Supplementary Information

Table S1. Detailed examination of the relationship between number of CD34+CD133+ cells (log transformed) and the risk of AD/dementia risk.

Table S2. Detailed examination of the relationship between CD34+CD133+ (log transformed) and the risk of diseases by using Cox proportional hazards regression analyses or Body Mass Index (BMI) and white matter hyperintensities (WMHI) by using linear regression analysis.

Table S3. Examination of the interactions between different progenitor or mature endothelial cells (log transformed) and vascular diseases on the risk of AD/dementia.

Table S4. Other SNPs from GWAS interaction results of KIRREL3 and EXOC6B.

Table S5. The association between CD34+CD133+ and AD incidences after stratification with the genotypes.

Table S6. Circulating CD34+CD133+ cells for Alzheimer's disease in the context of genetic background in FHS, stratified by each genotype (additive) adjusting for age, sex, years of education, APOE ε4 and PCs.

Table S7. Comparisons of incident Alzheimer's disease rates across CD34+CD133+ quartiles in the context of genetic background.

Figure S1. Flow chart of the study design.

Figure S2. Q-Q plot of the GWAS analyses.

Figure S3. The relationships between the *KIRREL3* SNPs, gene expression, and Alzheimer's disease.

Figure S4. The relationship between *KIRREL3* expression, SNPs and methylation in the ROSMAP study.

Figure S5. The relationships between the *EXOC6B* SNPs, gene expression, and Alzheimer's disease.

Table S1. Detailed examination of the relationship between number of CD34+CD133+ cells (log transformed) and the risk of AD/dementia risk

CD34+CD133+ cells plus Covariates	Alzheimer's disease		Dementia	
	HR (95% CI)	P value	HR (95% CI)	P value
Model 1: no covariates	0.66 (0.47, 0.92) n = 1597	**0.02**	0.64 (0.48, 0.85) n = 1619	**0.002**
Model 2: Age, sex, years of education	0.73 (0.53, 1.03) n = 1597	0.07	0.70 (0.53, 0.94) n = 1619	**0.02**
Model 3: Model 2 + *APOE ε4* + vascular diseases	0.72 (0.51, 1.03) n = 1325	0.07	0.68 (0.51, 0.93) n = 1346	**0.01**
Model 3 after stratification				
No vascular diseases[a]	1.88 (0.28, 12.75) n = 251	0.52	1.88 (0.28, 12.75) n = 251	0.52
Peripheral vascular diseases[b] only	0.68 (0.46, 0.99) n = 826	**0.04**	0.66 (0.48, 0.91) n = 844	**0.01**
Cerebrovascular diseases[c] only	0.70 (0.44, 1.13) n = 622	0.14	0.63 (0.42, 0.94) n = 635	**0.02**

Abbreviations: HR = hazard ratio

Cox proportional hazards regression models were used to study the relationship between Log transformed CD34+CD133+ cell numbers per mL and the risk of Alzheimer's disease (AD) or all-cause dementia after adjusting for the covariates. HR with 95% confidence interval (95% CI) with p values are shown.

Model 1: simple association without confounders

Model 2: Adjusting for age, sex and education

Model 3: Model 2 + *APOE ε4* + vascular diseases

a. Model 3 after the stratification for those with no CHD, no HTN, no stroke, no silent infarct, no CMB, and low level of WMHI.

b. Model 3 after the stratification for those with peripheral vascular diseases, e.g., CHD or HTN.

c. Model 3 after the stratification for those with cerebrovascular diseases, e.g., Stroke, silent infarct, CMB or high level of WMHI.

Table S2. Detailed examination of the relationship between CD34+CD133+ (log transformed) and the risk of diseases by using Cox proportional hazards regression analyses or Body Mass Index (BMI) and white matter hyperintensities (WMHI) by using linear regression analysis.

