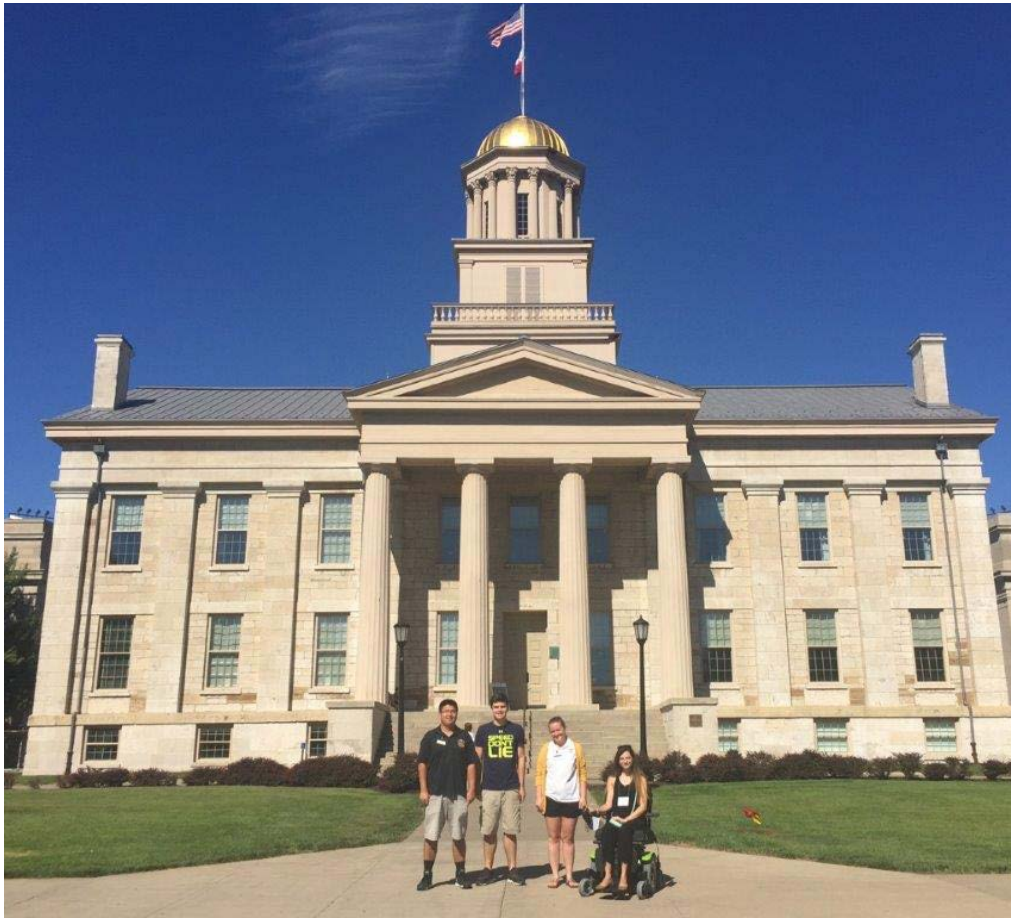
Welcome to the 2019 University of Iowa Wellstone Center Dystroglycanopathy Conference

