Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Dataset used for functional genomic analysis.

The Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP) enrolled more than 3,322 subjects free of dementia at baseline who have been examined longitudinally until death using a neuropsychological test battery. Their postmortem brains were examined neuropathologically [1,2] and RNA was extracted from the dorsolateral prefrontal cortex (DLPFC) for gene expression analysis [3,4]. DNA from brain tissue, whole blood or lymphocytes transformed with EBV virus was extracted for whole genome sequencing (WGS) [3]. Global cognition function at the last exam before death was calculated as the average of the Z scores for 19 cognitive tests which are described in detail elsewhere [5]. The present study included 1,072 subjects who have WGS and cognition function test data and neuritic plaque and neurofibrillary tangles, and a subset of 432 subjects have RNA sequencing data.

eTable 1. Characteristics of the discovery and replication samples.

				APOE ε4+ subjects					*APOE* ε4- subjects				
					Cases		Controls		All (N)	Cases		Controls	
Study	Genotyping platform	Total Sample (N)	Percent of *APOE* E4 positive (%)	All (N)	N	Age-at-onset (mean±SD)	N	Age-at-exam (mean±SD)		N	Age-at-onset (mean±SD)	N	Age-at-exam (mean±SD)
Discovery													
ADSP	Whole exome sequencing	10,441	29.53	3,083	2,377	71.62±7.77	706	87.36±3.47	7,358	3,145	79.34±8.83	4,213	86.39±4.61
Replication													
ADES-FR	Whole exome sequencing	2,275	34.86	793	555	72.16±8.28	238	79.12±7.22	1,482	619	77.37±8.95	863	80.49±7.73
CHARGE	Whole exome sequencing	2,398	31.65	759	323	80.39±4.41	436	79.44±6.76	1,639	269	82.04±4.76	1,370	80.53±6.82
ADGC	HRC imputation	18,536	45.99	8,525	5,886	70.07±18.19	2,639	73.88±7.12	10,011	2,842	70.46±22.18	7,169	74.96±8.26
Subtotal		23,209	43.82	10,077	6,764		3,313		13,132	3,730		9,402	
Total		33,650	39.11	13,160	9,141		4,019		20,490	6,875		13,615	
Functional analysis in ROSMAP	Whole genome sequencing	1,072	25.84	277	152	88.42±6.32*	125	87.35±5.96*	795	261	91.14±6.17*	530	88.35±6.69*

* Age at death

eTable 2. Results for SNVs and indels in the discovery sample.

							APOE E4+ subgroup						APOE E4- subgroup						Interaction with APOE E4		
Chr	Position	rsID	EA	Gene	Impact[%]	GnomAD Exomes MAF (%)	MAC	MAF (%)	OR (95%CI)[#]	*P1*[*]	*P2*[*]	*P3*[#]	MAC	MAF (%)	OR (95%CI)[#]	*P1*[*]	*P2*[*]	*P3*[#]	Beta[&]	Se[&]	P4[&]
APOE E4+ subgroup																					
1	16,073,527	rs199908593[M2]	T	SLC25A34-AS1 / TMEM82	frameshift	1.3 [@]	51	0.86	0.08 (0.03,0.22)	8.92E-07	1.98E-06	2.72E-06	134	0.94	0.72 (0.51,1.04)	8.20E-02	8.30E-02	7.70E-02	-1.41	0.51	5.44E-03
2	220,283,592	rs111828114[M1]	T	DES	synonymous	3.9	245	4.0	0.53 (0.41,0.7)	6.39E-06	1.46E-05	8.84E-06	523	3.6	0.89 (0.75,1.07)	2.19E-01	2.21E-01	2.19E-01	0.50	0.17	2.57E-03
4	100,460,531	rs41275705[M1]	A	C4ORF17	splice region	2.5	124	2.0	2.32 (1.62,3.32)	5.60E-07	2.69E-06	4.33E-06	380	2.6	1.26 (1.01,1.41)	2.86E-02	2.86E-02	3.81E-02	0.60	0.21	3.52E-03
7	4,830,463	rs11766611[M2]	A	AP5Z1	missense	2.5	92	1.6	8.41 (3.03,23.35)	8.34E-06	1.04E-06	4.32E-05	188	1.3	0.96 (0.69,1.14)	7.78E-01	7.90E-01	7.91E-01	-1.61	0.44	2.89E-04
10	3,143,667	rs11542777[M2]	T	PFKP	synonymous	1.8	67	1.1	6.34 (2.57,15.64)	7.06E-06	2.39E-05	6.23E-05	188	1.3	0.86 (0.62,1.03)	3.59E-01	3.66E-01	3.66E-01	-1.31	0.42	1.83E-03
13	77,672,926	rs116957494[M2]	A	MYCBP2	missense	0.1	10	0.16	NA	1.31E-06	4.79E-06	NA	15	0.1	0.89 (0.24,1.8)	8.58E-01	8.20E-01	8.60E-01	-13.55	129.03	9.16E-01
13	111,160,304	rs391859[M1]	A	COL4A2 / COL4A2-AS1	synonymous	8	301	5.3	0.58 (0.45,0.74)	6.67E-06	1.49E-05	1.54E-05	839	6.1	0.88 (0.76,1.01)	5.81E-02	5.83E-02	6.90E-02	0.40	0.14	5.31E-03
19	18,546,678	rs2303697[M1]	T	ISYNA1	synonymous	35.6	2139	34.9	0.73 (0.64,0.84)	3.19E-06	2.75E-06	3.49E-06	4988	66.0	1 (0.93,1.04)	9.83E-01	9.82E-01	9.79E-01	-0.31	0.07	3.88E-05
19	45,411,941	rs429358[M1]	C	APOE	missense	16.1	2599	47.6	5.95 (3.75-9.42)	6.89E-16	0	1.79E-14	72	0.5	1.96 (1.25,2.5)	2.53E-03	2.77E-03	3.48E-03	-1.05	0.32	1.17E-03
20	1,276,876	rs367658252[M2]	C	SNPH	5_prime_UTR	0.9	69	1.2	13.25 (4.52-38.83)	4.96E-07	1.27E-07	1.93E-06	182	1.3	0.94 (0.67,1.13)	6.78E-01	6.87E-01	7.10E-01	-1.99	0.51	8.46E-05
21	33,717,877	rs2833779[M2]	A	URB1	synonymous	9.7	496	8.8	2.14 (1.48,3.09)	2.08E-06	1.94E-05	5.16E-05	1197	8.7	1.1 (0.96,1.18)	1.67E-01	1.67E-01	1.54E-01	-0.48	0.17	3.79E-03
21	33,738,920	rs10222086[M2]	C	URB1	splice region	9.4	450	7.9	2.3 (1.54,3.45)	1.98E-06	1.46E-05	5.48E-05	1129	8.1	1.05 (0.91,1.13)	5.22E-01	5.20E-01	5.09E-01	-0.62	0.18	6.32E-04
APOE E4- subgroup																					
6	41,129,252	rs75932628[M1]	T	TREM2	missense	0.2	51	0.83	4.58 (1.43,8.6)	4.78E-03	2.24E-03	1.04E-02	68	0.50	4.85 (2.74-8.60)	2.12E-09	2.38E-09	4.59E-08	0.05	0.66	9.44E-01
6	142,468,449	rs2232299[M2]	C	VTA1	missense	0.02	6	0.1	0.86 (0.08,3.21)	9.51E-01	7.27E-01	9.04E-01	14	0.10	0.04 (0.01,0.2)	1.72E-06	4.01E-06	1.49E-04	3.79	1.44	8.64E-03
7	154,988,675	rs536940594[M2]	A	AC099552	synonymous	0	0	0	NA	NA	NA	NA	10	0.10	87.96 (9.08-851.98)	2.22E-07	8.80E-07	9.47E-05	NA	NA	NA

