



Genetic Predictors of Multimodal Brain Tau Pathology in Older Adults

Skylar Walters^{1*}, Ting-Chen Wang^{1,2*}, Derek Archer^{1,2}, Yiyang Wu¹, Paul K. Crane³, C. Dirk Keene⁴, Eric B. Larson³, Shubhabrata Mukherjee³, Andrew J. Saykin^{5,6}, Julie A. Schneider⁷, David A. Bennett⁷, Lisa L. Barnes⁷, Philip L. De Jager^{8,9,10,11}, Reisa A. Sperling^{12,13}, Elizabeth Mormino¹⁴, Gary Beecham¹⁵, Pedro Mena¹⁶, Thomas J. Montine¹⁷, Li-San Wang²⁰, Badri Vardarajan^{8,9,10,18}, Richard Mayeux^{8,9,10,18}, Brian W. Kunkle¹⁶, William S. Bush¹⁹, Gerard D. Schellenberg²⁰, Margaret A. Pericak-Vance¹⁶, Jonathan L. Haines¹⁹, Sarah Biber²¹, Walter A. Kukull²¹, Michael L. Cuccaro¹⁶, Arthur W. Toga²², Sterling C. Johnson²³, Corinne D. Engelman²⁴, Karly Cody²⁵, Andrzej Sokolowski²⁵, Rachel F. Buckley¹², Carlos Cruchaga²⁶, A4 Study Team, Alzheimer's Disease Neuroimaging Initiative (ADNI), Alzheimer's Disease Sequencing Project (ADSP), Timothy Hohman^{1,2}, Mary Ellen Koran^{27,28}, Logan Dumitrescu^{1,2}

¹Vanderbilt Memory and Alzheimer's Center, Department of Neurology, Vanderbilt Health, Nashville, Tennessee; ²Vanderbilt Genetics Institute, Vanderbilt Health, Nashville, Tennessee; ³School of Medicine, University of Washington, Seattle, Washington; ⁴Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA, USA; ⁵Department of Radiology and Imaging Sciences, Center for Neuroimaging, School of Medicine, Indiana University, Indianapolis; ⁶Department of Medical and Molecular Genetics, School of Medicine, Indiana University, Indianapolis; ⁷Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois; ⁸Department of Neurology, Columbia University Medical Center, New York, New York; ⁹Department of Neurology, The New York Presbyterian Hospital, New York; ¹⁰Taub Institute for Research on Alzheimer's Disease and The Aging Brain, Columbia University Medical Center, New York, New York; ¹¹Center for Translational and Computational Neuroimmunology, Department of Neurology, Columbia University Medical Center, New York, New York; ¹²Department of Neurology, Harvard Medical School, Boston, MA, USA; ¹³Brigham and Women's Hospital and Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; ¹⁴Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA, USA; ¹⁵Department of Biostatistics and Data Science, Wake Forest University School of Medicine, Winston-Salem, NC, USA; ¹⁶John P. Hussman Institute for Human Genomics, University of Miami School of Medicine, Miami, FL, USA; ¹⁷Department of Pathology, Stanford University, Stanford, CA, USA; ¹⁸The Institute for Genomic Medicine, Columbia University Medical Center, New York, New York; ¹⁹Department of Population and Quantitative Health Sciences, Institute for Computational Biology, School of Medicine, Case Western Reserve University, Cleveland, OH, USA; ²⁰Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; ²¹Department of Epidemiology, School of Public Health, University of Washington, Seattle; ²²Laboratory of Neuroimaging, USC Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; ²³Alzheimer's Disease Research Center, University of Wisconsin School of Public Health, Madison, WI, USA; ²⁴Department of Population Health Sciences, University of Wisconsin-Madison, School of Medicine and Public Health, Madison, WI, USA; ²⁵Department of Neurology and Neurological Sciences, Stanford University, Palo Alto, California, USA; ²⁶Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA; ²⁷Department of Radiology and Radiological Sciences, Vanderbilt Health, Nashville, TN, USA; ²⁸Department of Radiology, Mayo Clinic of Arizona, Scottsdale, AZ, USA; *Authors with equal contributions

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Background

- ❖ Tau proteinopathy is a hallmark of Alzheimer's disease (AD) pathology.
- ❖ Autopsy and biomarker studies have begun to characterize the underlying genetic architecture of tau proteinopathy, but genomic discovery is often limited by sample size.
- ❖ Recent genome-wide association studies (GWAS) linking neuropathology measured *in vivo* by positron emission tomography (PET) and at autopsy offer an exciting roadmap to combine tau definitions across modalities to increase GWAS sample size (Maass et al.; Schöhl et al.; Pascoal et al.; Theriault et al.).
- ❖ This study combined autopsy and PET measures of tau neuropathology to perform GWAS meta-analysis across 8 cohorts of aging and AD, enhancing sample size and better characterizing the genetic architecture of tau.

