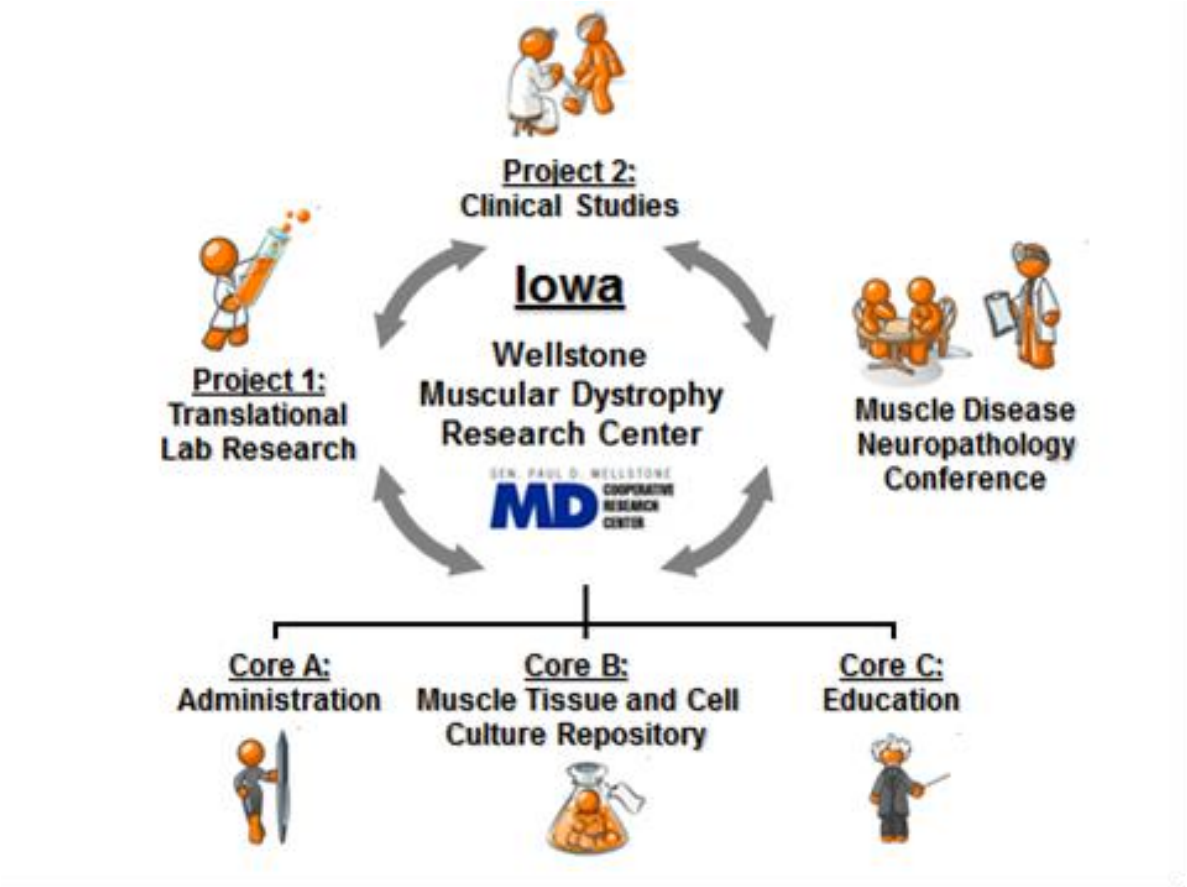
Introduction

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

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