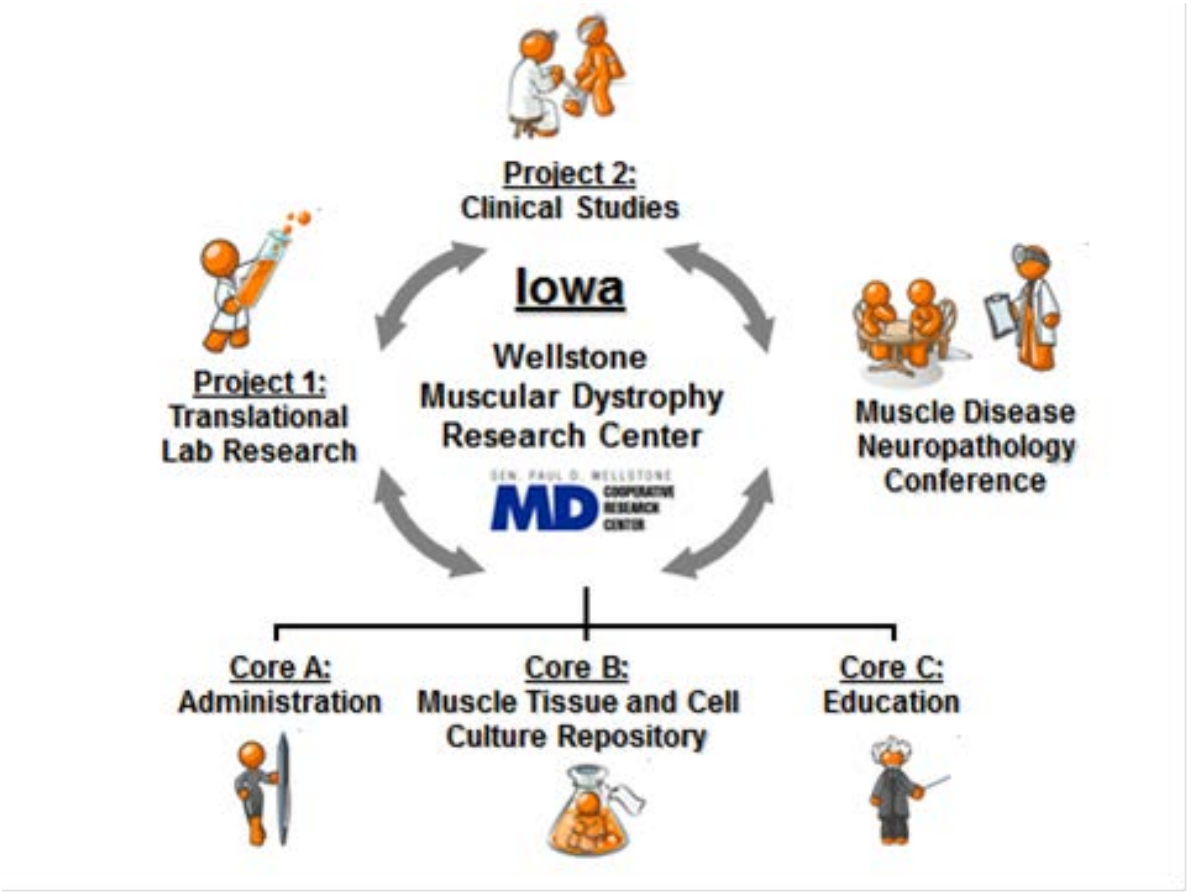
- Restrooms
- WiFi
  - Marriott_ Conference
  - Password: 12345
- Translators
- Life Hacks
- Information Tables
- Concurrent Sessions
- Ponies ~2:30 pm (weather permitting)
- Group Photo 4:30 pm
- Thank you to Advisory Board members!
- Please complete evaluations
- 2020 date: TBD



Sorry about the rainy weather but it could be worse!

