Alzheimer's disease polygenic burden beyond APOE acts stronger on Tau than on Amyloid

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INTRODUCTION

- Polygenic risk scores (PRS) aim to capture a person's genetic disease risk.
- PRS have gained popularity in recent years and PRS for AD have been linked to various hallmarks of AD (diagnosis, progression, biomarkers, …)
- Recently, a novel score, the polygenic hazard score (PHS), was introduced[1].
- PHS was shown to be associated with amyloid burden and cognitive decline[2].
- **However**, studies on PHS adjusted only for APOE-ε4 carrier status.

We hypothesize that the effects of PRS and PHS are overestimated when only adjusting for APOE-ε4 carrier status.

METHODS

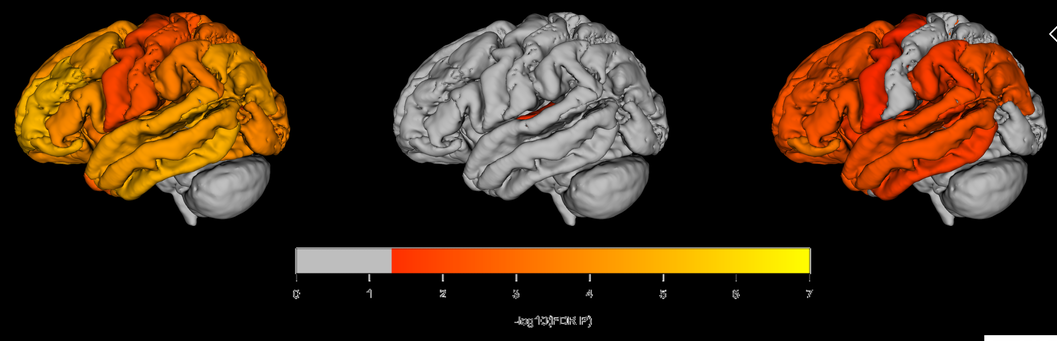
- N=995 subjects from ADNI
- PRS computed using most recent AD GWAS[3] at two cutoffs P=1e-05 (PRS1) and 0.05 (PRS2) and PRS-cs method[4]
- PHS obtained from ADNI directly
- Linear models to test association of scores with CSF biomarkers (Aβ, tau, p-tau) and cortical amyloid (AV45 PET)
- Adjusted for age, sex, education, APOE (ε4 status or ε2/ε4 allele count)
- Stratified by diagnosis (DX)
- Linear mixed effects model used to test effect on longitudinal decline in cognition (CDR-SB, memory & executive function)

RESULTS

- Adjustment for APOE locus and diagnosis stratification eliminated most effects of PHS on cortical amyloid
- Only PRS1 was associated with CDR-SB
- Scores strongly associated with CSF tau and p-tau but not Aβ

Adjusting only for APOE-ε4 status overestimates the effect of AD polygenic risk scores.

Polygenic risk in excess of *APOE* acts on tau pathology.



Association with regional amyloid burden. Left: PHS (APOE-ε4 status); middle: PHS (APOE ε2/ε4 count, DX); right: PRS1 (APOE ε2/ε4 count, DX)

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CONCLUSIONS

Findings in [2] regarding PHS were overestimated

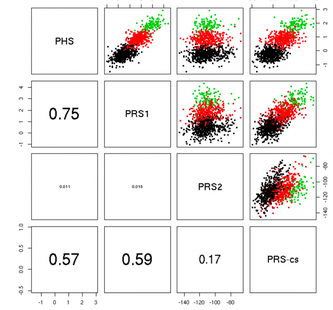
- Adjustment for APOE ε2/ε4 count needed
- Stratification for DX needed
- Linear mixed effects models require random slopes

Association of polygenic AD risk with CSF tau survived most stringent model adjustments.

ADDITIONAL INFORMATION

PHS and PRS1 are highly correlated

Scatter plots between different scores on 995 ADNI subjects with European ancestry, who did not contribute to the ADGC study. Colors indicate the number of APOE4 alleles (0:black, 1:red, 2:green)



Association of scores with **CSF biomarkers** in N=807 subjects. Adjustment for age, sex, education, APOE ε2/ε4 count. Uncorrected p-values.

Score	Aβ	tau	p-tau
PHS	4.20E-01	**3.78E-04**	**1.98E-04**
PRS1	3.50E-01	**2.12E-03**	**9.89E-04**
PRS2	3.54E-01	**2.97E-02**	**4.87E-02**
PRS-cs	5.90E-01	**3.16E-02**	**1.41E-02**

Association of scores with **cognitive decline** in N=601 CN/MCI subjects. Adj. for age, sex, edu., gray matter volume in Entorhinal cortex, amyloid, APOE ε2/ε4 count. Uncorrected p-values.

Score	CDR-SB	MEM	EF
PHS	8.00E-02	4.70E-01	5.50E-01
PRS1	**3.57E-03**	4.20E-01	6.50E-01
PRS2	4.50E-01	2.10E-01	7.10E-01
PRS-cs	3.40E-01	6.60E-01	6.50E-01

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