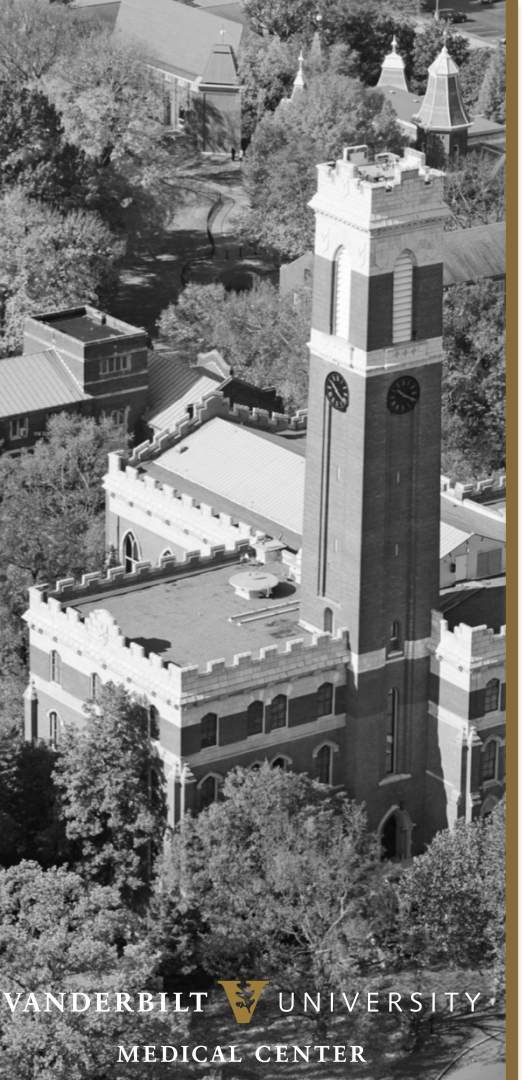
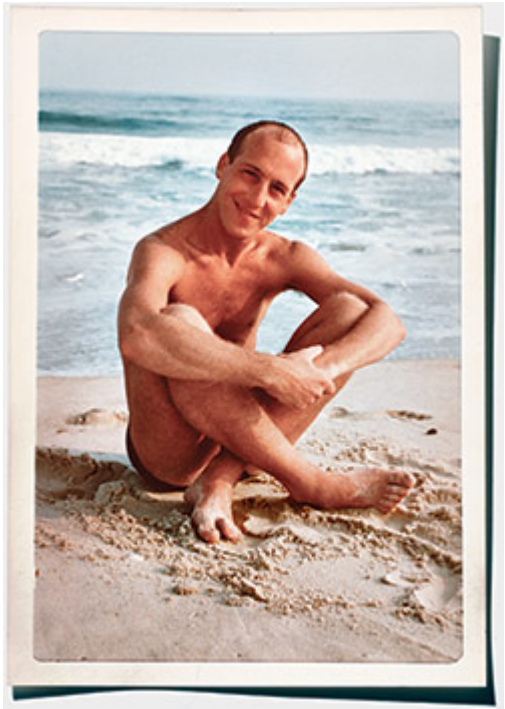



# Sex-Specific Drivers of Alzheimer's Disease Risk and Resilience

τimothy Hohman, PhD
Associate Professor
Vanderbilt Memory & Alzheimer's Center

Sex Differences in Brain Disorders Workshop
National Academies of Sciences, Engineering, and Medicine
September 23, 2020

# Pathways to Resilience





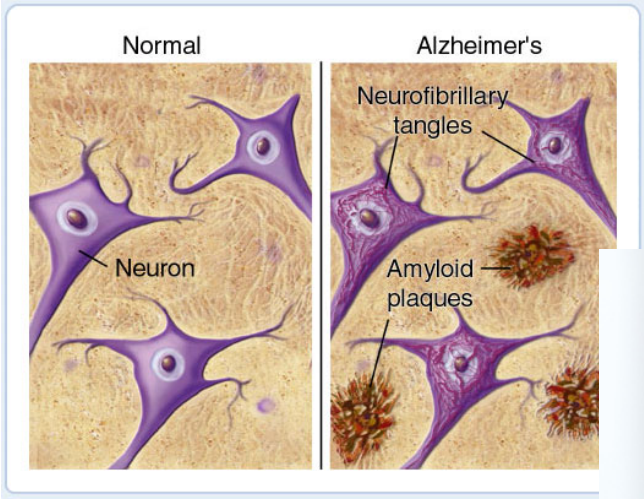
THE DALLAS HEART STUDY

*New York Magazine, The Man Who Was Immune to AIDS, 2014*
*Liu et al., 1996, Cell*

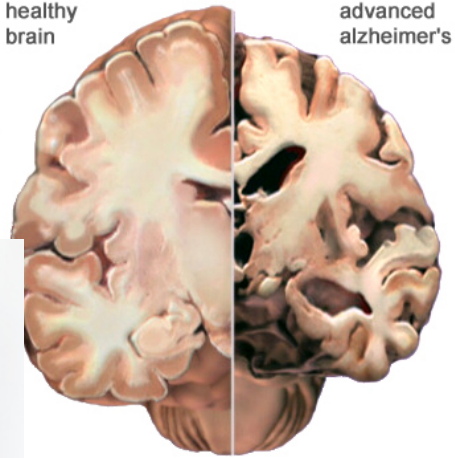
*Cohen et al., Nature Genetics, 2005*

# AD Neuropathological Cascade

## Neuropathology




## Neurodegeneration




## Cognitive Impairment

# Failed Clinical Trials in Alzheimer's Disease

TARGET TYPE | THERAPY TYPE

| Target Types | Timeline | Phase 1 | Phase 1/2 | Phase 2 | Phase 2/3 | Phase 3 | Phase 4 | Approved | Inactive | Discontinued | Not Regulated | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amyloid-Related | | 4 | 1 | 15 | 5 | 7 | 0 | 0 | 7 | 17 | 0 | 56 |
| Cholesterol | | 1 | 0 | 0 | 0 | 0 | | | | | | |

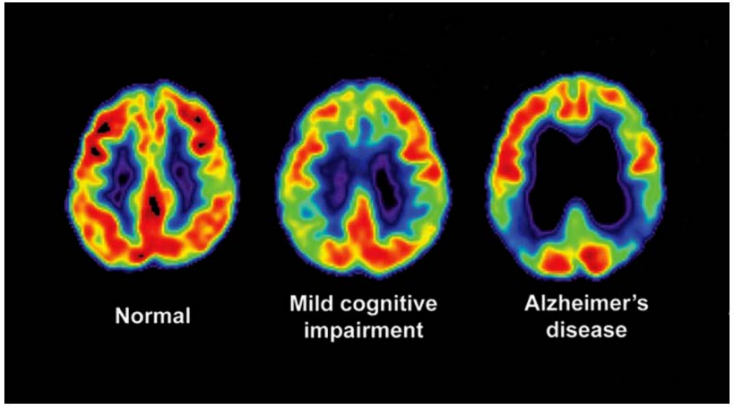
The New York Times

By MICHELLE

Poo
stuc
Alzh
bap

## *Eli Lilly's Experimental Alzheimer's Drug Fails in Large Trial*

Nov. 23, 2016




President Obar
additional $26
reports

Bloomberg

Markets

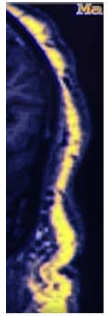
## Another Alzheimer's Drug Fails as Lilly, Astra Halt Tests

