Genome-wide Polygenic Risk for Alzheimer's Disease Is Associated With Rate of Metabolic Decline But Not With Rate Of Amyloid Deposition

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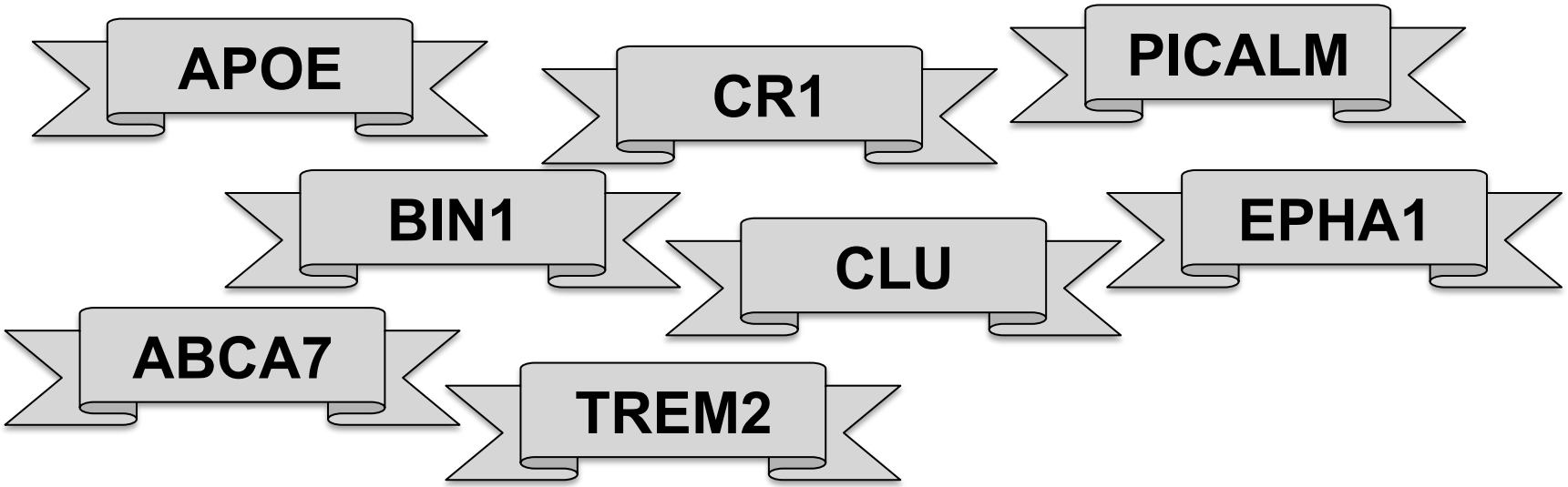
Genome-wide Polygenic Scores

