Individual Pathways of Resilience to Alzheimer's Disease: Embracing Complexity

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Outline

• Alzheimer's Disease Background
• Sex-Specific Genetic Predictors of Neuropathology
• Resistance and Resilience
• Molecular Drivers of Resilience

AD Neuropathological Cascade

Neuropathology

Neurodegeneration

Cognitive Impairment
Rare and Common Variants

Amyloid Cascade Hypothesis

Failed Trials


Failed Trials

ES Lilly's experimental Alzheimer's drug, bapineuzamab, fails study but shows potential
Challenges in Amyloid Treatments

- Lack of amyloidosis among those receiving treatment
- Heterogeneity in disease presentation
- A need for measures of target engagement

Opportunities for Precision Medicine

Amyloid Negative Individuals Included in Trial

Disease Heterogeneity

Reduced Efficacy of Anti-Aβ Immunotherapy in a Mouse Model of Amyloid Deposition and Vascular Cognitive Impairment Comorbidity

Jack et al., Lancet Neurology, 2013
Challenges in Amyloid Treatments

- Lack of amyloidosis among those receiving treatment
- Heterogeneity in disease presentation
- A need for measures of target engagement

Focus treatment at highest risk individuals
- Biomarker profile
- Genetic Background
- Sex

Identify Alternative Targets for Intervention
- Molecular Drivers of Resilience

Outline

- Alzheimer's Disease Background
- Sex-Specific Genetic Predictors of Neuropathology
- Resistance and Resilience
- Molecular Drivers of Resilience

Sex-Specific Framework
Two-thirds of AD cases are women

[Chart showing estimated risk for Alzheimer's Disease by sex at age 45 and age 85]
Females Have More AD Pathology at Autopsy

APP Transgenic Mice

***p<0.001

(Yue et al., Neurobiology of Aging, 2011)

Females with Pathology Decline More Rapidly

Neuropathology Association with Cognition

CSF Biomarker Association with Atrophy

APOE Association with AD is Stronger in Females

APOE

Farrer et al., JAMA Neurology, 1997

Neu et al., JAMA Neurology, 2017
Summary of Sex Differences

- Females have higher levels of plaques and tangles
- Females show stronger association between pathology and cognitive decline

Is there a Sex-Specific Genetic Architecture of AD Neuropathology?

Sex Differences in AD Neuropathology

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Tau</th>
<th>P-value</th>
<th>P-value</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age</td>
<td>0.36</td>
<td>0.001</td>
<td>0.30</td>
<td>0.001</td>
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<tr>
<td>APOE ε4</td>
<td>0.20</td>
<td>&lt;0.001</td>
<td>0.20</td>
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</table>

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Braak</th>
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<table>
<thead>
<tr>
<th>Predictor</th>
<th>CERAD</th>
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<td>APOE ε4</td>
<td>0.20</td>
<td>&lt;0.001</td>
<td>0.20</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CSF Sample Size: 2,798 (Male: 936, Female: 862)
Autopsy Sample Size: 5,470 (Male: 2,296, Female: 2,813)

Hohman et al., JAMA Neurology, 2018
Sex Specific Effects of APOE

<table>
<thead>
<tr>
<th>Predictor</th>
<th>CSF Sample Size</th>
<th>P-value</th>
<th>tTest</th>
<th>P-value</th>
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<tbody>
<tr>
<td>APOE</td>
<td>1,798</td>
<td>0.001</td>
<td></td>
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<tr>
<td>APOE (4)</td>
<td>2,880</td>
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Autopsy Sample Size:

<table>
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<tr>
<th>Predictor</th>
<th>CSF Sample Size</th>
<th>P-value</th>
<th>tTest</th>
<th>P-value</th>
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<td>APOE</td>
<td>5,470</td>
<td>0.001</td>
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<tr>
<td>APOE (4)</td>
<td>9,090</td>
<td>0.001</td>
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<td>0.001</td>
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</tbody>
</table>

Summary of Sex Differences

- Females have higher levels of plaques and tangles
- Females show stronger association between pathology and cognitive decline
- APOE has a strong association with amyloid
  - Consistent across men and women
- APOE has a strong association with tau, particularly among females

What about other Genetic Predictors of AD Pathology?

