FSHD Patient Day 2014!
What we know, what we think we know, what we have left to learn

Jeffrey Statland, MD
Overview

- Clinical Features
- Natural History
- Future Directions
Facioscapulohumeral Muscular Dystrophy (FSHD)

- One of the most common muscular dystrophies
  - Prevalence 1:15,000 to 1:20,000
  - or ~ 21,000 in US
- Slowly progressive
- Facio = face, Scapulo = scapular girdle, Humeral = upper arms
- Diagnosis is based on characteristic clinical presentation and genetic testing
FSHD: there are 2 types

- Two genetically distinct forms
  - Clinically identical
- Type 1: ~95%
  - Deletion of repeated DNA sequence on chromosome 4
    (normal >10 repeats, FSH 1-10 repeats)
  - Autosomal dominant inheritance, but up to 1/3 spontaneous
- Type 2: ~5%
  - No deletion on chromosome 4
  - ~80% associated with mutations in SMCHD1
  - Digenic inheritance
Patterns of Muscle Involvement

- Typically descending pattern
  - First affecting the face, shoulders, and upper arms
  - Followed by distal legs (e.g. tibialis anterior), quads and hamstrings
  - Hip muscles
- Can have marked axial and abdominal weakness
- Striking side to side asymmetry
- No or minimal contractures
- Often presence of pectus excavatum (hollowed chest)
- Other initial presentations have been described
Estimates of lung involvement have varied greatly (0-25%).

Review of Dutch registry of ventilator dependent patients

- Estimated 1% of Dutch FSHD population requiring mechanical ventilation (researchers took the number of ventilator dependent patients with FSHD, and compared to Dutch FSHD prevalence)

Reduced Lung Capacity in ~10%: Who is at Risk?

- Associated with higher disease severity score and lower extremity/ pelvic girdle involvement

FSHD: Cardiac Involvement

- No association with structural changes
  - No cardiomyopathy
- Cardiac (mainly atrial) arrhythmias ~ 5-10%?
- Typically not symptomatic
  - Most common symptom palpitations
- Severe cardiac conduction deficit or cardiomyopathy = revisit diagnosis
Extramuscular manifestations

- Retinal vascular changes
- Hearing changes
Retinal Disease

- Although retinal vascular changes can be seen in over half of patients (peripheral telangiectasias)
  - Coats disease = Symptomatic retinal vasculopathy
  - quite rare <1% (aneurysmal dilations, exudates, retinal detachment, blindness)
Idiopathic Coats disease tends to be:
- Unilateral
- Mostly male

In FSHD
- Often bilateral
- Mostly women
- Small residual D4Z4 fragments
- Typically the more severe infantile onset disease

Who do we screen?

<table>
<thead>
<tr>
<th></th>
<th>FSHD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case No.</td>
<td>n=14</td>
<td></td>
</tr>
<tr>
<td>Age Coats</td>
<td>10 (1, 15)</td>
<td></td>
</tr>
<tr>
<td>FSHD Dx years</td>
<td>12 (5, 18)</td>
<td></td>
</tr>
<tr>
<td>D4Z4 Fragment Kb</td>
<td>13 (12, 13)</td>
<td></td>
</tr>
<tr>
<td>Gender Female</td>
<td>92.9%</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>64.3%</td>
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FSHD: Hearing Loss

- Older studies suggested high frequency hearing loss in up to 60% of patients; however more recent studies suggest may not be different than general population
  - Largely asymptomatic
- However symptomatic hearing loss in small proportion of FSHD
  - Typically infantile onset, more severe disease
  - Smallest residual D4Z4 fragments (1-3 repeats)
- May affect language development if not detected early in childhood onset disease

Natural History: Data from a large US Registry of FSHD Patients
US Registry of FSHD Patients and Family Members

- Limited data about progression of functional impairment in FSHD
- 313 genetically confirmed and clinically affected FSHD1 participants
  - An average of 6 years of follow up
- Mean age 51.5 years, range 9-91 years
- Roughly equal number men and women
- Geographically distributed across the US
- Mostly well educated (>60% some college or beyond)

