# Molecular drivers of Alzheimer's disease resilience through genomic and proteomic analyses

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Vanderbilt University Medical Center

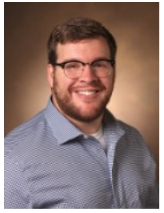
May 14, 2024

# Computational Neurogenomics Team (CNT)

## Faculty

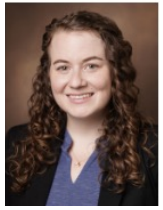
Timothy Hohman
PhD

Logan Dumitrescu
MS, PhD



Derek Archer
PhD

## Program Managers



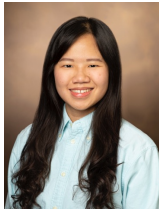
Shannon Turner

Jane Zyski
MHA

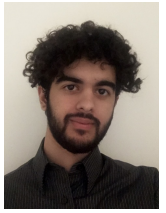
## Graduate Students

Anna Lorenz
MsC

Jared Phillips



Ting-Chen Wang



Alex Contreras

Emma Nolan
MS

## Staff Scientists and Staff Data Analysts

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Tonnar Castellano
MS

Michelle Clifton
MS

Alaina Durant

Vaibhav Janve
PhD

Alexis Smith
MS

Hui Shi, MS

Edward Miller
MIT

## Past Trainees

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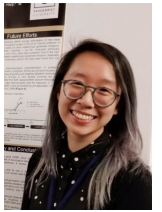
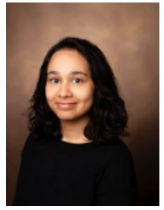
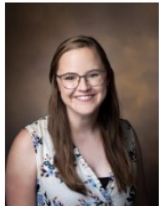
PhD



Mabel Seto
PhD



Aditi Sathe
MS

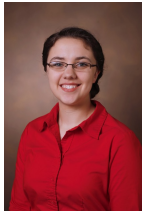


Julia Libby

Skylar Walters,
MS

Yiyang Wu
MD, PhD

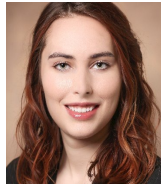
Melisa Lara Gomez



Emily Mahoney

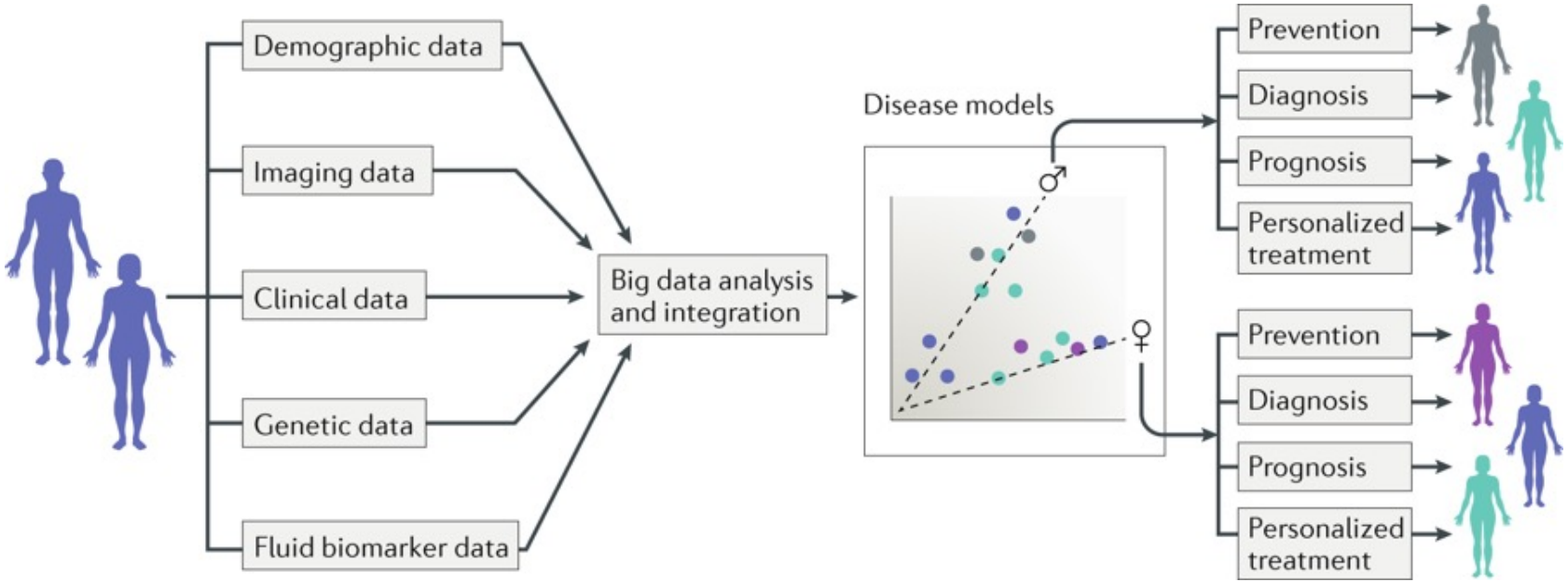
Dimitrios Zaras
PhD

Jackie Eissman
PhD



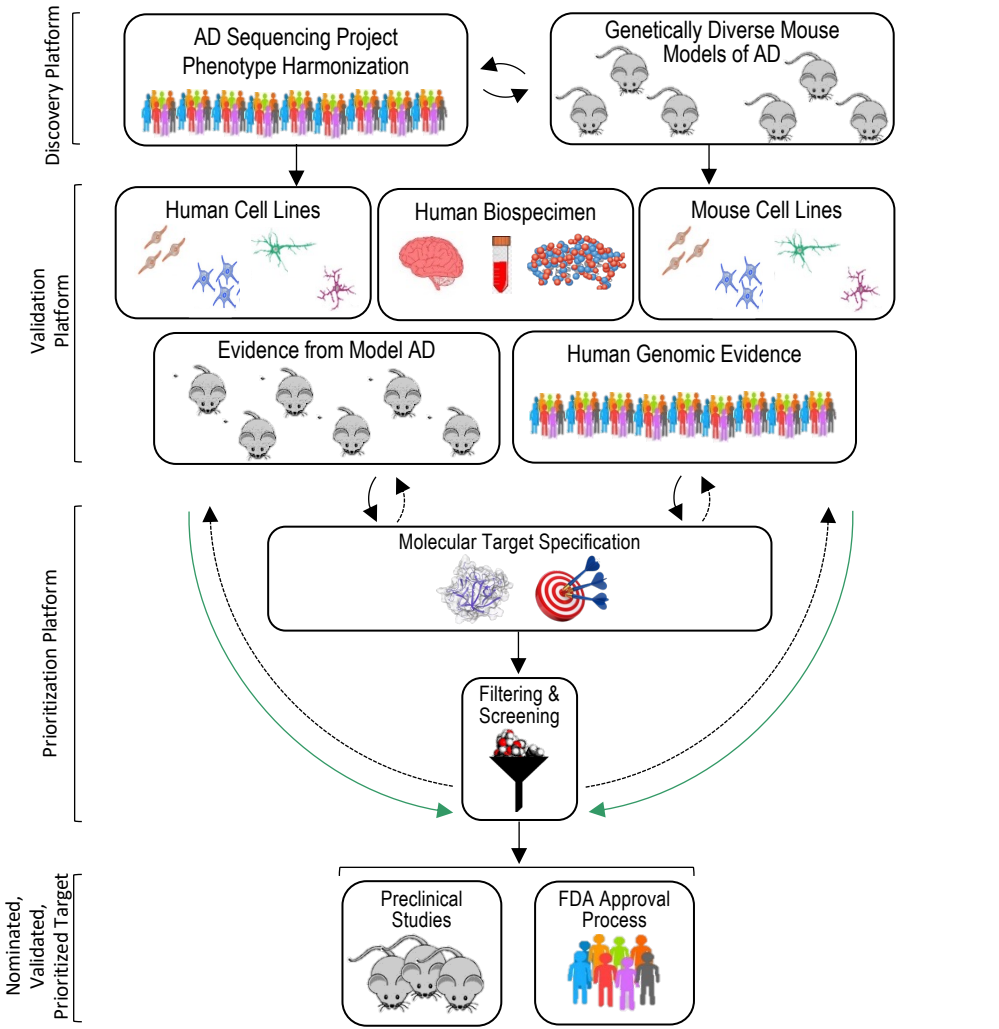
Annah Sclafani
PhD

# Precision Medicine in AD

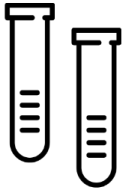


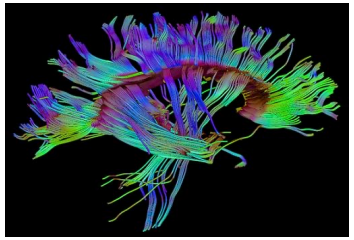

*Ferretti et al., Nature Reviews Neurology, 2018*

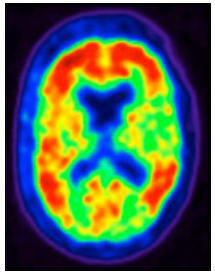
# Drug Discovery Framework in the Computational Neurogenomics Team

