Pleiotropy testing identifies genetic variants with pleiotropic evidence in Alzheimer's disease

Noah Lorincz-Comi, Xiaofeng Zhu, Ph.D

National Heart, Lung, and Blood Institute

Case Western Reserve University School of Medicine

Cleveland Institute for Computational Biology

INTRO

- We tested for genome-wide SNP effects on Alzheimer's disease (AD) using a novel pleiotropy test. This test makes use of the estimated causal effects of brain region volumes on AD.

METHODS

1. *Data*
   - EUR GWAS summary statistics from UKBB, ABCD, HCP, PNC, ADNI, PING study cohorts (acronyms, bottom right)
2. *Phenotypes*
   - Alzheimer's disease (outcome)
   - 7 brain region volumes (exposures)
3. *Tests*
   - Mendelian Randomization (MR) for causal effects using selected instruments
   - Pleiotropy T-test (genome-wide)

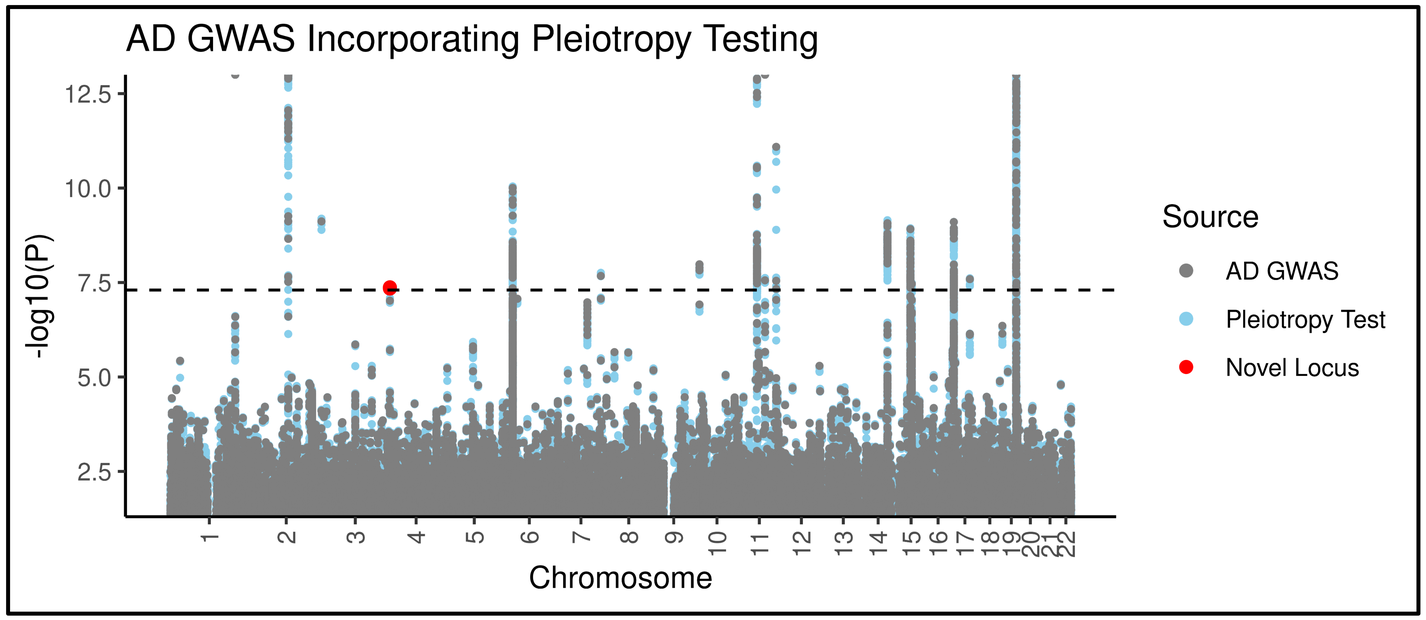
MR Causal Estimates for AD risk

ROI name	n_a	OR (P)
Cuneus (L)	3	0.98 (0.346)
Lingual (R)	3	1.01 (0.685)
Caudate (R)	**4**	**0.37 (0.006)**
Lat. Ventricle (R)	1	1.00 (0.932)
Cuneus (R)	5	0.99 (0.373)
Caudate (L)	**5**	**0.51 (0.024)**
Lingual (L)	3	1.00 (0.826)
Ventral DC (R)	6	0.99 (0.643)

a: *n* instruments from univariable MR with IVW

DISCUSSION

- MR pleiotropy testing can identify novel SNP associations with disease undetected by standard GWAS. These SNPs potentially have pleiotropic effects on both the MR exposure and outcome.



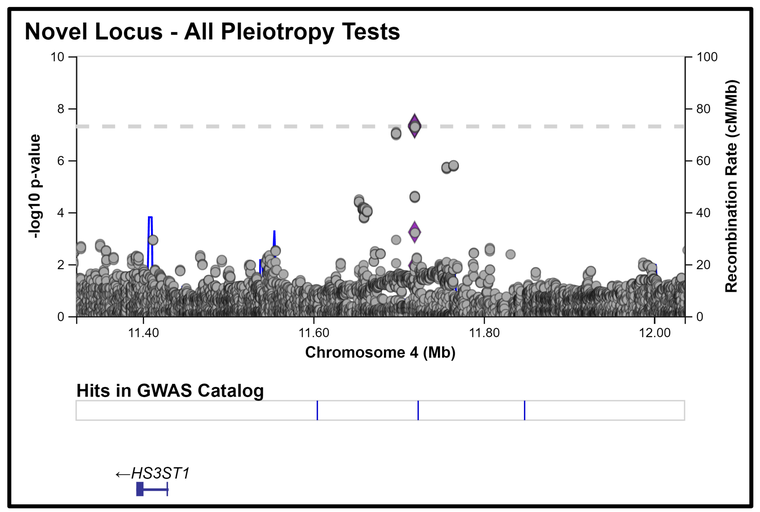
CHR 4 locus undetected in Alzheimer's GWAS but found in pleiotropy testing.

Novel SNPs

rsID	Pleiotropy P_a	AD GWAS P	ROI GWAS P_b
rs13133131	4.34E-08	5.10E-08	0.297
rs13133301	4.23E-08	5.01E-08	0.270
rs13134197	4.56E-08	5.37E-08	0.289

a,b: Min. of all pleiotropy test (a) and ROI GWAS (b) P-values

Nearest protein-coding gene, ***HS3ST1***, associated with CAD, BMI, cholesterol, sleep, albumins, and lateral sclerosis. Expressed mostly in ovary, bladder tissues.



Selected brain regions

- 7 brain regions (ROIs) selected as having the largest genetic correlations with AD (estimated using LD score regression), and at least one genome-wide significant SNP.

Mendelian Randomization

- Performed with IVW using instruments from ROI GWAS with P<5e-8 uncorrelated with other genetic variants.

Pleiotropy t-test

- Let:
  - β_j be the effect of ROI *j* on AD
  - Γ_i, γ_i respectively be instrument *i*'s effect on the outcome and exposure, *i*=1, …, *n* in MR analysis.
- H_0: $\gamma_i - \Gamma_i \beta_j = 0$ for each i, j
- Performed genome-wide after MR using instruments estimated a causal effect

Acronyms

MR: Mendelian Randomization
UKBB: UK Biobank
ABCD: Adolescent Brain Cognitive Development
HCP: Human Connectome Project
PNC: Philadelphia Neurodevelopmental Cohort
ADNI: Alzheimer's Disease Neuroimaing Initiative
PING: Pediatric Imaging, Neurocognition, and Genetics

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