Supplementary Method

The combined ADGC imputed datasets (data freeze in September 2014) were created as following steps outlined below.

1. Convert Oxford GEN/SAMPLE format from 32 studies with each study divided by autosomal chromosome (i.e., 704 GEN files) to PLINK format
    a. Filter SNPs with low info (info < 0.5)
    b. Treat calls with uncertainty greater than 0.1 as missing
    c. Remove duplicate SNPs

2. Merge datasets into one PLINK format dataset
    a. Flip SNPs with strand error
    b. Filter MAF < 0.01

3. Address known and cryptic relatedness
    a. Remove related individuals identified using a kinship coefficient cut-off of 0.0442 (i.e., 3rd degree relatives) in KING-Robust

Supplementary Table 1. Single nucleotide polymorphisms for Alzheimer's Disease identified in the previous studies

Gene	CHR	SNP	Position	Annotation	1000 Genomes			References
					MAF	r^2	D'	
CR1	1	**rs6656401**	207,692,049	Intron	0.17			[1, 2]
		rs3818361	207,784,968	Intron	0.18	0.83	0.94	[3, 4]
		rs6701713	207,786,289	Intron	0.18	0.83	0.94	[3, 5, 6]
		rs1408077	207,804,141	Intron	0.18	0.83	0.93	[3, 7]
BIN1	2	**rs6733839**	127,892,810	Regulatory region variant	0.38			[1]
		rs744373	12,789,4615	Intergenic variant	0.27	0.49	0.90	[3, 4, 8]
		rs7561528	127,889,637	Intergenic variant	0.31	0.35	0.69	[3, 5, 7]
INPP5D	2	**rs35349669**	234,068,476	Intron	0.46			[1]
MEF2C	5	**rs190982**	88,223,420	Intron	0.37			[1]
HLA-DRB5-DBR1	6	**rs9271192**	32,578,530	Intergenic variant	0.26			[1]
CD2AP	6	**rs10948363**	47,487,762	Intron	0.25			[1]
		rs9296559	47,452,270	Intron	0.25	1	1	[4]
		rs9349407	47,453,378	Intron	0.25	1	1	[4-6]
NME8	7	**rs2718058**	37,841,534	Intron	0.37			[1]
ZCWPW1	7	**rs1476679**	100,004,446	Intron	0.30			[1]
EPHA1	7	**rs11771145**	143,110,762	Intron	0.36			[1]
		rs11767557	143,109,139	Intron	0.22	0.25	0.71	[4, 5]
PTK2B	8	**rs28834970**	27,195,121	Intron	0.34			[1]
CLU	8	**rs9331896**	27,467,686	Intron	0.40			[1]
		rs11136000	27,464,519	Intron	0.39	0.91	0.97	[2, 3]
		rs9331888	27,468,862	5 prime UTR	0.30	0.28	1	[2, 9]
		rs2279590	27,456,253	Non coding transcript exon	0.41	0.83	0.93	[2]

		rs7982	27,462,481	Missense	0.39	0.90	0.97	
		rs7012010	27,448,729	Downstream gene variant	0.28	0.18	0.83	
		rs1532278	27,466,315	Non coding transcript exon variant	0.39	0.91	0.97	[5]
CELF1	11	**rs10838725**	47,557,871	Intron	0.28			[1]
		rs1057233	47,376,448	3 prime UTR variant	0.32	0.17	0.97	[10]
MS4A	11	**rs983392**	59,923,508	Downstream intergenic	0.41			[1]
		rs670139	59,971,795	Intron	0.40	0.44	0.97	[4, 5]
		rs4938933	60,034,429	Intergenic	0.40	0.70	0.85	[5]
		rs610932	59,939,307	3 prime UTR variant	0.44	0.72	0.89	[3, 4]
		rs662196	59,942,757	Intron	0.44	0.69	0.88	[3]
		rs583791	59,947,252	Missense	0.48	0.68	0.87	[3]
PICALM	11	**rs10792832**	85,867,875	Downstream intergenic	0.37			[1]
		rs3851179	85,868,640	Downstream gene variant	0.37	0.99	0.99	[3, 11]
		rs541458	85,788,351	Intergenic	0.32	0.64	0.90	[2]
		rs561655	85,800,279	Upstream gene variant	0.35	0.77	0.92	[5]
SORL1	11	**rs11218343**	121,435,587	Intron	0.043			[1]
FERMT2	14	**rs17125944**	53,400,629	Intron	0.081			[1]
SLC24A4-RIN3	14	**rs10498633**	92,926,952	Intron	0.22			[1]
DSG2	18	**rs8093731** [a]	29,088,958	Intron	0.012			[1]
ABCA7	19	**rs4147929**	1,063,443	Intron	0.19			[1]
		rs3764650	1,046,520	Intron	0.11	0.77	0.92	[4, 6]
		rs72973581	1,043,103	Missense	0.053	0.012	1	[12]

