Dystroglycanopathies: Introduction and updates

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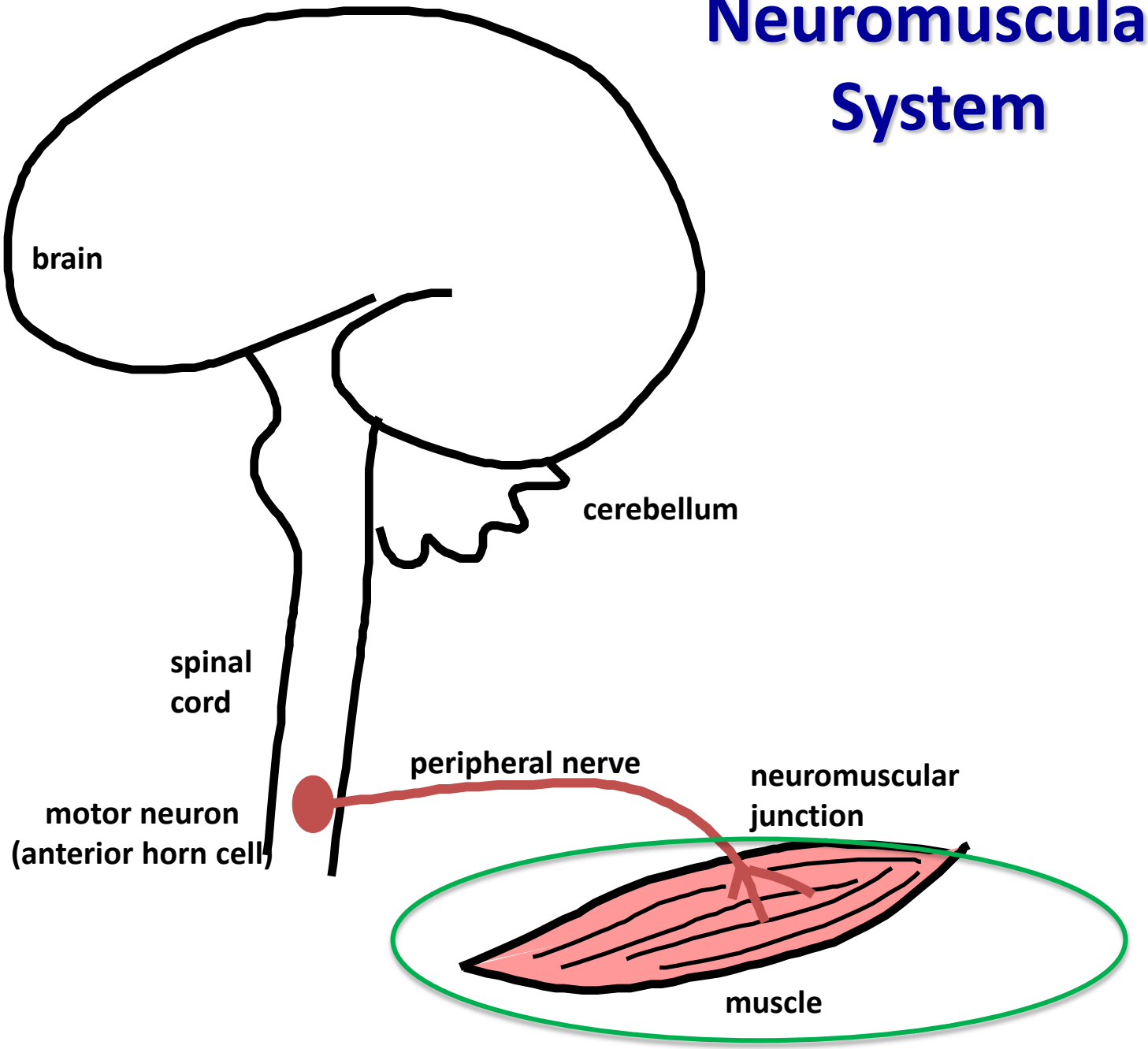
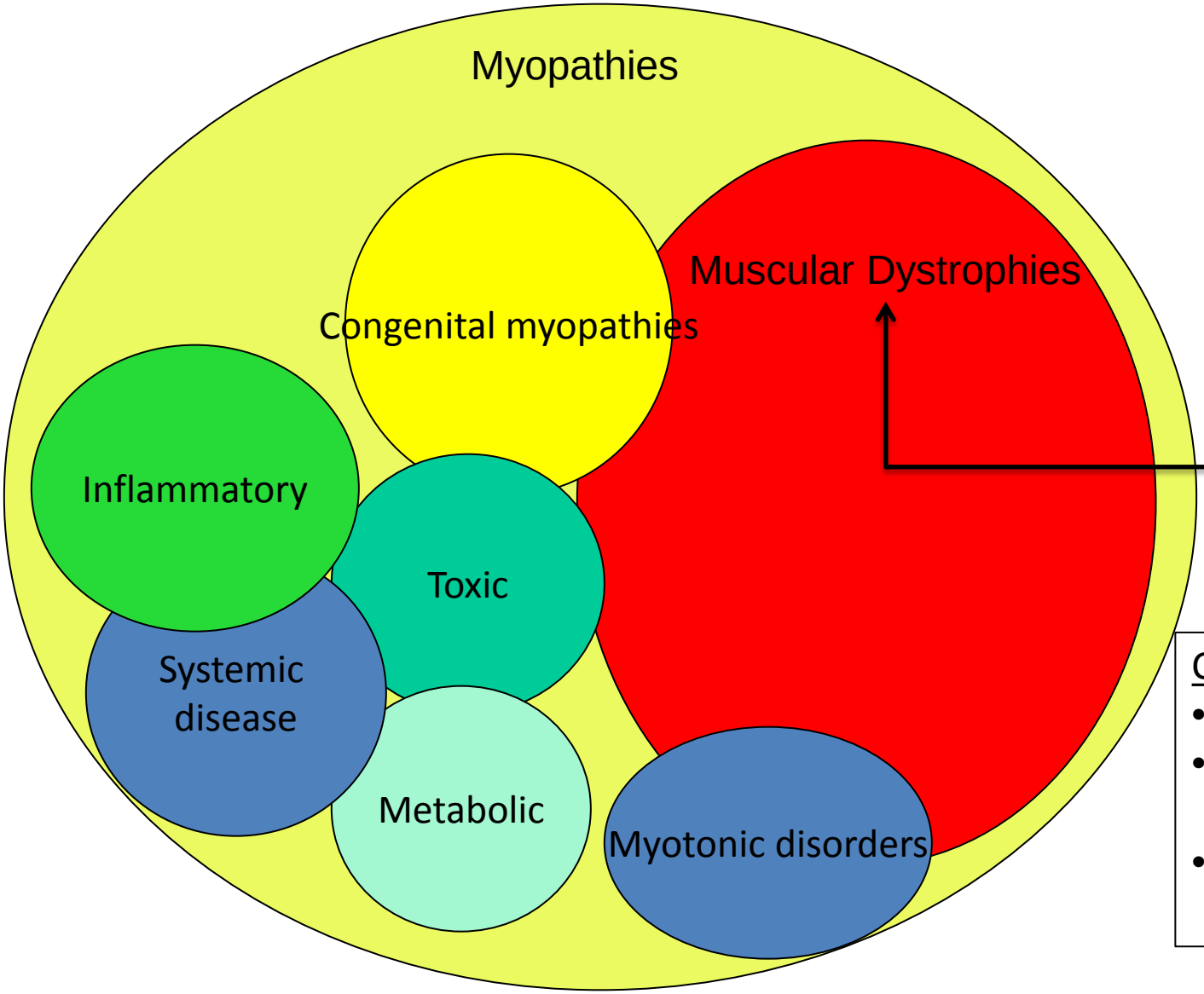
Neuromuscular System