CD34+CD133+ cells plus Covariates	Model 1: no covariates		Model 2: Age, sex, education		Model 3: Model 2 + *APOE ε4*	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Peripheral vascular diseases	1.10 (0.99-1.21)	0.07	1.15 (1.04-1.27)	**0.0072**	1.15 (1.03-1.27)	**0.009**
Hypertension	1.12 (1.01-1.24)	**0.04**	1.17 (1.06-1.31)	**0.0032**	1.17 (1.05-1.30)	**0.0039**
CHD	0.88 (0.73-1.05)	0.15	0.92 (0.77-1.11)	0.40	0.91 (0.76-1.10)	0.34
Diabetes	1.06 (0.83-1.36)	0.64	1.09 (0.85-1.40)	0.49	1.09 (0.85-1.40)	0.49
Cerebrovascular diseases	1.01 (0.90-1.13)	0.83	1.08 (0.97-1.22)	0.17	1.09 (0.97-1.22)	0.16
Stroke	1.04 (0.79-1.37)	0.78	1.15 (0.87-1.52)	0.33	1.20 (0.91-1.59)	0.20
Silent brain infarcts	0.94 (0.74-1.20)	0.63	0.97 (0.76-1.24)	0.80	0.99 (0.77-1.26)	0.92
CMB	0.97 (0.71-1.34)	0.86	1.06 (0.76-1.49)	0.72	1.10 (0.78-1.54)	0.59
	Beta (SE)	**P value**	**Beta (SE)**	**P value**	**Beta (SE)**	**P value**
BMI	0.024 (0.006)	**0.0002**	0.020 (0.006)	**0.0019**	0.018 (0.006)	**0.005**
WMHI	-0.11 (0.05)	**0.02**	-0.03 (0.04)	0.43	-0.03 (0.04)	0.41

Model 1: simple association without confounders; Model 2: Adjusting for age, sex and education; Model 3: Model 2 + *APOE ε4*

Table S3. Examination of the interactions between different progenitor or mature endothelial cells (log transformed) and vascular diseases on the risk of AD/dementia

Circulating cells	Alzheimer's disease		All-cause Dementia	
	HR (95% CI)	P value	HR (95% CI)	P value
CD34+CD133+ × vascular diseases	0.48 (0.06, 3.91)	0.49	0.48 (0.09, 2.68)	0.40
CD34+CD133- × vascular diseases	0.23 (0.02, 3.04)	0.26	0.45 (0.05, 3.91)	0.47
CD34-CD133+ × vascular diseases	72.19 (0.36, 1.45e+04)	0.11	8.96 (0.25, 317.46)	0.23
CD34+ × vascular diseases	0.36 (0.02, 8.26)	0.52	0.39 (0.02, 7.99)	0.54
CD34+/KDR+ × vascular diseases	0.85 (0.14, 5.07)	0.86	0.81 (0.14, 4.71)	0.82
CD31+/CD45- × vascular diseases	1.45 (0.21, 10.18)	0.71	0.83 (0.21, 3.33)	0.79
CD31+ ×vascular diseases	0.23 (0.004, 14.47)	0.48	2.05 (0.22, 18.78)	0.53
CD31- × vascular diseases	13.50 (0.34, 541.95)	0.17	3.88 (0.20, 76.21)	0.37
CD31+DIM × vascular diseases	0.07 (0.00, 46.63)	0.42	0.06 (0.00, 11.28)	0.30
CD31+Lymphoid × vascular diseases	540.46 (0.001, 3.80e+08)	0.36	0.29 (0.00, 8.58e+04)	0.85

Cox proportional hazards regression models were used to study the interactions between the proportions (%) of different subtypes of EPCs and EMCs (log transformed) and the vascular diseases on the risk of Alzheimer's disease (AD) or all-cause dementia after adjusting for age, sex, years of education and APOE ε4. Due to the imbalanced distributions of CD34-CD133- cells, the interactive data analysis on this type of cells was not able to be conducted for the meaningful conclusion. HR with 95% confidence interval (95% CI) for the interactive effects with p values are shown.