CD33	19	**rs3865444** [a]	51,727,962	Upstream gene variant	0.31			[1, 4, 5]
		rs3826656	51,726,613	Upstream gene variant	0.22	0.13	1	
		rs12459419	51,728,477	Missense	0.31	1	1	
CASS4	20	**rs7274581**	55,018,260	Intron	0.080			[1]

[a] The SNPs were reported not to reach statistical significance on meta-analysis [1].
Bold SNP ID represents the SNP identified the International Genomics of Alzheimer's Project reported by Lambert et al [1].

Key: CHR, chromosome; SNP, single nucleotide polymorphism; 1000 Genomes, 1000 Genomes Project Phase 3 in individuals of European ancestry; MAF, minor allele frequency

Supplementary Table 2. ADGC and CHARGE studies in ADSP WES data and ADGC imputed data

Consortium	Study	WES data	Imputed data
ADGC			
	ACT	X	X
	ADC	X	X
	ADNI		X
	BIOCARD		X
	CHAP	X	X
	EAS		X
	EFIGA	X	
	GDF	X	
	GSK		X
	MAP	X	X
	MAYO	X	X
	MAYO PD	X	X
	MIA	X	
	MIRAGE	X	X
	NBB		X
	NCRAD	X	
	NIA-LOAD	X	X
	OHSU		X
	RAS	X	
	ROS	X	X
	TAR		X
	TARCC	X	
	TGEN		X
	TOR	X	
	UKS		X
	UMVUMSSM		X
	UPITT		X
	VAN	X	X
	WASHU		X
	WHICAP	X	X
CHARGE			
	ARIC	X	
	ASPS	X	
	CHS	X	
	ERF	X	
	FHS	X	
	RS	X	

Supplementary Table 3. Subject (age at death ≥ 65 years) information of each expression datasets of entorhinal cortex (EC), frontal cortex (FCTX), hippocampus (HIPP), and temporal cortex (TCTX)

Brain region	Study	# of AD cases	# of AD controls	# of male	# of female	Mean age ± SD
EC	GSE48350	15	17	16	16	83.9 ± 8.3
	GSE5281	10	12	9	13	83.5 ± 7.4
	Total	25	29	25	29	
FCTX	GSE48350	21	25	19	27	84.1 ± 8.8
	GSE5281	23	10	14	19	79.7 ± 7.9
	GSE66333	8	0	5	3	83.1 ± 7.0
	GSE53890	0	21	11	10	88.0 ± 11.2
	Total	52	56	49	59	
HIPP	GSE48350	18	24	22	20	83.4 ± 8.3
	GSE5281	10	12	7	15	79.5 ± 7.3
	GSE28146	22	8	12	18	86.3 ± 7.7
	Total	50	44	41	53	
TCTX	GSE5281	16	11	10	17	80.1 ± 7.3
	GSE29652	18	0	5	13	84.7 ± 9.9
	Total	34	11	15	30	

Key: SD, standard deviation; EC, entorhinal cortex; FCTX, frontal cortex; HIPP, hippocampus; TCTX, temporal cortex

