

Supplementary Materials for

The *FAM171A2* gene is a key regulator of progranulin expression and modifies the risk of multiple neurodegenerative diseases

Wei Xu, Si-Da Han, Can Zhang, Jie-Qiong Li, Yan-Jiang Wang, Chen-Chen Tan, Hong-Qi Li, Qiang Dong, Cui Mei, Lan Tan, Jin-Tai Yu*

*Corresponding author. Email: jintai_yu@fudan.edu.cn

Published 21 October 2020, *Sci. Adv.* **6**, eabb3063 (2020)
DOI: 10.1126/sciadv.abb3063

This PDF file includes:

Figs. S1 to S5
Tables S1 to S10

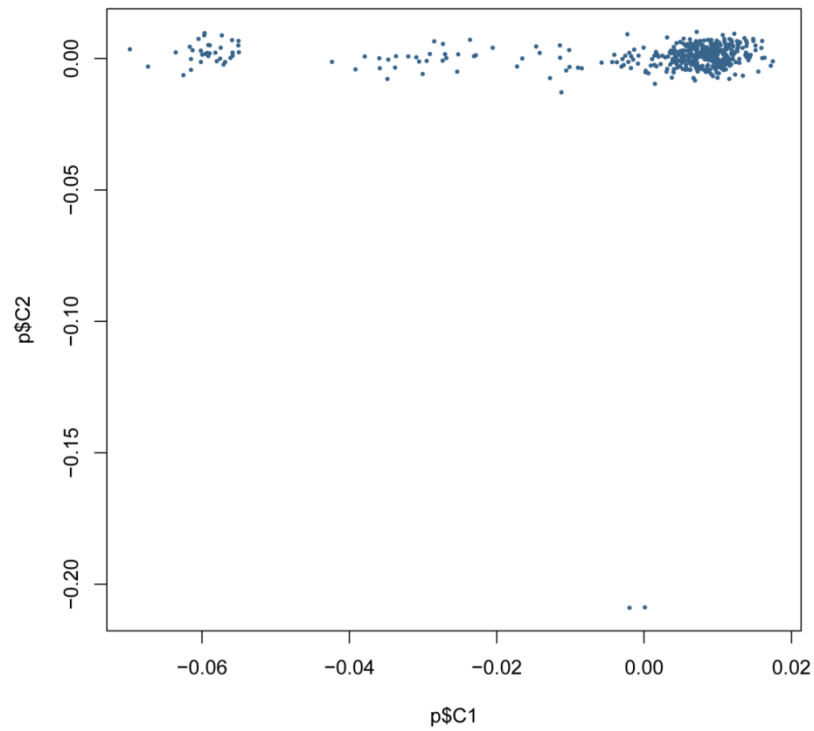


Figure S1 MDS plot of ADNI non-Hispanic Caucasian samples. The unanticipated duplicates and cryptic relatedness among samples were examined using pairwise genome-wide estimates of proportion identity-by-descent. Samples seemed to form generally tight clusters except for two outliers based on the second MDS component (at bottom of plot; IID = 024_S_4084 and 024_S_2239), suggesting potential population substructure.

Table S1 Suggestive loci associated with CSF PGRN levels

CHR	SNP	BP	AI	BETA	STAT	Source	GWAS p-value	empiric p-value	permutation based corrected empiric p-value
17	rs11654428	42555787	G	-0.002345	-5.52	Imputation	5.92E-08	0.0002	0.03459
17	rs9891016	42555485	A	-0.002308	-5.435	Genotyping	9.27E-08	0.0002	0.05559
17	rs575341342	42590812	C	-0.002219	-5.232	Imputation	2.65E-07	0.0002	0.147
17	rs4793113	42580061	C	0.0021	5.202	Imputation	3.08E-07	0.0002	0.1678
17	rs28614047	42583651	A	0.0021	5.202	Imputation	3.08E-07	0.0002	0.1678
17	rs7216502	42589924	A	0.0021	5.202	Imputation	3.08E-07	0.0002	0.1678
17	rs72824760	42560209	A	0.002085	5.133	Imputation	4.35E-07	0.0002	0.2288
17	rs9899573	42549880	T	0.002075	5.119	Imputation	4.68E-07	0.0002	0.2448
17	rs11867692	42570346	T	0.002075	5.119	Genotyping	4.68E-07	0.0002	0.2448
17	rs201470041	42596255	TAA	-0.002136	-5.111	Imputation	4.87E-07	0.0002	0.2501
17	rs11657509	42598428	G	-0.002136	-5.111	Imputation	4.87E-07	0.0002	0.2501
17	rs2045087	42482291	A	0.002065	5.068	Imputation	6.02E-07	0.0002	0.2977
17	rs11079122	42485044	C	0.002065	5.068	Imputation	6.02E-07	0.0002	0.2977
17	rs67633759	42515327	A	0.002065	5.068	Imputation	6.02E-07	0.0002	0.2977
17	rs9905022	42601674	C	-0.002103	-5.061	Imputation	6.23E-07	0.0002	0.3045
17	rs12103601	42601849	C	-0.002103	-5.061	Imputation	6.23E-07	0.0002	0.3045
17	rs200400827	42602225	C	-0.002103	-5.061	Imputation	6.23E-07	0.0002	0.3045
17	rs112190958	42602517	G	-0.002103	-5.061	Imputation	6.23E-07	0.0002	0.3045
17	rs4130977	42603714	G	-0.002103	-5.061	Imputation	6.23E-07	0.0002	0.3045
17	rs55753235	42605737	C	-0.002103	-5.061	Imputation	6.23E-07	0.0002	0.3045
17	rs9889793	42608923	G	-0.002103	-5.061	Imputation	6.23E-07	0.0002	0.3045
17	rs3924066	42589478	C	-0.002109	-5.048	Imputation	6.64E-07	0.0002	0.3201
17	rs8071155	42592202	A	-0.002109	-5.048	Imputation	6.64E-07	0.0002	0.3201
17	rs9890329	42594762	G	-0.002109	-5.048	Imputation	6.64E-07	0.0002	0.3201
17	rs8064751	42596589	A	-0.0021	-5.027	Imputation	7.37E-07	0.0002	0.3501
17	rs62081230	42530868	G	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs62081232	42532761	C	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs6503373	42538690	T	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs11347764	42539230	TG	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs7502443	42546874	C	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs9911079	42547688	C	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs7219873	42547981	C	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs4792945	42552832	C	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs9901031	42553667	G	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs7223739	42554600	T	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs7223781	42554675	T	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs150526952	42555366	TGGGGTGG	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs7503521	42560907	G	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs7502468	42562632	C	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs62078767	42568013	T	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs4793112	42572457	C	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs7223926	42578882	G	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs7210568	42578965	T	-0.00209	-4.973	Imputation	9.58E-07	0.0002	0.4295
17	rs148261873	42542461	A	-0.002073	-4.965	Imputation	9.98E-07	0.0002	0.4415
17	rs4792946	42582577	T	-0.002073	-4.965	Imputation	9.98E-07	0.0002	0.4415
17	rs4793114	42583236	G	-0.002073	-4.965	Imputation	9.98E-07	0.0002	0.4415
17	rs4793115	42584716	T	-0.002073	-4.965	Imputation	9.98E-07	0.0002	0.4415
17	rs12936626	42584877	T	-0.002073	-4.965	Imputation	9.98E-07	0.0002	0.4415
17	rs8064662	42588083	A	-0.002073	-4.965	Imputation	9.98E-07	0.0002	0.4415
17	rs7212357	42589008	C	-0.002073	-4.965	Imputation	9.98E-07	0.0002	0.4415
17	rs8071245	42592632	C	-0.002073	-4.965	Imputation	9.98E-07	0.0002	0.4415
17	rs7219216	42593325	C	-0.002073	-4.965	Imputation	9.98E-07	0.0002	0.4415
17	rs147058394	42502390	AAAC	-0.002081	-4.942	Imputation	1.12E-06	0.0002	0.4825
17	rs55758339	42471631	T	-0.002074	-4.922	Imputation	1.23E-06	0.0002	0.5171
17	rs147675276	42561193	TTTG	0.001996	4.921	Imputation	1.24E-06	0.0002	0.5207
17	rs4793107	42533404	A	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs4793108	42533790	G	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs6503371	42536147	C	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs6503372	42538053	C	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs28688303	42539569	C	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs9748120	42540484	T	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs11079156	42541131	A	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs8071032	42542693	T	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs7214894	42543705	C	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs7501858	42549992	G	-0.002054	-4.89	Genotyping	1.43E-06	0.0002	0.5723
17	rs8077743	42550603	T	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs4792944	42551549	G	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs7502979	42554890	G	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs7503752	42560910	A	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs7503804	42561152	A	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs4793110	42561923	A	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs9905790	42565329	T	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs9901244	42567468	C	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs8074093	42568770	G	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs4793111	42571104	G	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs7213453	42574898	A	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs10532706	42579727	GTTT	-0.002054	-4.89	Imputation	1.43E-06	0.0002	0.5723
17	rs850728	42464337	A	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs850727	42464915	C	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765