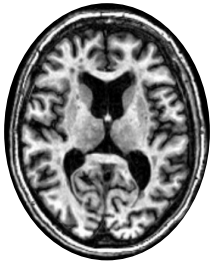


# Explosion of Big Data in Alzheimer's Disease



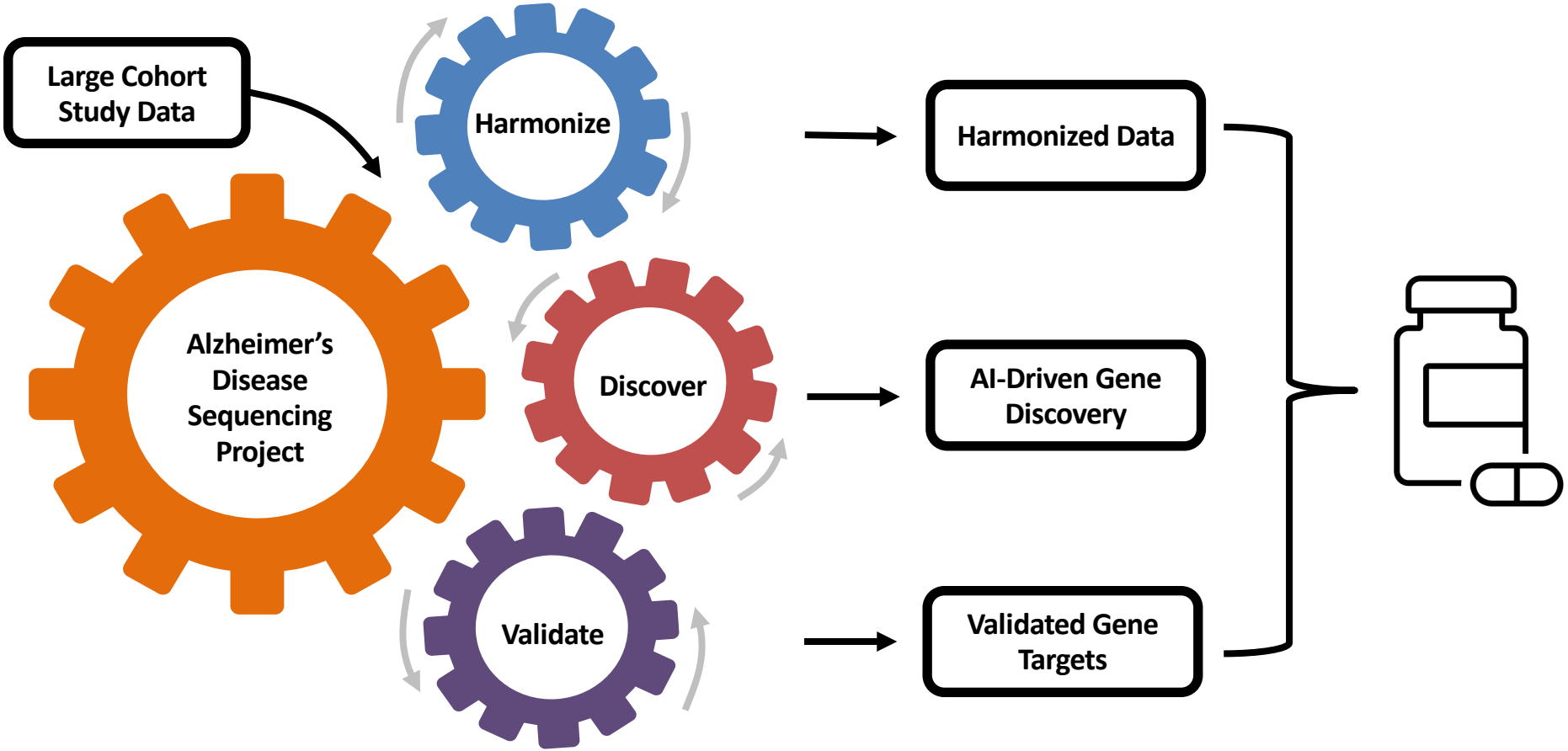




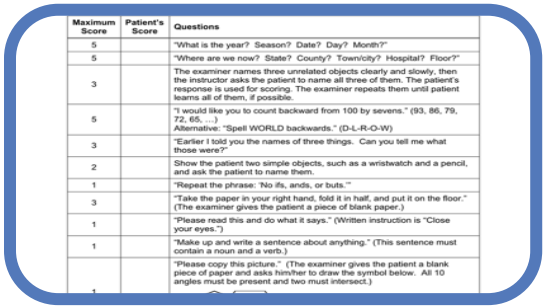


Genomics → Molecular Biomarkers → Structural Brain Imaging → Cognition

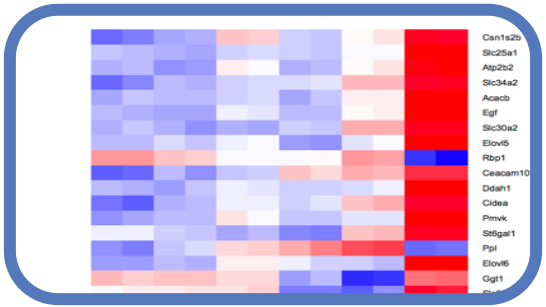
# Integrating AI into Genomic Discovery at NIA

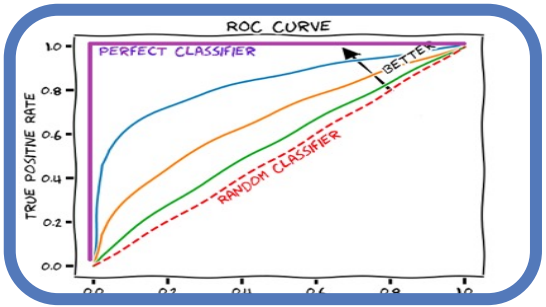


# New ADSP Programs



| Maximum Score | Patient's Score | Questions |
|---|---|---|
| 5 | | "What is the year? Season? Date? Day? Month?" |
| 5 | | "Where are we now? State? County? Town/city? Hospital? Floor?" |
| 3 | | The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. |
| 5 | | "I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...)<br>Alternative: "Spell WORLD backwards." (D-L-R-O-W) |
| 3 | | "Earlier I told you the names of three things. Can you tell me what those were?" |
| 2 | | Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them. |
| 1 | | "Repeat the phrase: 'No ifs, ands, or buts.'" |
| 3 | | "Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.) |
| 1 | | "Please read this and do what it says." (Written instruction is "Close your eyes.") |
| 1 | | "Make up and write a sentence about anything." (This sentence must contain a noun and a verb.) |
| 1 | | "Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) |



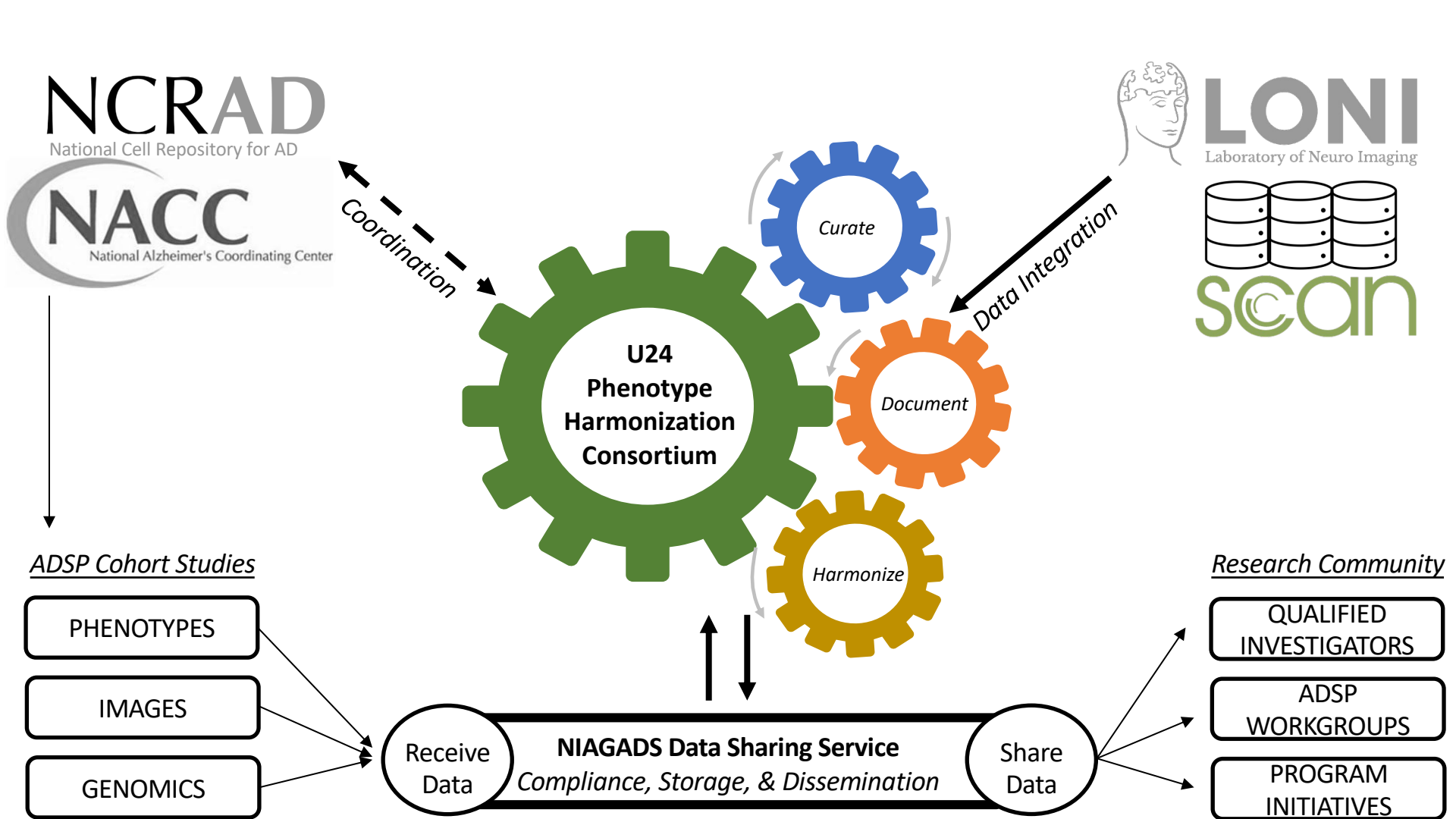

ADSP PHC
PHENOTYPE HARMONIZATION CONSORTIUM

FunGen-AD
ADSP Functional Genomics Consortium

AI4AD
GENETICS IMAGING COGNITION TREATMENT

adsp
Alzheimer's Disease Sequencing Project

NIAGADS
The National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site


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

# ADSP-PHC Teams

## Fluid Biomarker Harmonization

**Carlos Cruchaga, PhD**
Washington University

## Coordinating Center

**Timothy Hohman, PhD**
Vanderbilt University Medical Center
Contact-PI

**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

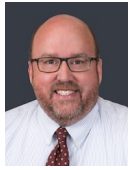
**Richard Mayeux, MD, MSc**
Columbia University

## Integration & Analytics

**Paul Thompson, PhD**
University of Southern California

**Andrew Saykin, PsyD**
Indiana University

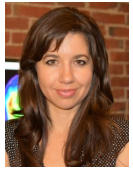
## Neuropathology Harmonization



**Thomas Montine, MD, PhD**
Stanford University

**Gary Beecham, PhD**
University of Miami

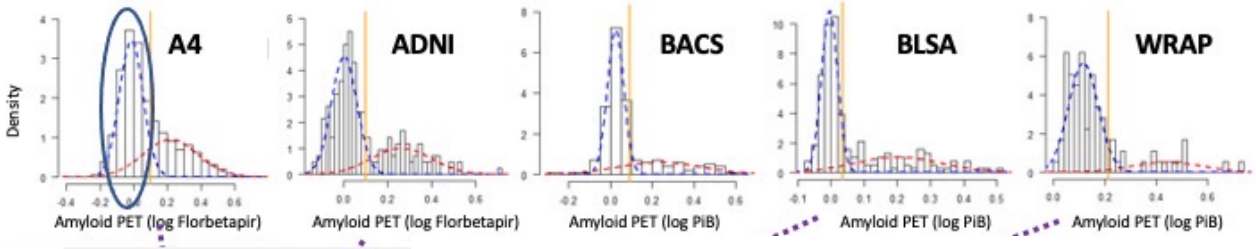
## PET Harmonization

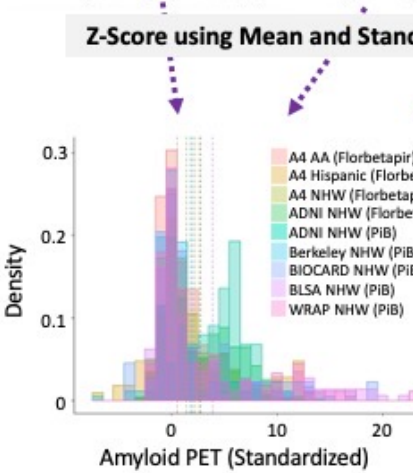


**Elizabeth Mormino, PhD**
Stanford University

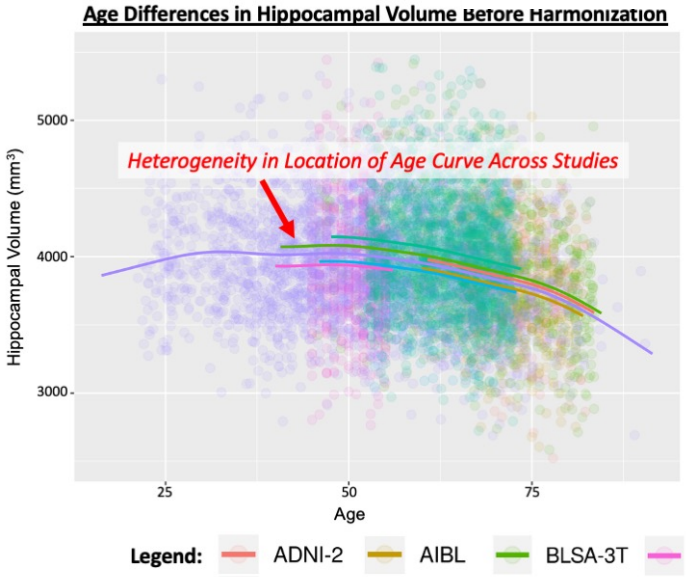
**Duygu Tosun, PhD**
University of California San Francisco

