Welcome to the 2019 University of Iowa Wellstone Center Dystroglycanopathy Conference

- Restrooms
- WiFi
  - Marriott_Conference
  - Password: 12345
- Translators
- Life Hacks
- Information Tables
- Concurrent Sessions
- Ponies ~2:30 pm (weather permitting)
- Group Photo 4:30 pm
- Thank you to Advisory Board members!
- Please complete evaluations
- 2020 date: TBD
Sorry about the rainy weather but it could be worse!
Overall goal: Improve treatment for patients now and in the future
Acknowledgements to key people

• Steve Moore, Kevin Campbell, and lab members

• Organizers
  • Carrie Stephan, nurse coordinator
  • Shelley Mockler, PT
  • Katie Laubscher, PT

• Research coordinators:
  • Chandra Miller
  • Corey McDaniel
  • Evgenia Folts

• Volunteer child supervisors

• Visiting healthcare providers
  • Linda Lowes
  • Megan Iammarino
  • Dimah Saade

• Photographers

• Many other students and health care professionals
Wellstone Medical Student Fellows

Jamie Eskuri (2010-2011)  
Child Neurology Resident  
Boston Children’s Hospital

Steve McGaughey (2011-2012)  
Emergency Med Fellow  
University of Oregon

Katie Lutz (2012-2013)  
Child Neurology Resident  
University of Iowa

Cameron Crockett (2013-2014)  
Child Neurology Resident  
Washington University, St. Louis

University of Iowa  
General surgery resident

Brianna Brun (2015-2016)  
Ohio State University  
Child Neurology resident

Courtney Carlson (2016-2017)  
Mayo clinic  
Orthopedic surgery resident

Angela Lee (2017-2018)  
CCOM medical student, M4  
Genetics
Thank you to those who support this conference financially

• NIH
• CURELGMD2i Foundation (Kelly and Keith Brazzo)
• LGMD2i Fund (John Pierre Laurent)
• PTC Therapeutics
• Private donors

• Please visit tables in the hallway to get more information and thank these people for their support.

• Britt Bergquist from U of Iowa Foundation
Ways to Support

1. THANK YOU!

2. If interested in discussing philanthropic support, contact Britt below:

   **BRITT BERGQUIST**
   Assistant Director of Development
   UI Stead Family Children’s Hospital

   #319.467.3871
   britt.bergquist@foriowa.org
Wellstone Dystroglycanopathy Project Updates

Katherine Mathews
June 2019
2018 Iowa Wellstone Center
Dystroglycanopathy Family Conference

2014 Family conference
Iowa Wellstone enrollment continues to grow

136 subjects consented

2019 Conference Trivia
- 163 Registrants
- 18 States
- 3 Countries
- 2 Continents
- 50 Research Exams

+ Canada, Brazil, South Africa, France and Mexico
Distribution of Wellstone enrollees by genotype

- 84 subjects have *FKRP* mutations (62%)
  - 48 (57%) are homozygous for the common mutation, c. 826C>A
- 41 subjects have mutations in other dystroglycanopathy genes
  - POMT1 & 2 (12%)
  - GMPPB (7%)
  - POMGNT1 (5%)
Big picture in neuromuscular and genetic disease therapy

• FDA approved genetic modifying treatments for Duchenne muscular dystrophy and spinal muscular atrophy
• FDA approved gene replacement therapy for young children with spinal muscular atrophy
• Rare and ultrarare diseases are viewed as potential treatment targets by the pharmaceutical industry

• Treatments are evolving: interesting and novel approaches in coming to the clinic
High level view of therapeutic options in LGMD2I

- Myostatin inhibitor (K. Wagner talk)
- Tamoxifen ?
- Ribitol
  - A human preparation is in development
- Corticosteroid
  - Deflazacort trial has started (see PTC table)
- Gene replacement
  - At least 4 companies are exploring gene replacement in LGMD2I
  - Expect human trials in the next 1-5 years

- What does this mean for other genotypes?
  - It depends on what works, but progress in related diseases is always good.
The data you have helped to generate about your diseases is being used

• Up to 13 years of data from the Iowa Wellstone Dystroglycanopathy project
• We are able to describe the variation between people and between years in one person
• This information helps companies design studies or determine if their treatment is feasible
• Small and large companies have used this information
Can retinal function be used as an outcome measure for future trials?

• Glycosylated alpha dystroglycan is found in the retina
• In Duchenne muscular dystrophy, abnormal retinal function can be seen on electroretinogram (ERG), even though vision is normal.
• We wanted to determine if dystroglycanopathy patients also have abnormal ERGs.
  • If so, ERG might be a non-invasive biomarker that could show change with certain therapies.
• We tested 7 subjects and got an ERG report on one additional subject
• No consistent or significant variation in ERGs seen in dystroglycanopathy subjects.
Are corticosteroids beneficial in patients with dystroglycanopathy?

