Genetic association between epigenetic aging-acceleration and the progression of mild cognitive impairment to Alzheimer's disease

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Original Article

Genetic Association Between Epigenetic Aging-Acceleration and the Progression of Mild Cognitive Impairment to Alzheimer's Disease

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Introduction

- Aging is one of the leading risk factors for AD.
- Previous studies found the detrimental relationship between accelerated brain aging and AD early-stage neurodegeneration.
- Epigenetic age acceleration (EAA): the difference between the estimated age by methylation data and the chronological age.
- EAA is an effective biomarker for the prediction of multiple aging-related phenotypes, including telomere length, cancer, obesity, metabolic syndrome, PTSD, morbidity and mortality.

Introduction (Cont’d)

Two EAA measures:

- Intrinsic epigenetic age acceleration (IEAA): a derivative variation of Horvath EAA with adjustment for white blood cell composition and can be used as a biomarker of cell-intrinsic aging.

- Extrinsic epigenetic age acceleration (EEAA): a derivative variation of Hannum EAA that can track age-related changes in blood cells, and be correlated with lifestyle and health-span related factors.

- Inconsistent results were reported by previous studies on the association of EAA and dementia risk.

Hypothesis

EAA related genetic variants are associated with the progression from MCI to AD.

Populations

- Patients diagnosed with MCI at baseline or during follow-up were selected from the ADNI study (as a discovery set) and the NACC (as a replication set).

- From ADNI: N=767 with available genotype and clinical data, 294 subjects developed dementia.

- From NACC: N=1,373, 864 subjects developed dementia.

EAA SNP selection and imputation

- Selected 275,716 and 277,045 SNPs associated with IEAA and EEAA, respectively, with $P < 0.05$ and minor allele frequency (MAF) ≥ 0.05 in European population.

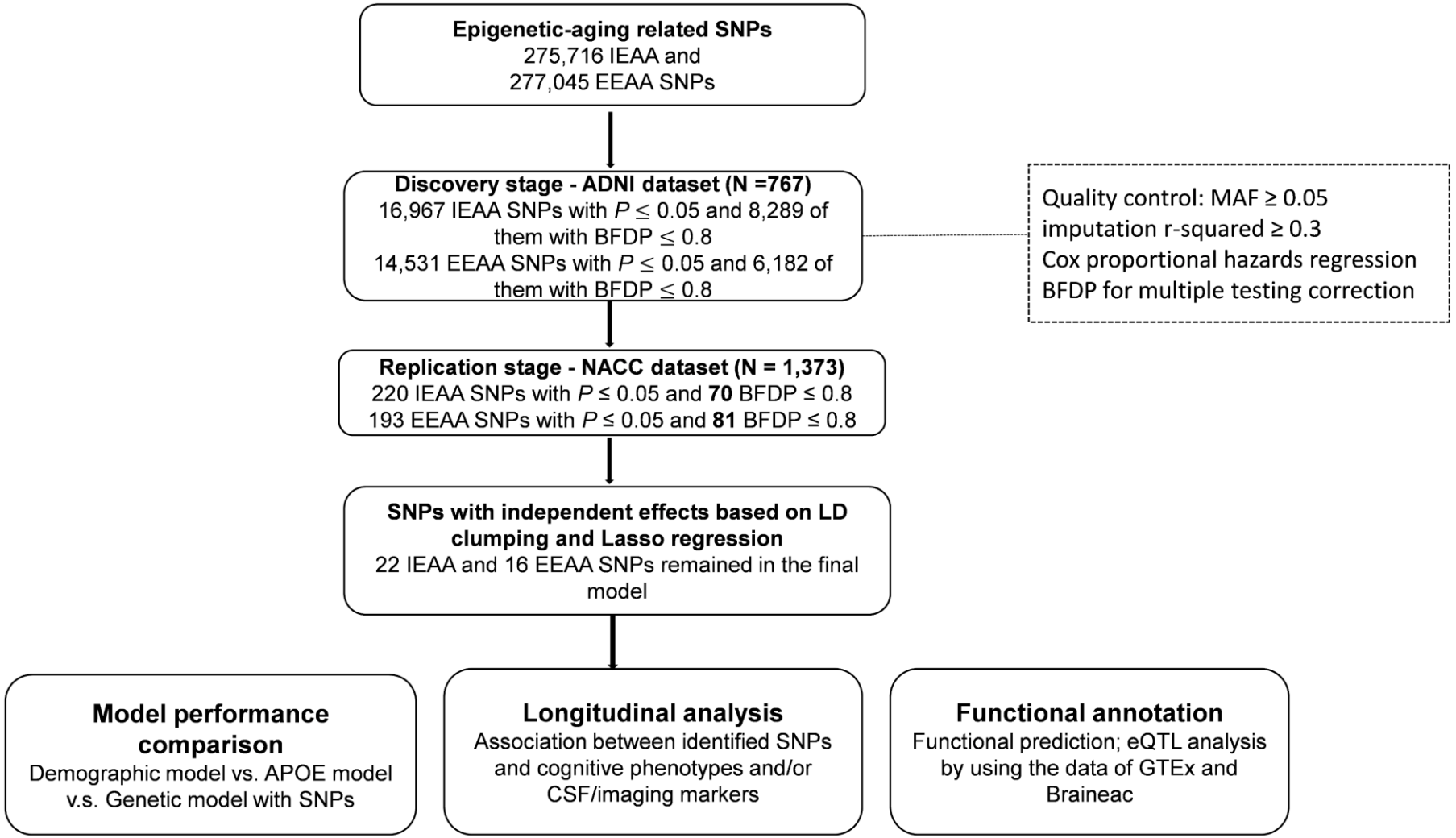
- Performed imputation with *minimac4* by using a set of high-quality genotyped SNPs : MAF ≥ 0.01; call rate ≥ 95%; HWE test P ≥ 10^{-6}; allele frequency difference ≤ 0.20 between the sample data and the reference panel.

