Ambulatory function in Duchenne muscular dystrophy

The characteristic trajectory and variation across individuals

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Duchene muscular dystrophy: progressive muscle wasting leads to weakness, loss of motor function and early death
Heterogeneity in rates of disease progression -- a challenge for drug development

The Collaborative Trajectory Analysis Project

Clinical experts and registries
- Eugenio Mercuri
- Nathalie Goemans
- Francesco Muntoni
- Brenda Wong
- Hank Meyer
- Craig McDonald
- Krista Vandenborne

Drug Developers

Patient Groups

Collaboration
- Susan J. Ward, PhD

Data Science
- James Signorovitch, PhD
Mission

• Learn from patient data to inform all stages of Duchenne drug development
• Make insights and tools available to everyone
• Deliver near-term impact

Research objectives discussed today

• Describe common patterns of disease progression
• Quantify variation across individuals
• Explore relationships across different functional measures
Data

Patients

• NorthStar UK Clinical Network database
• 323 boys
• 2,007 assessments
• 3.3 yrs median follow-up

North Star Ambulatory Assessment (NSAA)
(17 items scores 0, 1 or 2; e.g., walk, run, jump, climb step...)

Methods

▪ Linear mixed effects (LME) models
  • Function vs. age
  • Patient-specific random splines
  • Autocorrelation
▪ Superimposition by Translation and Rotation (SITAR)
  • Parameterize characteristic trajectory (spline)
  • Model individual variation as transformations of the time scale (shift + velocity) as well as vertical translation of the outcome scale
Results – NSAA total score

**Observed trajectories**

- **NSAA total score**
- **Age (years)**

**Re-scaled trajectories based on LME**

- **Model explained 92% of variability in NSAA scores**
- **Age (years)**

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**Results – NSAA total score**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at peak function (years)</td>
<td>6.8 (5.9 to 7.8)</td>
</tr>
<tr>
<td>Years from peak to 50% loss</td>
<td>4.0 (3.6 to 4.6)</td>
</tr>
</tbody>
</table>
## Relationships between features

### Pearson correlations

<table>
<thead>
<tr>
<th></th>
<th>Age at peak</th>
<th>Years to 50% loss</th>
<th>Height of peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at peak</td>
<td></td>
<td>0.60</td>
<td>0.30</td>
</tr>
<tr>
<td>Years to 50% loss</td>
<td>0.60</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Height of peak</td>
<td>0.30</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

- Later age at peak is associated with slower subsequent progression
- Later age at peak is modestly associated with higher peak function
- Height of peak is not strongly associated with the rate of subsequent decline

### Associations across measures

- Age at peak NSAA and age at peak 10 meter walk/run speed were **similar**
- Age at peak rise from floor speed was **earlier** by 1.3 (0.7 to 1.8) years compared with peak NSAA
Conclusions

• Despite variability across individuals, ambulatory progression in DMD follows common patterns
• The large majority of cross-patient variation in progression can be explained by differences in age at peak function, peak level achieved and subsequent rates of decline
• Different functional abilities peak at different ages, but with a predictable ordering, suggesting that they reflect different aspects of a consistent underlying disease process
• The SITAR approach was appealing but faced convergence issues in these data; Bayesian versions of SITAR are of interest
• Characterization of progression can help inform the design and interpretation of clinical studies (e.g., by enrichment for certain disease stages), and serve as a reference point for further research in DMD disease modeling

Acknowledgments and disclosures

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  o Parent Project Muscular Dystrophy, Charley's Fund, and CureDuchenne, a founding patient advocacy partner and provider of initial seed funding to cTAP
Extra slides

Data accessed by cTAP

>2,500 boys  >16,000 clinic visits  >5,000 patient-years
Other cTAP research

- Trajectories of change in clinical endpoints
- Consistency between real-world and clinical trial settings
- Prognostic models
- Minimal clinically important differences in endpoints