17	rs9903206	42466043	C	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs2037958	42472045	T	-0.002052	-4.887	Genotyping	1.45E-06	0.0002	0.5765
17	rs1018358	42472588	C	-0.002052	-4.887	Genotyping	1.45E-06	0.0002	0.5765
17	rs936019	42475983	G	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs11868742	42479392	T	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs7223275	42481493	C	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs2045088	42483233	T	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs8076720	42484319	C	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs4792941	42493020	A	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs9897984	42497027	A	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs9902493	42497737	G	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs11658173	42499153	G	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs9899760	42500602	C	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs1869495	42501692	C	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs11079133	42502129	A	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs9911487	42506397	T	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs11079138	42506960	C	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs28412336	42507844	C	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs4793102	42511518	A	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs4793103	42511682	A	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs79092888	42518758	C	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs11652426	42521607	T	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs9896740	42526970	C	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs11871577	42528530	C	-0.002052	-4.887	Imputation	1.45E-06	0.0002	0.5765
17	rs850735	42448180	A	0.002062	4.866	Imputation	1.61E-06	0.0002	0.6139
9	rs146782711	79732264	TAAATA	-0.002013	-4.844	Imputation	1.79E-06	0.0002	0.6139
3	rs9258	194361556	A	0.002091	4.823	Imputation	1.97E-06	0.0002	0.6853
17	rs4792940	42482623	A	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs11323148	42482882	GT	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs1377808	42483531	T	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs11469796	42485610	GGT	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs3065774	42491426	CATAT	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs3065772	42491485	GTA	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs9905969	42492556	C	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs9907524	42492860	A	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs35752663	42493687	AT	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs28571240	42494708	T	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs9902085	42495690	C	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs9903243	42497376	C	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs71361570	42504203	AAC	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs9903906	42504526	A	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs11079137	42506828	A	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs9913207	42507346	A	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs11079140	42509990	G	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs11448727	42514114	A	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs62081226	42514116	G	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs4793105	42514259	G	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs148920267	42519453	G	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs4793106	42522230	G	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs34090973	42524892	C	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs59861211	42526428	T	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs11283092	42527953	A	-0.002017	-4.805	Imputation	2.16E-06	0.0002	0.7121
17	rs74472815	42508941	A	-0.002019	-4.796	Imputation	2.25E-06	0.0002	0.7269
17	rs11650338	42515331	C	0.001966	4.787	Imputation	2.34E-06	0.0002	0.7393
17	rs74548808	42491525	G	-0.002005	-4.777	Imputation	2.46E-06	0.0002	0.7552
17	rs11305518	42531299	CA	-0.001997	-4.734	Imputation	3.01E-06	0.0002	0.8246
17	rs4793119	42624404	A	0.001958	4.694	Genotyping	3.62E-06	0.0002	0.8748
14	rs1484081	42823074	G	0.00205	4.682	Imputation	3.83E-06	0.0002	0.8874
17	rs545616723	12260128	GGAA	-0.002353	-4.662	Imputation	4.21E-06	0.0002	0.9084
17	rs202099152	42519581	T	-0.001945	-4.619	Imputation	5.13E-06	0.0002	0.9438
19	rs34163270	14264394	A	-0.002089	-4.613	Imputation	5.27E-06	0.0002	0.9464
12	rs6581710	67042317	A	-0.002161	-4.607	Genotyping	5.42E-06	0.0002	0.9506
3	rs711995	194360927	T	0.002024	4.584	Genotyping	6.00E-06	0.0002	0.964
17	rs200988896	42557333	CA	-0.001907	-4.573	Imputation	6.34E-06	0.0002	0.9708
3	rs56173723	194361299	C	0.001989	4.518	Imputation	8.10E-06	0.0002	0.9882
9	rs1044214	86275559	A	0.001993	4.507	Imputation	8.53E-06	0.0002	0.992
12	rs11320802	67041982	CT	-0.002109	-4.489	Imputation	9.24E-06	0.0002	0.995
17	rs200198398	42469795	ATTTTTT TTT	-0.001879	-4.484	Imputation	9.43E-06	0.0002	0.9956
11	rs10897273	62200069	T	0.00198	4.479	Imputation	9.67E-06	0.0002	0.996
3	rs1675955	194353875	T	0.001954	4.473	Genotyping	9.94E-06	0.0002	0.9968