- Imputed SNPs with MAF ≥ 0.05 and imputation quality score (r^2) > 0.3 were selected for further analysis.

Statistical methods

- SNP-heritability and genetic correlations of IEAA/EEAA and AD risk were estimated by using the LDAK model (http://dougspeed.com/) .
- The association between single SNP and the progression from MCI to AD was tested by using Cox proportional hazards regression with adjustment for age at baseline, sex, years of education, race, top significant principal components (PCs), and the number of allele copies of APOE E2 and E4.
- LD clumping and survival LASSO regression was applied to select SNPs with independent effect to construct PRS with PRSICE-2 by using the effect size estimates from the previous EAA GWAS.
- The correlations between PRSs and the longitudinal changes of these CSF and imaging biomarkers were investigated with a linear mixed model by including a random intercept and a random slope of time with adjustment for covariates.
- Functional annotations were performed by using the results from two eQTL database (GTEx and BRAINEAC), and one mQTL database (http://www.mqtldb.org/cgi-bin/search.cgi).

Study workflow



Abbreviations: IEAA = intrinsic-epigenetic-age-acceleration; EEAA = extrinsic-epigenetic-age-acceleration; ADNI = the Alzheimer's Disease Neuroimaging Initiative study; NACC = the National Alzheimer's Coordinating Center studies; MAF = minor allele frequency; BFDP = Bayesian false-discovery probability; eQTL = expression quantitative trait locus; GTEx = The Genotype-Tissue Expression (GTEx) project.

Distributions of the demographic variables in both ADNI and NACC dataset

ADNI

Variables	Total	Event (AD, %)	Beta[1]	Se[1]	*P*[1]
Overall	767	294 (38.3)			
Follow-up time (Years)					
Median (Min-max)	3.00 (0.39-13.00)	2.03 (0.46-11.50)			
AGE (Years old)			0.028	0.008	**0.001**
Mean ± SD	73.4±7.40	74.3±7.00			
Median (Min-max)	73.6 (55.0-91.4)	74.4 (55.0-88.4)			
Sex			-0.013	0.119	0.912
Female	299	114 (38.1)			
Male	468	180 (38.5)			
Education (Years)			-0.001	0.021	0.951
mean ± SD	15.9±2.82	15.9±2.69			
Race[2]			-0.249	0.238	0.295
Non-Hispanic White	700	275 (39.3)			
Other races	67	19 (28.4)			
APOE-E4			0.554	0.08	**3.35E-12**
0	385	108 (28.1)			
1	302	143 (47.4)			
2	80	43 (53.8)			
APOE-E2			-0.492	0.25	**0.049**
0	708	277 (39.1)			
1	59	17 (28.8)			