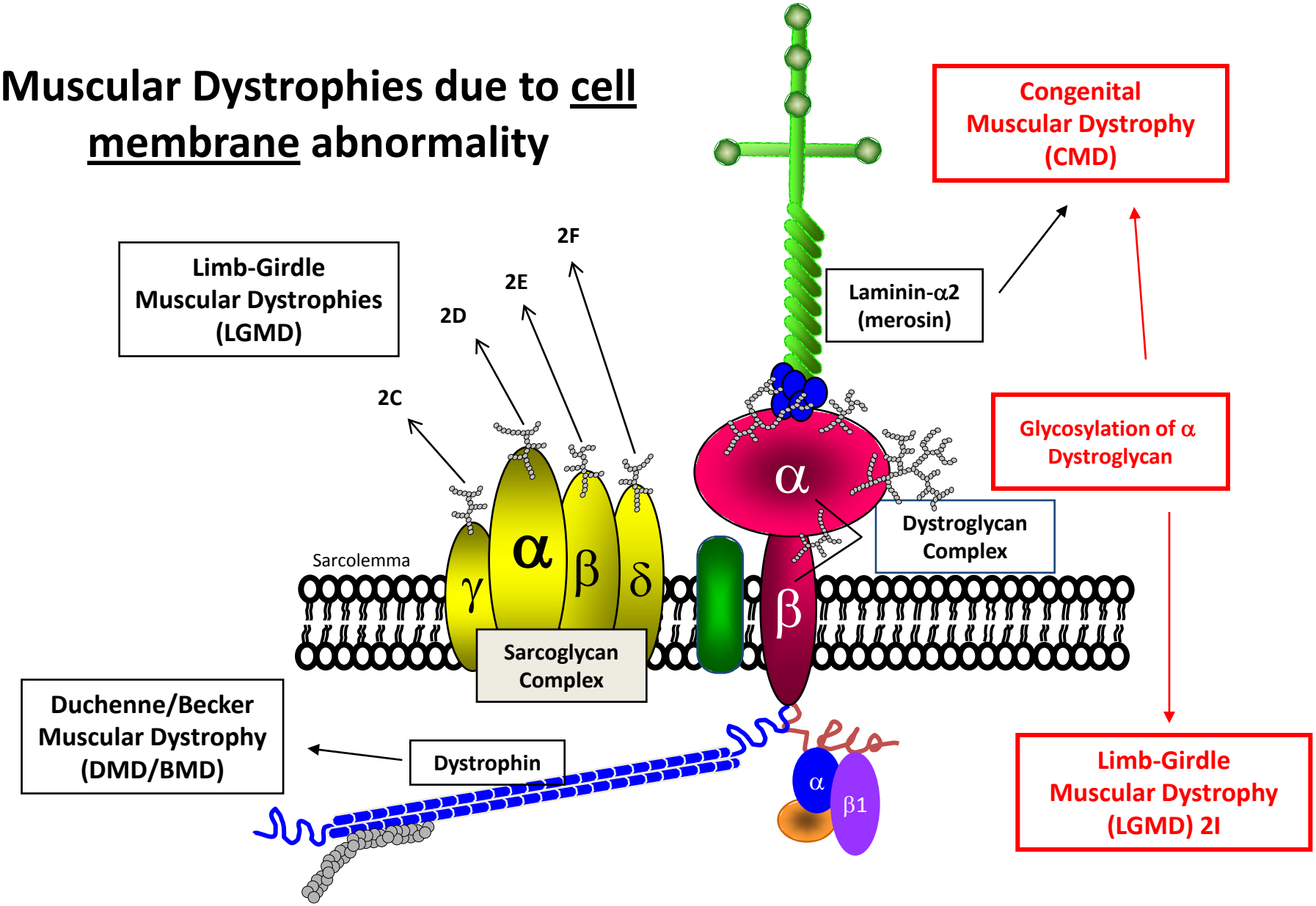
The Myopathies



Classification systems

- Inheritance
- Pattern of weakness
- Part of the cell affected

Muscular Dystrophies due to cell membrane abnormality



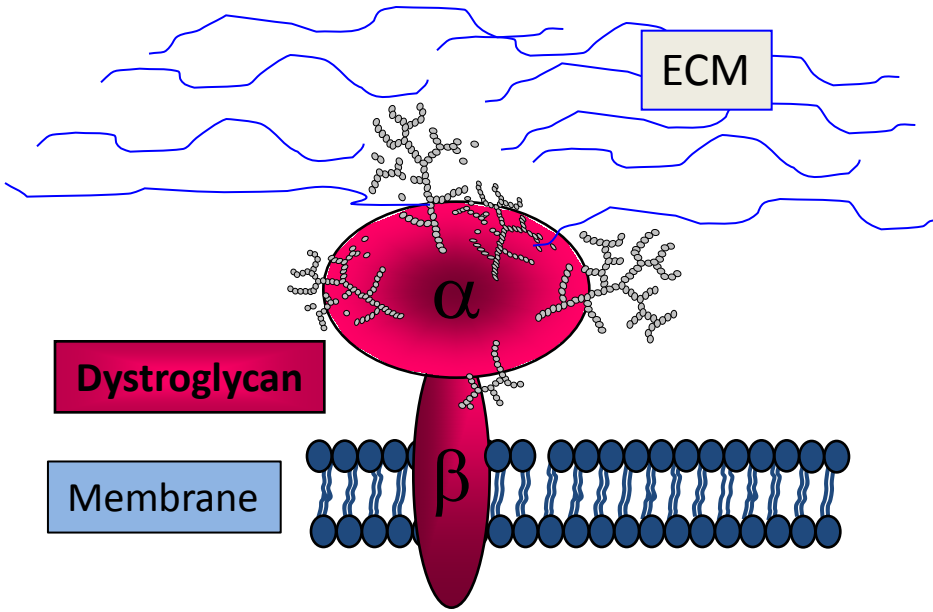
(Courtesy of Kevin Campbell laboratory)

Dystroglycanopathies
What are they?

