

Relationship of genetic variants and gene expression of *SLC16A7* with cognitive decline in older adults

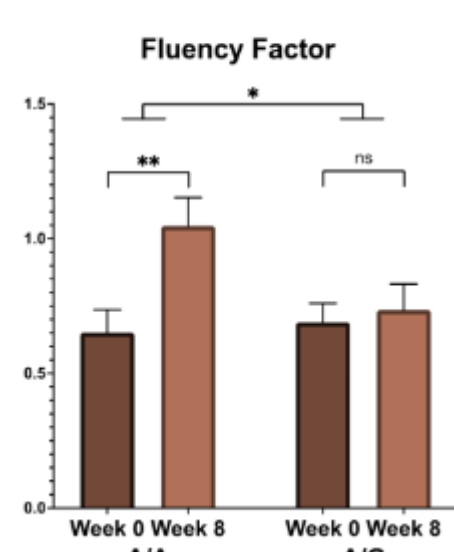
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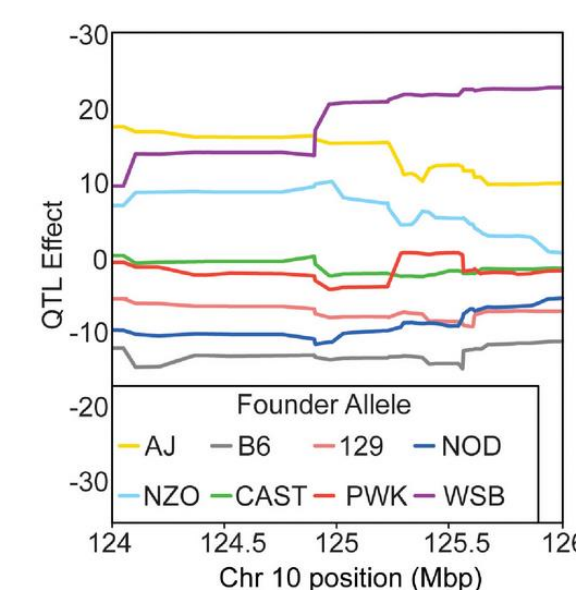
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Introduction

- In mice, *Slc16a7* genetic variants were associated with changes in late-life cognitive performance after dietary intervention (Ouellette AR, 2022)



- In a human clinical trial of intermittent fasting, *SLC16A7* variants modulated diet impacts on executive function (Kapogiannis D, 2025)

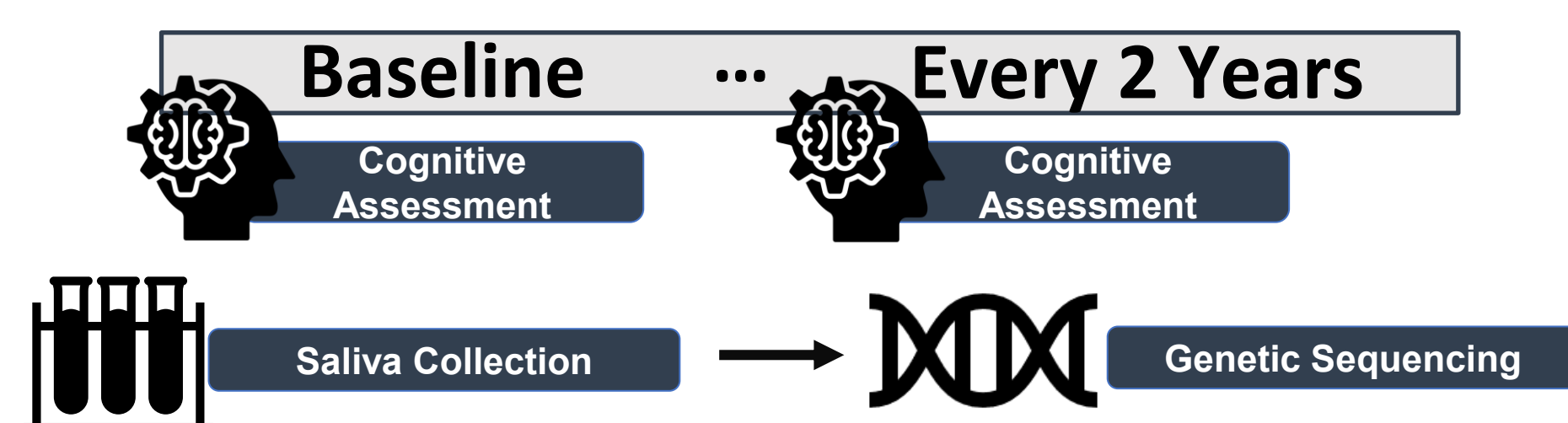


Do *SLC16A7* genetic variants impact cognitive decline in older adults?