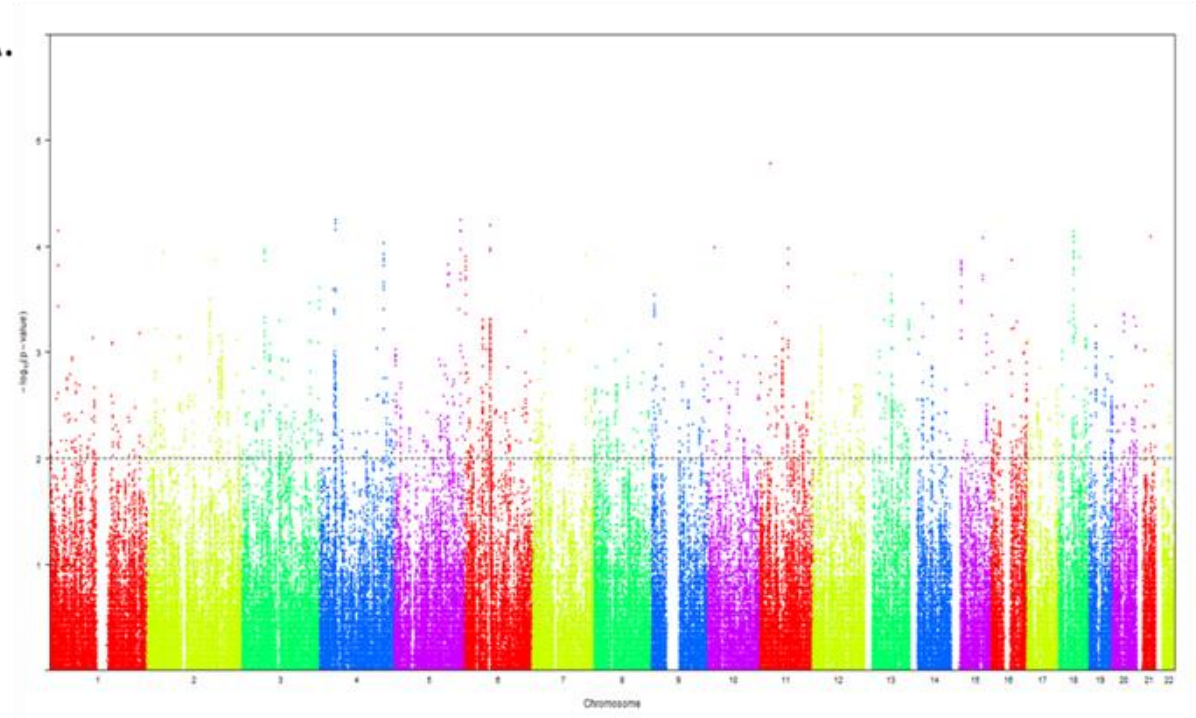
1.Univariate Cox regression

NACC

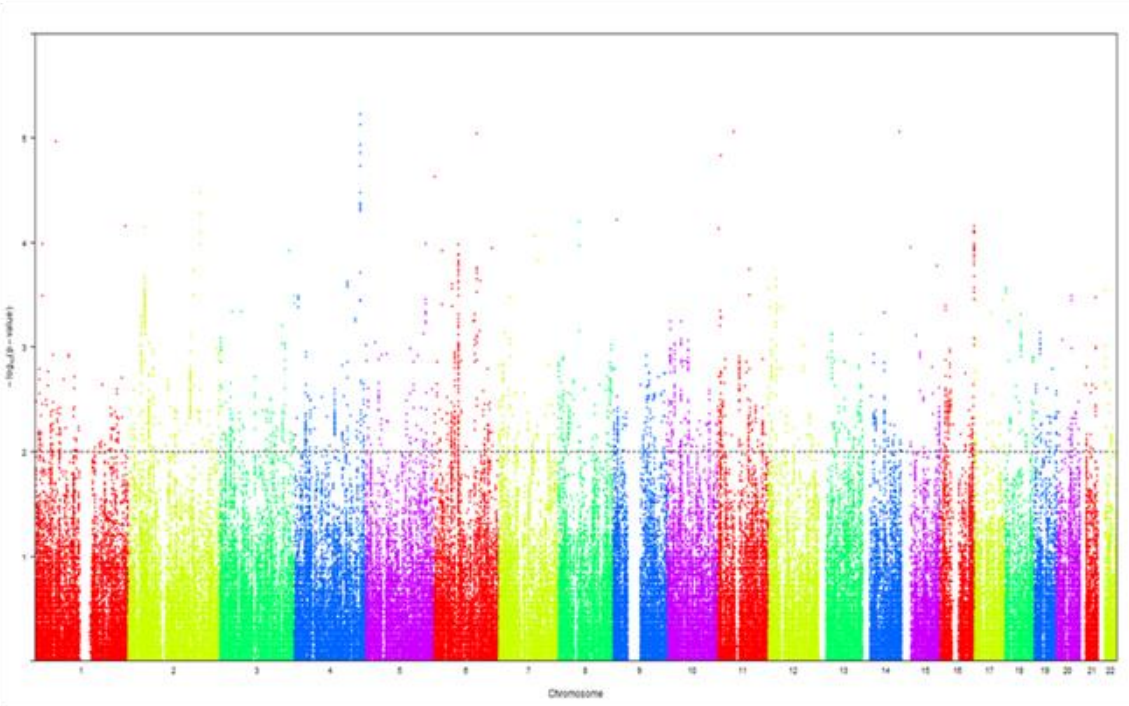
Variables	Total	Event (AD, %)	Beta[1]	Se[1]	*P*[1]
Overall	1373	864 (62.9)			
Follow-up time (Years)					
Median (Min-max)	2.35 (0.45-13.26)	2.76 (0.45-13.26)			
AGE (Years old)			0.001	0.004	0.777
Mean ± SD	77.2±8.21	77.2±7.95			
Median (Min-max)	77 (41-109)	77 (46-109)			
Sex			-0.008	0.068	0.906
Female	724	449 (62.0)			
Male	649	415 (63.9)			
Education (Years)[2]			-0.012	0.012	0.311
mean ± SD	15.7±2.94	15.7±2.89			
Race[2]			-1.476	0.578	**0.011**
Non-Hispanic White	1357	860 (63.4)			
Other races	15	3 (20.0)			
APOE-E4[2]			0.369	0.051	**4.28E-13**
0	744	406 (54.6)			
1	526	368 (70.0)			
2	100	88 (88.0)			
APOE-E2[2]			-0.234	0.113	**0.038**
0	1220	779 (63.9)			
1	146	83 (56.8)			
2	4	0 (0)			

Manhattan plots of the association results of IEAA/EEAA SNPs and AD progression time

A.



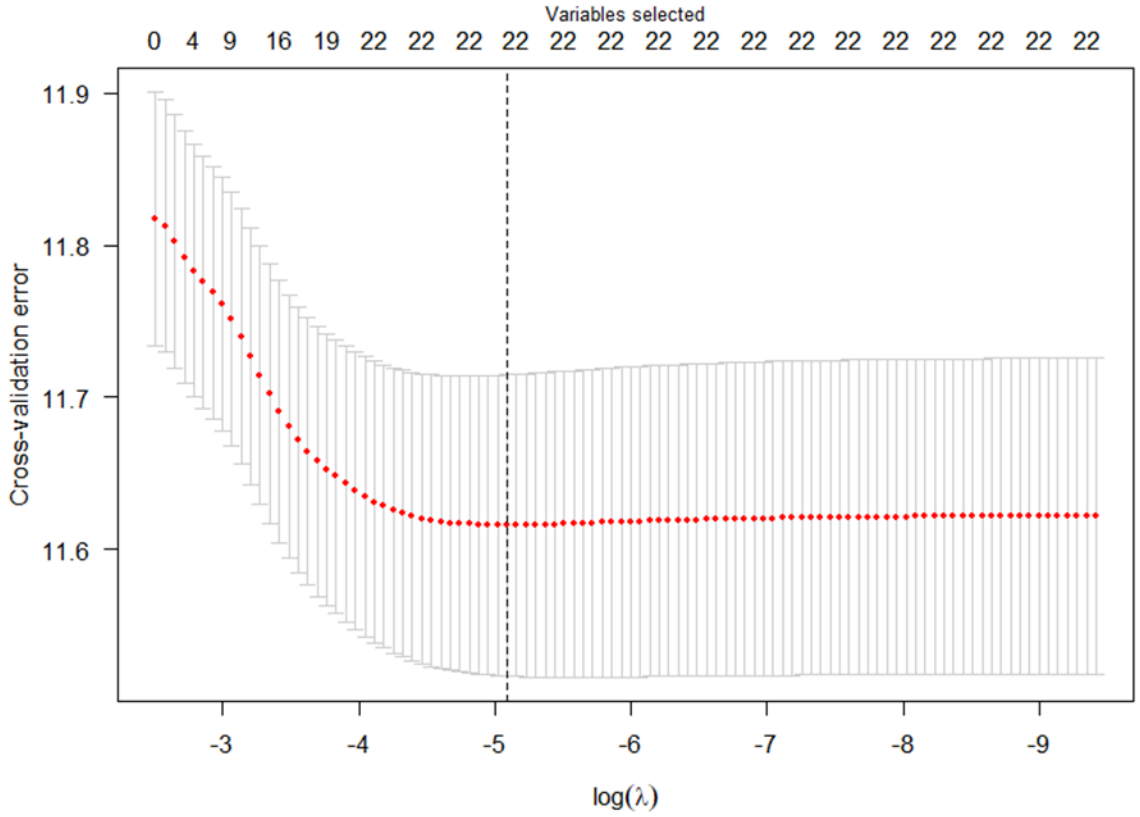
B.