Iowa Wellstone Muscular Dystrophy Center

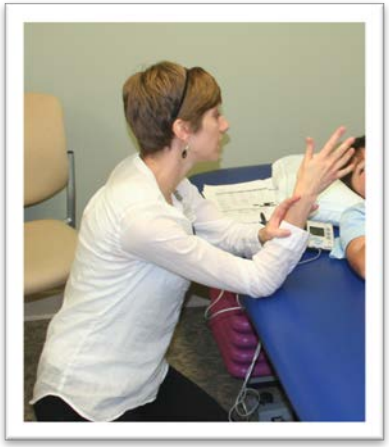
National Institutes of Health



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

Braden Jensen (2014-2015)
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

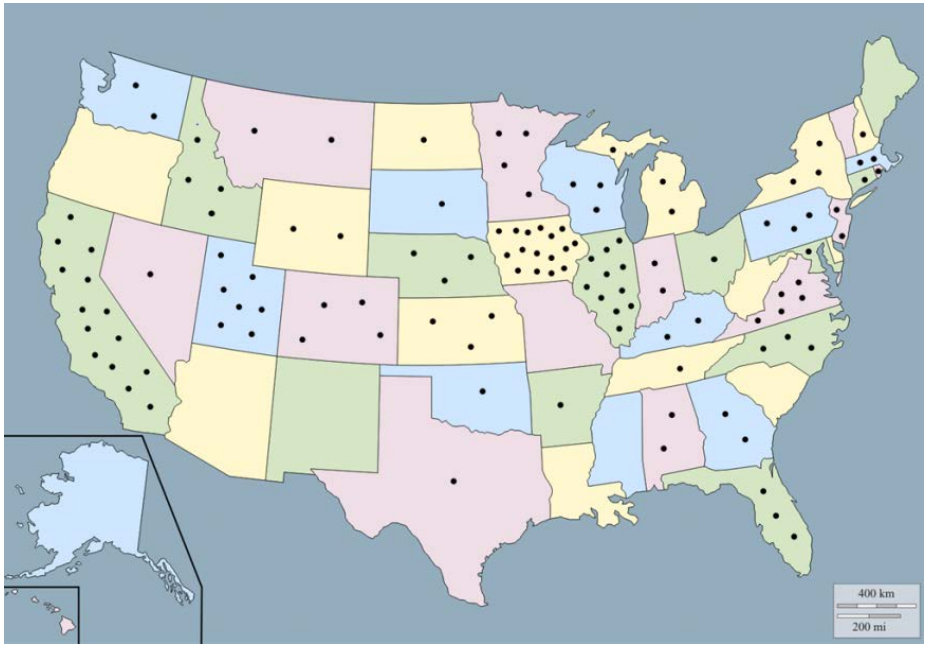
Katherine Mathews

June 2019

2018 Iowa Wellstone Center Dystroglycanopathy Family Conference

2014 Family conference

Iowa Wellstone enrollment continues to grow



+ Canada, Brazil, South Africa, France and Mexico

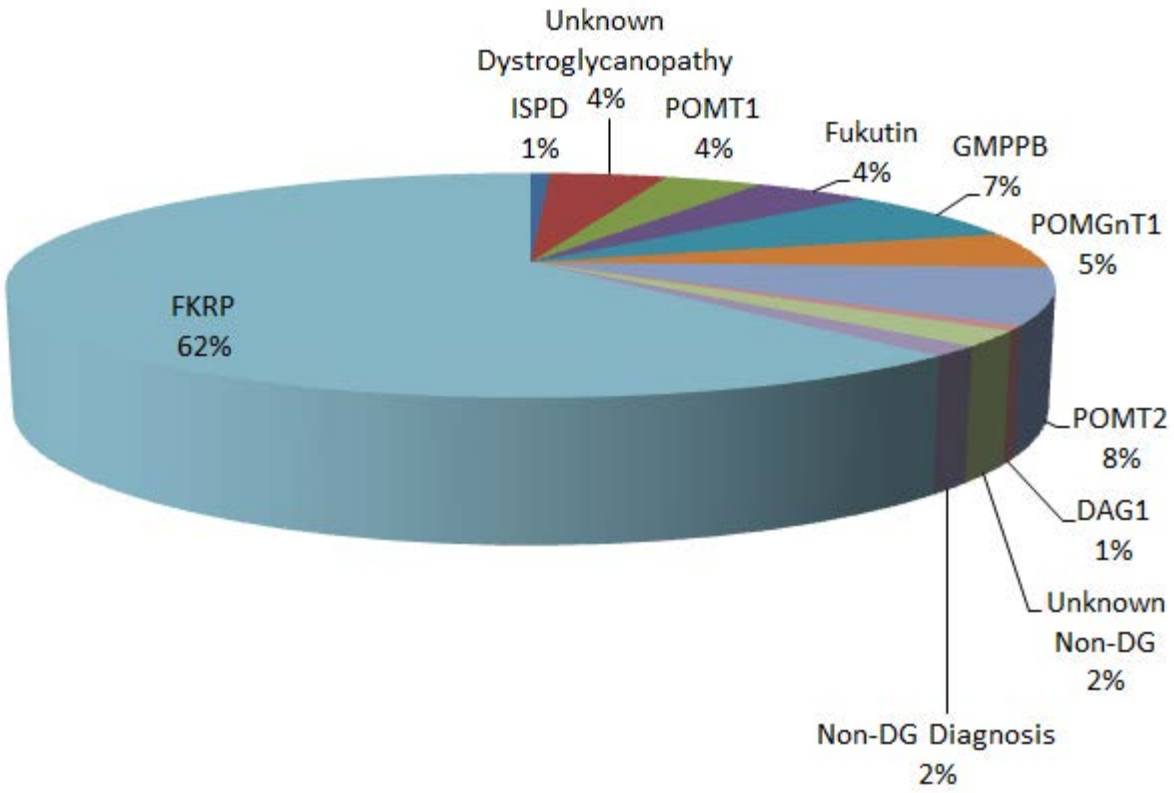
136 subjects consented