• Corticosteroids are beneficial in related forms of muscular dystrophy (Duchenne muscular dystrophy)
• Mechanism of action is predicted to be similar in dystroglycanopathies
• Corticosteroids have significant side effects and require careful weighing of risks and benefits.
• We reviewed what we know about people in the study who have taken corticosteroids continuously for >1 year
  • Limited this analysis to those with FKRP mutations
  • 14 people’s experience reviewed
Are corticosteroids beneficial in patients with FKRP mutations?

- 12/14 subjects report specific improvements while on steroids
- 7 subjects noted increased weakness with decrease in steroid dose (due to side effects), and increased dose again as a result
- 7/14 subjects experienced specific negative side effects
  - 5 subjects with 2 or more negative side effects

<table>
<thead>
<tr>
<th>Benefits:</th>
<th>Side effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved functional strength (transfers, fewer falls, more energy)</td>
<td>Decreased bone density/fractures</td>
</tr>
<tr>
<td>Stabilized function</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Reduced muscle soreness</td>
<td>Mood change (lability or hypomanic)</td>
</tr>
<tr>
<td>Improved appetite</td>
<td>Cataracts</td>
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</tbody>
</table>

Katie Laubscher, Karen Eilers, Kimberly Kroeze
Are corticosteroids beneficial in patients with *FKRP* mutations? Limitations of this review

• Highly selected population--a small subset is taking a steroid

• Mixture of *FKRP* genotypes
  • Only 2 of 14 are homozygous for common c.826C>A mutation

• Different doses and dosing regimens
  • 3 daily
  • 3 weekend only
  • 8 every other day

• Started at different ages
  • 3-42 years at start

• Data is subjective (few patients with before/after formal testing)

• Conclusion: Individual balance of risks and benefits
What other things have we learned about symptoms of care of patients with dystroglycanopathies?

• Rhabdomyolysis, myoglobinuria are common in LGMD2i
• GI/GU symptoms can be problems for some patients
• Heart disease (cardiomyopathy) typically occurs in adulthood in patients with LGMD2i
  • Genotype impacts age at onset
• Raised awareness of brain MRI findings in congenital muscular dystrophy patients and showed relationships with function.
• Level of childhood exercise doesn’t impact adult motor function in LGMD2i
• There is a syndrome of illness associated weakness in children with dystroglycanopathy across genotypes
• While patients with GMPPB mutations can have a myasthenia gravis-like syndrome, other dystroglycanopathy patients do not
• Most people with dystroglycanopathy don’t have significant osteoporosis in the absence of other risk factors
Nomenclature in muscular dystrophy

- The way we name disease reflects the way we organize disease for communication and remembering
- Nomenclature for LGMD is in evolution.....
Limb Girdle and Congenital Muscular Dystrophies

Onset of weakness:
- Before 4 weeks
- Before 6 months
- Before age 2 years
- Before walking

Onset of weakness after CMD criteria:
- Dystroglycanopathies
- Collagen 6
- LMNA
- Merosin (a2 chain of laminin)

LGMD/CMD overlap
- Dystroglycanopathies
- Collagen 6
- LMNA
- Merosin (a2 chain of laminin)
In this paper a new classification of the myopathies is proposed, based upon a review of the clinical features and natural history of the disease in 105 cases of myopathy of various types.
LGMD history, the genetic era

• 1986: *DMD* identified by positional cloning
• 1991: linkage of a form of LGMD to chromosome 15 (now LGMD 2A)
  • Beckmann, J.S.. et al
• 1992: 50kD dystrophin-associated glycoprotein (now α-sarcoglycan) is the cause of severe childhood onset autosomal recessive muscular dystrophy (SCARMD; later LGMD 2D)
## Limb Girdle Muscular Dystrophy, 1999

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Inheritance</th>
<th>Genetic Location</th>
<th>Protein</th>
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<tbody>
<tr>
<td>LGMD1C</td>
<td>AD</td>
<td>3p25</td>
<td>Caveolin 3</td>
</tr>
<tr>
<td>LGMD2A</td>
<td>AR</td>
<td>15qq5-21</td>
<td>Calpain 3</td>
</tr>
<tr>
<td>LGMD2B (and Myoshi myopathy)</td>
<td>AR</td>
<td>2p</td>
<td>Dysferlin</td>
</tr>
<tr>
<td>LGMD2C-F</td>
<td>AR</td>
<td>13q12</td>
<td>Sarcoglycans α,β,δ,γ dystrophin</td>
</tr>
<tr>
<td>DMD/BMD</td>
<td>X-LR</td>
<td>Xp21</td>
<td></td>
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</tbody>
</table>
### Dominant
- **1A**: Myotilin; 5q31
- **1B**: Lamin A/C; 1q21
- **1C**: Caveolin-3; 3p25
- **1D**: DNAJB6; 7q36
- **1E**: Desmin; 2q35
- **1F**: TNPO3; 7q32
- **1G**: HNRPNL; 4q21
- **1H**: 3p23