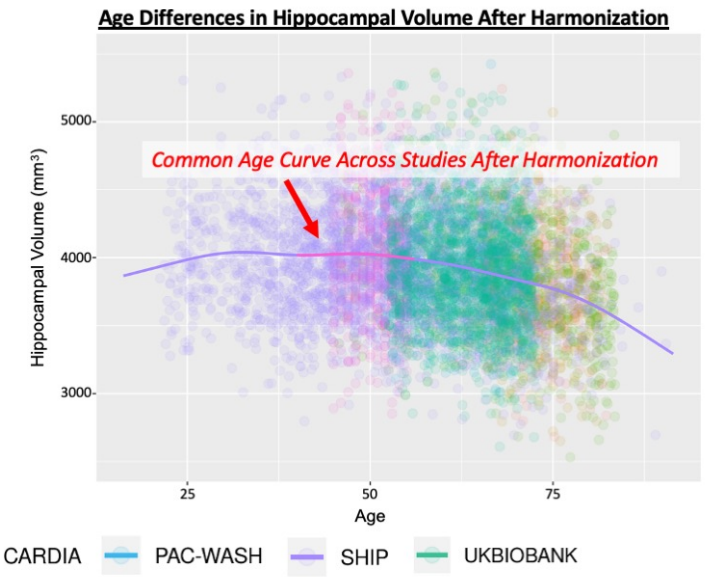
## Amyloid PET Harmonization




## Stuctural T1 MRI Harmonization




# Data Harmonized in Year 2

| Cohort | Autopsy | Vascular Risk Factors | Cognition | Fluid Biomarker | Diffusion Tensor Imaging (DTI) | Fluid Attenuated Inversion Recovery (FLAIR) | Magnetic Resonance Imaging (MRI) Freesurfer | Magnetic Resonance Imaging (MRI) MUSE | Positron Emission Tomography (PET) Amyloid | Positron Emission Tomography (PET) Tau |
|---|---|---|---|---|---|---|---|---|---|---|
| **TOTAL** | **23,020** | **57,083** | **83,548** | **3,047** | **2,830** | **10,020** | **7,679** | **10,590** | **7,602** | **1,836** |
| A4 | 0 | 0 | 6,595 | 0 | 0 | 1,198 | 0 | 0 | 4,486 | 447 |
| ACT | 532 | 0 | 5,546 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ADNI | 0 | 1,577 | 3,539 | 1,249 | 1,198 | 7,054 | 2,560 | 2,592 | 1,803 | 944 |
| EFIGA | 0 | 5,965 | 6,903 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Knight ADRC | 0 | 0 | 2,477 | 64 | 0 | 0 | 0 | 0 | 0 | 0 |
| NACC | 19,899 | 41,172 | 41,538 | 2,094 | 646 | 0 | 3,690 | 5,004 | 920 | 102 |
| NIA-AD FBS | 570 | 405 | 4,564 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ROS/MAP/ MARS | 2,019 | 4,500 | 4,550 | 0 | 643 | 0 | 0 | 1,183 | 0 | 0 |
| WHICAP | 0 | 1,830 | 6,257 | 0 | 0 | 1,768 | 929 | 1,197 | 0 | 0 |
| WRAP | 0 | 1,634 | 1,579 | 0 | 343 | 0 | 500 | 614 | 393 | 343 |

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# Freeze 2: Harmonized Data with Sequence Data

| Cohort | Autopsy | Vascular Risk Factors | Cognition | Fluid Biomarker | Diffusion Tensor Imaging (DTI) | Fluid Attenuated Inversion Recovery (FLAIR) | Magnetic Resonance Imaging (MRI) Freesurfer | Magnetic Resonance Imaging (MRI) MUSE | Positron Emission Tomography (PET) Amyloid | Positron Emission Tomography (PET) Tau |
|---|---|---|---|---|---|---|---|---|---|---|
| **TOTAL** | **6,795** | **15,565** | **25,278** | **2,034** | **967** | **3,278** | **3,630** | **4,329** | **4,955** | **912** |
| A4 | 0 | 0 | 3,373 | 0 | 0 | 963 | 0 | 0 | 3,378 | 345 |
| ACT | 532 | 0 | 1,337 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ADNI | 0 | 876 | 1,546 | 1,165 | 502 | 1,009 | 1,558 | 1,564 | 1,128 | 321 |
| EFIGA | 0 | 1,183 | 1,248 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Knight ADRC | 0 | 0 | 837 | 64 | 0 | 0 | 0 | 0 | 0 | 0 |
| NACC | 4,908 | 10,872 | 10,615 | 805 | 203 | 0 | 1,056 | 1,462 | 213 | 26 |
| NIA-AD FBS | 262 | 28 | 553 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ROS/MAP/ MARS | 1,093 | 1,254 | 1,271 | 0 | 77 | 0 | 0 | 165 | 0 | 0 |
| WHICAP | 0 | 604 | 3,786 | 0 | 0 | 1,306 | 712 | 770 | 0 | 0 |
| WRAP | 0 | 748 | 712 | 0 | 185 | 0 | 304 | 368 | 236 | 220 |

https://dss.niagads.org/
December 2023

Sample sizes reflect individuals with ADSP sequencing data, with exception to A4, which will have sequenced data available in R5.

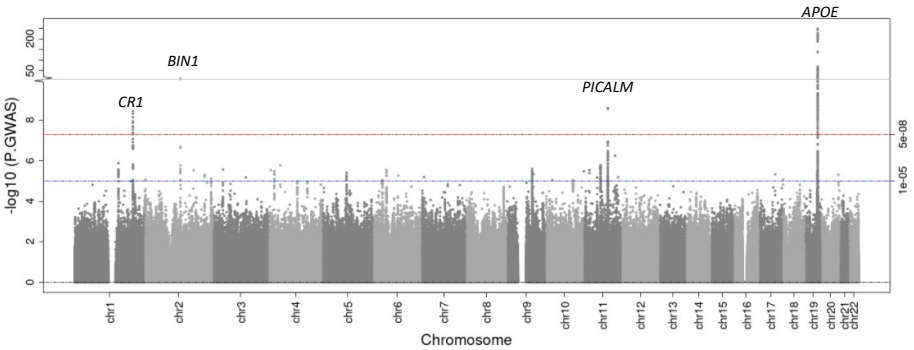
adsp PHC PHENOTYPE HARMONIZATION CONSORTIUM

dss NIAGADS

# Exploring the Genetic Architecture of AD Leveraging Endophenotypes

# Explorations into the Genetic Architecture of Memory

## GWAS of Memory Performance




*Archer et al., Alzheimer's & Dementia, In Press*

**26,633** participants over
**129,201** longitudinal visits

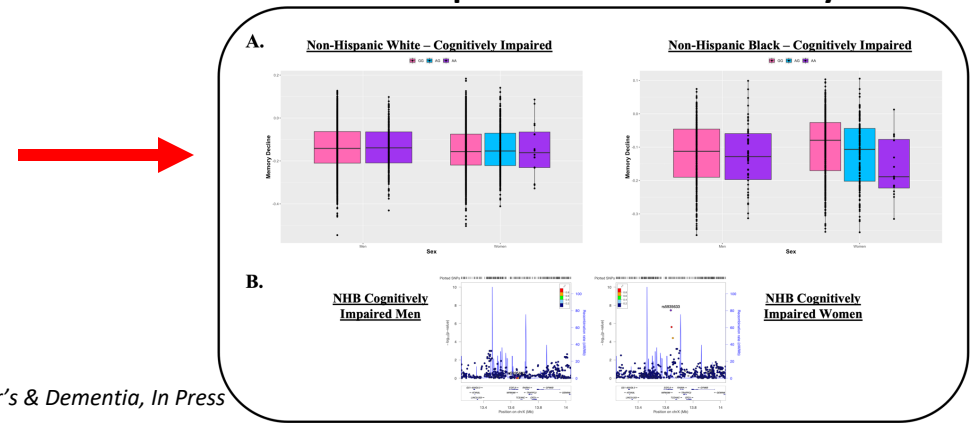
## Sex Differences in APOE

| | Memory Performance | Executive Functioning | Language Performance |
|---|---|---|---|
| *APOE-ε4* | ↑F M | F M | ↑F M |
| *APOE-ε2* | F M | F M | F M |