Table S4. Other SNPs from GWAS interaction results of *KIRREL3* and *EXOC6B*

Gene/Closest gene	Chr	Position ((GRCh37)	Major Allele	Minor Allele	rs ID	Beta	se	P value
KIRREL3								
KIRREL3	11	126436966	C	T	rs605226	1.6199	0.2677	1.60e-08
KIRREL3	11	126436922	G	T	rs605162	1.6169	0.2678	1.70e-08
KIRREL3	11	126437834	T	A	rs578463	1.4686	0.2458	2.40e-08
KIRREL3	11	126437941	G	A	rs619996	1.4646	0.2452	2.40e-08
KIRREL3	11	126439019	C	T	rs634964	1.7946	0.3006	2.50e-08
EXOC6B								
EXOC6B	2	73082263	G	A	rs55802296	1.4881	0.2686	2.30e-07
EXOC6B	2	73079675	T	C	rs12614041	1.4343	0.2594	2.44e-07
EXOC6B	2	73079965	T	A	rs56711961	1.4348	0.2596	2.45e-07
EXOC6B	2	73079989	G	C	rs56181835	1.4349	0.2596	2.45e-07
EXOC6B	2	73081791	T	A	rs12615875	1.4381	0.2602	2.45e-07
EXOC6B	2	73080639	G	C	rs2063168	1.4556	0.2643	2.70e-07
EXOC6B	2	73076311	T	C	rs4852897	1.4127	0.2570	2.84e-07
EXOC6B	2	73075651	T	C	rs57264301	1.4119	0.2569	2.86e-07
EXOC6B	2	73075644	A	G	rs59615613	1.4114	0.2568	2.86e-07
EXOC6B	2	73075206	C	T	rs67919884	1.4057	0.2559	2.90e-07
EXOC6B	2	73069299	C	T	rs12619068	1.3876	0.2530	3.04e-07
EXOC6B	2	73069973	G	T	rs1876488	1.3875	0.2530	3.04e-07
EXOC6B	2	73068205	T	A	rs67927720	1.3876	0.2530	3.04e-07
EXOC6B	2	73065894	C	T	rs2135983	1.3875	0.2530	3.04e-07
EXOC6B	2	73073494	A	C	rs4852896	1.3855	0.2527	3.04e-07
EXOC6B	2	73072728	C	T	rs60584321	1.3855	0.2527	3.04e-07
EXOC6B	2	73071304	A	T	rs12614455	1.3896	0.2534	3.04e-07

EXOC6B	2	73062631	G	C	rs11126386	1.3878	0.2531	3.05e-07
EXOC6B	2	73064491	G	A	rs6707107	1.3878	0.2531	3.05e-07
EXOC6B	2	73061305	C	T	rs58448780	1.3876	0.2531	3.07e-07
EXOC6B	2	73061116	G	A	rs4564798	1.3876	0.2531	3.07e-07
EXOC6B	2	73060352	T	G	rs7577528	1.3876	0.2532	3.11e-07
EXOC6B	2	73060015	A	G	rs7586886	1.3875	0.2532	3.11e-07
EXOC6B	2	72998061	T	C	rs6716335	1.4199	0.2593	3.15e-07
EXOC6B	2	72998075	C	T	rs6761253	1.4194	0.2592	3.15e-07
EXOC6B	2	73034553	C	T	rs11126382	1.3861	0.2537	3.34e-07
EXOC6B	2	73072819	A	G	rs112345272	1.4133	0.2588	3.39e-07
EXOC6B	2	73030396	A	G	rs10204141	1.3839	0.2534	3.41e-07
EXOC6B	2	73030674	C	T	rs10496187	1.3840	0.2535	3.42e-07
EXOC6B	2	73027972	A	T	rs12619565	1.3835	0.2534	3.43e-07
EXOC6B	2	73013879	T	A	rs7607226	1.3819	0.2532	3.45e-07
EXOC6B	2	73013836	C	T	rs7593084	1.3819	0.2532	3.45e-07
EXOC6B	2	73006888	A	G	rs4597553	1.3897	0.2547	3.49e-07
EXOC6B	2	73003486	C	T	rs58890506	1.3998	0.2566	3.49e-07
EXOC6B	2	72997442	R	D	NA	1.4036	0.2573	3.49e-07
EXOC6B	2	73005579	T	C	rs970577	1.3899	0.2548	3.50e-07
EXOC6B	2	73007522	T	C	rs2068410	1.3889	0.2546	3.50e-07
EXOC6B	2	73029379	A	G	rs7586339	1.3936	0.2564	3.88e-07
EXOC6B	2	73082129	C	T	rs11886503	1.4540	0.2680	4.07e-07
EXOC6B	2	73082562	G	T	rs4852899	1.4756	0.2731	4.51e-07
EXOC6B	2	73082563	C	A	rs4852900	1.4760	0.2732	4.51e-07
EXOC6B	2	73023457	T	C	rs111636941	1.3785	0.2551	4.52e-07
EXOC6B	2	73071303	R	D	NA	1.4171	0.2635	5.11e-07
EXOC6B	2	73082956	T	A	rs7567893	1.4785	0.2785	7.12e-07

Table S5. The association between CD34+CD133+ and AD incidences after stratification with the genotypes

SNP (Gene)	Genotype	HR (95% CI)	P value
rs4144611 (***KIRREL3)***	TT	0.29 (0.15-0.57)	**4.0e-04**
	GG+TG	1.13 (0.68-1.89)	0.64
rs580382 (***KIRREL3)***	CC	0.31 (0.17-0.57)	**2.0e-04**
	TT+CT	1.55 (0.89-2.68)	0.12
rs61619102 (***EXOC6B)***	CC	0.49 (0.31-0.75)	**1.2e-03**
	GG+GC	2.72 (1.17-6.28)	0.02