Methods

HRS | HEALTH AND RETIREMENT STUDY

- Longitudinal panel cohort nationally representative of US adults age 50 years and older
- Cognitive assessments every 2 years
- Genetic sequencing from saliva samples



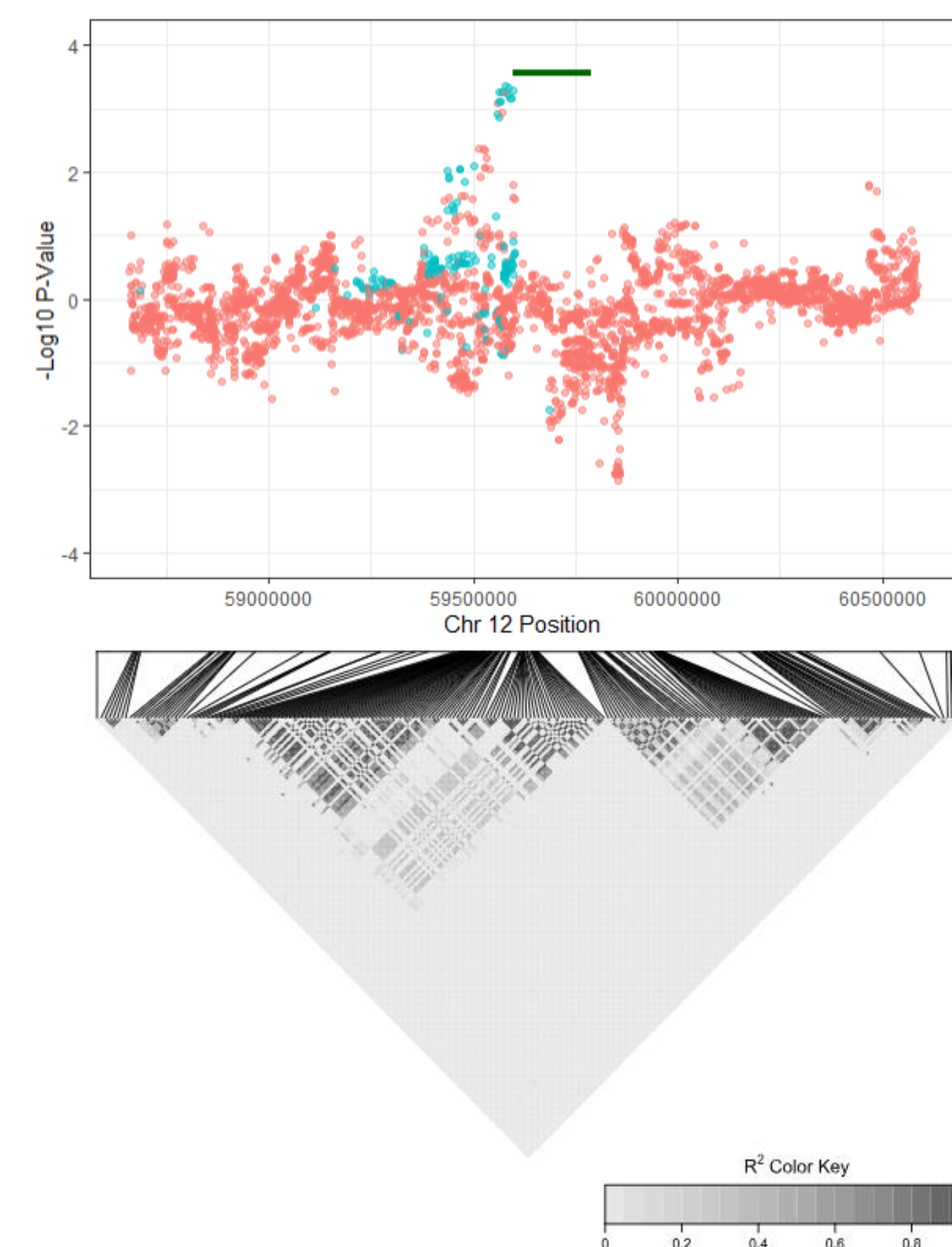
Religious Orders Study and Rush Memory and Aging Project