By Phil Serafino
June 12, 2018, 1:49 AM CDT *Updated on June 12, 2018, 5:06 AM CDT*

- Lanabecestat was unlikely to meet goals of advanced studies
- Both drugmakers reiterate guidance, see no financial impact

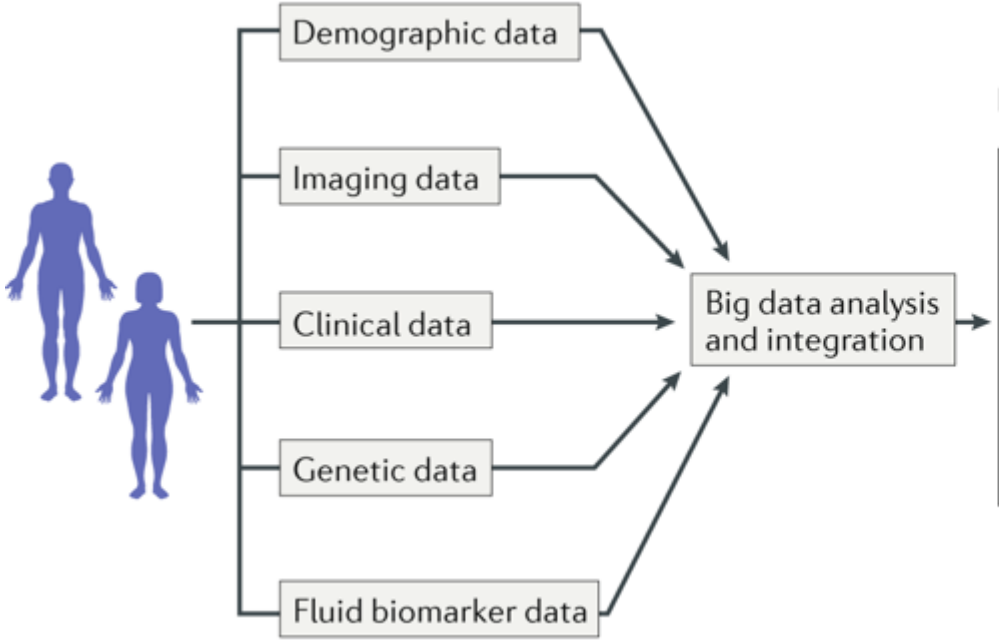
Source: Nomadsoul1/iStockphoto

but



Jon LaPook reports
bank in

# Embracing Complexity

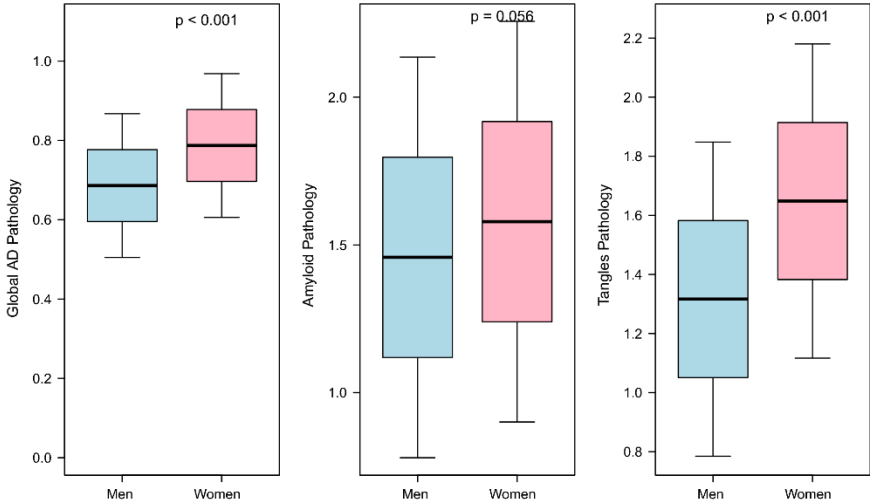



*Ferretti et al., Nature Reviews Neurology, 2018*

# Are there a Sex Differences in AD Neuropathology?

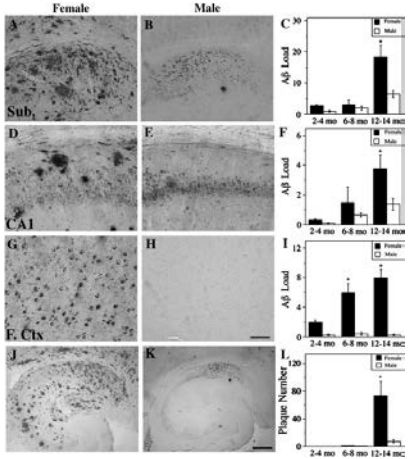
# Females Have More AD Pathology at Autopsy