- Assessing a subject's genetic risk for AD



- Genetic AD burden

burden = APOE + BIN1 + CR1 + PICALM + CLU + EPHA1 + ABCA7 + TREM2

$$\text{burden} = \sum_{i=1}^{N} \text{SNP}_i$$

0
1
2

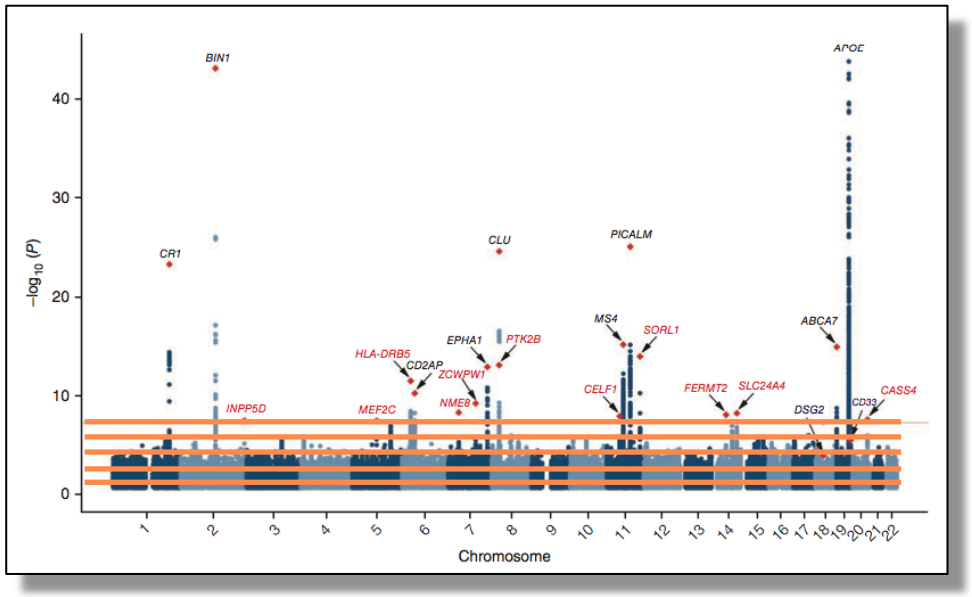
Genome-wide Polygenic Scores

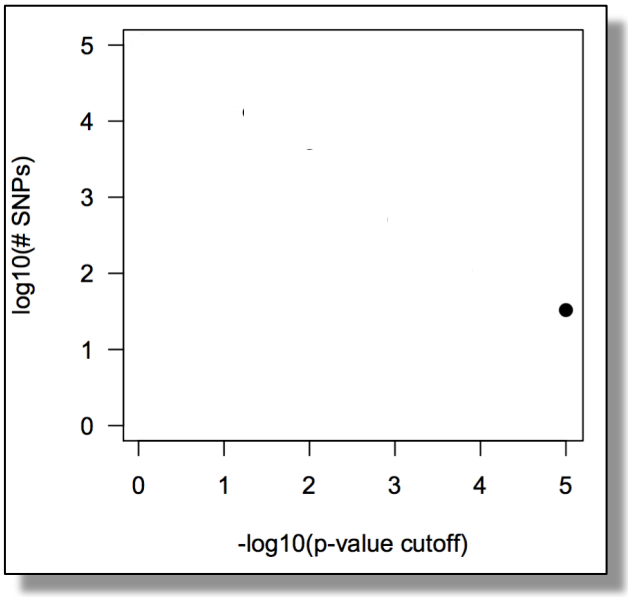
- Different genes have different ‘impact’

$$\mathrm{GPS} = \sum_{i=1}^{N} w_i \times \mathrm{SNP}_i$$

log(OR) from GWAs

- How to select the genes (SNPs)?



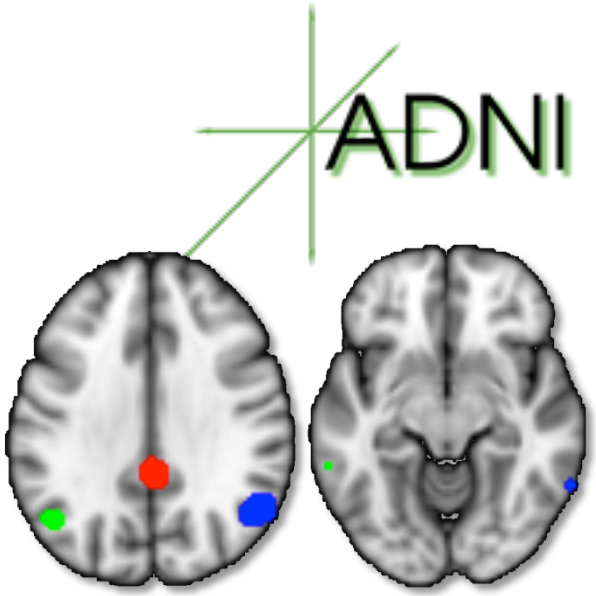


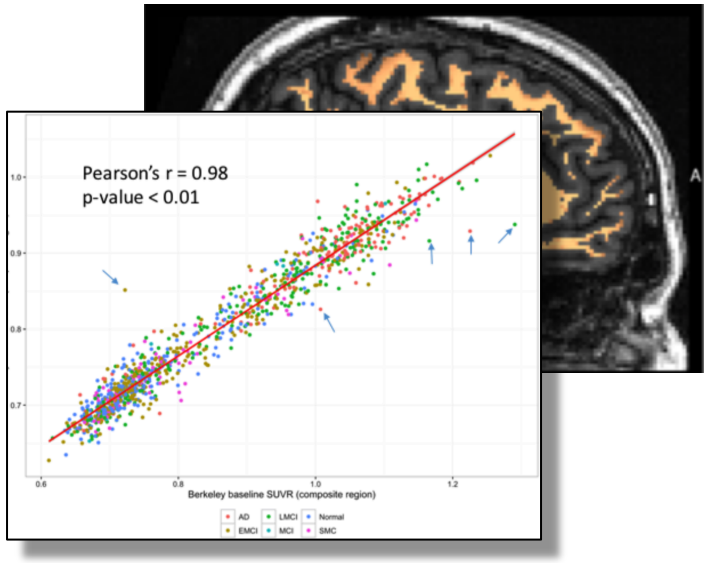
Rationale

- GPS is known to be associated with AD diagnosis
  - Identify people at risk for developing AD
  - Additional tool for patient screening for trails
- We do not know which biomakers respond to increased genome-wide risk for AD
  - Would help to select endpoints for trials
  - Which biomarkers to screen for people at risk
- How genome-wide risk affects the brain
  - Do biomarkers respond uniformly?