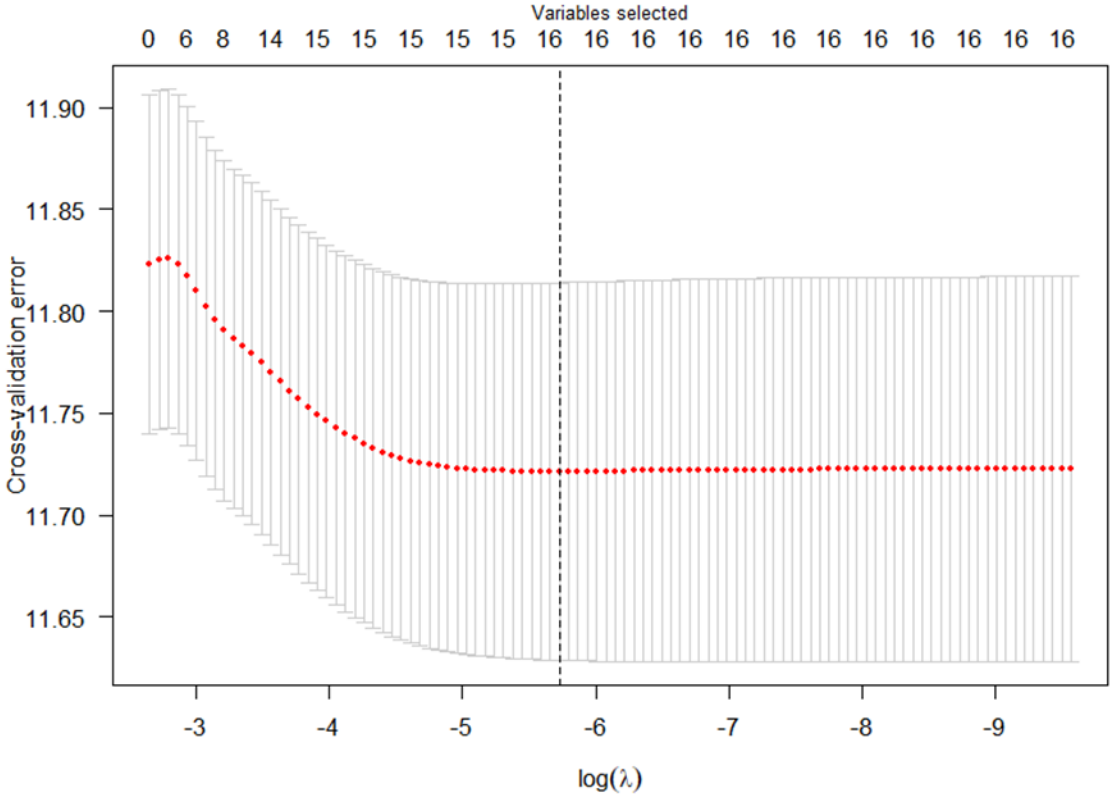
By using Bayesian false-discovery probability (BFDP) for multiple testing correction, in the ADNI dataset, we found 8,289 IEAA SNPs and 6,182 EEAA SNPs with BFDP ≤ 0.8.
There were 70 IEAA SNPs and 81 EEAA SNPs were replicated in the NACC dataset with BFDP ≤ 0.8.

Independent SNPs selection with lasso regression

ADNI IEAA: 22 SNPs with independent effects



ADNI EEAA: 16 SNPs with independent effects



Results of 22 IEAA SNPs associated with AD progression in both ADNI and NACC studies