Methods

- ❖ Data from eight cohorts of aging and AD were included: the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study; the Adult Changes in Thought study (ACT); the Alzheimer's Disease Neuroimaging Initiative (ADNI); the Knight Alzheimer's Disease Research Center (Knight ADRC); the National Alzheimer's Coordinating Center (NACC); the National Institute of Aging Alzheimer's Disease Family Based Study (NIA-AD FBS); the 3 harmonized cohorts of the Religious Orders Study, the Rush Memory and Aging Project, and the Minority Aging Research Study (ROS/MAP/MARS); and the Wisconsin Registry for Alzheimer's Prevention (WRAP) study.
- ❖ 9,200 European (EUR) individuals were included ($N_{\text{tau PET Imaging}}=1,982$; $N_{\text{Autopsy}}=7,218$; mean age at death [autopsy]=83.7; mean age at scan [tau PET]=73.23) (Table 1).
- ❖ Binarized tau status (negative/positive) was determined based on either medial temporal lobe composite of *in vivo* tau PET imaging (Figure 1A) or BRAAK≥III at autopsy (Figure 1B).
- ❖ GWAS was performed across cohorts per modality (per tracer in tau PET analyses) and then meta-analyzed across modalities. Covariates included: age, sex, and the first five genetic principal components.
- ❖ Follow-up single nucleus RNA sequencing analyses were performed in ROS/MAP using linear regression models testing for gene associations with AD pathologies for candidate genes identified through GWAS analyses. Covariates included: age at death, sex, postmortem interval (PMI), and interval between last visit and death.
- ❖ Follow-up analyses were performed using linear regression models with an ordinal tau definition (defined by either Braak staging in the autopsy datasets or an individual's highest Braak stage in tau PET imaging) for significant genome-wide variants identified in GWAS. Covariates included age, sex, and the first five genetic principal components.
- ❖ Validation models using linear regression in R were performed with cerebrospinal fluid (CSF) phosphorylated tau (p-tau) and total tau (t-tau) [$N=3,212$] to test associations of genome-wide significant loci identified through GWAS. Covariates included: age (at CSF visit), sex, and the first five principal components.
- ❖ Genome-wide significant variants were queried in the GTEx database for expression quantitative trait loci (eQTL), and candidate genes were queried in the AD Knowledge Portal (AGORA) for differential expression in the AD brain.

Table 1. Participant Characteristics

	Tau PET Imaging (N=1,982)	Autopsy (N=7,218)
Sex, N (%)		
Males	860 (43.39)	3,461 (47.95)
Females	1,122 (56.61)	3,757 (52.05)
Mean age/age at death, yrs (SD)	73.23 (8.72)	83.66 (10.79)
Discordant, N (%)	65 (3.28)	N/A
Tau positivity, N (%)		
Negative	1,362 (68.72)	1,672 (23.16)
Positive	620 (31.28)	5,546 (76.84)
Amyloid positivity, N (%)		
Negative	691 (34.86)	1,567 (21.71)
Positive	638 (32.19)	5,645 (78.21)
Missing	653 (32.95)	6 (0.08)

Continuous variables are presented in mean (SD). Categorical variables are presented in N (%). PET: positron emission tomography; SD: standard deviation.