After the stratification with each genotype of *KIRREL3* or *EXOC6B* genes in FHS, Cox proportional hazards regression model was used to examine the relationship between CD34+CD133+ EPCs proportion (log transformed) and the AD risk adjusted by age, sex, and years of education, as well as *APOE* ε4 and PCs

Table S6. Circulating CD34+CD133+ cells for Alzheimer's disease in the context of genetic background in FHS, stratified by each genotype (additive) adjusting for age, sex, years of education, *APOE* ε4 and PCs

rs4144611 (*KIRREL3*)				rs580382 (*KIRREL3*)				rs61619102 (*EXOC6B*)			
genotype	**CD34+CD133+ cutoffs**	**HR (95% CI)**	**P value**	**genotype**	**CD34+CD133+ cutoffs**	**HR (95% CI)**	**P value**	**genotype**	**CD34+CD133+ cutoffs**	**HR (95% CI)**	**P value**
TT (N=532, AD=24)	25%	0.18 (0.07-0.46)	**3.3e-04**	**CC** (N=598, AD=29)	25%	0.21 (0.09-0.47)	**1.7e-04**	**CC** (N=1023, AD=44)	25%	0.48 (0.26-0.88)	**0.02**
	50%	0.11 (0.03-0.42)	**0.001**		50%	0.16 (0.05-0.47)	**9.6e-04**		50%	0.38 (0.19-0.74)	**0.005**
	75%	*N/A* (Zero AD)	**0.006***		75%	*N/A* (Zero AD)	**0.002**[a]		75%	0.25 (0.08-0.81)	**0.02**
TG (N=702, AD=22)	25%	0.71 (0.29-1.75)	0.46	**CT** (N=670, AD=17)	25%	1.35 (0.43-4.23)	0.60	**GC** (N=372, AD=10)	25%	1.50 (0.27-8.45)	0.64
	50%	0.80 (0.34-1.88)	0.60		50%	1.23 (0.46-3.27)	0.68		50%	7.92 (1.39-45.20)	**0.02**
	75%	1.16 (0.43-3.10)	0.77		75%	1.65 (0.60-4.58)	0.33		75%	5.31 (1.39-20.28)	**0.01**
GG (N=208, AD=10)	25%	4.17 (0.39-44.56)	0.24	**TT** (N=174, AD=10)	25%	3.82 (0.35-41.05)	0.27	**GG**[b] (N=47, AD=2)	25%	0.00 (0.00-lnf)	NA
	50%	20.27 (1.71-240.88)	**0.02**		50%	25.55 (2.26-288.65)	**0.009**		50%	Infinite (0.00-lnf)	NA
	75%	2.31 (0.53-10.13)	0.27		75%	4.05 (0.84-19.55)	0.08		75%	0.39 (0.00-lnf)	NA

Cox proportional hazards regression model, AD incidence ~ (CD34+CD133+ cutoffs) + age + sex + years of education + *APOE* ε4 + PCs, stratified by genotype.

a. When CD34+CD133+ higher than 75% percentile, there are no AD cases among these genotypes, so log-rank statistics is used instead to compare groups.

b. Not enough subjects to perform the analysis.

Table S7. Comparisons of incident Alzheimer's disease rates across CD34+CD133+ quartiles in the context of genetic background

SNP (Gene)	Genotype	Overall	Blood CD34+CD133+ Endothelia Progenitor Cells frequency, %				P-value[a]
			1st Q	2nd Q	3rd Q	4th Q	
		[0.002,0.609]	[0.002,0.020]	[0.020,0.032]	[0.032,0.049]	[0.049,0.609]	
		AD, n (%)	AD, n (%)	AD, n (%)	AD, n (%)	AD, n (%)	
rs4144611 (*KIRREL3*)	TT	35 (6.23%)	20 (13.25%)	8 (5.52%)	7 (4.90%)	0 (0.00%)	**8.8e-05**
	TG	30 (4.11%)	13 (6.95%)	4 (2.50%)	6 (3.02%)	7 (3.83%)	0.14
	GG	14 (6.45%)	1 (1.64%)	4 (7.41%)	5 (10.00%)	4 (7.69%)	0.30
rs580382 (*KIRREL3*)	CC	40 (6.36%)	24 (14.55%)	8 (5.10%)	8 (4.85%)	0 (0.00%)	**2.1e-06**
	CT	28 (4.01%)	9 (4.86%)	5 (3.21%)	6 (3.24%)	8 (4.62%)	0.79
	TT	11 (6.11%)	1 (2.04%)	3 (6.52%)	4 (9.52%)	3 (6.98%)	0.51
rs61619102 (*EXOC6B*)	CC	59 (5.53%)	31 (10.23%)	13 (5.51%)	10 (3.70%)	5 (1.94%)	**1.1e-04**
	GC	18 (4.60%)	3 (3.57%)	3 (2.68%)	7 (6.48%)	5 (5.75%)	0.52
	GG	2 (4.08%)	0 (0.00%)	0 (0.00%)	1 (7.14%)	1 (8.33%)	0.60