Supplementary Table 4. The numbers of probes in each platform

Chromosome	ADNI	NABEC GPL6947	UKBEC GPL5175
1	4,339	3,244	2,606
2	2,792	2,025	1,809
3	2,381	1,654	1,495
4	1,731	1,212	1,000
5	1,991	1,457	1,125
6	2,224	1,575	1,383
7	1,934	1,449	1,363
8	1,429	1,120	923
9	1,654	1,292	1,077
10	1,693	1,261	1,035
11	2,559	1,871	1,590
12	2,283	1,566	1,353
13	774	567	484
14	1,339	939	840
15	1,286	1,066	872
16	1,639	1,309	1,124
17	2,405	1,776	1,541
18	629	461	450
19	2,390	1,908	1,476
20	1,108	871	728
21	517	454	332
22	923	799	603
Total	40,020	29,879	25,479

ADNI platform = Affymetrix Human Genome U219 Array platform; GPL6947 = Illumina HumanHT-12 V3.0 expression beadchip; GPL5175 = Affymetrix Human Exon 1.0 ST Array [transcript (gene) version]

Key: ADNI, Alzheimer's Disease Neuroimaging Initiative; NABEC, North American Brain Expression Consortium; UKBEC, United Kingdom Brain Expression Consortium

Supplementary Table 5. Characteristics of the individual in ADGC and ADSP

Variable	Overall n (%)	AD cases n (%)	AD controls n (%)
ADGC (n = 15,330)		7,364 (48.0)	7,966 (52.0)
Sex			
Male	6,107 (39.8)	2,880 (52.8)	3,227 (47.2)
Female	9,223 (60.2)	4,484 (51.4)	4,739 (48.6)
Age at the last visit or at death			
65-69	2,023 (13.2)	687 (34.0)	1,336 (66.0)
70-74	3,300 (21.5)	1,275 (38.6)	2,025 (61.4)
75-79	4,091 (26.7)	1,712 (41.8)	2,379 (58.2)
80-84	2,932 (19.1)	1,689 (57.6)	1,243 (52.4)
84-90	1,826 (11.9)	1,205 (66.0)	621 (34.0)
90+	1,158 (7.6)	796 (68.7)	362 (31.3)
APOE			
-/-	7,805 (54.2)	2,372 (30.4)	5,433 (69.6)
-/ε4	5,212 (36.2)	3,451 (66.2)	1,761 (33.8)
ε4/ε4	1,389 (9.6)	1,238 (89.1)	151 (10.9)
ADSP (n = 10,407)		5,350 (51.4)	5,057 (48.6)
Sex			
Male	4,366 (42.0)	2,308 (52.9)	2,058 (47.1)
Female	6,041 (58.0)	3,042 (50.4)	2,999 (49.6)
Age at the last visit or at death			
65-69	568 (5.5)	535 (94.2)	33 (5.8)
70-74	1,123 (10.8)	1,058 (94.2)	65 (5.8)
75-79	1,348 (13.0)	1,147 (85.1)	201 (14.9)
80-84	2,634 (25.3)	1,088 (41.3)	1,546 (58.7)
84-90	3,120 (30.0)	892 (28.6)	2,228 (71.4)
90+	1,614 (15.5)	630 (39.0)	984 (61.0)
APOE			
-/-	7,431 (71.4)	3,128 (42.1)	4,303 (57.9)
-/ε4	2,886 (27.7)	2,148 (74.4)	738 (25.6)
ε4/ε4	90 (0.9)	74 (82.2)	16 (17.8)

Key: ADSP, Alzheimer's Disease Sequencing Project; ADGC, Alzheimer's Disease Genetic Consortium; *APOE*, apolipoprotein E