Data – Imaging

- ADNI database
  - Longitudinal PET imaging & genetics
  - FDG PET
    - 5 ROIs (UC Berkeley)
  - Amyloid PET (AV45)
    - Cortex-wide uptake
    - Composite reference region
    - UC Berkeley and in-house pipeline

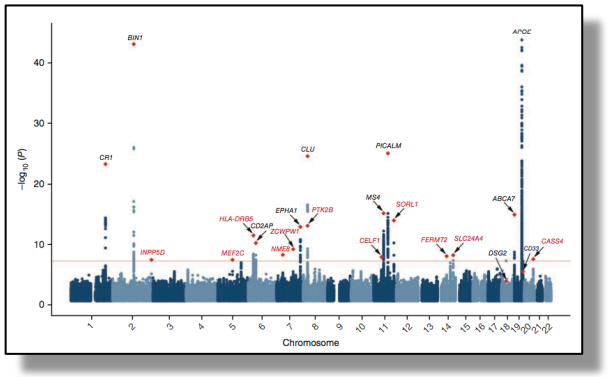


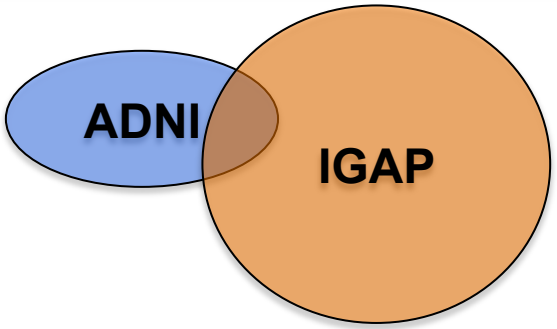


		HC	MCI	AD	total
FDG	all	271	543	139	953
	2+	**140**	**321**	**37**	**498**
AV45	all	250	457	137	844
	2+	**186**	**319**	**32**	**537**