### Recessive
- **2A**: Calpain-3; 15q15
- **2B**: Dysferlin; 2p13
- **2C**: γ-Sarcoglycan; 13q12
- **2D**: α-Sarcoglycan; 17q21
- **2E**: β-Sarcoglycan; 4q12
- **2F**: δ-Sarcoglycan; 5q33
- **2G**: Telethonin; 17q12
- **2H**: TRIM32; 9q33
- **2I**: (MDDGC5): FKRP; 19q13
- **2J**: Titin; 2q24
- **2K**: (MDDGC1): POMT1; 9q34
- **2L**: ANO5; 11p14
- **2M**: (MDDGC4): Fukutin; 9q31
- **2N**: (MDDGC2): POMT2; 14q24
- **2O**: (MDDGC3): POMGnT1; 1p32
- **2P**: (MDDGC9): DAG1; 3p21
- **2Q**: Plectin 1f; 8q24
- **2R**: Desmin; 2q35
- **2S**: TRAPPCL; 4q35
- **2T**: GMPPB; 3p21
- **2U**: (Cerebellum small): ISPD; 7p21
- **2V**: GAA; 17q25
- **2W**: LIMS2; 2q14
- **2X**: POPDC1; 6q21
- **2Y**: TOR1AIP1; 1q25
- **2Z**: POGLUT1; 3q13
- **MDDGC12**: POMK; 8p11

### X-linked
- Duchenne and Becker MD
Pull out the dystroglycanopathies and call them type C
Autosomal Recessive LGMD, Type C
OMIM, 2017

<table>
<thead>
<tr>
<th>Location</th>
<th>Phenotype</th>
<th>Gene/Locus</th>
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<tr>
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<td>19q13.32</td>
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<td>FKRP</td>
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Proposed refined definition of LGMD

“Limb girdle muscular dystrophy is a genetically inherited condition that primarily affects skeletal muscle leading to progressive, predominantly proximal muscle weakness at presentation caused by a loss of muscle fibres.

To be considered a form of LGMD the condition must be described in at least two unrelated families with affected individuals achieving independent walking, must have an elevated serum creatinine kinase activity, must demonstrate degenerative changes on muscle imaging over the course of the disease, and have dystrophic changes on muscle histology ultimately leading to end-stage pathology for the most affected muscles.”

2016 ENMC Workshop on LGMD Nomenclature and Reformed Classification.
**Proposed Nomenclature for LGMD**

"LGMD, inheritance (R or D), order of discovery (number), affected protein"

from 2016 ENMC Workshop on LGMD Nomenclature and Reformed Classification.

<table>
<thead>
<tr>
<th>LGMD D</th>
<th>LGMD R</th>
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<tbody>
<tr>
<td>LGMD D1</td>
<td>calpain 3-related</td>
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<tr>
<td>LGMD D2</td>
<td>dysferlin-related</td>
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<tr>
<td>LGMD D3</td>
<td>α-sarcoglycan-related</td>
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<tr>
<td>LGMD D4</td>
<td>β-sarcoglycan-related</td>
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<tr>
<td>LGMD D5</td>
<td>γ-sarcoglycan-related</td>
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<td>δ-sarcoglycan-related</td>
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<td>collagen 6-related</td>
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<td></td>
<td>laminin α2-related</td>
</tr>
</tbody>
</table>
Nomenclature
(screen shot from OMIM for LGMD2I, June 2018)

Stay tuned for the next stage in the definition and nomenclature saga...meanwhile, feel free to continue to call it LGMD2i or whatever you wish!
MDA-funded LGMD infrastructure project
GRASP-LGMD, PI Nick Johnson

• To bring to other forms of LGMD the clinical and diagnostic research under a single umbrella
  • Extend what we have in LGMD2I to other LGMDs
• Multiple sites in US and one in England
• First investigator meeting Sept 2019 in conjunction with first US national LGMD meeting
  (https://nationallimbgirdlemusculardystrophyconference.com)
Questions?
(or ask any time during the weekend!)

• WiFi
  • Marriott_ Conference
  • Password: 12345

• Please complete evaluation forms

2017 conference photo