

Multi-ancestry genome-wide pleiotropy analysis

P4-03

identifies novel loci for amyloid-beta deposition and brain atrophy

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Introduction

- GWAS have identified more than 80 loci for Alzheimer’s disease (AD)
- The underlying genetic basis of AD and AD-related dementia (ADRD) remains largely unknown
- Identifying loci associated with amyloid beta (A β) deposition, brain atrophy, or both (*i.e.*, pleiotropy) may improve our understanding of the underlying AD mechanisms

Methods

- Structural MRI data were obtained from 6,304 Korean participants of the Gwangju Alzheimer’s and Related Dementias (GARD) study and 2,708 European ancestry participants of the Alzheimer’s Disease Sequencing Project (ADSP)
- 2,829 GARD and 1,763 ADSP participants had standardized uptake value ratio (SUVR) measures derived from amyloid PET exams
- GWAS for pleiotropy in structural MRI paired with amyloid PET scans were conducted for variants with MAF > 0.01 in linear mixed models using the R package PLACO
- Results were combined across ancestry groups using METAL
- Colocalization analyses were performed for top-ranked pleiotropic loci to differentiate horizontal pleiotropy from mediated pleiotropy
- Expression of genes containing top-ranked pleiotropic variants was compared among brain tissue from cognitively normal controls and pathologically confirmed AD cases with/without clinical symptoms

	GARD	ADSP			
		ADNI	NACC	WRAP	Combined
Participants, n					
Participants with structural MRI	6,304	1,654	745	309	2,708
Participants with amyloid PET	2,829	1,295	178	290	1,763
Age, years (mean $\pm$ SD)	74.1 $\pm$ 6.2	77.5 $\pm$ 7.1	77.1 $\pm$ 7.9	68.6 $\pm$ 5.5	76.3 $\pm$ 7.7
Sex, female, n (%)					
Male	2,530 (40.1)	906 (54.8)	332 (44.6)	104 (33.7)	1,342 (49.6)
Female	3,774 (59.9)	748 (45.2)	413 (55.4)	205 (66.3)	1,366 (50.4)
Structural MRI (mean $\pm$ SD) [†]					
Global cortical thickness, mm	2.558 $\pm$ 0.141	2.410 $\pm$ 0.182	2.386 $\pm$ 0.170	2.386 $\pm$ 0.107	2.401 $\pm$ 0.172
Superior frontal thickness, mm	2.590 $\pm$ 0.132	2.432 $\pm$ 0.179	2.414 $\pm$ 0.175	2.414 $\pm$ 0.127	2.425 $\pm$ 0.173
Middle temporal thickness, mm	2.720 $\pm$ 0.174	2.585 $\pm$ 0.228	2.558 $\pm$ 0.207	2.558 $\pm$ 0.131	2.575 $\pm$ 0.213
Inferior parietal thickness, mm	2.363 $\pm$ 0.158	2.213 $\pm$ 0.193	2.186 $\pm$ 0.193	2.186 $\pm$ 0.128	2.203 $\pm$ 0.187
Entorhinal thickness, mm	3.326 $\pm$ 0.397	3.038 $\pm$ 0.532	2.982 $\pm$ 0.477	2.982 $\pm$ 0.265	3.016 $\pm$ 0.494
Hippocampal volume, cm ³	3.735 $\pm$ 0.472	3.297 $\pm$ 0.582	3.219 $\pm$ 0.529	3.219 $\pm$ 0.404	3.267 $\pm$ 0.551
Intracranial volume, cm ³	1446.3 $\pm$ 152.2	1535.1 $\pm$ 169.5	1533.4 $\pm$ 163.4	1533.4 $\pm$ 135.5	1534.4 $\pm$ 164.3
Amyloid PET, SUVR (mean $\pm$ SD) [‡]					
Global lobe	1.323 $\pm$ 0.207	1.173 $\pm$ 0.191	1.184 $\pm$ 0.326	1.184 $\pm$ 0.221	1.176 $\pm$ 0.214
Frontal lobe	1.348 $\pm$ 0.229	1.220 $\pm$ 0.231	1.231 $\pm$ 0.395	1.231 $\pm$ 0.279	1.223 $\pm$ 0.260
Medial temporal lobe	1.122 $\pm$ 0.094	1.076 $\pm$ 0.150	1.082 $\pm$ 0.240	1.082 $\pm$ 0.148	1.078 $\pm$ 0.161
Lateral temporal lobe	1.268 $\pm$ 0.212	1.158 $\pm$ 0.211	1.166 $\pm$ 0.358	1.166 $\pm$ 0.254	1.160 $\pm$ 0.237
Lateral parietal lobe	1.316 $\pm$ 0.207	1.220 $\pm$ 0.235	1.236 $\pm$ 0.419	1.236 $\pm$ 0.284	1.225 $\pm$ 0.268
Occipital lobe	1.345 $\pm$ 0.180	1.190 $\pm$ 0.187	1.205 $\pm$ 0.278	1.205 $\pm$ 0.189	1.194 $\pm$ 0.198
Cognitive status, n (%)					
Normal cognition	3,635 (57.7)	549 (33.2)	397 (53.3)	300 (97.1)	1,246 (46.0)
MCI	1,749 (27.7)	516 (31.2)	155 (20.8)	8 (2.6)	679 (25.1)
AD	910 (14.4)	488 (29.5)	174 (23.4)	1 (0.3)	663 (24.5)
Other dementia	10 (0.2)	101 (6.1)	19 (2.6)	0 (0.0)	120 (4.4)