a. Chi-squared test p-value.

The FHS participants were stratified by genotypes, rs4144611 (*KIRREL3*), rs580382 (*KIRREL3*) or rs61619102 (*EXOC6B*). The AD incident rates across CD34+CD133+ EPC quartiles were compared in each genotype by using Chi-squared test. P values are shown.

Figure S1. Flow chart of the study design

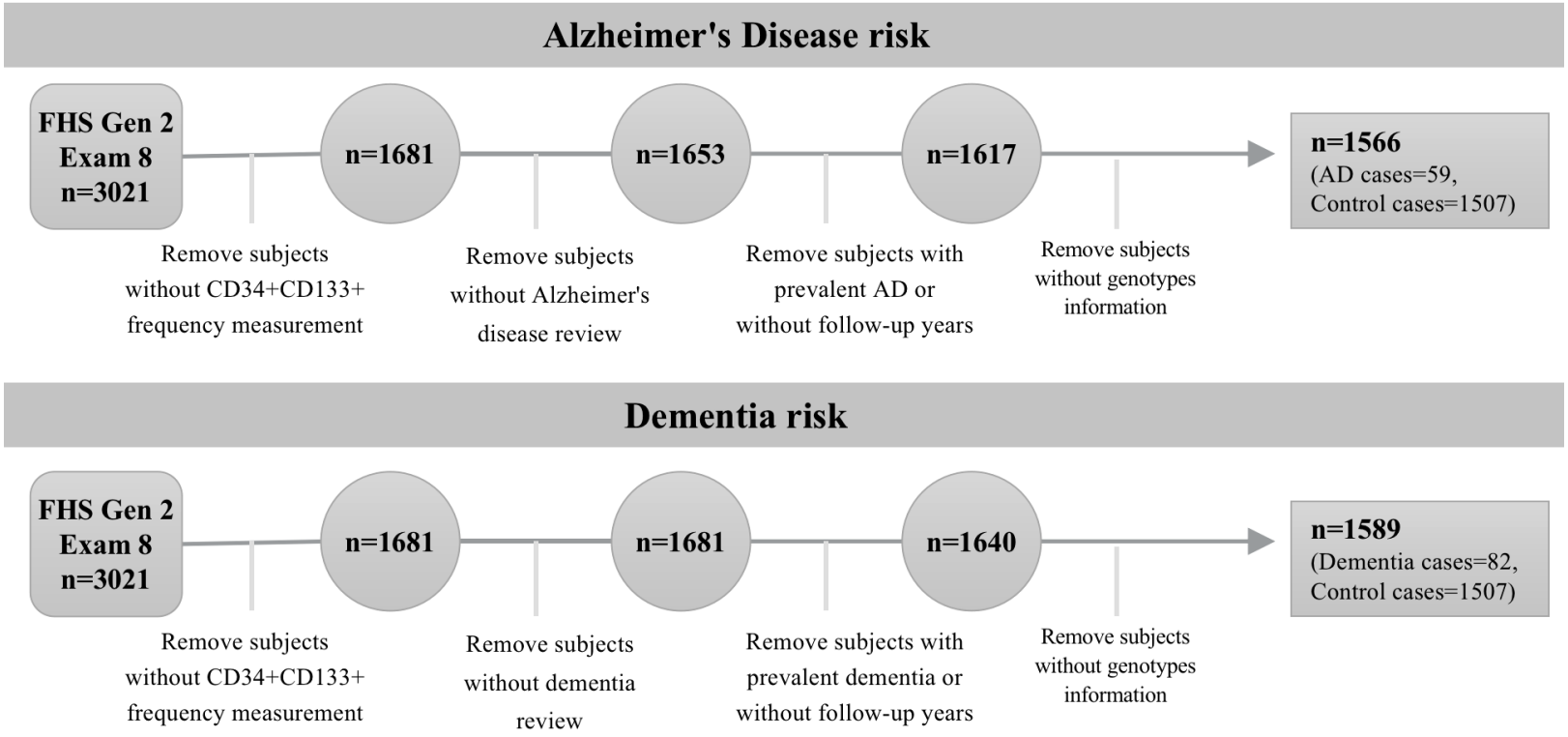
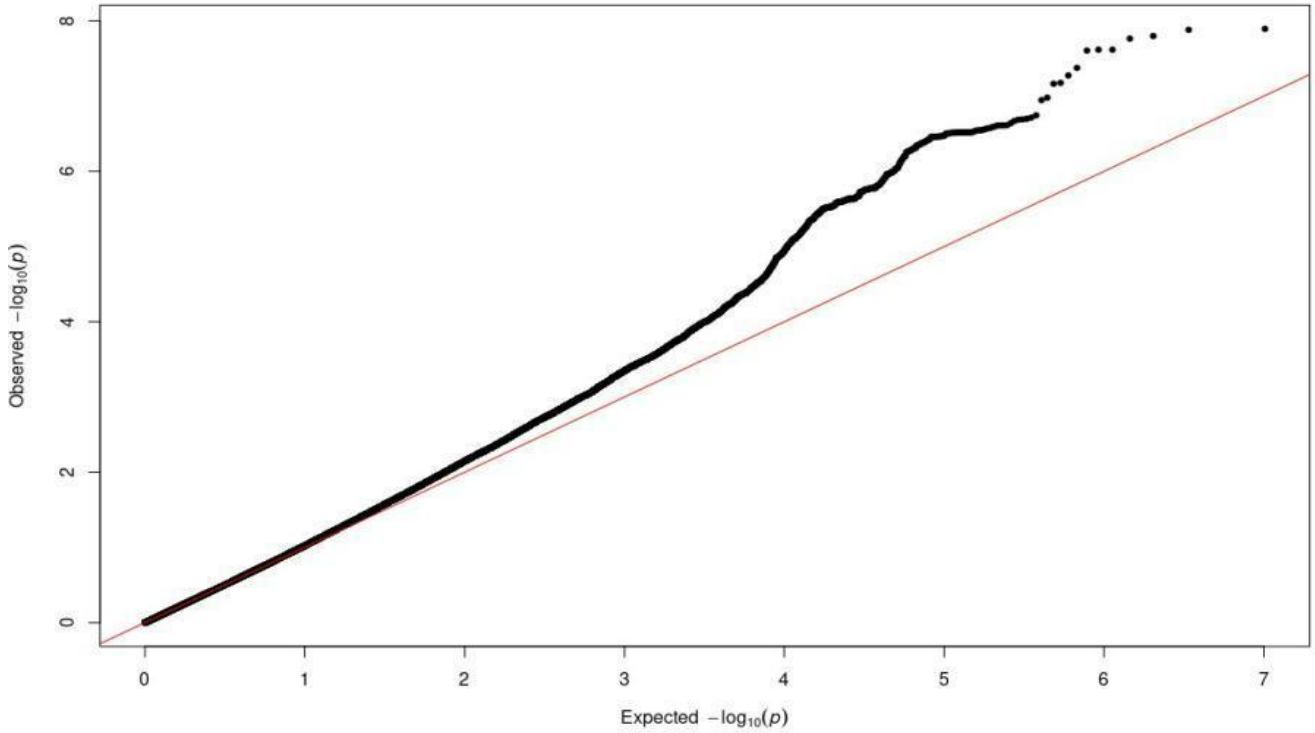


Figure S2. Q-Q plot of the GWAS analyses



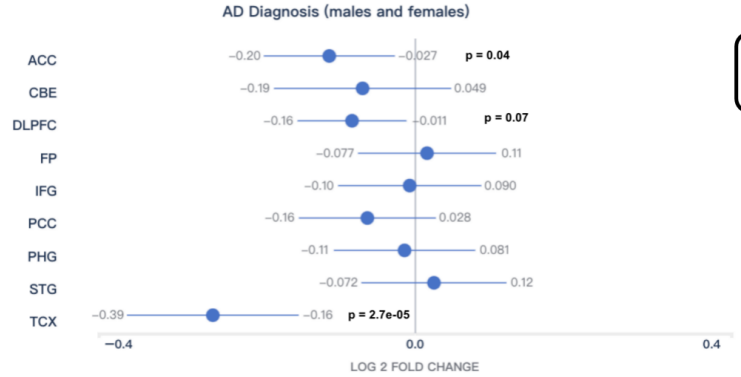
Genomic inflation (λ=1.15 before genomic control)