Figure 1A. Defining Tau in PET Imaging

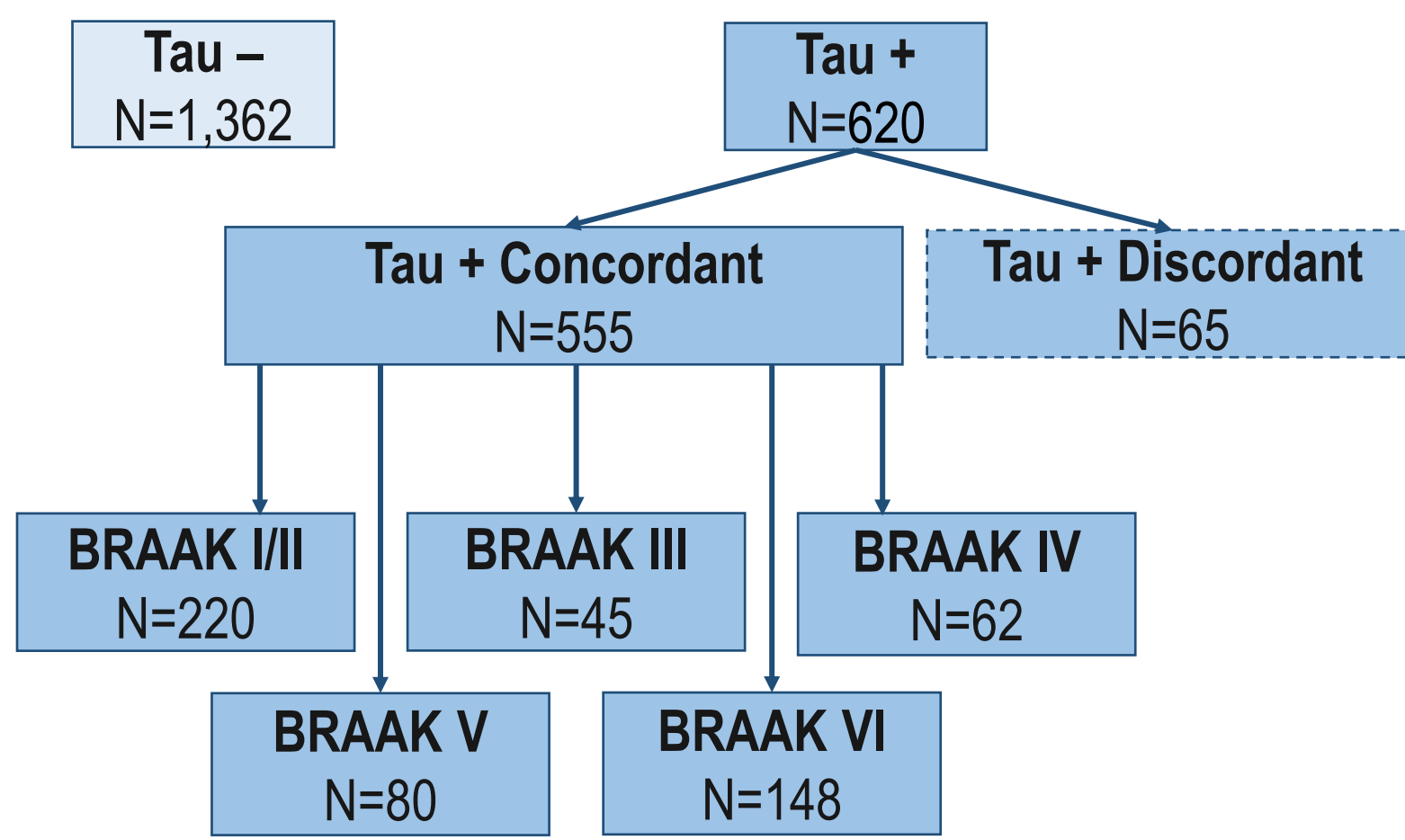
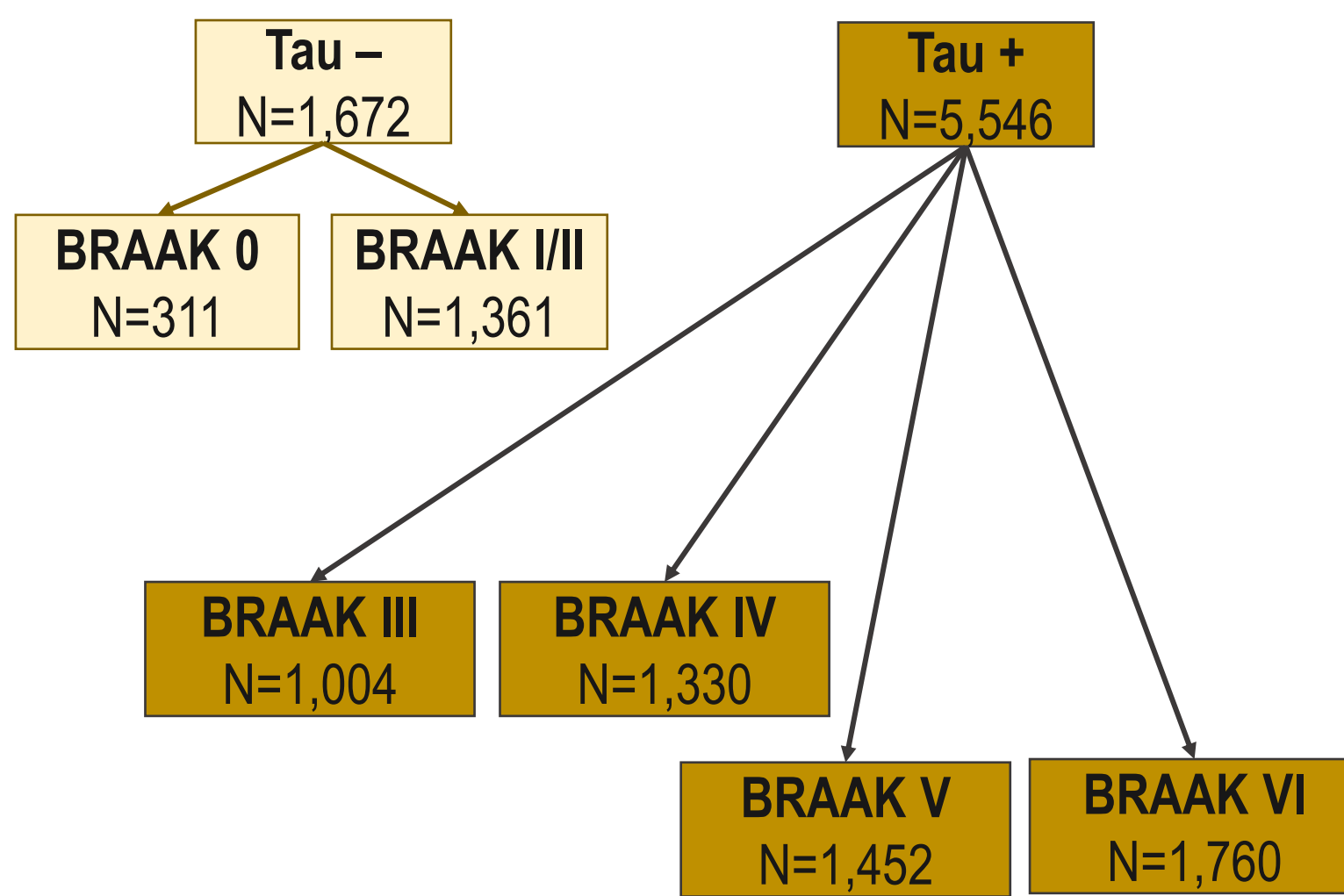


