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

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Assistant Professor
Vanderbilt Memory & Alzheimer’s Center

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New York, NY
Outline

- Alzheimer’s Disease Background
- Sex-Specific Genetic Predictors of Neuropathology
- Resistance and Resilience
- Molecular Drivers of Resilience
AD Neuropathological Cascade

Neuropathology

Normal

Alzheimer’s

Neurofibrillary tangles

Amyloid plaques

Neurodegeneration

healthy brain

advanced alzheimer’s

Cognitive Impairment
Rare and Common Variants

Biological Psychiatry 2015 77, 43-51
Amyloid Cascade Hypothesis

Jack et al., Lancet Neurology, 2013
<table>
<thead>
<tr>
<th>TARGET TYPE</th>
<th>TIMELINE</th>
<th>PHASE 1</th>
<th>PHASE 1/2</th>
<th>PHASE 2</th>
<th>PHASE 2/3</th>
<th>PHASE 3</th>
<th>PHASE 4</th>
<th>APPROVED</th>
<th>INACTIVE</th>
<th>DISCONTINUED</th>
<th>NOT REGULATED</th>
<th>TOTAL</th>
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<td>4</td>
<td>1</td>
<td>15</td>
<td>5</td>
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<td>0</td>
<td>56</td>
</tr>
<tr>
<td>Cholesterol</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<td>0</td>
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</table>

**Poor results halt production, studies on promising Alzheimer’s drug bapineuzumab**

**Eli Lilly’s experimental Alzheimer’s drug solanezumab 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-Ab Immunotherapy in a Mouse Model of Amyloid Deposition and Vascular Cognitive Impairment Comorbidity

Liu et al., Neurology, 2015

Arvanitakis et al., Lancet Neurology, 2016
Opportunities for Precision Medicine

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

Genetic Risk Factor → Amyloid → Tau → Brain Atrophy → Cognitive Impairment

Dumitrescu et al, Current Genetic Medicine Reports, 2019
Sex-Specific Framework

Female-Specific Risk

Shared Genetic Risk

Male-Specific Risk

Amyloid

Tau

Brain Atrophy

Cognitive Impairment

Dumitrescu et al, Current Genetic Medicine Reports, 2019
Sex-Specific Framework

Female-Specific Risk

Shared Genetic Risk

Male-Specific Risk

Amyloid → Tau → Brain Atrophy → Cognitive Impairment

Dumitrescu et al, Current Genetic Medicine Reports, 2019
Two-thirds of AD cases are women

Estimated Lifetime Risk for Alzheimer’s Dementia, by Sex, at Age 45 and Age 65

Percentage  Men  Women

Age  45  10.3%  19.5%

Age  65  11.6%  21.1%

Created from data from Chene et al.110

Females Have More AD Pathology at Autopsy

**Neuropathology at Autopsy**

- APP Transgenic Mice
  - (Carroll et al., Brain Research, 2010)

- Tau Transgenic Mice
  - (Yue et al., Neurobiology of Aging, 2011)

(Oveisgharan et al., Acta Neuropathologica, 2018)
Females with Pathology Decline More Rapidly

Neuropathology Association with Cognition

![Graph showing the association between global AD pathology score and global cognition score for males and females.](image)

CSF Biomarker Association with Atrophy

![Graph showing the association between cerebrospinal fluid Aβ42 levels and annual change in left hippocampal volume for males and females.](image)

(Barnes et al., Archives of General Psychology 2005)

(Koran, Wagener, & Hohman, Brain Imaging and Behavior, 2016)
APOE Association with AD is Stronger in Females

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

### CSF Biomarker Results

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Total Tau</th>
<th></th>
<th>Phosphorylated Tau</th>
<th></th>
<th>Aβ-42</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P-value</td>
<td>β</td>
<td>P-value</td>
<td>β</td>
<td>P-value</td>
</tr>
<tr>
<td>sex</td>
<td>0.11</td>
<td>&lt;0.001</td>
<td>0.07</td>
<td>0.004</td>
<td>0.01</td>
<td>0.60</td>
</tr>
<tr>
<td>APOE ε2</td>
<td>-0.10</td>
<td>&lt;0.001</td>
<td>-0.10</td>
<td>&lt;0.001</td>
<td>0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>0.28</td>
<td>&lt;0.001</td>
<td>0.28</td>
<td>&lt;0.001</td>
<td>-0.48</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Boldface** font signifies associations that remain statistically significant after correcting for multiple comparisons.