						ADNI					NACC		
SNP	Gene	Chr	Pos (hg19)	A1[1]	A2[1]	beta[2]	se[2]	*P*[2]	FDR	BFDP	beta[2]	se[2]	*P*[2]
rs76670701	*PTGFRN*	1	117494279	G	A	0.380	0.118	0.001	0.743	0.242	0.191	0.075	0.011
rs57789409	*LAX1*	1	203728206	C	T	-0.255	0.103	0.013	0.743	0.716	-0.181	0.072	0.011
rs1441837	*LOC107984934/ LINC01648*	1	30172441	T	C	-0.397	0.167	0.017	0.743	0.699	-0.327	0.121	0.007
rs10904575	*LARP4B*	10	890252	G	A	0.203	0.076	0.007	0.743	0.666	0.137	0.052	0.008
rs61905163	*SORL1*	11	121266600	G	C	0.452	0.162	0.005	0.743	0.470	0.281	0.107	0.008
rs7968623	*RP11-439H13.2/RASSF3*	12	64934166	G	C	0.289	0.119	0.015	0.743	0.719	0.186	0.078	0.017
rs7229512	*BRUNOL4/LOC388474*	18	36353977	A	G	0.393	0.186	0.034	0.767	0.792	0.259	0.113	0.022
rs62193947	*KIAA2012*	2	202945280	G	A	-0.408	0.140	0.004	0.743	0.404	-0.220	0.094	0.019
rs13407491	*LINC01800*	2	65095571	A	C	0.500	0.154	0.001	0.743	0.202	0.217	0.091	0.017
rs6772965	*NLGN1*	3	173945890	A	C	0.195	0.076	0.010	0.743	0.725	0.150	0.049	0.002
rs12509085	*FSTL5*	4	163048511	T	G	-0.347	0.137	0.011	0.743	0.649	-0.233	0.091	0.010
rs621356	*CTD-2247C11.2*	5	4931128	T	G	-1.633	0.662	0.014	0.743	0.768	-1.104	0.371	0.003
rs13172823	*KIAA0947*	5	5599662	C	G	-0.237	0.103	0.021	0.743	0.794	-0.193	0.070	0.006
rs9480937	*CD164*	6	109679832	G	A	0.431	0.201	0.032	0.760	0.776	0.259	0.114	0.023
rs77702925	*TBXT*	6	166630734	A	C	0.387	0.170	0.023	0.743	0.745	0.354	0.114	0.002
rs3892832	*RREB1*	6	7142488	G	A	-0.377	0.126	0.003	0.743	0.361	-0.290	0.093	0.002
rs10237105	*SHH*	7	155644686	T	A	-0.380	0.154	0.013	0.743	0.664	-0.247	0.103	0.017
rs10093080	*RNF19A/ANKRD46*	8	101509461	C	G	-0.251	0.097	0.010	0.743	0.674	-0.179	0.064	0.005
rs79608085	*SGCZ*	8	14681337	A	G	-0.361	0.126	0.004	0.743	0.460	-0.197	0.083	0.018
rs28874035	*SH2D4A*	8	19236870	T	A	0.298	0.130	0.022	0.743	0.768	0.230	0.081	0.004
rs2654014	*DLGAP2*	8	934539	G	A	-0.295	0.081	2.56E-04	0.743	0.083	-0.150	0.055	0.007
rs11138749	*LOC107987084/ LOC105376103*	9	83195753	A	T	-0.413	0.164	0.012	0.743	0.637	-0.242	0.097	0.012

Abbreviations: IEAA = intrinsic-epigenetic-age-acceleration; EEAA = extrinsic-epigenetic-age-acceleration; AD = Alzheimer's disease; ADNI = the Alzheimer's Disease Neuroimaging Initiative study; NACC = the National Alzheimer's Coordinating Center studies; chr = chromosome; pos = position.

1. A1= effect allele, A2 = reference allele.

2. Adjusted for age, sex, education, race, the copy numbers of APOE E2 and E4, and significant principal components.

Results of 16 EEAA SNPs in both ADNI and NACC studies

						ADNI					NACC		
SNP	Gene	Chr	Pos (hg19)	A1[1]	A2[1]	beta[2]	se[2]	*P*[2]	FDR	BFDP	beta[2]	se[2]	*P*[2]
rs147449969	*ATP2B4*	1	203720905	C	T	-0.476	0.129	2.14E-04	0.898	0.057	-0.207	0.085	0.015
rs75269594	*PAK1*	11	77096603	G	A	-0.415	0.157	0.008	0.941	0.565	-0.375	0.117	0.001
rs4293193	*ZNF705A*	12	8307358	G	A	-0.215	0.079	0.006	0.941	0.619	-0.160	0.051	0.002
rs187776	*ALDH1A2*	15	58646011	G	C	-0.289	0.088	0.001	0.941	0.224	-0.148	0.057	0.009
rs112837743	*GALNS*	16	88902931	G	C	-0.328	0.144	0.022	0.941	0.758	-0.352	0.091	1.02E-04
rs4972565	*CDCA7*	2	174314089	G	A	-0.316	0.126	0.012	0.941	0.672	-0.243	0.080	0.002
rs72853313	*LOC107985792/ KLHL29*	2	23215521	C	T	0.404	0.174	0.020	0.941	0.720	0.303	0.114	0.008
rs2590959	*CNBD2*	20	34615776	T	C	-0.251	0.093	0.007	0.941	0.615	-0.159	0.063	0.011
rs45473297	*APP*	21	27541906	A	G	-0.247	0.085	0.004	0.941	0.501	-0.143	0.056	0.010
rs11924725	*EPHB1*	3	134505041	G	A	-0.363	0.158	0.022	0.941	0.744	-0.293	0.099	0.003
rs7707210	*LINC02039/GRAMD2B*	5	125334086	A	G	-0.380	0.145	0.009	0.941	0.590	-0.357	0.112	0.001
rs13172823	*KIAA0947*	5	5599662	C	G	-0.237	0.103	0.021	0.941	0.794	-0.193	0.070	0.006
rs4959195	*LINC01600/MYLK4*	6	2596934	C	T	-0.218	0.092	0.017	0.941	0.780	-0.253	0.060	2.32E-05
rs17162828	*MGC4859/ LOC105375149*	7	10299150	A	G	-0.270	0.076	4.13E-04	0.898	0.127	-0.142	0.056	0.011
rs7011999	*DLGAP2*	8	1008446	A	G	-0.227	0.080	0.005	0.941	0.553	-0.167	0.053	0.001
rs79608085	*SGCZ*	8	14681337	A	G	-0.361	0.126	0.004	0.941	0.460	-0.197	0.083	0.018