2019 Conference Trivia

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

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

Benefits:	**Side effects:**
Improved functional strength (transfers, fewer falls, more energy)	Decreased bone density/fractures
Stabilized function	Weight gain
Reduced muscle soreness	Mood change (lability or hypomanic)
Improved appetite	Cataracts
	Prediabetes, amenorrhea

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)

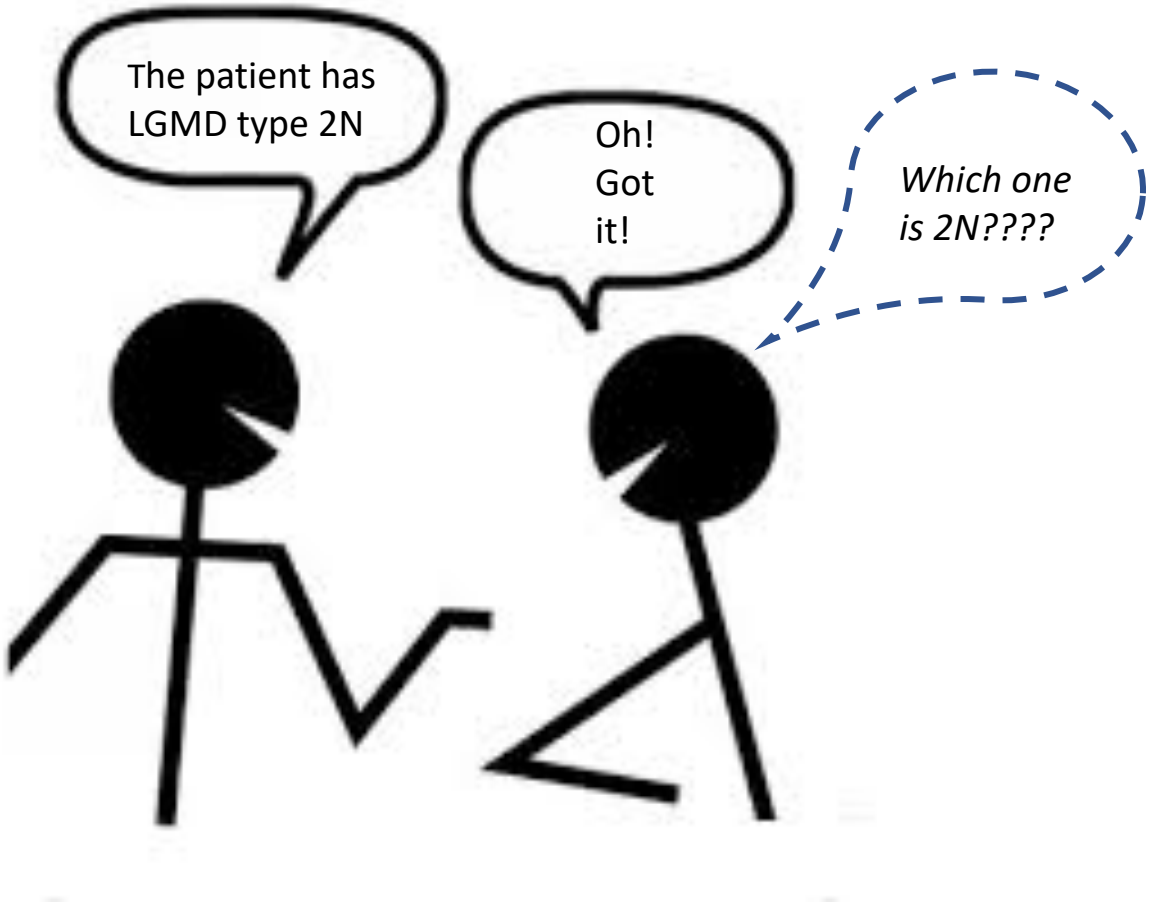
- Conclusion: Individual balance of risks and benefits