<table>
<thead>
<tr>
<th>Disease Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age initial symptom (SD)</td>
<td>21.1 (15.0)</td>
</tr>
<tr>
<td>Age diagnosed (SD)</td>
<td>31.3 (17.3)</td>
</tr>
<tr>
<td>D4Z4 contraction (kb)</td>
<td>24.8 (5.7)</td>
</tr>
<tr>
<td>Facial weakness (%)</td>
<td>282 (90.1%)</td>
</tr>
<tr>
<td>Scapular weakness (%)</td>
<td>303 (96.8%)</td>
</tr>
<tr>
<td><strong>Functional Burden</strong></td>
<td></td>
</tr>
<tr>
<td>Dry or irritated eyes (%)</td>
<td>152 (48.6%)</td>
</tr>
<tr>
<td>Difficulty whistling or drinking through a straw (%)</td>
<td>188 (60.1%)</td>
</tr>
<tr>
<td>Difficulty raising arms above shoulder height (%)</td>
<td>228 (72.8%)</td>
</tr>
<tr>
<td>Difficulty getting out of a chair (%)</td>
<td>108 (34.5%)</td>
</tr>
</tbody>
</table>
FSHD: Age at diagnosis

- Men show peak in diagnosis around 20 years of age, women diagnosed on average older

Dx Age: Relationship to contraction

- Median: 14 years (1-3 repeats)
- Median 30 years (4-7 repeats)
- Median 37 years (8-10 repeats)

Proportion of population not yet diagnosed with FSHD

P<0.0001

Years

Proportion of population not yet diagnosed with FSHD
WC Use by Decade and D4Z4 Deletion

Wheelchair Use Anytime

Decade
Prevalence
6 Year Risk
Average D4Z4 Contraction (kb)

Frequency

Average D4Z4 Contraction

Prevalence
6 Year Risk
Average D4Z4 Contraction
Relationship of Age to First WC Use

![Box plot showing the distribution of age at first wheelchair use for different repeat sizes. The x-axis represents the repeat size categories: Large (≤18 kb), Medium (19-28 kb), and Small (>28 kb). The y-axis represents the age at first wheelchair use. The box plot indicates significant differences among the groups, with F = 31.99 and Prob > F < .0001.](image-url)
# Linear Relationship to Age for Other Assistive Devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Age at First Use in Years</th>
</tr>
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<tbody>
<tr>
<td>Ankle Foot Orthotic (SD) n=91</td>
<td>40.2 (15.2)</td>
</tr>
<tr>
<td>Ankle Knee Orthotic (SD) n=48</td>
<td>43.2 (14.6)</td>
</tr>
<tr>
<td>Cane (SD) n=124</td>
<td>49.1 (14.1)</td>
</tr>
<tr>
<td>Walker (SD) n=79</td>
<td>56.8 (15.5)</td>
</tr>
</tbody>
</table>
This risk of using a WC is not distributed evenly across the FSHD population
  - Higher risk in people with small residual fragments
  - And older people

Risk for other assistive devices related to age

Unless we can find other markers to determine who is most at risk
  - The ability to use WC use as endpoint in study will be limited due to the long time needed for such studies
Natural History: outcomes

- What have we learned about the Natural History of FSHD as measured by clinical trial outcome measures?
- Natural history study 3 year prospective longitudinal study (1997) n=81

Background: QMT

- Technique for testing strength against fixed resistance
- Uses a digital force transducer
- Connected by an inelastic strap to metal frame
- Standardized positions for different muscles

Personius et al. (1994) Phys Ther 74: 253-63
Background: QMT

- Reliable: What you measure one day you measure the next
- Can be standardized to normal expected strength based on gender, height, and age
  - E.g. Create percent predicted of normal
  - Advantages: makes changes in individual muscles comparable
- Standardized scores can be averaged across muscle groups to create combined score to follow progression over time
Background: MMT