## Neuropathology at Autopsy



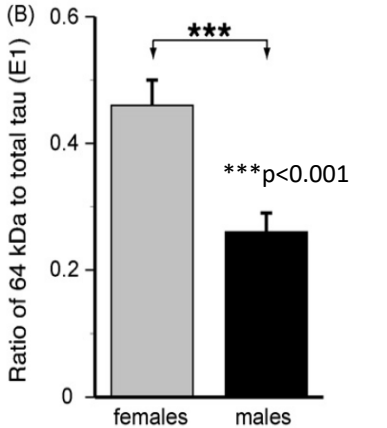

*Oveisgharan et al., Acta Neuropathologica, 2018*

## APP Transgenic Mice




*Carroll et al., Brain Research, 2010*

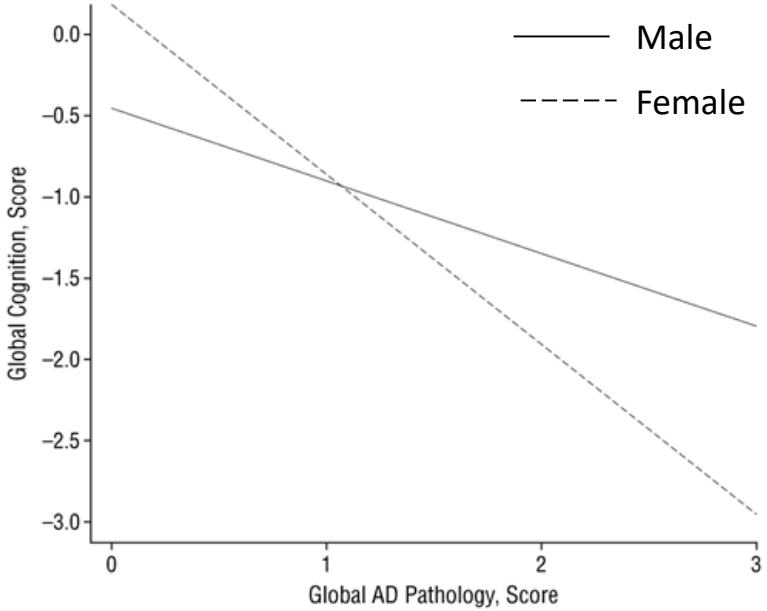
## Tau Transgenic Mice



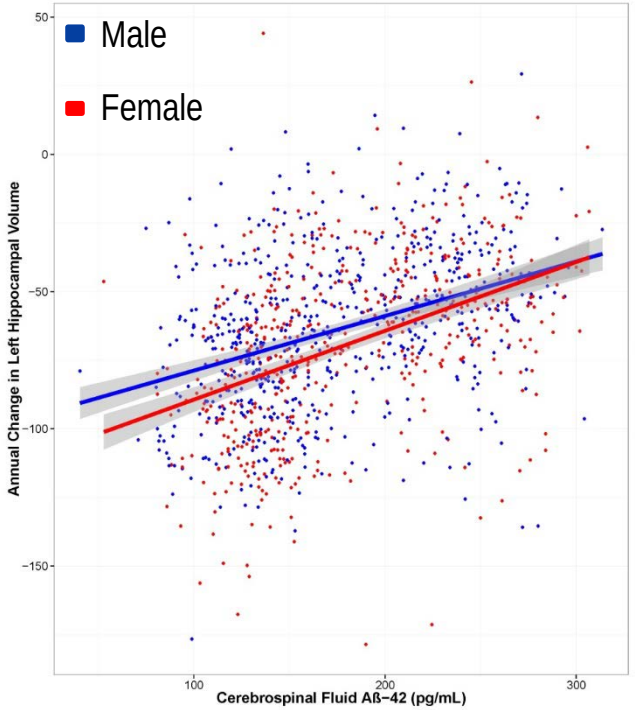

*Yue et al., Neurobiology of Aging, 2011*

# Females with Pathology Decline More Rapidly

## Neuropathology Association with Cognition



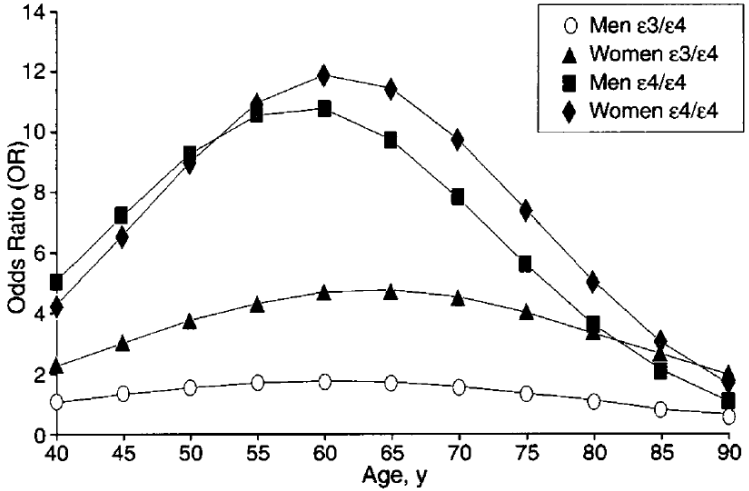

## CSF Biomarker Association with Atrophy



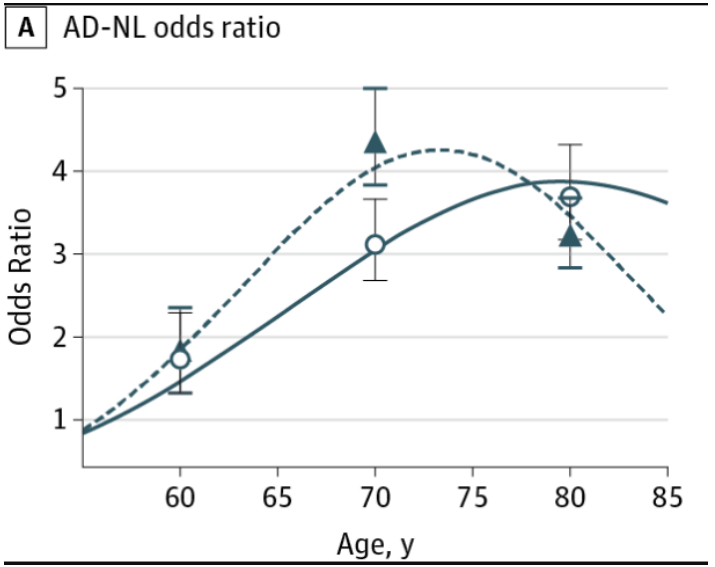

*Barnes et al., Archives of General Psychology 2005*