Curtsey M. Scelsi

Methods

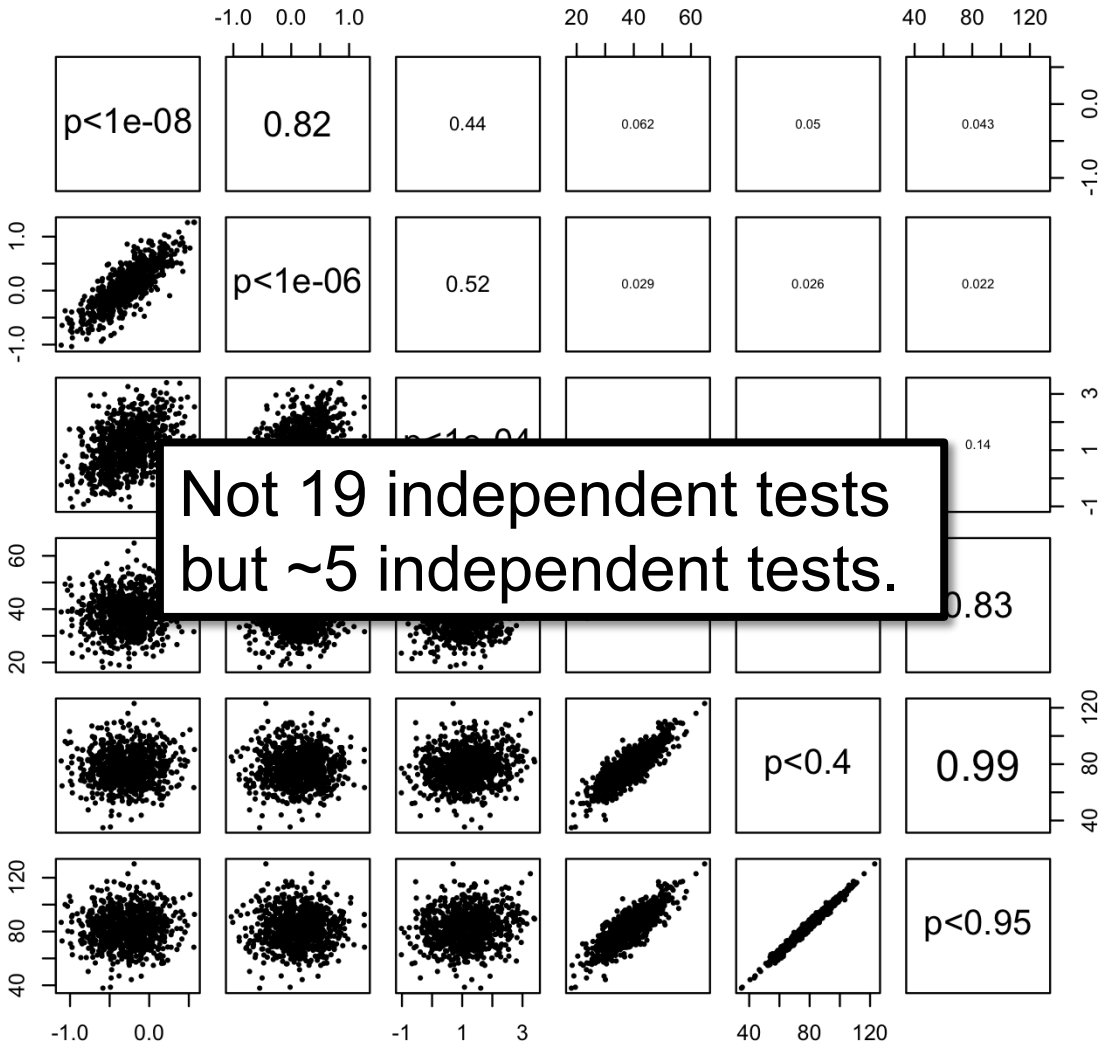




- IGAP GWAS 54k subjects
  - Some ADNI subjects excluded
- 19 GPS scores
  - 1e-8, 1e-7, …, 0.95, 1.0
  - ADNI SNPs imputed (~ 5 mio)
  - PLINK function to '*clump results*'
- Linear mixed effects model
  - Biomarker at time t_n as a function of time
  - Predictors: time, EDU, SEX, PC1-3, imgAGE, imgDX, APOE-e4 x time, GPS x time
  - Random effect for subject
  - Test for **GPS x time** effect (reported *p*-value)

Results (GPS)

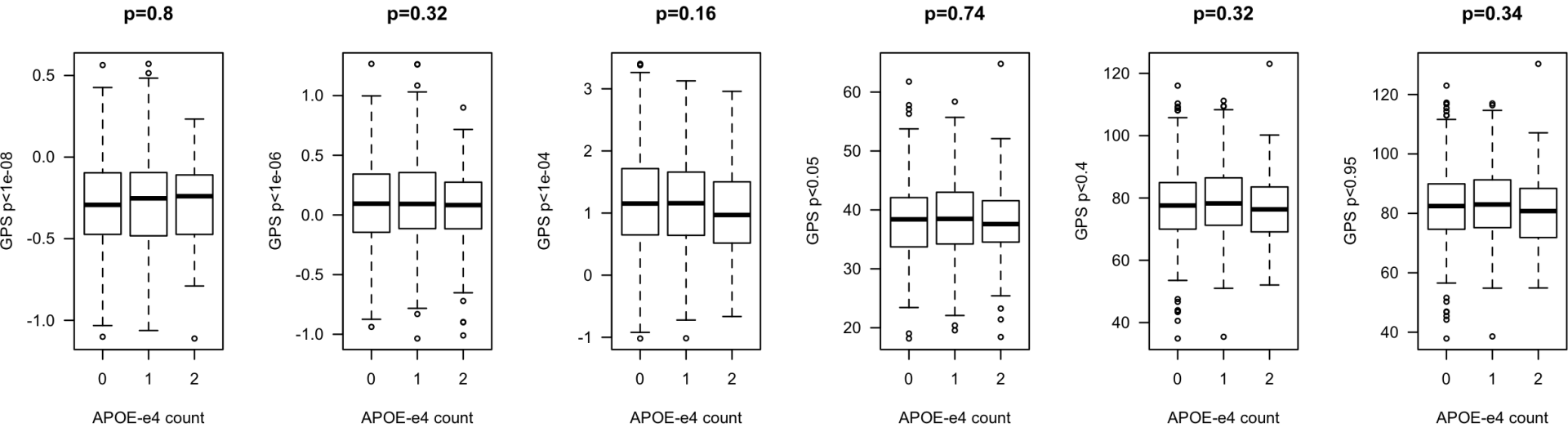
- Scores from similar cut-offs are highly correlated