Supplementary Table 6. IGAP SNPs and its proxies

IGAP SNP	Closest Gene	Exonic SNP					1000 Genomes EUR		
		SNP ID	Position	Variant [a]	Major/minor alleles	Gene	MAF	r^2	D'
Strong LD ($r^2 \geq 0.8$)									
rs6656401	*CR1*	rs4844600	207,679,307	E60E	G/A	*CR1*	0.19	0.88	0.99
		rs2296160	207,795,320	A2419T	G/A	*CR1*	0.18	0.84	0.93
rs9271192	*HLA-DRB5*	rs9270303	32,557,483	A13T	C/T	*HLA-DRB1*	0.25	0.92	0.99
rs1476679	*ZCWPW1*	rs2405442	99,971,313	L12L	C/T	*PILRA*	0.32	0.85	0.97
		rs1859788	99,971,834	G78R	G/A	*PILRA*	0.32	0.85	0.97
rs9331896	*CLU*	rs7982	27,462,481	H263H	G/A	*CLU*	0.39	0.90	0.97
rs10838725	*CELF1*	rs2293576	47,434,986	A191A	G/A	*SLC39A13*	0.31	0.84	0.99
rs983392	*MS4A6A*	rs12453	59,945,745	L137L	T/C	*MS4A6A*	0.40	0.80	0.91
rs4147929	*ABCA7*	rs3752246	1,056,492	A1527G	C/G	*ABCA7*	0.19	0.97	1
rs3865444	*CD33*	rs12459419	51,728,477	A14V	C/T	*CD33*	0.31	1	1
Moderate LD ($0.4 \leq r^2 < 0.8$)									
rs9271192	*HLA-DRB5*	rs2308759	32,549,596	V130V	C/T	*HLA-DRB1*	0.14	0.45	1
		rs1049092	32,629,802	D201D	G/A	*HLA-DQB1*	0.40	0.51	0.97
		rs1049086	32,629,904	D167D	G/A	*HLA-DQB1*	0.40	0.50	0.97
rs2718058	*NME8*	rs2722372	37,890,267	R43K	G/A	*NME8*	0.25	0.49	0.93
		rs2598044	37,890,316	D59D	C/T	*NME8*	0.25	0.49	0.93
rs1476679	*ZCWPW1*	rs909152	100,175,473	G337G	C/T	*LRCH4*	0.31	0.53	0.75
rs10838725	*CELF1*	rs12286721	47,701,528	I671M	A/C	*AGBL2*	0.28	0.48	0.97
rs983392	*MS4A6A*	rs7232	59,940,599	T213S	T/A	*MS4A6A*	0.36	0.68	0.92
rs8093731	*DSG2*	rs16961975	29,046,606	V509M	G/A	*DSG3*	0.012	0.51	0.75
		rs61730311	29,049,138	R575W	C/T	*DSG3*	0.010	0.67	0.90
rs4147929	*ABCA7*	rs4147930	1,064,193	L1995L	A/G	*ABCA7*	0.28	0.56	1
		rs4147934	1,065,018	S2045A	T/G	*ABCA7*	0.28	0.55	0.98

		rs2074442	1,074,000	D275E	T/A	*HMHA1*	0.27	0.56	0.97
		rs2074454	1,080,311	P603P	C/G	*HMHA1*	0.26	0.49	0.88
		rs10404947	1,081,617	Q769Q	G/A	*HMHA1*	0.22	0.44	0.74
rs3865444	*CD33*	rs35112940	51,738,917	G304R	G/A	*CD33*	0.21	0.57	0.98

[a] The first amino acid is linked to major allele and the second one to minor allele.

Key: IGAP, International Genomics of Alzheimer's Project; SNP, single nucleotide polymorphism; MAF, minor allele frequency; LD, linkage disequilibrium; 1000 Genomes, 1000 Genomes Project Phase 3 in individuals of European ancestry

Supplementary Table 7. Association of IGAP SNPs and the coding SNPs moderately correlated with the IGAP SNPs with Alzheimer's disease in two datasets: ADGC [a] and ADSP [b]