- Two longitudinal clinical-pathologic cohort studies with unified diagnostic processes
- Cognitive assessments yearly
- Older adult participants who agree to clinical evaluations and organ donations after death
- Bulk RNA-sequencing of postmortem brain tissue



SLC16A7 Genetic Variants Associated with Cognitive Decline

	Normal Cognition N = 13,743 ¹	Cognitive Impairment N = 5,421 ¹	P-value
Follow Up Time (Years)	14.71 (6.5)	16.48 (5.9)	<0.001
Sex			<0.001
F	7,777 (57%)	2,920 (54%)	
M	5,966 (43%)	2,501 (46%)	
Baseline Age (Years)	56.18 (7.7)	63.11 (8.9)	<0.001
Ever Had Diabetes	4,135 (30%)	1,905 (35%)	<0.001



GTEx

Expression quantitative trait loci in brain from Genotype-Tissue Expression Consortium

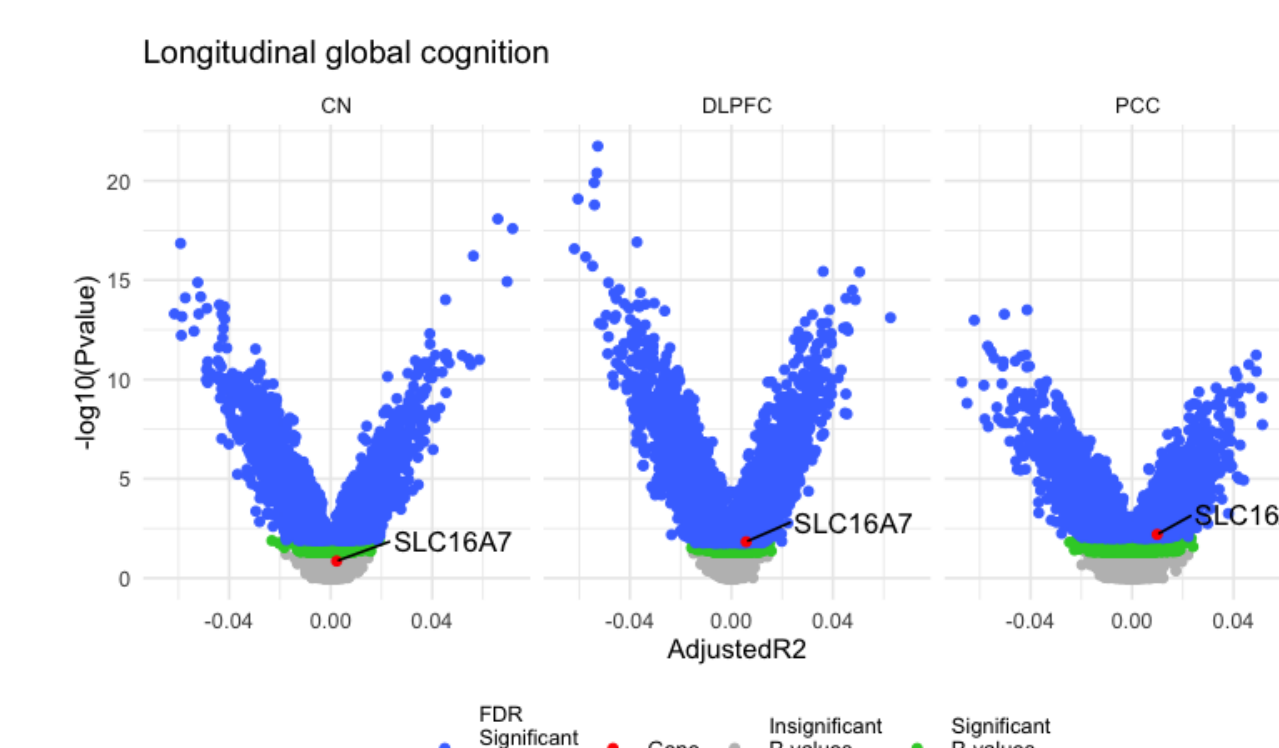
eQTL
FALSE
TRUE

Results

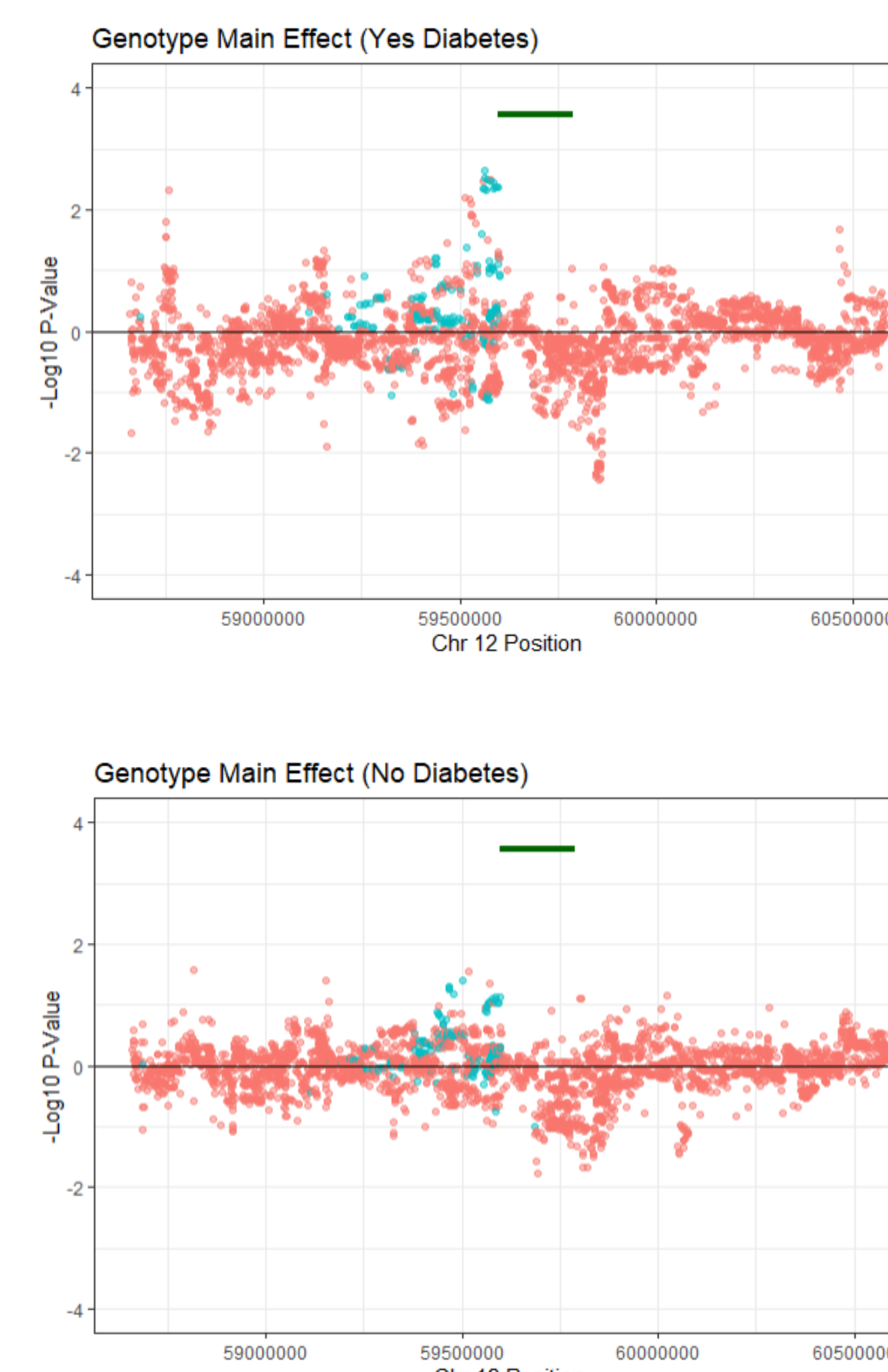
SLC16A7 Gene Expression in Postmortem Brain Associated with Higher Longitudinal Cognition

	Caudate Nucleus (n=688)	Dorsolateral Prefrontal Cortex (n=890)	Posterior Cingulate Cortex (n=500)
Education (years)	16.36 (3.57)	16.46 (3.54)	16.44 (3.54)
Male	277 (33%)	285 (32%)	180 (36%)
Age at death	89.24 (6.44)	89.34 (6.67)	89.27 (6.44)
Global cognition	-0.79 (1.09)	-0.83 (1.09)	-0.74 (1.07)
Postmortem Interval (hours)	7.62 (4.41)	7.57 (4.32)	7.08 (4.09)