8	144,995,964	rs35139934[M1]	A	PLEC	synonymous	7.4	476	7.8	1.13 (0.89,1.28)	3.15E-01	3.25E-01	3.16E-01	1131	7.8	1.34, (1.19,1.51)	1.88E-06	2.09E-06	2.23E-06	0.18	0.13	1.82E-01
8	145,138,063	rs138412600[M2]	A	GPAA1	synonymous	2	106	1.7	0.64 (0.31,1.35)	2.66E-01	1.99E-01	2.43E-01	239	2.0	2.13 (1.59-2.87)	2.70E-07	3.85E-07	3.91E-07	1.10	0.33	8.12E-04
17	44,076,665	rs62063857[M1]	A	MAPT / STH	missense	18.8	749	14.7	1.22 (1.03,1.33)	2.13E-02	2.25E-02	2.41E-02	2063	16.3	1.25 (1.14,1.37)	1.83E-06	1.67E-06	4.23E-06	-0.05	0.10	5.83E-01
17	44,828,931	rs199533[M1]	A	NSF	synonymous	17.8	1239	20.2	0.89 (0.77,1.03)	1.25E-01	1.26E-01	1.24E-01	2983	20.3	0.82 (0.76,0.89)	3.97E-06	3.79E-06	4.28E-06	-0.09	0.09	2.82E-01
19	1,047,507	19:1047507[M1]	A	ABCA7	frameshift	NA	26	0.43	2.23 (0.66,4.29)	1.88E-01	2.16E-01	1.95E-01	40	0.28	4.64 (2.2,9.8)	9.76E-06	9.75E-06	5.51E-05	0.71	0.72	3.31E-01
19	45,316,588	rs28399654[M1]	A	BCAM	missense	2.9	121	2.0	0.71 (0.48,1.07)	1.01E-01	1.01E-01	1.03E-01	538	3.7	0.66, (0.55,0.79)	6.70E-06	5.40E-06	7.93E-06	-0.09	0.23	7.05E-01
19	45,395,714	rs157581[M12]	T	TOMM40	synonymous	22.3	2871	53.1	1 (0.73,1.19)	8.18E-01	7.57E-01	9.92E-01	1501	10.2	1.36 (1.2,1.54)	1.43E-06	1.26E-06	1.61E-06	-0.38	0.15	8.82E-03

[%]Variant impact annotated by SnpEff and VEP. High: splice acceptor, splice donor, stop gained, frameshift, stop lost, start lost, or transcript amplification; Moderate: inframe insertion inframe deletion, missense variant, or protein altering; Low: initiator condon, stop retain, in splice region, 5' UTR premature start codon gain, synonymous variant, start retain; Modifier: the variant hits the coding sequence or a gene, upstream or downstream gene, intron, exon, intergenic region, conserved intergenic or intron region, miRNA, transcript, regulatory region, 3' or 5' UTR region.

[@]ExAC European MAF reference

*P1 and P2 represent the P-value for score and firth test, respectively

[#]OR (95%CI) represent the estimate of the odds ratio of AD cases and its 95% confidence interval based on generalized linear model, and P3 represents the corresponding P value

[&]Beta, SE, and P4 represent the estimate of the regression coefficient, standard error, and significance level of the interaction term of SNV*APOE4 in the generalized linear model

[M1]All the statistics and estimates are based on Model 1, which adjusted for principle components only

[M2]All the statistics and estimates are based on Model 2, which adjusted for age, sex, and principle components

[M12]The SNP is significant in both Model 1 and 2, but the statistics in Model 2 is presented.

EA = effect allele; MAC = minor allele count; MAF = minor allele frequency.

eTable 3. Meta-analysis results for SNVs and indels in the discovery and replication samples.