Figure 1B. Defining Tau in Autopsy



Results

Table 2. Genetic Loci With A Significant Genome-Wide Effect on Tauopathy

Phenotype	CHR	BP	A1:A2	SNP	MAF	OR	P	Gene
Multi-Modal Tau	2	127135234	T:C	rs6733839	0.402	1.260	1.48x10⁻⁹	<i>BIN1</i>
	14	92486336	T:C	rs7156885	0.280	0.799	2.35x10⁻⁸	<i>SLC24A4/RIN3</i>

Boldface indicates significant genome-wide effect ($P < 5.0 \times 10^{-8}$). CHR=chromosome; BP=base pair position; A1=minor allele; A2=other allele; MAF=minor allele frequency

Figure 2. Chromosome 2 Locus Association With Tauopathy

A. rs6733839

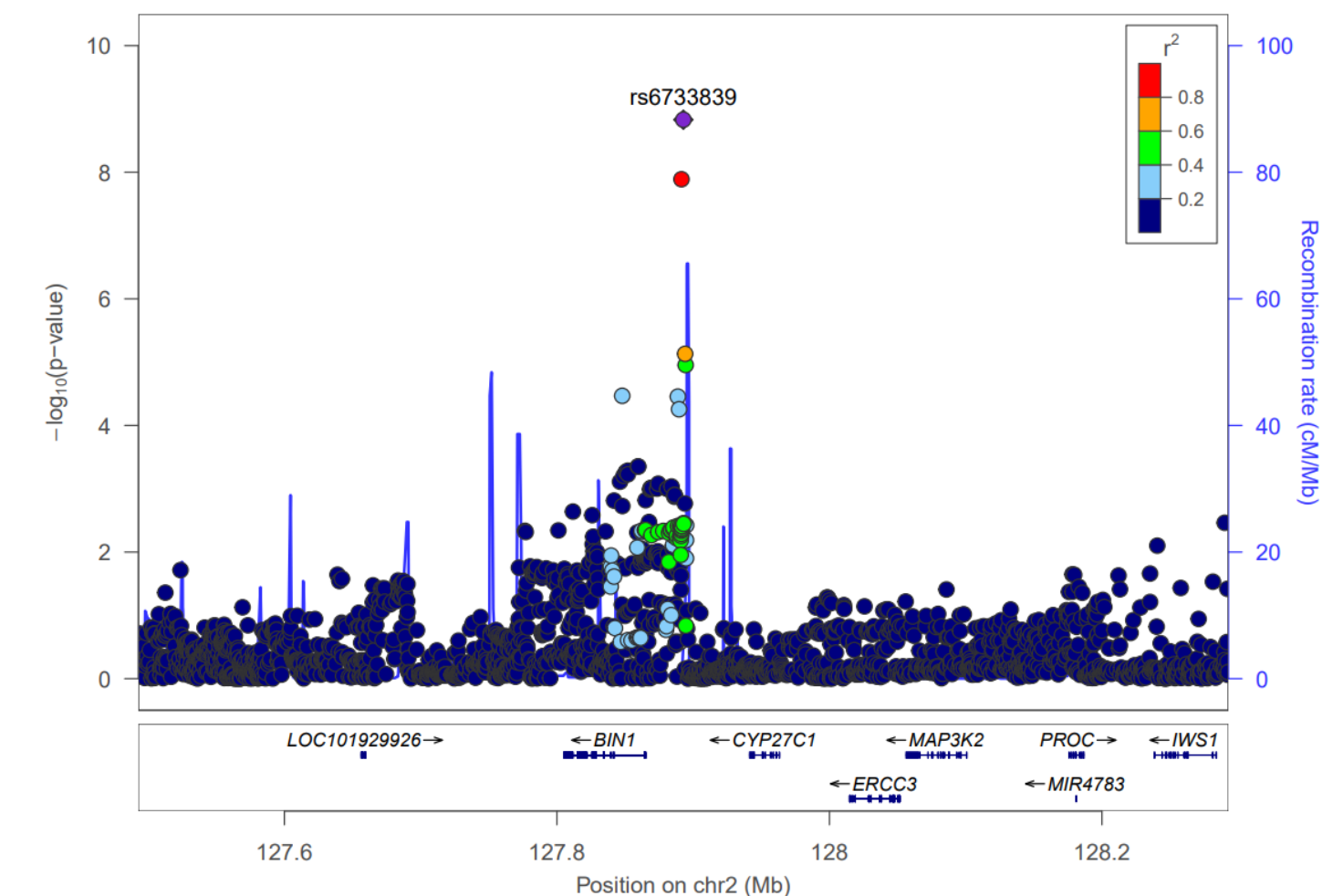


Figure 3. Chromosome 14 Locus Association With Tauopathy

A. rs7156885

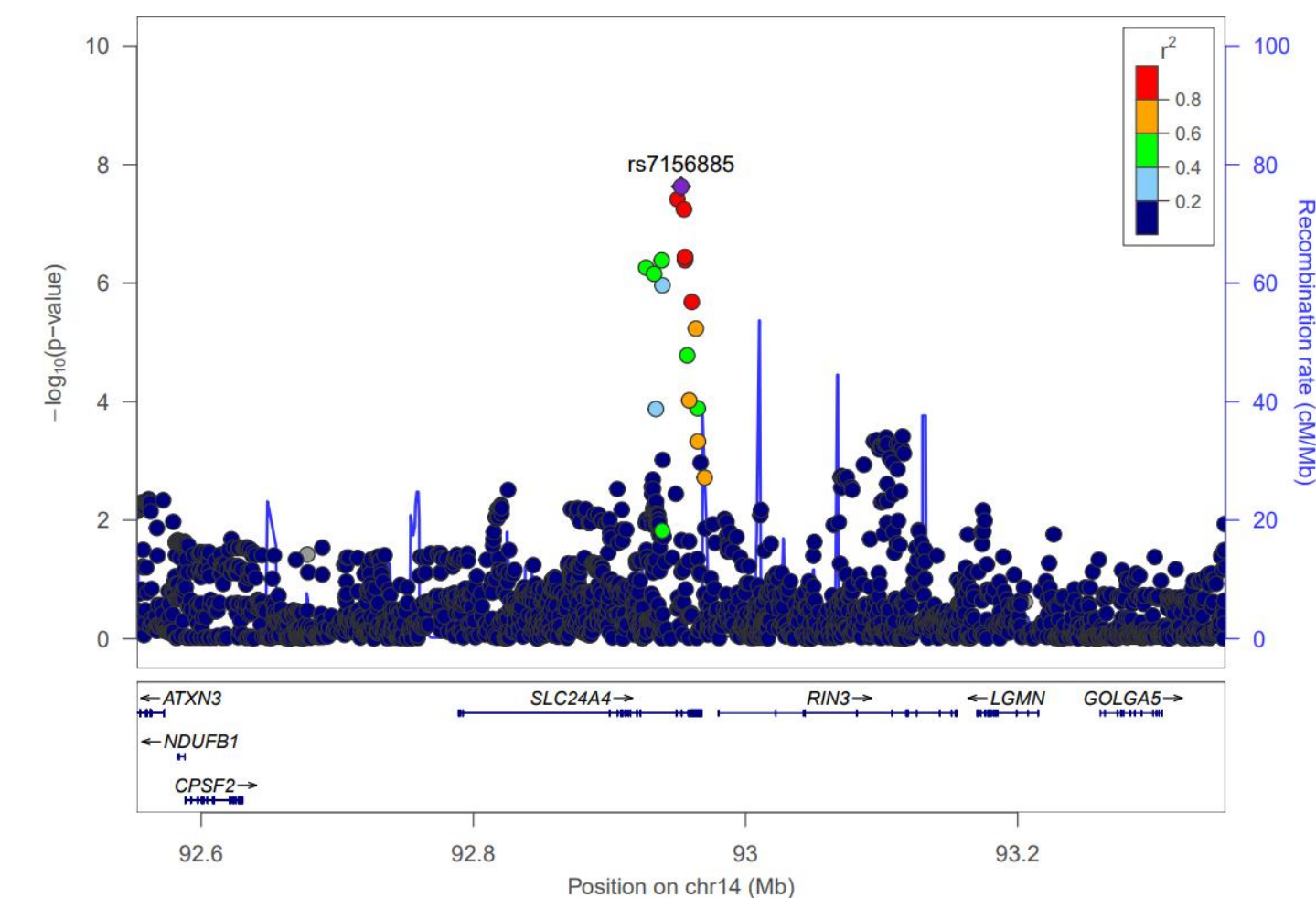
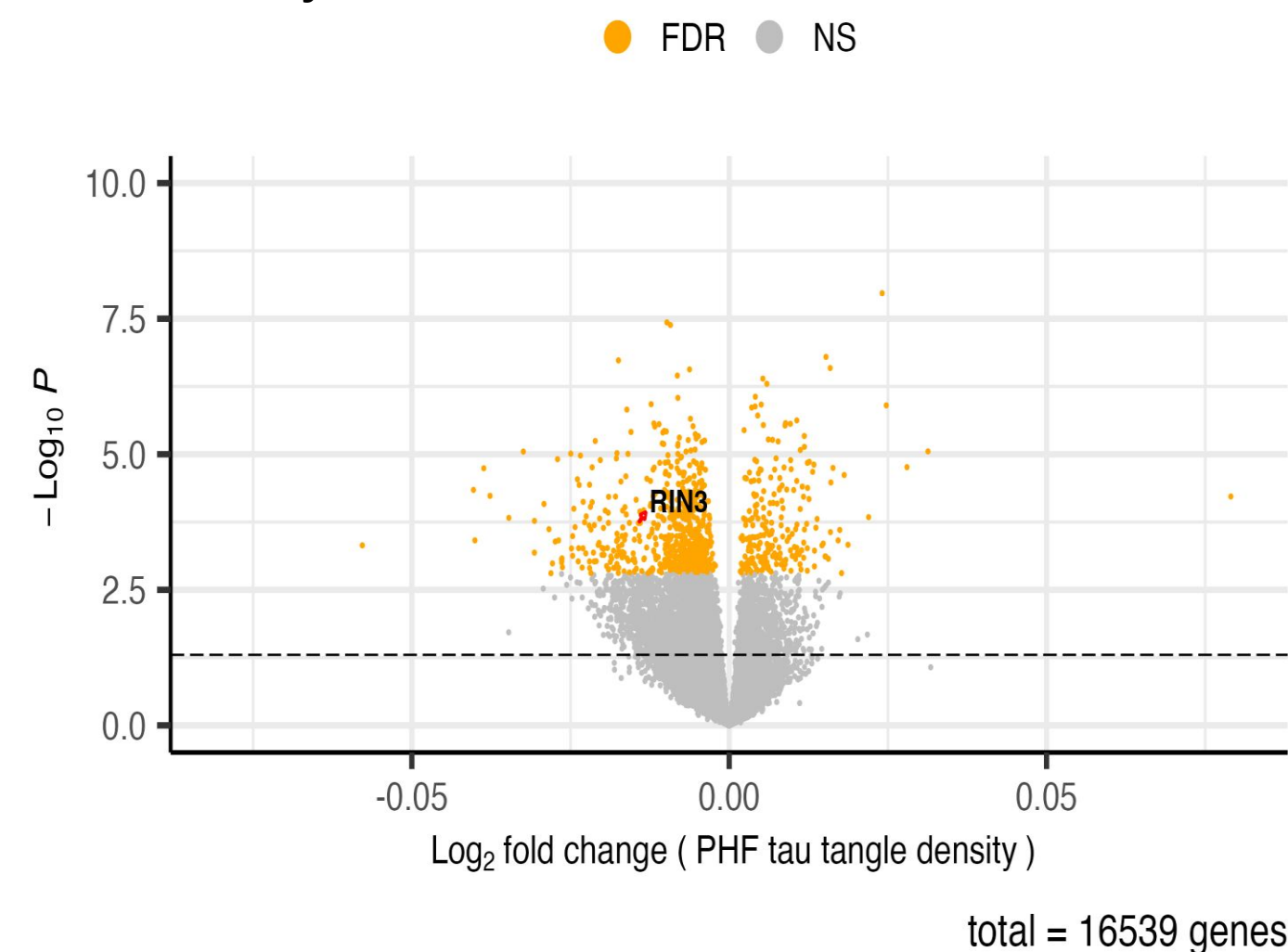