First conference 2011
First photo 2014

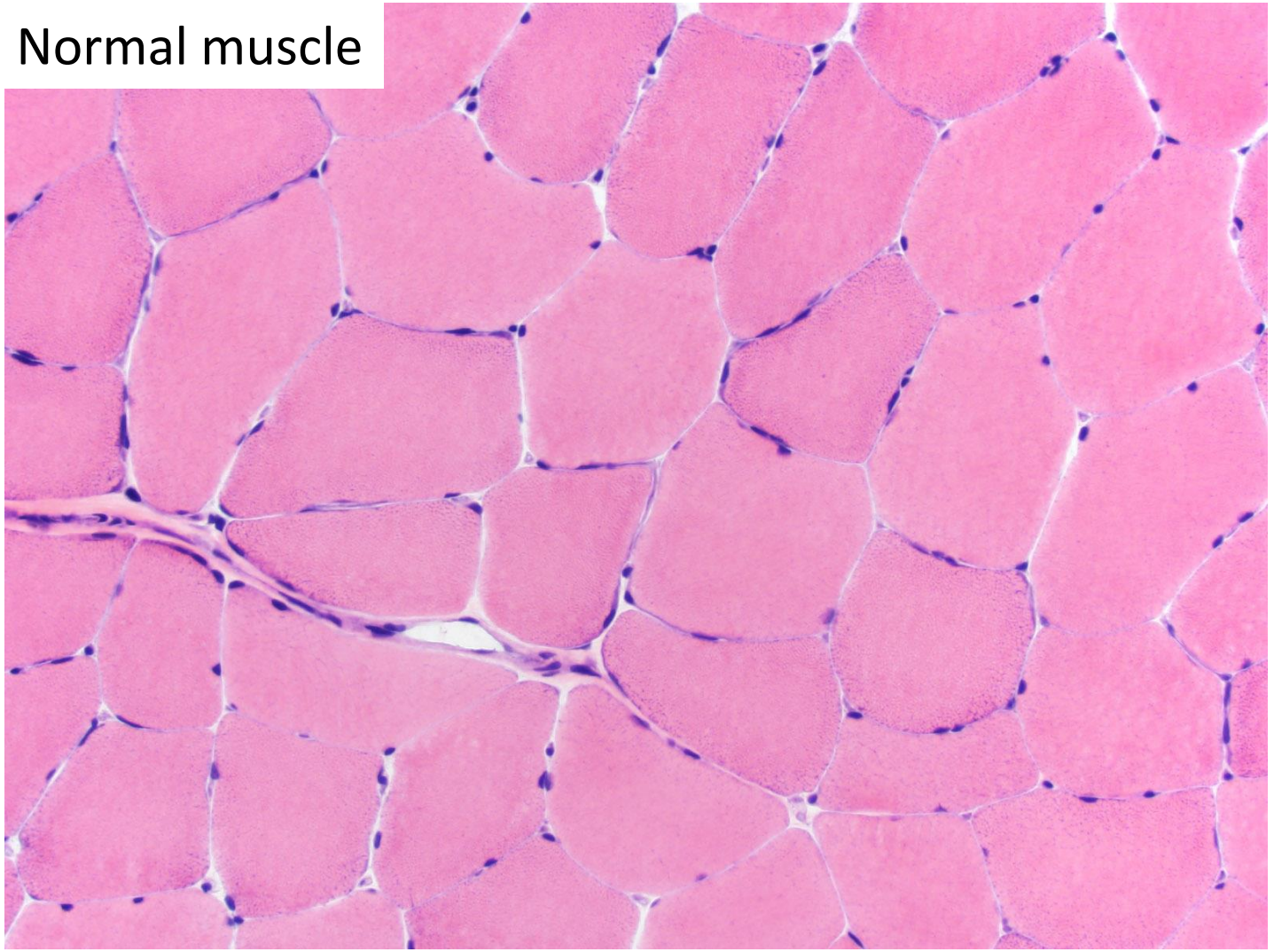
2017 Family Conference

What are the Dystroglycanopathies???