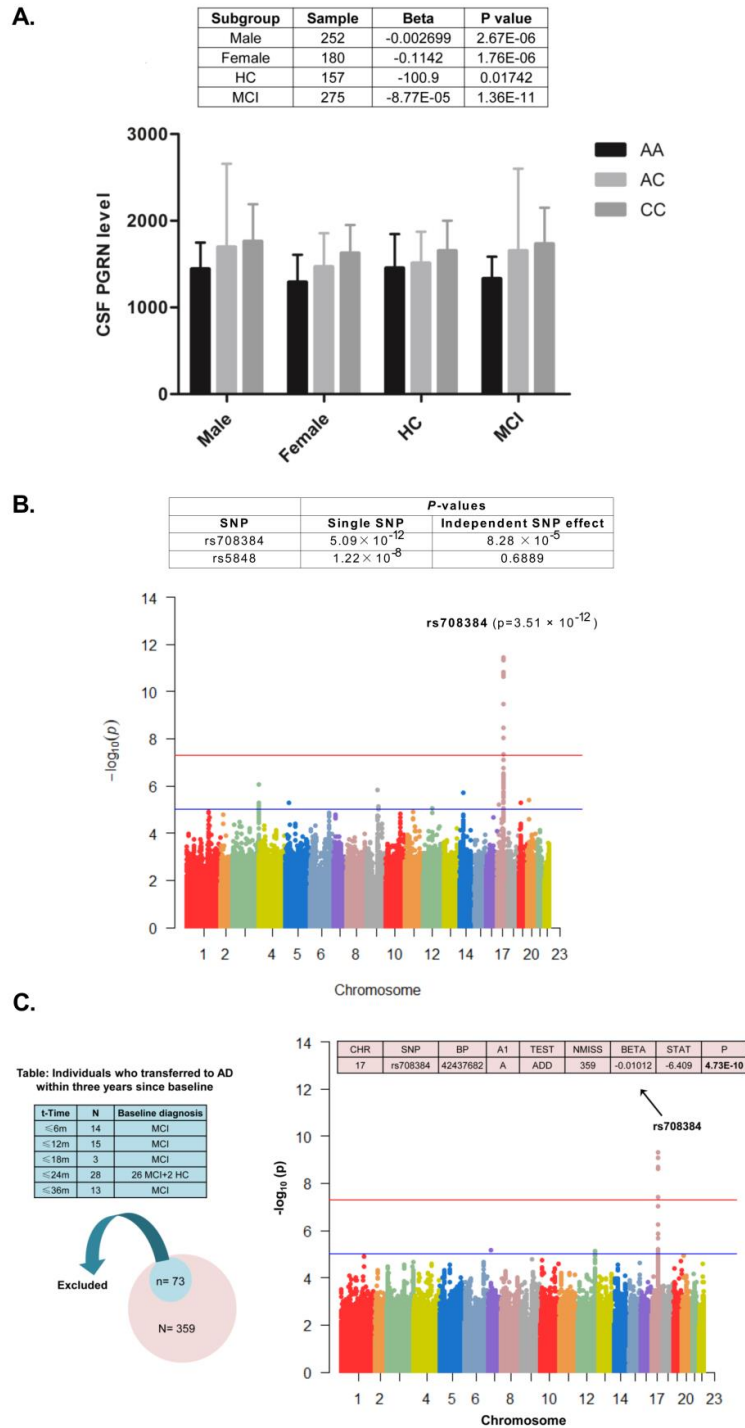


Figure S2 Subgroup and sensitivity analysis. **a** In the subgroup analyses, the minor allele (C) of rs708384 was associated with higher CSF levels of PGRN in different strata according to gender (Male, $p = 2.67 \times 10^{-6}$; Female, $p = 1.76 \times 10^{-6}$) and diagnosis at baseline (HC, $p = 0.01742$; MCI, $p = 1.36 \times 10^{-11}$). Notably, the effect size was drastically enlarged in HC population (beta for HC = -100.9 and beta for MCI = -8.77×10^{-5}). **b** Sensitivity analyses further adjusting these confounders are performed. Adjusting for age and baseline diagnosis did not significantly change the results ($p = 3.51 \times 10^{-12}$ for rs708384). After adjusting for rs5848, we also found a strong, but less significant, association for rs708384 with CSF PGRN levels ($p = 8.28 \times 10^{-5}$). **c** After excluding 73 individuals who progressed to AD within three years since baseline, rs708384 was still the top SNP ($n = 359$, $p = 4.73 \times 10^{-10}$).

Table S2 Specificity for the association with PGRN in ADNI sample (or replicate sample/?please

clarify)

CSF biomarkers	Other CSF biomarkers as covariates			Correlations between PGRN and other CSF biomarkers			Single variable linear regression based on other CSF biomarkers		
	N	beta	<i>p</i> -value	N	r	<i>p</i> -value	N	beta	<i>p</i> -value
Abeta42	432	-0.002935	4.62E-12	432	0.04010273	0.4063	432	0.06533	0.774
T-tau	432	-0.003021	5.92E-13	432	0.09929248	0.0394	431	0.01252	0.103
P-tau	432	-0.002925	4.28E-12	432	0.06797563	0.1589	432	0.01174	0.724
α -synuclein	96	5.647 E-05	0.00839	96	0.3604819	0.0003	262	-0.0677	0.305
NFL	102	5.652E-05	0.01	102	0.2187118	0.0272	278	-0.0016	0.087
sTREM2	432	3.064 E-03	5.53 E-14	432	0.2706483	1.134 E-08	703	-0.0464	0.773

Table S3 Associations results in the replication sample

SNP	Single SNP	Independent effect*
rs708384 (AA vs. AC vs. CC)	1.25×10^{-5}	0.100
rs708384 (AA vs. CC)	5.04×10^{-4}	0.045
rs5848	4.11×10^{-5}	0.88
rs660240	0.14	NA
rs4747197	0.64	NA
rs646776	0.14	NA

All analyses were adjusted for age, sex, education, *APOE* epsilon4 status, and MMSE score at baseline.

*Both rs708384 and rs5848 were added in the regression model.

