The Limb Girdle Muscular Dystrophies

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Disclosure of Relevant Financial Relationships

I have the following financial relationships to disclose:

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- Employee of: None

Disclosure of Off-Label and/or investigative Uses

I may discuss the following off label use and/or investigational use in my presentation: Corticosteroids and genetic-based therapies in muscular dystrophies.
History

• 1954 - Walton and Nattrass
  – Proposed LGMD as a distinct clinical entity
  – Initially distinguished cases from the 3 most common muscular dystrophies…
Definition

• “Post-natal onset of progressive weakness and muscle atrophy affecting proximal muscles of the upper and lower extremities”
Variability

- Genetic
- Pathogenic
- Phenotypic
- Regional/Ethnic
Limb Girdle, Distal, or what?

- 19 autosomal recessive LGMDs
- 8 autosomal dominant LGMDs
Limb Girdle, Distal, or what?

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- 8 autosomal dominant LGMDs
- 9 distal myopathies
Limb Girdle, Distal, or what?

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- 8 autosomal dominant LGMDs
- 9 distal myopathies
- 6 Emery Dreifuss muscular dystrophies
Limb Girdle, Distal, or what?

- 19 autosomal recessive LGMDs
- 8 autosomal dominant LGMDs
- 9 distal myopathies (1A, 1E, 2B, 2L)
- 6 EDMD (1B)
- 7 myofibrillar myopathies (1A, 1E)

Over 50 genes in total
Relative Prevalence in USA

- Calpain 25%
- Sarcoglycans 15%
- Dysferlin 15%
- FKRP 15%
- Anoctamin 10%
- Lamin A/C 10%
- All others 10%
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<th>DISEASE</th>
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LGMD1B – Lamin A/C

• ~5-10% of LGMD
• Onset:
  – Congenital – 3rd decade
• Contractures
  – Elbows
  – Achilles
  – Neck extensors
  – Hip flexors
• Rigidity of the spine
• Scapular winging
• Variable rates of progression
• Frequent *cardiac* involvement

Colomer et al Neuromusc Disord 2002;12:19-25
Lamin A/C

- Lamins A & C
  - Inner nuclear envelope proteins
  - Mechanosctructural functions, signaling and gene regulation

- Mutations in LMNA also cause:
  - AR LGMD
  - Familial partial lipodystrophy
  - AD & AR axonal polyneuropathies
  - Mandibuloacral dysplasia syndrome
  - Progeria syndromes
  - Isolated dilated cardiomyopathy with A-V block (CMD1A)
  - Heart-hand syndrome of the Slovenian type
  - Restrictive dermopathy
  - Metabolic syndrome
  - Cerebral white matter disease
LGMD2A - Calpain

- Overall most common LGMD, ~20-30%
- Onset 2\textsuperscript{nd} or 3\textsuperscript{rd} decade
  - 75% between 5-20 yo
  - Range (2-55 yo)
- Scapular winging
- Finger extensor weakness
- **Posterior thigh involvement**
  - KF < KE, HE < HF, HAD < HAB
- ~50% wheelchair confined after 20 years of disease
- May be confused clinically with DMD/BMD
- Lack of cardiac involvement

Fardeau et al
Brain 1996;119:295-308
Calpainopathy

- CK
  - 1000-5000 U/L
  (450-12,500 U/L)

- Muscle biopsy
  - Dystrophic
  - **Lobulated** fibers
  - Eosinophilic myositis
    - Early in disease

Fardeau et al
Brain 1996;119:295-308
Dysferlinopathy

• Phenotype
  – Limb girdle pattern
  – Also causes *distal myopathies*:
    • Miyoshi myopathy (gastrosoleus complex)
    • Distal anterior compartment myopathy (tib ant)
  – Scapuloperoneal or proximodistal pattern
  – Biceps atrophy
  – Bent spine syndrome
  – Carriers may be symptomatic

• Identical mutations may present with different phenotypes
  – Even within the same family

Mahjneh et al
Neuromusc Disord 2001;11:20-26
Dysferlinopathy

- Anterior tibial
  - 13/76 cases
Dysferlinopathy

Calf hypertrophy early in course

Prominent deltoids with biceps atrophy

Rosales, X
Muscle Nerve 2010;42:14

Rosales, X
Muscle Nerve 2010;42:14
Dysferlinopathy

Diamond on Quadriceps Sign
- 21/33 cases

Pradhan, S
Neurology 2009;57:172

Pradhan, S
Neurology 2008;70:332
Dysferlinopathy

Paradas, C
Neurology 2010;75:316
Dysferlinopathy
Dysferlinopathy

• Mechanism of action
  – Dysferlin-associated membrane repair
  – Mitochondrial health
  – Stabilizes stress-induced Ca\(^{2+}\) signaling in the T-tubule membrane
    • Diltiazem ↓ muscle fiber inflammation & injury

Bansal and Campbell
Dysferlinopathy

- No scapular winging
- No contractures
- No cardiac manifestations
- PFTs ↓ over decades
  - Rarely symptomatic
- CK may be markedly elevated
  - Mean = 3800 U/L (generally 1-30K U/L)