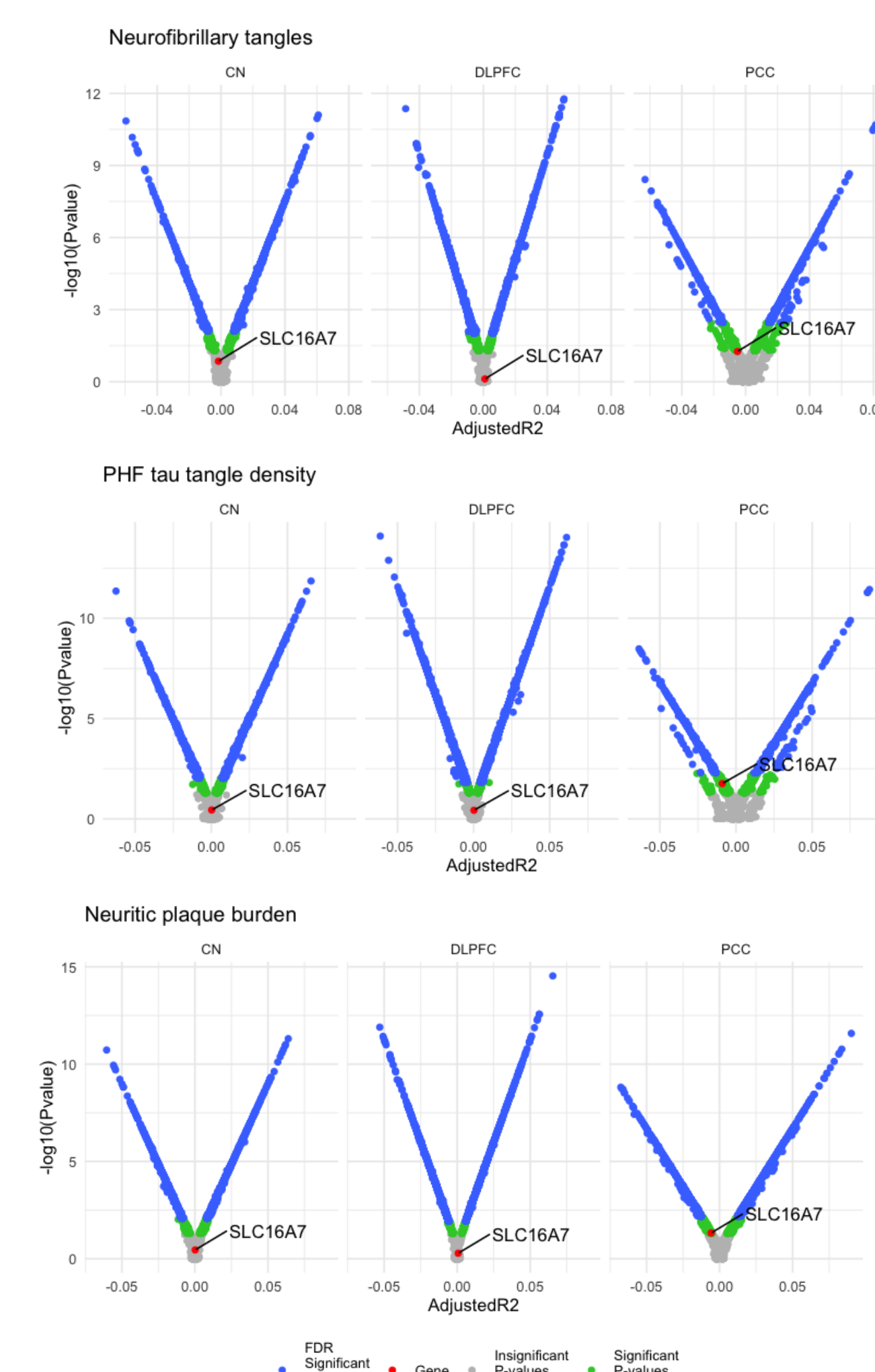
¹ n (%); Mean (SD)



SLC16A7 Genetic Variant Associations Stronger in Diabetes Group



Expression in Posterior Cingulate Cortex Associated with Lower Alzheimer's Pathology Marker Levels in Brain



Summary

- Suggestive associations of cognitive decline and *SLC16A7* variants, some of which previously identified as genetically influencing gene expression in brain
- Expression of *SLC16A7* in postmortem brain is associated with longitudinal global cognition, and marginally with AD pathology
- Genetic associations involving eQTL SNPs, and brain RNA-expression associations both implicate *SLC16A7* levels in influencing cognition

Acknowledgements

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