Figure S3. The relationships between the *KIRREL3* SNPs, gene expression, and Alzheimer's disease

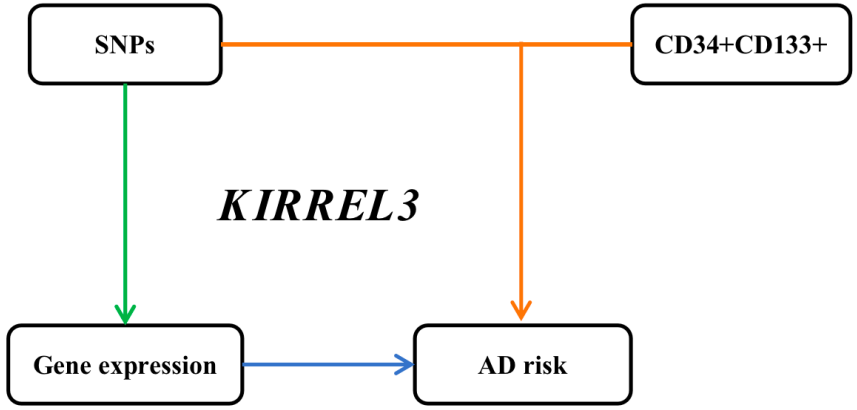
A. The relationship between KIRREL3 expression and AD in Monocytes and Brain

Outcome	Region	Gene	OR (95% CI)	P-value
AD	Monocytes	*KIRREL3*	0.80 (0.51-1.25)	0.32
AD	Brain	*KIRREL3*	0.66 (0.47-0.93)	0.02

B. KIRREL3 mRNA levels at brain regions: AD vs. controls[1]



[1] Agora (https://agora.adknowledgeportal.org/genes)



C. Interaction between SNPs and CD34+CD133+ on AD risk in FHS[2]

Interaction Effect				
Predictor 1 (SNP id)	Predictor 2	Outcome	HR (95% CI)	P-value
rs4144611	CD34+CD133+	AD	2.85 (1.77-4.57)	1.5e-05
rs580382	CD34+CD133+	AD	3.89 (2.37-6.37)	7.1e-08

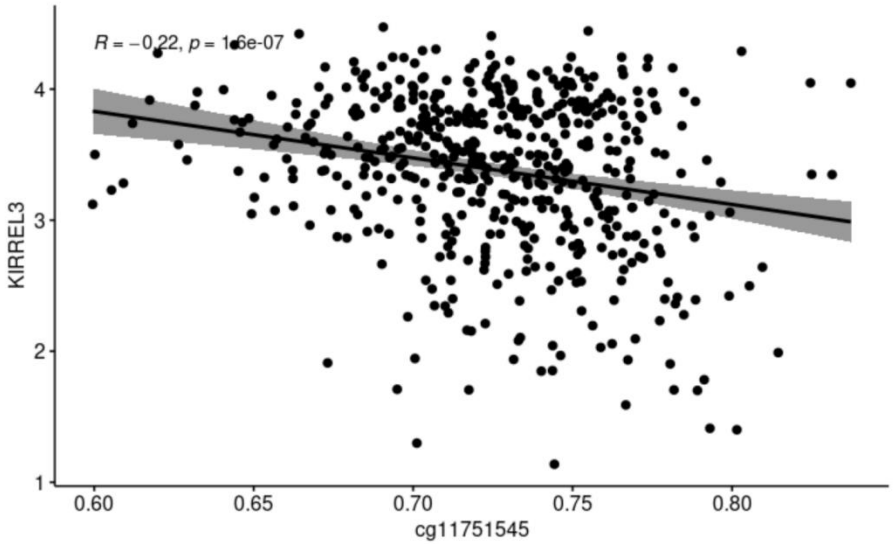
[2] Cox proportional hazards regression model, AD incidence ~ SNP + (CD34+CD133+) + SNP:(CD34+CD133+) + age + sex + years of education + APOE ε4 + PCs.

We hypothesized that the gene expression levels of KIRREL3 are involved in AD pathology, thus leading to their genotypes having interactive effects with circulating CD34+CD133+ endothelial progenitors for AD risk.