*Walters et al., JAMA Neurology, 2023*

**32,427** Participants including
**4,453** non-Hispanic Black

## Sex-Specific GWAS of Memory

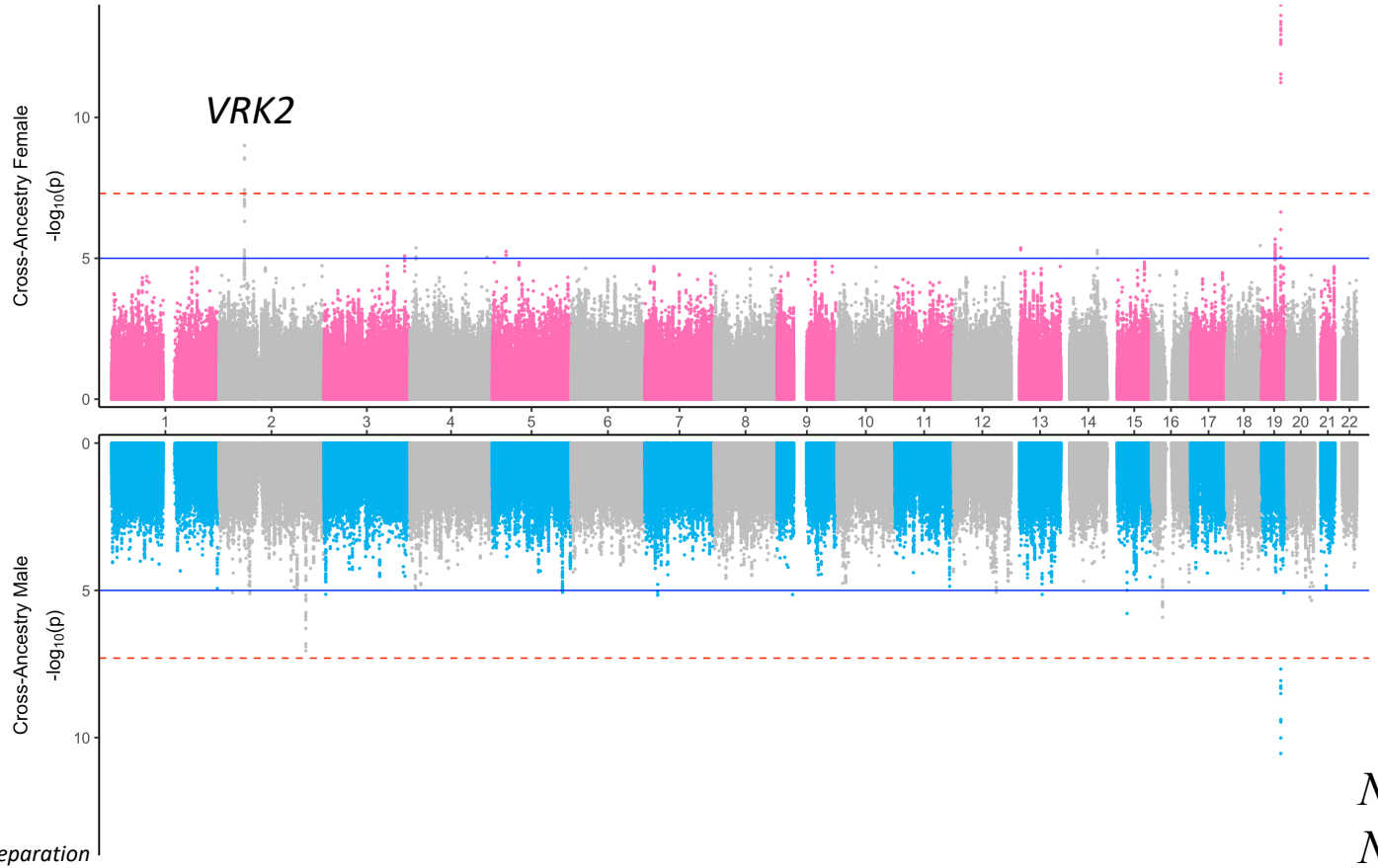



*Eissman et al., Alzheimer's & Dementia, In Press*

**26,633** participants over
**129,201** longitudinal visits

# Sex-Specific Genetic Drivers of Language

Jackie Eissman
PhD



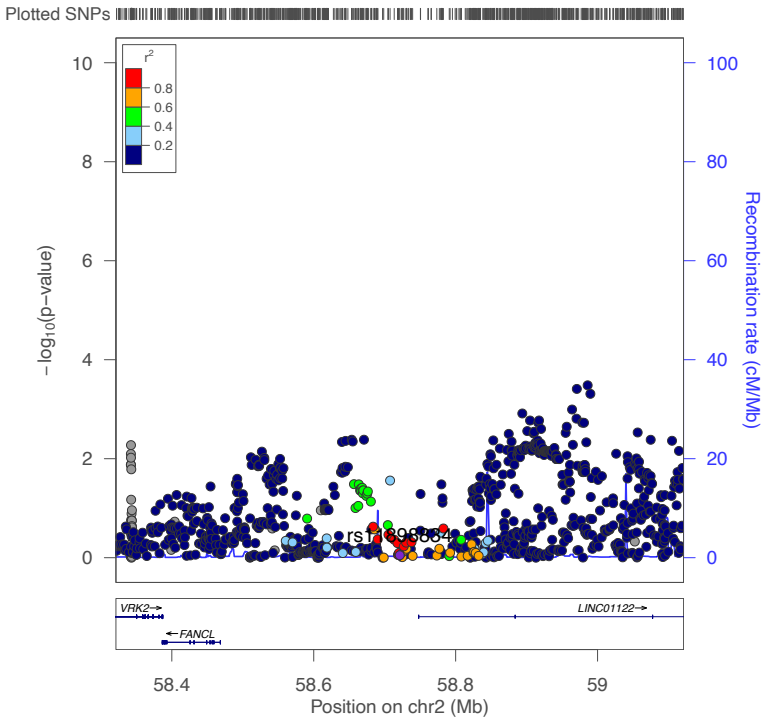

$N_{males} = 15,493$

$N_{females} = 20,681$

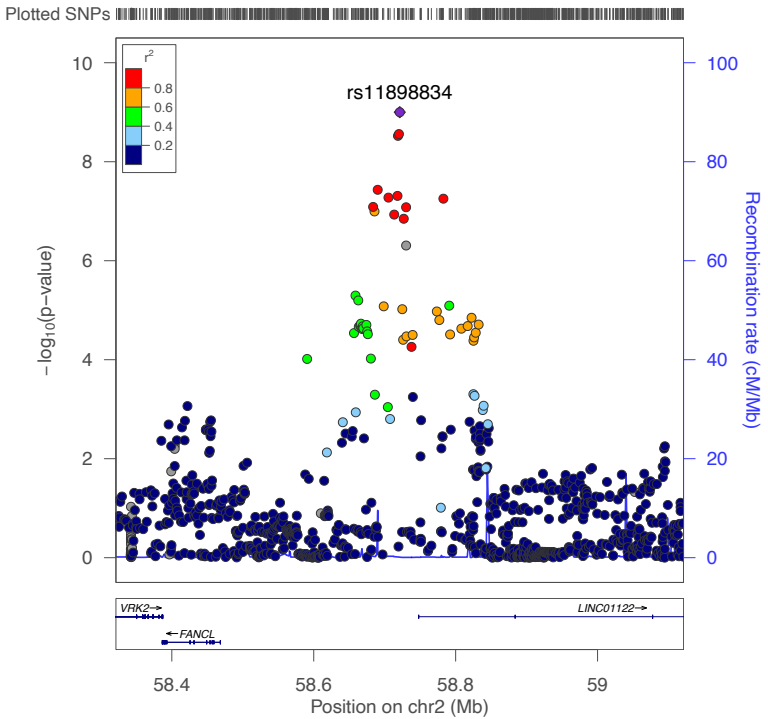
*Eissman et al., In Preparation*

# Sex Differences in VRK2 Association with Language

## Males



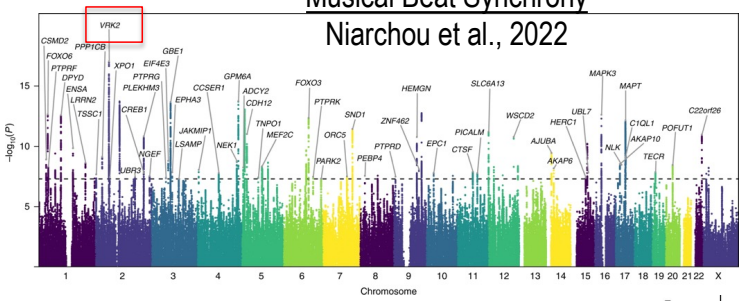

## Females



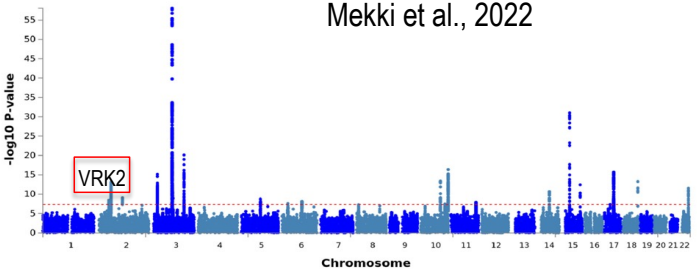

*Eissman et al., In Preparation*

# VRK2 Association with other Neuropsychiatric Traits

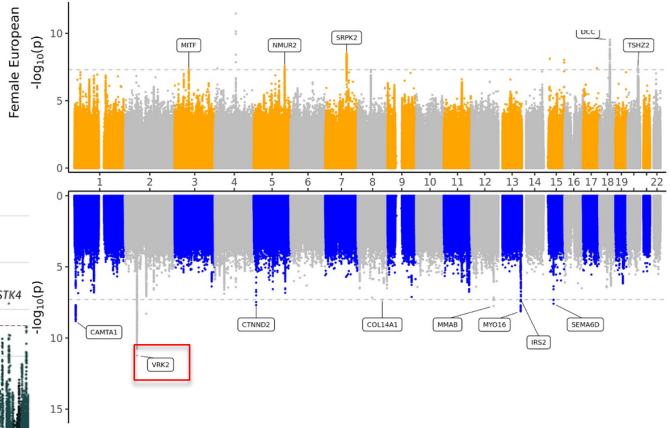
Musical Beat Synchrony
Niarchou et al., 2022



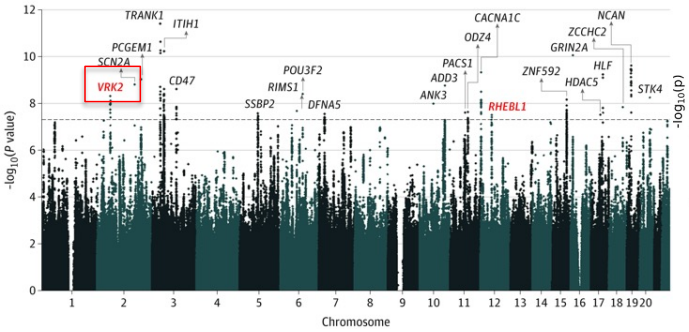

Language Connectivity
Mekki et al., 2022



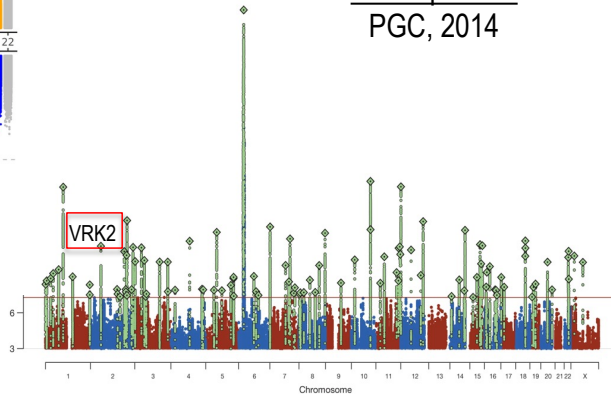

Developmental Stuttering
Below et al., 2023




Bipolar Disorder
Li et al., 2021




Schizophrenia
PGC, 2014

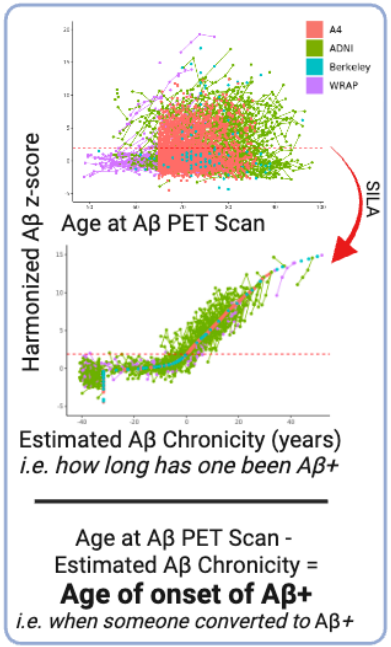


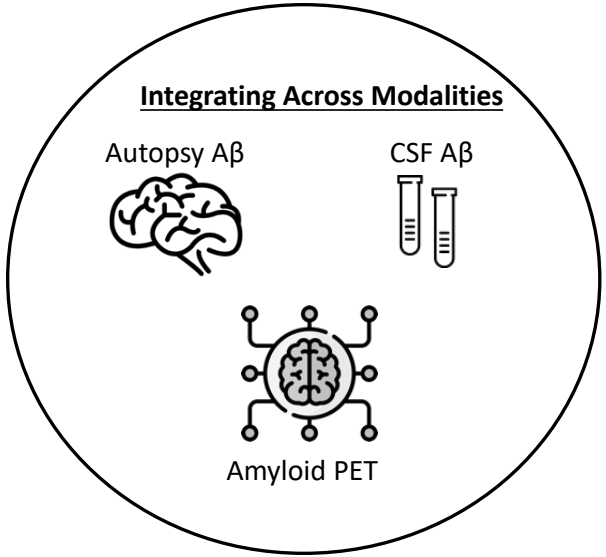
# Integrative Analysis for More Precise Phenotypes

# Integrative Analytics

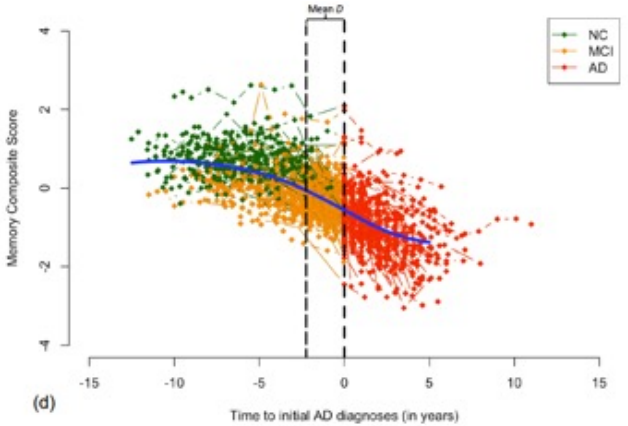
## Applying Advanced Algorithms to Increase Statistical Power