- Clinically heterogeneous group of muscular dystrophies that result from abnormality of α-dystroglycan

α and β Dystroglycan

- *DAG1* (chr 3p21); single propeptide cleaved to
  - α (extracellular)
  - β dystroglycan (transmembrane)
- α dystroglycan requires extensive glycosylation (addition of sugar) for binding to components of extracellular matrix (ECM)



Muscular Dystrophy and α DG Glycosylation

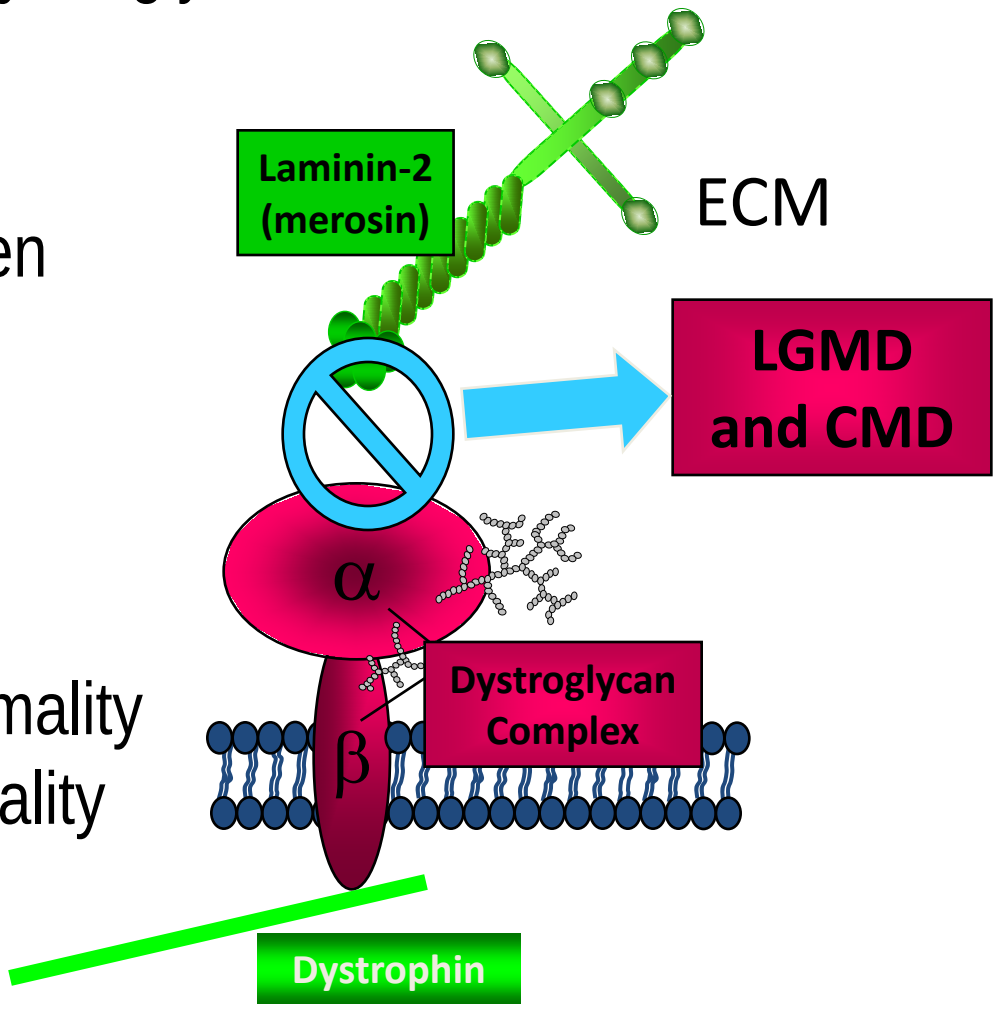
Abnormal glycosylation of α-dystroglycan

↓

Disruption of the link between inside the cell and ECM

↓

- Muscular dystrophy
- +/- Developmental brain abnormality
- +/- Developmental eye abnormality