					Discovery						Replication								Discovery + Replication	
					ADSP		ADGC				ADES-FR			CHARGE			Total Replication			
Chr	BP	rsID	EA	Gene	OR (95%CI)#	*P*#	R^{2*}	MAF Range (%)*	OR (95%CI)#	*P*#	MAF (%)	OR (95%CI)#	*P*#	MAF (%)	OR (95%CI)#	*P*#	OR (95%CI)#	*P*#	OR (95%CI)#	*P*#
Top variants identified in APOE E4+ subgroup																				
1	16,073,527	rs199908593[M2]	T	SLC25A34-AS1 / TMEM82	0.08 (0.03,0.22)	2.72E-06	NA	NA	NA	NA	2.4	1.19 (0.59,2.4)	0.64	2.20	1.3 (0.6,2.83)	0.51	1.13 (0.59,2.15)	0.71	0.56 (0.32,0.97)	0.04
2	220,283,592	rs111828114[M1]	T	DES	0.53 (0.41,0.7)	8.84E-06	(0.45,0.72)	(1.3, 5.7)	0.84 (0.64,1.09)	0.18	3.7	0.82 (0.48,1.42)	0.48	3.0	1.03 (0.55,1.93)	0.92	0.88 (0.7,1.11)	0.27	0.72 (0.6,0.85)	2.18E-04
4	100,460,531	rs41275705[M1]	A	C4ORF17	2.32 (1.62,3.32)	4.33E-06	(0.81,0.99)	(1.5, 7.1)	1.11 (0.92,1.35)	0.28	3.4	1.95 (1.11,3.44)	0.02	3.6	1.41 (0.76,2.59)	0.28	1.19 (0.99,1.42)	0.06	1.36 (1.16,1.6)	1.80E-04
7	4,830,463	rs11766611[M2]	A	AP5Z1	8.41 (3.03,23.35)	4.32E-05	(0.41,0.56)	(1.6, 2.7)	0.72 (0.41,1.26)	0.26	2.7	1.17 (0.54,2.51)	0.70	1.7	2.07 (0.89,4.81)	0.09	0.96 (0.63,1.48)	0.86	1.34 (0.9,1.99)	0.15
10	3,143,667	rs11542777[M2]	T	PFKP	6.34 (2.57,15.64)	6.23E-05	(0.47,0.99)	(0.23, 2.8)	0.94 (0.67,1.33)	0.73	2.4	0.67 (0.32,1.4)	0.29	1.3	1.02 (0.39,2.66)	0.98	0.87 (0.64,1.17)	0.35	1.06 (0.79,1.41)	0.70
13	77,672,926	rs116957494[M2]	A	MYCBP2	NA	NA	(0.41,0.84)	(0.03, 0.35)	1.05 (0.1,11.16)	0.97	0.32	Inf (0,Inf)	0.98	0.13	0.06 (0,1.14)	0.06	1.05 (0.1,11.15)	0.97	1.05 (0.1,11.15)	0.97
13	111,160,304	rs391859[M1]	A	COL4A2 / COL4A2-AS1	0.58 (0.45,0.74)	1.54E-05	(0.81,0.999)	(6.2, 14.2)	1.04 (0.92,1.18)	0.51	9.7	0.98 (0.67,1.41)	0.90	7.5	0.99 (0.67,1.49)	0.98	1.03 (0.92,1.16)	0.60	0.93 (0.84,1.03)	0.17
19	18,546,678	rs2303697[M1]	T	ISYNA1	0.73 (0.64,0.84)	3.49E-06	(0.9,0.997)	(30.7, 39.8)	0.88 (0.81,0.95)	6.84E-04	35.9	0.96 (0.76,1.2)	0.72	32.5	1.02 (0.81,1.28)	0.87	0.89 (0.83,0.96)	1.26E-03	0.85 (0.8,0.91)	4.61E-07
19	45,411,941	rs429358[M1]	C	APOE	5.95 (3.75-9.42)	1.79E-14	(0.41,0.7)	(37.6, 39.1)	4.13 (3.24-5.25)	2.60E-31	44.3	3.67 (1.91,7.05)	9.54 E-05	NA	NA	NA	3.99 (3.21,4.96)	1.99E-35	4.3 (3.53,5.23)	9.83E-48
20	1,276,876	rs367658252[M2]	C	SNPH	13.25 (4.52-38.83)	1.93E-06	(0.65,0.97)	(0.07, 2.0)	0.77 (0.55-1.06)	0.11	1.1	0.66 (0.23,1.92)	0.45	0.59	0.41 (0.08,2.03)	0.27	0.79 (0.58,1.07)	0.13	0.98 (0.73,1.31)	0.87
21	33,717,877	rs2833779[M2]	A	URB1	2.14 (1.48,3.09)	5.16E-05	(0.8,0.998)	(9.2, 17.8)	0.93 (0.83,1.04)	0.20	11.1	1.03 (0.7,1.51)	0.90	11.9	0.81 (0.57,1.14)	0.23	0.93 (0.84,1.04)	0.21	1 (0.9,1.1)	0.92
21	33,738,920	rs10222086[M2]	C	URB1	2.3 (1.54,3.45)	5.48E-05	(0.9,0.995)	(8.8, 15.2)	0.93 (0.83,1.04)	0.20	10.4	0.96 (0.64,1.42)	0.82	10.8	0.75 (0.52,1.07)	0.12	0.93 (0.83,1.04)	0.19	0.99 (0.89,1.1)	0.84
Top variants identified in APOE E4- subgroup																				
6	41,129,252	rs75932628[M1]	T	TREM2	4.85 (2.74-8.60)	4.59E-08	(0.6,0.99)	(0.08, 1.1)	2.84 (1.37-5.89)	4.67E-03	0.34	NA	NA	0.12	0.29 (0.02,3.75)	0.34	2.4 (1.2,4.81)	0.01	3.66 (2.36,5.68)	6.84E-09
6	142,468,449	rs2232299[M2]	C	VTA1	0.04 (0.01,0.2)	1.49E-04	(0.56,0.998)	(0, 0.77)	0.07 (0,16.18)	0.34	0.03	0 (0,Inf)	0.97	0.06	2.98 (0,2189.88)	0.75	0.32 (0,21.34)	0.59	0.05 (0.01,0.24)	2.08E-04
7	154,988,675	rs536940594[M2]	A	AC099552	87.96 (9.08-851.98)	9.47E-05	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
8	144,995,964	rs35139934[M1]	A	PLEC	1.34, (1.19,1.51)	2.23E-06	(0.4,0.77)	(6.3, 11.4)	1.31 (1.11,1.53)	1.06E-03	8.1	0.84 (0.64,1.11)	0.23	6.8	0.71 (0.49,1.03)	0.07	1.1 (0.97,1.25)	0.1416	1.22 (1.12,1.34)	8.17E-06
8	145,138,063	rs138412600[M2]	A	GPAA1	2.13 (1.59-2.87)	3.91E-07	(0.42,0.91)	(0.81, 2.4)	1.5 (1.03-2.38)	0.03	1.5	1.08 (0.6,1.97)	0.79	2.2	1.79 (0.92,3.47)	0.08	1.47 (1.08,1.98)	0.01	1.78 (1.44,2.2)	7.81E-08

17	44,076,665	rs62063857[M1]	A	MAPT / STH	1.25 (1.14,1.37)	4.23E-06	(0.8,0.998)	(17.9, 27.4)	1.12 (1.03,1.22)	5.42E-03	25.0	1.06 (0.89,1.25)	0.53	9.6	1.38 (0.97,1.96)	0.07	1.12 (1.04,1.2)	2.03E-03	1.17 (1.1,1.23)	1.59E-07
17	44,828,931	rs199533[M1]	A	NSF	0.82 (0.76,0.89)	4.28E-06	(0.85,0.997)	(16.3, 25.4)	0.89 (0.82,0.97)	8.64E-03	23.5	0.96 (0.8,1.14)	0.61	20.0	0.83 (0.66,1.05)	0.12	0.9 (0.83,0.96)	3.38E-03	0.86 (0.82,0.91)	1.66E-07
19	1,047,507	chr19bp1047507[M1]	A	ABCA7	4.64, (2.2,9.8)	5.51E-05	NA	NA	NA	NA	0.24	0.24 (0.03,2.03)	0.19	NA	NA	NA	NA	NA	3.36 (1.66,6.79)	7.49E-04
19	45,316,588	rs28399654[M1]	A	BCAM	0.66, (0.55,0.79)	7.93E-06	(0.61,0.99)	(1.2, 5.6)	0.92 (0.75,1.14)	0.44	3.3	0.74 (0.48,1.13)	0.17	3.2	0.74 (0.43,1.28)	0.28	0.87 (0.73,1.04)	0.1154	0.76 (0.67,0.86)	2.25E-05
19	45,395,714	rs157581[M12]	T	TOMM40	1.36 (1.2,1.54)	1.61E-06	(0.41,0.999)	(6.2, 14.8)	1.14 (1.01,1.29)	0.04	8.7	NA	NA	10.4	0.99 (0.72,1.35)	0.93	1.12 (1,1.26)	0.05	1.22 (1.13,1.33)	2.50E-06

@ ExAC European MAF reference

*R2 and MAF represent the range of imputation quality and minor allele frequency (minimum value, maximum value) across cohorts of replication ADGC.

#OR (95%CI) represent the estimate of the odds ratio of AD cases and its 95% confidence interval based on generalized linear model, and P represents the corresponding P value

M1 All the statistics and estimates are based on Model 1, which adjusted for principle components only.

M2 All the statistics and estimates are based on Model 2, which adjusted for age, sex, and principle components

M12 The SNP is significant in both Model 1 and 2, but the statistics in Model 2 is presented.