A. by using the ROSMAP dataset and logistic regression, the relationships between KIRREL3 expression in monocytes and brain and AD pathology are shown; B. KIRREL3 mRNA levels across brain regions were compared between AD and controls obtained from Agora; C. interaction between two KIRREL3 SNPs and CD34+CD133+ on AD risk in FHS. ACC = The anterior cingulate cortex; CBE = cerebellum; DLPF = The dorsolateral prefrontal cortex; FP = The frontal pole; IFG = The inferior frontal gyrus; PCC = The posterior cingulate cortex; PHG = The parahippocampal gyrus; STG = The superior temporal gyrus; TCX = The temporal cortex

Figure S4. The relationship between *KIRREL3* expression, SNPs and methylation in the ROSMAP study

A. The relationship between *KIRREL3* expression and the methylation site cg11751545 in the DLPFC region



B. The relationships between SNPs and DLPFC methylation in ROSMAP

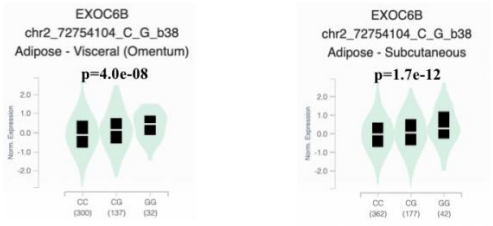
SNP id	SNP chr	SNP pos	A1	A2	feature Name	feature PositionStart	beta	se	P-value
rs4144611 (*KIRREL3*)	11	126434673	G	T	cg11751545	126434315	-0.28	0.04	3.5e-11
					cg04445570	126456651	-0.10	0.04	0.02
rs580382 (*KIRREL3*)	11	126438111	T	C	cg11751545	126434315	-0.28	0.04	1.9e-11

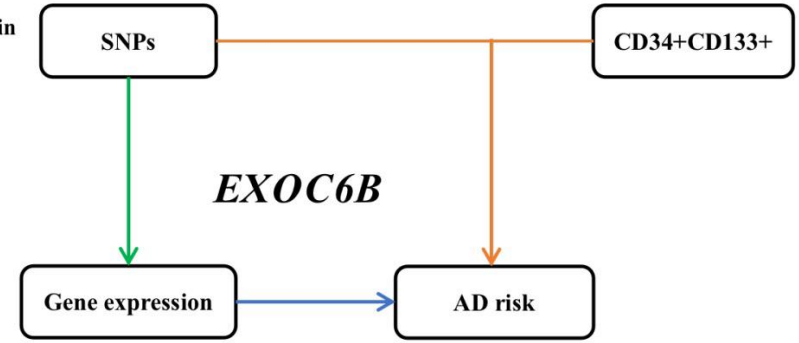
Figure S5. The relationships between the *EXOC6B* SNPs, gene expression, and Alzheimer's disease

A. The relationship between EXOC6B expression and AD in Monocytes and Brain

Outcome	Region	Gene	OR (95% CI)	P-value
AD	Monocytes	*EXOC6B*	1.38 (1.16-1.64)	2.9e-04
AD	Brain	*EXOC6B*	0.63 (0.40-0.99)	0.05

B. The relationships between EXOC6B rs61619102 (eQTLs) and EXOC6B expression in two types of adiposes from GTEx





C. Interaction between SNP and CD34+CD133+ on AD risk in FHS[1]

Interaction Effect				
Predictor 1 (SNP id)	Predictor 2	Outcome	HR (95% CI)	P-value
rs61619102	CD34+CD133+	AD	4.87 (2.13-11.15)	1.8e-04

[1] Cox proportional hazards regression model, AD incidence ~ SNP + (CD34+CD133+) + SNP:(CD34+CD133+) + age + sex + years of education + APOE ε4 + PCs.

We hypothesized that the gene expression levels of EXOC6B are involved in AD pathology, thus leading to their genotypes having interactive effects with circulating CD34+CD133+ endothelial progenitors for AD risk.

A. by using the ROSMAP dataset and logistic regression, the relationships between EXOC6B expression in monocytes and brain and AD pathology are shown, thus indicating that high peripheral expression of EXOC6B expression was significantly associated with AD risk; B. peripheral eQTL results for the EXOC6B genotype in two types of adipose tissues from GTEx are illustrated, thus suggesting that the EXOC6B cc allele with low peripheral expression and AD risk can be rescued by circulating CD34+CD133+ endothelial progenitor cells for AD risk; C. the interaction between the EXOC6B SNP and CD34+CD133+ cells impacted AD risk in FHS.