Figure 4. ROS/MAP Single Nucleus RNA Sequencing Results in Excitatory and Inhibitory Neurons for *RIN3* in the Dorsolateral Prefrontal Cortex

A. Excitatory Neurons



B. Inhibitory Neurons

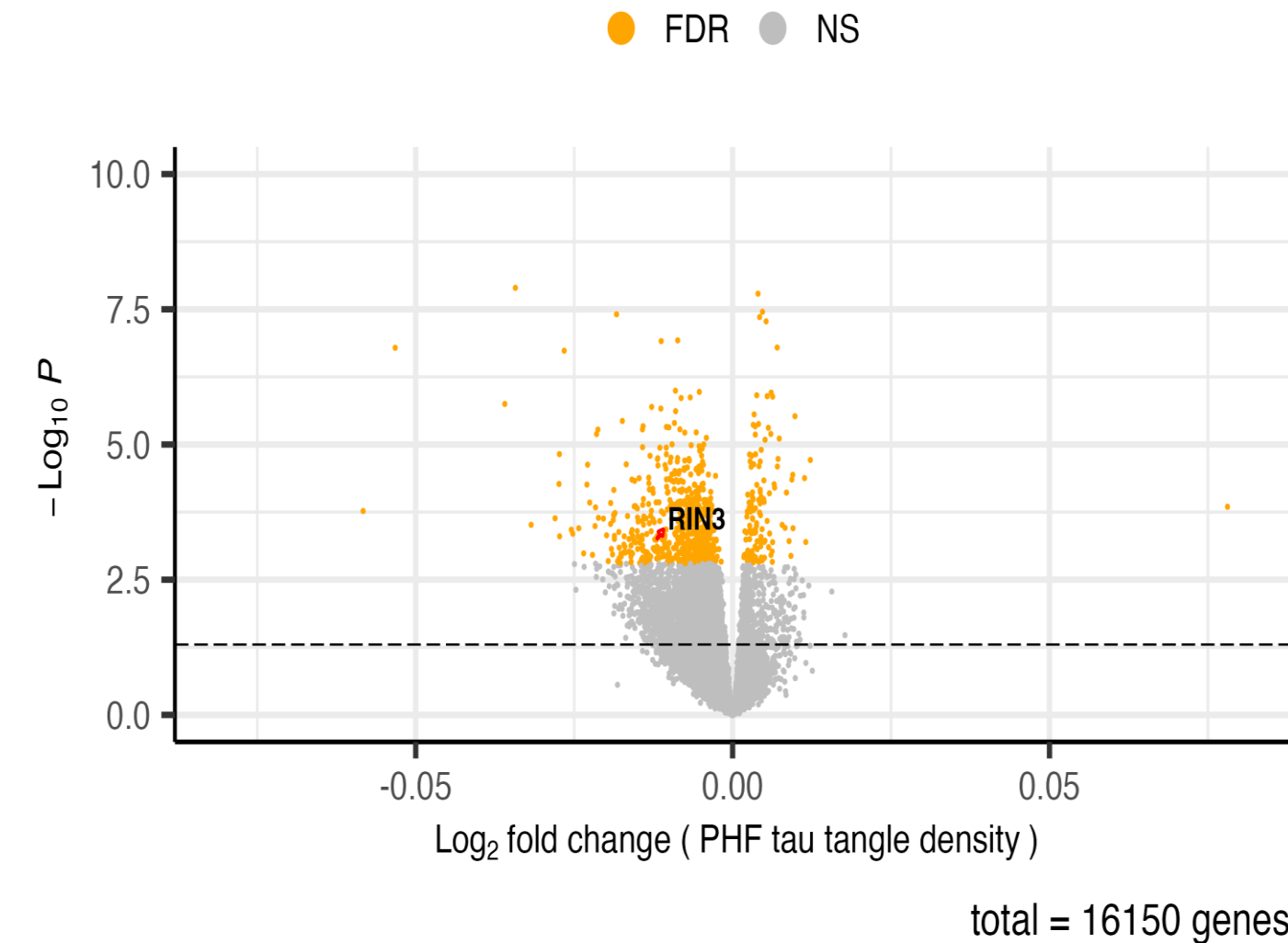


Table 3. Analysis of Top SNP Associations Using Ordinal Tau Definition

Outcome	SNP	OR (SE)	P
Tau (Ordinal)	rs6733839	1.22 (0.03)	4.55x10⁻¹²
	rs7156885	0.86 (0.03)	1.20x10⁻⁶

Boldface indicates significant Bonferroni-corrected p-values ($P < 0.05$). SNP: single nucleotide polymorphism; OR: odds ratio; SE: standard error; P: p-value.

