Alzheimer’s Disease and Down Syndrome: Research Today and What the Future May Hold

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• Extra copy of chromosome 21 (trisomy 21), on which the APP gene resides.
• Glenner and Wong - plaques in AD same as plaques in DS (beta-amyloid).
• By the age of 40, virtually all people with DS show AD-related neuropathological changes including plaques and tangles. By the age of 65, about 80% have dementia\(^1\).
• Dementia is cause of death in 70% of people with DS over age 35.
• There are 6 million people with DS worldwide.
• APP – Disomic in DS– NO AD

1. Head et al, 2012
1/695 live births in US
~450,000 with DS in US
~6 million worldwide

**Life Expectancy**
- 10 yrs born in 1961
- 25 yrs born in 1983
- 49 yrs born in 1997
- 61 yrs born in 2005
- 65 yrs born in 2010

**Age Specific Rates**
- 40-49 Years: 9.4%
- 50-59 Years: 50.1%
- 60-69 Years: 80.4%

CDC MMWR, 2007

day et al, 2005
Healthy Brain

AD Brain

Plaques and Tangles define Alzheimer’s disease
### Pathogenogenesis

<table>
<thead>
<tr>
<th>PS 1, PS 2, AND APP MUTATIONS</th>
<th>β-SECRETASE</th>
<th>OXIDATIVE STRESS; INFLAMMATION</th>
<th>SYNAPTIC FAILURE; NEURON DEATH</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOWN SYNDROME (TRISOMY 21)</td>
<td>γ-SECRETASE</td>
<td>DIRECT TOXICITY; EXCITOTOXICITY</td>
<td></td>
</tr>
</tbody>
</table>

↑ Abeta levels

![Diagram showing the pathogenesis of Alzheimer's disease](image)

**Icelandic mutation in BACE**

↓ Abeta levels
CLINICAL STAGES OF ALZHEIMER’S DISEASE
CLINICAL STAGES OF ALZHEIMER’S DISEASE

Jack et al, Lancet 2009. ADNI Biomarkers in normal aging, MCI and AD
<table>
<thead>
<tr>
<th>Condition</th>
<th>PiB Aβ</th>
<th>T807 Tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ−neg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ−pos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ−pos</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Preclinical/Prodromal**
Tau PET enables visualization of the spread of AD neuropathology

59 year-old MCI
MMSE 26 → 24, over 13.2 months

Baseline

+13.2 months

SUVR: 1.0

Johnson et al, 2017
## Multimodal AD Biomarker Analysis in Down Syndrome

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Mental Age</th>
<th>ApoE 4</th>
<th>Amyloid PET Clinical Read</th>
<th>Grey matter Amyloid PET (SUVr)</th>
<th>FDG PET clinical read</th>
<th>Avg Hippocampus Volume (cm³)</th>
<th>Retinal Amyloid Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP06</td>
<td>37</td>
<td>9</td>
<td>E3-E3</td>
<td>Negative</td>
<td>0.938</td>
<td>Normal</td>
<td>3.19</td>
<td>1.63</td>
</tr>
<tr>
<td>DP01</td>
<td>32</td>
<td>7</td>
<td>E3-E3</td>
<td>Negative</td>
<td>0.97</td>
<td>Mildly Hypo</td>
<td>3.22</td>
<td>2</td>
</tr>
<tr>
<td>DP07</td>
<td>34</td>
<td>7</td>
<td>E2-E4</td>
<td>Negative</td>
<td>0.988</td>
<td>Normal</td>
<td>3.53</td>
<td>2.47</td>
</tr>
<tr>
<td>DP08</td>
<td>39</td>
<td>5</td>
<td>E3-E3</td>
<td>Positive</td>
<td>1.054</td>
<td>Hypo</td>
<td>3.48</td>
<td>1.8</td>
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<tr>
<td>DP02</td>
<td>45</td>
<td>3</td>
<td>E2-E3</td>
<td>Positive</td>
<td>1.171</td>
<td>Hypo</td>
<td>2.91</td>
<td>2.2</td>
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<tr>
<td>DP12</td>
<td>45</td>
<td>6</td>
<td>E3-E4</td>
<td>Positive</td>
<td>1.176</td>
<td>Hypo</td>
<td>3.37</td>
<td>1.83</td>
</tr>
<tr>
<td>DP05</td>
<td>48</td>
<td>8</td>
<td>E3-E3</td>
<td>Positive</td>
<td>1.177</td>
<td>Hypo</td>
<td>3.47</td>
<td>1.68</td>
</tr>
<tr>
<td>DP11</td>
<td>47</td>
<td>7</td>
<td>E3-E4</td>
<td>Positive</td>
<td>1.245</td>
<td>Hypo</td>
<td>2.99</td>
<td>2.34</td>
</tr>
<tr>
<td>DP13</td>
<td>50</td>
<td>8</td>
<td>E3-E4</td>
<td>Positive</td>
<td>1.344</td>
<td>Hypo</td>
<td>3.14</td>
<td>1.58</td>
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<tr>
<td>DP04</td>
<td>55</td>
<td>6</td>
<td>E3-E4</td>
<td>Positive</td>
<td>1.385</td>
<td>Hypo</td>
<td>3.25</td>
<td>1.7</td>
</tr>
<tr>
<td>DP03</td>
<td>52</td>
<td>7</td>
<td>E3-E4</td>
<td>Positive</td>
<td>1.401</td>
<td>Hypo</td>
<td>3.01</td>
<td>2.2</td>
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<tr>
<td>DP09</td>
<td>60</td>
<td>7</td>
<td>E3-E3</td>
<td>Positive</td>
<td>1.457</td>
<td>Hypo</td>
<td>2.73</td>
<td>--</td>
</tr>
</tbody>
</table>