Table 1. Characteristics of the study sample

Results

- Genome-wide significant (GWS) pleiotropy was identified with rs9730555 between *FMN2* and *GREM2* for global cortical thickness paired with SUVR measures of global ($P=8.62\times 10^{-23}$) lobe and medial temporal lobe ($P=4.04\times 10^{-11}$)
- GWS and suggestive pleiotropy for middle temporal thickness and medial temporal lobe SUVR was identified with *HTR1E* (rs7769652, $P=1.29\times 10^{-8}$) and *UNC5B* (rs10999738, $P=1.45\times 10^{-7}$)
- Suggestive pleiotropy for middle temporal thickness paired with global lobe SUVR was also identified with *C3orf56* (rs12494418, $P=2.28\times 10^{-7}$) and *ADAMTS17* (rs12909096, $P=3.21\times 10^{-7}$)
- Many variants in the *APOE* region had GWS pleiotropy for the pairs of structural MRI and amyloid PET (rs404935, $P < 4.22\times 10^{-15}$)
- Colocalization analyses indicated that *APOE*, *HTR1E*, and *FMN2* influence cortical thinning directly or through mechanisms that bypass A β deposition
- Four genes, *FMN2* (FDR= 9.45×10^{-3}), *HTR1E* (FDR= 1.55×10^{-2}), *UNC5B* (FDR= 1.77×10^{-5}), and *ADAMTS17* (FDR= 9.81×10^{-3}) were differentially expressed between cognitively normal controls and pathologically confirmed AD cases with and without clinical symptoms

Conclusions

- Our findings provide some insight into the genetic basis and shared genetic architecture of cerebral A β burden and cortical atrophy, two correlated but distinct measures of AD pathogenesis which starts long before onset of clinical symptoms
- Increasing the sample of WGS data and harmonized neuroimaging measures would likely enhance the discovery of additional genetic factors and pleiotropy underlying AD/ADRD pathologies

Neuroimaging [†]		Variant (chr:position)	A1/A2 [‡]	MAF		Nearest gene	GWAS (MRI)		GWAS (PET)		Pleiotropy
MRI	PET			GARD	ADSP		Est (SE)	P	Est (SE)	P	
GCT	GL	rs12036337 (1:4515228)	A/G	0.031	0.098	<i>LINC01646</i>	-0.165 (0.033)	4.14×10^{-7}	-0.156 (0.066)	1.75×10^{-2}	2.62×10^{-7}
		rs9730555 (1:240478432)	C/T	0.060	0.644	<i>FMN2</i>	-0.185 (0.022)	1.88×10^{-17}	-0.228 (0.045)	2.81×10^{-7}	8.62×10^{-33}
		rs12404655 (19:44869537)	A/G	0.236	0.165	<i>NECTIN2</i>	-0.081 (0.019)	2.12×10^{-5}	0.226 (0.028)	2.32×10^{-16}	4.22×10^{-15}
	MTL	rs9730555 (1:240478432)	C/T	0.060	0.644	<i>FMN2</i>	-0.185 (0.022)	1.88×10^{-17}	-0.112 (0.045)	1.14×10^{-2}	4.04×10^{-11}
		rs72910602 (6:86869198)	A/C	0.153	0.075	<i>HTR1E</i>	-0.074 (0.023)	1.59×10^{-5}	0.170 (0.036)	2.03×10^{-6}	8.07×10^{-8}
		rs412776 (19:44876259)	A/G	0.223	0.129	<i>NECTIN2</i>	-0.095 (0.020)	2.04×10^{-6}	0.190 (0.028)	4.50×10^{-12}	1.33×10^{-10}
MTT	GL	rs12494418 (3:127147593)	A/G	0.067	0.021	<i>C3orf56</i>	-0.119 (0.033)	2.90×10^{-4}	0.205 (0.049)	3.17×10^{-5}	2.28×10^{-7}
		rs12909096 (15:99958995)	T/G	0.464	0.381	<i>ADAMTS17</i>	0.074 (0.017)	1.00×10^{-5}	0.070 (0.026)	6.62×10^{-3}	3.21×10^{-7}
		rs395908 (19:44870308)	A/G	0.231	0.163	<i>NECTIN2</i>	-0.093 (0.019)	1.33×10^{-6}	0.214 (0.028)	6.35×10^{-15}	2.56×10^{-16}
	MTL	rs7769652 (6:86860758)	G/A	0.153	0.070	<i>HTR1E</i> <i>SNHG5</i>	-0.080 (0.024)	6.02×10^{-4}	0.173 (0.036)	1.51×10^{-6}	1.29×10^{-8}
		rs10999738 (10:71238362)	A/C	0.322	0.335	<i>UNC5B</i>	-0.067 (0.018)	1.42×10^{-4}	-0.098 (0.026)	1.90×10^{-4}	1.45×10^{-7}
		rs412776 (19:44876259)	A/G	0.223	0.129	<i>NECTIN2</i>	-0.107 (0.020)	1.33×10^{-7}	0.190 (0.028)	4.50×10^{-12}	1.82×10^{-17}