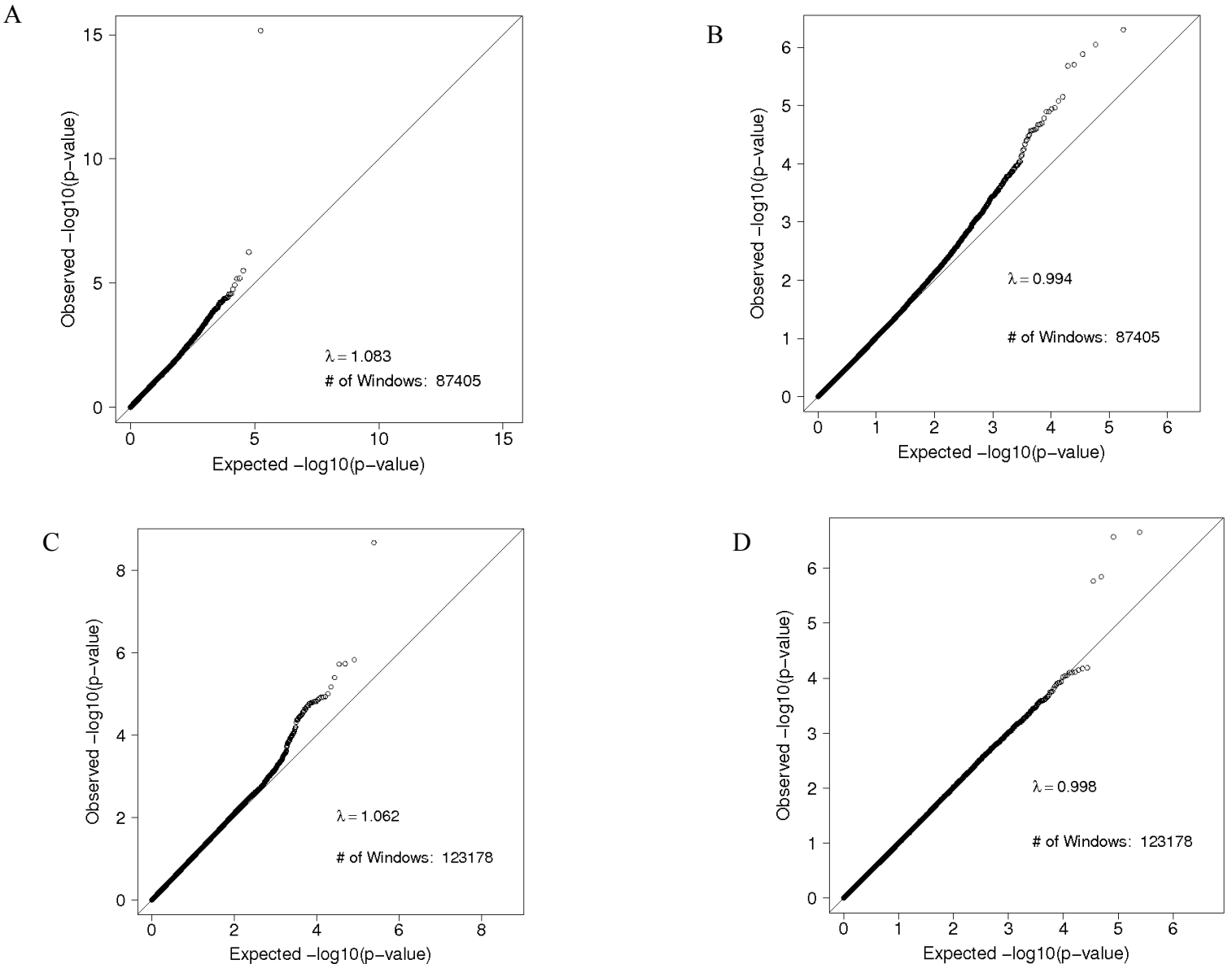
EA = effect allele; MAC = minor allele count.

eTable 4. Results of gene-based tests in the discovery and replication samples

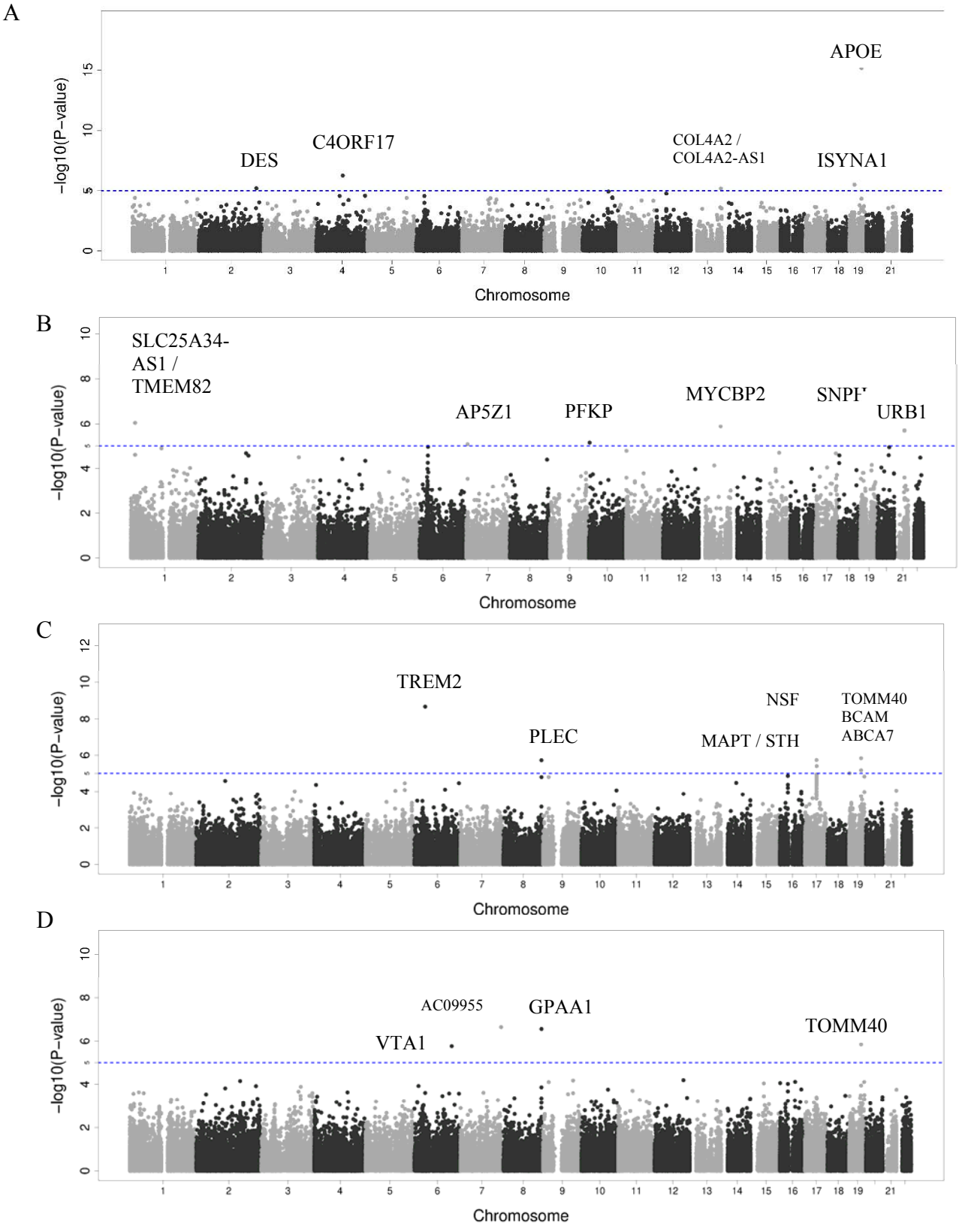
APOE Group	Chr	Start	End	Gene	SNV impact	Model	P values						Sentinel SNP in Replic.[a]
							ADSP	Replication Cohorts				All	
								ADGC	ADES-FR	CHARGE	Meta		
ε4+	11	124134751	124135752	*OR8G5*	High + Moderate	2	4.67E-07	7.77E-02	6.58E-01	4.79E-01	0.05	3.54E-05	No
	14	106518415	106518824	*IGHV3-7*	All	2	9.75E-16	6.06E-02	NA	8.90E-01	0.07	3.69E-08	No
	20	19261606	19261724	*SLC24A3*	All	2	2.67E-12	4.58E-01	7.97E-01	3.97E-02	0.19	5.73E-06	No
ε4-	6	41126505	41130815	*TREM2*	High + Moderate	1	2.75E-08	1.11E-03	2.51E-02	8.00E-01	2.25E-04	4.75E-10	Yes

