Introduction

Katherine Mathews
Iowa Wellstone Muscular Dystrophy Center

Overall goal: Improve treatment for patients now and in the future
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
2017 Family Conference
What are the Dystroglycanopathies???

• A group of muscular dystrophies characterized by decreased glycosylation (sugar groups) of alpha dystroglycan.
  – Alpha dystroglycan is a protein associated with the muscle cell membrane
  – Lack of sugar groups results in failure to bind to supportive tissue outside the muscle cell, weakening the muscle cell membrane
  – The leaky muscle cell membrane is prone to injury and over time can’t recover from repeated injury

• No (sadly) this doesn’t mean that eating more sugar will cure this muscular dystrophy
Muscle is affected in all types of dystroglycanopathy

Normal muscle
atrophy/hypertrophy
endomysial fibrosis/fatty replacement
Necrotizing Muscular Dystrophy - Later
atrophy/hypertrophy
Muscular Dystrophies due to cell membrane abnormality

- Duchenne/Becker Muscular Dystrophy (DMD/BMD)
- Limb-Girdle Muscular Dystrophies (LGMD)
- Congenital Muscular Dystrophy (CMD)

(Courtesy of Kevin Campbell laboratory)
Without glycosylation, a-DG does not bind to the extracellular matrix.
Genes that can cause dystroglycanopathy

- B3GALNT2
- GMPPB
- B3GNT1 (B4GAT1)
- ISPD
- DAG1
- LARGE
- DOLK
- POMGNT1
- DPM1
- POMGNT2 (GTDC2)
- DPM2
- POMK (SGK196)
- DPM3
- POMT1
- FKRP
- POMT2
- FKTN
- TMEM5

Autosomal recessive—require 2 abnormal copies to have disease
**FKRP: Fukutin Related Protein**

- Chromosome 19q13.3
- Common mutation
  - c.826C>A, Protein change: leucine to isoleucine at amino acid 276 (L276I)
  - seen in almost 100% of patients with LGMD 2I

- **Homozygous** for common mutation: 2 copies of c.826C>A
- **Heterozygous**: one copy of c.826C>A and one copy of some different mutation
Dystroglycanopathies encompass a huge phenotypic spectrum

- Walker-Warburg
- Muscle-Eye-Brain
- Fukuyama
- Congenital MD

Congenital Muscular Dystrophies

Limb Girdle Muscular Dystrophies

Clinical Severity

All Dystroglycanopathy Genes
Dystroglycan-related Congenital Muscular Dystrophies

• Onset of weakness before age 2 years
  – Progressive weakness in most cases

• When severe, can result in
  – Brain malformation
  – Severe learning problems
  – Seizures
  – Malformation of eyes

• When mild
  – Normal brain formation
  – Normal eyes

• Can affect heart and breathing
Dystroglycan-related
Limb girdle muscular dystrophies (LGMD)

- Progressive muscle weakness involving shoulders and hips first, starting after 2 years old
- Muscle hypertrophy or enlargement is common (calves particularly)
- Muscle pain, muscle breakdown (brown colored urine) with exercise is common
- Normal intelligence, typically
- Can affect heart and breathing
Iowa Wellstone Center
Dystroglycanopathy Clinical Study

• Overall goal is to improve care for patients with dystroglycanopathies
  – Determine the natural history
  – Identify problems
  – Improve monitoring and management
• Determine how to measure disease progression
• Prepare for testing new potential treatments
Thank you for attending!