- Also reliable
- Standardized procedure for positioning
- Uses standard strength scale
  - Range: 0 = no strength; 3= strength against gravity but no resistance; 5= normal strength
- Scores averaged across muscles to create combined score

<table>
<thead>
<tr>
<th>MMT Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Normal strength</td>
</tr>
<tr>
<td>5–</td>
<td>Uncertain muscle weakness</td>
</tr>
<tr>
<td>4+</td>
<td>Inability to resist against maximal pressure throughout range of motion</td>
</tr>
<tr>
<td>4</td>
<td>Ability to resist against moderate pressure throughout range of motion</td>
</tr>
<tr>
<td>4–</td>
<td>Ability to resist against minimal pressure throughout range of motion</td>
</tr>
<tr>
<td>3+</td>
<td>Ability to move through full range of motion against gravity and to resist against minimal pressure through partial range of motion, then contraction breaks abruptly</td>
</tr>
<tr>
<td>3</td>
<td>Ability to move through full range of motion against gravity</td>
</tr>
<tr>
<td>3–</td>
<td>Ability to move through greater than one half range of motion against gravity</td>
</tr>
<tr>
<td>2+</td>
<td>Ability to move through less than one half range of motion against gravity</td>
</tr>
<tr>
<td>2</td>
<td>Ability to move through full range of motion with gravity eliminated</td>
</tr>
<tr>
<td>2–</td>
<td>Ability to move in any arc of motion with gravity eliminated</td>
</tr>
<tr>
<td>1</td>
<td>A flicker of movement is seen or felt in the muscle</td>
</tr>
<tr>
<td>0</td>
<td>No contraction palpable</td>
</tr>
</tbody>
</table>
Natural History Combined Scores

- Followed subjects at 6 months intervals for 3 years
- Most responsive to disease progression: compared to functional measures, functional grades, and muscle mass
Extension of Natural History

- Extending natural history in 15 subjects who subsequently enrolled in albuterol trial
  - Confirmed slow but steady loss of strength over 2-7 years follow up (~ 2-4% per year)

How Many For Clinical Trial?

- How many people needed to show a difference in strength depends on how big an effect you think you’re going to see with a treatment?
  - For example to show halt of progression would need ~160 people per treatment arm
  - On the other hand for an effect twice as large would only need ~40 per treatment arm

Summary – Measures of Strength

- QMT and MMT are reliable measures of strength
- Both showed significant disease progression at 1 year
  - However the ‘clinical importance’ of this change is not known
- Variability measurements can be used for power and sample size estimates
  - But ~160 people per group to demonstrate halt of disease progression a large number for rare disease
- The ability to identify specific people or ‘muscles at risk’ for progression would increase the sensitivity of strength outcomes in future trials
Functional Measures

- Include measures like:
  - Time to ascend 4 stairs
  - walk 30 feet
  - get up from a chair
  - Drink 6 ounces of water
  - Brooks and Vignos functional scales

- Good face validity
  - A change in a functional activity would intuitively seem meaningful
Functional Measures in FSHD

- Reliable
- Typically moderate to strong linear relationship to disease severity or measures of strength
- But do not change over periods of time as long as 3 years
Future Challenges for the Design of Therapeutic Trials
Challenges: Biomarkers

- Biomarkers are things like gene expression, or levels of proteins in your blood which can predict changes in the disease.
- Biomarkers are important for proof of concept studies, or as an early signal a drug is working.
- DUX4 is hard to measure directly.
- Targets of DUX4 may be easier to measure:
  - Downstream changes appear to be more persistent.
- However more work is needed to determine which biomarkers will work best in FSHD.
MRI: non-invasive biomarker of disease progression?

- MRI uses magnetic fields and radio waves to look at muscle
- Changes on MRI might indicate active disease
  - May help target muscles at risk for progression
- Relationship between DUX4 expression and inflammation seen on MRI?