- Biopsies:
  - Inflammation
    - Treatment refractory polymyositis
    - Deflazacort not effective
  - Amyloid
    - 20-30%

Gallardo, E
Neurology 2001;57:2136

Spuler, S
Ann Neurol 2008;63:323
Dysferlin

Polymyositis

Duchenne Muscular Dystrophy
Dysferlinopathy

• Diagnosis
  – Western blot on muscle or monocytes

• Best to use genetic testing
  – Gene sequencing
  – Next generation gene panel
  – Exome/genome sequencing
LGMD2C-F - Sarcoglycans

- $\gamma$, $\alpha$, $\beta$, and $\delta$-sarcoglycan
- ~10-15% of LGMD
- Form a tetrameric transmembrane subcomplex within the dystrophin glycoprotein complex
  - links the extracellular matrix to the subsarcolemmal cytoskeletal proteins

Bushby
Brain 1999;122:1403-1420
LGMD2C-F - Sarcoglycans

• Onset
  – in first decade in lower extremities

• Phenotypes:
  – SCARMD (Duchenne-like)
  – Mild, later onset (Becker-like)
  – Aches / pains / cramps syndrome
  – Recurrent myoglobinuria
  – Asymptomatic hyperCKemia
  – Dilated cardiomyopathy

• Calf hypertrophy in ½

• Scapular winging frequent

Bushby
Brain 1999;122:1403-1420
Sarcoglycanopathies

- May develop cardiac dysfunction (conduction defect and/or dilated cardiomyopathy)
- CK markedly elevated 1,000-25,000 IU
- Muscle biopsy dystrophic
  - Eosinophilic myositis reported early in \( \gamma \)-sarcoglycanopathy
LGMD2I – FKRP

• Fukutin-related protein (FKRP)

• Prevalence = 6-20%
  – Highly prevalent LGMD subtype in Northern Europeans

• Phenotypes:
  – Congenital muscular dystrophy – Fetal / neonatal
  – LGMD – Onset 3-55 years
  – Asymptomatic hyperCKemia

Mercuri et al
Ann Neurol 2003;53:537-542
Defective glycosylation in muscular dystrophy

Muntoni et al, Lancet 2002 Nov 2;360(9343):1419-21
LGMD2I - FKRP

Mercuri et al
Ann Neurol 2003;53:537-542

Poppe et al
Neurology 2003;60:1246-1251
LGMD2I - FKRP

- Highly variable progression
- Calf and tongue hypertrophy
- Muscle pain & cramps
- **Cardiac** dysfunction
- **Respiratory** involvement
  - Nocturnal ventilation in 30-50%
- Myoglobinuria not uncommon
- CK = NL => 50 x ULN
- May be confused with DMD/BMD
α-dystroglycanopathies

- POMT1
- POMT2
- POMGnT1
- Fukutin
- FKRP
- LARGE
- ISPD
- GTDC2
- DAG1
- TMEM5
- B3GALNT2
- SGK196
- B3GNT1
- GMPPB

- Muscle biopsy: dystrophic
  - Reduced
    - Laminin α2
    - Glycosylated α-dystroglycan

Brockington et al.
Am J Hum Genet 2001;69:1198-1209
LGMD2L – Anoctamin 5

- **ANO5** – Anoctamin 5

- Putative calcium-activated chloride channel
  - Involved in membrane repair

- More common than dysferlinopathy in Northern England

Bolduc et al.  
*Am J Hum Genet* 2010;86:213-221
LGMD2L – Anoctamin 5

- 10-20% LGMD in Northern Europeans
- AR inheritance:
  - LGMD2L
  - Distal myopathy (MMD3)
  - Asymptomatic hyperCKemia
- LGMD clinical
  - Onset 11-77 yo (70% < 40 yo)
  - ↑ prevalence & severity in males
  - **Quadriiceps** & biceps atrophy
  - **Muscle pain** in 85%
  - No cardiorespiratory involvement
  - Most remain ambulatory
- CK = 4-80 x ULN
- Bx = Dystrophic

Jarry et al
Brain 2007;130:368-380
LGMD2J - Titin

- TTN – titin
  - Largest single polypeptide in humans
  - Multiple binding sites for calpain
- Mutation on one allele ⇒ distal tibial myopathy (Finns)
  - Onset in 5th to 8th decade
- Mutations on both alleles lead to LGMD
  - Onset < 20 years
  - Typical LGMD distribution of weakness
  - Some patients become wheelchair confined
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What else looks like LGMD?

