Genetic Drivers of Resilience to Alzheimer’s Disease

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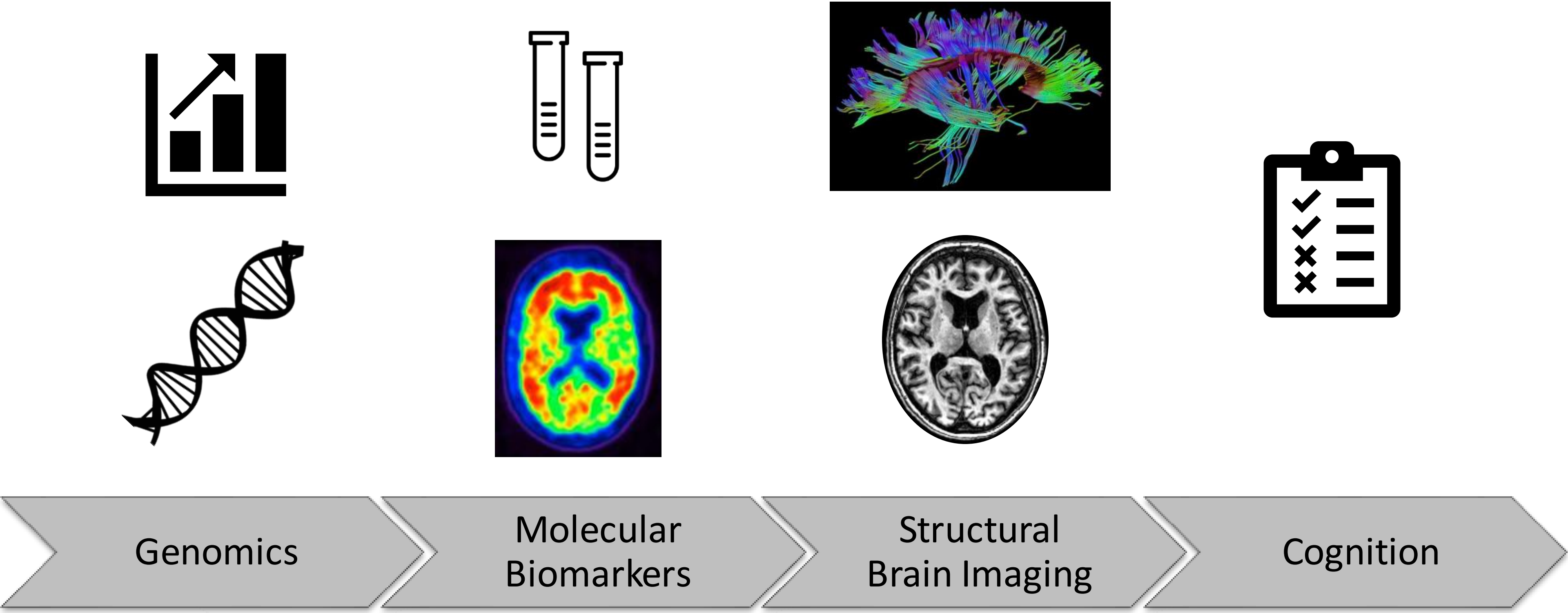
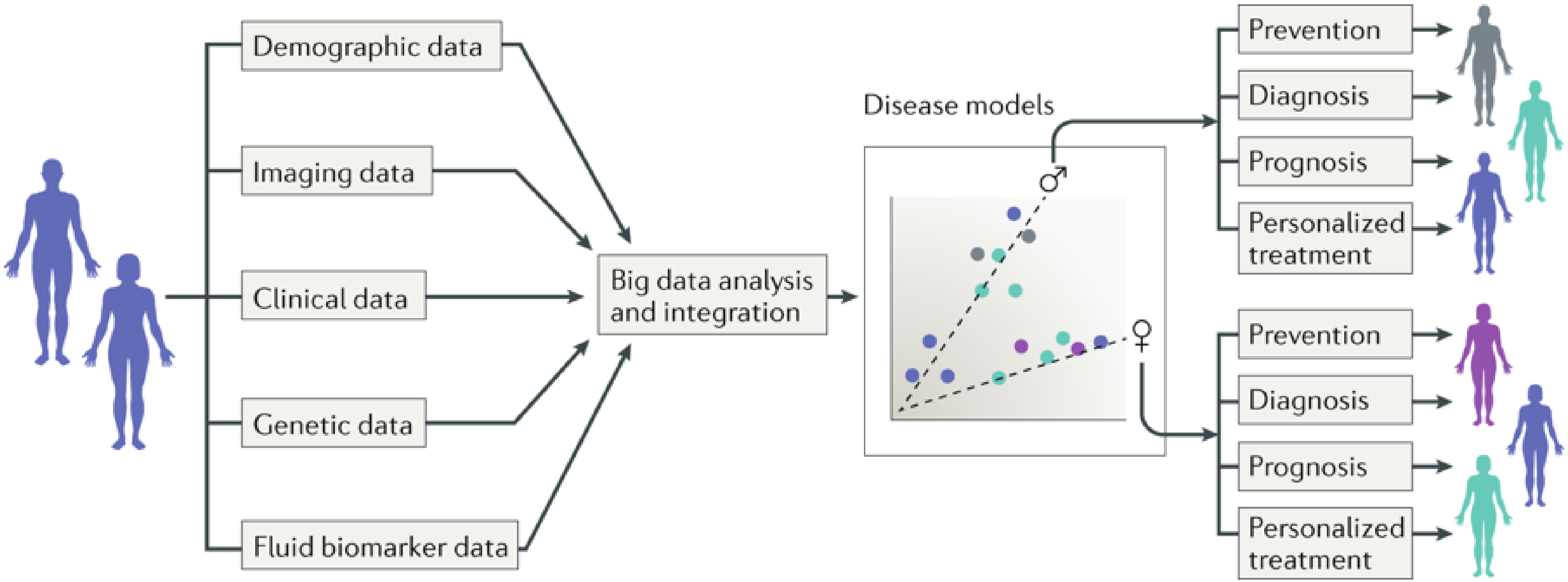
Disclosures