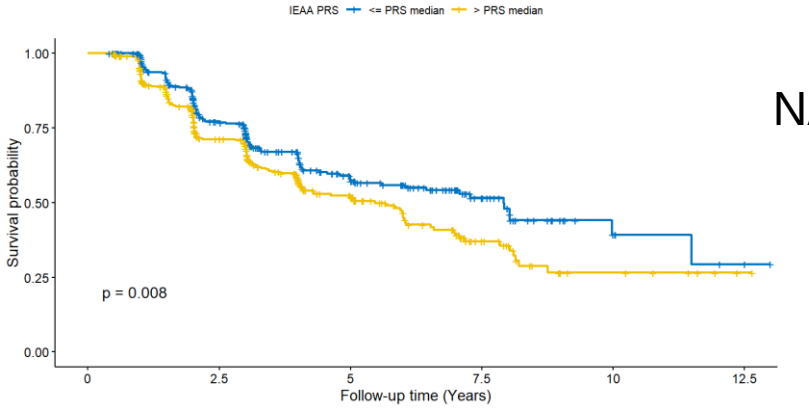
Abbreviations: IEAA = intrinsic-epigenetic-age-acceleration; EEAA = extrinsic-epigenetic-age-acceleration; AD = Alzheimer's disease; ADNI = the Alzheimer's Disease Neuroimaging Initiative study; NACC = the National Alzheimer's Coordinating Center studies; chr = chromosome; pos = position.

1. A1= effect allele, A2 = reference allele.

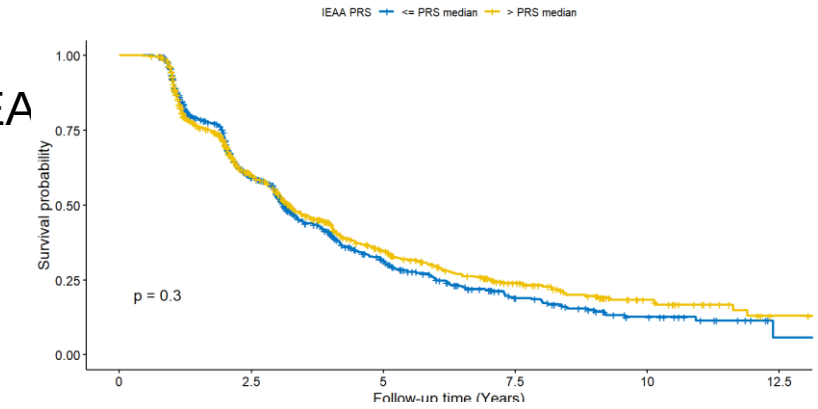
2. Adjusted for age, sex, education, race, the copy numbers of APOE E2 and E4, and significant principal components.

Association between IEAA and EEAA PRSs and the progression of MCI to AD

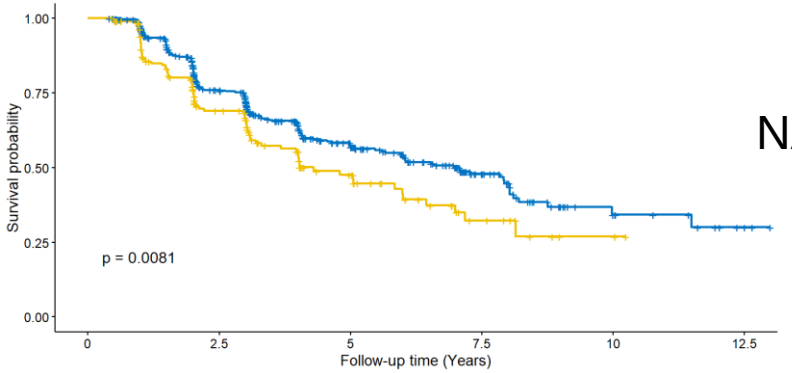
ADNI IEAA



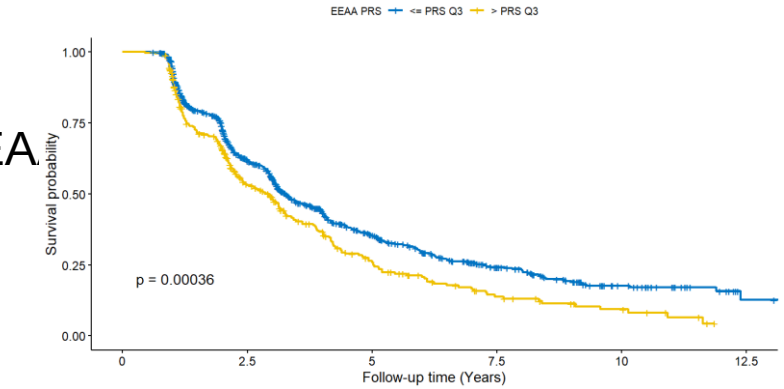
NACC IEA



ADNI EEAA



NACC EEA



	ADNI			NACC		
Variable	beta[1]	se[1]	*P*[1]	beta[1]	se[1]	*P*[1]
IEAA-PRS	0.123	0.062	**0.048**	0.013	0.034	0.699
EEAA-PRS	0.134	0.064	**0.036**	0.11	0.037	**0.003**