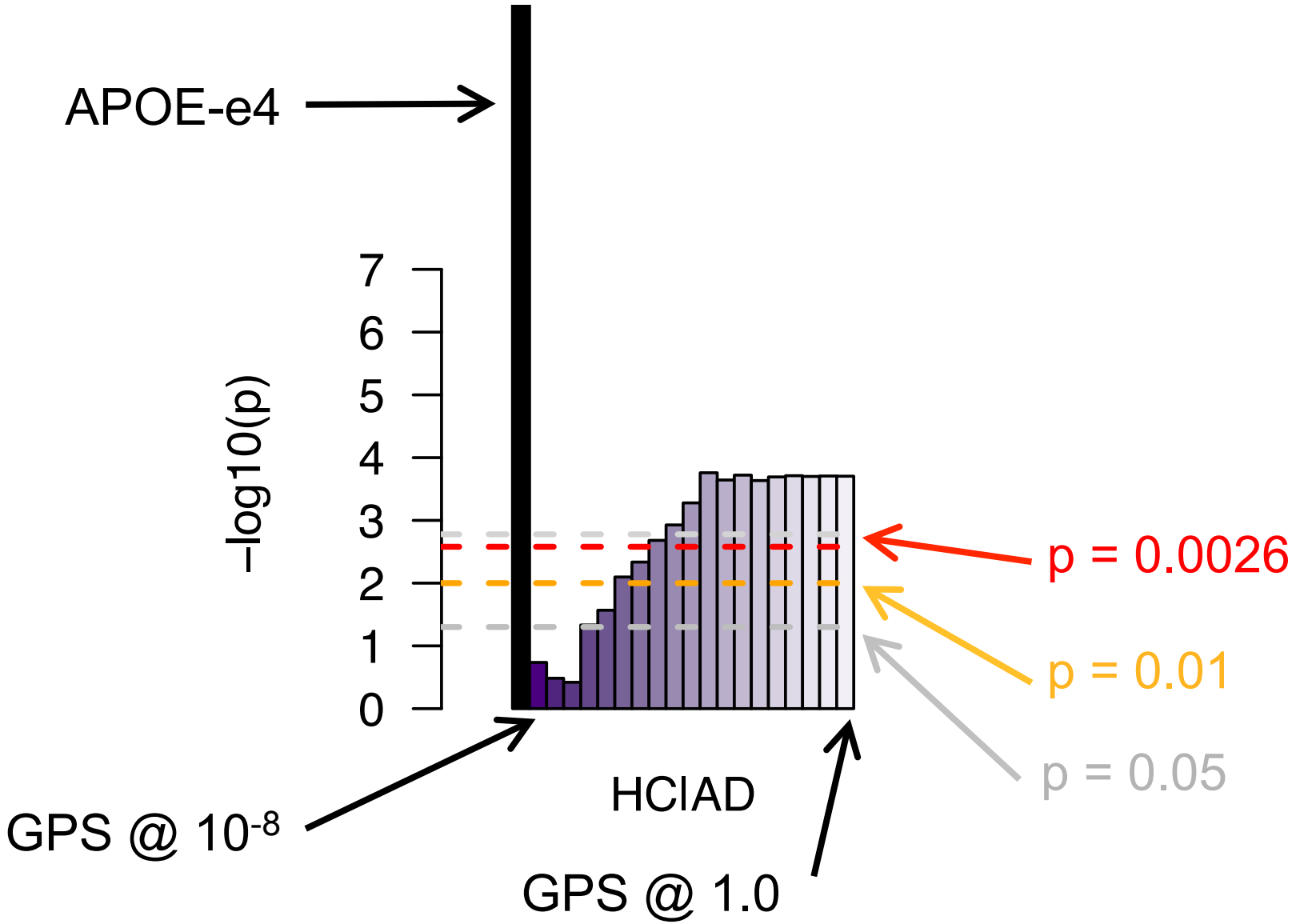
Results (GPS)