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

# *APOE* Association with AD is Stronger in Females

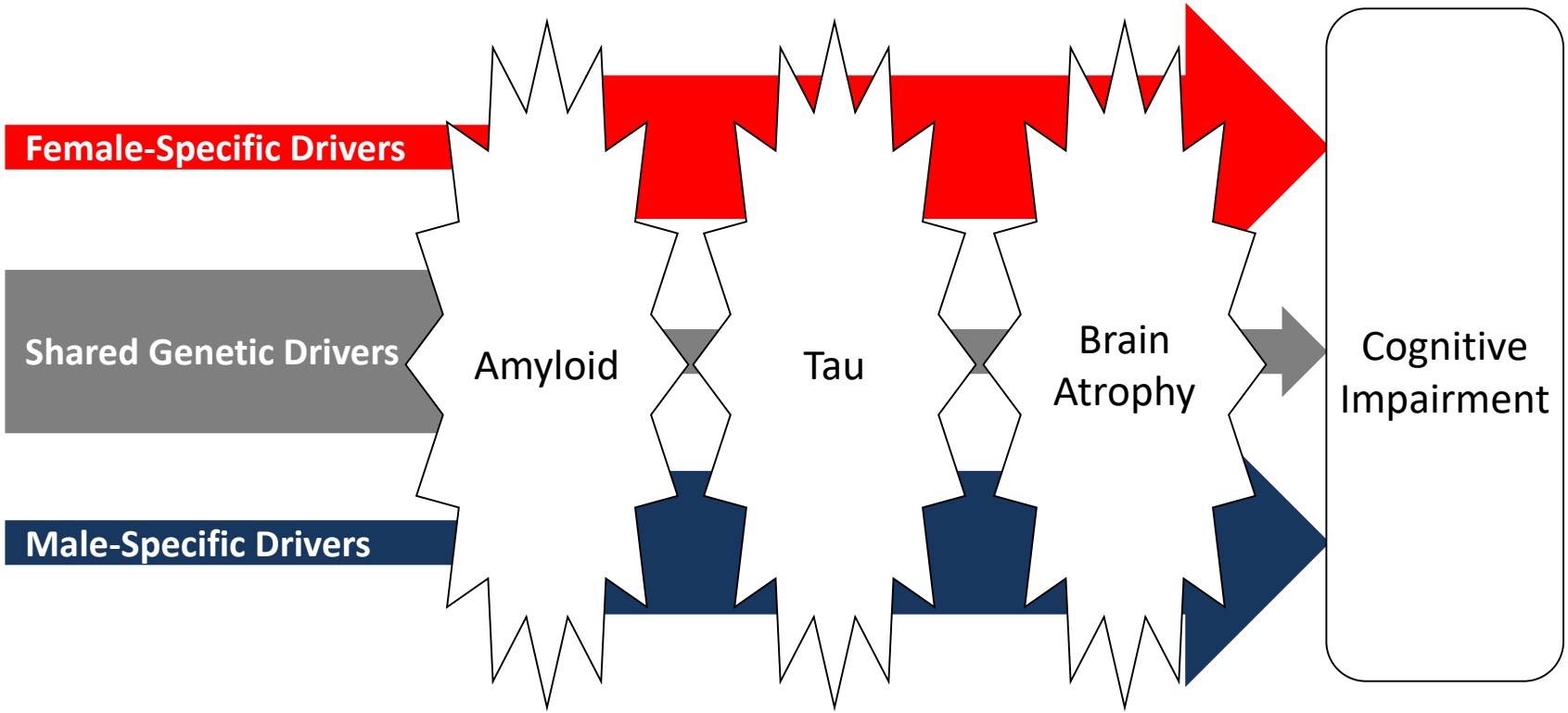



*Farrer et al., JAMA Neurology, 1997*




*Neu et al., JAMA Neurology, 2017*

# Summary of Sex Differences

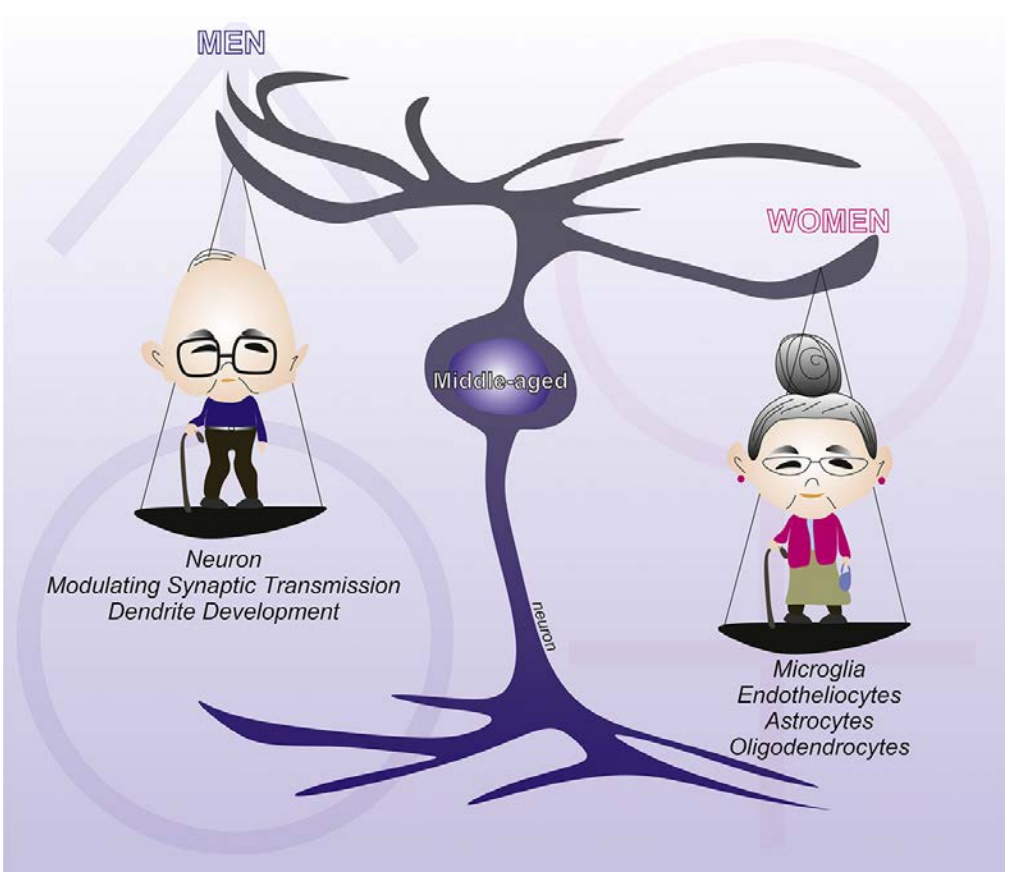


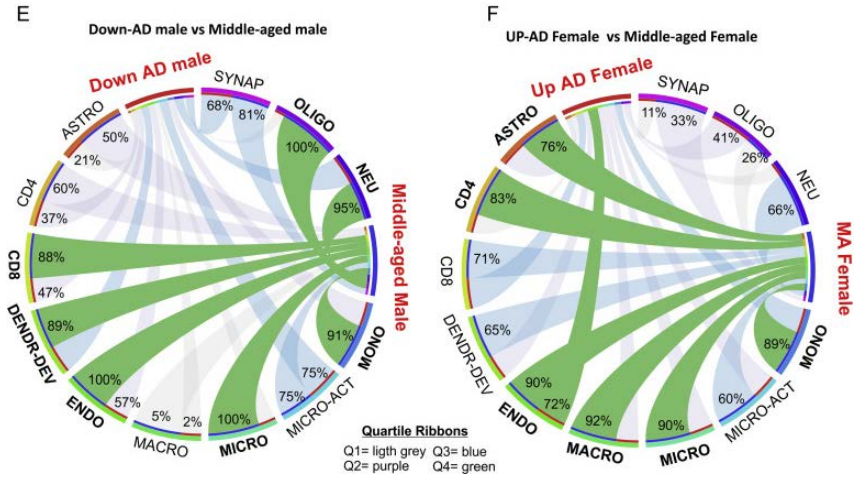
# Summary of Sex Differences

- Females have higher levels of plaques and tangles
- Females show more rapid neurodegeneration and cognitive decline in presence of AD neuropathology
- *APOE* has a strong association with amyloid
  - *Consistent across men and women*
- *APOE* has an association with tau, particularly among females