IGAP SNP				Exonic SNP				
SNP	Closest gene	ADGC [a]		SNP ID	ADGC [a]		ADSP [b]	
		OR	P-value		OR	P-value	OR	P-value
Moderate LD ($0.4 \leq r^2 < 0.8$)								
rs9271192	*HLA-DRB5*	1.11	2.66×10^{-4}	rs2308759	-	-	1.09	0.072
				rs1049092	-	-	1.11	**1.04×10^{-3}**
				rs1049086	1.07	**0.015**	1.11	**1.90×10^{-3}**
rs2718058	*NME8*	0.95	0.024	rs2722372	0.93	**9.02×10^{-3}**	0.90	**4.79×10^{-3}**
				rs2598044	0.93	**6.64×10^{-3}**	0.90	**5.41×10^{-3}**
rs1476679	*ZCWPW1*	0.92	1.41×10^{-3}	rs909152	0.93	**0.010**	0.96	0.28
rs10838725	*CELF1*	1.05	0.054	rs12286721	1.08	**2.58×10^{-3}**	1.05	0.14
rs983392	*MS4A6A*	0.86	7.22×10^{-9}	rs7232	0.87	**8.47×10^{-7}**	0.87	**4.08×10^{-5}**
rs8093731	*DSG2*	0.99	0.90	rs16961975	1.23	0.074	1.22	0.22
				rs61730311	-	-	1.14	0.47
rs4147929	*ABCA7*	1.12	1.39×10^{-3}	rs4147930	1.07	**0.024**	1.10	**7.50×10^{-3}**
				rs4147934	1.08	**8.45×10^{-3}**	1.11	**4.28×10^{-3}**
				rs2074442	1.07	**0.023**	1.08	0.037
				rs2074454	1.05	0.13	1.09	**0.016**
				rs10404947	1.06	0.092	1.07	0.089
rs3865444	*CD33*	0.91	4.49×10^{-4}	rs35112940	0.94	0.045	0.98	0.59

[a] Imputed genotype data from ADGC

[b] Whole exome sequencing data from ADSP

Bold p-value represents the statistical significance after FDR adjustment.

Key: IGAP, International Genomics of Alzheimer's Project; SNP, single nucleotide polymorphism; ADSP, Alzheimer's Disease Sequencing Project; ADGC, Alzheimer's Disease Genetic Consortium; OR, odds ratio; LD, linkage disequilibrium

Supplementary Table 8. Coding single nucleotide polymorphisms significantly associated with Alzheimer's disease

Coding SNP	Gene	Major/minor allele	Strand	# of transcripts	# of consequence type		
					Missense	Synonymous	Others [a]
Strong LD ($r^2 \geq 0.8$)							
rs2296160	*CR1*	G/A	+	6	6	0	0
rs2405442	*PILRA*	C/T	+	7	0	5	2
rs1859788	*PILRA*	G/A	+	7	5	0	2
rs7982	*CLU*	A/G	-	18	0	8	10
rs12453	*MS4A6A*	T/C	-	22	0	8	14
rs3752246	*ABCA7*	C/G	+	7	3		4
Moderate LD ($0.4 \leq r^2 < 0.8$)							
rs1049086	*HLA-DQB1*	G/A	-	10	0	5	5
rs2722372	*NME8*	G/A	+	6	2	0	4
rs2598044	*NME8*	C/T	+	6	0	2	4
rs7232	*MS4A6A*	T/A	-	13	9	0	4
rs4147930	*ABCA7*	A/G	+	16	0	4	12
rs4147934	*ABCA7*	T/G	+	15	4	0	11

[a] Including non-coding transcript exon variant, upstream gene variant, downstream gene variant, stop retained variant, and intron variant

Key: SNP, single nucleotide polymorphism

Supplementary Table 9. Association of the coding rare variants with Alzheimer's disease in ADSP [a]

IGAP SNP		Exonic rare variant					
SNP	Closest gene	Rare variant ID	Position	1000 Genomes EUR	ADSP [a]		
				MAF [b]	MAF [c]	OR	P-value
rs9271192	*HLA-DRB5*	rs11575848	31,686,943	0.0061	0.0049	1.55	0.030
		rs2070600	32,151,443	0.051	0.043	1.17	0.022
rs1476679	*ZCWPW1*	rs62483572	100,319,633	0.0061	0.0040	0.53	5.77×10^{-3}
rs10792832	*PICALM*	rs74547795	85,431,954	0.0091	0.011	0.72	0.015
rs8093731	*DSG2*	rs111986709	29,054,294	0.024	0.038	0.85	0.024

