BACKGROUND

Duchenne Muscular Dystrophy (DMD) is caused by a lack of the dystrophin protein which leads to progressive muscle degeneration.

• Secreted Phosphoprotein 1 (SPP1) gene codes for Osteopontin (OPN) protein which is pro-inflammatory.
• A specific SNP (TT) in SPP1 gene have been shown to be beneficial for slowing disease progression.
• A specific haplotype of LTBP4, IIAAMM, is suspected to be beneficial because it may bind better to TGFβ than other haplotypes.
• TGFβ inhibits satellite cell differentiation and causes fibrosis unless it is bound to Latent TGFβ Binding Protein 4 (LTBP4).
• The purpose of this research is to determine if variations of these polymorphisms are beneficial and to be able to predict the different rates of disease progression in participants with DMD.

METHODS

Genotyping

• Collaborators at University of Pennsylvania performed targeted genotyping of genes of interest.

MRS Analysis

• Utilizes ratio between water and fat in muscle to calculate fat fraction.

\[ FF = \frac{\text{Lipid}}{\text{Water + Lipid}} \]

Dixon MRI Analysis

• Dixon MRI images were analyzed to determine the intramuscular fat fraction at the maximum cross-sectional area of the soleus (SOL), vastus lateralis (VL), and biceps femoris longhead (BF).

MRI T₂

• Transverse relaxation time measured to collect information about the microenvironments within muscles.

Statistical Analysis

• Mann-Whitney test were utilized to analyze differences between groups.

RESULTS

AIM 1: Determine if specific SNP variations of the SPP1 gene are linked to slower muscle degeneration in boys with DMD utilizing Dixon MRI Fat Fraction and MRS.

A. VL Relative One Year Change

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Percent Relative Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>0.05 ± 0.02</td>
</tr>
<tr>
<td>TG/GG</td>
<td>0.00 ± 0.00</td>
</tr>
</tbody>
</table>

B. BF Relative One Year Change

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Percent Relative Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>0.10 ± 0.03</td>
</tr>
<tr>
<td>TG/GG</td>
<td>0.05 ± 0.01</td>
</tr>
</tbody>
</table>

Figure 1: One year relative fat fraction changes in BF (A) and VL (B).

AIM 2: Investigate the relationship between DMD patients with variations of the SPP1 gene and T₂ values.

A. BF T₂ One Year Change

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Change in T₂ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>TG/GG</td>
<td>1.5 ± 0.3</td>
</tr>
</tbody>
</table>

B. VL T₂ One Year Change

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Change in T₂ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>3.0 ± 0.7</td>
</tr>
<tr>
<td>TG/GG</td>
<td>2.5 ± 0.6</td>
</tr>
</tbody>
</table>

Figure 2: One Year T₂ Changes in BF. A) in BF. B) in VL.

AIM 3: Determine if a particular haplotype in the LTBP4 is associated with slower muscle degeneration in boys with DMD.

\[ T₂ \text{ Baseline IIAAMM vs. other haplotypes} \]

Figure 3: T₂ at Baseline for IIAAMM and other haplotypes in SOL, VL, and BF muscles.

AIM 4: Verify if the combination of both protective polymorphisms results in a slower muscle degeneration

Change in Fat Fraction with Varying Numbers of Protective Genetic Modifiers

Figure 4: 1 yr change in fat fraction shows significant differences between subjects with and without protective modifiers.

REFERENCES


Acknowledgements:

• Funded by NIH (U54R052646; R01 AR056973) and NSF (DMR 1157490)