# A Sex-Specific Genetic Architecture of Alzheimer's Disease?

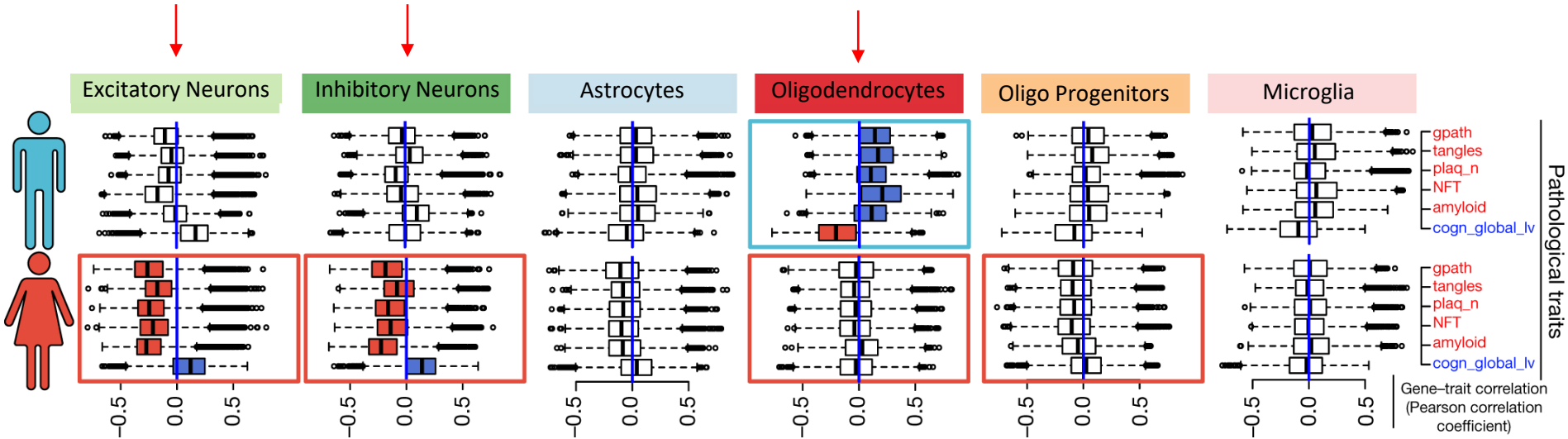
# Sex-Specific Changes in Transcription



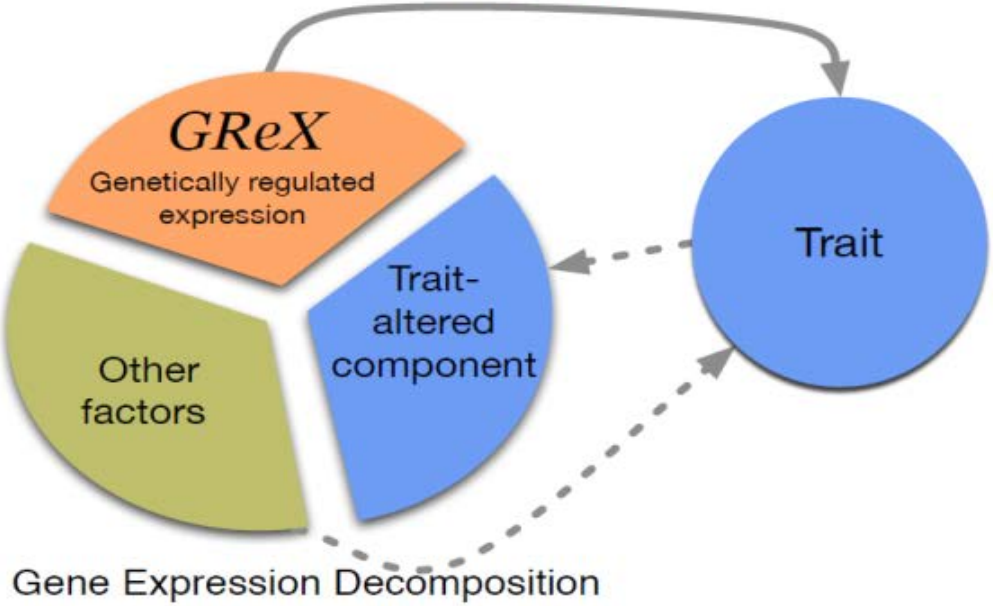

*Sanfilippo et al., Neuroscience, 2019*