- Scientific Advisory Board for Vivid Genomics

Explosion of Big Data in Alzheimer's Disease

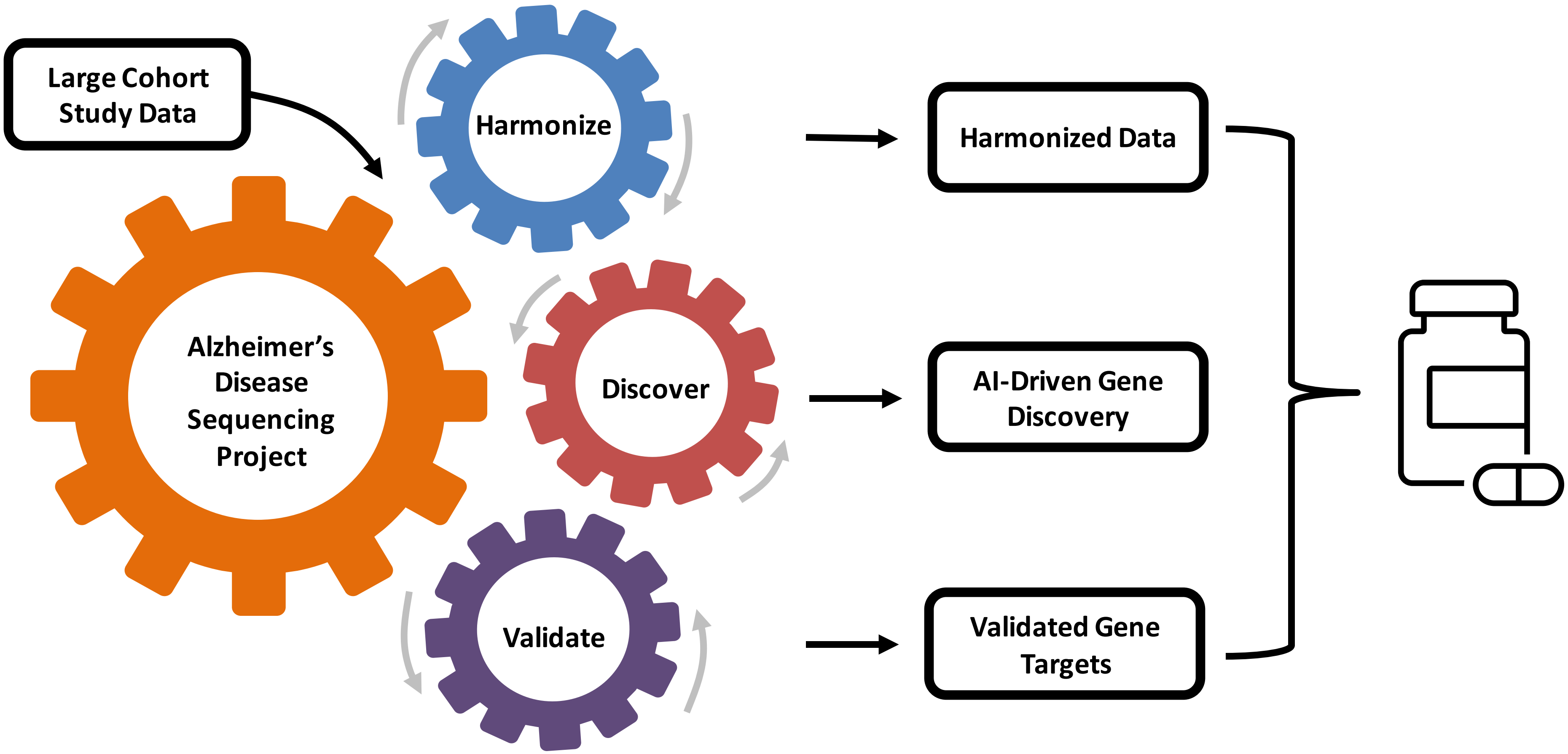


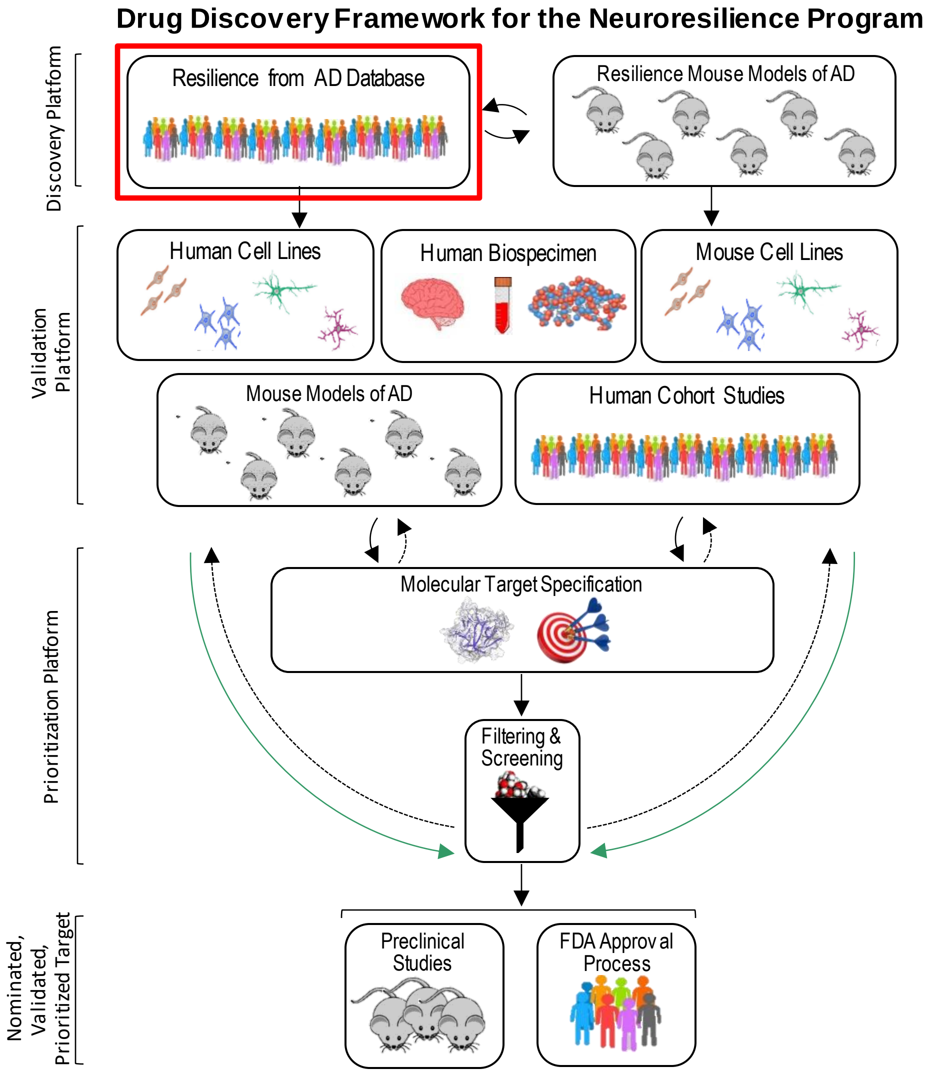
Precision Medicine in AD



Ferretti et al., Nature Reviews Neurology, 2018

Integrating AI into Genomic Discovery at NIA



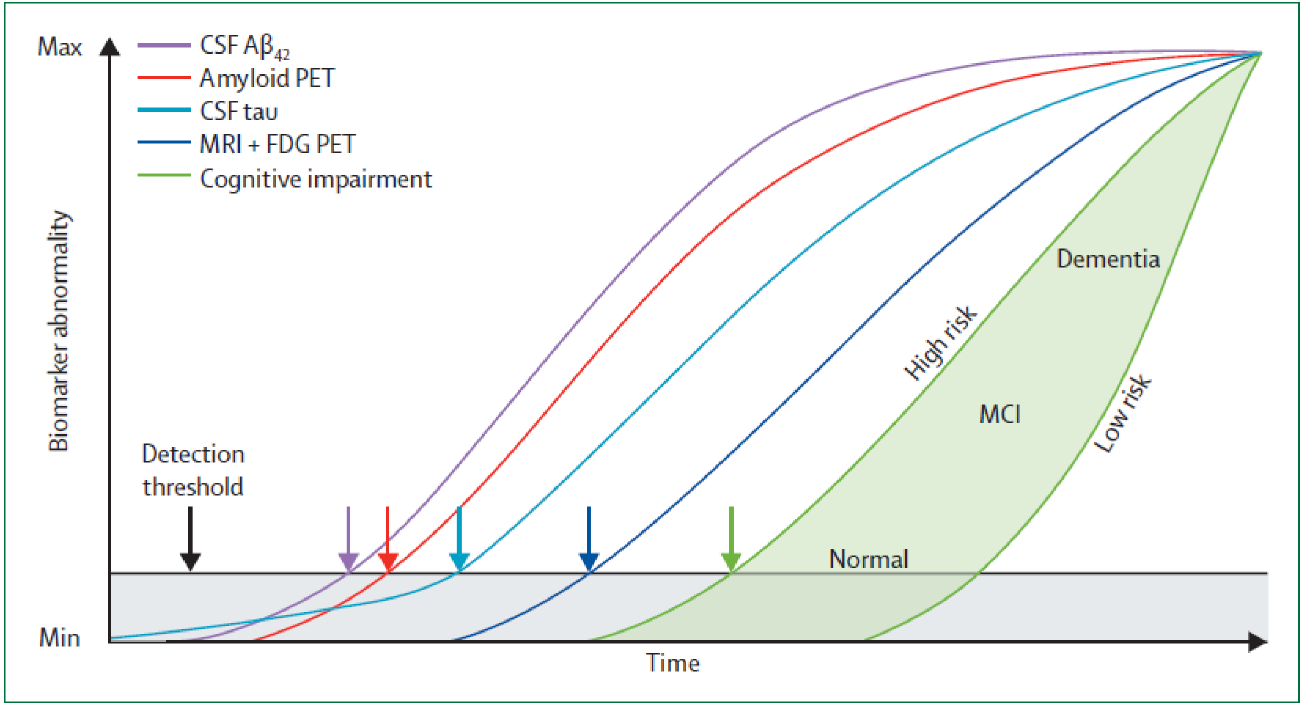


Drug Discovery Framework for the Neuroresilience Program
Discovery Platform
Resilience from AD Database
Resilience Mouse Models of AD
Validation Platform
Human Cell Lines
Human Biospecimen
Mouse Cell Lines
Mouse Models of AD
Human Cohort Studies
Prioritization Platform
Molecular Target Specification
Filtering & Screening
Nominated, Validated, Prioritized Target
Preclinical Studies
FDA Approval Process

Outline

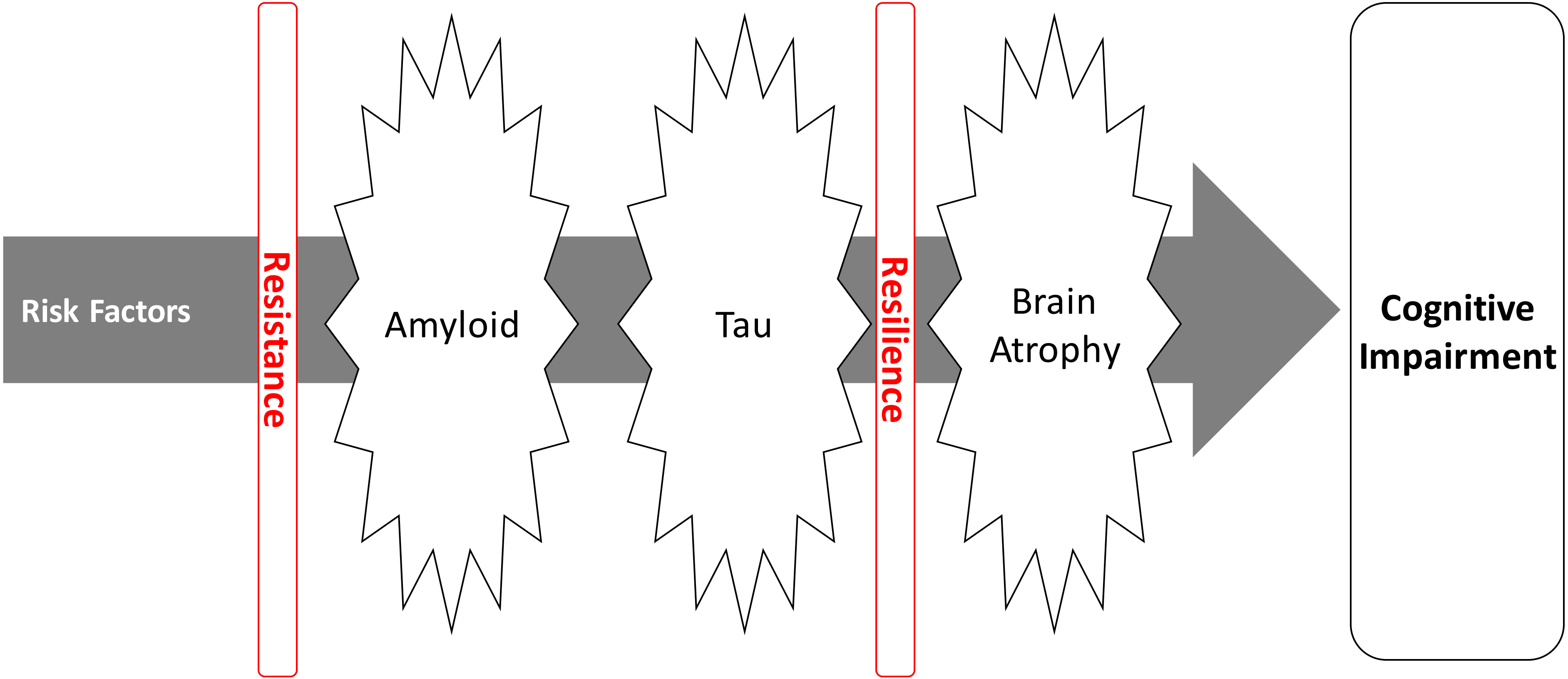
- Defining Resilience
- Genetic Drivers of Resilience
- Future Directions

Amyloid Cascade Hypothesis

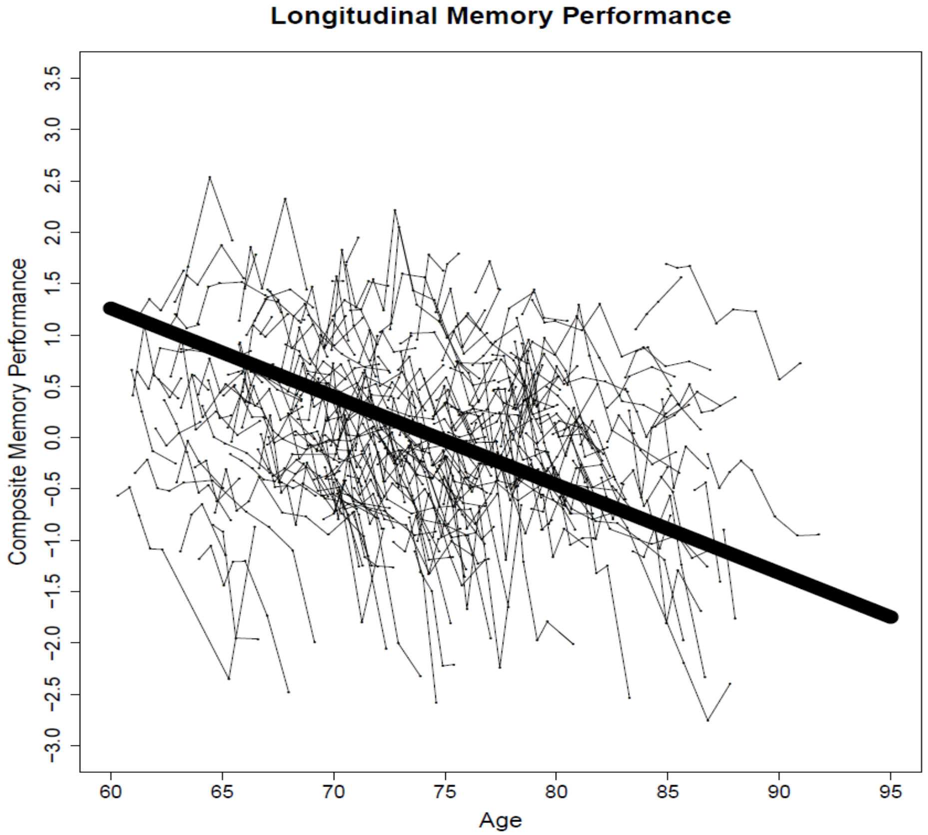


Jack et. al, Lancet Neurology, 2013

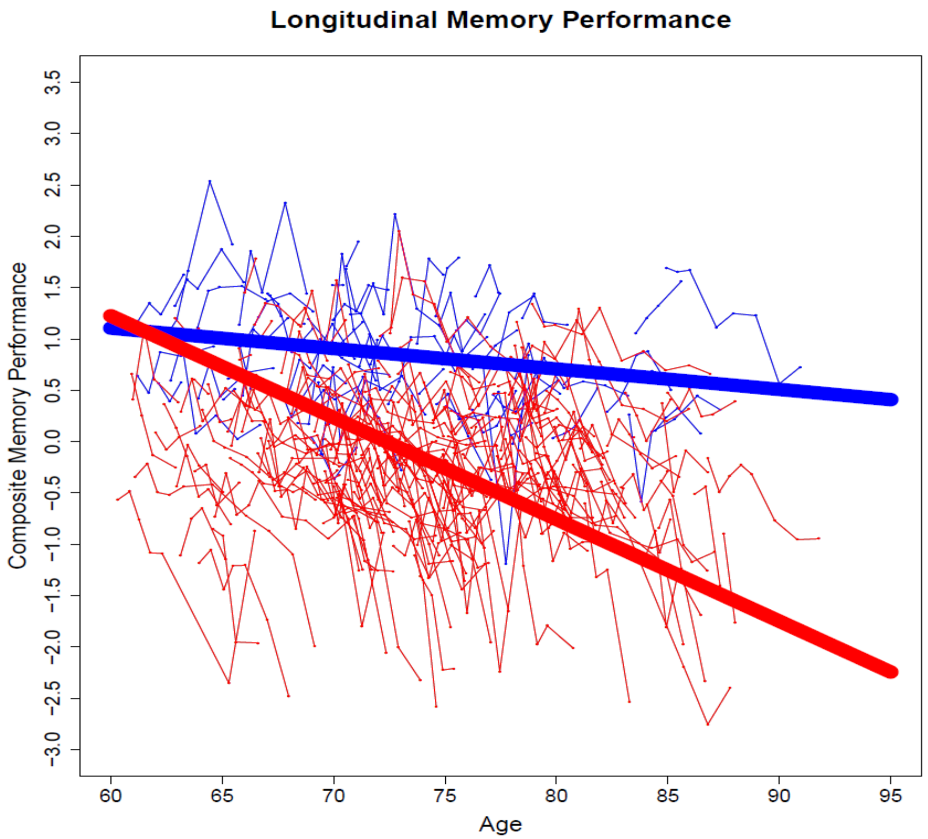
Resistance and Resilience



Heterogeneity in Cognitive Performance



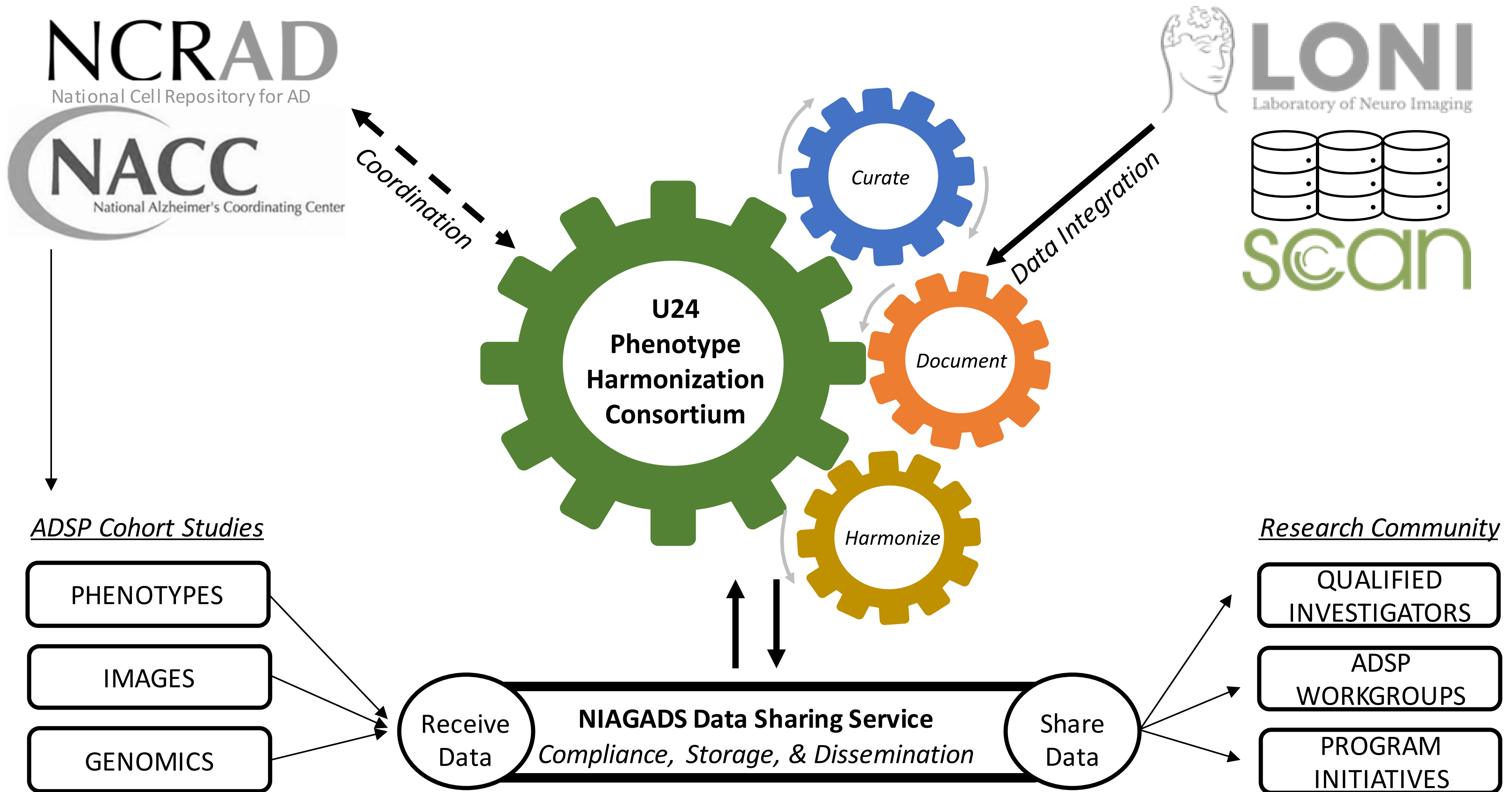
Resilience as a Pathway to New Targets



All Participants:

- Amyloid⁺
- Tau⁺
- *APOE ε4*⁺

Harmonizing Data to Increase Sample Size



NCRAD
National Cell Repository for AD
NACC
National Alzheimer's Coordinating Center
Coordination
LONI
Laboratory of Neuro Imaging
scan
Data Integration
Curate
U24
Phenotype
Harmonization
Consortium
Document
Harmonize
ADSP Cohort Studies
PHENOTYPES
IMAGES
GENOMICS
Research Community
QUALIFIED INVESTIGATORS
ADSP WORKGROUPS
PROGRAM INITIATIVES
Receive Data
NIAGADS Data Sharing Service
Compliance, Storage, & Dissemination
Share Data

Fluid Biomarker Harmonization

Carlos Cruchaga, PhD
Washington University

Coordinating Centers

Timothy Hohman, PhD
Vanderbilt University
Medical Center
MPI

Michael Cuccaro, PhD
University of Miami
MPI

Diffusion MRI Harmonization

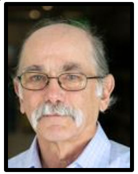
Bennett Landman, PhD
Vanderbilt University

Cognitive Harmonization

Paul Crane, MD, MPH
University of Washington

Jesse Mez, MD, MS
Boston University

Storage & Informatics



Arthur Toga, PhD
University of Southern California
MPI

CHARGE Coordination

Mohamad Habes, PhD
University of Texas Health
San Antonio

Structural MRI Harmonization

Shannon Risacher, PhD
Indiana University

Christos Davatzikos, PhD
University of
Pennsylvania

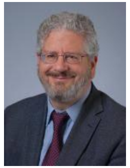
Vascular Harmonization

Adam Brickman, PhD
Columbia University

Richard Mayeux, MD, MSc
Columbia University

Integration & Analytics

Paul Thompson, PhD
University of Southern
California



Andrew Saykin, PsyD
Indiana University

Neuropathology Harmonization

Thomas Montine, MD, PhD
Stanford University

Gary Beecham, PhD
University of Miami

PET Harmonization

Elizabeth Mormino, PhD
Stanford University

Duygu Tosun, PhD
University of California
San Francisco

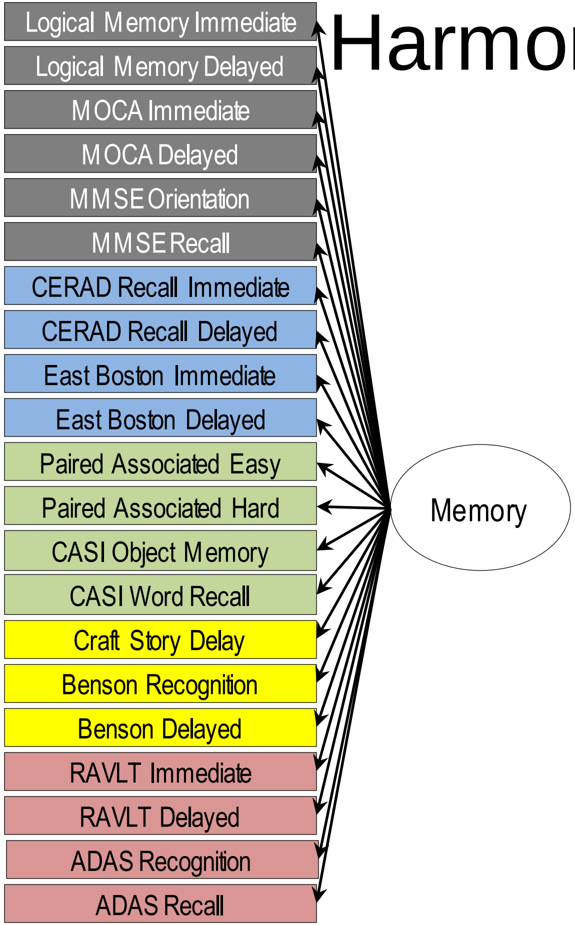
Example Domain: Cognition

	NACC	ACT	ADNI	ROSMAP & MARS	**TOTAL**
Total Cog N	41459	5546	3189*	4386	**54,580**
Total ADSP N	10486	1392	1574	1575	**15,027**
Total Cog & ADSP N	8458	1340	1574	1560	**12,932**

Paul Crane, MD, MPH
University of Washington

Harmonization Approach

Anchor Items
- Tests administered consistently across studies serve as anchor items



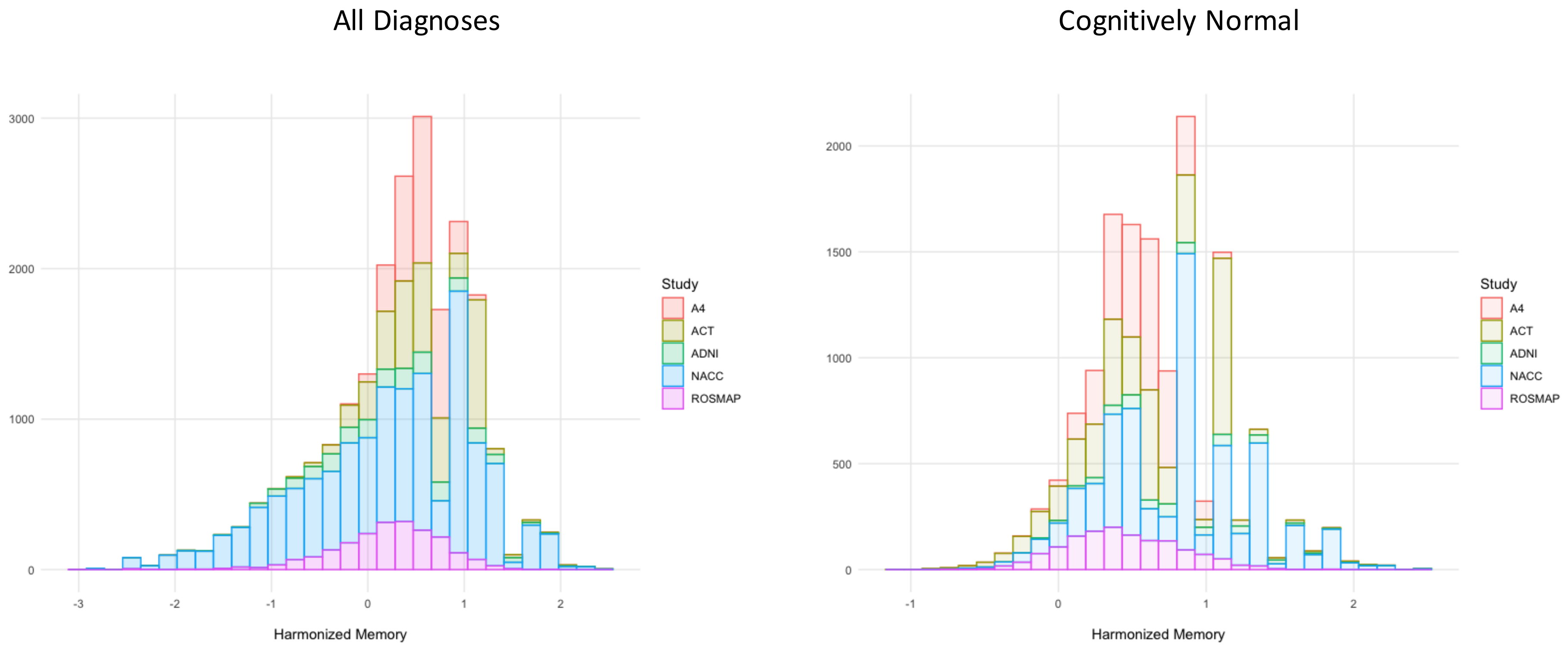
<u>Applied Psychometrics</u>

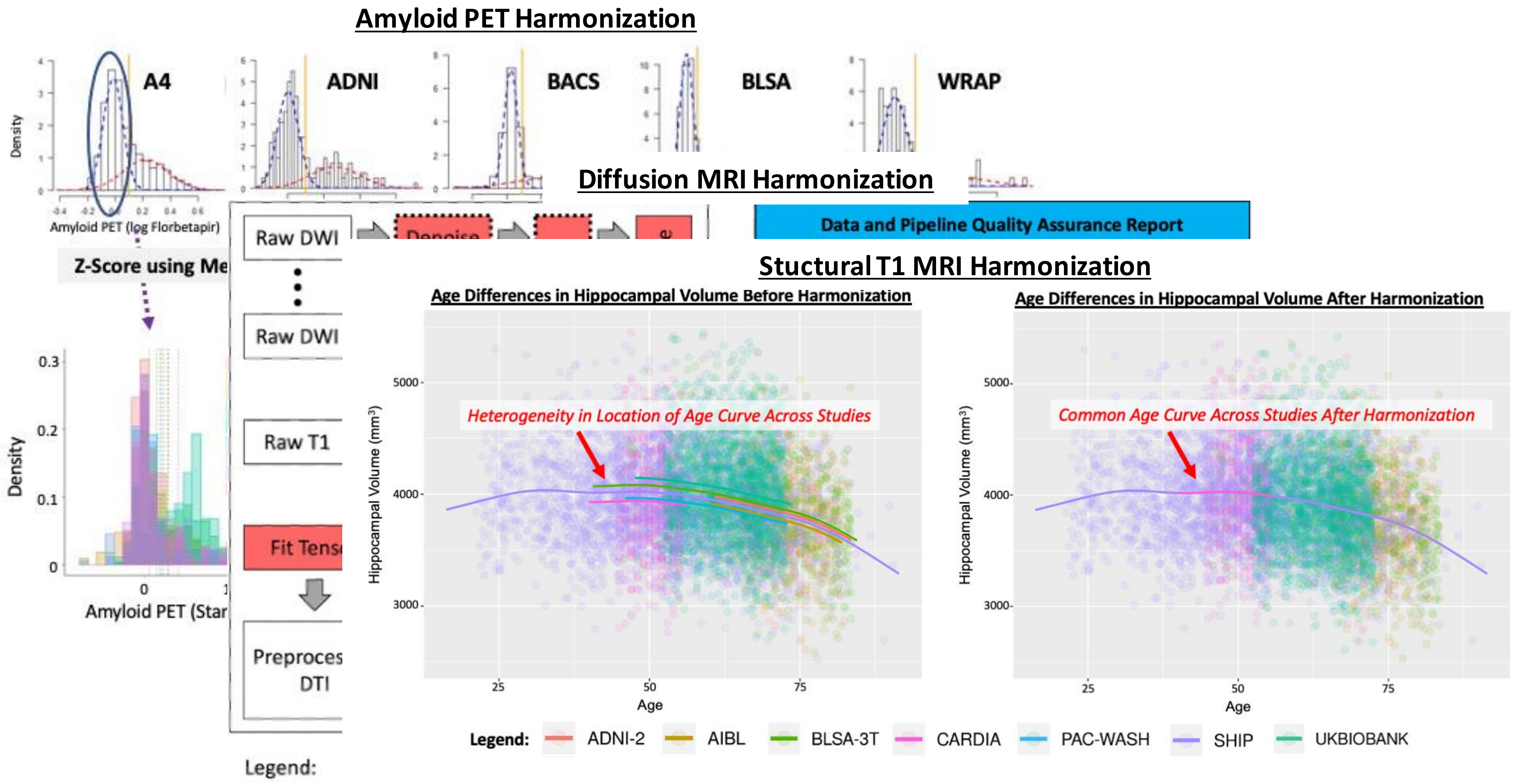
- An expert panel assigns items to one of 4 domains
  - Memory
  - Language
  - Executive functioning
  - Visuospatial ability