Dystroglycanopathy clinical classification

(basis for new OMIM classification)

- Walker Warburg Syndrome (and WWS-like)
- Muscle Eye Brain/Fukuyama CMD-like
- CMD with cerebellar involvement (cysts, hypoplasia, dysplasia)
- CMD with mental retardation (normal brain structure)
- CMD with no mental retardation
- LGMD (>6 months) with mental retardation
- LGMD (> 6 months) with no mental retardation

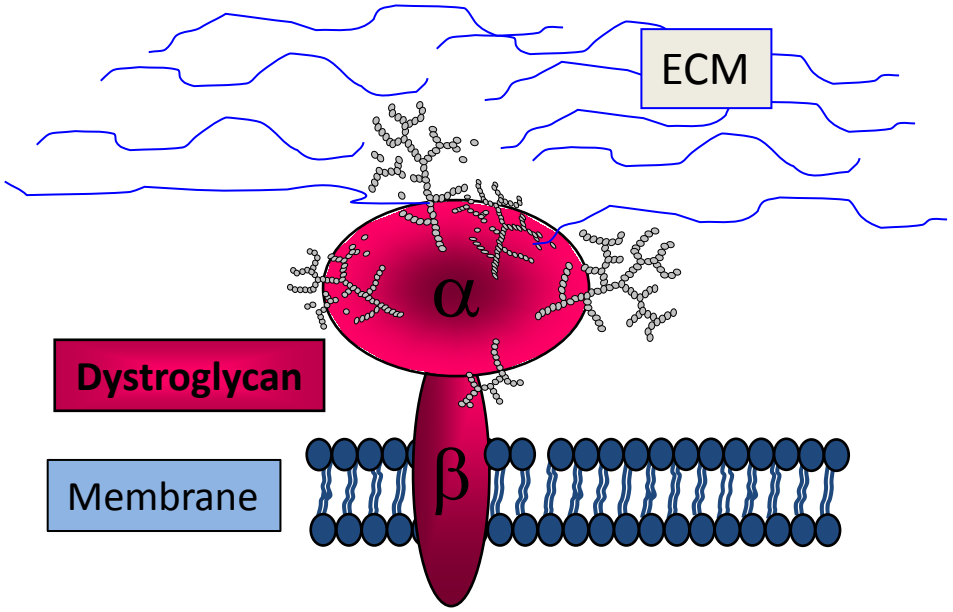
Godfrey, et al. Brain (2007)

Dystroglycanopathies

Genes involved in α DG glycosylation:

- FKRP
- FKTN
- POMT1
- POMT2
- POMTGnT1
- LARGE
- ISPD

- Others to be found



FKRP: Fukutin Related Protein

- Chromosome 19q13.3
- Small gene—12 kb
- One common mutation
  - C826A
  - Protein change: leucine to isoleucine at amino acid 276 (L276I)

Iowa Dystroglycanopathy Clinical Study

- Overall goal is to prepare for treatment trials in the dystroglycanopathies
  - Facilitate diagnosis
  - Identify new patients
    - Gene finding for patients without known mutation
  - Determine which outcome measures are useful in specific populations
  - Determine the natural history, using those outcome measures and based on observations

Muscle Pain

- 61% report muscle pain significant enough to affect their activities
  - Typically pain occurs with exercise
  - Mean age at onset of reported pain is 14 years (range 2 – 45 yrs)
- Muscle pain is usually an early symptom
  - 30% reported pain as one of the first symptoms

– Mathews, et al. *Neurology* 2011;76;194

Myoglobinuria

- Myoglobinuria
  - Muscle breakdown products in urine
  - Urine appears brown
  - Often suggests a metabolic muscle disease (not a muscular dystrophy)
- 27% reported myoglobinuria
  - Most have had multiple episodes.
  - Age at first episode 6-43 years, mean 14 years.

- Mathews, et al. *Neurology* 2011;76;194

Muscle pain and myoglobinuria are more common in those with 2 copies of common mutation (C826A)