[a] Sentinel SNP accounting for significance in ADSP discovery sample present in any replication datasets (yes/no)

eFigure 1. QQ plots for association in the discovery sample by analysis model and *APOE* genotype. (A) *APOE* ε4+, Model 1; (B) *APOE* ε4+, Model 2; (C) *APOE* ε4-, Model 1; (D) *APOE* ε4-, Model 2.

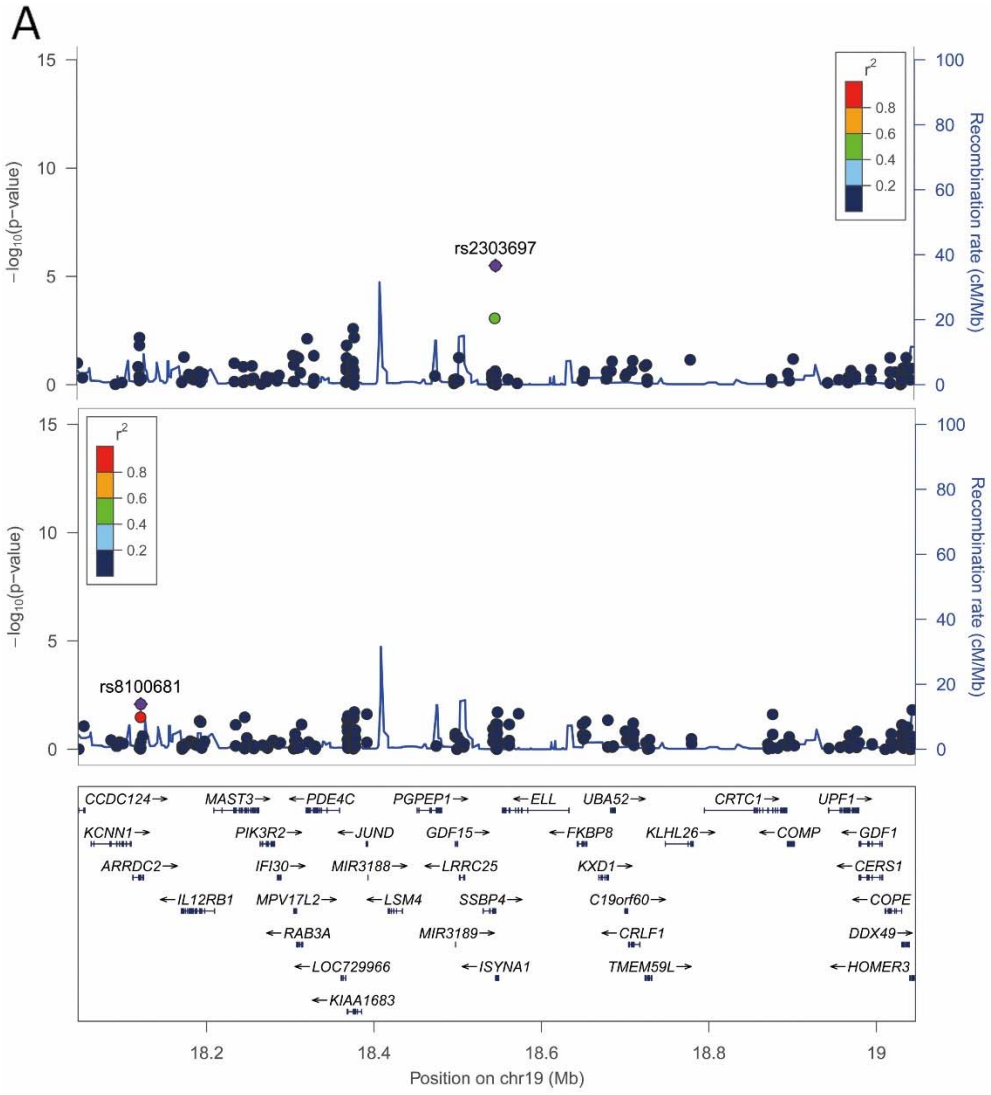


eFigure 2. Manhattan plots for association in the discovery sample by analysis model and *APOE* genotype. Observed –log *P*-values (y-axis) are shown for each variant grouped by chromosome (x-axis). (A) ε4+, Model 1; (B) ε4+, Model 2; (C) ε4-, Model 1; (D) ε4-, Model 2. Model 1 adjusts for principle components (PCs) and Model 2 adjusts for PCs, age and sex. Variants with discovery *P*-values < 1×10^{-5} are shown above the dotted line and were further evaluated in the replication sample.



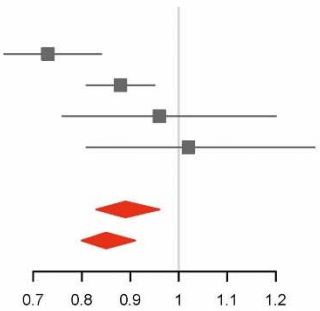
eFigure 3. Association of Alzheimer disease with variants in the *ISYNA1* region. (A) Regional Manhattan plot in the *APOE* ε4+ (upper) and *APOE* ε4- (lower) subgroups in the discovery ADSP sample. SNPs with the lowest *P*-value are indicated with a purple diamond, and the estimated linkage

disequilibrium (r^2) between the top SNP and other SNPs in the region are shown as circles with the color coding: red = $r^2 \geq 0.8$, orange = $0.6 \leq r^2 < 0.8$, green = $0.4 \leq r^2 < 0.6$, light blue = $0.2 \leq r^2 < 0.4$, and blue = $r^2 < 0.2$. Grey circles represent unannotated SNPs. (B) Forest plot of association results in each cohort in the *APOE* ε4+ group. OR = odds ratio. The filled symbol and horizontal line indicate the estimated odds ratio and its 95% confidence interval per dosage of the rs2303697 *T* allele on the risk of AD. Both plots show the results using Model 1, which adjusts for principle components of ancestry.