### Autopsy Results

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Braak</th>
<th>CERAD</th>
<th>NFT Positivity¹</th>
<th>Neuritic Plaque Positivity²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>P-value</td>
<td>OR</td>
<td>P-value</td>
</tr>
<tr>
<td>sex</td>
<td>1.36</td>
<td>&lt;0.001</td>
<td>1.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APOE ε2</td>
<td>0.45</td>
<td>&lt;0.001</td>
<td>0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>2.60</td>
<td>&lt;0.001</td>
<td>3.03</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

¹Neurofibrillary tangle positivity was defined as Braak stage III,IV,V, or VI. ²Neuritic plaque positivity was defined as CERAD neuritic plaque stage of "moderate" or "frequent".

**CSF Sample Size**: 1,798 (Male: 936, Female: 862)
**Autopsy Sample Size**: 5,470 (Male: 2296, Female: 2813)

Hohman et al., JAMA Neurology, 2018
### CSF Biomarker Results

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<td>P-value</td>
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<td>0.01</td>
<td>0.60</td>
</tr>
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<td>&lt;0.001</td>
<td>-0.10</td>
<td>&lt;0.001</td>
<td>0.14</td>
<td>&lt;0.001</td>
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<tr>
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<td>0.28</td>
<td>&lt;0.001</td>
<td>0.28</td>
<td>&lt;0.001</td>
<td>-0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sex x APOE ε2</td>
<td>-0.10</td>
<td>0.20</td>
<td>-0.10</td>
<td>0.19</td>
<td>0.01</td>
<td>0.88</td>
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<tr>
<td>sex x APOE ε4</td>
<td>0.41</td>
<td>&lt;0.001</td>
<td>0.24</td>
<td>0.001</td>
<td>0.01</td>
<td>0.87</td>
</tr>
</tbody>
</table>

**Boldface** font signifies associations that remain statistically significant after correcting for multiple comparisons. 

1Neurofibrillary tangle positivity was defined as Braak stage III, IV, V, or VI. 2Neuritic plaque positivity was defined as CERAD neuritic plaque stage of "moderate" or "frequent".

### Autopsy Results

| Predictor       | Braak |                 | CERAD |                 | NFT Positivity¹ |                 | Neuritic Plaque Positivity² |
|-----------------|-------|-----------------|-------|-----------------|-----------------|--------------------------|
|                 | OR    | P-value         | OR    | P-value         | OR              | P-value                  | OR                          | P-value                  |
| sex             | 1.36  | <0.001          | 1.32  | <0.001          | 1.33            | <0.001                  | 1.23                        | 0.003                    |
| APOE ε2         | 0.45  | <0.001          | 0.39  | <0.001          | 0.43            | <0.001                  | 0.37                        | <0.001                  |
| APOE ε4         | 2.60  | <0.001          | 3.03  | <0.001          | 3.76            | <0.001                  | 3.24                        | <0.001                  |
| sex x APOE ε2   | 0.85  | 0.31            | 0.94  | 0.72            | 0.91            | 0.63                     | 0.85                        | 0.43                     |
| sex x APOE ε4   | 0.85  | 0.06            | 1.12  | 0.27            | 0.76            | 0.04                     | 1.06                        | 0.67                     |

CSF Sample Size: 1,798 (Male: 936, Female: 862)  
Autopsy Sample Size: 5,470 (Male: 2296, Female: 2813)  