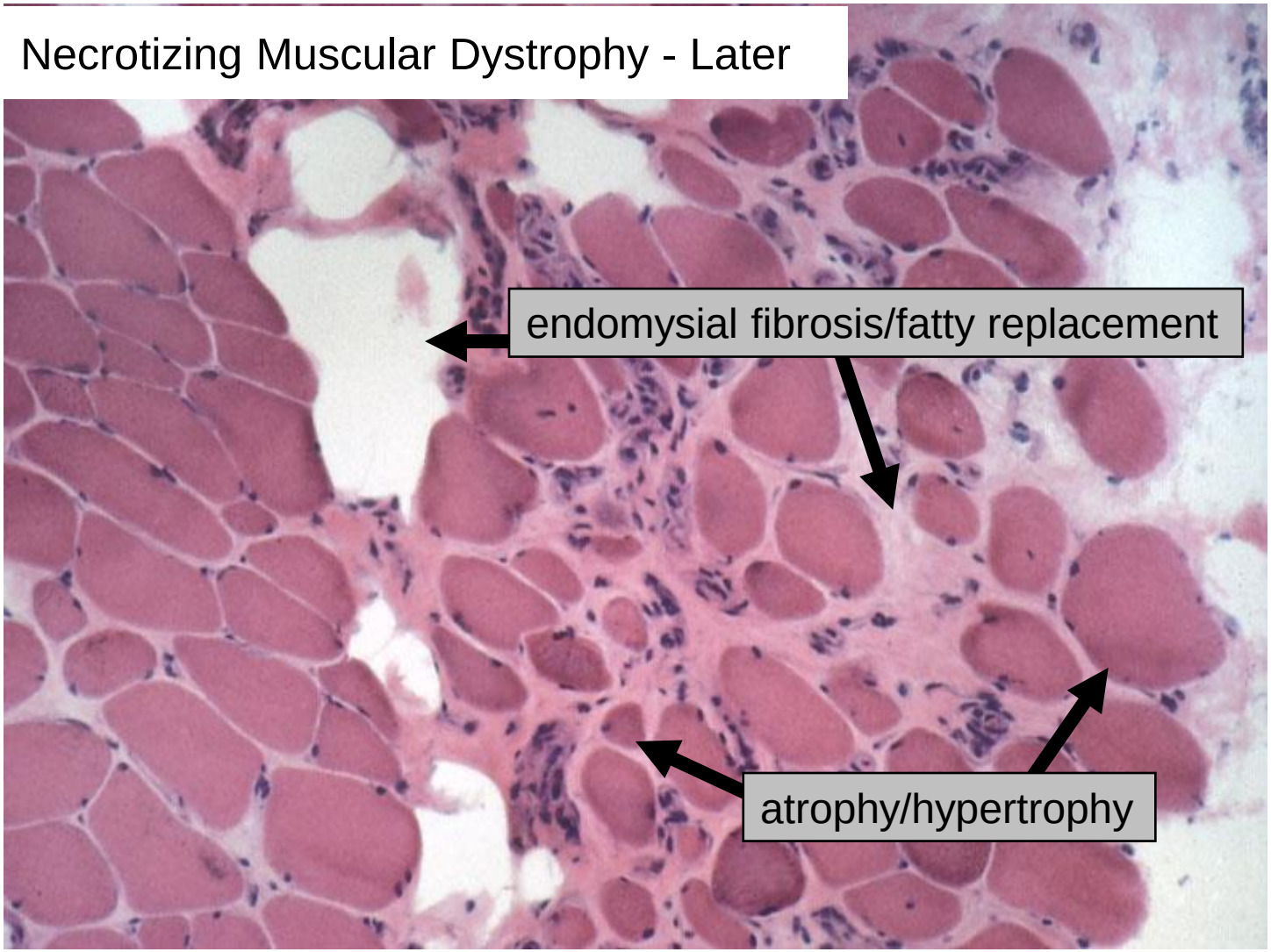
- A group of muscular dystrophies characterized by decreased glycosylation (sugar groups) of alpha dystroglycan.
  - Alpha dystroglycan is a protein associated with the muscle cell membrane
  - Lack of sugar groups results in failure to bind to supportive tissue outside the muscle cell, weakening the 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

