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Association of CAG Repeats With Long-term Progression in Huntington Disease

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Association of CAG Repeats With Long-term Progression in Huntington Disease


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Jefin Jose
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Abstract Abstracted

• Huntington’s disease is neurodegenerative disease caused by a single mutation in the Huntingtin gene

• The number of CAG repeats can be used to predict the severity of degeneration in the brain as well the age of disease onset

• Disease progression can be defined in terms of a number of variables (including performance on tests and brain volume), but the most basic one is time

• Langbehn et al. found that putamen and caudate volumes best tracked disease progression at any given time
Introduction

• Huntington’s disease is a neurodegenerative disease characterized by expansion of the CAG trinucleotide sequence in the huntingtin gene of chromosome 4

• Therefore, Huntington’s disease is inherently a genetic disease
Introduction

Huntingtin gene

Htt pools/inclusions
Intracellular and extracellular inclusions develop (Jimenez-Sanchez et al., 2017)

↓ brain volume in the striatum (Alila Medical, 2021)
Introduction

• The primary clinical markers of the disease are cognitive and motor deficits
  • Perform worse on a tapping task
  • Perform worse on a Stroop word reading task

• The expression of the disease symptomatically based on the genetic underpinning is known as **penetrance**
  • 10-26 repeats → no penetrance
  • 26-25 repeats → intermediate penetrance
  • 39-39 repeats → reduced penetrance
  • 40+ repeats → full penetrance
Introduction

• Langbehn et al. claim that few disease characteristics can be determined using just the CAG repeat length and age
• The goal of the research was to determine the clinical and morphometric implications of CAG repeat length
• Hopefully, the results would help determine:
  • 1. Which variables are best associated with CAG repeat length and age (highest $R^2$)
  • 2. How the progression of Huntington’s disease looks like (Quadratic? Linear? Flat?)
Methods

• The researchers did not sample individuals themselves
• Rather, they obtained data through the TRACK-HD/TRACK-ON studies

<table>
<thead>
<tr>
<th>TRACK-HD</th>
<th>TRACK-ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>• four academic institutions first recruited 123 healthy controls, 120</td>
<td>• a follow up of TRACK</td>
</tr>
<tr>
<td>pre-HD carriers, and 123 with early HD subjects</td>
<td>• still occurring</td>
</tr>
<tr>
<td></td>
<td>• maximum time of consideration: 6 years</td>
</tr>
</tbody>
</table>

**Combined**

• 2065 patient visits
• 443 participants
• Used UHDRS variables + morphometric data
Methods

- **UHDRS – Clinical**
  - A clinical battery of tests used to assess disease severity
  - Involves motor, cognitive, and neuropsychiatric tasks/tests
  - 74 total items

- **Morphometric data (MRI)**
  - Brain volumes (caudate and putamen, total brain volume)
  - Given that people naturally have different-sized heads, the **ratios** of these volumes to the total intracranial volume

\[
Volume\ Considered = \frac{Actual\ Volume}{Total\ Intracranial\ Volume}
\]
Methods

• Principal component analysis was used to derive summary scores for clinical and morphometric data
  • “the weighted sum of the original set of variables that has the highest possible mean correlation with those same variables”
  • That statistics themselves are described using linear algebra

\[
\mathbf{w}_{(1)} = \arg \max_{\|\mathbf{w}\|=1} \left\{ \sum_i (t_i)_{(i)}^2 \right\} = \arg \max_{\|\mathbf{w}\|=1} \left\{ \sum_i (\mathbf{x}_{(i)} \cdot \mathbf{w})^2 \right\}
\]

\[
\mathbf{w}_{(1)} = \arg \max_{\|\mathbf{w}\|=1} \left\{ \|\mathbf{Xw}\|^2 \right\} = \arg \max_{\|\mathbf{w}\|=1} \left\{ \mathbf{w}^T \mathbf{X}^T \mathbf{X} \mathbf{w} \right\}
\]

\[
\mathbf{w}_{(1)} = \arg \max \left\{ \frac{\mathbf{w}^T \mathbf{X}^T \mathbf{X} \mathbf{w}}{\mathbf{w}^T \mathbf{w}} \right\}
\]
### Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Motor-Cognitive Score</th>
<th>UHDRS Motor-Cognitive Score</th>
<th>White Matter-Ventricle Score</th>
<th>Caudate-Putamen Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbol Digit Modalities Test, No. correct</td>
<td>-0.795</td>
<td>-0.903</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Stroop word reading, No. correct</td>
<td>-0.770</td>
<td>-0.879</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Spot the Change 5 s, corrected for guessing</td>
<td>-0.582</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>UHDRS total motor score</td>
<td>0.872</td>
<td>0.891</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Paced tapping 3-Hz SD of intertap intervals, log</td>
<td>0.808</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Q-Motor speeded tapping intertap interval, mean</td>
<td>0.829</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Q-Motor speeded tapping interonset interval, log SD</td>
<td>0.885</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Q-Motor speeded tapping tap duration, log SD</td>
<td>0.889</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Q-Motor speeded tapping interonset interval, log mean</td>
<td>0.918</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Putamen volume, ratio to ICV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-0.947</td>
</tr>
<tr>
<td>Caudate volume, ratio to ICV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-0.947</td>
</tr>
<tr>
<td>Total brain volume, ratio to ICV</td>
<td>NA</td>
<td>NA</td>
<td>-0.926</td>
<td>NA</td>
</tr>
<tr>
<td>Ventricle volume, ratio to ICV</td>
<td>NA</td>
<td>NA</td>
<td>0.818</td>
<td>NA</td>
</tr>
<tr>
<td>White matter volume, ratio to ICV</td>
<td>NA</td>
<td>NA</td>
<td>-0.870</td>
<td>NA</td>
</tr>
<tr>
<td>Gray matter volume, ratio to ICV</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Variance explained by the first PC, %</td>
<td>67.6</td>
<td>79.4</td>
<td>76.1</td>
<td>89.7</td>
</tr>
</tbody>
</table>
Results

Quadratic, Accelerating

Quadratic, Accelerating

Quadratic, Accelerating

Non-linear, low slope
Results

- Previous graphs depicted motor-cognitive, caudate-putamen, and gray matter scores as a function of time
- These graphs indicate the relationship between the PCs themselves
- The inflection point at PC = 0 indicates shift from healthy to HD subjects
Conclusion

• Phenotype declines in a CAG-dependent manner
  • However, different acceleration rates between CAG repeat lengths indicate that a relationship is present
• Clinical predictors do not as strongly track disease progression as morphometric predictors do
• Variance can be decreased using a smaller subset of variables
• Neurodegeneration in the caudate and putamen is linear over time
Discussion Questions

• Why do you think brain matter volume tracked age in a quadratic manner?

• Why do you think neurodegenerative diseases have no cure? (Keep in mind genetics)

• What directions do you think neuroscience/neurology should take in the future?