1. Adjusted for age, sex, education, race, the copy numbers of APOE E2 and E4, and significant principal components.

Performance of models integrating demographic variables and IEAA/EEAA PRSs

Model	Harrell's C (95% CI)	*P*
ADNI		
Demographic model[1]	0.555 (0.521-0.590)	
APOE model[2]	0.636 (0.600-0.671)	5.72E-07[5]
IEAA-PRS model[3]	0.641 (0.606-0.676)	0.216[6]
EEAA-PRS model[4]	0.639 (0.604-0.675)	0.409[6]
NACC		
Demographic model[1]	0.524 (0.502 - 0.546)	
APOE model[2]	0.575 (0.554-0.597)	3.52E-04[5]
IEAA-PRS model[3]	0.575 (0.553-0.596)	0.435[6]
EEAA-PRS model[4]	0.578 (0.557-0.600)	0.519[6]

1. Demographic model including age, sex, education and race
2. APOE model including age, sex, education, race, the copy numbers of APOE E2, and E4.
3. Genetic model including age, sex, education, race, the copy numbers of APOE E2/E4, and IEAA-PRS
4. Genetic model including age, sex, education, race, the copy numbers of APOE E2/E4, and EEAA-PRS
5. Results of APOE model vs. Demographic model.
6. Results of PRS model vs. APOE model.

Association results of IEAA PRS, EEAA PRS and cognitive phenotypes in ADNI dataset

Phenotype	#Subjects	#Observations	IEAA-PRS beta[1]	IEAA-PRS se[1]	IEAA-PRS *P*[1]	EEAA-PRS beta[1]	EEAA-PRS se[1]	EEAA-PRS *P*[1]
Cognitive phenotypes								
CDRSB	767	3,960	0.038	0.034	0.272	0.008	0.034	0.810
ADAS11	767	3,988	0.074	0.165	0.654	0.127	0.162	0.434
ADAS13	767	3,966	0.153	0.246	0.534	0.209	0.242	0.388
ADASQ4	767	3,993	0.098	0.089	0.267	0.072	0.087	0.409
MMSE	767	3,993	-0.121	0.067	0.071	0.031	0.066	0.641
MOCA	513	2,403	0.043	0.125	0.734	-0.012	0.124	0.923
FAQ	767	3,956	-0.034	0.144	0.812	0.084	0.142	0.555
CSF biomarkers								
ABETA[2]	295	712	-0.052	0.023	**0.028**	-0.030	0.024	0.210
tau[2]	289	695	-0.007	0.023	0.760	-0.009	0.023	0.688
ptau[2]	288	693	0.005	0.026	0.863	-0.008	0.027	0.776
Imaging biomarkers								
PIB	34	81	0.044	0.087	0.618	-0.008	0.027	0.776
FDG	385	1,278	0.004	0.007	0.510	0.000	0.006	0.997
AV45	312	817	0.016	0.011	0.146	0.005	0.011	0.621
Ventricles[3]	700	2,878	0.002	0.041	0.958	-0.024	0.040	0.543
Hippocampus[3]	652	2,553	0.002	0.003	0.500	-0.001	0.003	0.647
Entorhinal[3]	626	2,431	0.000	0.002	0.809	-0.002	0.002	0.311
Fusiform[3]	626	2,431	-0.001	0.006	0.938	-0.013	0.006	**0.032**
MidTemp[3]	626	2,431	0.003	0.007	0.697	-0.008	0.007	0.245

1. Adjusted for age at baseline, sex, years of education, race, significant principal components, and the allele copies of APOE E4 and APOE E2.
2. Log-transformed.

3. These dependent variables were expressed as the percentages to intracranial volume (ICV).

eQTL results of the identified SNPs in different brain tissues

Gene	rsid	exprID	chr	aveALL[1]	CRBL[1]	FCTX[1]	HIPP[1]	MEDU[1]	OCTX[1]	PUTM[1]	SNIG[1]	TCTX[1]	THAL[1]	WHMT[1]
KISS1	rs147449969	2451920	chr1	0.075	0.23	0.045	0.98	0.15	0.94	0.9	8.30E-06	0.3	0.5	0.68
CHIT1	rs57789409	2451620	chr1	0.17	4.80E-05	0.95	0.35	1	0.91	0.29	0.74	0.76	0.25	0.94
CDCA7	rs4972565	t2516023	chr2	0.26	0.76	0.08	**9.30E-06**	0.95	0.86	0.44	0.78	0.35	0.8	0.44
BMPR2	rs62193947	2523250	chr2	0.0095	0.45	0.19	0.11	0.65	0.049	0.44	2.50E-05	0.035	0.033	0.64
CASP8	rs62193947	2522752	chr2	0.00016	0.58	7.00E-05	0.68	0.64	0.034	0.024	0.024	0.0049	0.43	0.31
MPP4	rs62193947	2595006	chr2	0.99	0.8	0.92	**7.30E-05**	0.061	0.038	0.22	0.92	0.39	0.027	0.22
NOP58,SN	rs62193947	2523152	chr2	0.00083	0.052	0.0061	**0.0073**	0.41	0.024	0.051	0.062	8.20E-05	0.041	0.39
STRADB	rs62193947	2522795	chr2	0.00084	0.47	0.03	0.28	0.55	0.5	0.014	3.60E-05	0.028	0.051	0.34
WDR12	rs62193947	2595454	chr2	0.0015	0.93	0.033	0.29	0.27	0.12	0.092	1.30E-08	0.048	0.22	0.61
CPNE1,RBI	rs2590959	3904143	chr20	1.30E-05	2.60E-05	0.012	**2.00E-04**	0.00092	0.012	0.0034	0.047	0.00037	0.00087	0.00037
ERGIC3	rs2590959	3883395	chr20	2.50E-08	0.12	0.00057	**7.20E-05**	0.0044	0.048	0.055	0.056	0.0054	0.0045	1.20E-05
LOC25516	rs13172823	2800461	chr5	0.72	0.76	0.2	0.15	0.28	0.19	0.48	0.034	0.67	2.20E-05	0.7
NDUFA4	rs17162828	t3038617	chr7	0.13	0.59	0.79	0.71	0.066	0.77	0.68	0.61	0.00025	0.62	0.59
PHF14	rs17162828	t2990043	chr7	0.043	0.95	0.91	0.76	0.49	0.15	0.19	0.31	2.00E-04	0.26	0.14
PHF14	rs17162828	2990102	chr7	0.027	0.78	0.47	0.56	0.47	0.11	0.14	0.095	4.00E-04	0.24	0.24
THSD7A,TI	rs17162828	3038699	chr7	0.013	0.063	0.9	0.69	0.14	0.37	0.17	0.31	7.30E-05	0.22	0.1
PSD3	rs28874035	3126331	chr8	0.93	0.57	9.10E-05	0.58	0.89	0.87	0.72	0.87	0.4	0.87	0.21

