr>
<td>SGCD</td>
<td>LGMD2F</td>
<td>LGMDR6 δ-sarcoglycan-related</td>
</tr>
<tr>
<td>FMRP</td>
<td>LGMD2I</td>
<td>LGMDR9 FMRP-related</td>
</tr>
<tr>
<td>ANO5</td>
<td>LGMD2L</td>
<td>LGMDR12 anoctamin-5-related</td>
</tr>
<tr>
<td>DNAJB6</td>
<td>LGMD1D</td>
<td>LGMD12 DNAJB6-related</td>
</tr>
<tr>
<td>TNP03</td>
<td>LGMD1F</td>
<td>LGMD2 TNP03-related</td>
</tr>
</tbody>
</table>

US prevalence of LGMD subtypes

• Older study 2006:
  • 18% DYSF (LGMD2B), 15% SGCA (LGMD2C-F), 15% FKRP (LGMD2I), 12% CAPN3 (LGMD2A), and 1.5% CAV3 (LGMD1C)

• More recent free testing programs

• Meta analysis 2018 using large WES/WGS data bases

• But common to all the most frequent include:
  • CAPN3, DYSF, SGCA (group), ANO5, FKRP
  • DNAJB6


Courtesy of MDA and Jain Foundations
Clinical Features of LGMD

• In theory each subtype has its own trajectory
• Disease progression = variable
• Age of onset  = variable
• Incidence in both males and females
• Progressive weakness and wasting in limb musculature
• CK on average higher in recessive LGMD
• If cardiac (arrythmia, cardiomyopathy) think: sarcoglycan, CAV3, LMNA, DES, FKRP
• If pulmonary think: sarcoglycan,
  • In most respiratory follows limb weakness – late feature

Management of LGMD: Supportive Care

• Multi-disciplinary care
• PT/OT/orthotics – assistive devices / mobility aids
• Pulmonary / RT -respiratory aids if required
• Cardiology – if affected
• Orthopedics/pain – for some
• Management approaches aim to improve quality of life and prolong survival
• Genetic counseling

➢ No FDA approved medications
• Our ability to diagnose LGMD has improved
  • Advocacy groups/Genzyme supporting free genetic testing programs ~ 6K tested
  • The cost of commercial testing has lowered (~$250)
• This has increased the prevalence of LGMD in the US
  • But also increasing the number of individuals with variants of unknown significance or negative testing = great deal of uncertainty, often no clear path forward

Courtsy of the Jain Foundation and MDA
At the same time, advances in gene therapy technology have

- Made systemic AAV-delivered gene replacement therapy a reality (FDA approved Zolgensma for SMA)
- Virtually all recessive LGMDs could be amenable to gene replacement (dominant LGMD to other approaches, RNAi)—making them targets for future drug development
  - Industry involved: Myonexus/Sarepta, Genethon, etc
• Gene replacement therapy is happening now for sarcoglycanopathies (LGMD2C-F)
• Proof of concept in single muscles
• Press Releases from Sarepta’s LGMD2E program
  • 3 individuals dosed and 2 month biopsy results released
  • 51% sarcoglycan positive fibers by immunohistochemistry / +Western Blot
  • 90% drop in serum CK

Limbg-girdle muscular dystrophy type 2D

The pace of therapeutic development has outpaced our efforts to prepare for clinical trials

Leaving several gaps which need to be addressed:

- Gap 1: In how we diagnose people with LGMD
- Gap 2: In the tools we will use to measure a response to therapy in a clinical trial
- Gap 3: In our understanding of the patient experience of living with LGMD

Barriers: rarity, heterogeneity, and broad age range affected
Genetic Resolution and Assessments Solving Phenotypes in LGMD (GRASP-LGMD)

• Funding for a smaller network of sites from the MDA and industry funds = growing quickly from 6 to 11 sites

• Close relationship with advocacy group partners who are tremendous help (Jain Foundation, Coalition to Cure Calpain, LGMD1D, LGMD2L, Team Titin)
  • First ever combined LGMD patient and family day: Aug30-Sep2, 2019, Chicago, IL

• The Goal: hasten therapeutic development for LGMD by:
  • Improving diagnostics (Gap1)
  • Developing outcome measures (Gap2)
  • Understanding the patient reported impact (Gap3)
  • Training the next generation of LGMD researchers

• Common network efficiencies
  • Streamlined regulatory oversite
  • Data management
  • Training sites and patient engagement
Gap 1: Improved diagnostics