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

LGMD/CMD overlap
- Dystroglycanopathies
- Collagen 6
- LMNA
- Merosin (a2 chain of laminin)

Limb girdle muscular dystrophy

JUNE, 1954

BRAIN

VOL. 77, PART 2.

ON THE CLASSIFICATION, NATURAL HISTORY AND TREATMENT OF THE MYOPATHIES

BY

JOHN N. WALTON AND F. J. NATTRASS

(*From the Department of Medicine, King's College, University of Durham and the Royal Victoria Infirmary, Newcastle upon Tyne*)

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)
    - Matsumura, et al, Nature 1992

Limb Girdle Muscular Dystrophy, 1999

Nomenclature	**Inheritance**	**Genetic location**	**Protein**
LGMD1C	AD	3p25	Caveolin 3
LGMD2A	AR	15qq5-21	Calpain 3
LGMD2B (and Myoshi myopathy)	AR	2p	Dysferlin
LGMD2C-F	AR	13q12	Sarcoglycans $\alpha,\beta,\delta,\gamma$
DMD/BMD	X-LR	Xp21	dystrophin

LGMDs Sept 2017

http://neuromuscular.wustl.edu/musdist/lg.html

Dominant

- 1A: Myotilin; 5q31
- 1B: Lamin A/C; 1q21
- 1C: Caveolin-3; 3p25
- 1D: DNAJB6; 7q36
- 1E: Desmin; 2q35
- 1F: TNPO3; 7q32
- 1G: HNRPDL; 4q21
- 1H: 3p23

X-linked

- Duchenne and Becker MD

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: TRAPPC11; 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

Pull out the dystroglycanopathies and call them type C
Autosomal Recessive LGMD, Type C
OMIM, 2017

Location	Phenotype	Gene/Locus
1p34.1	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 3	POMGNT1
3p21.31	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 9	DAG1
3p21.31	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 14	GMPPB
7p21.2	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 7	ISPD
8p11.21	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 12	POMK
9q31.2	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 4	FKTN
9q34.13	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 1	POMT1
14q24.3	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 2	POMT2
19q13.32	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 5	FKRP

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.