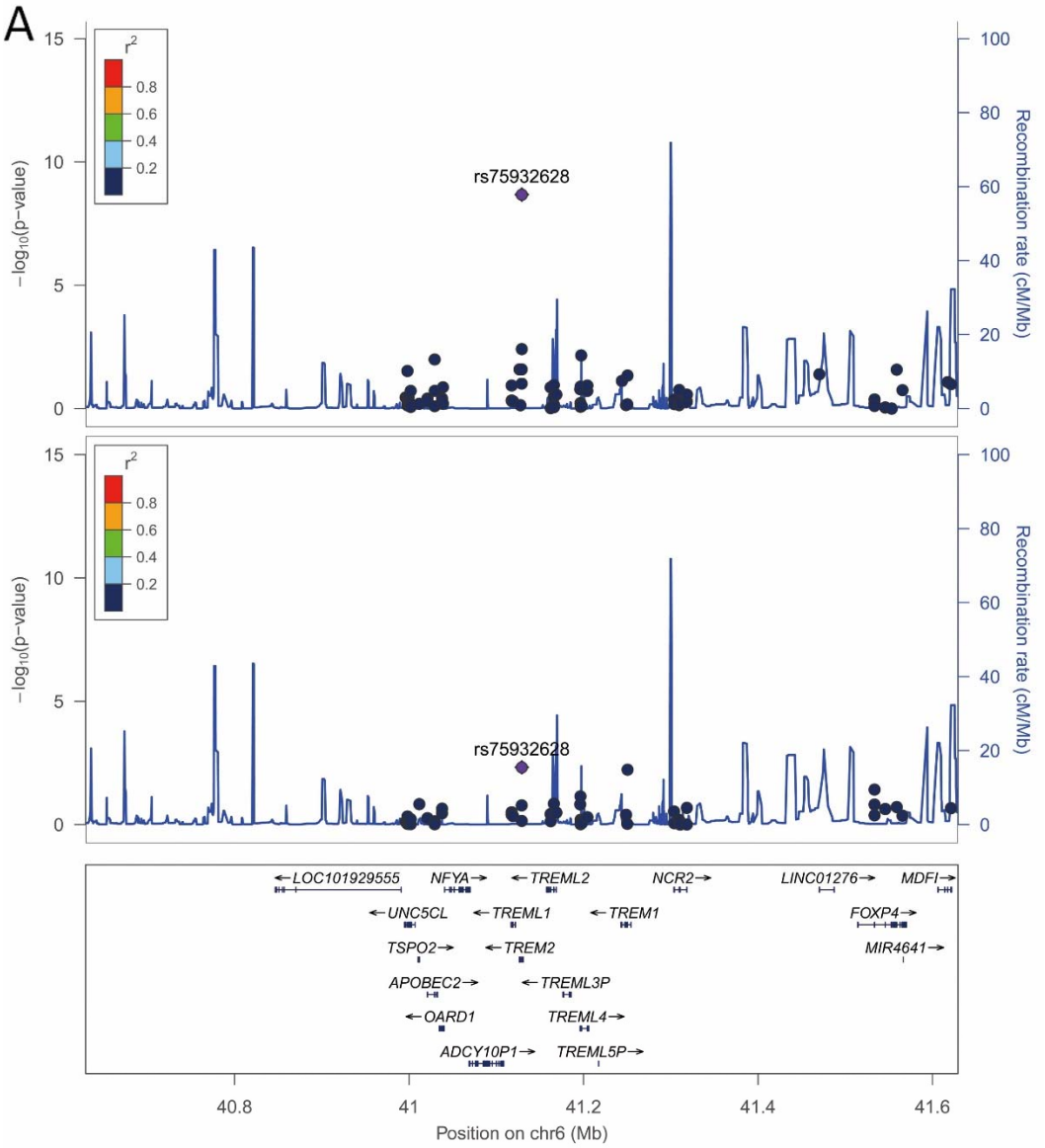


B

Cohort	N	OR	P value
Discovery_ADSP	3068	0.73	3.19e-06
Replication_ADGC	8284	0.88	6.84e-04
Replication_ADES-FR	793	0.96	7.20e-01
Replication_CHARGE	759	1.02	8.70e-01
Meta_Replication	**9836**	**0.89**	**1.23e-03**
Meta_All	**12904**	**0.85**	**4.61e-07**

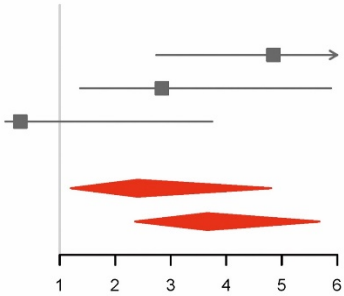


eFigure 4. Association of Alzheimer disease with variants in the *TREM2* region. (A) Regional Manhattan plot in the *APOE* ε4+ (upper) and *APOE* ε4- (lower) subgroups in the discovery ADSP sample. SNPs with the lowest *P*-value are indicated with a purple diamond, and the estimated linkage disequilibrium (r^2) between the top SNP and other SNPs in the region are shown as circles with the color coding: red = $r^2 \geq 0.8$, orange = $0.6 \leq r^2 < 0.8$, green = $0.4 \leq r^2 < 0.6$, light blue = $0.2 \leq r^2 < 0.4$, and blue = $r^2 < 0.2$. Grey circles represent unannotated SNPs. (B) Forest plot of association results in each cohort in the *APOE* ε4+ group. OR = odds ratio. The filled symbol and horizontal line indicate the estimated odds ratio and its 95% confidence interval per dosage of the rs75932628 *A* allele on the risk of AD. Both plots show the results using Model 1, which adjusts for principle components of ancestry.