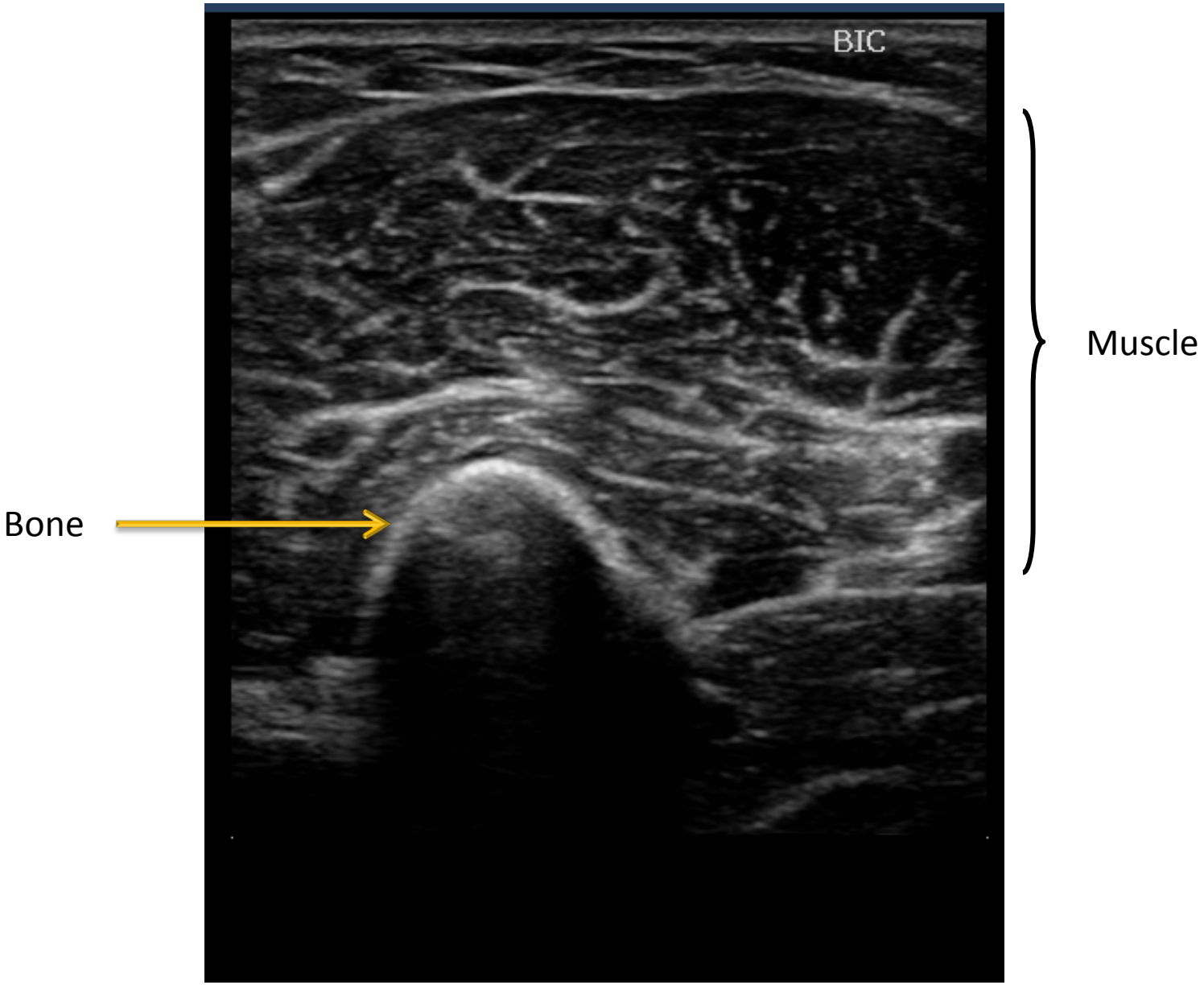
	826 C>A, 826 C>A	826 C>A, Unique	2 Unique
Whole cohort	15 (55%)	11 (41%)	1 (4%)
Muscle pain	11 (59%)	5 (31%)	0
Myoglobinuria	6 (86%)	1 (14%)	0

