Genetic Drivers of Resilience to Alzheimer’s Disease

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Disclosures

• Scientific Advisory Board for Vivid Genomics
Explosion of Big Data in Alzheimer’s Disease

- Genomics
- Molecular Biomarkers
- Structural Brain Imaging
- Cognition
Precision Medicine in AD

Ferretti et al., Nature Reviews Neurology, 2018
Integrating AI into Genomic Discovery at NIA

- Large Cohort Study Data
- Harmonize
- Discover
- Validate
- Alzheimer’s Disease Sequencing Project
- Harmonized Data
- AI-Driven Gene Discovery
- Validated Gene Targets
Drug Discovery Framework for the Neuroresilience Program

- Resilience from AD Database

- Human Cell Lines

- Human Biospecimen

- Mouse Cell Lines

- Mouse Models of AD

- Human Cohort Studies

- Molecular Target Specification

- Filtering & Screening

- Preclinical Studies

- FDA Approval Process

- Nominated, Validated, Prioritized Target
Outline

• Defining Resilience
• Genetic Drivers of Resilience
• Future Directions
Amyloid Cascade Hypothesis

Jack et. al, Lancet Neurology, 2013
Heterogeneity in Cognitive Performance

Longitudinal Memory Performance

Composite Memory Performance

Age
Resilience as a Pathway to New Targets

All Participants:
- Amyloid$^+$
- Tau$^+$
- $APOE \varepsilon4^+$
Harmonizing Data to Increase Sample Size
U24 Phenotype Harmonization Consortium

Coordination

Data Integration

Curate

Document

Harmonize

NIAGADS Data Sharing Service
Compliance, Storage, & Dissemination

Receive Data

Share Data

Research Community
QUALIFIED INVESTIGATORS
ADSP WORKGROUPS
PROGRAM INITIATIVES

ADSP Cohort Studies
PHENOTYPES
IMAGES
GENOMICS

ADSP
National Cell Repository for AD
NACC
National Alzheimer's Coordinating Center
LONI
Laboratory of Neuro Imaging
SCAN
National Cell Repository for AD

## Example Domain: Cognition

<table>
<thead>
<tr>
<th></th>
<th>NACC</th>
<th>ACT</th>
<th>ADNI</th>
<th>ROSMAP &amp; MARS</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cog N</td>
<td>41459</td>
<td>5546</td>
<td>3189*</td>
<td>4386</td>
<td>54,580</td>
</tr>
<tr>
<td>Total ADSP N</td>
<td>10486</td>
<td>1392</td>
<td>1574</td>
<td>1575</td>
<td>15,027</td>
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<tr>
<td>Total Cog &amp; ADSP N</td>
<td>8458</td>
<td>1340</td>
<td>1574</td>
<td>1560</td>
<td>12,932</td>
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</tbody>
</table>
Anchor Items
- Tests administered consistently across studies serve as anchor items

Applied Psychometrics
- An expert panel assigns items to one of 4 domains
  - Memory
  - Language
  - Executive functioning
  - Visuospatial ability

Harmonization Approach
- Anchor Items
  - Logical Memory Immediate
  - Logical Memory Delayed
  - MOCA Immediate
  - MOCA Delayed
  - MMSE Orientation
  - MMSE Recall
  - CERAD Recall Immediate
  - CERAD Recall Delayed
  - East Boston Immediate
  - East Boston Delayed
  - Paired Associated Easy
  - Paired Associated Hard
  - CASI Object Memory
  - CASI Word Recall
  - Craft Story Delay
  - Benson Recognition
  - Benson Delayed
  - RAVLT Immediate
  - RAVLT Delayed
  - ADAS Recognition
  - ADAS Recall
Harmonization Approach

