Dystroglycanopathies: Introduction and updates
August 18, 2012
Katherine Mathews, MD
Neuromuscular System

- brain
- cerebellum
- spinal cord
- motor neuron (anterior horn cell)
- peripheral nerve
- neuromuscular junction
- muscle
The Myopathies

Myopathies

Congenital myopathies

Muscular Dystrophies

Inflammatory

Toxic

Systemic disease

Metabolic

Myotonic disorders

Classification systems
- Inheritance
- Pattern of weakness
- Part of the cell affected
Muscular Dystrophies due to cell membrane abnormality

Limb-Girdle Muscular Dystrophies (LGMD)

Duchenne/Becker Muscular Dystrophy (DMD/BMD)

Sarcoglycan Complex

Dystroglycan Complex

Laminin-α2 (merosin)

Dystrophin

Sarcolemma

Glycosylation of α Dystroglycan

Limb-Girdle Muscular Dystrophy (LGMD) 2I

Congenital Muscular Dystrophy (CMD)

(Courtesy of Kevin Campbell laboratory)
Dystroglycanopathies
What are they?

• Clinically heterogeneous group of muscular dystrophies that result from abnormality of $\alpha$-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 $\alpha$ DG Glycosylation

Abnormal glycosylation of $\alpha$-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

Dystroglycanopathies

Genes involved in $\alpha$ 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)

<table>
<thead>
<tr>
<th></th>
<th>826 C&gt;A, 826 C&gt;A</th>
<th>826 C&gt;A, Unique</th>
<th>2 Unique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole cohort</td>
<td>15 (55%)</td>
<td>11 (41%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>11 (59%)</td>
<td>5 (31%)</td>
<td>0</td>
</tr>
<tr>
<td>Myoglobinuria</td>
<td>6 (86%)</td>
<td>1 (14%)</td>
<td>0</td>
</tr>
</tbody>
</table>

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....

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

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

Funding
LGMD2i Foundation
NIH (NINDS)