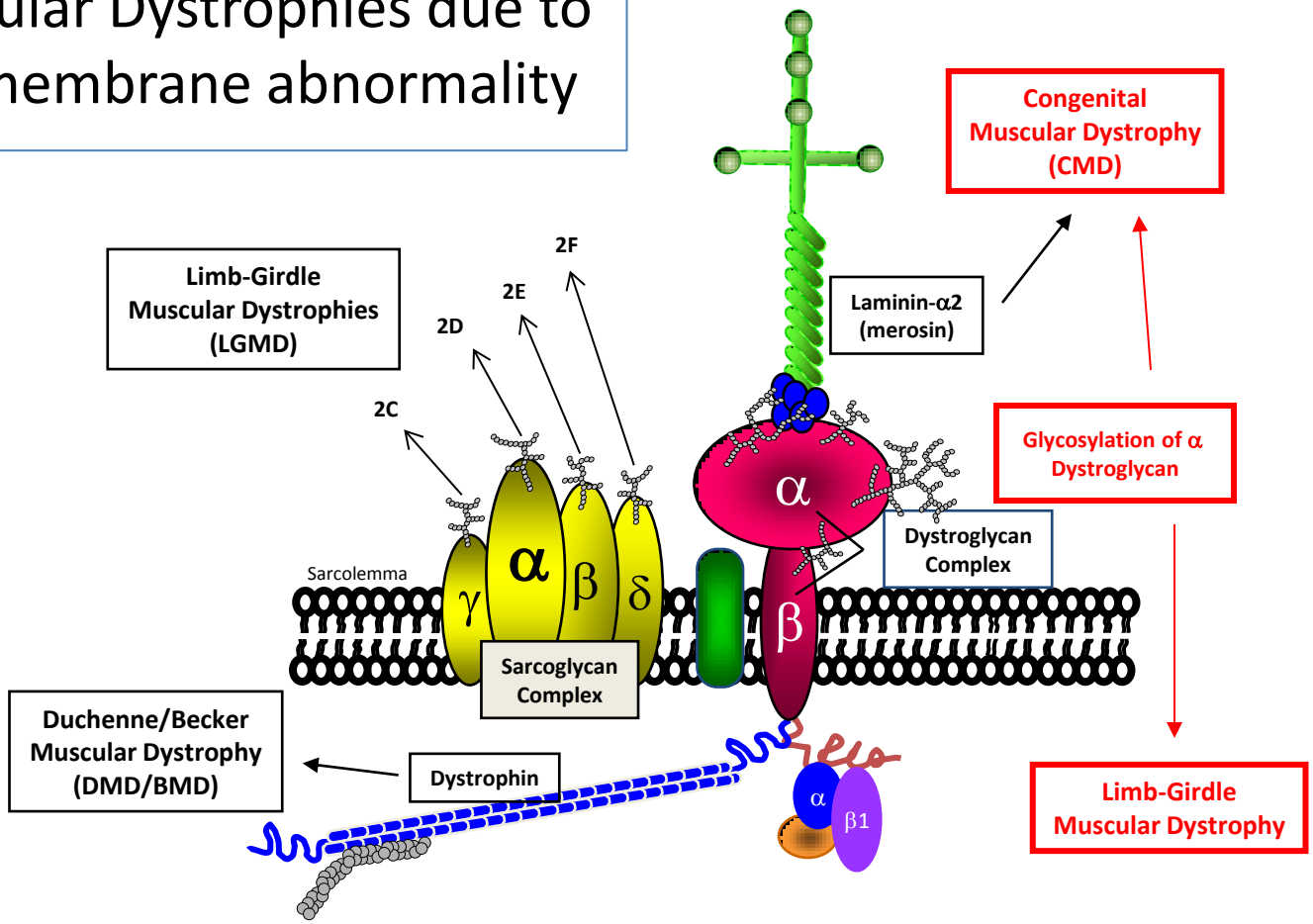
Normal muscle



Necrotizing Muscular Dystrophy - Later

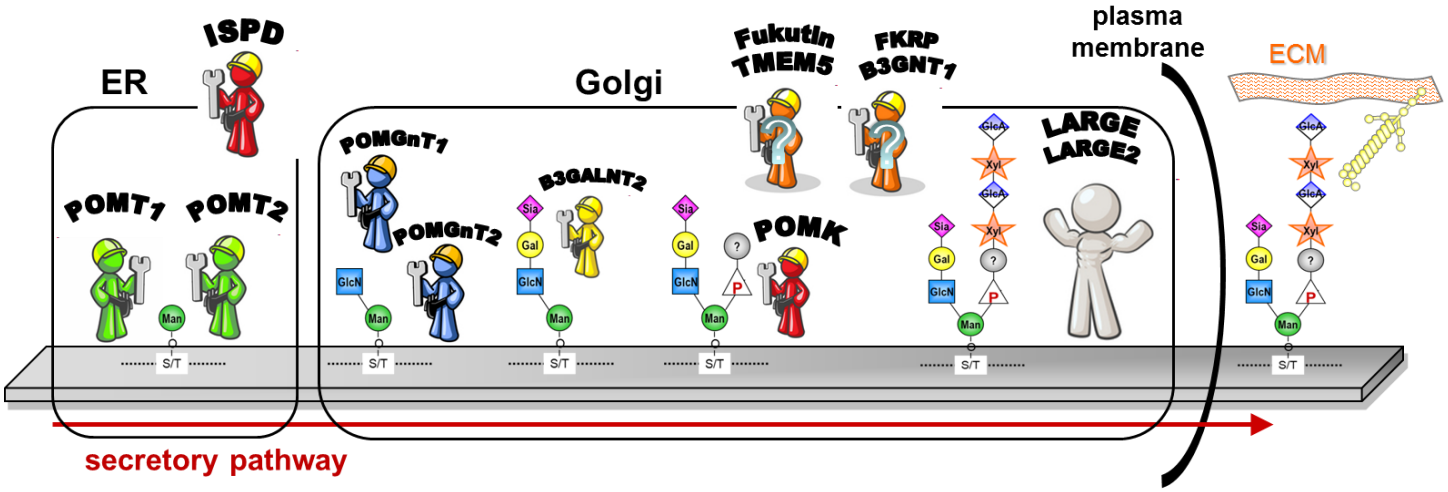


Muscular Dystrophies due to cell membrane abnormality



(Courtesy of Kevin Campbell laboratory)

Dystroglycan Glycosylation Process



Without glycosylation, a-DG does not bind to the extracellular matrix.