All Diagnoses

Cognitively Normal
Amyloid PET Harmonization

Diffusion MRI Harmonization

Structural T1 MRI Harmonization

Age Differences in Hippocampal Volume Before Harmonization

Heterogeneity in Location of Age Curve Across Studies

Age Differences in Hippocampal Volume After Harmonization

Common Age Curve Across Studies After Harmonization

Legend:
- ADNI-2
- AIBL
- BLSA-3T
- CARDIA
- PAC-WASH
- SHIP
- UKBIOBANK
Data Integration to Define Resilience

Amyloid Burden

Memory Performance

Dumitrescu et al., *Brain*, 2020
Genetic Architecture of Resilience
Analytical Plan

Resilience GWAS Workflow

Harmonization of cognition and amyloid metrics

- ACT
  Total=407
  CN=284
- ROSMAP
  Total=1031
  CN=337
- ADNI
  Total=688
  CN=217
- A4
  Total=2,982
  CN=2,982

GWAS

- Autopsy
  Total=1,438
  CN=621
- PET
  Total=3,670
  CN=3,199

Meta-analysis

- Combined results from both sets
  Total=5,108
  CN=3,820

Post-GWAS Analytical Workflow

- Genetic correlation
  - BADGERS
  - GNOVA
- Gene- and pathway-based tests
  - PrediXcan
  - VEGAS2
- Variant level tests
  - Post-hoc analyses
  - Functional annotation

Stratified Analyses:
- APOE-ε4
- Cognitively Normal

Dumitrescu et al., Brain, 2020
Cognitively Normal Resilience Results

ATP8B1

rs2571244 0.20 -0.22 0.04 3.69E-08
rs2850228 0.20 -0.22 0.04 3.69E-08
rs2663860 0.20 -0.22 0.04 3.91E-08

Dumitrescu et al., *Brain*, 2020
Gene Mapping and Functional Annotation

Methylation targets for rs2571244 (18:55473651)

<table>
<thead>
<tr>
<th>target</th>
<th>target start position</th>
<th>Spearman’s ρ</th>
<th>P</th>
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<tr>
<td>cg19596477</td>
<td>18:55472454</td>
<td>0.33</td>
<td>2.24x10^{-13}</td>
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<td>cg16310513</td>
<td>18:55471075</td>
<td>0.17</td>
<td>1.79x10^{-4}</td>
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<td>cg16141316</td>
<td>18:55469758</td>
<td>-0.12</td>
<td>8.14x10^{-3}</td>
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Prefrontal Cortex Methylation

Dumitrescu et al., Brain, 2020
ATP8B1 Function and Posthoc Analyses

• ATPase phospholipid transporting 8B1
  – Codes an aminophospholipid translocase protein
  – Operates in the Liver to maintain **bile acid homeostasis**

<table>
<thead>
<tr>
<th>Bile Acid</th>
<th>β</th>
<th>DF</th>
<th>P</th>
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<tbody>
<tr>
<td>TCA</td>
<td>0.40</td>
<td>1019</td>
<td>0.01</td>
</tr>
<tr>
<td>GLCA</td>
<td>0.33</td>
<td>1019</td>
<td>0.02</td>
</tr>
<tr>
<td>GCA</td>
<td>0.31</td>
<td>1019</td>
<td>0.02</td>
</tr>
<tr>
<td>TDCA</td>
<td>0.33</td>
<td>1019</td>
<td>0.04</td>
</tr>
<tr>
<td>TCDCA</td>
<td>0.30</td>
<td>1019</td>
<td>0.04</td>
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• Exome sequencing identified risk variants in **ATP8B4** (Holstege, 2020)
Summary of Genetic Resilience

- Genetic architecture of resilience is distinct from clinical AD
  - Small contribution of \textit{APOE}
- Observed a shared architecture with \textit{cognition} and \textit{education}
- Modest genetic correlation with \textit{vascular} and \textit{psychiatric} phenotypes
- \textit{ATP8B1} is a novel resilience gene along the \textit{bile acid metabolism} and phospholipid transport pathway
Gene Modifiers of Neuropathology
Data Integration to Identify Gene Modifiers