- Chris Weihl (Wash U) and Monkol Lek (Yale) – lead
- Proposal to:
  - **Aim 1:** Identify patients with an LGMD phenotype and negative or indeterminate genetic testing with panel based sequencing. Using national MDA clinics, and ability to reach out to previously sequenced individuals in Jain/MDA programs if available
  - **Aim 2:** Resolve LGMD gene variants and establish LGMD diagnoses. Workflows for variant resolution
  - **Aim 3:** Identify new genes associated with LGMD. WES/WGS/RNA seq
Proposed workflow

Suspected LGMD
- Negative gene testing
  - Gene discovery with WES, WGS, and RNAseq
    - Unresolved

Genetic testing shows VOUS
- Enhanced clinical phenotyping
  - Bioinformatic analysis
    - Functional testing for certain LGMDs
      - Resolved

Genetically confirmed LGMD
- Enroll in Studies
Example

- Collected clinical information and existing muscle tissue

- Informatics
  - DYSF in general pop; CAPN3 not
  - CAPN3 VOUS near splice site junction

- Clinical: progressive LG weakness, no prior family history

- Functional study
  - Normal DYSF staining, reduction in CAPN3 by immunoblot
  - Consider RT PCR for cryptic splicing

- Result: compound heterozygous LGMD2A

Example courtesy of Chris Weihl, Washington University, St Louis, MO
Gap 2 - Development of COAs for LGMDs

• Nicholas Johnson (VCU) and Jeff Statland (KUMC) - lead
• Common protocol (platform study) regardless of LGMD mutation
• COAs chosen by experienced PT leads at Nationwide Children’s (Lindsay Alfano, PT, DPT, PCS, and Linda Lowes, PT, PhD)

• Proposal for 12-24 months study:
  • To define a common set of pelvic and shoulder girdle COAs, and COAs useful for capturing phenotypic diversity. To establish multi-site training, test-retest reliability, cross sectional associations
  • To determine the sensitivity to longitudinal disease progression. We will use statistical and anchoring methods to determine what will be a minimally important clinical difference. We will use factor analysis to identify which COAs capture variation in disease severity across the cohort.
  • To refine clinical trial strategies (i.e. inclusion criteria) based on baseline and longitudinal phenotypic characteristics. We will determine which baseline characteristics, mutation, age, gender, and baseline functional status are most likely to predict progression, using regression trees to assess subgroups likely to progress.

• Data useful for understanding natural history and trial planning
Two pathways: LEXT v UEXT

- NorthStar Ambulatory Assessment for Dysferlin
  - Combined NSAA + elements from MFM domain 1
- ACTIVE
  - Video game and stereographic camera to define workspace volume (i.e. reachable workspace)

More: Next Talk Jay Han

Figure courtesy of COS1 Study, and Nationwide Children’s
Gap3: The patient perspective

- The choice of what you measure needs to match a person's perception of LGMD.
- We are in the process of developing an LGMD-specific health inventory—a questionnaire for use in clinical trials.
- Strategy outline in FDA Guidance to Industry for PROs:
  - Open ended interviews: themes we need to address.
  - Other themes like respiratory issues, or cardiac issues may not apply to all LGMD, but will be important for people for whom it is an issue.
- GRASP-LGMD:
  - The next step is a large (several 100s) survey to determine how common each symptom is and how impactful on someone's life.
  - Then the instrument needs to be included in a prospective study.

![Figure 2. Patient Reported Impact in LGMD](image-url)
GRASP-LGMD Today and in the Future

• Funded pilot of n=20 for CAPN3, DYSF, ANO5, and DNAJB6 at 8 sites
• Industry funded study for sarcoglycans, n=100, 11 sites in US and UK
• Proposal out for larger CAPN3
• Proposal out for variant resolution and genetic discovery
• Anticipate 1st patient enrolled 2019
• Working on establishing training program
• Future projects:
  • MRI
  • Biomarkers
  • Additional LGMD subtypes
LGMD patients and family members!!

Organizations
- MDA
- Jain Foundation
- Coalition to Cure Calpain
- Other LGMD advocacy groups

Proposed GRASP-LGMD Sites:
- University of Kansas Medical Center (Jeffrey Statland);
- Virginia Commonwealth University (Nick Johnson);
- Washington University (Conrad Weihl);
- University of Colorado (Matthew Wicklund);
- Kennedy Krieger Institute (Kathryn Wagner);
- Brigham and Women's Hospital (Anthony Amato);
- UC-Irvine (Tahseen Mozaffar)
- University of Iowa (Katherine Matthews);
- University of Florida (Peter Kang);
- Yale University (Monkol Lek);
- Newcastle, UK (Volker Straub)

Thank You!