Table S4 Enhancer enrichment analysis

Cell	15-state core model			25-state core model			H3K4me1/H3K4me3			H3K27ac/H3K9ac		
	O	E	p	O	E	p	O	E	p	O	E	p
E062 BLD.PER.MONUC.PC (Primary mononuclear cells from peripheral blood)	0	0.1	1	0	0.4	1	0	0.6	1	0	0.3	1
E034 BLD.CD3.PPC (Primary T cells from peripheral blood)	0	0.4	1	0	0.4	1	5	1.1	0.003315	0	0.6	1
E045 BLD.CD4.CD25I.CD127.TMEMPC (Primary T cells effector/memory enriched from peripheral blood)	0	0.2	1	0	0.4	1	2	0.9	0.223534	0	0.5	1
E033 BLD.CD3.CPC (Primary T cells from cord blood)	0	0.3	1	0	0.5	1	0	0.5	1	0	0	1
E044 BLD.CD4.CD25.CD127M.TREGPC (Primary T regulatory cells from peripheral blood)	0	0.2	1	0	0.4	1	0	1	1	0	0.6	1
E043 BLD.CD4.CD25M.TPC (Primary T helper cells from peripheral blood)	0	0.4	1	0	0.4	1	2	1.2	0.323081	0	0.6	1
E039 BLD.CD4.CD25M.CD45RA.NPC (Primary T helper naive cells from peripheral blood)	0	0.4	1	0	0.4	1	1	1.1	0.698727	0	0.6	1
E041 BLD.CD4.CD25M.IL17M.PL.TPC (Primary T helper cells PMA-I stimulated)	0	0.4	1	0	0.4	1	2	1.3	0.366131	0	0.9	1
E042 BLD.CD4.CD25M.IL17P.PL.TPC (Primary T helper 17 cells PMA-I stimulated)	0	0.3	1	0	0.4	1	2	1	0.276351	1	0.5	0.404939
E040 BLD.CD4.CD25M.CD45RO.MPC (Primary T helper memory cells from peripheral blood 1)	0	0.3	1	0	0.4	1	1	1.1	0.669157	0	0.5	1
E037 BLD.CD4.MPC (Primary T helper memory cells from peripheral blood 2)	0	0.4	1	0	0.4	1	0	1.1	1	0	0.7	1
E048 BLD.CD8.MPC (Primary T CD8+ memory cells from peripheral blood)	0	0.3	1	0	0.4	1	1	1	0.66336	1	0.5	0.409628
E038 BLD.CD4.NPC (Primary T helper naive cells from peripheral blood)	0	0.3	1	0	0.4	1	2	1	0.268209	0	0.4	1
E047 BLD.CD8.NPC (Primary T CD8+ naive cells from peripheral blood)	0	0.4	1	0	0.4	1	0	1.1	1	0	0.4	1
E029 BLD.CD14.PC (Primary monocytes from peripheral blood)	0	0.5	1	0	0.4	1	0	0.8	1	4	0.4	0.000495
E031 BLD.CD19.CPC (Primary B cells from cord blood)	0	0.3	1	0	0.5	1	0	0.7	1	0	0	1
E035 BLD.CD34.PC (Primary hematopoietic stem cells)	1	0.3	0.298827	0	0.5	1	0	0.6	1	0	0	1
E051 BLD.MOB.CD34.PC.M (Primary hematopoietic stem cells G-CSF-mobilized Male)	0	0.5	1	0	0.4	1	2	1	0.261655	0	0	1
E050 BLD.MOB.CD34.PC.F (Primary hematopoietic stem cells G-CSF-mobilized Female)	2	0.5	0.086018	0	0.5	1	2	1.2	0.349199	0	0.8	1
E036 BLD.CD34.CC (Primary hematopoietic stem cells short term culture)	0	0.5	1	0	0.5	1	2	1	0.270402	0	0	1
E032 BLD.CD19.PPC (Primary B cells from peripheral blood)	0	0.5	1	0	0.4	1	1	1	0.647086	0	0.4	1
E046 BLD.CD56.PC (Primary Natural Killer cells from peripheral blood)	0	0.4	1	0	0.4	1	1	1	0.631329	0	0.4	1
E030 BLD.CD15.PC (Primary neutrophils from peripheral blood)	0	0.4	1	0	0.6	1	0	0.8	1	0	0	1
E123 BLD.K562.CNCR (K562 Leukemia Cells)	1	0.4	0.317035	0	0.4	1	4	0.8	0.006489	0	0.3	1
E124 BLD.CD14.MONO (Monocytes-CD14+ RO01746 Primary Cells)	0	0.4	1	0	0.5	1	0	1	1	0	1.2	1
E054 BRN.GANGEM.DR.NRSPHR (Ganglion Eminence derived primary cultured neurospheres)	3	0.3	0.003593	2	0.4	0.060306	2	0.9	0.234081	0	0	1
E053 BRN.CRTX.DR.NRSPHR (Cortex derived primary cultured neurospheres)	2	0.5	0.075201	2	0.4	0.047011	3	1.1	0.084211	0	0	1
E071 BRN.HIPP.MID (Brain Hippocampus Middle)	0	0.4	1	0	0.6	1	2	1.7	0.521587	4	1.2	0.028108
E074 BRN.SUB.NIG (Brain Substantia Nigra)	0	0.4	1	0	0.6	1	2	1.4	0.413045	2	1.2	0.323858
E068 BRN.ANT.CAUD (Brain Anterior Caudate)	0	0.3	1	2	0.6	0.117324	2	1.6	0.477345	2	1.4	0.404137
E069 BRN.CING.GYR (Brain Cingulate Gyrus)	0	0.3	1	0	0.6	1	2	1.4	0.424189	3	1.3	0.143567
E072 BRN.INF.TMP (Brain Inferior Temporal Lobe)	0	0.3	1	2	0.6	0.123737	2	0.9	0.238612	5	1.4	0.009549
E067 BRN.ANG.GYR (Brain Angular Gyrus)	0	0.3	1	2	0.6	0.112296	3	1.4	0.159161	4	1.3	0.030831
E073 BRN.DL.PFRNTL.CRTX (Brain Dorsolateral Prefrontal Cortex)	0	0.3	1	2	0.6	0.127101	5	1.4	0.009242	5	1.4	0.00872
E070 BRN.GRM.MTRX (Brain Germinal Matrix)	2	0.3	0.031041	2	0.4	0.059423	2	0.7	0.156719	0	0	1
E082 BRN.FET.F (Fetal Brain Female)	2	0.2	0.017854	3	0.3	0.003956	3	1	0.076469	0	0	1
E081 BRN.FET.M (Fetal Brain Male)	4	0.4	0.000566	3	0.4	0.008491	6	1.2	0.000519	0	0	1
E125 BRN.NHA (NH-A Astrocytes Primary Cells)	0	0.4	1	0	0.5	1	2	1.2	0.358956	0	0.7	1

Significant associations with $p < 0.05$ are bolded. O, observed; E, expected; BLD, blood; BRN, brain

Table S5 Tagged variants and gene expression in human blood samples

SNP	Dataset	Samples	Beta	Z	log10 (p)	Gene
rs708384	[1]	5311	NA	4.736784776	-5.663540266	<i>GRN</i>
rs850730	[1]	5311	NA	4.949722813	-6.128624639	<i>GRN</i>
rs5910	[1]	5311	NA	4.954245083	-6.138893076	<i>GRN</i>
rs5911	[1]	5311	NA	4.973844543	-6.182745132	<i>GRN</i>
rs708382	[1]	5311	NA	4.526124495	-5.221049085	<i>GRN</i>
rs850736	[2]	2765	0.2	7.1429	-11.55284197	<i>GRN</i>
rs5848	[3]	5257	0.0225	NA	-9.1853	<i>GRN</i>

Significance level $p < 0.05$; NA, not available; Z-score = effect (beta)/standard error; Beta is the regression coefficient based on the effect allele. Beta > 0 and Beta < 0 means that this effect allele regulates increased and reduced gene expression, respectively. [1] <http://www.genenetwork.nl/bloodqtlbrowser/> [2]

<http://cnsgenomics.com/shiny/CAGE/> [3] <https://preview.ncbi.nlm.nih.gov/gap/eqt/studies/>