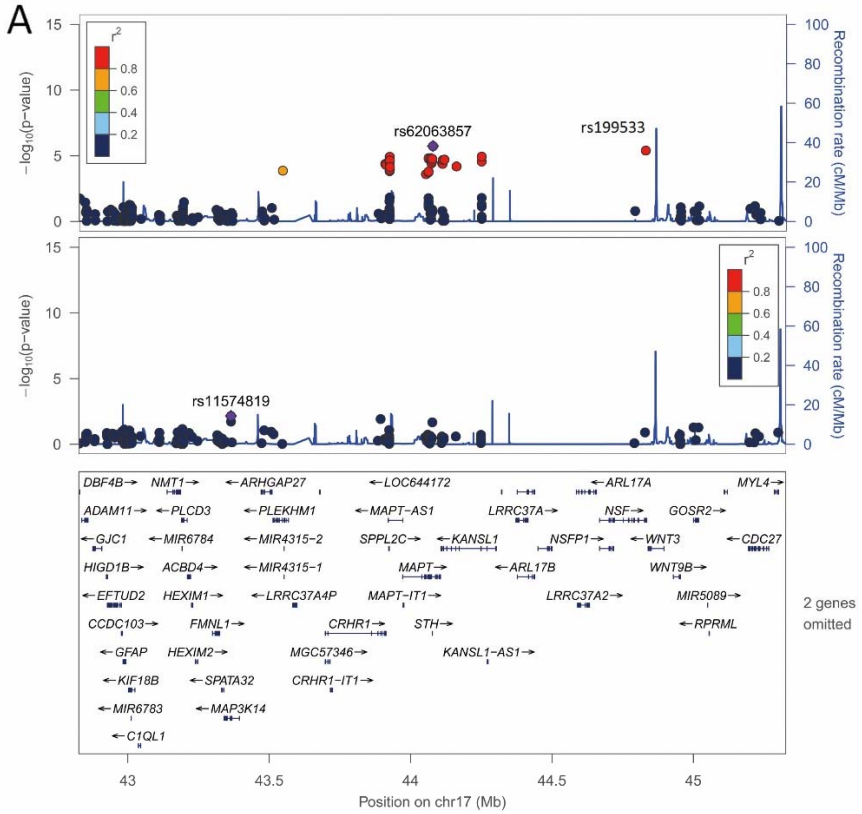
B

Cohort	N	OR	P value
Discovery_ADSP	7317	4.85	4.59e-08
Replication_ADGC	9256	2.84	4.67e-03
Replication_CHARGE	1639	0.29	3.40e-01
Meta_Replication	**10895**	**2.4**	**1.00e-02**
Meta_All	**18212**	**3.66**	**6.84e-09**



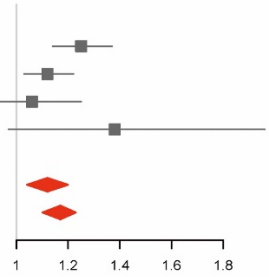
eFigure 5. Association of Alzheimer disease with variants in the region including *MAPT* and *NSF*. (A) Regional Manhattan plot in the *APOE* ε4+ (upper) and *APOE* ε4- (lower) subgroups in the discovery ADSP sample. SNPs with the lowest *P*-value are indicated with a purple diamond, and the estimated linkage disequilibrium (r^2) between the top SNP and other SNPs in the region are shown as circles with the color coding: red = $r^2 \geq 0.8$, orange = $0.6 \leq r^2 < 0.8$, green = $0.4 \leq r^2 < 0.6$, light blue = $0.2 \leq r^2 < 0.4$, and blue = $r^2 < 0.2$. Grey circles represent unannotated SNPs. (B) Forest plot of association results for *MAPT* in each cohort in the *APOE* ε4- group. The filled symbol and horizontal line indicate the estimated odds ratio (OR) and its 95% confidence interval per dosage of the rs62063857 *A* allele on the risk of AD. (C) Forest

plot of association results for *NSF* in each cohort in the *APOE* ε4- group. The filled symbol and horizontal line indicate the estimated odds ratio (OR) and its 95% confidence interval per dosage of the rs199533 *A* allele on the risk of AD. All plots show the results using Model 1, which adjusts for principle components of ancestry.



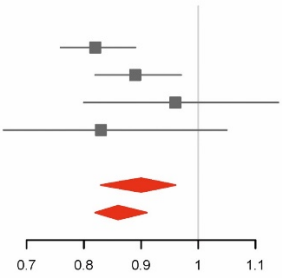
B

Cohort	N	OR	P value
Discovery_ADSP	6318	1.25	1.83e-06
Replication_ADGC	9975	1.12	5.42e-03
Replication_ADES-FR	1482	1.06	5.30e-01
Replication_CHARGE	1639	1.38	7.00e-02
Meta_Replication	**13096**	**1.12**	**2.03e-03**
Meta_All	**19414**	**1.17**	**1.59e-07**



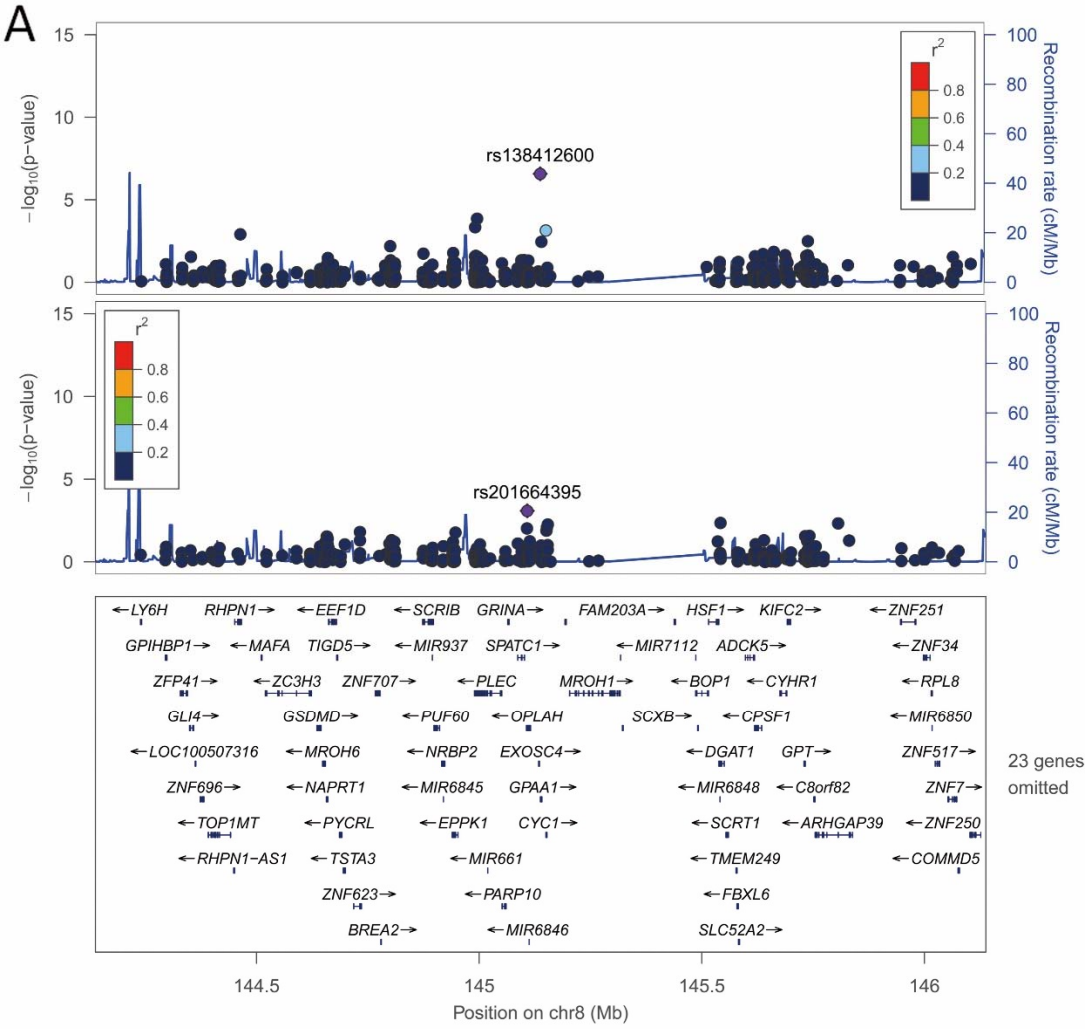
C

Cohort	N	OR	P value
Discovery_ADSP	7330	0.82	4.28e-06
Replication_ADGC	9528	0.89	8.64e-03
Replication_ADES-FR	1482	0.96	6.10e-01
Replication_CHARGE	1639	0.83	1.20e-01
Meta_Replication	**12649**	**0.9**	**3.384e-03**
Meta_All	**19979**	**0.86**	**1.660e-07**