Mathews, et al. *Neurology* 2011;76;194

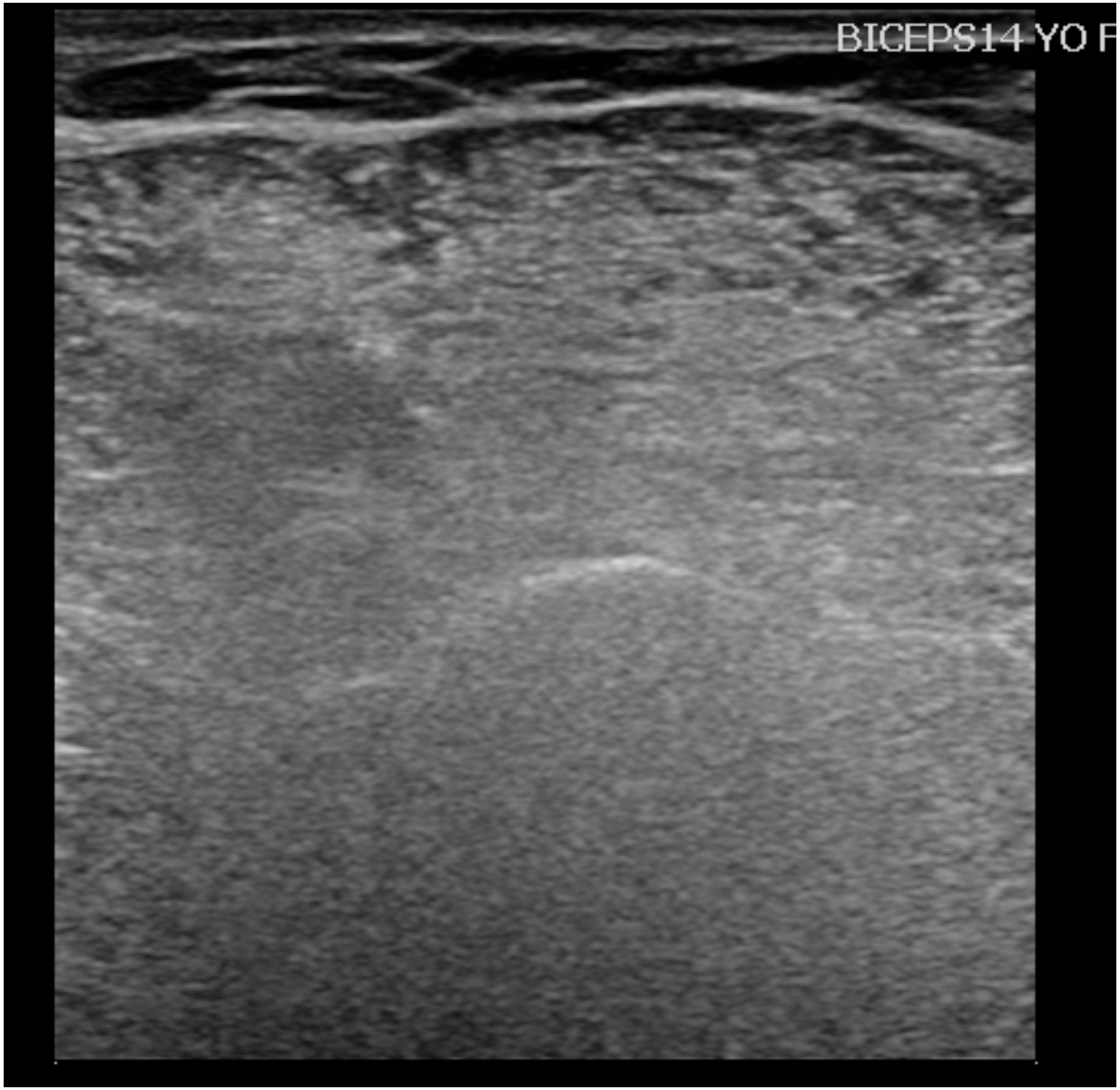
Muscle ultrasound

- Why are we doing them?
  - To determine if this might be a way to monitor disease progression or assist in diagnosis
  - Portable, cheap, painless, can be done on children
- Not sensitive enough to be used as a measure of disease progression for a trial?
- Ultrasound does demonstrate differences