[a] Whole exome sequencing data from ADSP
[b] MAF calculated by using 1000 Genomes Project Phase 3 in individuals of European ancestry
[c] MAF calculated by using the study subjects in ADSP

Key: IGAP, International Genomics of Alzheimer's Project; SNP, single nucleotide polymorphism; ADSP, Alzheimer's Disease Sequencing Project; MAF, minor allele frequency; OR, odds ratio

Supplementary Table 10. Coding single nucleotide polymorphisms significantly associated with Alzheimer's disease

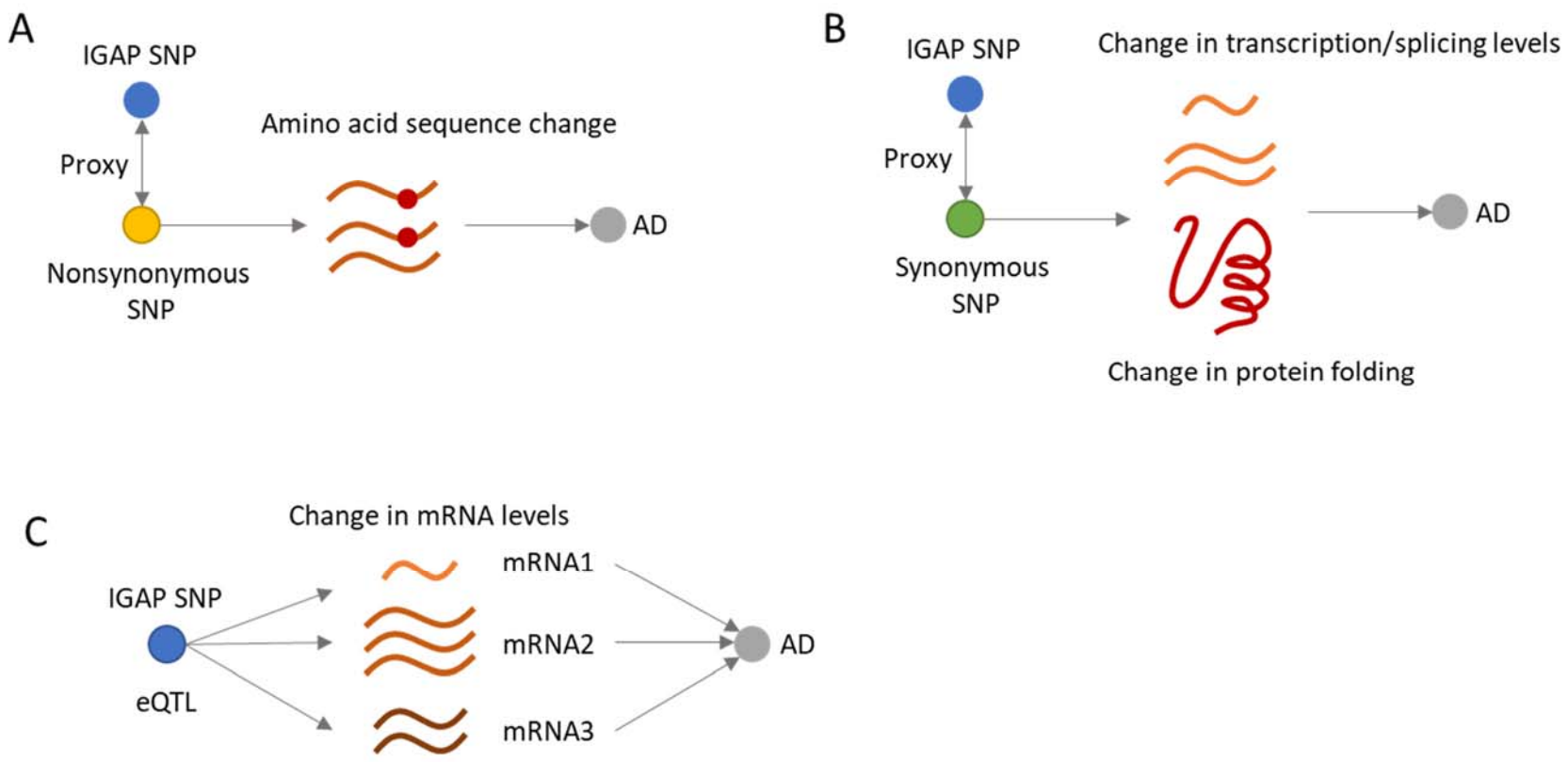
Rare coding variants	Gene	Major/minor allele	Strand	# of transcripts	# of consequence type		
					Missense	Synonymous	Others [a]
rs11575848	*LY6G6C*	C/T	-	18	2	0	16
rs2070600	*AGER*	C/T	-	23	9	0	14
rs62483572	*EPO*	G/A	+	1	1	0	0
rs74547795	*SYTL2*	G/T	-	24	10	0	14
rs111986709	*DSG3*	C/T	+	1	1	0	0