Hohman et al., JAMA Neurology, 2018
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></th>
<th>ADNI1</th>
<th>ADNI2</th>
<th>BIOCARD</th>
<th>HB</th>
<th>MAYO</th>
<th>SWEDEN</th>
<th>UPENN</th>
<th>UW</th>
<th>WU</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td><strong>Sample Size</strong></td>
<td>390</td>
<td>397</td>
<td>183</td>
<td>105</td>
<td>433</td>
<td>293</td>
<td>164</td>
<td>375</td>
<td>804</td>
<td>3144</td>
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<tr>
<td><strong>Males</strong></td>
<td>234</td>
<td>218</td>
<td>76</td>
<td>57</td>
<td>262</td>
<td>110</td>
<td>68</td>
<td>190</td>
<td>370</td>
<td>1585</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>156</td>
<td>179</td>
<td>107</td>
<td>48</td>
<td>171</td>
<td>183</td>
<td>96</td>
<td>185</td>
<td>434</td>
<td>1559</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>77 ± 7</td>
<td>73 ± 8</td>
<td>62 ± 11</td>
<td>65 ± 16</td>
<td>79 ± 6</td>
<td>75 ± 9</td>
<td>72 ± 9</td>
<td>62 ± 17</td>
<td>70 ± 9</td>
<td>72 ± 11</td>
</tr>
<tr>
<td><strong>% AD cases</strong></td>
<td>24%</td>
<td>7%</td>
<td>5%</td>
<td>N/A</td>
<td>22%</td>
<td>100%</td>
<td>85%</td>
<td>33%</td>
<td>29%</td>
<td>32%</td>
</tr>
<tr>
<td><strong>% APOE4 carriers</strong></td>
<td>50%</td>
<td>38%</td>
<td>34%</td>
<td>54%</td>
<td>28%</td>
<td>76%</td>
<td>56%</td>
<td>43%</td>
<td>41%</td>
<td>44%</td>
</tr>
</tbody>
</table>

### Original Sample exclusions

- Missingness (5%)
- Sex Inconsistency
- Relatedness (PI-hat 25%)

### SNP QC

<table>
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<tbody>
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<td>Genotype Missingness: 5%</td>
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<td>HWE: 1x10-6</td>
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<td><strong>Final:</strong></td>
<td>5,166,244</td>
</tr>
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</table>

(Deming et al., 2017)
GWAS of CSF Aβ-42

(Deming et al., Acta Neuropathologica, 2017)
GWAS of CSF Aβ-42

(Deming et al., Acta Neuropathologica, 2018)
rs316341 is eQTL for SERPINB1, SERPINB6, and SERPINB9 in Braineac and GTex

(Deming et al., Acta Neuropathologica, 2018)
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

(Deming et al., Acta Neuropathologica, 2018)
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
GWAS of CSF Tau

(Deming et al., Acta Neuropathologica, 2017)
GWAS of CSF Tau

(Deming et al., Acta Neuropathologica, 2018)
Locus Zoom

(Deming et al., Acta Neuropathologica, 2018)
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

Braineac Results

<table>
<thead>
<tr>
<th>geneSymbol</th>
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<td>A4R3</td>
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<td>B7R2</td>
<td>2991115</td>
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<tr>
<td>TSPAN13</td>
<td>2991165</td>
<td>9.80E-04</td>
</tr>
</tbody>
</table>
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

Shared Genetic Drivers

Male-Specific Drivers

Amyloid

Tau

Brain Atrophy

Cognitive Impairment

Atrophy

Cognitive
Impairment
First Steps Toward Precision Intervention

(Ferretti et al., Nature Reviews Neurology, 2018)
Outline

- Alzheimer’s Disease Background
- Sex-Specific Genetic Predictors of Neuropathology
- Resistance and Resilience
- Molecular Drivers of Resilience
Heterogeneity in Cognitive Performance

Longitudinal Memory Performance

Composite Memory Performance vs. Age
Resilience as a Pathway to New Targets

All Participants:
- Amyloid$^+$
- Tau$^+$
- $APOE \varepsilon 4^+$
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

(Stern, 2013, Lancet Neurology)
Resistance and Resilience

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

Resistance
- Amyloid

Resilience
- Tau

Neurodegeneration

Cognitive Impairment

Arenaza-Urquijo & Vemuri, Neurology, 2018
Resistance and Resilience

Risk Factors → Resistance → Amyloid → Tau → Resilience → Brain Atrophy → Cognitive Impairment
Outline