Table S6 Tagged variants and gene expression in human brain tissues

	Study name	CHR	SNP	BP(GRCh37)	NMISS	BETA	STAT	log10(P)	PROBE	Start	End	Gene Symbol (Probe)
Brain expression GWAS	CER_AD	17	rs708384	39793208	195	-0.03916	-1.225	-6.53E-01	ILMN_1724250	39778016	39785996	GRN
		17	rs708384	39793208	195	0.01018	0.4469	-1.83E-01	ILMN_1811702	39778016	39785996	GRN
	CER_Control	17	rs708384	39793208	176	0.03721	1.245	-6.68E-01	ILMN_1811702	39778016	39785996	GRN
		17	rs708384	39793208	176	0.03757	0.9701	-4.77E-01	ILMN_1724250	39778016	39785996	GRN
		17	rs850737	39799310	174	-0.01797	-0.4062	-1.64E-01	ILMN_1721888	39805075	39822399	ITGA2B
	CER_All	17	rs708384	39793208	371	-0.009667	-0.3946	-1.59E-01	ILMN_1724250	39778016	39785996	GRN
		17	rs850737	39799310	369	-3.48E-02	-1.463	-8.40E-01	ILMN_1724250	39778016	39785996	GRN
	TX_AD	17	rs708384	39793208	200	-0.03545	-1.123	-5.80E-01	ILMN_1724250	39778016	39785996	GRN
		17	rs708384	39793208	200	0.01123	0.5591	-2.39E-01	ILMN_1811702	39778016	39785996	GRN
		17	rs708384	39793208	190	0.03955	1.193	-6.30E-01	ILMN_1811702	39778016	39785996	GRN
	TX_Control	17	rs708384	39793208	190	-0.02466	-0.6202	-2.71E-01	ILMN_1724250	39778016	39785996	GRN
		17	rs708384	39793208	390	-0.03414	-1.374	-7.69E-01	ILMN_1724250	39778016	39785996	GRN
	TX_All	17	rs708384	39793208	390	0.02373	1.275	-6.92E-01	ILMN_1811702	39778016	39785996	GRN
		17	rs850737	39799310	389	3.34E-02	1.838	-1.17E+00	ILMN_1811702	39778016	39785996	GRN
1000 Genomes Project	Brain_Caudate_basal_ganglia	17	rs708384	39793208	NA	-0.1515	NA	-1.68E+00	NA	39778016	39785996	FAM171A2
	Brain_Anterior_cingulate_cortex_BA24	17	rs708384	39793208	NA	-0.3589	NA	-2.40E+00	NA	39778016	39785996	GRN
	Brain_Frontal_Cortex_BA9	17	rs708384	39793208	NA	-0.2582	NA	-1.78E+00	NA	39778016	39785996	GRN

CER = cerebellum; TX = temporal cortex

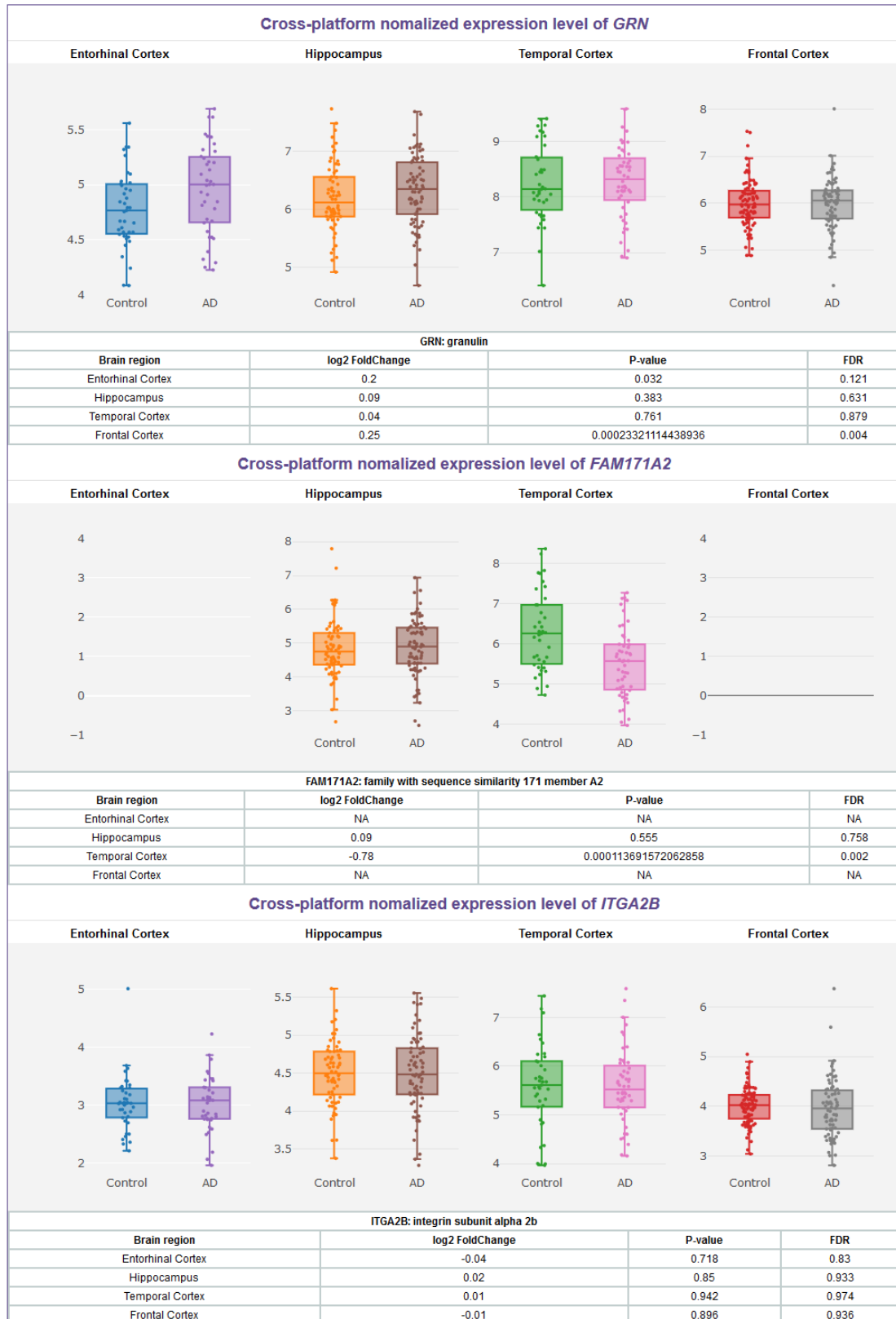


Figure S3 Differential expression analysis for GRN, FAM171A2, and ITGA2B. All results were adjusted for age and sex. Dataset of Entorhinal cortex: GSE26927, GSE26972, GSE48350, GSE5281; Dataset of Hippocampus: GSE28146, GSE29378, GSE36980, GSE48350, GSE5281; Dataset of Temporal cortex: GSE29652, GSE36980, GSE37263, GSE5281; Dataset of Frontal cortex: GSE12685, GSE36980, GSE5281, GSE53890, GSE66333

Table S7 Influences of rs708384 and rs5848 on expression of *GRN-FAM171A2-ITGA2B*