Table 2. Top-ranked pleiotropic variants for MRI paired with amyloid PET

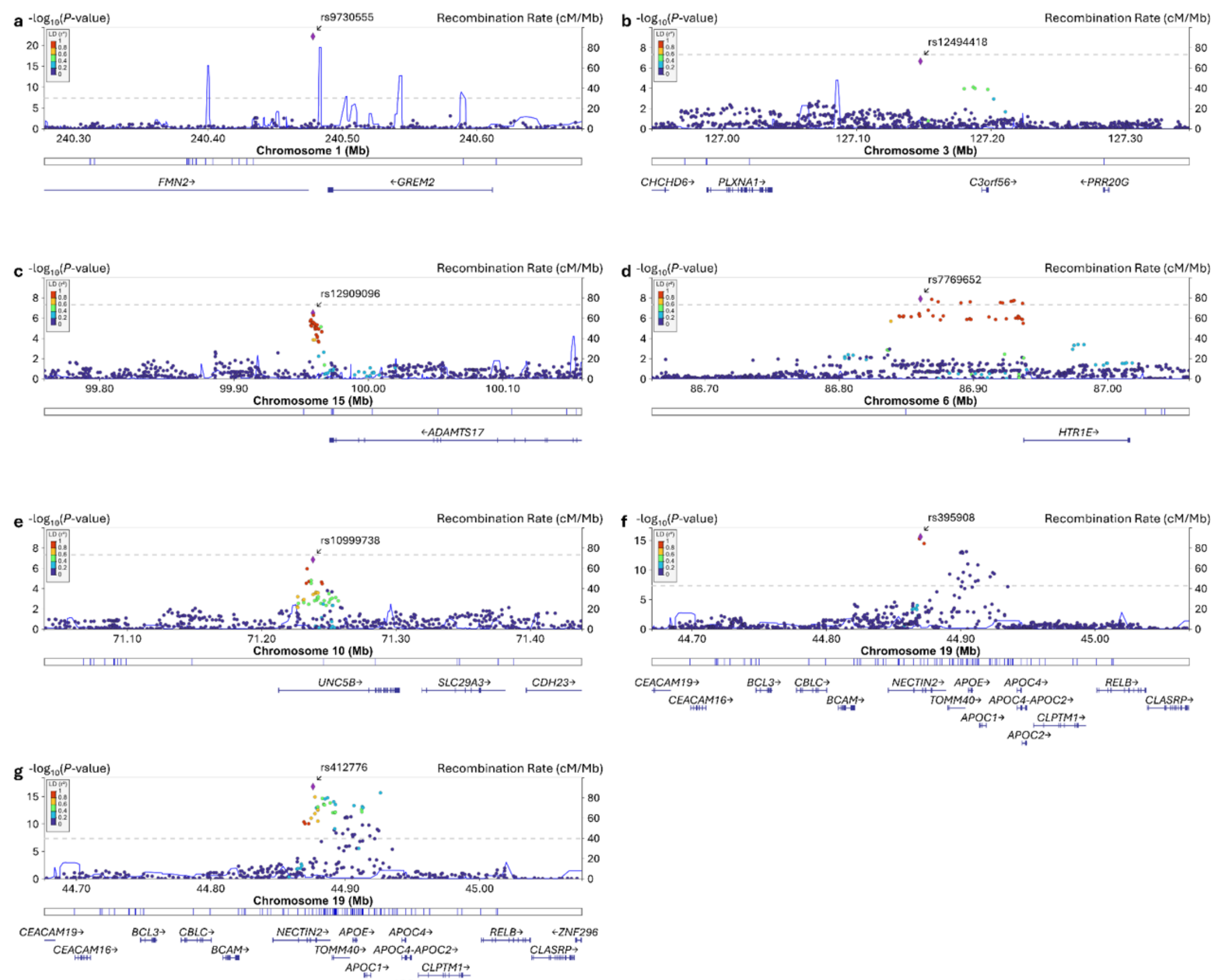


Figure 1. Top-ranked pleiotropic variants for MRI paired with amyloid PET

