

Supplementary Material

Association of candidate genetic variants and circulating levels of ApoE/ApoJ with common neuroimaging features of Cerebral Amyloid Angiopathy

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Supplemental Table 1.

	Global Population *	Study Population
ABCA7 rs3764650 (G allele, MAF)	0.20	0.23
ABCA7 rs4147929 (A allele, MAF)	0.18	0.44
ACE rs4311 (A allele, MAF)	0.33	0.79
BIN1 rs6733839 (T allele, MAF)	0.40	0.58
BIN1 rs744373 (G allele, MAF)	0.36	0.46
CD2AP rs10948363 (G allele, MAF)	0.19	0.49
CD2AP rs9349407 (C allele, MAF)	0.19	0.49
CD33 rs3865444 (A allele, MAF)	0.21	0.47
CLU rs11136000 (T allele, MAF)	0.38	0.37
CLU rs7012010 (C allele, MAF)	0.33	0.55
CLU rs9331888 (G allele, MAF)	0.33	0.44
CLU rs9331896 (C allele, MAF)	0.38	0.63
CR1 rs6656401 (A allele, MAF)	0.07	0.29
CR1 rs6701713 (A allele, MAF)	0.25	0.31
EPHA1 rs11767557 (C allele, MAF)	0.20	0.28
EPHA1 rs11771145 (A allele, MAF)	0.43	0.51

HLA-DRB5/HLA-DRB1 rs9271192 (C allele, MAF)	0.24	0.41
MS4A4A-MS4A6A rs4938933 (C allele, MAF)	0.38	0.76
MS4A4A-MS4A6A rs983392 (G allele, MAF)	0.23	0.75
PICALM rs10792832 (A allele, MAF)	0.31	0.44
PICALM rs3851179 (T allele, MAF)	0.31	0.56
PTK2B rs28834970 (C allele, MAF)	0.32	0.64
SORL1 rs11218343 (C allele, MAF)	0.11	0.05
TREM1 rs6910730 (G allele, MAF)	0.27	0.26
TREM2 rs75932628 (T allele, MAF)	< 0.01	< 0.01
TREML2 rs3747742 (C allele, MAF)	0.31	0.52

ST1. Allelic frequency of minor alleles in Global Population and the Population studied. MAF: Minor allele frequency. Data are expressed as frequency per 1. *Global Population MAF was obtained from 1000 Genome Project phase 3 (Auton et al., 2015).

Supplemental Table 2

	cSS	cSS extent	CSO-EPVS	CSO-EPVS degree	BG-EPVS	BG-EPVS degree	Lobar CMB	Lobar CMB >5	WMH deep burden	WMH PV burden	Atrophy	CAA-SVD burden score (low vs. high)
Sex	0.635	0.758	0.111	0.876	0.16	0.144	0.584	0.473	0.252	0.078	0.473	0.753
Age	0.946	0.256	0.538	0.282	0.669	0.086	0.759	0.458	0.173	0.126	0.144	0.483
HT	0.972	0.228	0.311	0.678	1	0.691	0.723	0.565	0.739	0.276	0.989	0.629
DM	0.233	0.647	0.561	0.438	0.686	0.304	0.229	0.076	0.962	0.682	0.401	0.183
DL	1.000	0.822	0.895	0.827	0.764	0.322	0.218	0.300	0.441	0.524	0.703	0.591
ABCA7 rs3764650 (G allele, MA)	0.143	1.000	0.614	0.215	0.495	0.593	0.009	0.029	0.488	0.229	0.079	0.013
ABCA7 rs4147929 (A allele, MA)	0.630	0.133	0.663	0.502	0.653	0.789	0.013	0.079	0.992	0.227	0.017	0.132
ACE rs4311 (T allele, MA)	0.684	0.570	0.648	0.446	0.487	0.481	0.988	0.31	0.958	0.467	0.949	0.855
BIN1 rs6733839 (T allele, MA)	0.837	0.927	0.128	0.973	0.878	0.832	0.639	0.656	0.088	0.721	0.032	0.748
BIN1 rs744373 (G allele, MA)	0.328	0.641	0.201	0.425	0.523	0.447	0.462	0.565	0.146	0.421	0.117	0.964