[a] Including non-coding transcript exon variant, upstream gene variant, downstream gene variant, stop retained variant, and intron variant

Supplementary Table 11. Coding common single nucleotide polymorphisms and rare variants significantly associated with Alzheimer's disease

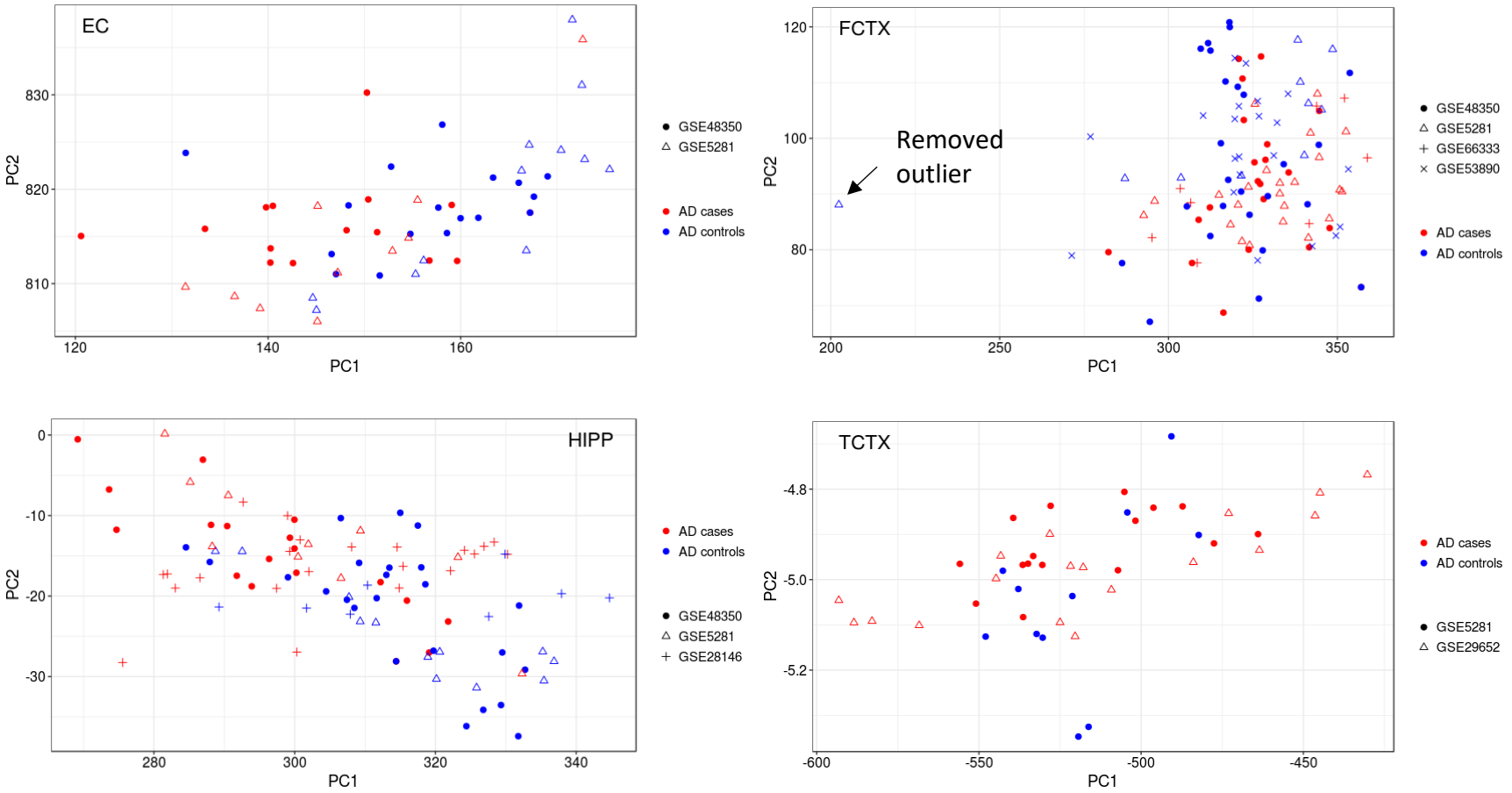
Coding SNP/variant	Gene	Exon	Variant [a]	SIFT	PolyPhen-2 (HumDiv)	PROVEAN	GERP++ RS score
Common SNP							
rs2296160	*CR1*	44/47	A2419T	Tolerated (0.8)	Benign (0.0)	Neutral (-0.10)	-8.25
rs9270303	*HLA-DRB1*	1/6	A13T	Tolerated (1.0)	Benign (0.0)	Neutral (1.46)	1.62
rs2722372	*NME8*	5/18	R43K	Tolerated (1.0)	Benign (0.0)	Neutral (1.39)	3.85
rs1859788	*PILRA*	2/7	G78R	Tolerated (1.0)	Benign (0.0)	Neutral (6.98)	3.28
rs7232	*MS4A6A*	7/7	T213S	Tolerated (0.08)	Possibly damaging (0.573)	Neutral (-2.07)	-5.11
rs3752246	*ABCA7*	33/47	A1527G	Tolerated (0.79)	Benign (0.0)	Neutral (2.70)	1.57
rs4147934	*ABCA7*	46/47	S2045A	Tolerated (0.97)	Benign (0.057)	Neutral (0.06)	1.15
Rare variant							
rs11575848	*LY6G6C*	3/3	R103Q	Tolerated (0.28)	Probably damaging (0.999)	Neutral (-0.83)	3.83