SNP	Gene	P-value (-log10)	Effect size	Tissue
rs5848	<i>FAM171A2</i>	2.65	0.43	Brain_Cortex
rs5848	<i>FAM171A2</i>	1.98	-0.19	Skin_Not_Sun_Exposed_Suprapubic
rs708384	<i>FAM171A2</i>	1.48	0.13	Adipose_Subcutaneous
rs708384	<i>FAM171A2</i>	1.68	-0.15	Brain_Caudate_basal_ganglia
rs708384	<i>FAM171A2</i>	2.40	0.10	Cells_Transformed_fibroblasts
rs708384	<i>FAM171A2</i>	1.96	0.25	Esophagus_Gastroesophageal_Junction
rs708384	<i>FAM171A2</i>	1.44	0.16	Muscle_Skeletal
rs708384	<i>FAM171A2</i>	1.76	0.12	Nerve_Tibial
rs708384	<i>FAM171A2</i>	1.87	0.18	Skin_Not_Sun_Exposed_Suprapubic
rs708384	<i>FAM171A2</i>	2.17	0.15	Skin_Sun_Exposed_Lower_leg
rs708384	<i>FAM171A2</i>	2.93	-0.17	Thyroid
rs5848	<i>GRN</i>	6.29	-0.20	Adipose_Subcutaneous
rs5848	<i>GRN</i>	4.09	-0.26	Adrenal_Gland
rs5848	<i>GRN</i>	8.60	-0.34	Artery_Aorta
rs5848	<i>GRN</i>	1.65	-0.13	Artery_Coronary
rs5848	<i>GRN</i>	13.58	-0.29	Artery_Tibial
rs5848	<i>GRN</i>	1.95	-0.35	Brain_Anterior_cingulate_cortex_BA24
rs5848	<i>GRN</i>	2.17	-0.25	Brain_Caudate_basal_ganglia
rs5848	<i>GRN</i>	3.33	-0.44	Brain_Cortex
rs5848	<i>GRN</i>	1.77	-0.30	Brain_Frontal_Cortex_BA9
rs5848	<i>GRN</i>	1.65	-0.29	Brain_Putamen_basal_ganglia
rs5848	<i>GRN</i>	2.88	-0.18	Breast_Mammary_Tissue
rs5848	<i>GRN</i>	6.46	-0.17	Cells_Transformed_fibroblasts
rs5848	<i>GRN</i>	3.43	-0.24	Colon_Sigmoid
rs5848	<i>GRN</i>	3.20	-0.26	Esophagus_Gastroesophageal_Junction
rs5848	<i>GRN</i>	6.23	-0.29	Esophagus_Muscularis
rs5848	<i>GRN</i>	9.31	-0.41	Heart_Atrial_Appendage
rs5848	<i>GRN</i>	4.16	-0.25	Heart_Left_Ventricle
rs5848	<i>GRN</i>	15.86	-0.43	Nerve_Tibial
rs5848	<i>GRN</i>	2.87	-0.30	Ovary
rs5848	<i>GRN</i>	1.97	-0.14	Pancreas
rs5848	<i>GRN</i>	1.36	-0.11	Skin_Not_Sun_Exposed_Suprapubic
rs5848	<i>GRN</i>	2.74	-0.14	Skin_Sun_Exposed_Lower_leg
rs5848	<i>GRN</i>	2.91	-0.18	Stomach
rs5848	<i>GRN</i>	10.44	-0.35	Thyroid
rs708384	<i>GRN</i>	3.42	-0.13	Adipose_Subcutaneous
rs708384	<i>GRN</i>	3.65	-0.23	Adrenal_Gland
rs708384	<i>GRN</i>	4.84	-0.21	Artery_Aorta
rs708384	<i>GRN</i>	2.27	-0.14	Artery_Coronary
rs708384	<i>GRN</i>	9.43	-0.22	Artery_Tibial
rs708384	<i>GRN</i>	2.40	-0.36	Brain_Anterior_cingulate_cortex_BA24
rs708384	<i>GRN</i>	1.78	-0.26	Brain_Frontal_Cortex_BA9
rs708384	<i>GRN</i>	2.06	-0.13	Breast_Mammary_Tissue

rs708384	<i>GRN</i>	4.01	-0.12	Cells_Transformed_fibroblasts
rs708384	<i>GRN</i>	1.53	-0.13	Colon_Sigmoid
rs708384	<i>GRN</i>	1.52	-0.14	Esophagus_Gastroesophageal_Junction
rs708384	<i>GRN</i>	4.32	-0.21	Esophagus_Muscularis
rs708384	<i>GRN</i>	4.76	-0.27	Heart_Atrial_Appendage
rs708384	<i>GRN</i>	2.09	-0.15	Heart_Left_Ventricle
rs708384	<i>GRN</i>	8.05	-0.28	Nerve_Tibial
rs708384	<i>GRN</i>	1.95	-0.23	Ovary
rs708384	<i>GRN</i>	1.89	-0.12	Pancreas
rs708384	<i>GRN</i>	1.71	-0.09	Skin_Sun_Exposed_Lower_leg
rs708384	<i>GRN</i>	2.60	-0.15	Stomach
rs708384	<i>GRN</i>	5.83	-0.23	Thyroid
rs708384	<i>GRN</i>	1.35	0.07	Whole_Blood
rs5848	<i>ITGA2B</i>	1.34	-0.18	Adipose_Subcutaneous
rs5848	<i>ITGA2B</i>	1.35	0.22	Colon_Sigmoid
rs5848	<i>ITGA2B</i>	1.90	-0.30	Heart_Left_Ventricle
rs5848	<i>ITGA2B</i>	1.74	-0.17	Lung
rs5848	<i>ITGA2B</i>	1.45	-0.18	Skin_Sun_Exposed_Lower_leg
rs5848	<i>ITGA2B</i>	1.83	0.19	Testis
rs5848	<i>ITGA2B</i>	4.31	-0.17	Thyroid
rs708384	<i>ITGA2B</i>	1.54	-0.18	Adipose_Visceral_Omentum
rs708384	<i>ITGA2B</i>	1.63	-0.15	Lung
rs708384	<i>ITGA2B</i>	3.50	-0.14	Thyroid