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

Risk Factors

Amyloid

Tau

Resilience

Brain Atrophy

Cognitive Impairment
## Identifying Markers of Resilience

### Gene x Biomarker Interactions

<table>
<thead>
<tr>
<th>Author</th>
<th>Significant Genes/SNPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hohman et al 2016</td>
<td>CNTLN, PROK1, PRSS50, TMC4, HMBS</td>
</tr>
<tr>
<td>Hohman et al 2015</td>
<td>rs4866650, SPTLC1, WDR11-AS1, FTMT</td>
</tr>
<tr>
<td>Hohman et al 2014</td>
<td>POT1</td>
</tr>
</tbody>
</table>

### Gene x Gene Interactions

<table>
<thead>
<tr>
<th>Author</th>
<th>Significant Genes</th>
</tr>
</thead>
</table>
| Hohman et al 2016 | SIRT1 × ABCB1  
                        | PSAP × PEBP4  
                        | GRIN2B × ADRA1A  
                        | RYR3 × CACNA1C  |
| Hohman et al., 2015 + 2016 | APPB2 × GSK3β  
                          | APP × GSK3β  |
| Koran et al., 2015 + 2016 | RYR3 × CACNA1C  
                        | YNJ2 × PI4KA  
                        | PARD3 × MYH2  
                        | PDE3A × ABHD12B  
                        | OR2L13 × PRKG1  
                        | SYNJ2 × PI4KA |

### Protein x Biomarker Interactions

<table>
<thead>
<tr>
<th>Author</th>
<th>Significant Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varma et al 2017</td>
<td>A2M</td>
</tr>
<tr>
<td>Lane et al 2016</td>
<td>IGFBP-II</td>
</tr>
<tr>
<td>Hohman et al 2015</td>
<td>VEGF</td>
</tr>
</tbody>
</table>
Identifying Markers of Resilience in ADNI

Genotype (DNA) → Transcription → Gene Expression (RNA) → Translation → Protein

GWAS

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

https://commonfund.nih.gov/GTEX/index
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

Gamazon et al., Nature Genetics, 2015
Identifying Markers of Resilience in ADNI

- **Prokineticin 1 in the Coronary Artery and the Aorta**

  Prokineticin system modulation as a new target to counteract the amyloid beta toxicity induced by glutamatergic alterations in an *in vitro* model of Alzheimer's disease

  Silvia Caioli a, Cinzia Severini b, Teresa Ciotti c, Fulvio Florenzano c, Domenico Pimpinella a, Pamela Petrocchi Passeri b, Gianfranco Balboni d, Patrizio Polisca e, Roberta Lattanzi f, Robert Nisticò c g, Lucia Negri f, Cristina Zona a h *,

  (Hohman et al., Brain Imaging & Behavior, 2016)
How can we increase statistical power to identify the molecular drivers of resilience?
Statistical Frameworks to Quantify Resilience

Resilience
Incorporating AD Biomarkers into Resilience

Residual(Memory | Tau)
Residual(Memory | Amyloid)
Residual(Executive | Tau)
Residual(Executive | Amyloid)
Residual(Left Hippocampus | Tau)
Residual(Left Hippocampus | Amyloid)
Residual(Right Hippocampus | Tau)
Residual(Right Hippocampus | Amyloid)

(Hohman et al., Neurology, 2016)
Global Resilience Phenotype

(Hohman et al., Neurology, 2016)

Goodness of Fit = 0.76
Cross-loadings < 0.30
Dillon-Goldstein > 0.80
Diagnostic Conversion Results