# Sex-Specific Single Cell Transcriptomics



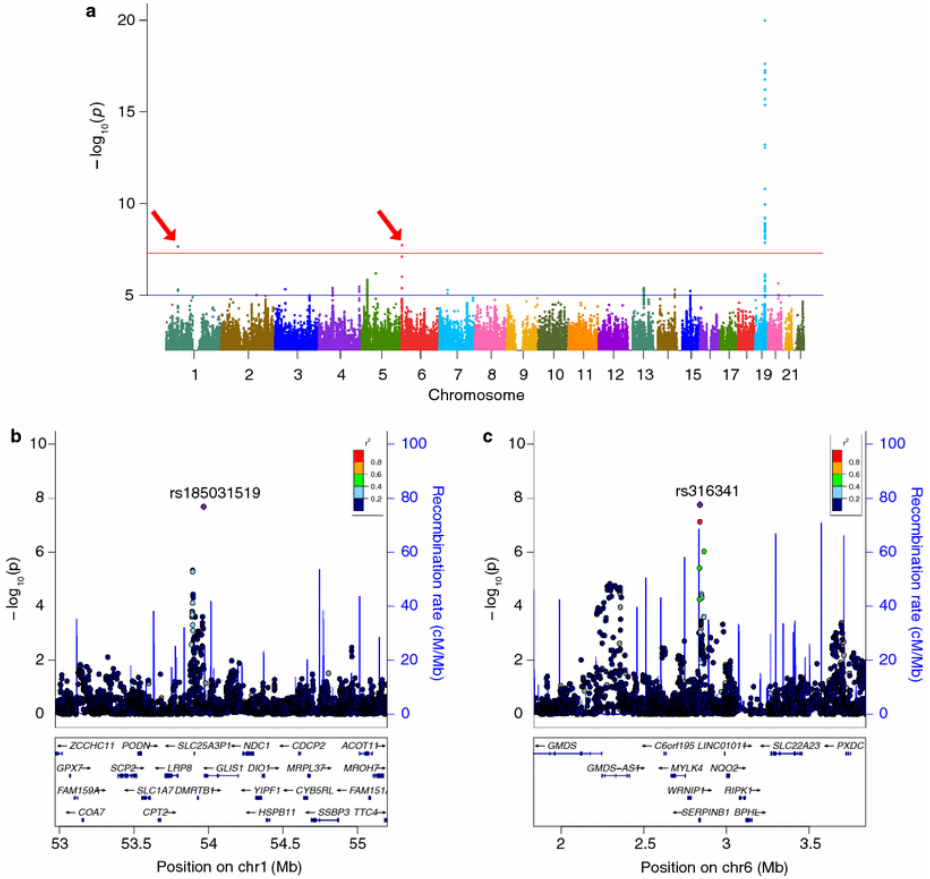

*Mathys et al., Nature, 2019*

# Cause or Effect?



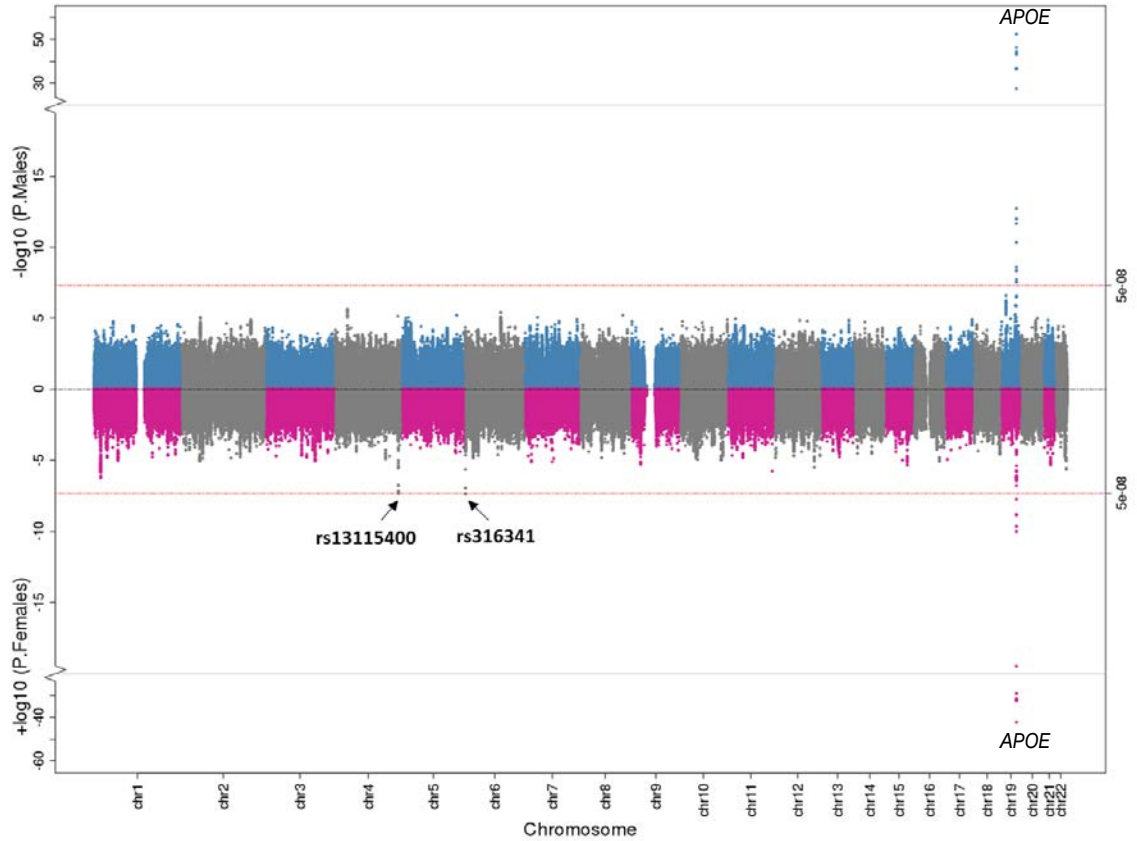
# Leveraging Genome-Wide Data to Explore Sex Differences in AD