Adapted from Annah Moore, Ph.D.
Study Design

- Identify genetic variants that confer neuroprotection from AD
Study Design

Annual Change in Hippocampal Volume (slopes)

VMAP → BIOCARD → ADNI → WRAP

Joint Analysis

Replication in ADNI PET Sample

Replication in MCSA Sample
Results

ADNI PET Replication: $\beta = -0.005; p = 0.004$

MCSA Replication: $\beta = -0.24, p = 0.0112$

Discovery: $\beta = 0.01; p = 1e^{-8}$
Semaphorin 5b

- Semaphorin 5B is a member of the semaphorin family
  - Development of nervous system
  - Regulation of neuronal proliferation and migration
- Overexpression of SEMA5B is associated with reduction in hippocampal synapse number (O’Connor et al. 2011)
- SEMA5B knock-out causes aberrant branching of neurons (Jung et al. 2019)
Summary of Genetic Resilience

- Genetic architecture of resilience is distinct from clinical AD
  - Small contribution of \textit{APOE}
- Observed a shared architecture with \textit{cognition} and \textit{education}
- Modest genetic correlation with \textit{vascular} and \textit{psychiatric} phenotypes
- \textit{ATP8B1} is a novel resilience gene along the \textit{bile acid metabolism} and phospholipid transport pathway
- \textit{SEMA5B} is a novel susceptibility gene that may be \textit{beneficial} in absence of amyloid, but \textit{detrimental} with onset of pathology
Incorporating Sex and Gender into Resilience Models
Females Have More AD Pathology at Autopsy

Neuropathology at Autopsy

Oveisgharan et al., Acta Neuropathologica, 2018

APP Transgenic Mice

Carroll et al., Brain Research, 2010

Tau Transgenic Mice

Yue et al., Neurobiology of Aging, 2011
Females with Pathology Decline More Rapidly

Neuropathology Association with Cognition

CSF Biomarker Association with Atrophy

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

Female-Specific Drivers

Shared Genetic Drivers

Male-Specific Drivers

Amyloid

Tau

Brain Atrophy

Cognitive Impairment
Leveraging Genome-Wide Data to Explore Sex Differences in AD
GWAS of CSF Aβ-42

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

Deming, ... Hohman, Acta Neuropathologica, 2018
rs316341 is eQTL for SERPINB1, SERPINB6, and SERPINB9 in Braineac and GTex

Deming, ... Hohman, 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.
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
### SERPINB1 in Brain Tissue

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>RNA expression (TPM)</th>
<th>Protein expression (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow &amp; Immune system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver &amp; gall bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; urinary bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female tissues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adipose &amp; soft tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin</td>
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</tr>
</tbody>
</table>

**SERPINB1 Staining in AD Cortex**
Hot off the Presses (or Computer... )
Sex-Stratified Memory GWAS

rs2590395 is eQTL for SERPINB2 and SERPINB10 in Blood
Precision Medicine through Collaboration

Sex-Specific Discovery in Mouse

Sex-Specific Discovery in Human Brain

Protocol Alignment

Identify Consensus Candidates Human and Mouse Brain

Genomic Association with AD Endophenotypes

Bioinformatic Filtering for Druggability & Known Therapeutics

RNA Scope Validation

Sex-Specific Mechanistic Exploration in Mouse

APOE  SERPINB6  KDM6A  ??  ??
Future Directions
Resilience from AD Database

APOE Modifiers

Extreme Phenotype

Sex Specific Genetic Resilience

Protective Proteomic Effects

Extreme Phenotypes in ADSP

Resilient

Risk

Time Interval (yrs)

Extreme Phenotype

Resilience from AD Database

Sex Specific Genetic Resilience

Protective Proteomic Effects

PGF
VEGFB
VEGFA
VEGFC
VEGFD

NRP2
NRP1
FLT4
FLT1

KDR
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