<u>LEGEND</u>

Anchor Items
ROS/MAP
ACT
NACC
ADNI

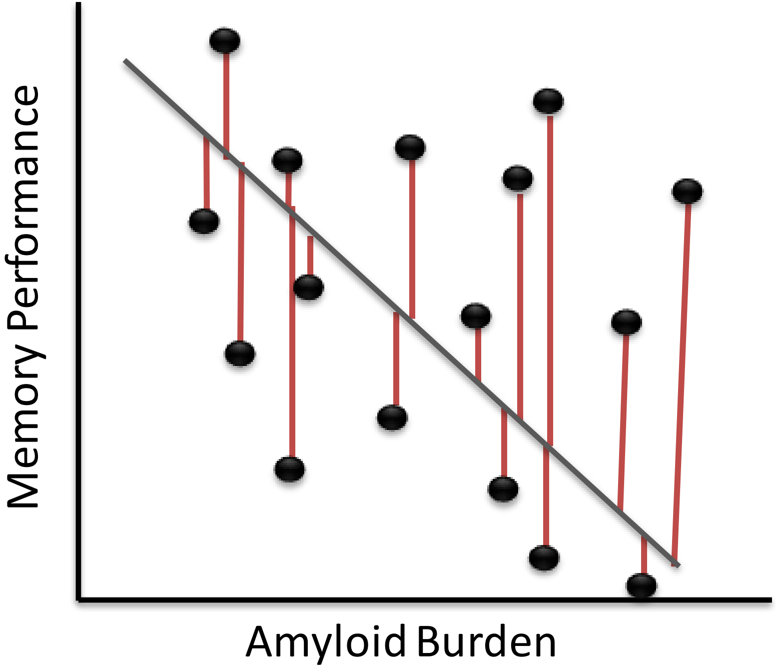
Harmonization Approach

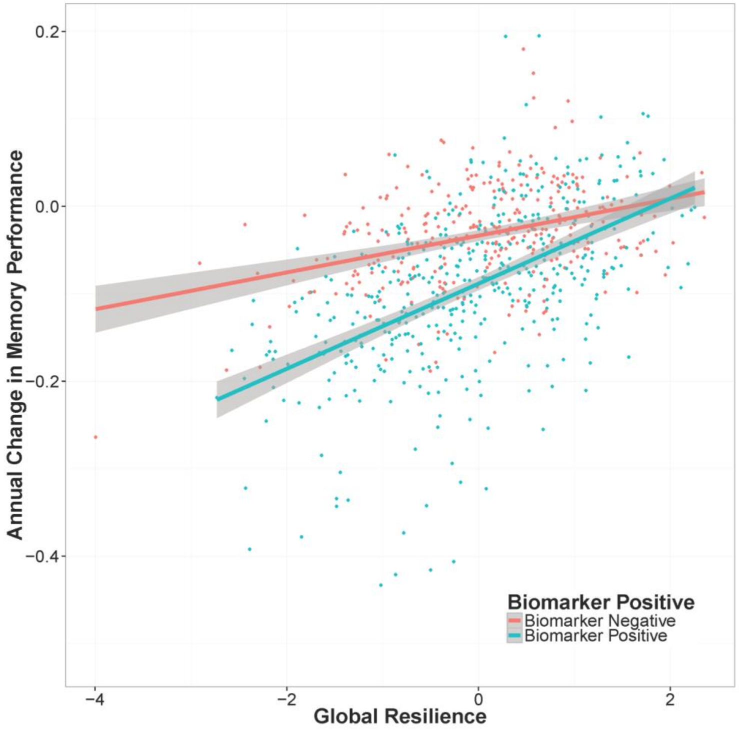




Amyloid PET Harmonization
A4
ADNI
BACS
BLSA
WRAP
Density
Amyloid PET (log Florbetapir)
Z-Score using Me
Density
Amyloid PET (Star
Diffusion MRI Harmonization
Raw DWI
Denoise
Raw DWI
Raw T1
Fit Tens
Preproces
DTI
Legend:
Data and Pipeline Quality Assurance Report
Stuctural T1 MRI Harmonization
Age Differences in Hippocampal Volume Before Harmonization
Heterogeneity in Location of Age Curve Across Studies
Hippocampal Volume (mm³)
Age
Age Differences in Hippocampal Volume After Harmonization
Common Age Curve Across Studies After Harmonization
Hippocampal Volume (mm³)
Age
Legend: ADNI-2 AIBL BLSA-3T CARDIA PAC-WASH SHIP UKBIOBANK

Data Integration to Define Resilience



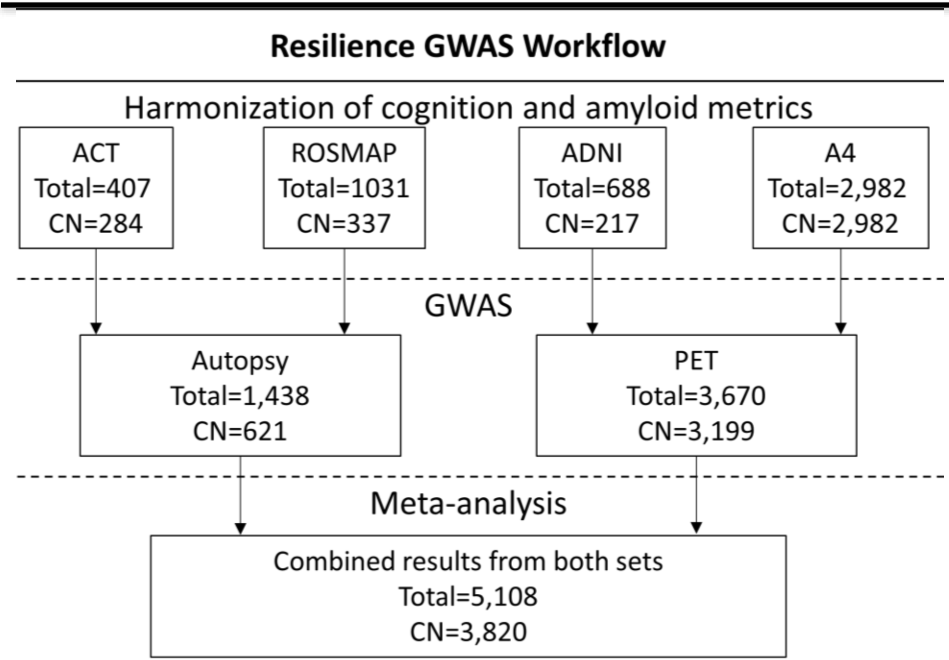


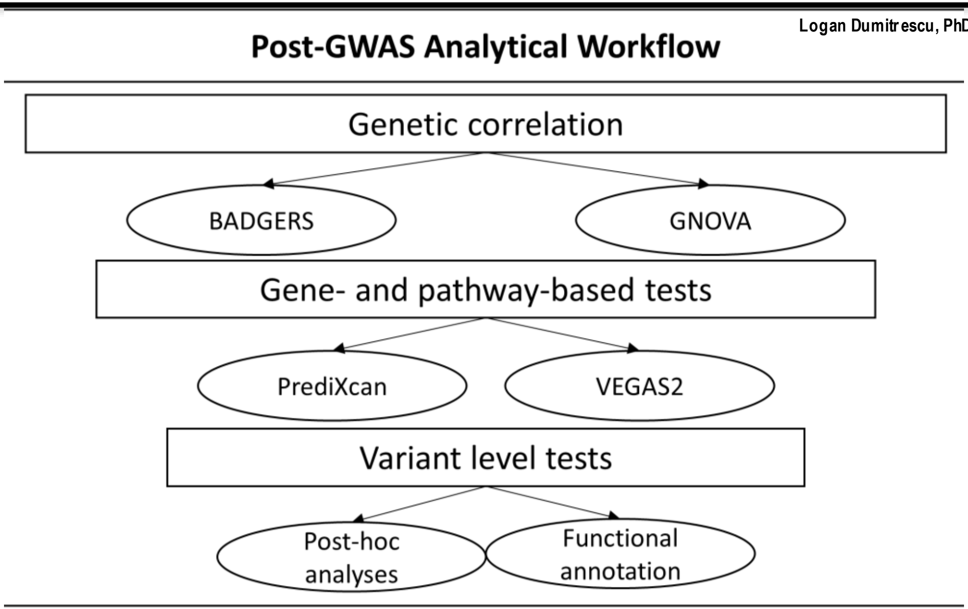
Dumitrescu et al., *Brain, 2020*

Genetic Architecture of Resilience

Analytical Plan

Logan Dumitrescu, PhD



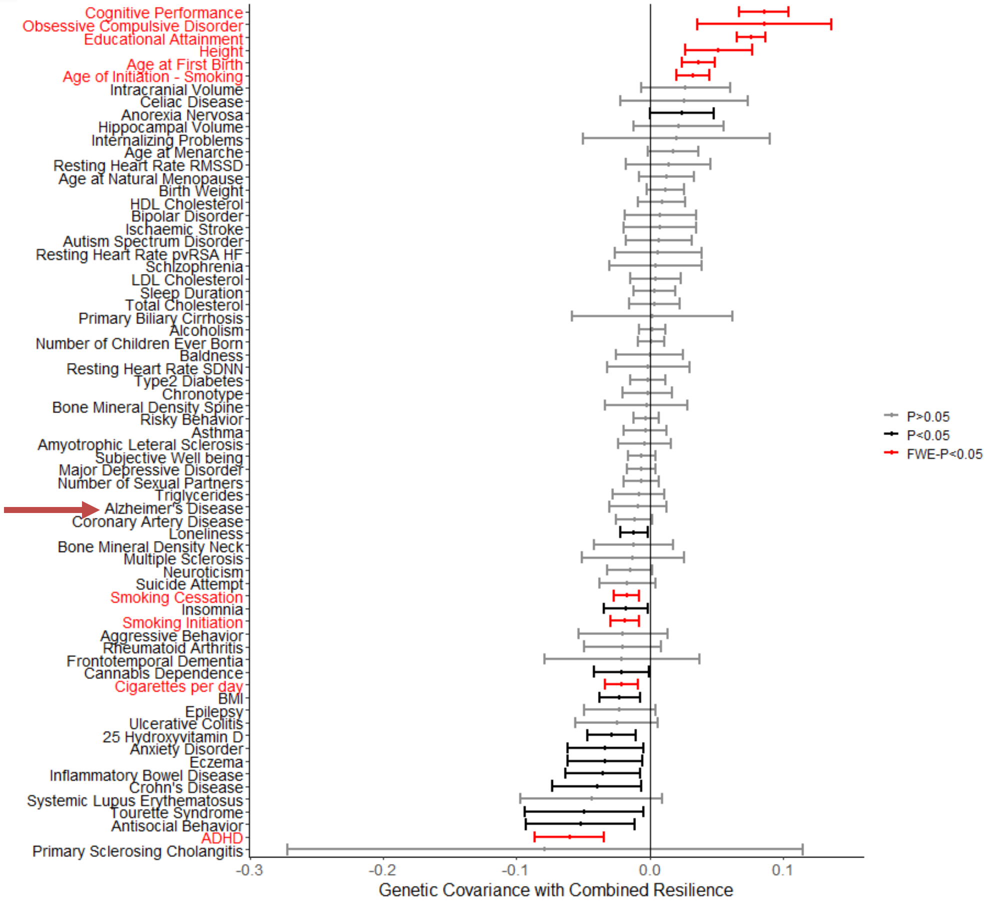


Stratified Analyses:

- ***APOE-ε4***
- **Cognitively Normal**

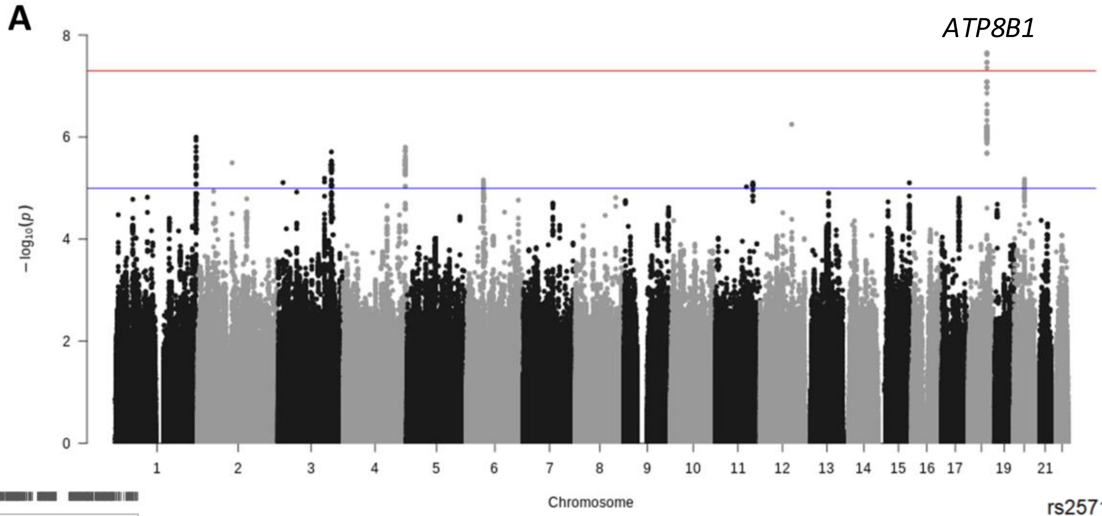
Dumitrescu et al., *Brain, 2020*

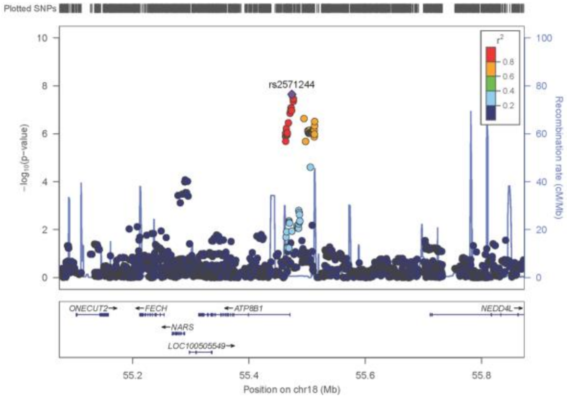
Genetic Correlation and Pathway Results



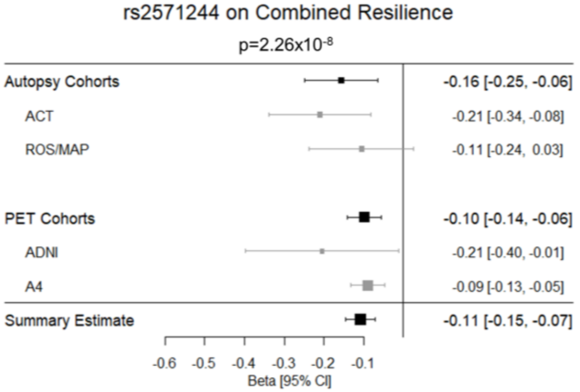
Dumitrescu et al., *Brain, 2020*

Cognitively Normal Resilience Results





SNP	MAF	β	SE	*p-value*
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**

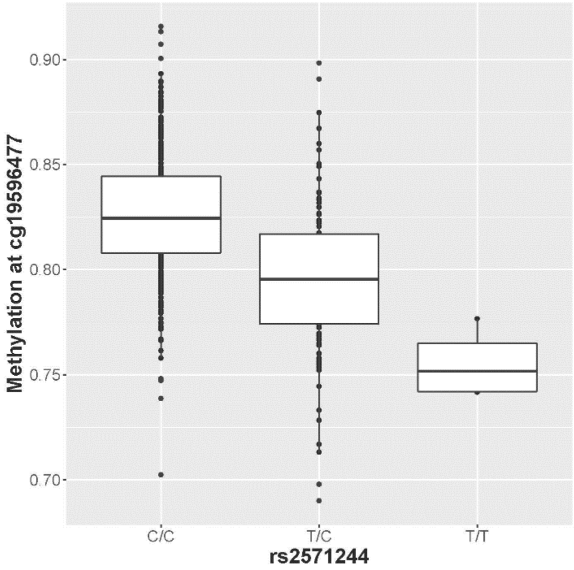


Dumitrescu et al., *Brain, 2020*

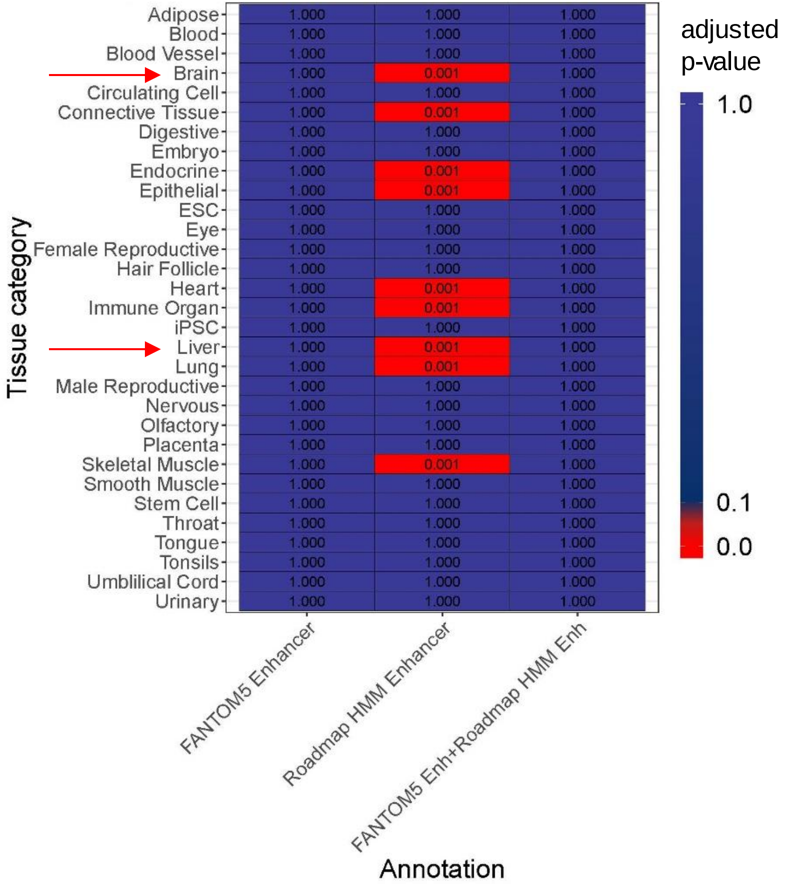
Gene Mapping and Functional Annotation

Methylation targets for rs2571244 (18:55473651)

target	target start position	Spearman's ρ	P
cg19596477	18:55472454	0.33	2.24×10^{-13}
cg16310513	18:55471075	0.17	1.79×10^{-4}
cg16141316	18:55469758	-0.12	8.14×10^{-3}



Prefrontal Cortex Methylation



Dumitrescu et al., *Brain, 2020*

ATP8B1 Function and Posthoc Analyses

- ATPase phospholipid transporting 8B1
  - Codes an aminophospholid translocase protein
  - Operates in the Liver to maintain **bile acid homeostasis**

	SNP Association with Bile Acids		
Bile Acid	β	DF	*P*
TCA	0.40	1019	**0.01**
GLCA	0.33	1019	**0.02**
GCA	0.31	1019	**0.02**
TDCA	0.33	1019	**0.04**
TCDCA	0.30	1019	**0.04**

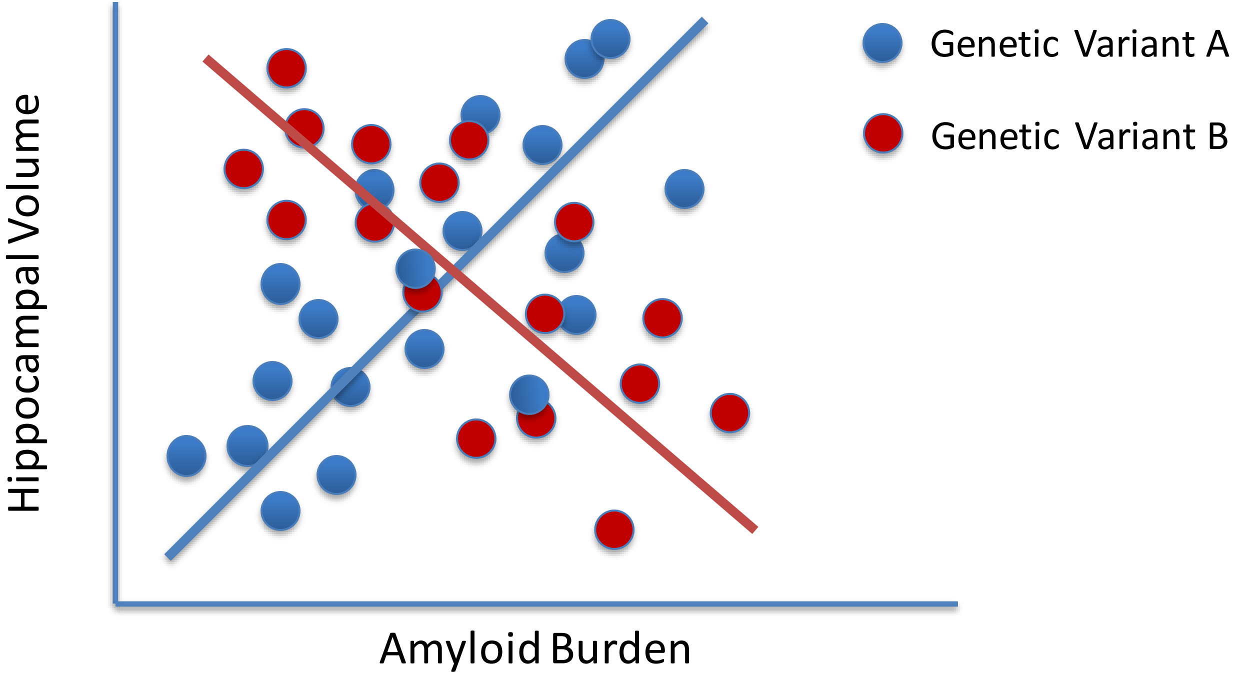
- Exome sequencing identified risk variants in *ATP8B4* (Holstege, 2020)

Summary of Genetic Resilience

- **Genetic architecture of resilience is distinct from clinical AD**
  - Small contribution of *APOE*
- Observed a shared architecture with <u>cognition</u> and <u>education</u>
- Modest genetic correlation with <u>vascular</u> and <u>psychiatric</u> phenotypes
- *ATP8B1* is a novel resilience gene along the <u>bile acid metabolism</u> and phospholipid transport pathway

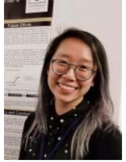
Gene Modifiers of Neuropathology

Data Integration to Identify Gene Modifiers



Adapted from Annah Moore, Ph.D.