Generated byTobias Willer

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

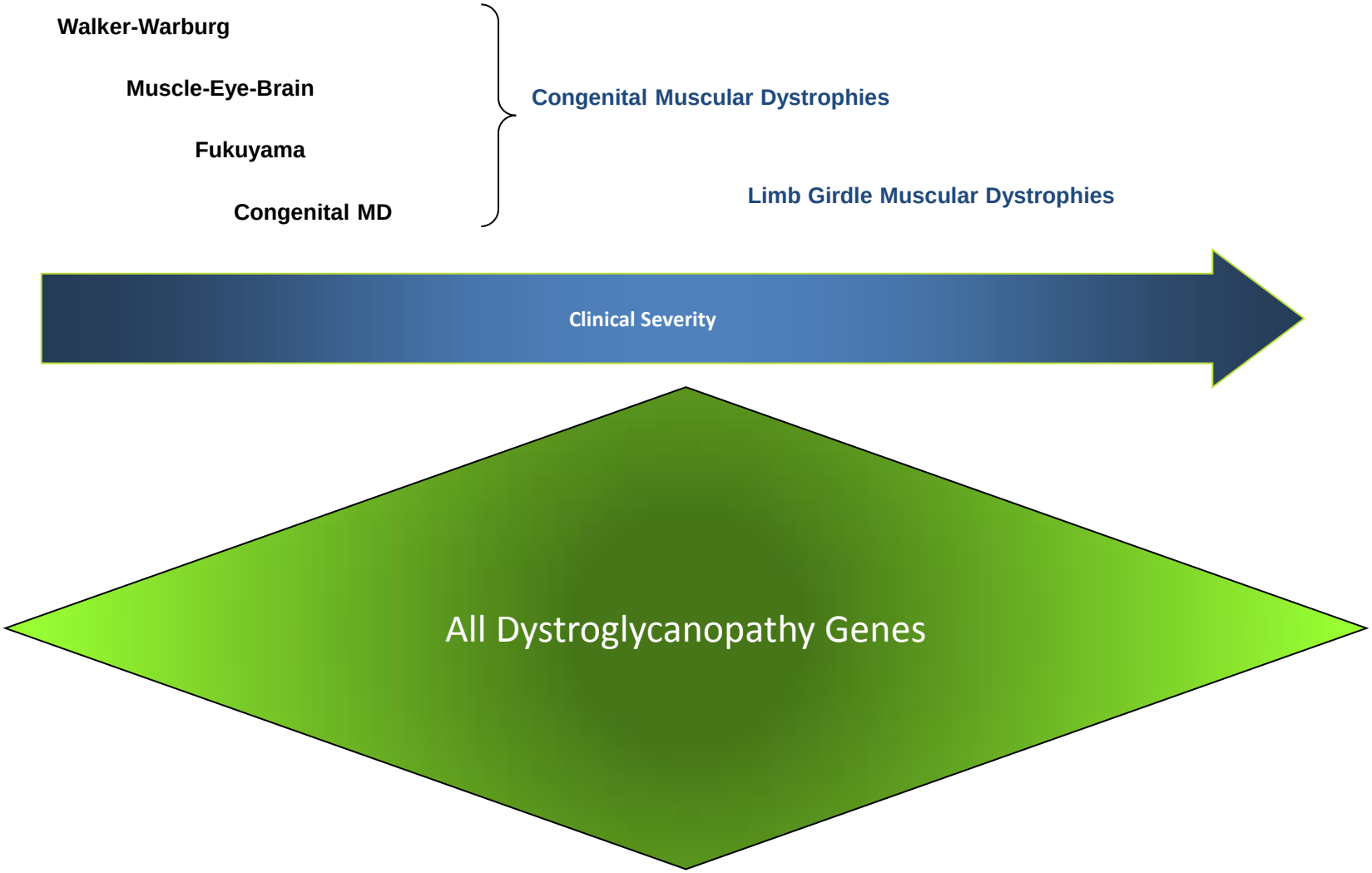
Autosomal recessive-—require 2 abnormal copies to have disease

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



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

SENATOR PAUL D. WELLSTONE
MD COOPERATIVE RESEARCH CENTER

Thank you for attending!