Non-invasive Biomarkers: MRI

- Alternatively can also use MRI to measure muscle mass and fat content in muscle
- As muscles become weaker the fat content goes up
- Changes in fat content might identify muscles at risk for progression


![Graph showing fat fraction distribution](image)
Other Non-Invasive Biomarkers

- Electrical impedance myography found to be a useful biomarker in motor neuron disease
  - Impedance is resistance to current flow
  - Largely determined by muscle structure
Current Studies

- Prospective 12 month longitudinal study
- To test: reliability, relationship to other measures of FSHD, and changes over time:
  - Disease specific health inventory
  - Disease specific functional rating scale
  - Electrical Impedance Myography
FSHD Health Inventory

- Developed by Chad Heatwole, MD
  - using FDA Guidance
- Patient interviews (1375 quotes) used to identify relevant symptoms
- National cross-sectional study of 328 FSHD patients
  - Rank importance of different symptoms identified in interviews
- Final questionnaire 116 questions in 14 subdomains

FSHD-Functional Outcome

- Evaluator administered functional tasks
- Chosen to represent areas of body affected by FSHD
- Combined to create a 72 point scale for use in clinical trials
- Preliminary data:
  - Reliable
  - Associations with other measures of disease (strength, clinical severity scores)

<table>
<thead>
<tr>
<th>Function</th>
<th>Task Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg Function</td>
<td>Sit to stand without hands</td>
</tr>
<tr>
<td></td>
<td>6 Minute Walk Test</td>
</tr>
<tr>
<td></td>
<td>Self-selected gait speed</td>
</tr>
<tr>
<td></td>
<td>Go’ 30 feet</td>
</tr>
<tr>
<td></td>
<td>Timed ascend/descend stairs</td>
</tr>
<tr>
<td>Arm Function</td>
<td>Shoulder abduction</td>
</tr>
<tr>
<td></td>
<td>Shoulder forward flexion</td>
</tr>
<tr>
<td></td>
<td>Elbow flexion</td>
</tr>
<tr>
<td></td>
<td>Time to don/doff coat</td>
</tr>
<tr>
<td>Trunk Function</td>
<td>Time to pick penny up from floor</td>
</tr>
<tr>
<td></td>
<td>Sit up with feet held</td>
</tr>
<tr>
<td></td>
<td>Timed supine to sit</td>
</tr>
<tr>
<td>Hand Function</td>
<td>Grip dynamometry (M/F)</td>
</tr>
<tr>
<td>Balance/Mobility</td>
<td>Timed Up and Go</td>
</tr>
</tbody>
</table>
Clinical Trials: Opportunities

- FSHD is one of the most common muscular dystrophies
  - Patient recruitment should not be an issue
- Established outcome measures and natural history using these outcome measures
- Current efforts to build networks of FSHD clinical trial sites
  - Standardizing protocols for biomarkers, imaging, strength and functional measures, and quality of life measures
  - If studies will be done at different sites at least they will be done the same way
Recent advances have elucidated a unified genetic model for FSHD1 and 2

Identifies potential disease-directed therapeutic targets

The slow disease progression and individual to individual variability present challenges when developing outcomes for future trials

- Identifying markers of disease activity to help stratify people will be key

International cooperation and standardization of procedures will be necessary for comparing interventions across studies
Thanks: everyone who came today

- **Organizations**
  - Experimental Therapeutics Program
  - MDA Clinical Research Training Program
  - FSH Society
  - Registry of FSH Patients and Family Members

- **URMC**
  - Rabi Tawil, MD – mentor
  - Robert Griggs, MD – mentor
  - Chad Heatwole, MD – collaborator
  - Kate Eichinger – PT
  - Shree Pandya – PT

- **KUMC**
  - Richard Barohn, MD – mentor

- **LUMC – the Netherlands**
  - Silvere van der Maarel – collaborator

- **Fred Hutchinson Cancer Center – Seattle**
  - Stephen Tapscott - collaborator

- **URMC**
  - Colleen Donlin-Smith – coordinator
  - Bharati Shah – Lab
  - Don Henderson – Lab