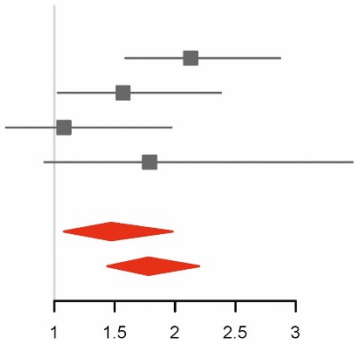
eFigure 6. Association of Alzheimer disease with variants in the *GPAA1* region. (A) Regional Manhattan plot in the *APOE* ε4+ (upper) and *APOE* ε4- (lower) subgroups in the discovery ADSP sample. SNPs with the lowest *P*-value are indicated with a purple diamond, and the estimated linkage disequilibrium (r^2) between the top SNP and other SNPs in the region are shown as circles with the color coding: red = $r^2 \geq 0.8$, orange = $0.6 \leq r^2 < 0.8$, green = $0.4 \leq r^2 < 0.6$, light blue = $0.2 \leq r^2 < 0.4$, and blue

= r^2<0.2. Grey circles represent unannotated SNPs. (B) Forest plot of association results in each cohort in the *APOE* ε4+ group. OR = odds ratio. The filled symbol and horizontal line indicate the estimated odds ratio and its 95% confidence interval per dosage of the rs138412600 *A* allele on the risk of AD. Both plots show the results using Model 2, which adjusts for principle components of ancestry, age, sex, and sequencing center.



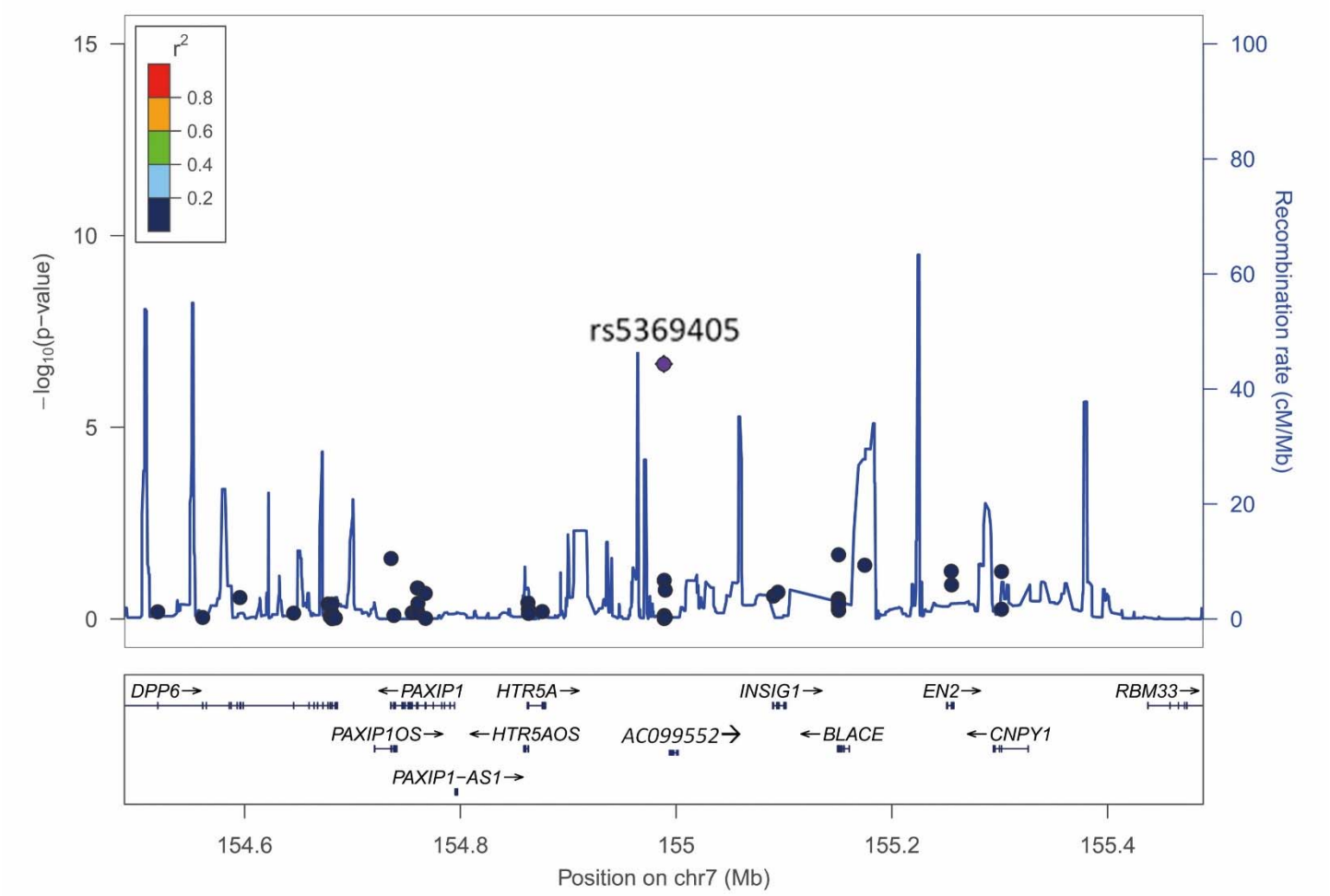
B

Cohort	N	OR	P value
Discovery_ADSP	7330	2.13	2.7e-07
Replication_ADGC	8524	1.57	3.0e-02
Replication_ADES-FR	1482	1.08	7.9e-01
Replication_CHARGE	1639	1.79	8.0e-02
Meta_Replication	**11645**	**1.47**	**1.00e-02**
Meta_All	**18975**	**1.78**	**7.81e-08**



eFigure 7. Regional Manhattan plot in the *APOE* ε4- subgroup showing association of Alzheimer disease with variants in the *AC099552* region using Model 2, which adjusts for principle components

of ancestry, age, sex, and sequencing center. SNPs with the lowest *P*-value are indicated with a purple diamond, and the estimated linkage disequilibrium (r^2) between the top SNP and other SNPs in the region are shown as circles with the color coding: red = $r^2 \geq 0.8$, orange = $0.6 \leq r^2 < 0.8$, green = $0.4 \leq r^2 < 0.6$, light blue = $0.2 \leq r^2 < 0.4$, and blue = $r^2 < 0.2$. Grey circles represent unannotated SNPs.



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2. Bennett DA, Schneider JA, Buchman AS, Barnes LL, Boyle PA, Wilson RS. Overview and findings from the rush Memory and Aging Project. *Curr Alzheimer Res.* 2012;9(6):646-663.
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