Table 4. Replication of Top SNP Association Results in CSF Tau

Outcome	SNP	Beta (SE)	P	P.Corrected
p-Tau	rs6733839	0.116 (0.059)	0.049	0.196
	rs7156885	-0.089 (0.063)	0.160	0.064
t-Tau	rs6733839	0.111 (0.194)	0.567	1.000
	rs7156885	-0.530 (0.208)	0.011	0.044

Boldface indicates significant Bonferroni-corrected p-values ($P_{\text{Corrected}} < 0.05$). SNP: single nucleotide polymorphism; CSF: cerebrospinal fluid; p-Tau: phosphorylated tau; t-Tau: total tau; SE: standard error; P: p-value; P.Corrected: Bonferroni-corrected p-value.

Table 5. GTEx eQTL Associations in Brain Tissues

SNP	Gene	Tissue	P	Direction
rs6733839	<i>BIN1</i>	Cerebellum	8.0x10⁻⁶	Downregulated
	<i>LOC105373604</i>	Spinal Cord (cervical-1)	5.2x10⁻⁷	Upregulated
rs7156885	<i>RIN3</i>	Cortex	3.8x10⁻⁵	Upregulated

Boldface indicates significant p-values ($P < 0.05$). SNP: single nucleotide polymorphism; P: p-value.

Table 6. AGORA Differential Gene Expression in the AD Brain

Gene	Brain Regions	P
<i>BIN1</i>	IFG, PHG, STG	<0.03
<i>LOC105373604</i>	ACC, IFG, PCC, PHG, TCX	<0.03
<i>SLC24A4</i>	PHG	<0.002
<i>RIN3</i>	ACC, DLPFC, IFG, PCC, PHG, STG, TCX	<0.04

Boldface indicates significant p-values ($P < 0.05$). P: p-value; IFG: inferior frontal gyrus; PHG: parahippocampal gyrus; STG: superior temporal gyrus; ACC: anterior cingulate cortex; PCC: posterior cingulate cortex; TCX: temporal cortex.

Results Summary

- ❖ Our multimodal Tau GWAS meta-analysis identified two genome-wide significant loci on chromosome 2 (previously known AD risk locus) and chromosome 14 (novel) associated with tauopathy.
- ❖ The chromosome 2 locus (index SNP: rs6733839) near *BIN1*, a previously known AD risk locus (Figure 2) demonstrates significant eQTL associations in GTEx brain tissues with *BIN1* and *LOC105373604* (Table 5). In the brain, *BIN1* is upregulated in AD individuals, and *LOC105373604* is downregulated in AD individuals [AGORA] (Table 6).
- ❖ The chromosome 14 locus (index SNP: rs7156885) near *SLC24A4/RIN3* (Figure 3) demonstrates significant eQTL associations in GTEx brain tissues with *RIN3* (Table 5). In the brain, *SLC24A4* and *RIN3* are upregulated in AD individuals [AGORA] (Table 6).
 - ❖ *SLC24A4* has been linked to AD risk in previous studies (Lambert et al.; Kunkle et al.; Karch et al.; Rosenthal et al.; Tan et al.; Yu et al.; Karlsson et al.). Interestingly, previous studies have suggested *RIN3*, which regulates endocytic processes through the encoding of guanine nucleotide exchange factor (GEF) proteins, to play a role in several conditions with cognitive impairment symptoms, including early and late onset AD (Meshref et al.; Boden et al.); *RIN3* has also been suggested to interact with *BIN1* (Kahijo et al.; Shen et al.; Maaser-Hecker et al.).
- ❖ Our ROS/MAP single-nucleus RNAseq analysis revealed that upregulated *RIN3* expression in both excitatory and inhibitory neurons is significantly associated with lower tau tangle burden (Figures 4A&4B).
- ❖ In follow-up analyses of our genome-wide significant loci using an ordinal definition of tau, both chromosome 2 and 14 signals remained significant, with the chromosome 14 signal slightly attenuated (Table 3).
- ❖ In replication analyses of our genome-wide significant loci in CSF t-tau and p-tau, only the chromosome 14 locus in CSF t-tau remained significant (Table 4).

Conclusions

- ❖ In this study, our findings identified the established index variant rs6733839 at the *BIN1* locus associated with tauopathy. We also identified a novel association between the chromosome 14 locus (*SLC24A4/RIN3*) and tauopathy.
- ❖ We provide cross-modality validation, via CSF t-tau, of a novel chromosome 14 locus associated with tauopathy identified through our GWAS meta-analysis of combined tau PET and autopsy measures.

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