Biomarkers for Parkinson’s Disease

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Objective

To discuss the importance of biomarkers for Parkinson’s disease, efforts that are underway to identify those markers, and potential diagnostic and progression markers.
Outline

- Need for biomarkers
- Biomarker investigations
  - PDBP, JHU Udall Center
- Potential biomarkers

What is a biomarker?

• A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.
A good biomarker should:

• Diagnose disease
• Predict change
• Change with treatment
• And be related to the underlying disease process

• Ideal example: Sugar levels for diabetes
### Non-PD examples of biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Disease state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>Fever and infection</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Stroke risk and heart attack</td>
</tr>
<tr>
<td>MRI brain</td>
<td>Stroke</td>
</tr>
<tr>
<td>Genetic testing for Huntington’s Disease</td>
<td>Huntington’s Disease</td>
</tr>
</tbody>
</table>
How do we diagnose PD now?

- History and examination
- Sometimes assisted by dopamine transporter scan (DaTScan)
- Wouldn’t it be great if there were a test or imaging study that:
  - Diagnosed PD?
  - Told us about disease progression?
  - Told us which medications would work or who would get medication side effects?
Biomarkers would have 3 uses

- **Diagnostic Markers**
  - Identify patients with PD
  - Assist with patient selection for clinical studies
  - Direct drug regimen and treatment strategies

- **Progression Markers**
  - Monitor patients as PD progresses
  - Measure disease-based modifications and drug response

- **Pharmacokinetic Markers**
  - Monitor therapeutic effect, and absorption of drug regimens
  - Interpret novel clinical trial results
Parkinson’s Disease biomarkers could improve all aspects of patient care
How does finding a biomarker work?

- See patients and assess their motor, cognitive, psychiatric symptoms
  - Usually involves lots of tests and scales
- Also get blood, sometimes spinal fluid, imaging, urine, DNA, etc
- Connect clinical changes or findings with molecules or imaging
- If the molecule or imaging correlates with the clinical assessments, it is a potential biomarker
A number of investigations are trying to find biomarkers
PDBP is a large consortium (n=\sim 1840)
There are a lot of biofluids available through the PDBP.
JHU PDBP has enrolled 121 participants, all of whom donated blood and spinal fluid.

<table>
<thead>
<tr>
<th></th>
<th>Parkinson’s disease (n=86)</th>
<th>Healthy Controls (n=35)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>66.08 (8.17)</td>
<td>66.84 (8.86)</td>
<td>0.65</td>
</tr>
<tr>
<td>Education, years (SD)</td>
<td>16.82 (2.39)</td>
<td>16.84 (2.33)</td>
<td>0.95</td>
</tr>
<tr>
<td>Gender, % Male</td>
<td>69.8</td>
<td>31.42</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Race, % Caucasian</td>
<td>95.34</td>
<td>88.57</td>
<td>0.17</td>
</tr>
<tr>
<td>MDS-UPDRS motor score, mean (SD)</td>
<td>32.13 (11.86)</td>
<td>1.51 (2.02)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MDS-UPDRS total score, mean(SD)</td>
<td>60.30 (24.19)</td>
<td>6.8 (6.18)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total LED, mean (SD)</td>
<td>731.00 (497.88)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Hamilton Anxiety total, mean (SD)</td>
<td>7.77 (4.31)</td>
<td>4.23 (4.01)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hamilton Depression total, mean (SD)</td>
<td>6.32 (4.62)</td>
<td>3.29 (3.75)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MoCA total score, mean (SD)</td>
<td>25.46 (4.54)</td>
<td>27.77 (1.24)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cognition, number of individuals</td>
<td>25 Normal Cognition 45 MCI 15 Dementia</td>
<td>27 Normal Cognition 8 MCI</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean follow-up time, years (SD)</td>
<td>2.96 (1.56)</td>
<td>3.02 (1.54)</td>
<td>0.71</td>
</tr>
<tr>
<td>Mean disease duration, years (SD)</td>
<td>6.79 (4.83)</td>
<td>--</td>
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</tbody>
</table>
### Active Longitudinal Cohort (n = 105*)

<table>
<thead>
<tr>
<th></th>
<th>PD (n = 49)</th>
<th>Atypical PD (n = 14)</th>
<th>Control (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years, mean (sd)</strong></td>
<td>62.4 (8.5)</td>
<td>68.5 (6.9)</td>
<td>69.8 (7.6)</td>
</tr>
<tr>
<td><strong>Sex (% male)</strong></td>
<td>44.9</td>
<td>64.3</td>
<td>42.9</td>
</tr>
<tr>
<td><strong>Race (% Caucasian)</strong></td>
<td>93.9</td>
<td>100</td>
<td>92.9</td>
</tr>
<tr>
<td><strong>Education in years, mean (sd)</strong></td>
<td>17.0 (3.1)</td>
<td>14.8 (2.9)</td>
<td>16.9 (2.4)</td>
</tr>
<tr>
<td><strong>Age at disease onset, mean (sd)</strong></td>
<td>54.7 (9.5)</td>
<td>63.5 (7.2)</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Disease duration, mean (sd)</strong></td>
<td>7.7 (6.2)</td>
<td>5.0 (3.4)</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Hoehn &amp; Yahr Stage distribution</strong></td>
<td>20% I, 74% II, 6% III, 0% IV, 0% V</td>
<td>0% I, 44% II, 21% III, 14% IV, 21% V</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Pathology

- Loss of dopamine producing cells is thought to be responsible for the motor changes observed in PD.

- Alpha-synuclein is the “bad” protein.

http://pathology.mc.duke.edu/neuropath/CNSlecture4/CNSlecture4.htm
Alpha-synuclein positive Lewy bodies are the primary pathology in PD
How do we get the “bad” alpha-synuclein and cell loss?

- Protein cascade is like a domino cascade
- Each domino is a potential biomarker
What happens when abnormal alpha-synuclein goes into the neuron?
PAR levels separate PD and control participants

![Graph showing mean PAR concentration over visits for Parkinson's Disease (blue) and Healthy Controls (red). The graph includes error bars and asterisks indicating significant differences.](image)
PAR levels may also relate to disease duration, severity
Different forms of alpha-synuclein may also predict cognitive changes
We can also look at numerous molecules at once in the blood.
So, have we found a biomarker?

- Maybe…
- Next steps including looking at whether each molecule is still a biomarker in other cohorts (groups of patients and controls)
- Also determine if the marker changes with newer treatments
- Also want to test each biomarker to see if it is specific to PD
Thank you and questions?