Age of Onset of Aβ+ Calculation

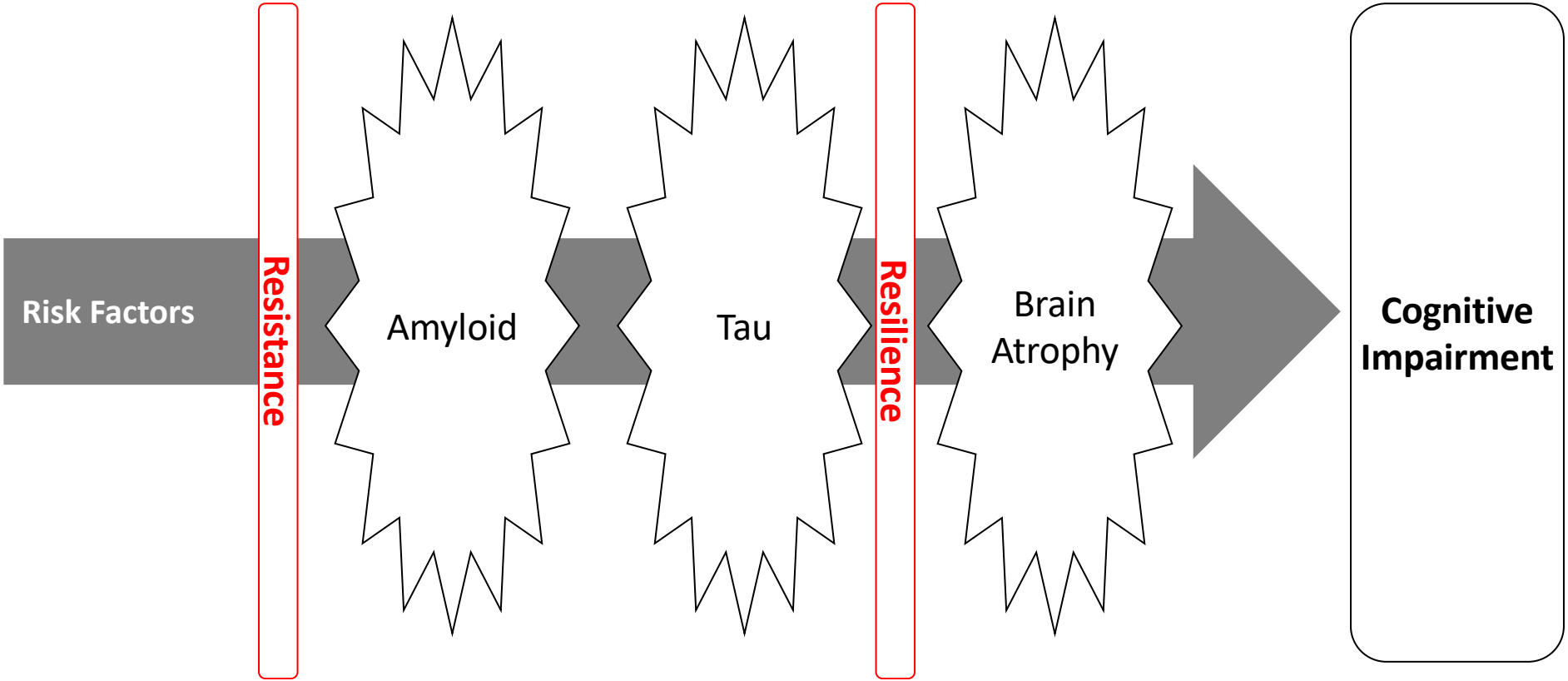



Mixed Effects Sigmoidal Model



# Resistance and Resilience



# Approximating Resilience w/o Path Measures

Jared Phillips
Graduate Student

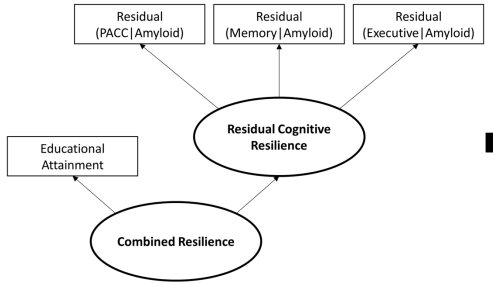
## Silver Model

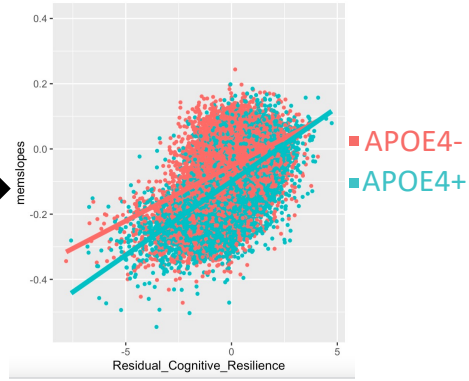
### Mixed Effects Model Predictors:

Age, Sex, Race, APOE, Baseline Performance, Time and 3-way Interactions

Variance explained = 26%

Sample Size (3+ Visits) = **20,339**



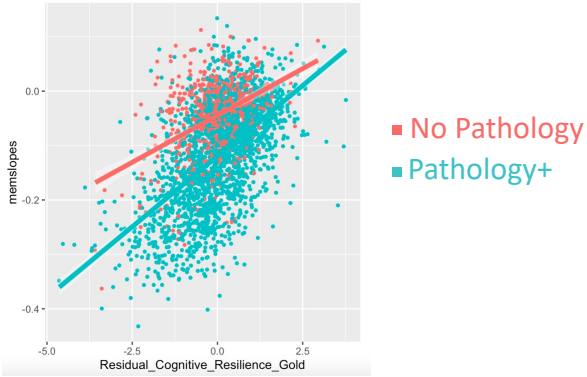

## Gold Model

### Mixed Effects Model Predictors:

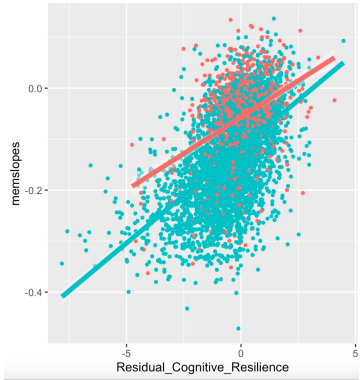
Age, Sex, Race, APOE, Pathology, Baseline Performance, Time
and 3-way Interactions