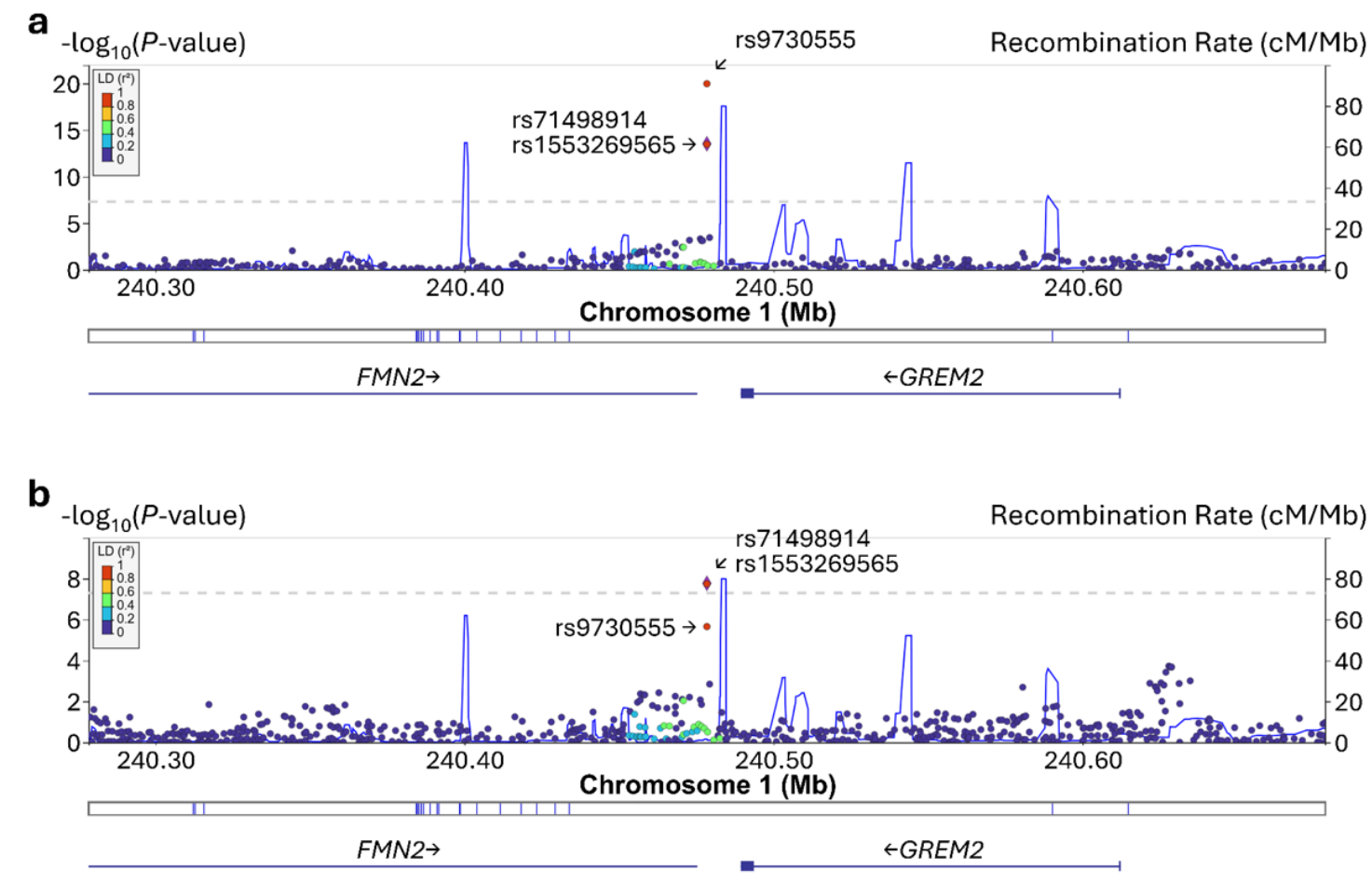


Figure 2. *FMN2* variants for GCT paired with GL and MTL SUVR in the GARD

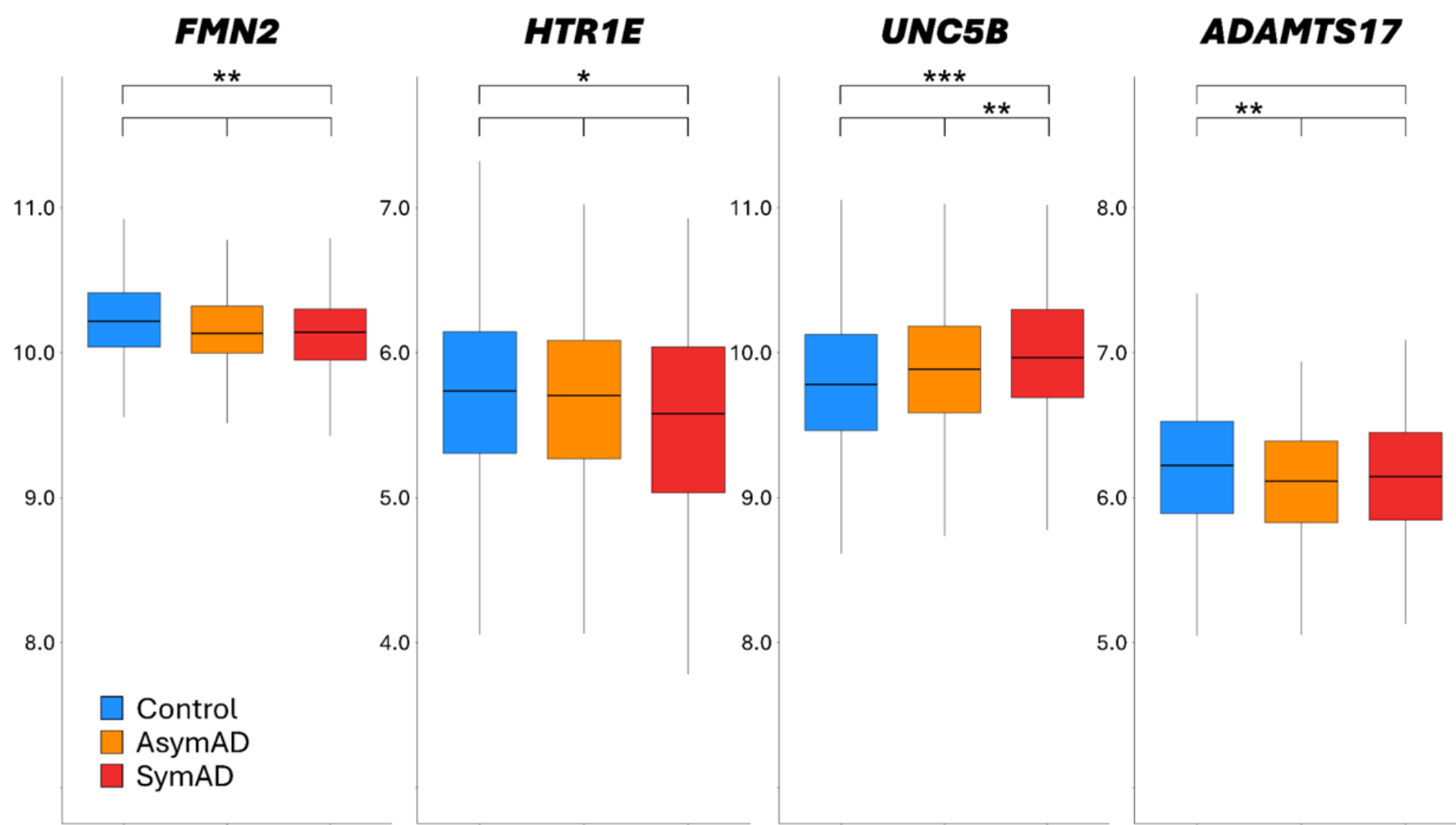


Figure 3. Pleiotropic genes differentially expressed in the DLPFC in controls and pathologically confirmed AD cases with and without clinical symptoms