# GWAS of CSF Aβ-42




*Deming et al., Acta Neuropathologica, 2017*

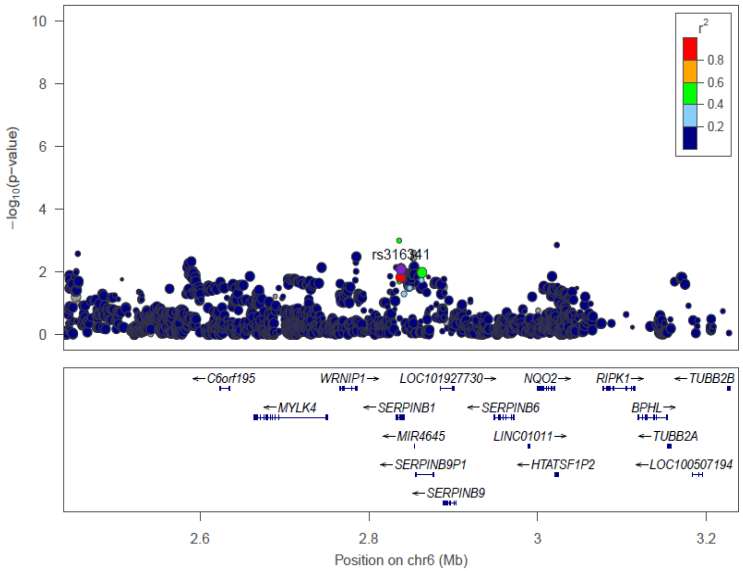
# GWAS of CSF Aβ-42



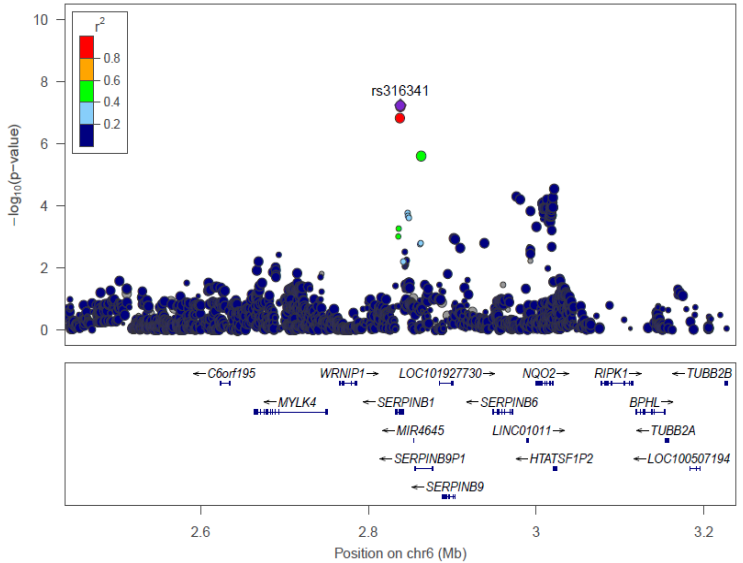

*Deming, … Hohman, Acta Neuropathologica, 2018*

# Locus Zoom

## Male




## Female

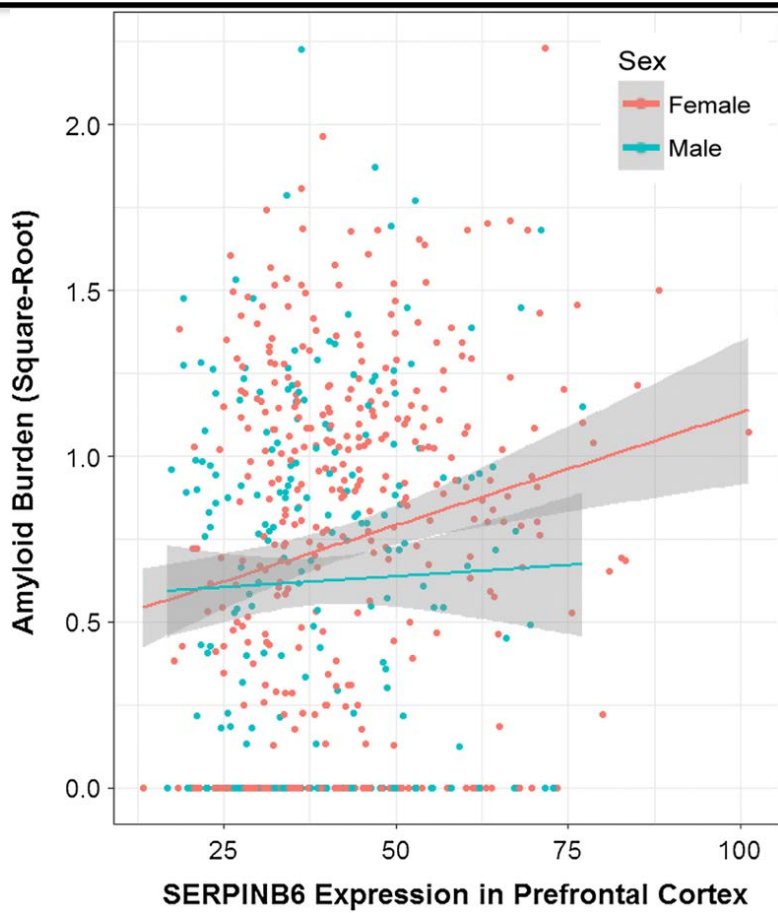



*rs316341 is eQTL for SERPINB1, SERPINB6, and SERPINB9 in Braineac and GTex*

*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

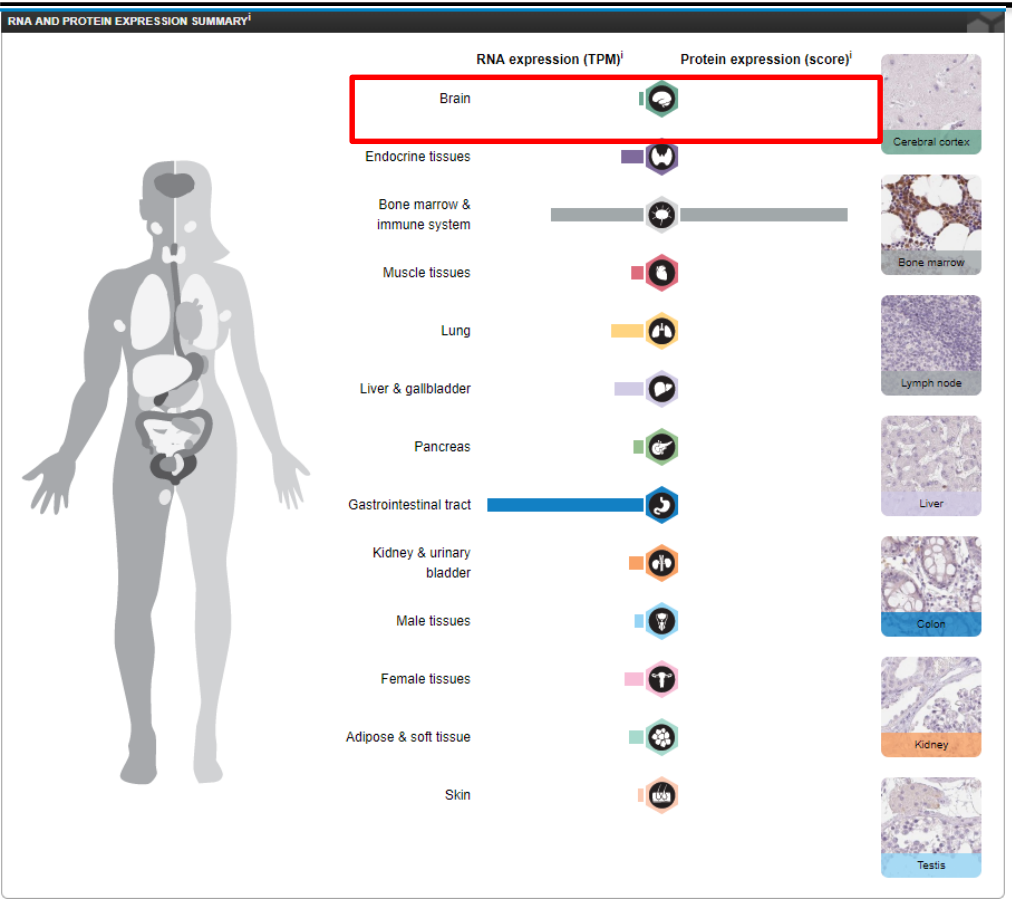



*Deming, ... Hohman, Acta Neuropathologica, 2018*

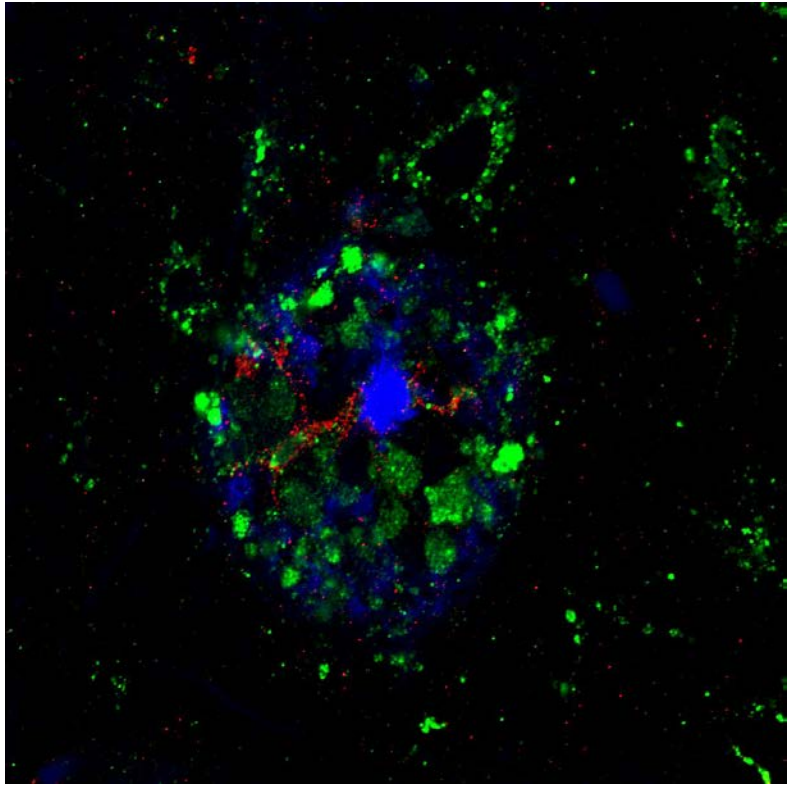
# Serpin Signaling and Amyloidosis

- 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



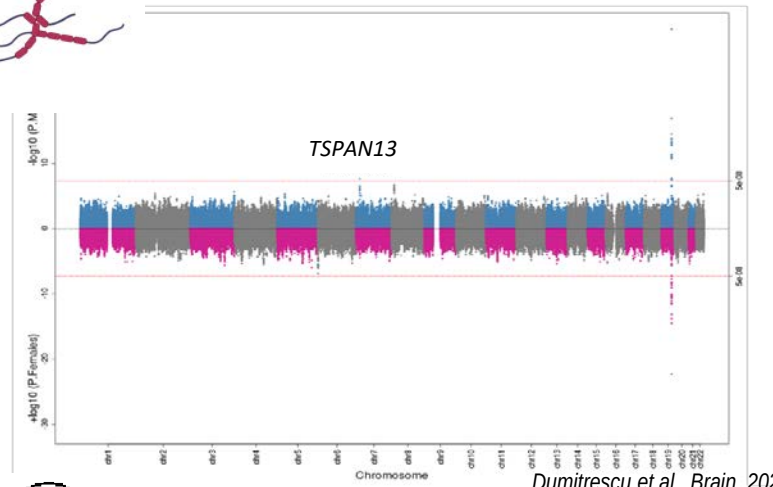

## SERPINB1 Staining in AD Cortex



# PET Amyloid




# Neurofibrillary Tangles




Dumitrescu et al., Brain, 2020