rs2070600	*AGER*	3/11	G82S	Damaging (0.01)	Possibly damaging (0.864)	Neutral (-1.43)	5.82
rs62483572	*EPO*	3/5	D70N	Tolerated (0.07)	Possibly damaging (0.924)	Neutral (-2.03)	4.38
rs74547795	*SYTL2*	2/13	A825D	Damaging (0.003)	Possibly damaging (0.69)	Deleterious (-3.21)	4.89
rs111986709	*DSG3*	15/16	S771F	Damaging (0.04)	Possibly damaging (0.516)	Deleterious (-3.62)	6.06

[a] The first amino acid is linked to major allele and the second one to minor allele, and the codon number is for the canonical transcript.
Key: SNP, single nucleotide polymorphism; RS, rejected substitutions



Supplementary Figure 1. Possible causal relationships between single nucleotide polymorphisms (SNPs), mRNA, and phenotype.

Keys: IGAP, International Genomics of Alzheimer's Project; SNP, single nucleotide polymorphism; eQTL, expression quantitative trait locus



Supplementary Figure 2. Principal component analysis of the merged datasets by using ComBat in "sva" Bioconductor R package

Keys: EC, entorhinal cortex; HIPP, hippocampus; FCTX, frontal cortex; TCTX, temporal cortex

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