Study Design



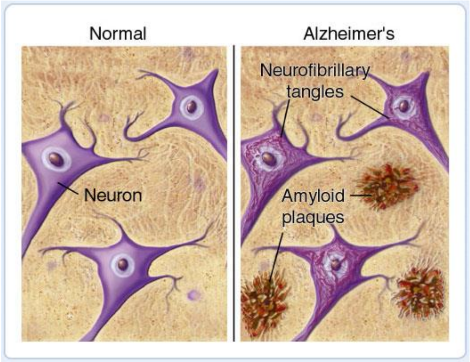
Mabel Seto, PhD

- Identify genetic variants that confer neuroprotection from AD

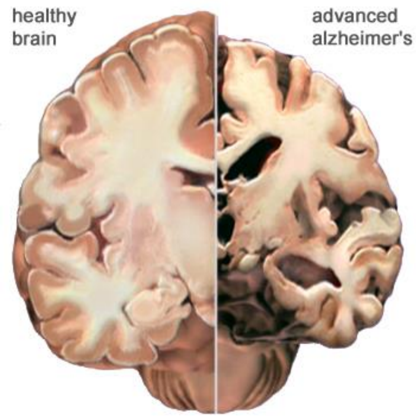
Genetic Variation

Enhance

Diminish



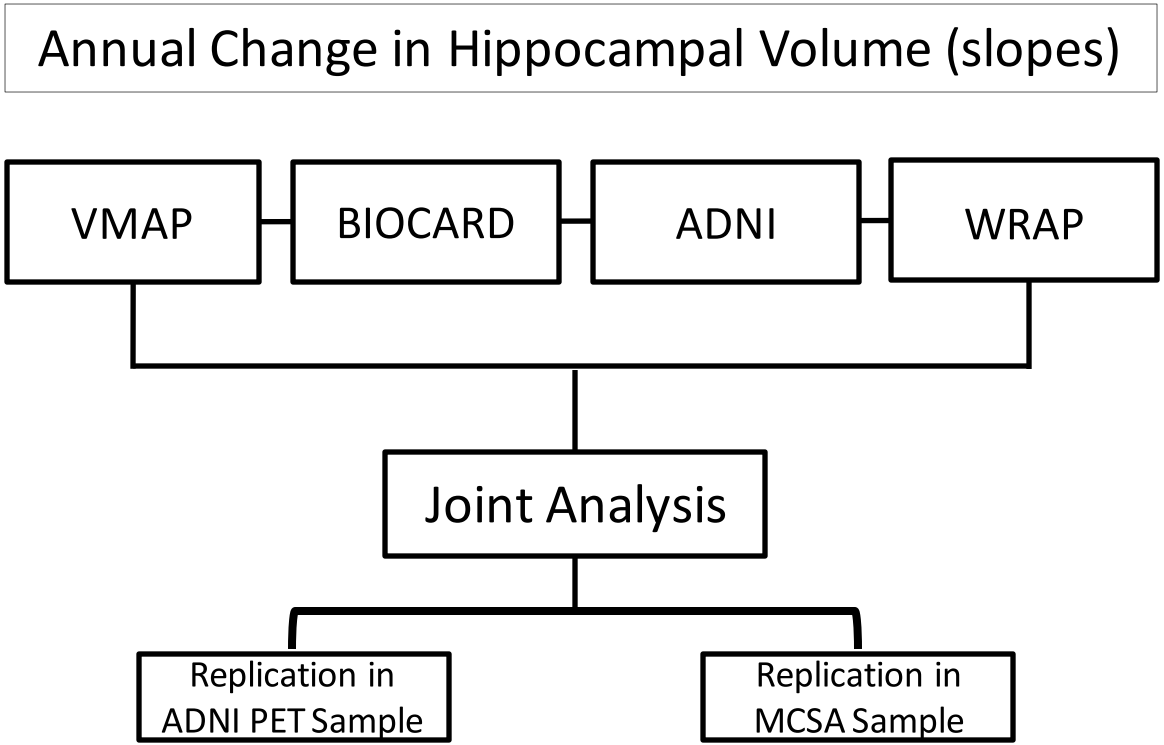
Neuropathology



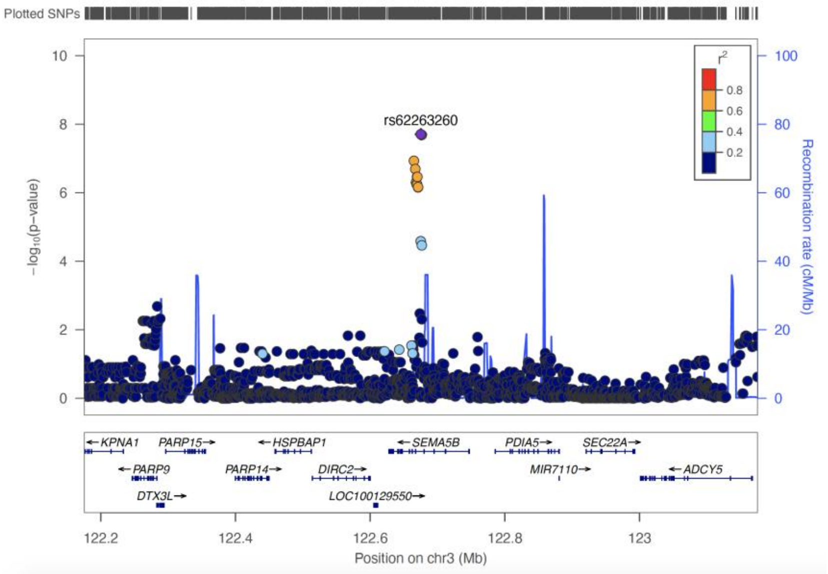
Neurodegeneration

Genome Wide Association Study

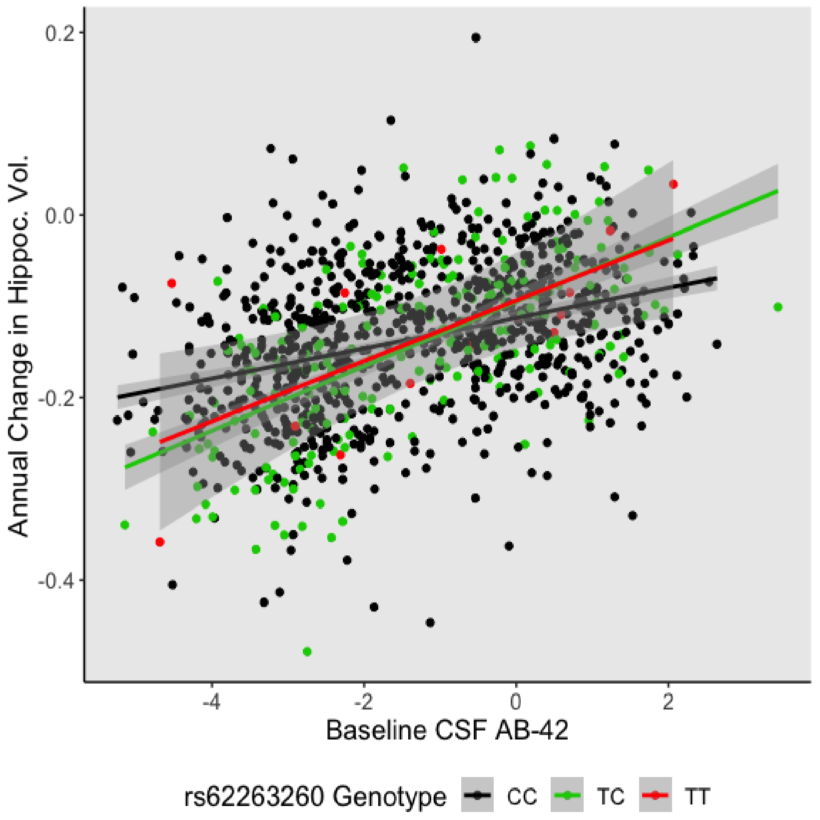
Study Design



Results



Discovery: β = 0.01; p = 1e-8

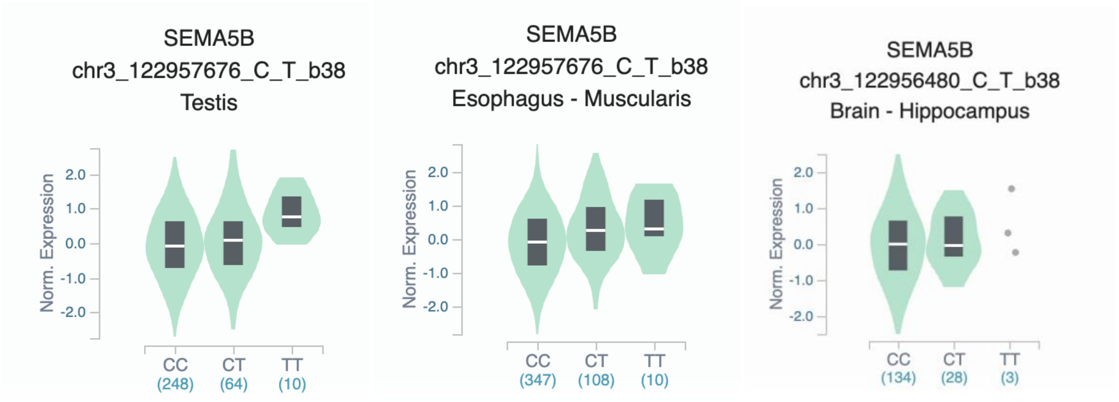


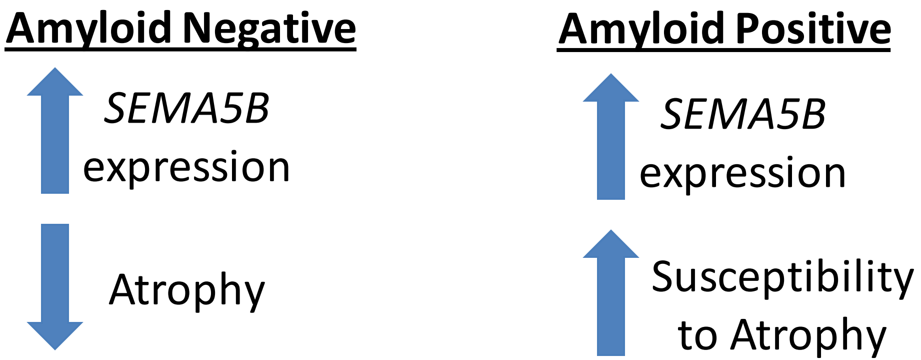
ADNI PET Replication:
β = -0.005; p = 0.004

MCSA Replication:
β = -0.24, p = 0.0112

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)





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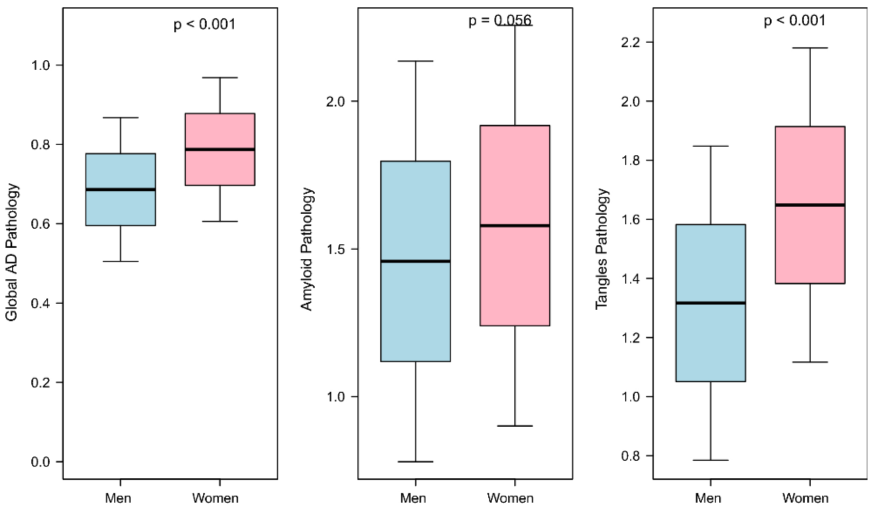
  - Small contribution of *APOE*
- Observed a shared architecture with <u>cognition</u> and <u>education</u>
- Modest genetic correlation with <u>vascular</u> and <u>psychiatric</u> phenotypes
- *ATP8B1* is a novel resilience gene along the <u>bile acid metabolism</u> and phospholipid transport pathway
- *SEMA5B* is a novel susceptibility gene that may be <u>beneficial</u> in absence of amyloid, but <u>detrimental</u> with onset of pathology

Incorporating Sex and Gender into Resilience Models

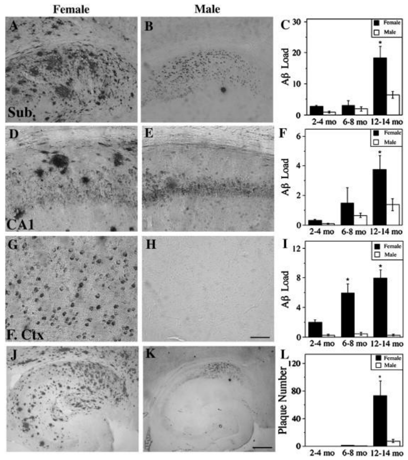
Females Have More AD Pathology at Autopsy

Neuropathology at Autopsy



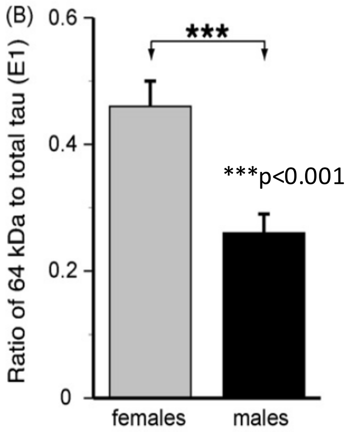
Oveisgharan et al., Acta Neuropathologica, 2018

APP Transgenic Mice



Carroll et al., Brain Research, 2010

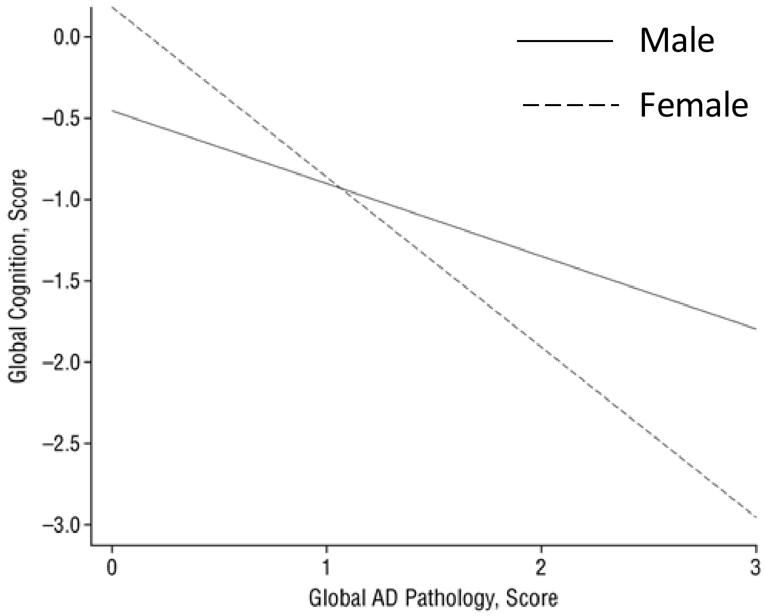
Tau Transgenic Mice



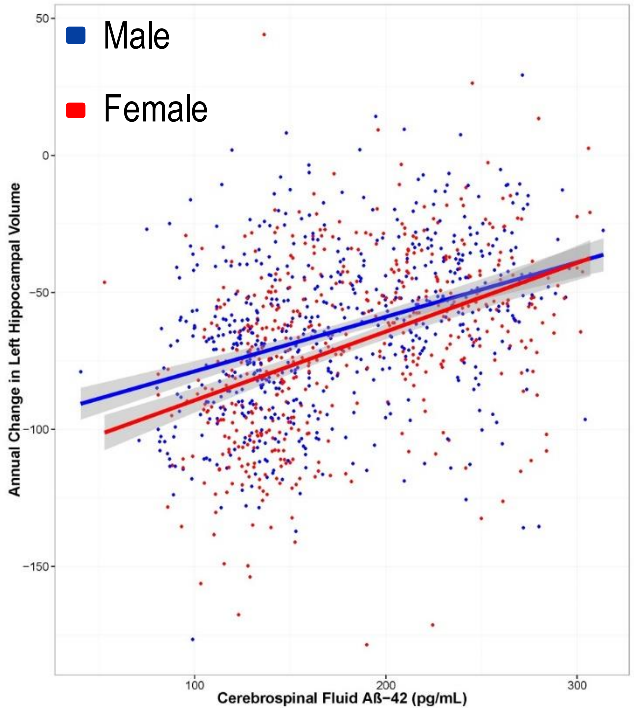
Yue et al., Neurobiology of Aging, 2011

Females with Pathology Decline More Rapidly

Neuropathology Association with Cognition



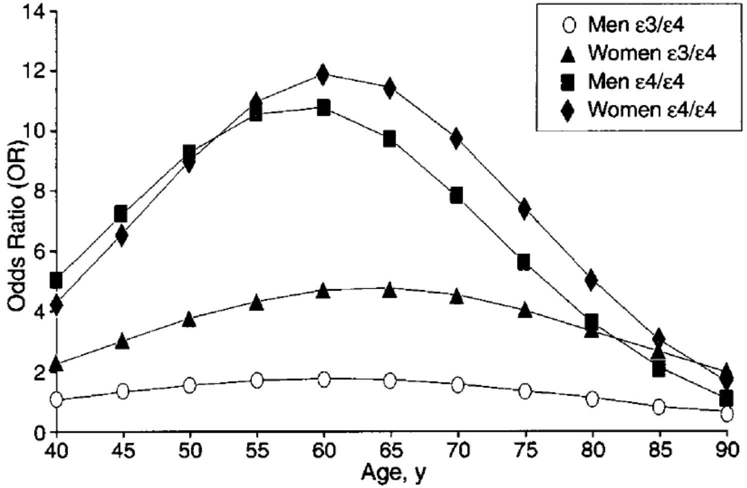
CSF Biomarker Association with Atrophy



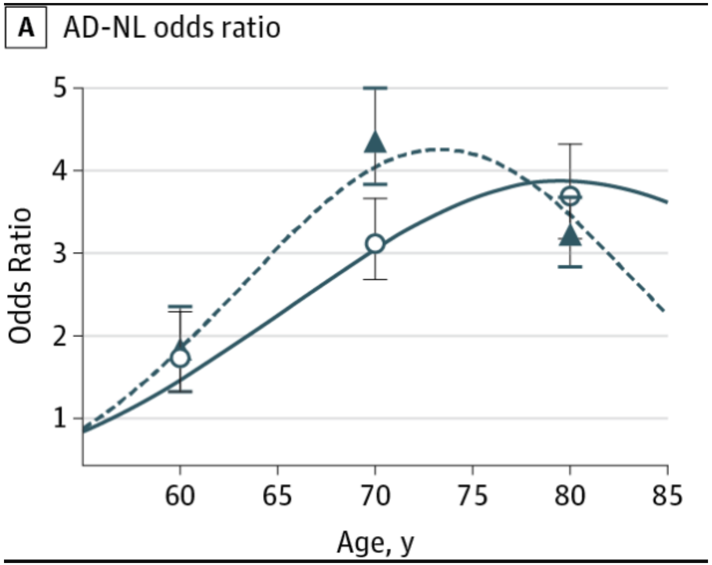
Barnes et al., Archives of General Psychology 2005