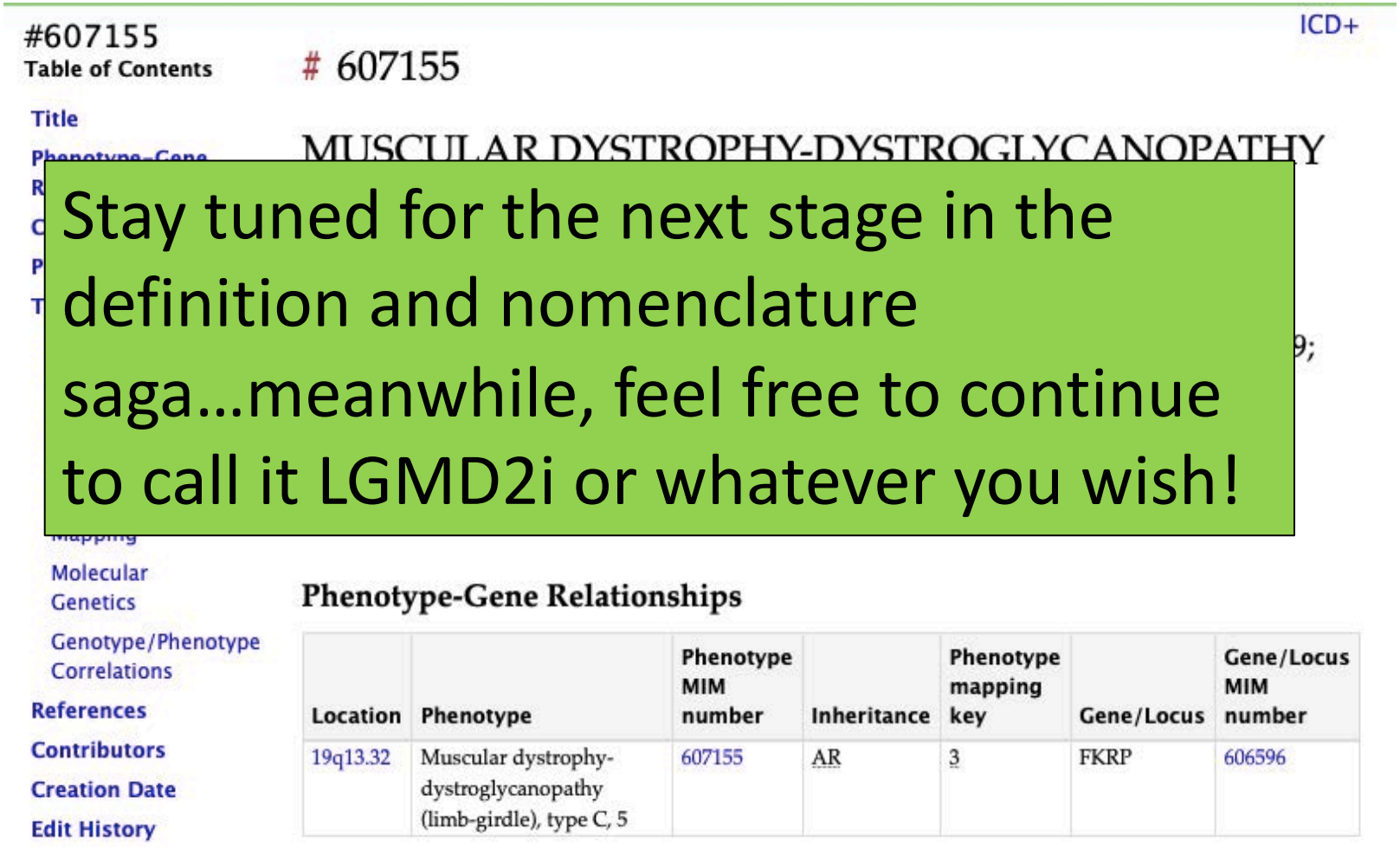
LGMD D

LGMD D1 DNAJB6-related
LGMD D2 TNPO3-related
LGMD D3 HNRNPDL-related
LGMD D4 calpain 3-related
LGMD D5 collagen 6-related

LGMD R

LGMD R1	calpain 3-related
LGMD R2	dysferlin-related
LGMD R3	α-sarcoglycan-related
LGMD R4	β-sarcoglycan-related
LGMD R5	γ-sarcoglycan-related
LGMD R6	δ-sarcoglycan-related
LGMD R7	telethonin-related
LGMD R8	TRIM32-related
LGMD R9	FKRP-related
LGMD R10	titin-related
LGMD R11	POMT1-related
LGMD R12	anoctamin 5-related
LGMD R13	fukutin-related
LGMD R14	POMT2-related
LGMD R15	POMGnT1 -related
LGMD R16	dystroglycan-related
LGMD R17	plectin-related
LGMD R18	TRAPPC11-related
LGMD R19	GMPPB-related
LGMD R20	ISPD-related
LGMD R21	POGLUT1-related
LGMD R22	collagen 6-related
LGMD R23	laminin α2-related

Nomenclature
(screen shot from OMIM for LGMD2I, June 2018)



#607155
Table of Contents

ICD+

607155

MUSCULAR DYSTROPHY-DYSTROGLYCANOPATHY

Title
Phenotype-Gene
R
C
P
T
Molecular Genetics
Genotype/Phenotype Correlations
References
Contributors
Creation Date
Edit History

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!

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
19q13.32	Muscular dystrophy-dystroglycanopathy (limb-girdle), type C, 5	607155	AR	3	FKRP	606596

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