Global Resilience

HR = 0.43 [0.35-0.51], p < 0.0001

Brain Resilience

HR = 0.56 [0.47-0.65], p < 0.0001

Cognitive Resilience

HR = 0.44 [0.36-0.54], p < 0.0001

Cognitive Reserve

HR = 0.90 [0.78-1.04], p = 0.148

Brain Reserve

HR = 0.95 [0.76-1.18], p = 0.626

(Hohman et al., Neurology, 2016)
**Longitudinal Cognition Results**

- **Global Resilience**: $t_{2656}=6.00, p<0.0001$
- **Brain Resilience**: $t_{2656}=7.19, p<0.0001$
- **Cognitive Resilience**: $t_{2656}=3.17, p=0.002$
- **Cognitive Reserve**: $t_{2656}=1.43, p=0.153$
- **Brain Reserve**: $t_{2656}=-1.82, p=0.069$

*(Hohman et al., Neurology, 2016)*
Global Resilience Phenotype

(Hohman et al., Neurology, 2016)
Global Resilience Phenotype

(Hohman et al., Neurology, 2016)
Resilience from Alzheimer’s Disease (RAD)

Dr. William Bush
- Variant Annotation
- PrediXcan Reference Panels

Dr. Marilyn Albert
- BIOCARD Dataset

Drs. Bennett & Schneider
- ROS/MAP
- Data Sharing

Dr. Sterling Johnson
- WRAP Dataset

Dr. Eric Larson
- ACT Dataset
- Data Sharing

Dr. Susan Resnick
- BLSA Dataset

Dr. Paul Crane
- ACT Dataset
- Data Harmonization

Dr. Walter Kukull
- NACC Dataset
## Dataset Descriptions

<table>
<thead>
<tr>
<th>Dataset</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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<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>
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<tr>
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<tr>
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<td>87±8</td>
<td>88±6</td>
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<tr>
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* 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

### Dataset Descriptions

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  - Include autopsy measures of neuropathology
## Preliminary Results

### Autopsy Discovery

![Autopsy Discovery](image)

### ADNI Replication

<table>
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<tr>
<th>Gene</th>
<th>Position</th>
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<td>CHD4</td>
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<td>Treh</td>
<td>11q23.3</td>
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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

VEGF in CSF and Serum are Associated AD and Amyloid Levels

Mateo et al., Acta Neurol Scand, 2007
Leung et al., Alzheimer's & Dementia, 2015
Molecular Drivers of Resilience

Brain Expression of Vascular Endothelial Growth Factor

[Graphs and diagrams showing expression patterns and genetic interactions]

GReX
Genetically regulated expression

Trait-altered component

Other factors

Gene Expression Decomposition

PrediXcan

Trait
Importance of Sex Differences

PROK1 and VEGF associations are only present among females

Female
Amyloid Positive Individuals

Male
Amyloid Positive Individuals

CSF Tau Positive

- CSF Vascular Endothelial Growth Factor (Log Transformed)
- Annual Change in Left Inferior Lateral Ventricular Volume
- Sex
  - Female
  - Male
Resistance and Resilience

Female-Specific Drivers

Shared Genetic Drivers

Male-Specific Drivers

Shared Resistance

Female-Specific Resistance

Male-Specific Resistance

Amyloid

Tau

Brain Atrophy

Cognitive Impairment

Female-Specific Resilience

Shared Resilience

Male-Specific Resilience
Future Goals

Systems genetics identifies modifiers of Alzheimer's disease risk and resilience

Donghui Yan, Bowen Hu, Burcu F. Duric, Subhabrata Mukherjee, Brian W. Kunkle, Yuexia Deng, Logan Dumitrescu, Turling Wang, Adam Njor, Amanda Kuzma, Yi Zhao, Hyungseung Kang, Sterling C. Johnson, Carlos Cruchaga, Timothy J. Hohman, Paul Crain, Corinne D. Engelman, Alzheimer's Disease Genetics Consortium,

Biobank-wide association scan identifies risk factors for late-onset Alzheimer's disease and endophenotypes

doi https://doi.org/10.1101/225714

doi https://doi.org/10.1101/468306
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- William Bush, PhD
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University of Michigan
- Laura Zahodne, PhD
National Institute on Aging
- Susan Resnick, PhD
University of Washington
- Paul Crane, MD
- Joey Mukherjee, PhD
- Eric Larson, MD
- Walter Kukull, PhD

Workgroup on Residual Cognitive Reserve
Postdoc Positions Available!

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