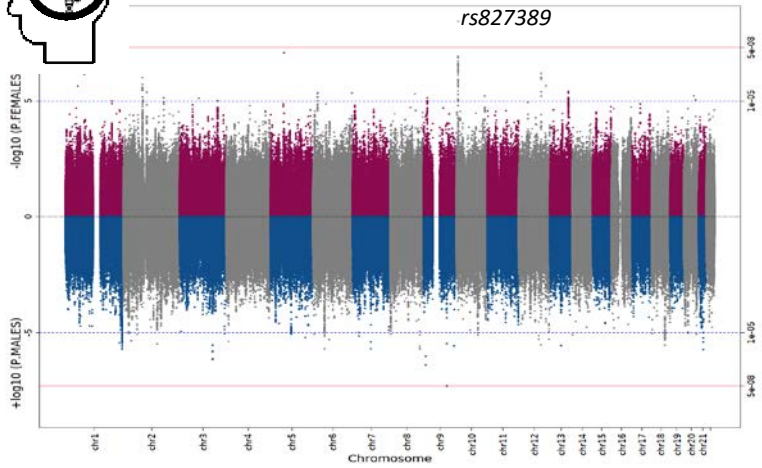
# Cognitive Decline

*IL16*




# Resilience to AD

*rs827389*



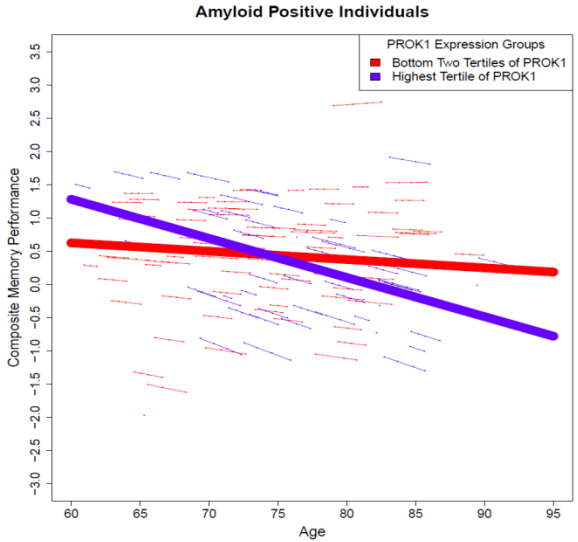
# Sex-Specific Genomic Pathways Summary

| | Amyloid | Tau | Cognitive Decline | Resilience |
|---|---|---|---|---|
| |  |  |  |  |
| Male ♂ | *APOE*<br>*HLA Region* | *α Secretase Pathway* | *APOE*<br>*Mitochondrial Transport* | *Glutamate* |
| Female ♀ | *APOE*<br>*Neutrophils*<br>*RNA Binding* | *APOE*<br>*Dendritic Growth* | *APOE*<br>*Metabolism (Gluconeogenesis)*<br>*Inflammation*<br>*Circadian Clock* | *Angiogenesis*<br>*Neurotrophic* |

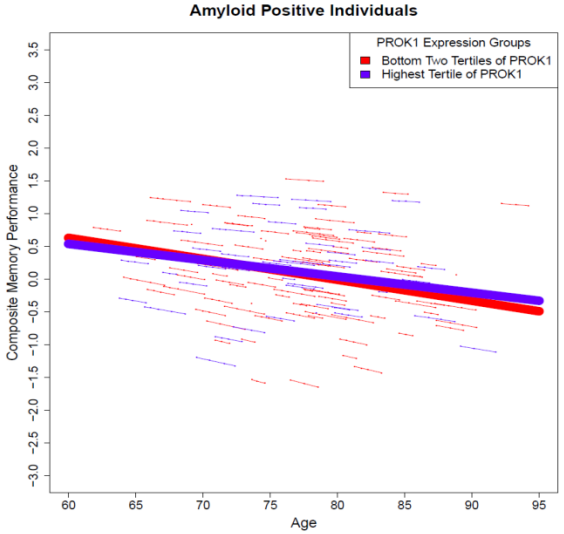
# Future Directions: Leveraging PrediXcan

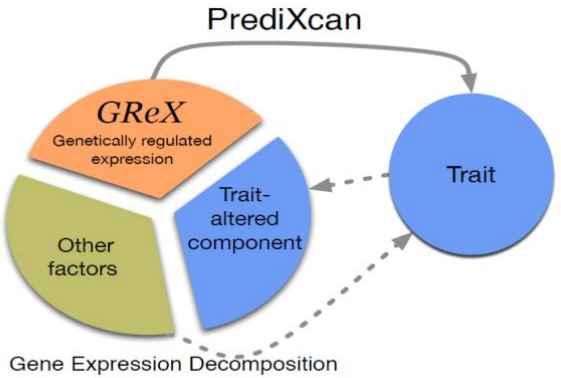
***Angiogenic Genes Interact with Amyloid among Females***

**Female**




**Male**



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