Quantitative Muscle Analysis in FSHD using Whole-Body MRI: Composite Muscle Measurements for Cross-Sectional Analysis

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- Board Certified Neurologist with subspecialty training in Neuromuscular Disease

- I am not presenting any data related to ReDUX4 and cannot take any questions related to the recently concluded randomized controlled ReDUX4 clinical trial.
Whole-Body MSK MRI Evaluation of FSHD Disease Heterogeneity and Progression

- WB-MSK-MRI Captures
  - Wholistic evaluation of skeletal musculature
  - Small quantitative changes in muscle health that correlate with functional measures
- Disease Heterogeneity
- Non-invasive
- Minimal burden on patient participation
- Changes in MSK MRI may be detected earlier than changes in clinical outcome assessments (COAs)
Objective

• Develop a whole-body MR imaging protocol and analysis algorithms to volumetrically measure fat replacement of skeletal muscle in FSHD feasible to use in multi-site clinical trials

• Generate a regional composite measurement that can correlate with clinical outcome measures
New Paradigm of Image analysis in NMD

- Imaging a slice(s) of select muscles in lower limbs
- Imaging of whole muscle, proximal to distal, in the whole body
- Personalized set of muscles to follow over time
Study Design

- Two Visits 4-12 weeks apart
- Assessments included
  - WB-MSK-MRI
  - Muscle Biopsy
    - Results presented in Ronco, et al. A Biomarker of DUX4 Activity to Evaluate Losmapimod Treatment Effect in FSHD Phase 2 Trials. At 2020 Virtual MDA Clinical and Scientific Congress.
- Clinical Outcome Assessments
  - TUG
  - FSHD TUG
  - Reachable Work Space
Main Inclusion Criteria

▪ Age 18-65 years old
▪ Confirmed diagnosis of FSHD1 with 1-7 repeats
▪ CSS 2 to 4 on Ricci’s scale (range 0-5)
▪ Presence of STIR positive signal in at least one leg muscle eligible for muscle biopsy
### Subject Demographics (N=17)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean(SD); range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>49.4 (13.02); 23-65</td>
</tr>
<tr>
<td><strong>Gender (Female) %</strong></td>
<td>29.4%</td>
</tr>
<tr>
<td><strong>Clinical Severity Score (CSS)</strong></td>
<td>3.0 (0.71); 2-4</td>
</tr>
<tr>
<td><strong>Average Repeats</strong></td>
<td>5.2 (1.46); 3-7</td>
</tr>
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</table>
Imaging Protocol for Whole Body MRI

Total examination time ~30 min
### Skeletal Muscle MRI

**Muscles Studied- 18 muscles bilaterally; 36**

<table>
<thead>
<tr>
<th>Neck</th>
<th>Torso</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraspinatus</td>
<td>Pectoralis Major</td>
</tr>
<tr>
<td>Infraspinatus</td>
<td>Rhomboideus</td>
</tr>
<tr>
<td>Subscapularis</td>
<td>Latissimus Dorsi &amp; Teres Major</td>
</tr>
<tr>
<td>Teres Minor</td>
<td>Trapezius</td>
</tr>
<tr>
<td></td>
<td>Serratus Anterior</td>
</tr>
<tr>
<td></td>
<td>Paraspinal (C3-Sacrum)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Legs</th>
<th>Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadriceps</td>
<td>Deltoid</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>Biceps Brachii</td>
</tr>
<tr>
<td>Adductors</td>
<td>Triceps Brachii</td>
</tr>
<tr>
<td>Tibialis Anterior</td>
<td></td>
</tr>
<tr>
<td>Gastrocnemius Medialis</td>
<td></td>
</tr>
</tbody>
</table>
Image Analysis

Calibration and merge

Muscle segmentation and QC

Measurement algorithms
Quantitative Muscle Measurement

- **LEAN MUSCLE VOLUME (cL)**
  - A measurement of the amount of lean/contractile muscle tissue

- **MUSCLE FAT INFILTRATION (%)**
  - A measurement of the diffuse fatty infiltration in the leaner/functioning parts of the muscle definition.

- **MUSCLE FAT FRACTION (%)**
  - A measurement of the overall fattiness of the muscle. Used to identify affected muscles or follow a muscle-to-fat replacement progress in muscle dystrophy.
Muscles Analyzed

- 478 out of 612 muscles analyzed
- 134 not analyzable
  - 64 Image Artifacts
    - Technical issues; e.g. streak artifact
  - 70 due to complete fat replacement
WB-MSK-MRI Captures Disease Heterogeneity

**RICCI 2.5**

1. Muscles clearly affected by disease, but not so severely fat replaced to have lost all function
   - MFI ≥ 10%; MFF ≤ 50%

2. Muscles do not appear to be affected by disease
   - MFF ≤ 10%

3. Muscles severely fat replaced and have likely lost most if not all function
   - MFF ≥ 50%

4. Excluded due to image artefacts

**RICCI 3.0**

5. Muscles clearly affected by disease, but not so severely fat replaced to have lost all function
   - MFI ≥ 10%; MFF ≤ 50%

6. Muscles do not appear to be affected by disease
   - MFF ≤ 10%

7. Muscles severely fat replaced and have likely lost most if not all function
   - MFF ≥ 50%

8. Excluded due to image artefacts

**RICCI 4.0**

9. Muscles clearly affected by disease, but not so severely fat replaced to have lost all function
   - MFI ≥ 10%; MFF ≤ 50%

10. Muscles do not appear to be affected by disease
    - MFF ≤ 10%

11. Muscles severely fat replaced and have likely lost most if not all function
    - MFF ≥ 50%

12. Excluded due to image artefacts
Quantitative Muscle Measurement is Consistent with FSHD Pattern

Circle and lines correspond to mean ± one standard deviation.
Good Reproducibility for All Muscle Measurements

- Good reproducibility across all muscles
- Higher reproducibility in larger muscles

Coefficient of variation

Within-subject standard deviation
### Regional Composite Measurement (MFF<sub>tot</sub> & MFI<sub>tot</sub>)

<table>
<thead>
<tr>
<th>Test</th>
<th>Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper Extremity</strong></td>
<td><strong>Trunk</strong></td>
</tr>
<tr>
<td>FHSD TUG</td>
<td>Supraspinatus, Infraspinatus, Subscapularis, Teres Minor, Deltoid, Biceps Brachii, Triceps Brachii</td>
</tr>
<tr>
<td>Classic TUG</td>
<td>N/A</td>
</tr>
<tr>
<td>RWS</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Regional Composite Measurements ($MFF_{tot}$ & $MFI_{tot}$) Show Strong Correlations with TUG, FSHD TUG and Moderate Correlations with RWS
Summary

- Developed WB-MSK- MRI protocol
  - Currently being performed in all Phase 2 clinical trials of losmapimod

- Reproducibility of quantitative muscle measurements was excellent

- Strong cross-sectional correlation between Regional Composite Measurement ($MFF_{tot}$ & $MFI_{tot}$) and TUG, FSHD-TUG and RWS.

- Whole Body-MSK MRI can capture the heterogeneity and provide important information about disease severity as it correlates with FSHD relevant clinical endpoints.
Thank you!

- **ALL PATIENTS WITH FSHD**

- **Participating Sites**
  - Kennedy Krieger Institute
  - University of Rochester Medical Center
  - Radboudumc University Medical Center
  - The University of Kansas Medical Center
  - UCLA Health
  - University of Washington

- **Collaborators**
  - UC Irvine