Variance explained = 55%

Sample Size: **5,107**

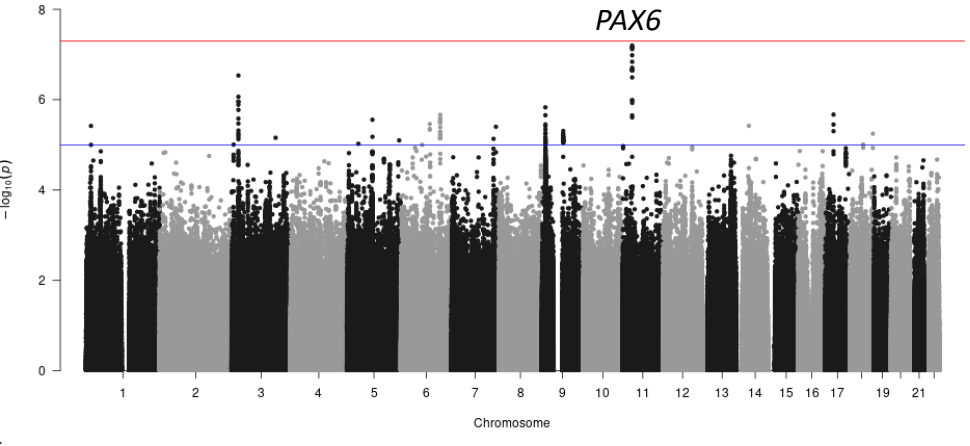


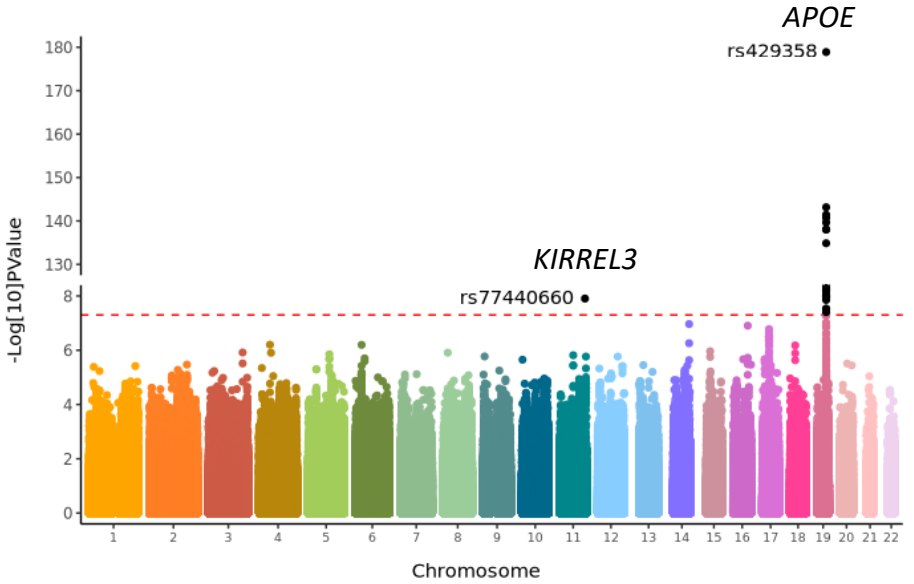

Gold Standard Results




Silver Standard Results

# New Resilience and Resistance Loci



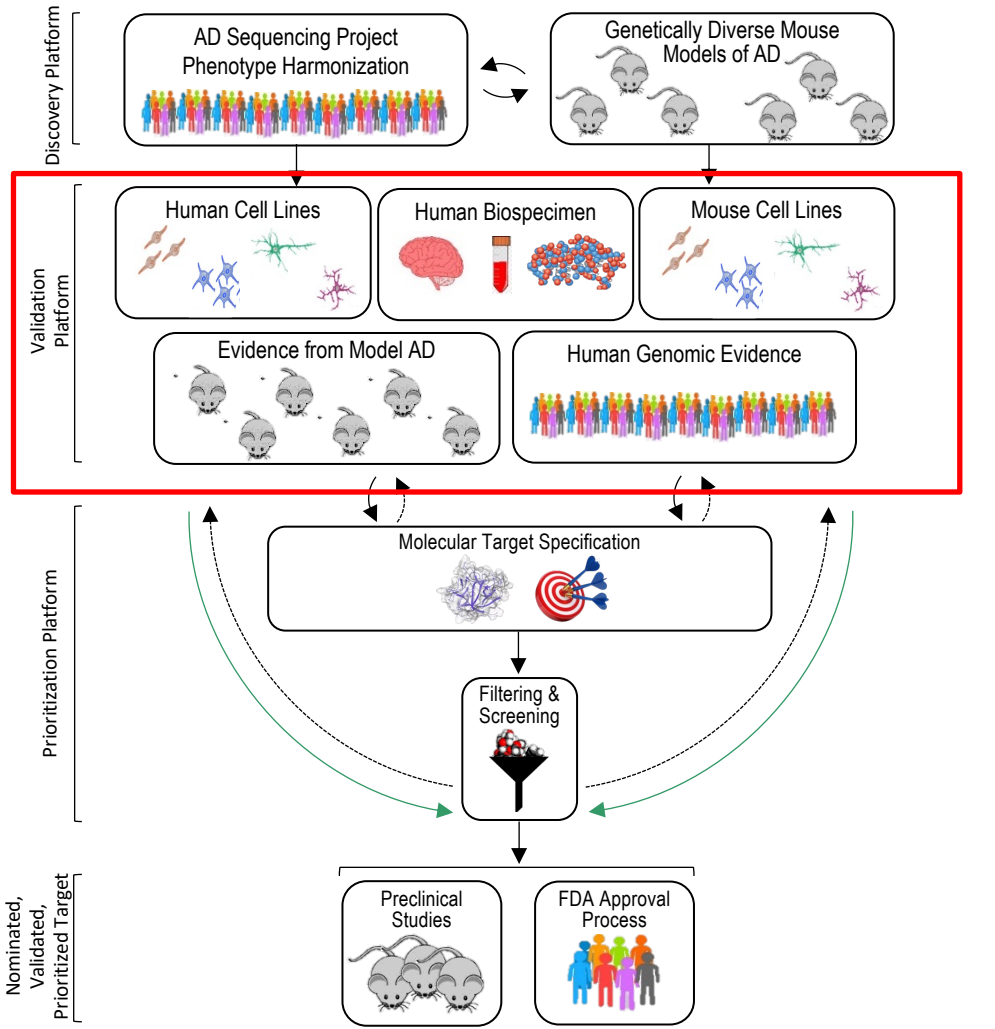




*Phillips et al, In Preparation*

*Castellano, ... Koran, In Preparation*

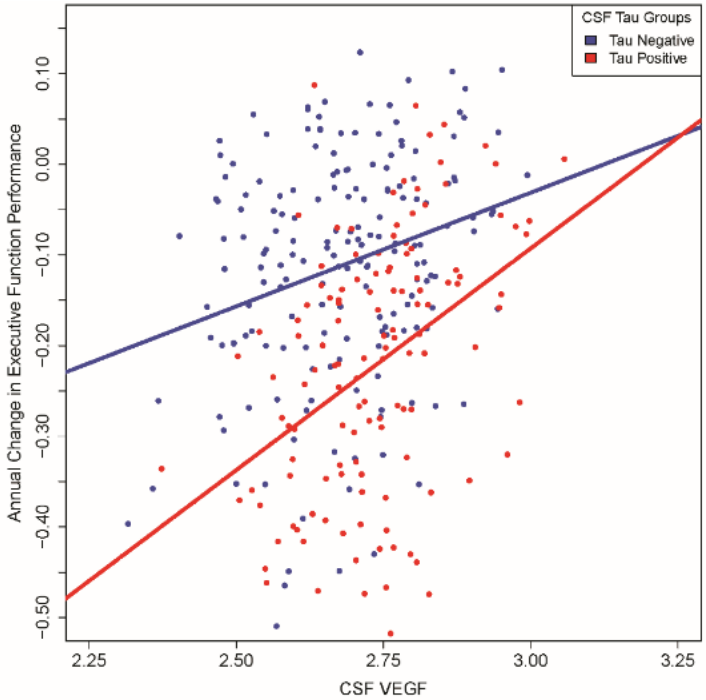
# Deep Molecular Characterization of High Quality Candidates

# Drug Discovery Framework in the Computational Neurogenomics Team

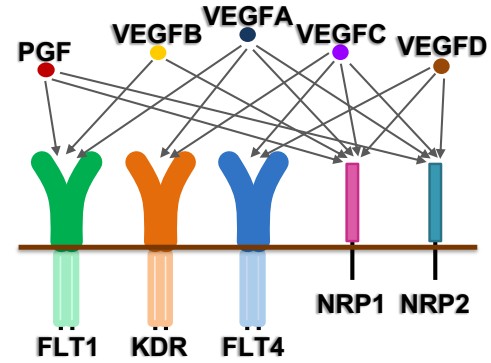


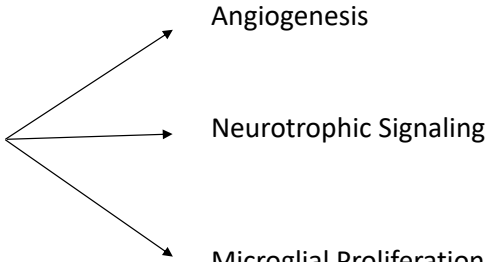
# Vascular Endothelial Growth Factor

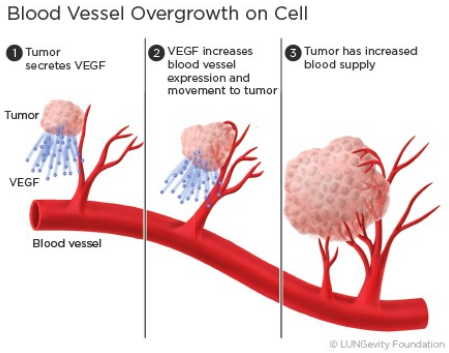
**CSF VEGF Levels Associated with Slower Future Cognitive Decline**

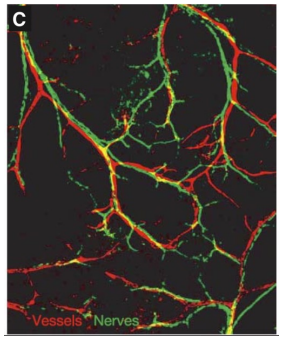



*(Hohman, Bell, & Jefferson, JAMA Neurology, 2015)*



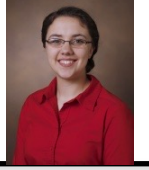



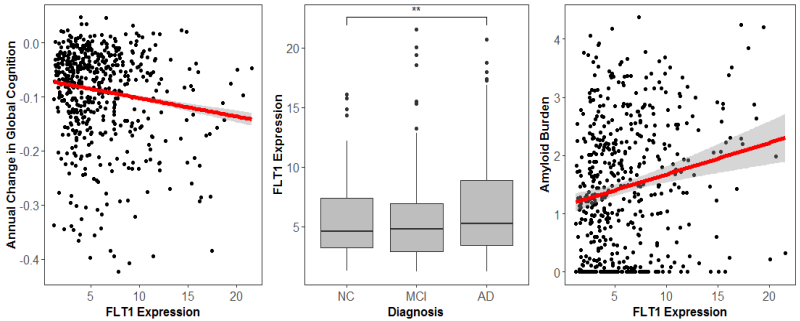

Ruiz et al., 2009. *Physiol Rev.*

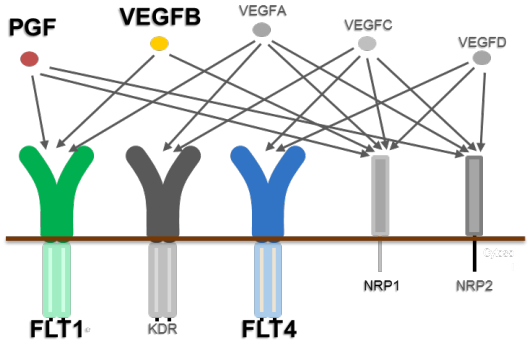
# VEGF Transcript Association in the Brain