Table S8 Significant GO categories overlapped in PANTHER and CPDB analyses

GO	Function	Total.genes number	Candidate.genes numl	Candidate.genes	P.value for PANTHE	P.value_CPDE
GO:005080	regulation of synapse organization	166	4	TIAM1; ADGRL1; NEURL1; ASIC2	9.01E-05	1.03E-04
GO:005080	regulation of synapse structure or activity	173	4	TIAM1; ADGRL1; NEURL1; ASIC2	1.06E-04	1.32E-04
GO:005196	regulation of nervous system development	866	7	FZD2; NEURL1; ASIC2; TIAM1; ADGRL1; GRIP1; DRAXIN	1.76E-04	1.72E-04
GO:009879	postsynapse	466	5	GRIP1; TIAM1; NEURL1; ASIC2	4.78E-04	4.47E-03
GO:005196	positive regulation of nervous system development	509	5	GRIP1; TIAM1; ADGRL1; NEURL1; ASIC2	7.12E-04	7.64E-04
GO:004866	neuron development	783	6	FZD2; NEURL1; CNGB1; TIAM1; FAT4; GRIP1; DRAXIN	7.29E-04	8.20E-04
GO:200002	regulation of multicellular organismal development	1905	9	FZD2; NEURL1; ITGA2B; ADGRL1; ASIC2; TIAM1; FAT4; GRIP1; DRAXIN	9.99E-04	1.37E-03
GO:005123	regulation of multicellular organismal process	2904	11	FZD2; NEURL1; ITGA2B; ADGRL1; ASIC2; TIAM1; FAT4; GRIP1; NOS1AP; DRAXIN	1.49E-03	6.78E-03
GO:005079	regulation of developmental process	2452	10	FZD2; NEURL1; ITGA2B; ADGRL1; ASIC2; TIAM1; FAT4; GRIP1; DRAXIN	1.51E-03	8.04E-03
GO:004319	dendritic spine	160	3	TIAM1; NEURL1; ASIC2	1.53E-03	1.55E-03
GO:004430	neuron spine	162	3	TIAM1; NEURL1; ASIC2	1.59E-03	1.61E-03
GO:000715	heterophilic cell-cell adhesion via plasma membrane cell adhesion mole	45	2	ADGRL1; FAT4	1.91E-03	2.89E-03
GO:006011	inner ear receptor cell development	46	2	FZD2; FAT4	2.00E-03	1.66E-03
GO:000760	phototransduction	46	2	CNGB1; ASIC2	2.00E-03	3.81E-03
GO:003018	neuron differentiation	963	6	FZD2; NEURL1; CNGB1; TIAM1; FAT4; GRIP1; DRAXIN	2.11E-03	2.72E-03
GO:004222	response to cocaine	53	2	EFTUD2; TIAM1	2.63E-03	2.68E-03
GO:005171	cellular response to stimulus	6433	17	GRIP1; FZD2; UBQLN1; NEURL1; CNGB1; ITGA2B; ADGRL1; ASIC2; EFTUD2; TIAM1; MACROD2	2.66E-03	2.72E-02
GO:000739	nervous system development	2245	9	FZD2; NEURL1; CNGB1; ADGRL1; NHSL1; ASIC2; TIAM1; MACROD2; FAT4; GRIP1; DRAXIN	3.16E-03	3.09E-04
GO:004249	mechanoreceptor differentiation	61	2	FZD2; FAT4	3.46E-03	3.69E-03
GO:000958	detection of light stimulus	61	2	CNGB1; ASIC2	3.46E-03	5.55E-03
GO:005196	positive regulation of synapse assembly	65	2	ADGRL1; ASIC2	3.92E-03	4.44E-03
GO:004869	generation of neurons	1470	7	FZD2; NEURL1; CNGB1; NHSL1; TIAM1; FAT4; GRIP1; DRAXIN	3.95E-03	1.00E-03
GO:000716	signal transduction	4878	14	GRIP1; FZD2; UBQLN1; NEURL1; CNGB1; ITGA2B; ADGRL1; ASIC2; TIAM1; FAT4; GRN; KSR2; N	3.99E-03	2.32E-02
GO:009859	plasma membrane region	1098	6	NEURL1; CNGB1; TIAM1; ADGRL1; GRIP1; NOS1AP	4.05E-03	4.67E-03
GO:001406	postsynaptic density	229	3	TIAM1; NEURL1	4.20E-03	4.58E-02
GO:009957	postsynaptic specialization	231	3	TIAM1; NEURL1	4.30E-03	4.65E-02
GO:003227	asymmetric synapse	234	3	TIAM1; NEURL1	4.46E-03	4.76E-02
GO:009898	neuron to neuron synapse	238	3	TIAM1; NEURL1	4.68E-03	4.87E-02
GO:002200	neurogenesis	1562	7	FZD2; NEURL1; CNGB1; NHSL1; TIAM1; FAT4; GRIP1; DRAXIN	5.51E-03	1.55E-03
GO:004846	cell development	1562	7	FZD2; NEURL1; CNGB1; TIAM1; FAT4; GRIP1; DRAXIN	5.51E-03	2.86E-02
GO:007234	response to anesthetic	78	2	EFTUD2; TIAM1	5.58E-03	5.55E-03
GO:015003	distal axon	267	3	CNGB1; TIAM1; ADGRL1	6.42E-03	7.50E-03
GO:005196	regulation of synapse assembly	86	2	ADGRL1; ASIC2	6.73E-03	7.60E-03
GO:005124	positive regulation of multicellular organismal process	1655	7	NEURL1; ASIC2; TIAM1; ADGRL1; GRIP1; NOS1AP	7.53E-03	2.50E-02

Table S9 Pathway analysis

gene_set_id	gene_set_name	p-value
REACTOME:R-HSA-373760	LICAM interactions	2.49E-06
REACTOME:R-HSA-190873	Gap junction degradation	3.90E-05
REACTOME:R-HSA-112308	Presynaptic depolarization and calcium channel opening	5.51E-05
REACTOME:R-HSA-5423646	Aflatoxin activation and detoxification	5.90E-05
REACTOME:R-HSA-437239	Recycling pathway of L1	7.37E-05
REACTOME:R-HSA-196025	Formation of annular gap junctions	1.41E-04
REACTOME:R-HSA-373752	Netrin-1 signaling	2.38E-04
REACTOME:R-HSA-381753	Olfactory Signaling Pathway	2.64E-04
REACTOME:R-HSA-428542	Regulation of commissural axon pathfinding by SLIT and ROBO	5.65E-04
REACTOME:R-HSA-3928665	EPH-ephrin mediated repulsion of cells	7.06E-04
REACTOME:R-HSA-2682334	EPH-Ephrin signaling	8.82E-04
REACTOME:R-HSA-157858	Gap junction trafficking and regulation	8.95E-04
KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY_ARVC	Arrhythmogenic right ventricular cardiomyopathy (ARVC)	1.01E-04
KEGG_ONE_CARBON_POOL_BY_FOLATE	One carbon pool by folate	2.07E-04
KEGG_CARDIAC_MUSCLE_CONTRACTION	Cardiac muscle contraction	4.39E-04
KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM	Hypertrophic cardiomyopathy (HCM)	7.33E-04