- Scores from similar cut-offs are highly correlated

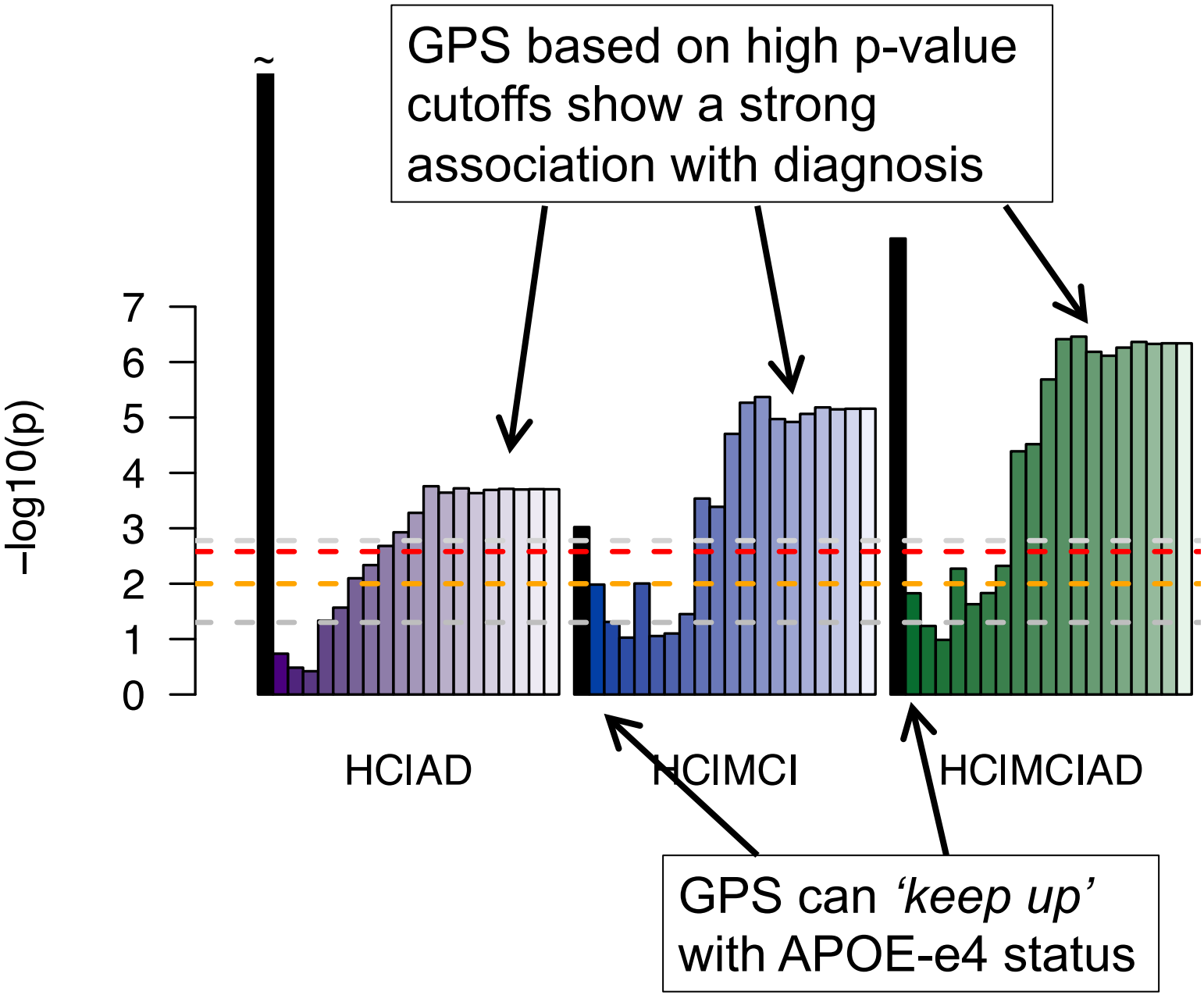
- APOE locus was excluded from GPS
  - None of these scores is correlated with the APOE-e4 genotype