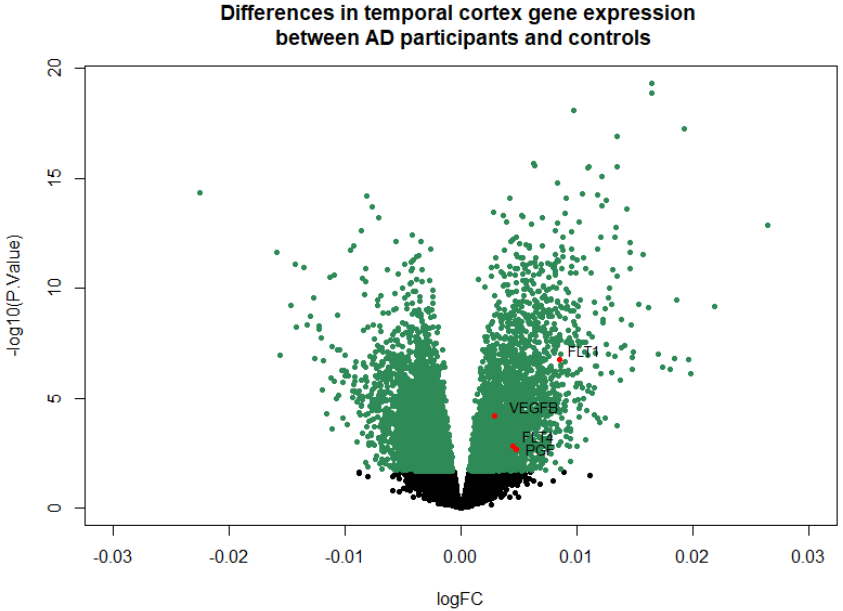
Emily Mahoney

## Brain Expression of Vascular Endothelial Growth Factor



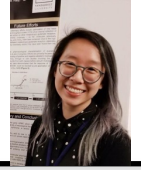




## Replication in Independent Dataset

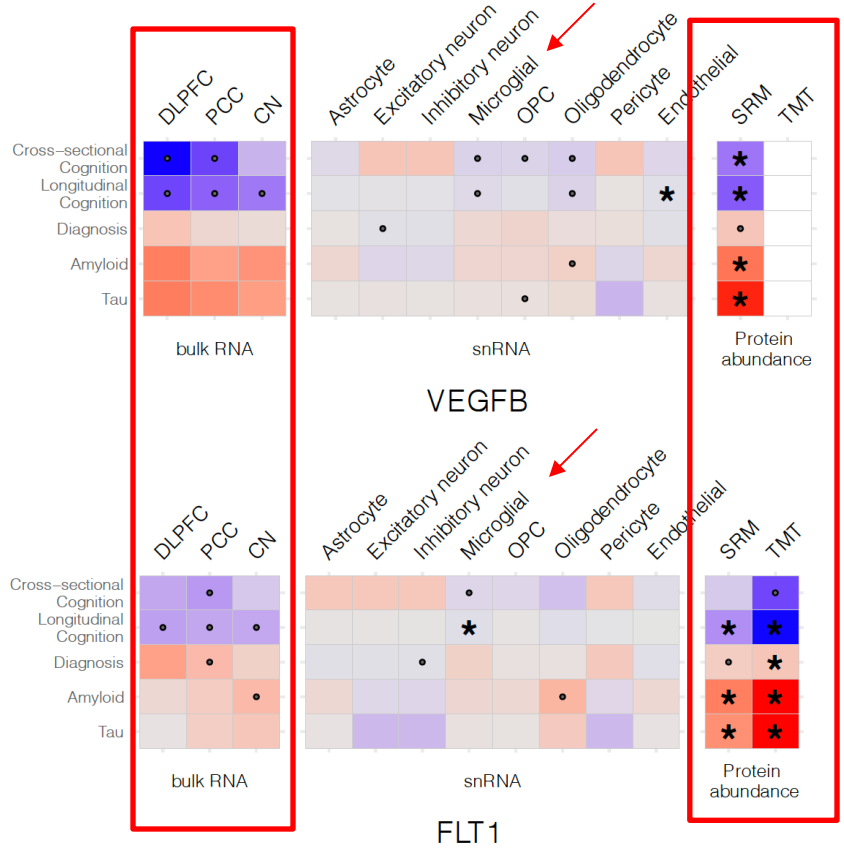


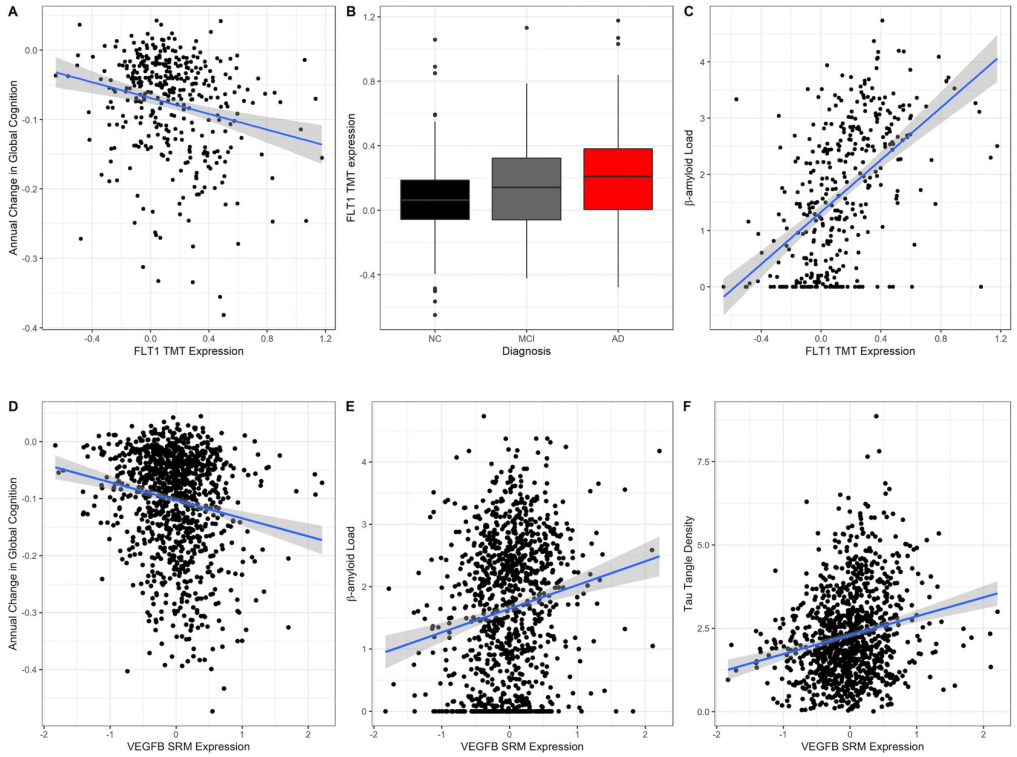

Mahoney et al., 2021, Molecular Psychiatry

# FLT1 and VEGFB Robustly Relate to AD outcomes



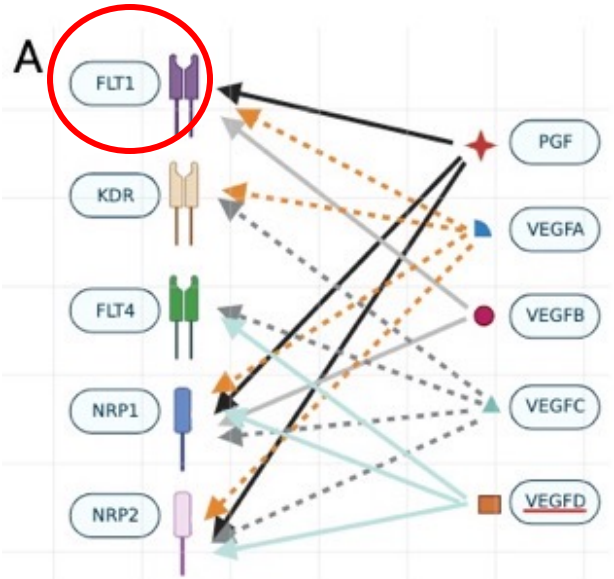
Mabel Seto, PhD

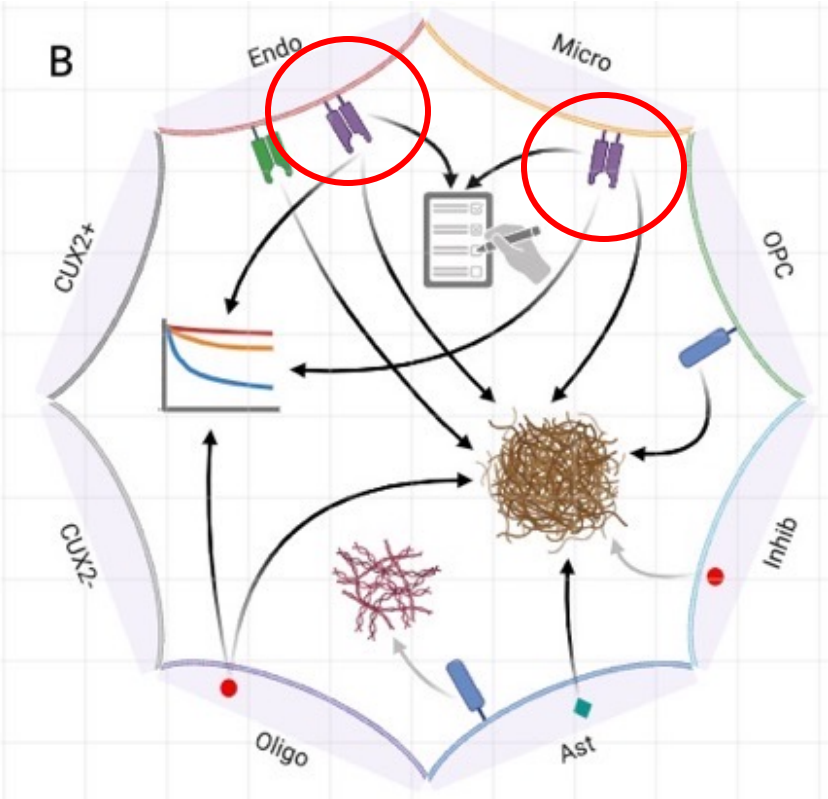



Seto et al., *Neurobiology of Aging*, 2023

# Confirming snRNA Associations in Prefrontal Cortex




Sample size: 424

Wu et al., *In Preparation*

# Post-translational Modifications

*The FASEB Journal* express article 10.1096/fj.03-0767fje. Published online March 4, 2004.

**The c-Cbl/CD2AP complex regulates VEGF-induced endocytosis and degradation of Flt-1 (VEGFR-1)**

Satsuki Kobayashi,*,† Asako Sawano,* Yoshihisa Nojima,† Masabumi Shibuya,* and Yoshiro Maru*,‡

PLOS ONE

OPEN ACCESS PEER-REVIEWED

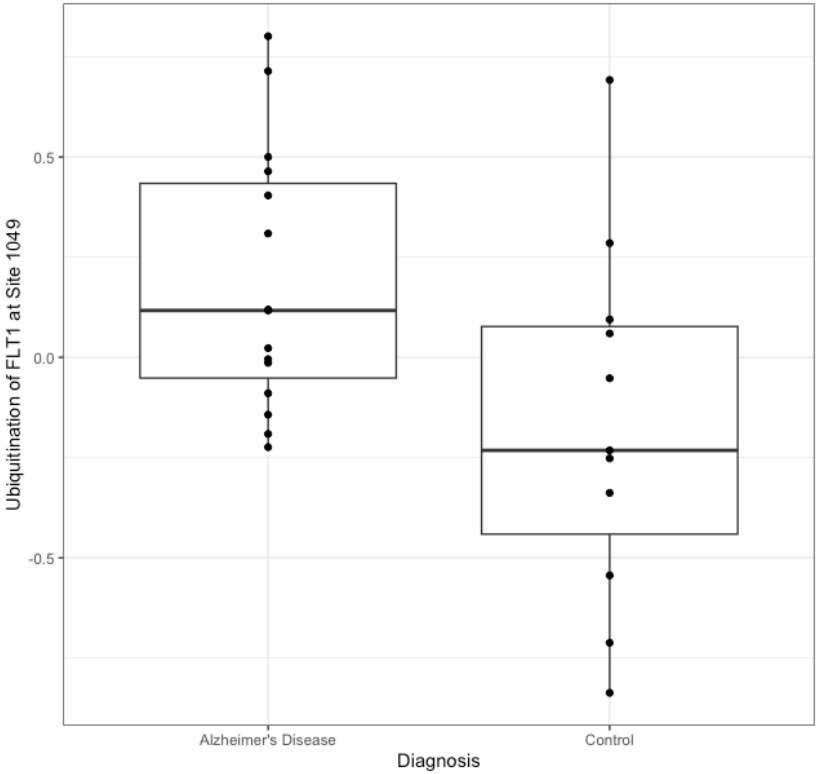
RESEARCH ARTICLE

**N-Terminal Cleavage and Release of the Ectodomain of Flt1 Is Mediated via ADAM10 and ADAM 17 and Regulated by VEGFR2 and the Flt1 Intracellular Domain**

Nandita S. Raikwar, Kang Z. Liu, Christie P. Thomas

Published: November 11, 2014 • https://doi.org/10.1371/journal.pone.0112794

FLT1 Ubiquitination is Upregulated in AD



# FLT1 is a Druggable Target

## Druggability of FLT1

AMP-AD pharmaceutical partners scored the tractability of targets using publicly-available resources and have generated ratings of small-molecule druggability, therapeutic antibody feasibility, and safety.

Learn more about the analysis

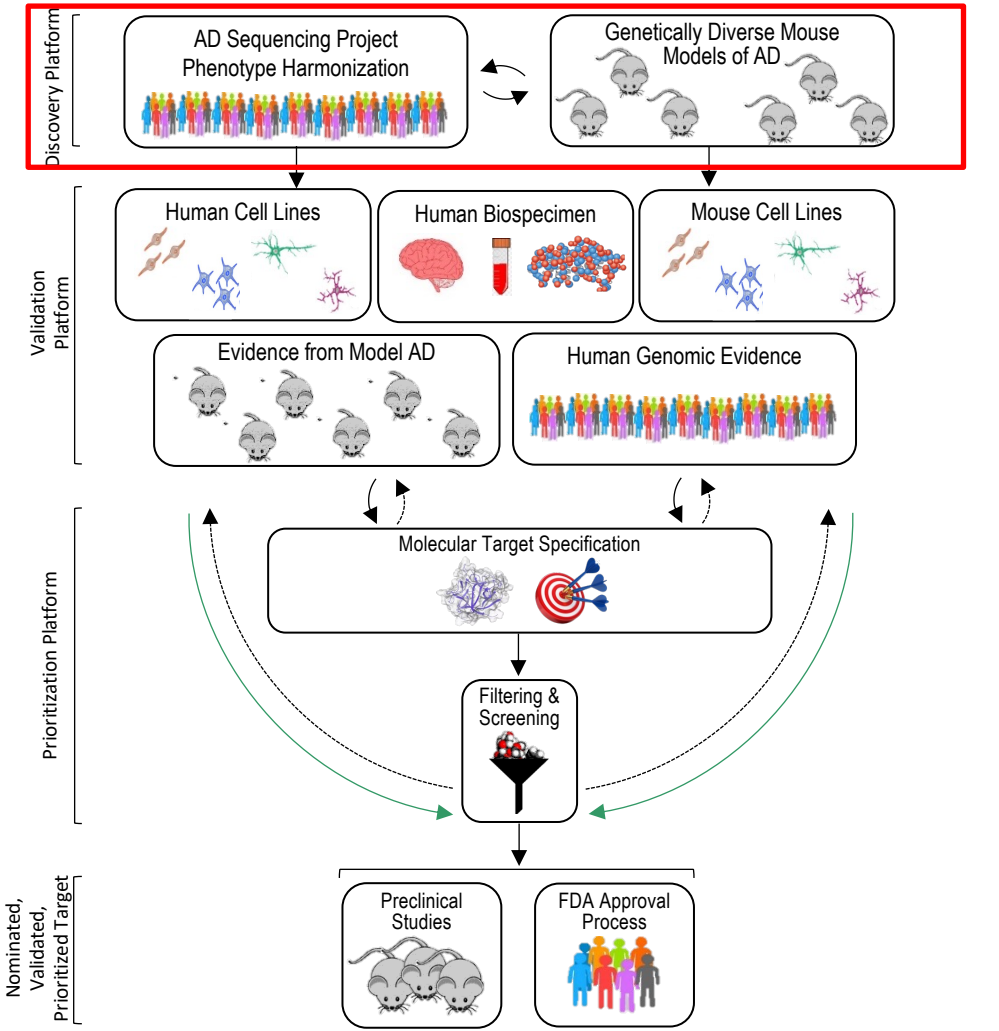
| | | |
|---|---|---|
| Small Molecule Modality | 1 | Small molecule druggable: Protein with a small molecule ligand identified from ChEMBL, meeting TCRD activity criteria. |
| Antibody Modality | 1 | Secreted protein. Highly accessible to antibody-based therapies. |
| Safety | 1 | Clinical data, evidence of tolerable safety profile in desired modality; target has a drug in phase IV in the appropriate modality, with good safety profile. |