FKRP: homozygous C826A mutation
11 yo ambulatory male

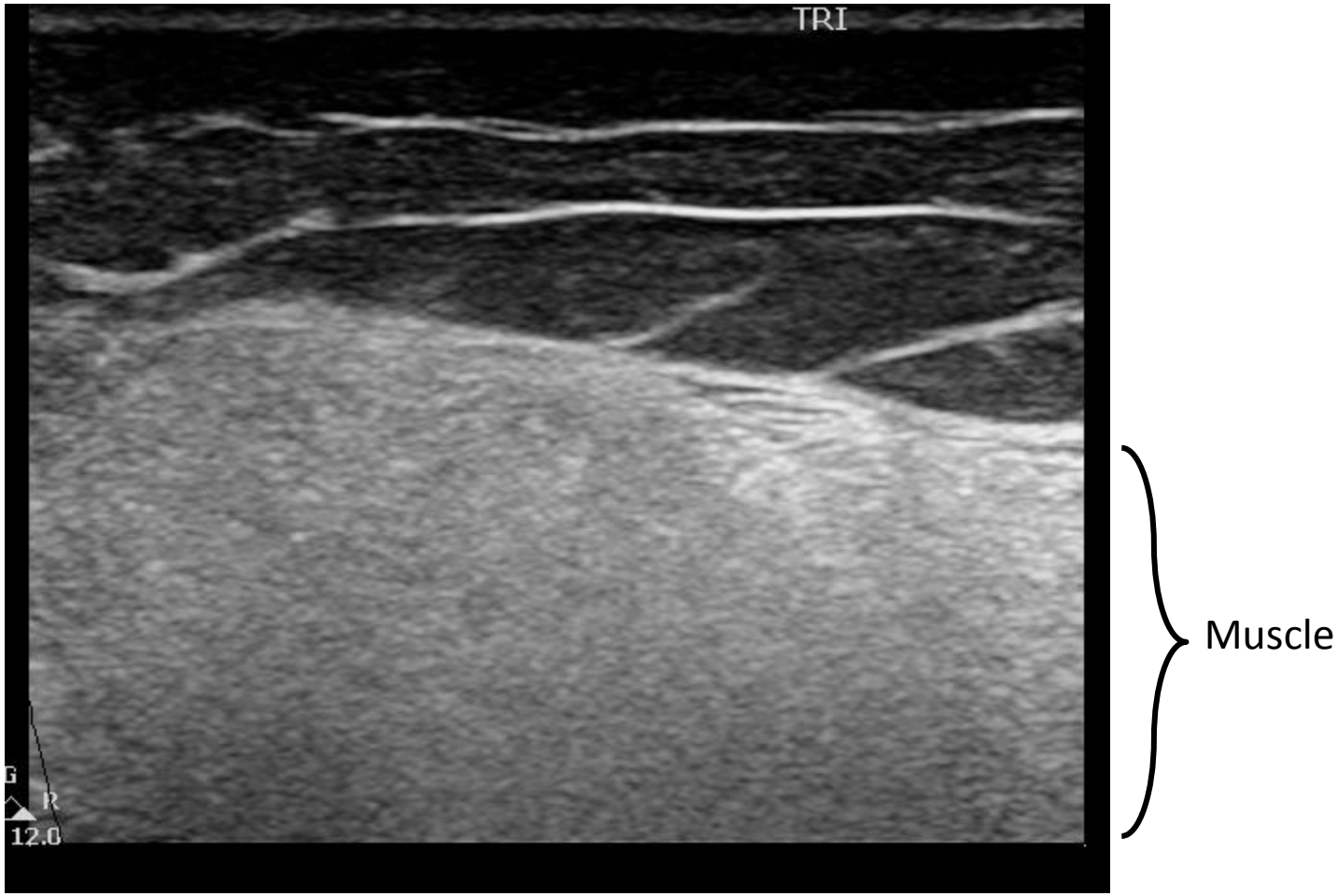


FKRP: C826A, and C217T leading to premature stop
14 yo ambulatory male



Muscle

triceps (all muscles identical)
Fukutin c.920G>A, c.1167 dupA
13 yo ambulatory male



Dystroglycanopathy—Steroids?? Anecdotal information….

Gene	mutation(s)	age at start of steroids
FKRP	C826A ; G472C	12 mo
FKRP	430A>G ; 469G>C	9 yo
FKRP	C826A; 947delC	5 yo
FKRP	C826A; 947delC	13 yo
FKRP	C826A; C826A	adulthood
FKRP	C826A; C826A	18 yo
POMT1	85A>C ; 1864C>T	8 yo
FKTN	c.920G>A, c.1167 dupA	13 mo
FKTN	c.920G>A, c.1167 dupA	12 mo

See poster for more information

Steroids in LGMD2I

- A number of case reports suggesting improvement
- C826A/C826A is particularly common in Scandinavian countries, so relatively large number of patients
- An international trial is in the planning stages
  - >18 years old
  - Supported in part by the LGMD2i foundation
  - Stay tuned!

Summary

- Dystroglycanopathies are diverse
  - Mutations in FKRP are the most common
- Muscle pain and myoglobinuria are rather common presentations
- The changes in function over time vary by affected gene and mutations in that gene (FKRP)
  - Those with 2 copies of C826A mutation in FKRP have milder disease

Thank You!

Families and study participants

Carrie Stephan
Meghan Lawler

Colleagues volunteering their time

- Anne Wallace
- Christina Trout
- Erik Edens
- Tim Starner

Wellstone center colleagues and trainees

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