GPS and Case-Control Status



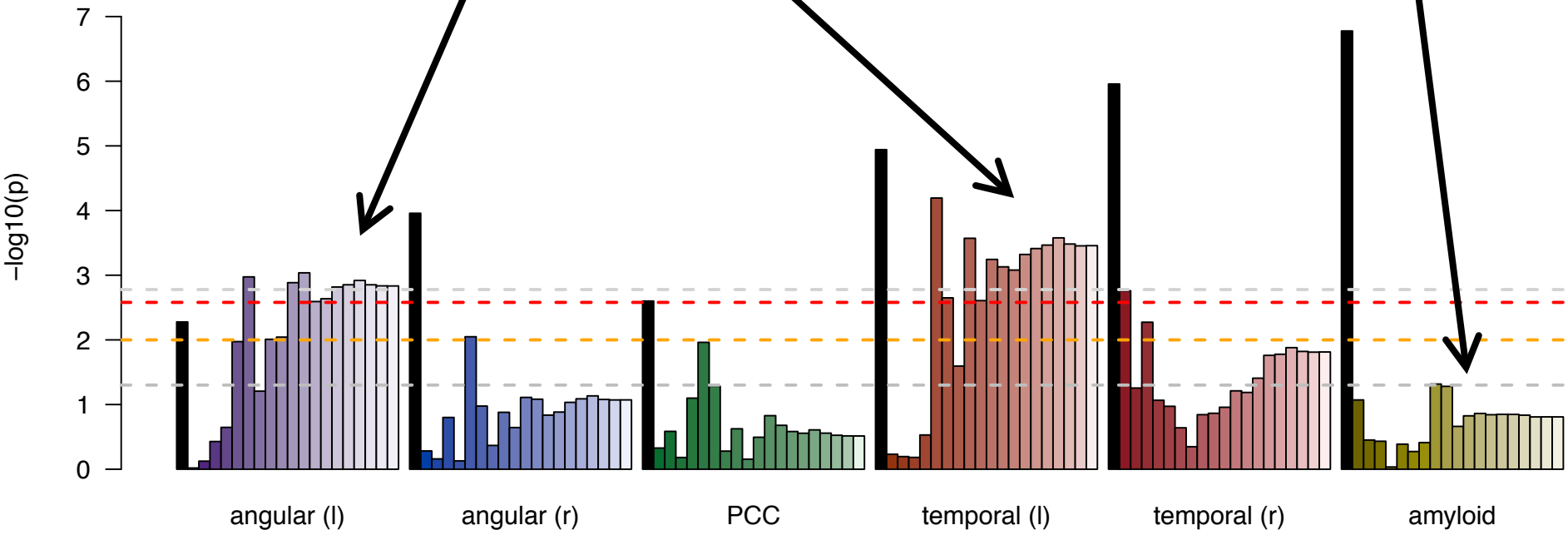
GPS and Case-Control Status



GPS and PET biomarkers

Effect on FDG decrease in some ROIs

No effect on amyloid increase

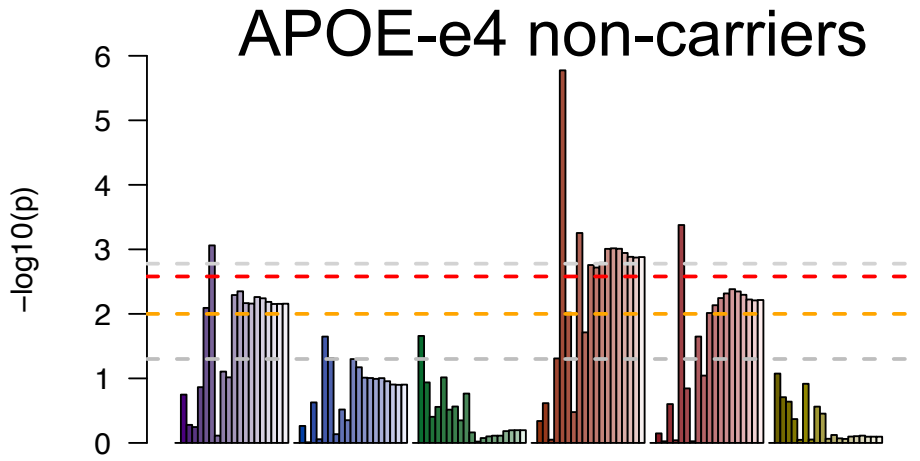


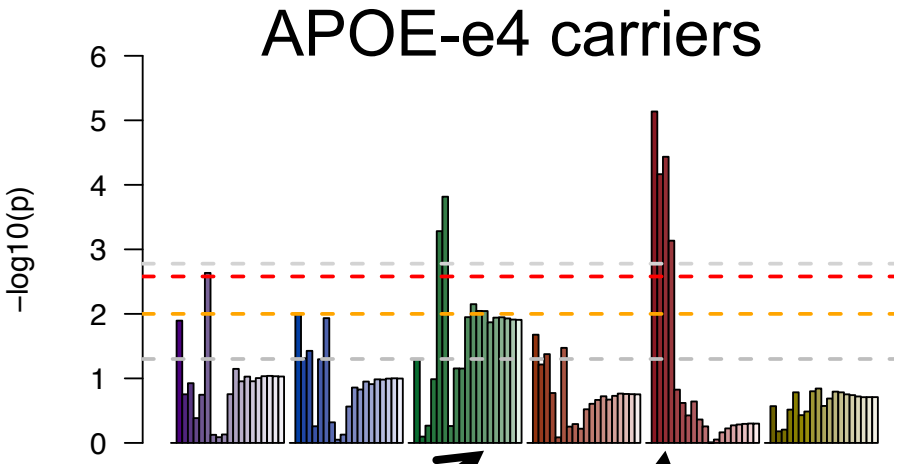
GPS with many SNPs show stronger associations