TREAT-AD
TaRget Enablement to Accelerate Therapy Development for AD

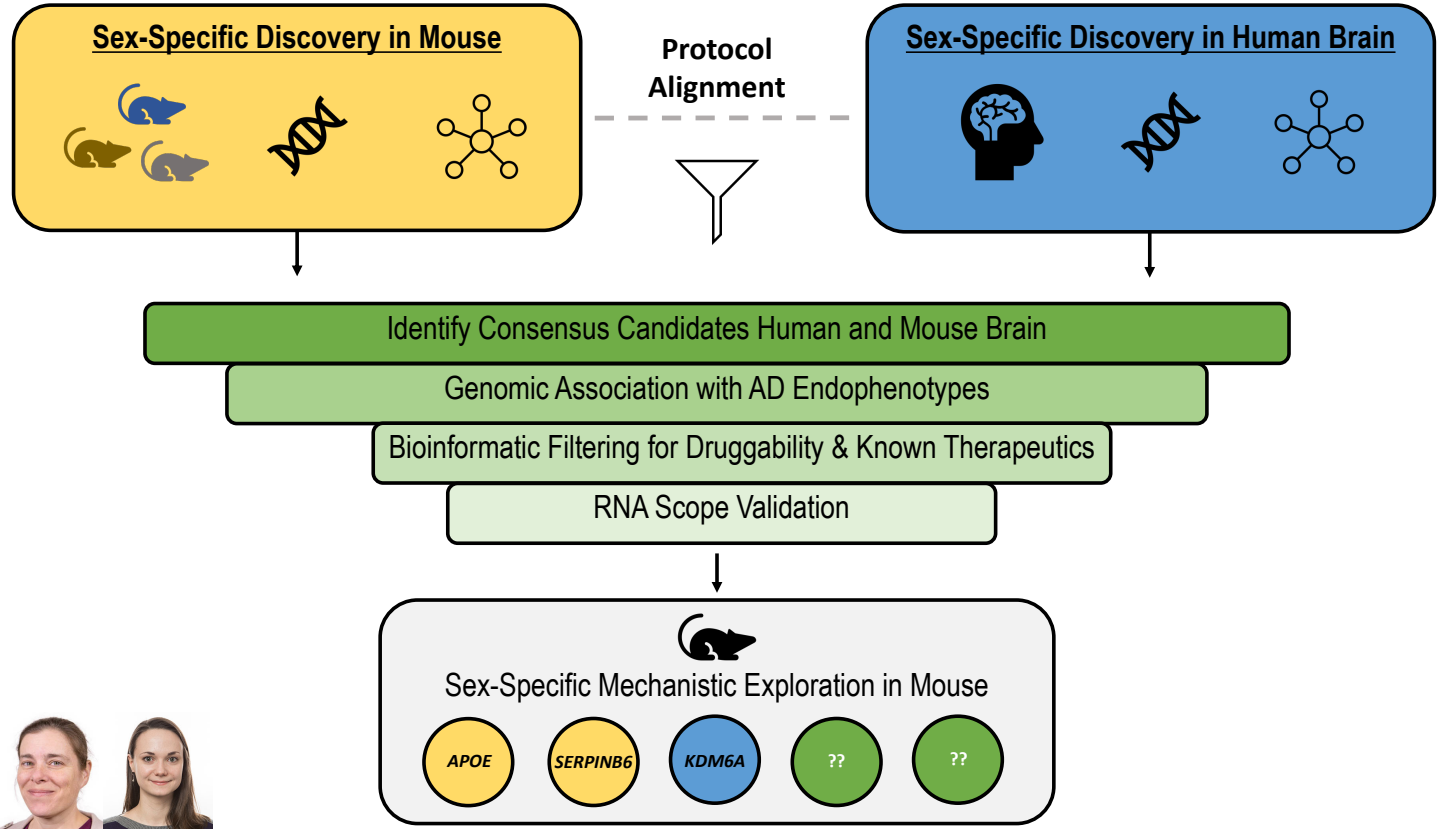
Agora

https://agora.adknowledgeportal.org/

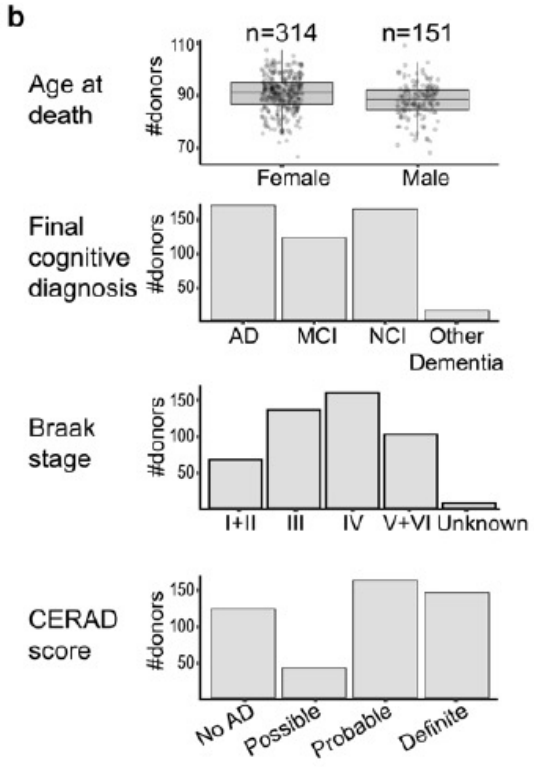
# Drug Discovery Framework in the Computational Neurogenomics Team

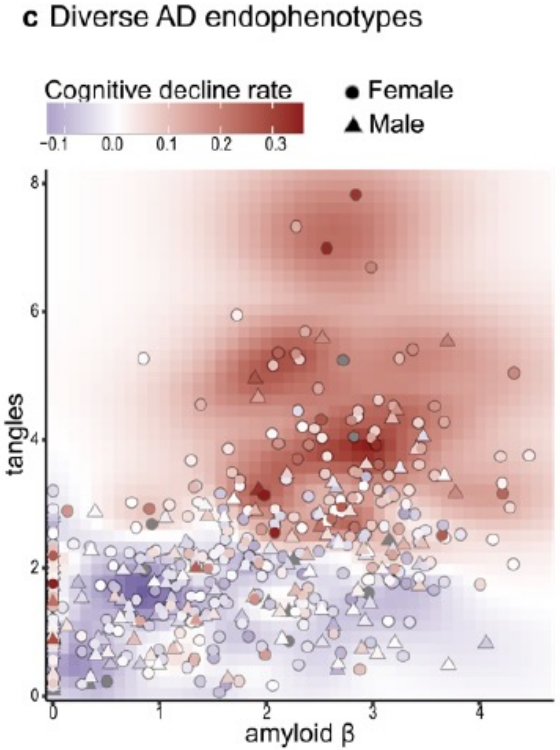


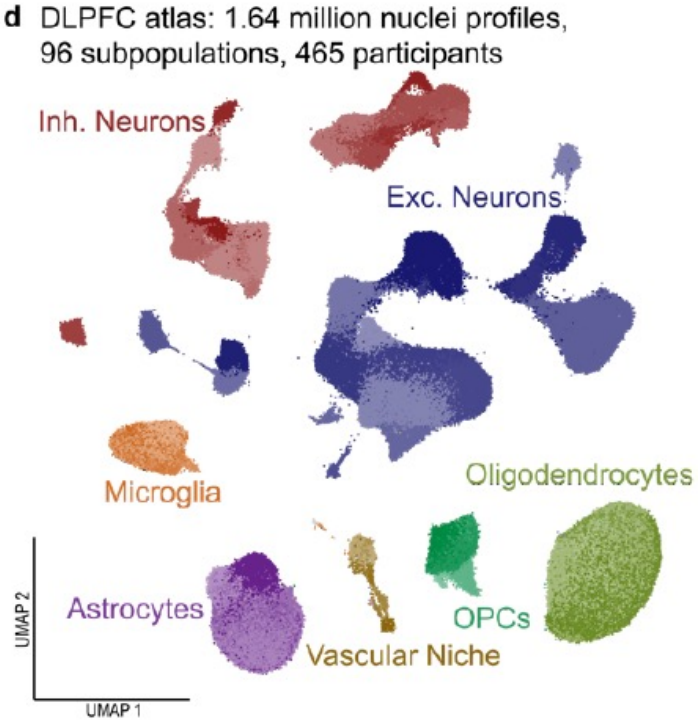
# Collaborations to Move Targets Forward




# Exploring Sex Differences with Single Cell Resolution



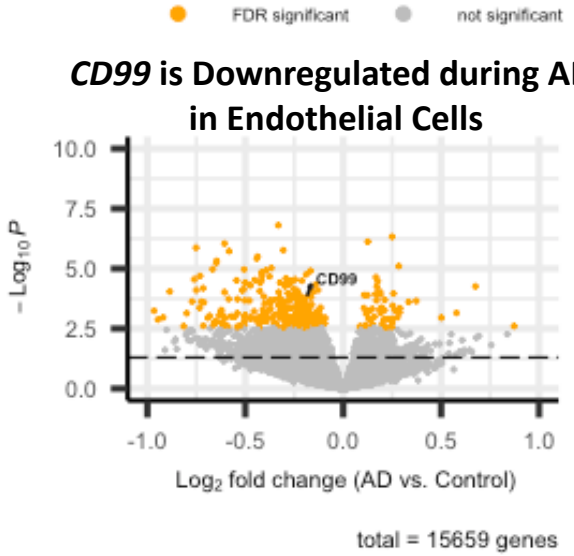



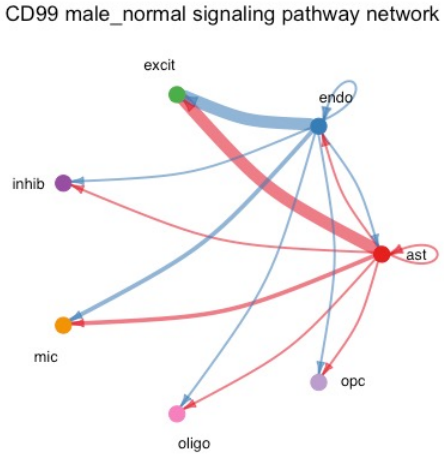



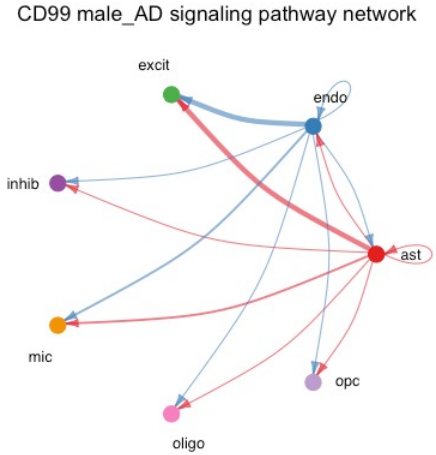

https://www.biorxiv.org/content/10.1101/2023.03.07.531493v1

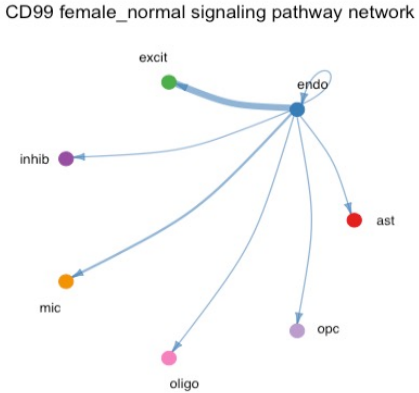
Green et al., preprint

# Striking Sex Differences in Immune Cells in AD




Yiyang Wu, MD, PhD

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