Rafii et al, 2015
Amyloid burden correlates with age and lower memory performance.

Spearman rank correlations (r) that are significant at the 0.05 level after false discovery rate adjustment.

Rafii et al, 2015
COMPARISON OF CEREBRAL GLUCOSE METABOLISM IN DS VERSUS AD

Violet: Relative hypometabolism DS  
Blue: Relative hypometabolism in AD  
(166 ADNI subjects)

Green: Relative hypermetabolism in DS  
Red: Relative hypermetabolism in AD  
(166 ADNI subjects)

Dissociation of DS and AD effects using imaging

Rafii et al, 2016
Tau positivity only seen in amyloid-positive subjects but to varying degrees

Rafii et al, 2017
Areas with greater tau burden have less regional glucose metabolism

Rafii et al, 2017
TAU PATHOLOGY CORRELATES WITH BASELINE COGNITIVE MEASURES

Higher tau correlates with lower cognitive and functional scores

Rafii et al, 2017
Scanning Laser Ophthalmoscope
(Operator View)

Retinal Amyloid Index

Courtesy of Neurovision
Down Syndrome  Non-Down Syndrome

Collaboration with Neurovision
Blood Biomarkers: Plasma NF-L and Age

![Graph showing the relationship between plasma NFL (pg/ml) and age for different groups: Control, DSBI, and Preclinical AD. The x-axis represents age, and the y-axis represents NFL concentration. The data points are scattered across the graph, with shaded areas indicating the range for each group.](image-url)
Correlations of Plasma NF-L with a. brain amyloid; b. CAMCOG total score; c. CANTAB PAL Errors; d. Vineland Score; e. Hippocampal volume; f. OMQ-PF score.

Rafii et al, 2019
Blood Biomarkers

• Plasma NF-L:
  • Correlates with age and clinical dementia status
  • Correlates with amyloid-burden, glucose hypometabolism, cognitive and functional decline
  • Levels greater than 50 pg/ml may indicate presence of neurodegeneration
  • Increases 25% per year once above threshold level 50 pg/ml

• Further studies are needed on larger sample size to confirm and extend these findings.
BIOMARKERS OF ALZHEIMER’S DISEASE IN DS

Jack et al, Lancet 2009. ADNI Biomarkers in normal aging, MCI and AD
# CLINICAL TRIALS FOR AD IN DS

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scyllo-inositol</td>
<td>Amyloid binding</td>
<td>2a</td>
<td>Published (Rafii et al, 2017)</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Anti-oxidant</td>
<td>2</td>
<td>Published (Sano et al, 2016)</td>
</tr>
<tr>
<td>ACI-24</td>
<td>Active vaccine against beta-amyloid</td>
<td>1b</td>
<td>Ongoing (PI: Rafii)</td>
</tr>
</tbody>
</table>
CONCLUSIONS

- Amyloid positive is nearly universal by age 40
- Tau PET positivity is seen only in the presence amyloid PET positivity, just as in sporadic AD
- Tau PET signal seems to correlate with age and amyloid burden and with greater cognitive decline in DS, just as in sporadic AD
- Many biomarkers of AD, including plasma NfL, behave similarly in adults with DS as in other preclinical AD populations.
- The data indicate that a large, multicenter longitudinal study is feasible to better understand the trajectories of AD biomarkers in this enriched population → NIH ABC-DS
- Such data will inform clinical trials for AD in DS