Effect is comparable to APOE-e4

APOE-e4 is the dominant genetic effect

GPS and PET biomarkers (subgroups)



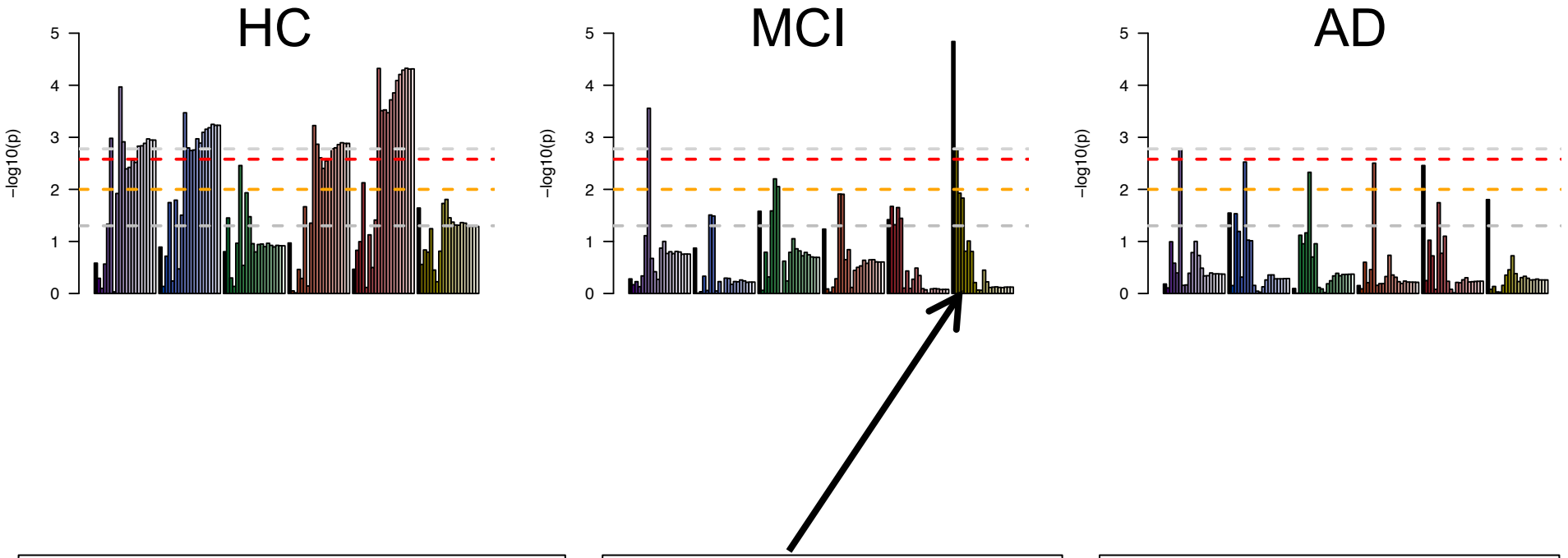


The effect appears to be stronger in non-carriers

PCC responds to GPS in APOE-e4 carriers

GPSs with few SNPs show stronger effects

GPS and PET biomarkers (subgroups)



Overall strong effect in healthy subjects. GPS with many SNPs

Effect of GPS with few variants on amyloid

No clear trend in AD – smallest sample size N~30

Summary

- The two PET biomarkers exhibited different association patterns regarding GPS
  - Increase in brain amyloid mainly driven by APOE-e4
  - Decrease of glucose metabolism in some regions associated with GPS
- Scores with many SNPs showed stronger associations – in accordance with DX
- Amyloid increases over 2 years may not be very sensitive – but APOE-e4 effect is visible
- Interactions of GPS with APOE-e4 status and DX
- FDG effect not uniform – follow-up studies needed

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