Participants: CSF GWAS Sample

<table>
<thead>
<tr>
<th>SNP</th>
<th>QC N_SNPs</th>
<th>Original Data</th>
<th>Final: 5,166,244</th>
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<tbody>
<tr>
<td></td>
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<td>7,359,341</td>
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<tr>
<td>Genotype Missingness: 5%</td>
<td>2,158,568</td>
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<tr>
<td>MAF: 1% - 34,529</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HWE: 1x10^-6</td>
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</table>

Original Sample exclusions

<table>
<thead>
<tr>
<th>Reason</th>
<th>Original Sample Size</th>
<th>Final Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missingness (5%)</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Sex Inconsistency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relatedness (PI - hat 25%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
GWAS of CSF Aβ-42

Locus Zoom

rs316341 is eQTL for SERPINB1, SERPINB6, and SERPINB9 in Brainac and GTex
**SERPINB1 Functional Evidence**

- Female-specific association between prefrontal cortex expression of SERPINB1 ($p=0.02$) and SERPINB6 ($p=0.00007$) and amyloid levels in brain tissue

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**Serpin Signaling and Amyloidosis**

- Serpins are Protease Inhibitors
  - Serpin-B1 Regulates Neutrophil Infiltration
- Serpins have been shown to inhibit Aβ toxicity
  - Likely through regulation of neutrophils
- Some evidence of sex difference in neutrophil infiltration and clearance
  - Female mice show more activated neutrophils than male mice following stroke
  - Estradiol modulates neutrophil infiltration and clearance

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**GWAS of CSF Tau**
GWAS of CSF Tau

Locus Zoom

OSTN/CLDN16 Functional Evidence

- rs1393060
  - eQTL for OSTN expression in the frontal cortex (p=0.0005)
  - Associated with tangle count at autopsy among females (p=0.047), but not males (p=0.96)
- OSTN and CLDN16 show sex-specific association with tangles
OSTN and CLDN16

- Osteocrin
  - Hormone that regulates dendritic growth
  - Secretion induced by depolarizations in human neurons
  - Some evidence of direct effects of estrogen on OSTN

- Claudin 16
  - Tight junction protein, primarily in the kidneys
  - Claudins have been implicated in AD and Vascular Dementia previously
  - Claudins have shown sex differences in gene expression in liver and kidneys

Neurofibrillary Tangles GWAS Results

Summary of Sex Differences

- Females have higher levels of plaques and tangles
- APOE has a strong association with amyloid
  - Consistent across men and women
- APOE has an association with tau, particularly among females
- Genetic predictors of amyloid and tau vary by sex
Summary of Sex Differences

- Female-Specific Drivers
- Male-Specific Drivers
- Shared Genetic Drivers
- Amyloid
- Tau
- Brain Atrophy
- Cognitive Impairment

First Steps Toward Precision Intervention

- Add in precision medicine figure

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- Molecular Drivers of Resilience
Heterogeneity in Cognitive Performance

Resilience as a Pathway to New Targets

Asymptomatic Alzheimer’s Disease

• 30% of Cognitively Normal Older Adults
• Reserve Hypothesis
  – Cognitive Reserve (Educational Attainment, IQ)
  – Brain Reserve (Premorbid Brain Volume)
• Molecular Drivers?
  – Neuroprotective Genetic Factors
  – Neural Repair
  – Angiogenesis

All Participants:
• Amyloid+ 
• Tau+ 
• APOE ε4+
Resistance and Resilience

Risk Factors:
- Age
- Sex
- Genetics
- Sleep
- Diet
- Exercise
- SES

Arenaza-Urquijo & Vemuri, Neurology, 2018

Outline

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Molecular Drivers of Resilience

Risk Factors

Amyloid  Tau  Brain Atrophy  Cognitive Impairment

Identifying Markers of Resilience

Gene x Biomarker Interactions

Protein x Biomarker Interactions

Gene x Gene Interactions

Identifying Markers of Resilience in ADNI

GWAS

Non-Coding Variant of Unknown Significance
Identifying Markers of Resilience in ADNI

- SNP → Gene Expression
  - Is my identified SNP associated with gene expression in the brain?
- Impute gene expression!
  - Build multi-SNP prediction models in GTEx
  - Use SNP prediction estimates to impute

Prokineticin 1 in the Coronary Artery and the Aorta

Prokinetinics system modulation as a new target to counteract the amyloid beta toxicity induced by glialmatogenetic alterations in an in vitro model of Alzheimer's disease
How can we increase statistical power to identify the molecular drivers of resilience?