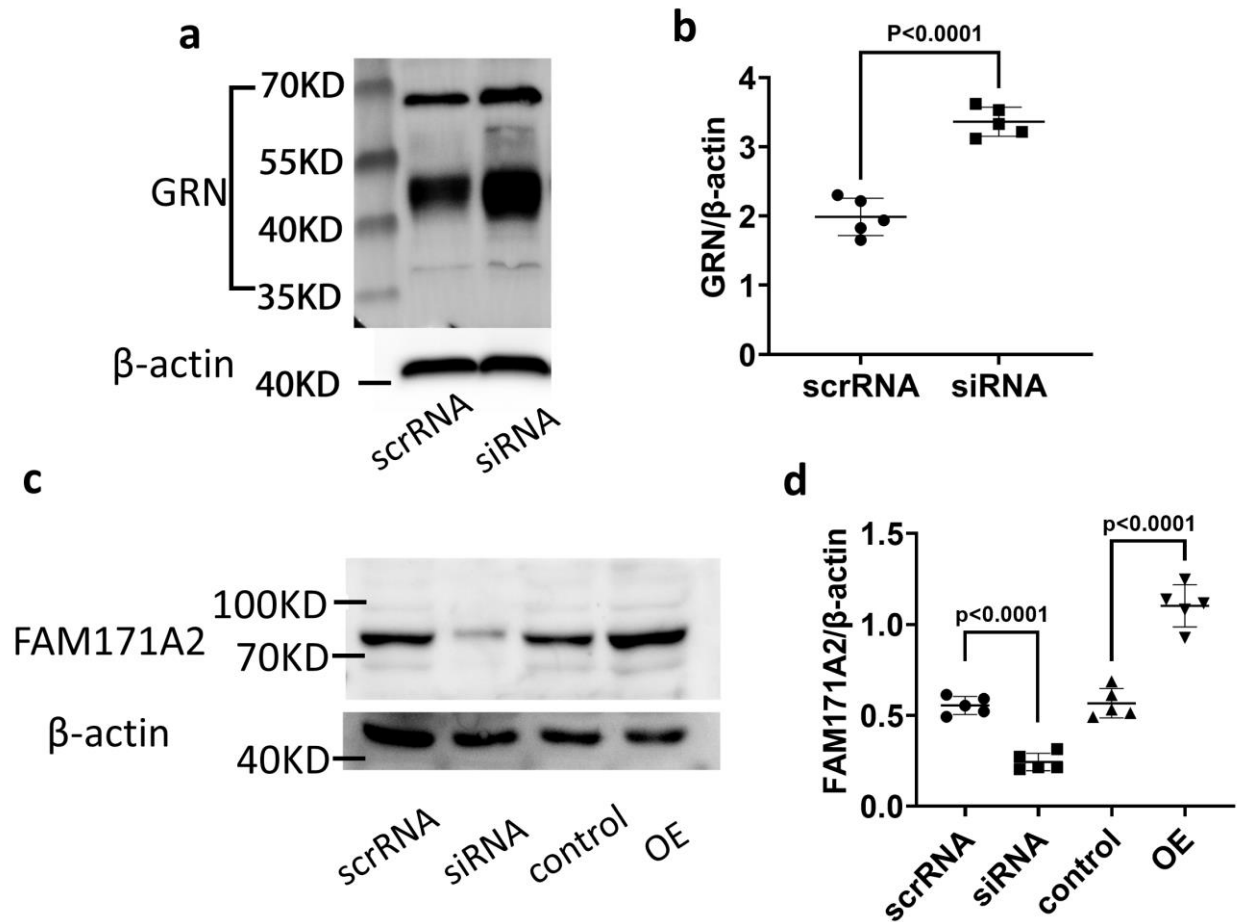


Figure S4 Knockdown of FAM171A2 stimulates intracellular GRN expression. a, b The intracellular expression of GRN. n = 5 per group. The data was analyzed by the t-test ($p < 0.0001$). c, d The efficiency of FAM171A2 siRNA and over-expression (OE). n = 5 per group. The data was analyzed by one-way ANOVA ($p < 0.0001$), followed by Tukey post hoc test ($p < 0.0001$ scrRNA vs siRNA; $p < 0.0001$ control vs OE).

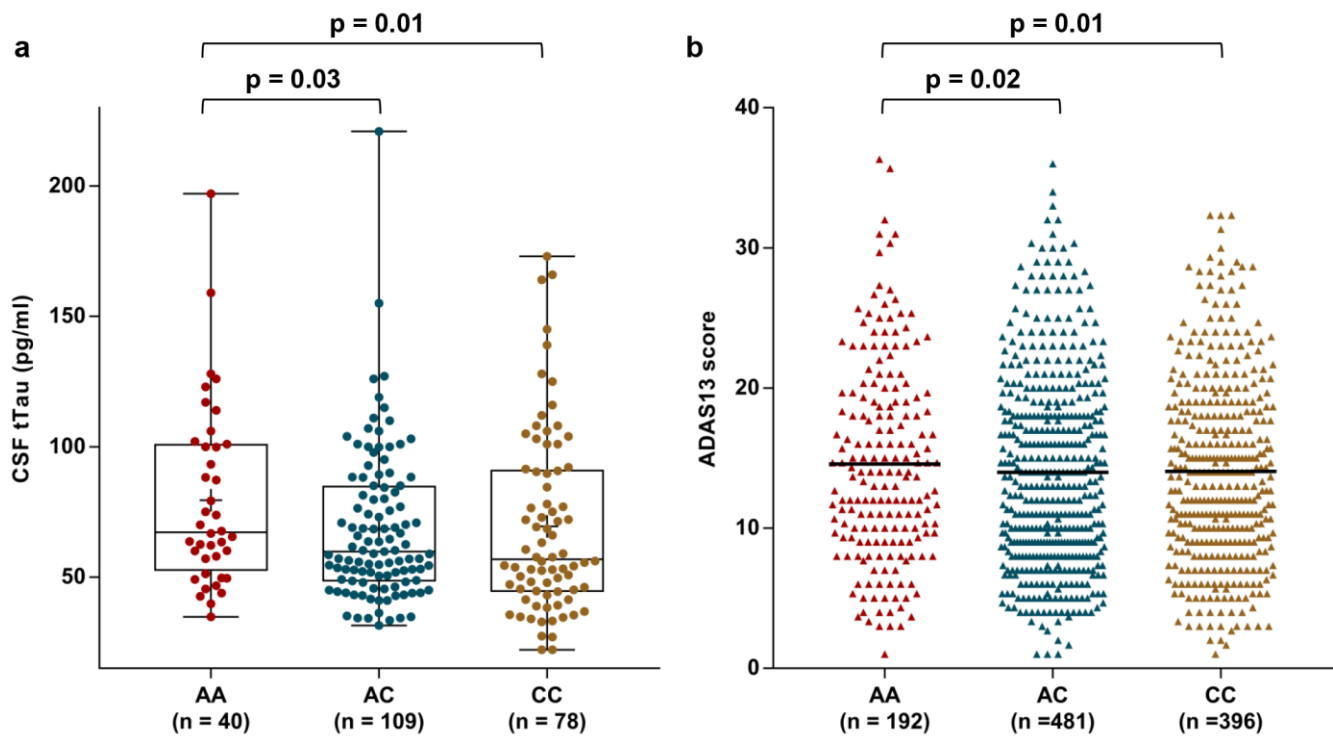


Figure S5 Association of rs708384 genotype with global cognition and CSF tau levels. The ‘AA’ genotype of the rs708384 was significantly associated with higher CSF tau levels in HC population (a) and poorer global cognition in total (b)

Table S10 Variants tagged by top SNP and susceptibility of neurodegenerative diseases

SNP	Position	Effect allele	Other allele	<i>p</i> value for AD*	<i>p</i> value for PD[#]	<i>p</i> value for ALS[#]	<i>p</i> value for FTD[#]
rs708384	17:42437682	A	C	<0.05	1.42e-05	>0.05	0.04
rs708383	17:42437754	A	G	<0.05	1.35e-05	NA	NA
rs850737	17:42443784	C	T	<0.05	3.41e-06	>0.05	0.04
rs850736	17:42446420	C	G	<0.05	<0.05	NA	NA
rs850734	17:42449025	G	C	<0.05	<0.05	NA	NA
rs5910	17:42449789	A	G	<0.05	2.51e-06	NA	0.04
rs850733	17:42451305	A	G	<0.01	3.00e-06	NA	NA
rs5911	17:42453065	C	A	<0.05	2.69e-06	NA	0.04
rs850732	17:42454243	T	C	<0.05	2.33e-06	NA	NA
rs850730	17:42454463	C	G	<0.05	<0.05	NA	0.04
rs850729	17:42454806	T	C	<0.05	2.49e-06	NA	NA

Significant associations with $p < 0.05$ were bolded. Beta, overall estimated effect size for the effect allele; SE, overall standard error for effect size estimate; *p* value, meta-analysis *p* value using regression coefficients (beta and standard error). Beta is the regression coefficient, based on the effect allele using an additive model. Position, chromosome 17 (GRCh37); Beta > 0 and Beta < 0 means that this effect allele increases and reduces AD risk, respectively. None of these variants were identified in stage 1+2 GWAS.

*IGAP stage-1 GWAS; the above loci cannot be found in stage-2 GWAS.

Meta *p* values in previous GWAS for PD, ALS, and FTD [14-16].