Abbreviations: chr=chromosome; aveALL = average of the ten tissues; CRBL = cerebellar cortex; FCTX = frontal cortex; HIPP = hippocampus; MEDU = medulla; OCT

1. *P* values of eQTL results in specific brain tissues (highlighted in bold if P values ≤ 0.05).

Five SNPs with significant mQTL results in blood samples at middle age

Time point	SNP	SNP Chr	SNP Pos	Gene	A1[1]	A2[1]	MAF	CpG	CpG Chr	CpG Pos	CpG Gene	beta	t-stat	p-value
Middle Age	rs7011999	8	1008446	*DLGAP2*	G	A	0.333	cg04851639	8	1020857	*ERICH1-AS1*	-0.709	-18.01	2.03E-60
Middle Age	rs7011999	8	1008446		G	A	0.333	cg06547541	8	962834	*ERICH1-AS1*	-0.1206	-2.664	7.89E-03
Middle Age	rs7011999	8	1008446		G	A	0.333	cg08648136	8	956695		0.5202	12.93	1.27E-34
Middle Age	rs7011999	8	1008446		G	A	0.333	cg20449379	8	968983	*ERICH1-AS1*	0.2765	5.911	5.19E-09
Middle Age	rs7011999	8	1008446		G	A	0.333	cg15309053	8	964076	*ERICH1-AS1*	0.6511	15.75	2.00E-48
Middle Age	rs4293193	12	8307358	*ZNF705A*	A	G	0.324	cg19723998	12	8337217	*FAM66C*	-0.3315	-7.56	1.20E-13
Middle Age	rs112837743	16	88902931	*GALNS*	C	G	0.043	cg10491452	16	88866627	*CDT1*	-0.6009	-6.626	6.66E-11
Middle Age	rs112837743	16	88902931		C	G	0.043	cg06353259	16	88937797	*CBFA2T3*	0.9488	8.813	8.58E-18
Middle Age	rs2590959	20	34615776	*CNBD2*	C	T	0.166	cg03833512	20	34543802	*SCAND1*	-0.6152	-11.5	2.79E-28
Middle Age	rs2590959	20	34615776		C	T	0.166	cg27632911	20	34205182	*SPAG4*	0.4607	8.266	6.40E-16
Middle Age	rs2590959	20	34615776		C	T	0.166	cg04508476	20	34239394	*CPNE1*	-0.527	-13.4	8.47E-37
Middle Age	rs2590959	20	34615776		C	T	0.166	cg03168614	20	34253242	*CPNE1/RBM12*	-0.4216	-7.139	2.25E-12
Middle Age	rs45473297	21	27541906	*APP*	A	G	0.272	cg01286133	21	27540106	*APP*	-0.2679	-6.31	4.81E-10

Genetic association between IEAA/EEAA and AD risk

SNP-heritability and genetic correlation analyses of AD, IEAA, and EEAA

Traits	Heritability	SD	Genetic correlation with AD	SD
AD	0.160	0.014		
IEAA	0.265	0.074	0.508	0.343
EEAA	0.263	0.074	-0.179	0.357

Mendelian randomization analyses of IEAA/EEAA on late onset AD risk.

Outcome	Exposure	Method	#SNP	beta	se	*P*
AD (late onset)	IEAA	MR Egger	1002	0.0078	0.0108	0.469
AD (late onset)	IEAA	Weighted median	1002	0.0010	0.0047	0.839
AD (late onset)	IEAA	Inverse variance weighted	1002	-0.0011	0.0034	0.753
AD (late onset)	EEAA	MR Egger	1046	-0.0013	0.0091	0.889
AD (late onset)	EEAA	Weighted median	1046	-0.0044	0.0038	0.255
AD (late onset)	EEAA	Inverse variance weighted	1046	-0.0036	0.0029	0.214

Conclusions

- We revealed multiple genetic variants with pleiotropic effects on EAAs and the progression time from MCI to AD, and suggested shared genetic architecture between these traits.
- Further PRS analysis revealed a combined effect of those SNPs on AD progression, longitudinal changes of ABETA in CSF, and the volume changes of fusiform gyrus.
- Functional annotation revealed multiple SNPs with potential functions on regulation of DNA methylation and mRNA expression.
- However, no significance was found for the associations of both PRSs and AD progression. Such results suggested that these identified SNPs do not contribute substantially to the effect of these epigenetic aging on AD progression.
- In the future, more genetic variants with causal effects on EAA may be identified with the application of different statistical learning methods and used for EAA PRS calculation to improve the performance of AD risk prediction model.

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