Koran, Wagener, & Hohman, Brain Imaging and Behavior, 2016

APOE Association with AD is Stronger in Females

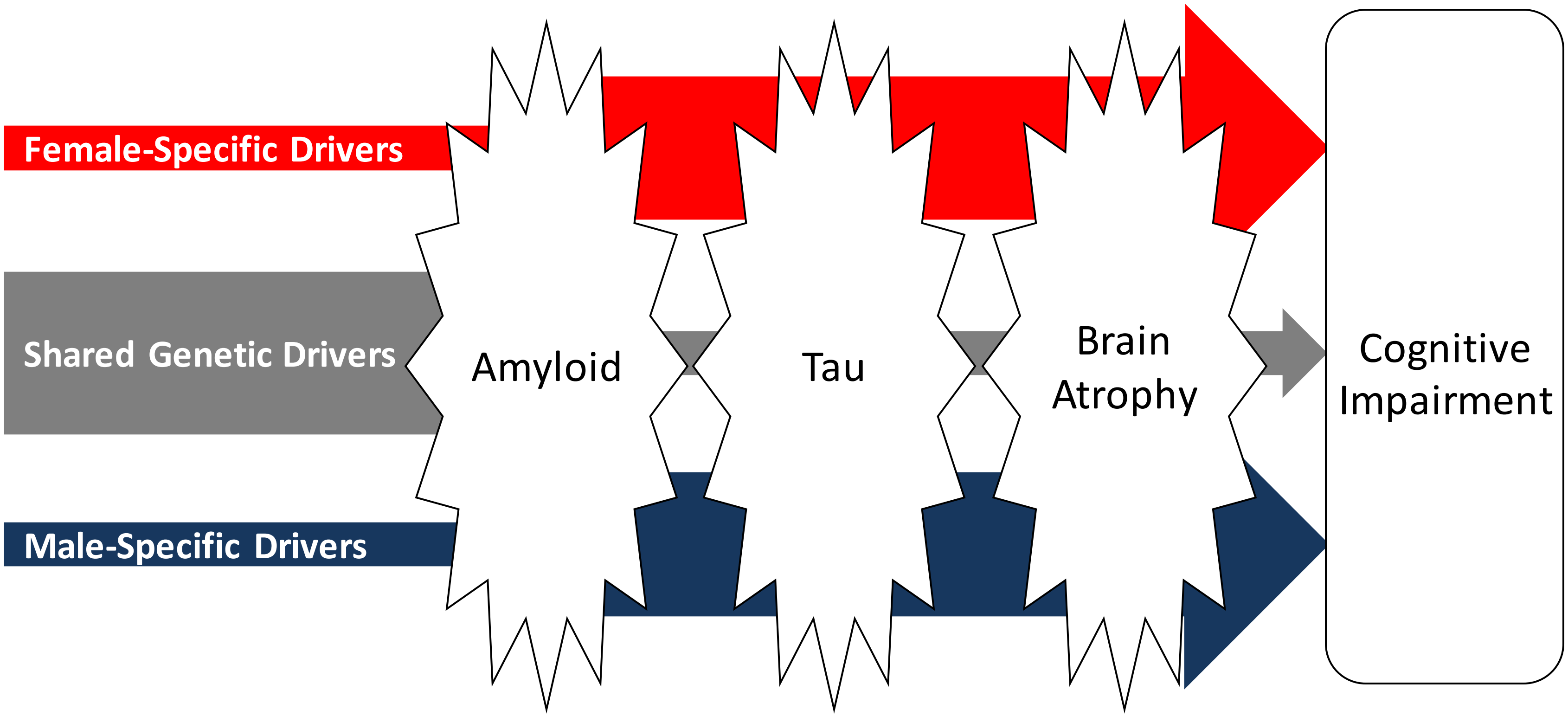


Farrer et al., JAMA Neurology, 1997



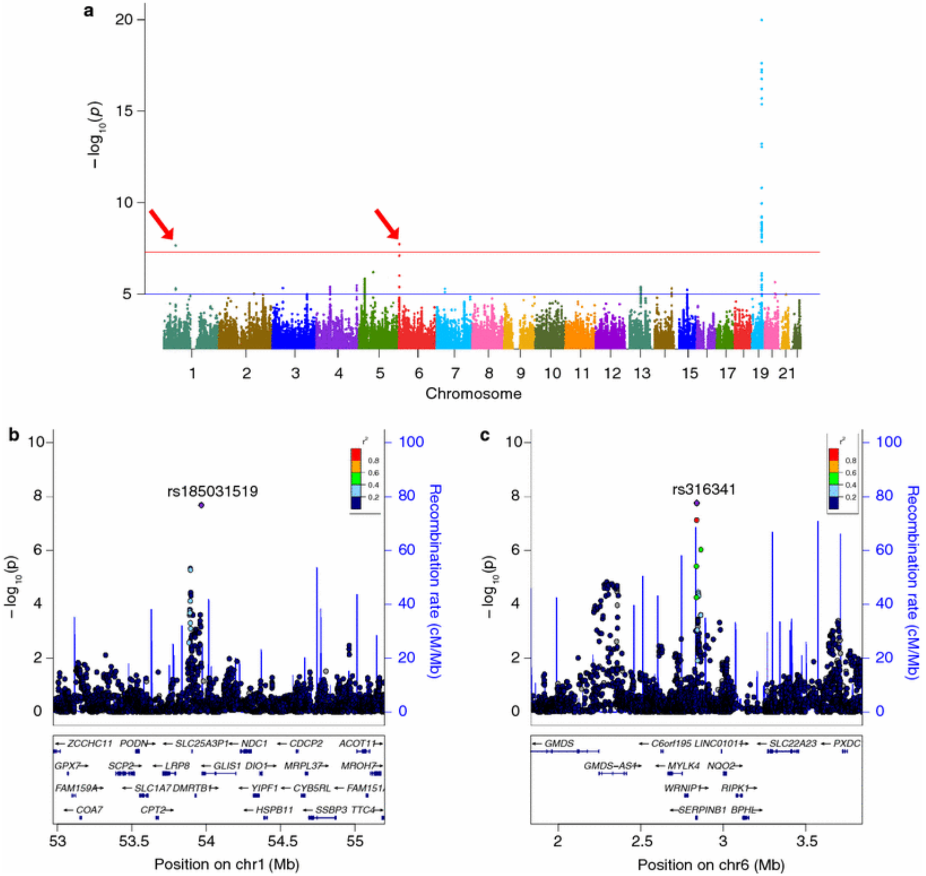
Neu et al., JAMA Neurology, 2017

Summary of Sex Differences



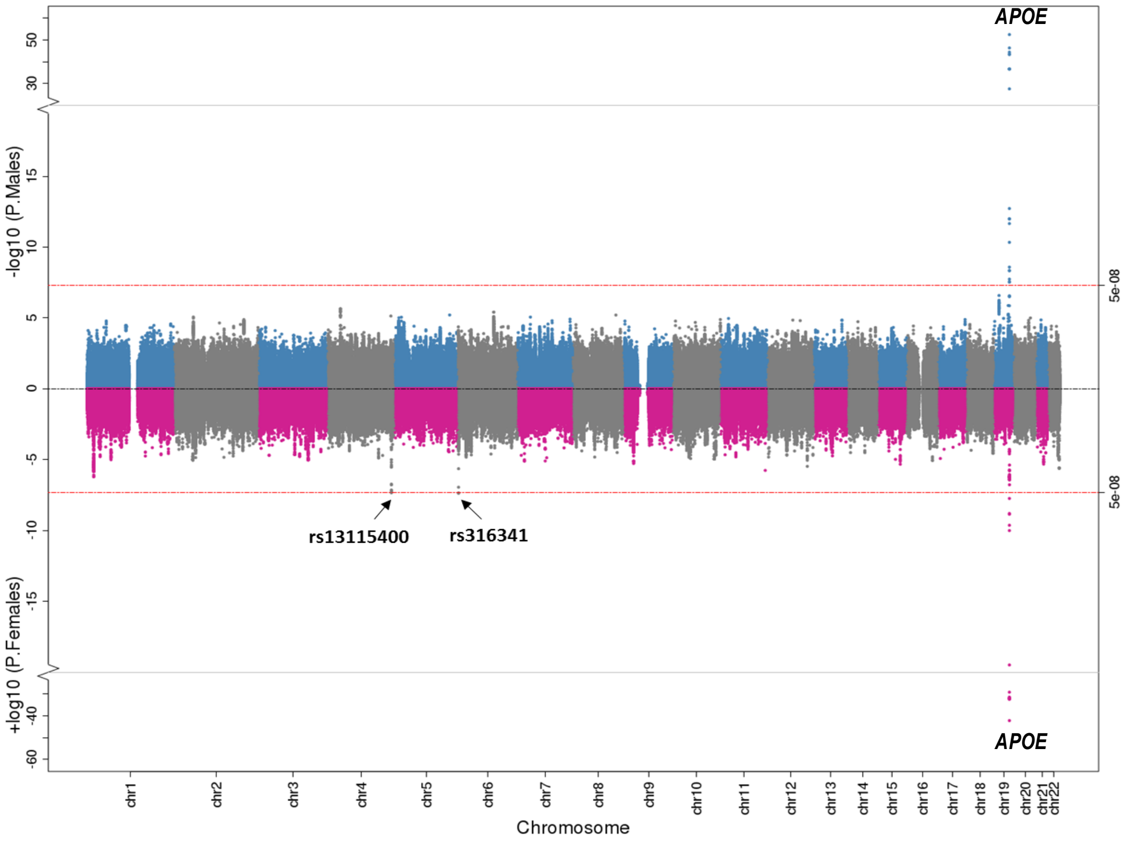
Leveraging Genome-Wide Data to Explore Sex Differences in AD

GWAS of CSF Aβ-42



Deming et al., Acta Neuropathologica, 2017

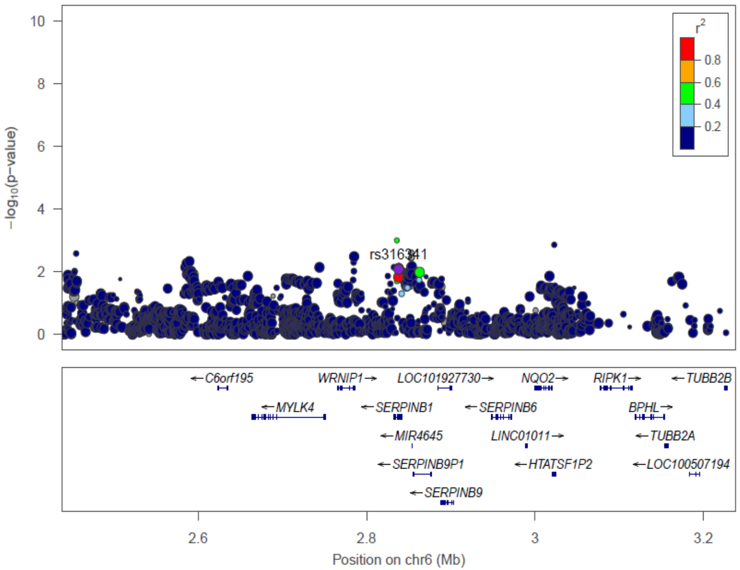
GWAS of CSF Aβ-42



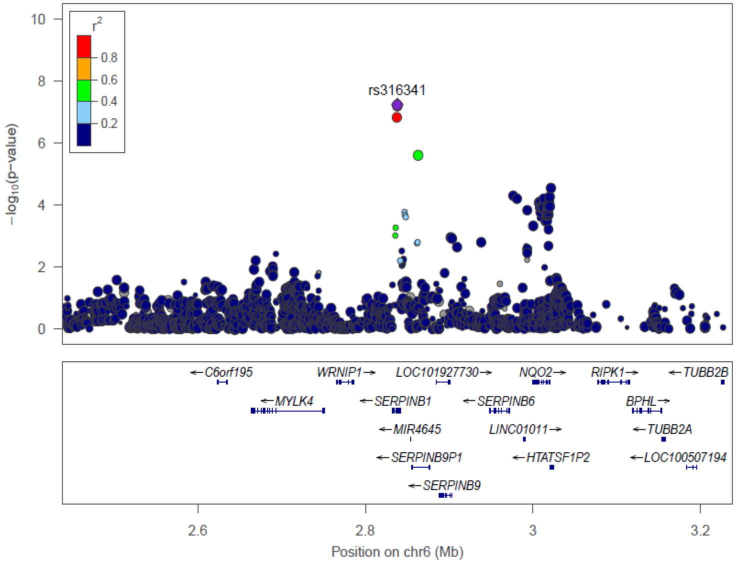
Deming, … Hohman, Acta Neuropathologica, 2018

