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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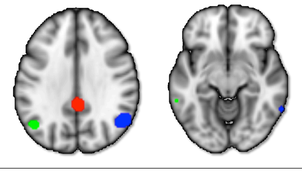
Background

Genome-wide association studies (GWAS) have revealed numerous genetic loci that are consistently associated with the risk to develop late-onset Alzheimer's disease (AD). Genome-wide polygenic scores (**GPS**) for diseases and traits are a recent development in statistical genetics and allow **aggregating the genetic risk into one single score**. In previous studies, an AD-GPS showed consistent and strong association with the disease in independent subjects. Here **we analyzed the association of an AD-GPS with brain metabolism and amyloid deposition** using fluorodeoxyglucose (FDG) positron emission tomography (PET) and florbetapir (AV45) PET, respectively, in a study sample from the Alzheimer's disease neuroimaging initiative (ADNI).

Methods

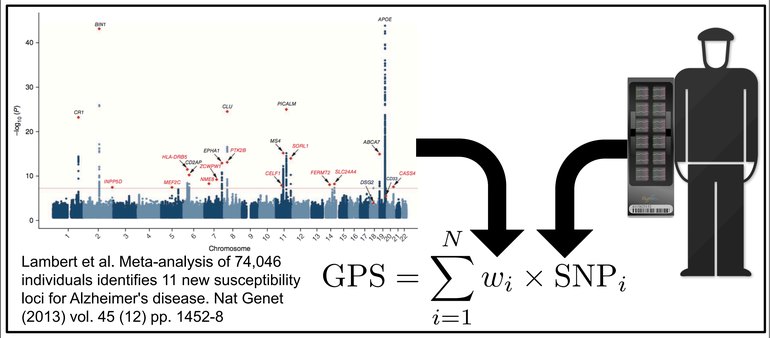
Study sample: We used subjects with available SNP data from the ADNI database that did not contribute to the GWAS used for GPS computation. **A total of 1,923 and 1495 FDG and AV45 PET scans were used**, respectively. The majority originating from subjects with 2 or more scans (2+): 1,471 (FDG) and 1,188 (AV45). From these scans we extracted glucose metabolism in five regions of interest and cortical amyloid uptake using a composite reference region.

		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



Methods (cont.)

GPS construction: The GPS is a weighted sum of the number of risk alleles present in a subject (SNP_i). The weights (w_i) are obtained from the summary statistics of a large GWAS.

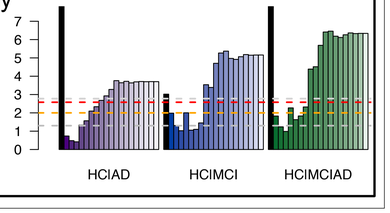


Lambert et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet (2013) vol. 45 (12) pp. 1452-8

The extended APOE locus was excluded from the GPS. We computed GPS for 19 *p*-value cutoffs in the range from 1 x 10^{-8} to 1.0.

Statistical analysis: The effect of the GPS on rate of biomarker changes was estimated using a linear mixed effects model with random intercepts and following fixed effects: diagnosis and age at 1st scan, sex, years of education, population structure (3 PCs), APOE-e4 status, GPS, time since 1st scan (t) and interactions between APOE-e4 status and t and between GPS and t. **We tested for a non-zero coefficient for the interaction between GPS and *t*.**

Figure 1: AD-GPSs based on many SNPs with weak effects (towards right) show a stronger association to the most recent diagnosis than GPSs using few SNPs with strong effects (towards left). APOE-e4 (black bar) shown as reference.



Results

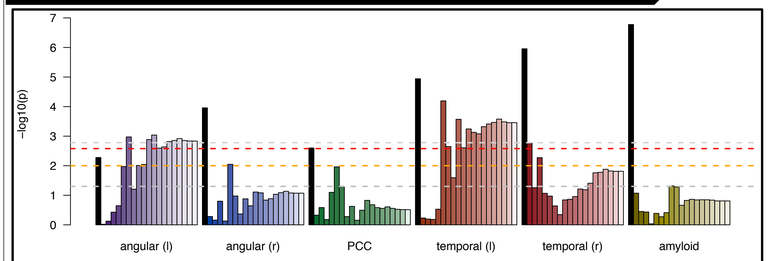


Figure 2: There is no association between GPS and rate of amyloid uptake (yellow); there are significant association between GPS based on many weak SNPs and metabolic decline.

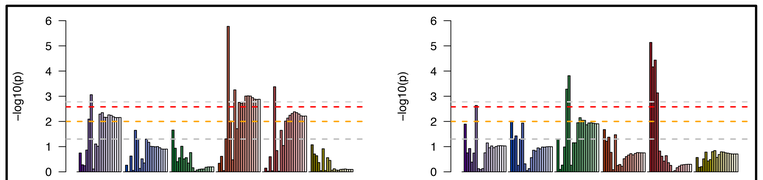


Figure 3: GPSs show stronger associations in non APOE-e4 carriers (left) than in APOE-e4 carriers (right).

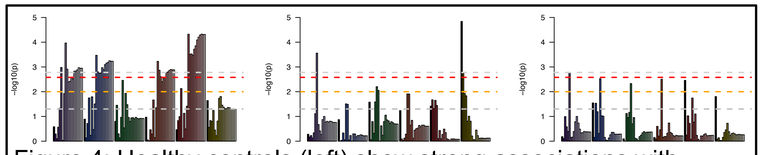


Figure 4: Healthy controls (left) show strong associations with metabolic decline in 4 of 5 ROIs; but not in amyloid uptake. MCIs (middle) show an association with amyloid uptake with GPS based on few significant SNPs.

Discussion

The AD-GPS, which excluded APOE, is strongly associated with rate of metabolic decline but not with rate of amyloid deposition. The associations are not uniform. There appears to be an interaction with APOE-status and/or disease status.

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