- Dystrophinopathies
- FSHD
- Bethlem myopathy
- X-linked EDMD
- Myofibrillar myopathies
- Mitochondrial myopathies
- Metabolic myopathies
- Pompe disease
Pompe Disease

- Affects all ages
- Treatable disorder
  - Enzyme replacement therapy

All undiagnosed LGMD patients should be tested for Pompe Disease.
Myopathy with Paget’s Disease

• Uncommon

• Adult onset – mean age of 42 years

• Slowly progressive proximodistal weakness
  • Early onset Paget’s disease
  • Premature frontotemporal dementia (FTD)

• 29yo F with AD proximodistal weakness and FH of Paget’s disease…

Kovach et al
Mol Genet Metab 2001;74:458-475
Extracellular Matrix-Related Myopathies

- Collagen VI
  - Bethlem and Ullrich
  - *COL6A1/A2/A3*
    - Hyperlaxity => contractures
    - Keloids
    - Keratosis pilaris
    - CK NL-2,000 U/L
    - Ultrasound “central cloud”
    - MRI – “outside in” pattern

- Collagen XII
  - Similar features
WHY IS IT IMPORTANT TO MAKE A DIAGNOSIS IN GENETIC MUSCLE DISEASE?
Top 7 Reasons to Make a Genetic Diagnosis

1. “Closure”
2. Efficient and cost effective use of medical resources*
   - Biopsy >$7-12K vs genetic testing $2-10K
3. Defining the long-term prognosis
4. Evaluations for other organ system involvement*
   - Especially cardiorespiratory
5. Avoid risks/costs of empiric immunotherapy trials*
6. Genetic counseling and family planning
7. Current and future therapeutic possibilities
RECOMMENDATIONS AS TO DIAGNOSTIC ALGORITHM
What if the CK is very high? (>10,000 U/L)

- LGMD2A - Calpain
- LGMD2B - Dysferlin
- LGMD2C-F - Sarcoglycans
- LGMD2I - FKRP
- LGMD2L - Anoctamin 5

- Dystrophinopathy (Duchenne/Becker)
Diagnostic Strategies

• If clinically FSHD, DM1 or OPMD => genetic testing

• If “limb-girdle” pattern of weakness
  – Use phenotype, PH, FH, CK & EMG => targeted genetic test(s)
    • Jain Foundation web-based “smart” algorithm (ALDA)

• Pompe disease testing – free

• Dystrophin gene testing
  – Including in women
Free Genetic Sequencing

The Quiz, or questionnaire, on this website was designed to determine whether you may have a type of muscular dystrophy. To help identify individuals who may have one of the diseases studied by the foundations in our consortium, we sponsor genetic sequencing for the diseases listed below. After taking the quiz, we will contact you if your answers suggest that you may have one of the diseases covered by our sequencing program and invite you to participate in our diagnosis program at no cost to you.

Diseases Tested by our Genetic Sequencing

- Limb girdle muscular dystrophies (LGMD1A-F and LGMD2A-Q)
- Nonaka/HIBM, Tibial muscular dystrophy
- Becker muscular dystrophy (BMD)
- Duchene muscular dystrophy (DMD)
- Facioscapulohumeral muscular dystrophy (FSHD)
- Emery-Dreifuss muscular dystrophy (EDMD)
- ISPD
- Pompe
- Bethlem myopathy

Associated Genes

MYOT, LMNA, CAV3, DNAJB6, DES, TNPO3, CAPN3, DYSF, SGCG, SGCA, SGCB, SGCD, TCAP, TRIM32, FKRIP, TTN, POMT1, ANO5, FKTN, POMT2, POMGnT1, DAG1, PLEC1, GNE, DMD, FSHD1, FSHD2, EMD, FHL1, SYNE1, SYNE2, ISPD, GAA, COL6A1, COL6A2, COL6A3
Diagnostic Strategies

• Muscle biopsy?
  – Muscle biopsy with immunostains - $7,000-$12,000
  – Or… multiple mutation analyses
    • Commercially available panels (26, 76 & 200+ genes)***
  – Or…
    • Exome sequencing – 3 affected & 3 unaffected family members***
    • Genome sequencing – now raw data available in < 1 week***
      – Cautionary tale…

• “Inverted Diagnosis”
  – Duchenne muscular dystrophy
Single Gene vs Panel vs Exome

- Diagnostic yields:
  - Single gene = 15-19%
  - Panel = 46%
  - Exome = ~37%

- Why is this?
Exome Sequencing

**Challenges**
- Copy number variations
  - Would miss 2/3 of all Duchenne patients
- Large truncations
  - Would miss FSHD
- Repeat sequences
  - Would not pick up myotonic dystrophy type 1
- So, would only pick up 1 in 9 of the 3 most common muscular dystrophies…

**The Future**
- Massively parallel, deep sequencing
  - >1,000x coverage of each nucleotide
  - Can pick up small and large duplications/deletions
  - Can recognize repeat sequence expansions
  - Can be expanded to include intronic and other sequences
- Orders of magnitude greater numbers of genes
LGMD Genetic Testing through MDA

• MDA now offering same panel of 35 genes to >5,000 LGMD patients registered with the MDA.

  – An explosion of diagnoses over the upcoming year!
“Whilst looking down the rabbit hole, all I saw was bunnies. But once my eyes gazed ‘bout the glen, the panoply of species I did see.”

(Old English Fairy Tale)
mwicklund@hmc.psu.edu