Locus Zoom

Male



Female

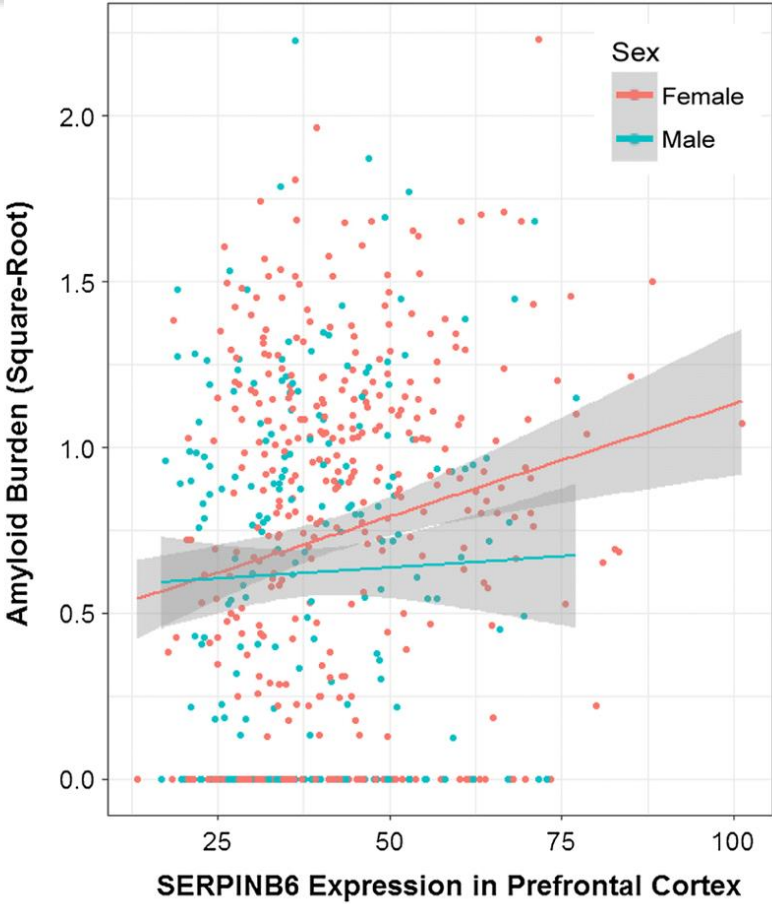


rs316341 is eQTL for SERPINB1, SERPINB6, and SERPINB9 in Braineac and GTex

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

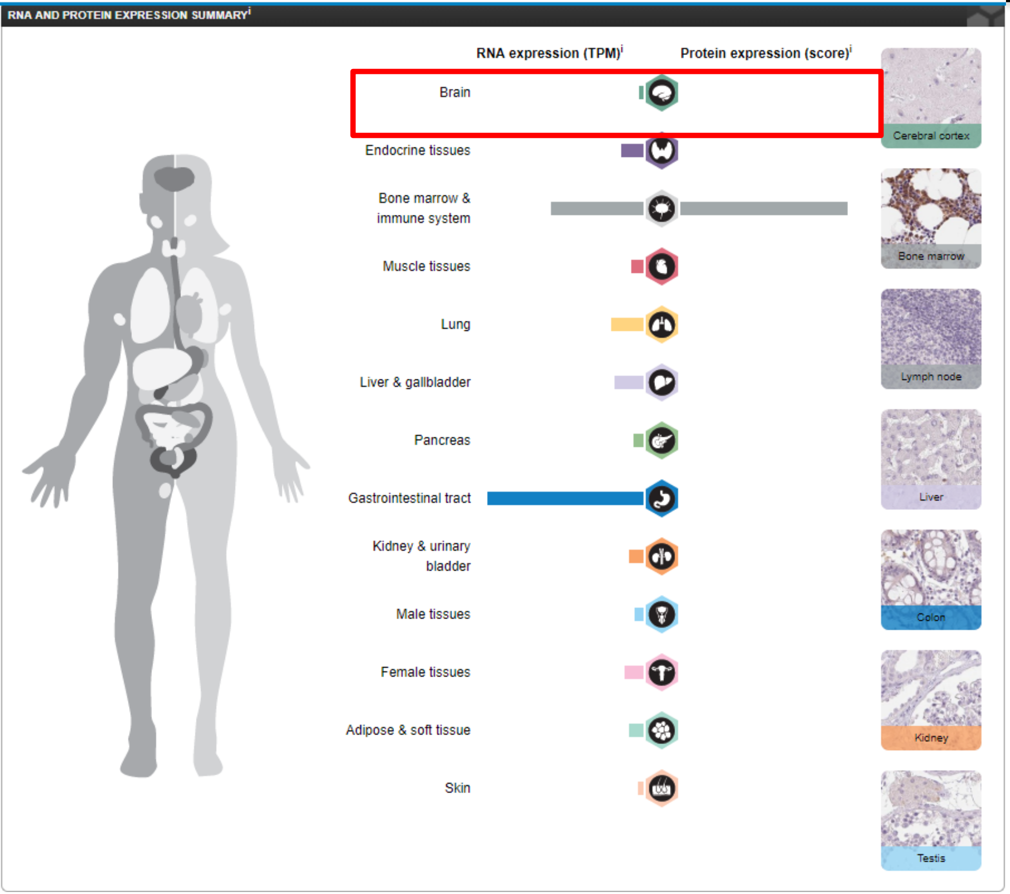


Deming, … Hohman, Acta Neuropathologica, 2018

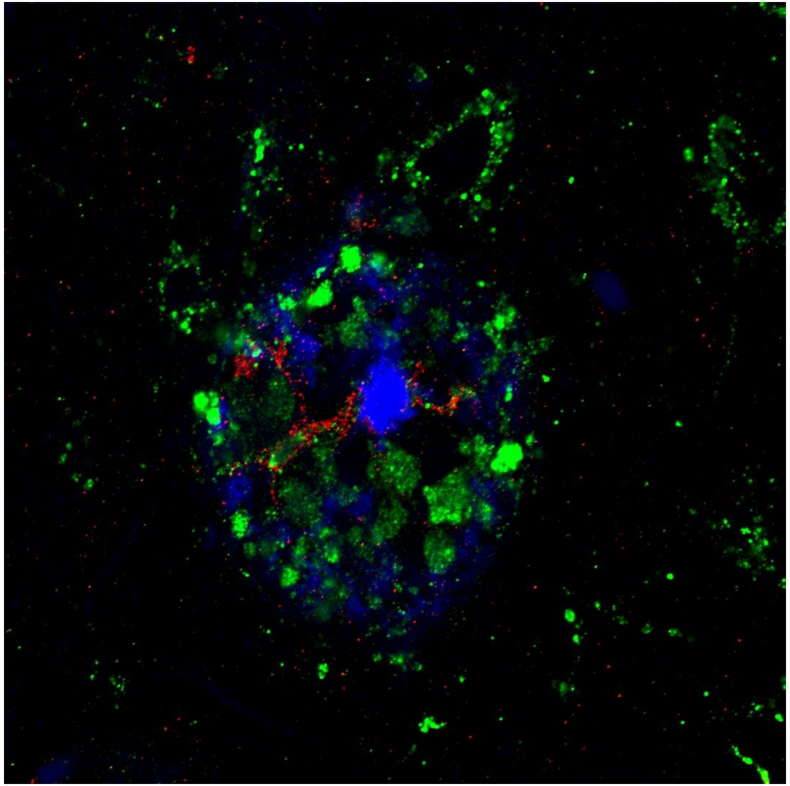
Serpin Signaling and Amyloidosis

- Serpins are Protease Inhibitors
  - Serpin-B1 Regulates Neutrophil Infiltration
- Serpins have been shown to inhibit Aβ toxicity *Schubert, 1997*
  - Likely through regulation of neutrophils *Zenaro et al., 2015*
- 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

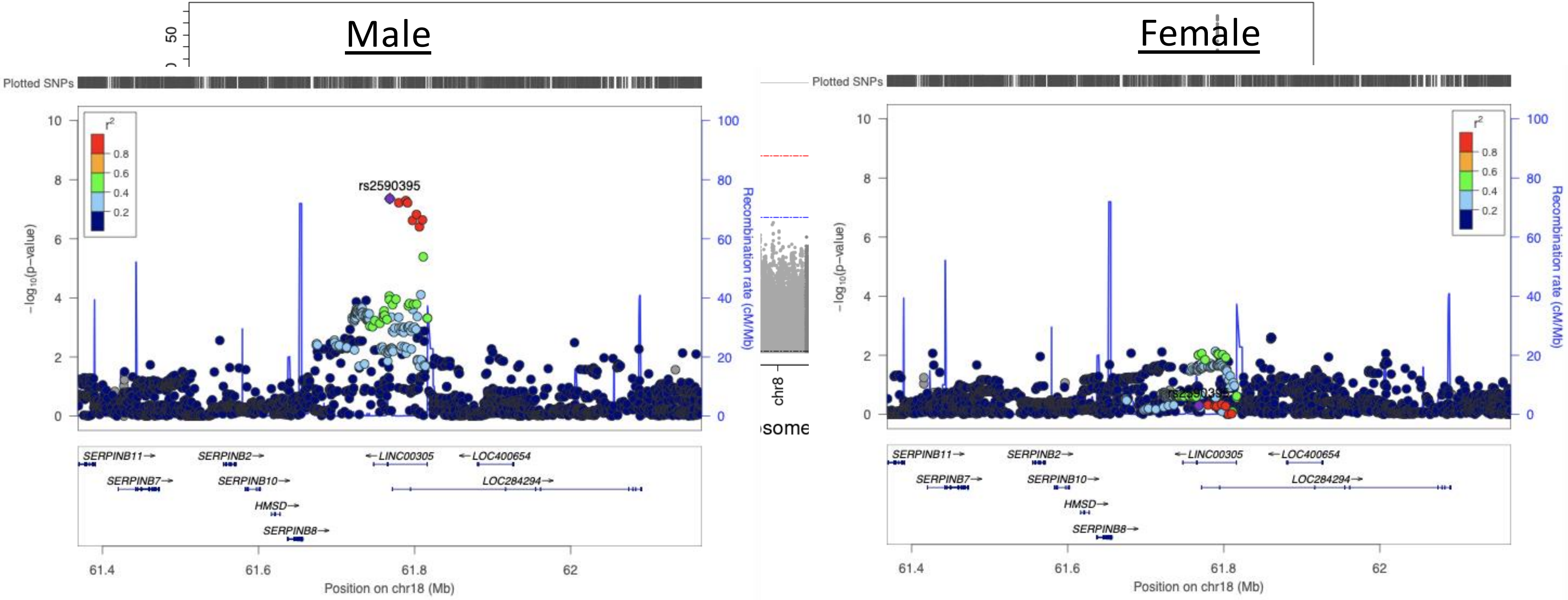


SERPINB1 Staining in AD Cortex



<u>Hot off the Presses (or Computer…)</u>

Sex-Stratified Memory GWAS



rs2590395 is eQTL for SERPINB2 and SERPINB10 in Blood

Precision Medicine through Collaboration

Sex-Specific Discovery in Mouse

Protocol Alignment

Sex-Specific Discovery in Human Brain

Identify Consensus Candidates Human and Mouse Brain

Genomic Association with AD Endophenotypes

Bioinformatic Filtering for Druggability & Known Therapeutics

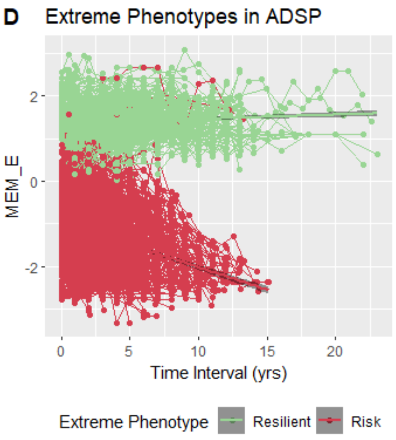
RNA Scope Validation

Sex-Specific Mechanistic Exploration in Mouse

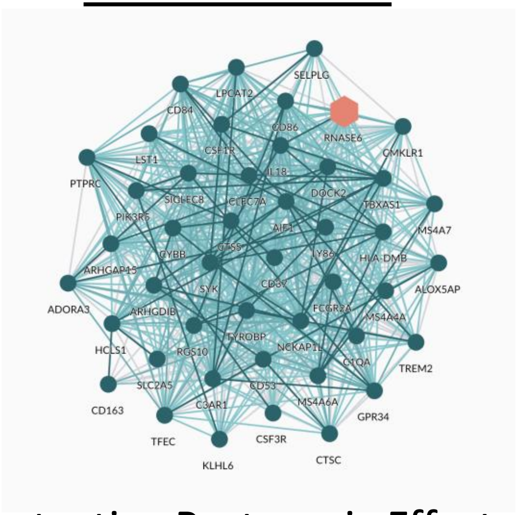
APOE — *SERPINB6* — *KDM6A* — ?? — ??

Future Directions

Extreme Phenotype

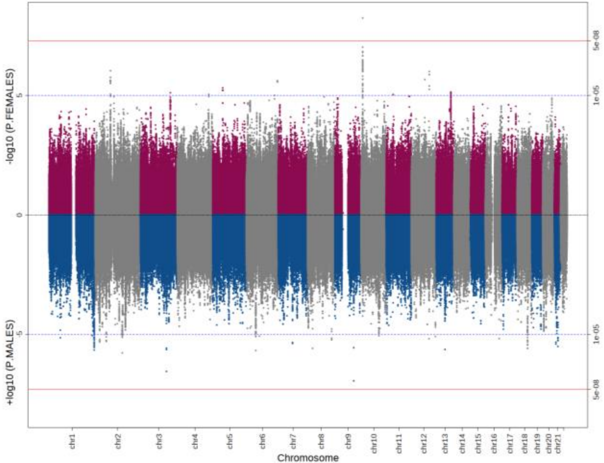


APOE Modifiers

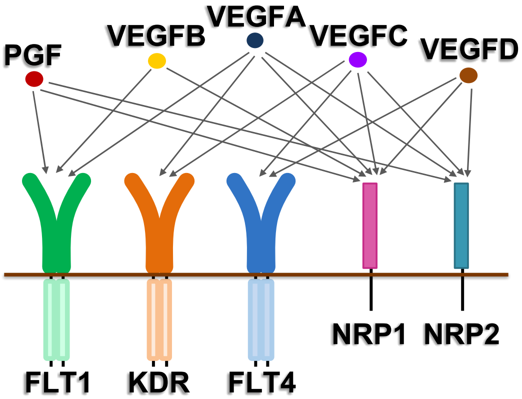


Resilience from AD Database

Sex Specific Genetic Resilience



Protective Proteomic Effects



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