Statistical Frameworks to Quantify Resilience

Incorporating AD Biomarkers into Resilience
Global Resilience Phenotype

Diagnosis Conversion Results

HR = 0.43 [0.35-0.51], p < 0.0001
HR = 0.56 [0.47-0.65], p < 0.0001
HR = 0.44 [0.36-0.54], p < 0.0001
HR = 0.90 [0.78-1.04], p = 0.148
HR = 0.95 [0.76-1.18], p = 0.626

Longitudinal Cognition Results

t_{2656} = 6.00, p < 0.0001

t_{2656} = 7.19, p < 0.0001

t_{2656} = 3.17, p = 0.002

t_{2656} = 1.43, p = 0.153

t_{2656} = -1.82, p = 0.069
RAD Participant Characteristics

<table>
<thead>
<tr>
<th>Dataset Description</th>
<th>ACT</th>
<th>NACC</th>
<th>ROS/MAP</th>
<th>ADNI</th>
<th>BIOCARD</th>
<th>BLSA</th>
<th>VMAP</th>
<th>WRAP</th>
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<tbody>
<tr>
<td>Sample Size*</td>
<td>418</td>
<td>479</td>
<td>713</td>
<td>768</td>
<td>202</td>
<td>139</td>
<td>141</td>
<td>179</td>
</tr>
<tr>
<td>Female</td>
<td>57%</td>
<td>49%</td>
<td>61%</td>
<td>42%</td>
<td>60%</td>
<td>63%</td>
<td>32%</td>
<td>68%</td>
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<tr>
<td>Age, years</td>
<td>84 ± 58</td>
<td>7 ± 88</td>
<td>8 ± 67</td>
<td>4 ± 75</td>
<td>6 ± 10</td>
<td>59 ± 17</td>
<td>72 ± 65</td>
<td>5 ± 6</td>
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<tr>
<td>Education, years</td>
<td>14 ± 31</td>
<td>5 ± 31</td>
<td>7 ± 41</td>
<td>6 ± 31</td>
<td>7 ± 21</td>
<td>7 ± 21</td>
<td>6 ± 31</td>
<td>3 ± 3</td>
</tr>
<tr>
<td>APOE-ε4, carrier</td>
<td>28%</td>
<td>38%</td>
<td>23%</td>
<td>44%</td>
<td>35%</td>
<td>24%</td>
<td>35%</td>
<td>40%</td>
</tr>
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</table>

* Number of European ancestry participants with genotype, autopsy or biomarker, and cognitive data. Age at death for ACT, NACC, and ROS/MAP; Age at biomarker acquisition for ADNI, BIOCARD, BLSA, VMAP, WRAP. #WGS: Whole Genome Sequencing.

• Biomarker Datasets (1,429 participants)
  • Include CSF biomarkers, neuroimaging, cognition
• Autopsy Datasets (1,610 participants)
  • Include autopsy measures of neuropathology

Leveraging RAD for Discovery

RAD Participant Characteristics

• Biomarker Datasets (1,429 participants)
  • Include CSF biomarkers, neuroimaging, cognition
• Autopsy Datasets (1,610 participants)
  • Include autopsy measures of neuropathology
Preliminary Results

<table>
<thead>
<tr>
<th>Gene</th>
<th>Position</th>
<th>P-value</th>
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<tbody>
<tr>
<td>PODNL1</td>
<td>19p13.12</td>
<td>0.30</td>
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<tr>
<td>UBTD2</td>
<td>5q35.1</td>
<td>0.0245</td>
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<tr>
<td>CHD4</td>
<td>12p13.31</td>
<td>0.0495</td>
</tr>
<tr>
<td>TREH</td>
<td>11q23.3</td>
<td>0.27</td>
</tr>
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</table>

Brain Expression Validation

Leveraging RAD for Deep Candidate Analyses
Vascular Endothelial Growth Factor

CSF VEGF Levels are Associated with Resilience and Slower Cognitive Decline

Mateo et al., Acta Neurol Scand, 2007

VEGF in CSF and Serum are Associated with AD and Amyloid Levels

Leung et al., Alzheimer's & Dementia, 2015

Molecular Drivers of Resilience

Brain Expression of Vascular Endothelial Growth Factor

Importance of Sex Differences

PROK1 and VEGF associations are only present among females