Welcome to Iowa City!
Thank you to those who make this conference possible

– Carrie Stephan  
  • Research coordinator  
  • Event planner  
  • Everything else

– Meghan Lawler  
  • Administrative assistant  
  • Event planner

– Bekah Walker  
  • Dr. Campbell’s administrative assistant  
  • Artist and designer of this year’s t-shirts

– Students and trainees

– Lab personnel

– Volunteer child supervisors

– Speakers (volunteers)

– Volunteers to help with study evaluations

– NIH and foundations for providing funding
Supervision of children

Meghan, Shelley, and Carrie
Iowa Wellstone Muscular Dystrophy Center
Iowa Wellstone Center Clinical Fellowship

• Why?
  – There is a shortage of pediatric neurologists and particularly of those with expertise in neuromuscular disease.

• The Wellstone Center supports one medical student fellow per year
  – One year taken out of medical school training
  – Focus on neuromuscular diseases (particularly dystroglycanopathies)
  – Opportunity for clinical and basic research
Iowa Clinical Fellows

Jamie Eskuri
Child neurology resident
Boston Children’s Hospital

Katie Lutz
Child neurology resident
University of Iowa Children’s Hospital

Cameron Crockett
Medical student
University of Iowa
Future child neurology resident

Steve McGaughey
Pediatric resident
Barnes Children’s Hospital

Not pictured:
Braden Jensen
This year’s fellow!

Katie Lutz
Child neurology resident
University of Iowa
Children’s Hospital
Clinical trial readiness in the dystroglycanopathies

- Project began 9 years ago, only studying patients with FKRP mutations
- Now there are ~17 dystroglycanopathy genes known and the patient population is greatly expanded.

Clinical spectrum of onset and severity

- **Congenital muscular dystrophy**
  - Weakness in infancy, possibly with brain and eye involvement

- **Limb girdle muscular dystrophy**
  - Onset of weakness in adulthood
Identification of dystroglycanopathy genes

- **dystrophin**
- **dystroglycan**
- **FKRP**
- **POMGnT1**
- **POMT2**
- **POMT1**
- **LARGE**
- **FKTN**
- **ISPD**
- **GTDC2**
- **DPM2**
- **DPM1**
- **DPM3**
- **TMEM5**
- **B3GNT1**
- **B3GALNT2**
- **GMPPB**
- **POMK**
- **DPM1**
Clinical trial readiness in the dystroglycanopathies

• Many ways to approach the information you have contributed to this study
• Overall goal: Learn about the natural history of this group of diseases
  – Identify outcome measures
    • Reproducible
    • Minimal equipment
    • Change fairly rapidly
  – Answer clinical questions
    • Muscle weakness-rate of progression, degree of weakness
    • Heart
    • Breathing
    • GI/GU symptoms
    • Quality of life
    • What else are you interested in???
Self reported activity vs genotype

activity history

Self reported activity

life stage, pre-K through adult

C826A, C826A
C826A, other
other
Pattern of change is similar across measures
Comparing 10 m walk with climb 4 stairs
Walking time for the whole group

10 meter walk time by age and genotype

Unable to complete

Walking time for the whole group

10 meter walk time by age and genotype

FKRP C826A/C826A
FKRP C826A/other
Other genes
**Step Activity Monitor**

**SAM: max steps/day vs age**

- **Not walking independently**
  - FKRP C826A/C826A: 2/23 (9%)
  - FKRP C826A/other: 3/20 (15%)
  - Other: 7/15 (50%)

The diagram illustrates the maximum steps/day vs age for individuals with different genetic conditions:

- **C826A. C826A**
- **C826A, other**
- **other gene**
Heart, the literature

• Retrospective European series of individuals with congenital muscular dystrophy due to dystroglycanopathy (mean age 9.3 yrs)
  – Many without specific genetic mutation
  – 5/115 with dilated cardiomyopathy
    • 3-FKPR (23%),
    • 1-POMT1 (7%)
    • 1-POMT2 (1%)

• LGMD2I (FKRP mutations, onset after infancy)
  – 2/11 (18%)
  – 14/23 (60%)
    • Neuromuscular Disorders 18 (2008) 650–655
Conclusions
(K. Lutz, submitted for publication)

• Our data support the recommendation for regular monitoring of heart function in people with dystroglycanopathies.

• Consideration should be given for the use of cardioprotective medications in this population.
Respiratory function, the literature

• European study—congenital muscular dystrophy
  – 13 getting respiratory support of some type (11%)
    • 7-unknown gene
    • 3-FKRP (6 m, 9 yrs, 13 yrs) 23%
    • 3-POMT2 (2 yrs, 7 yrs, 19 yrs) 3%

• LGMD2I
  – 5/14 (36%) with respiratory support
    • NEUROLOGY 2003;60:1246–1251
  – 6/11 (55%) FVC<50% predicted
    • J Neurol Neurosurg Psychiatry 2009;80:1405–1408
Our data, respiratory function

• LGMD2I
  – 4/43 (9%) with FVC <50% predicted

• Other mutations:
  – 1/6 (17%) of those able to cooperate with FVC <50% predicted.
Sitting FVC vs Age

Sitting FVC vs age, FKRP

Normal

Consider intervention
Clinical trial readiness in the dystroglycanopathies

• Overall goal: Learn about the natural history of this group of diseases
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  – Answer clinical questions
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    • Heart
    • Breathing
    • GI/GU symptoms
10 m walk time for individuals over time; outcome measure?

- All >5 year old
- All able to complete the 10 m walk
- 3-9 years of data

CONCLUSION:
- Very stable for years

**Graph:**
- Time to walk 10 m vs years of follow up
- Data for 10 m walk time for individuals over time
- Different colored lines represent different groups or data sets
Biomarker study

• Collaboration with Sebahattin Cirak, MD
• Why?
  – Clinical outcome measures are often slow to change
  – Clinical outcome measures can be highly variable
  – Difficult to measure in young children, individuals with cognitive impairment
• Try to find a laboratory test that changes faster or more reliably than the clinical measures
  – Blood
  – Urine
  – Imaging (MRI, ultrasound)
  – You are invited to give blood for this study today!!
Thank you for your participation!
Please complete your evaluation forms