Sex Differences in AD biomarker progression: the role of APOE

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Disclosures

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• Paid consultant to Eli Lilly, Roche, Neurotrack
Objectives

• Classify the major biomarkers for assessing dementia etiology.

• Identify the relationship between APOE genotypes and AD biomarkers.

• Describe findings of differential biomarker progression among men and women at risk for dementia.
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<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>Etiology</th>
<th>Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Amyloid plaques &amp; Tau tangles</td>
<td>PET, CSF, Plasma</td>
</tr>
<tr>
<td>Dementia with Lewy bodies (&amp; Parkinson’s with dementia)</td>
<td>Alpha-synuclein/Lewy bodies</td>
<td>CSF (Seed Amplification Assay)</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>Vascular Injury</td>
<td>MRI</td>
</tr>
<tr>
<td>LATE</td>
<td>TDP-43</td>
<td>In development; need validation</td>
</tr>
</tbody>
</table>
Alzheimer’s Disease **Amyloid/Tau/Neurodegeneration** Research Framework

- **Clinically Unimpaired (CU)**
  - Can measure with cerebrospinal fluid (CSF) via lumbar puncture
  - Can measure with plasma via blood draw

- **Mild Cognitive Impairment (MCI)**

- **Dementia**

- **In Vivo Biomarkers**
  - Amyloid → Tau → Neuronal Dysfunction → Neuronal Degeneration
Alzheimer’s Disease Amyloid/Tau/Neurodegeneration Research Framework

Clinically Unimpaired (CU)

Amyloid → Tau → Neuronal Dysfunction → Neuronal Degeneration

Mild Cognitive Impairment (MCI)

Dementia

FDA Approved Amyloid PET
- 2012: Florbetapir (Amyvid)
- 2013: Flutemetamol (Vizamyl)
- 2014: Florbetaben (Neuroceq)

FDA Approved Tau PET
- 2020: Flortaucipir FDA approved (Tauvid)
AD Plasma Biomarkers

A  A- MCI vs A+ MCI

[Graph showing ROC curves and corresponding AUC values for various p-tau biomarkers.

Janelidze 2022]
Co-Etiology is Common

Capturing AD etiologies in isolation is a limitation of current biomarker research and interpretation of biomarkers in clinic.
Objectives

• Classify the major biomarkers for assessing dementia etiology.

• Identify the relationship between APOE genotypes and AD biomarkers.

• Describe findings of differential biomarker progression among men and women at risk for dementia.
APOE genotype is a strong predictor of AD dementia risk

Farrer 1998

Reiman 2020
(ADGC Path Confirmed Data)
APOE is a strong predictor of amyloid-positivity.
APOE Effects on Tau

Reduced Tau Clearance in APOE4+ > APOE4-

Shi 2017
Does APOE contribute to this variability?
APOE effects on regional tau PET among Amyloid+ individuals

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimate</th>
<th>Allele</th>
<th>e2</th>
<th>e4</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC</td>
<td>-0.10</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Amygdala</td>
<td>-0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IT</td>
<td>0.00</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IP</td>
<td>0.05</td>
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<td></td>
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</tr>
<tr>
<td>Precuneus</td>
<td>0.00</td>
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</table>

Young 2023
Additional APOE Effects among Amyloid- : Blood Brain Barrier

Montagne 2020
Amyloid

Tau

Neuro Dysfunction

Neuro Degeneration

Mild Cognitive Impairment (MCI)

Clinically Unimpaired (CU)

Blood Brain Integrity

Microglial Pathways

APOE Effects

Dementia
Objectives

• Classify the major biomarkers for assessing dementia etiology.

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Greater risk of AD in women with APOE4+ women

A  AD-NL odds ratio

Neu 2017 JAMA Neurology
Greater tau pathology in women
Greater decline in women with risk factor

Higher Tau PET levels

Meta temporal ROI lower tertile  Meta temporal ROI middle tertile  Meta temporal ROI upper tertile

PACC change (SD/yr)

Time from tau scan (years)

Sex

Buckley 2020
Differential progression in women and men?

APOE 4>3>2 → Amyloid → Tau → Dementia

Women

Men

??? Co-pathology Lifestyle
Risk profiles change at older ages

APOE

Farrer 1998

APOE risk in Women

Neu 2017

Tau Tangles

Savva 2009
Summary

• Robust PET and biofluid biomarkers for assessing Alzheimer’s disease etiology.

• Current missing biomarkers to capture other common age-related etiologies.

• APOE genotype influences multiple components of the Alzheimer’s disease cascade.

• Increased risk of AD dementia in women may be mediated by APOE genotype and/or elevated tau burden.

• Need to integrate multiple factors to understand disease progression and underlying mechanisms in humans (sex, age, co-pathologies).
Thank you

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Career Development NIH K99-AG071837 (C. Young)
NIH K99-AG075184 (A. Trelle)

Mormino Lab
Limitations with generalizability

<table>
<thead>
<tr>
<th></th>
<th>Caucasians: Population-based Studies</th>
<th></th>
<th>African Americans</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε3/ε3</td>
<td>2683</td>
<td>1.0 (Referent)</td>
<td>...</td>
</tr>
<tr>
<td>ε2/ε2</td>
<td>36</td>
<td>0.9 (0.3-2.8)</td>
<td>.94</td>
</tr>
<tr>
<td>ε2/ε3</td>
<td>568</td>
<td>0.6 (0.5-0.9)</td>
<td>.93</td>
</tr>
<tr>
<td>ε2/ε4</td>
<td>152</td>
<td>1.2 (0.8-2.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ε3/ε4</td>
<td>1226</td>
<td>2.7 (2.2-3.2)</td>
<td>.15</td>
</tr>
<tr>
<td>ε4/ε4</td>
<td>193</td>
<td>12.5 (8.8-17.7)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Farrer 1998
FDA approved F18 Amyloid PET tracers

(First research amyloid scans=2004)

**Florbetapir (Amyvid)**
2012
- Aβ-
- Aβ+

**Flutemetamol (Vizamyl)**
2013
- Aβ-
- Aβ+

**Florbetaben (Neuroceq)**
2014
- Aβ-
- Aβ+

→ F18 tracers highly correlated with postmortem amyloid neuritic plaques (moderate/frequent).
Tau Ligand Timeline

- 2013: T807/AV1451/Flortaucipir publication
- 2014: T808 publication (⇒ GTP-1)
- 2016: THK5351 publication
- 2017: THK5351 MAO-B binding discovered
- 2016/17: First MK6240 scans
- 2017: First PI2620 scans presented
- 2020: First JNJ scans presented
- 2020: Flortaucipir FDA approved (Tauvid)
Additional APOE Effects among Amyloid-: Microglia gene expression

"microglia-APOE cluster" phagocytosis & proinflammatory genes

Serrano-Pozo 2021