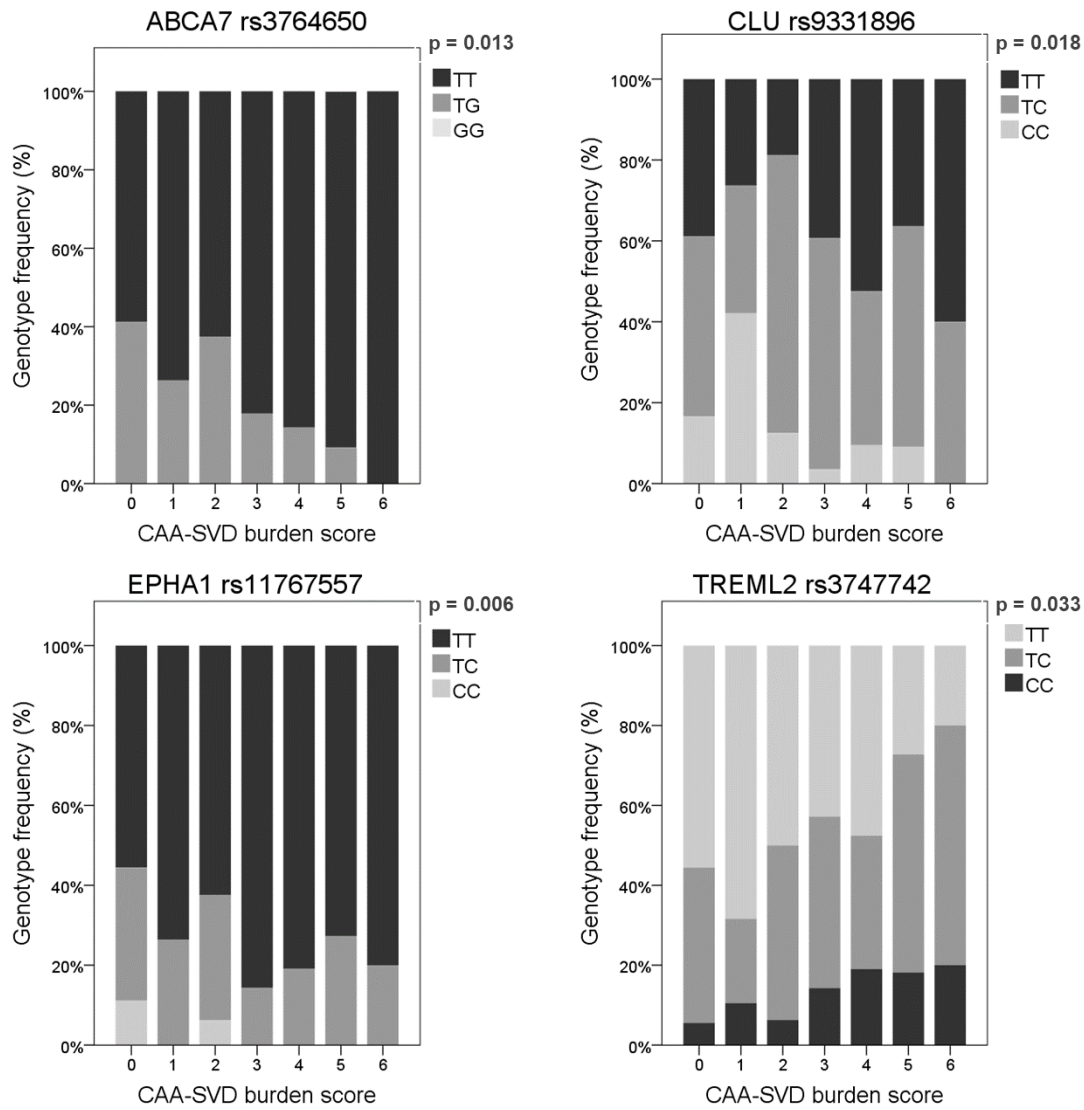
CD2AP rs10948363 (G allele, MA)	0.180	0.008	0.622	0.416	0.503	0.585	0.710	0.329	0.430	0.813	0.013	0.597
CD2AP rs9349407 (C allele, MA)	0.180	0.008	0.622	0.416	0.503	0.585	0.710	0.329	0.430	0.813	0.013	0.597
CD33 rs3865444 (A allele, MA)	0.729	0.302	0.611	0.036	0.92	0.005	0.090	0.317	0.468	0.489	0.591	0.676
CLU rs11136000 (T allele, MA)	0.046	0.031	0.305	0.176	0.84	0.113	0.139	0.017	0.090	0.009	0.198	0.006
CLU rs7012010 (C allele, MA)	0.559	0.146	0.672	0.025	0.694	0.176	0.034	0.142	0.937	0.321	0.009	0.101
CLU rs9331888 (G allele, MA)	0.033	0.852	0.300	0.274	0.136	0.844	0.714	0.120	0.010	0.020	0.534	0.023
CLU rs9331896 (C allele, MA)	0.041	0.042	0.235	0.248	0.91	0.264	0.149	0.028	0.147	0.010	0.417	0.006
CR1 rs6656401 (A allele, MA)	0.331	0.601	0.260	0.315	0.216	0.153	0.527	0.373	0.290	0.990	0.612	0.786
CR1 rs6701713 (A allele, MA)	0.299	0.201	0.279	0.671	0.385	0.567	0.397	0.503	0.043	0.360	0.761	0.491
EPHA1 rs11767557 (C allele, MA)	0.043	0.272	0.784	0.881	0.544	0.98	0.308	0.305	0.072	0.124	0.520	0.012
EPHA1 rs11771145 (A allele, MA)	0.813	0.496	0.924	0.406	0.606	0.476	0.480	0.916	0.101	0.541	0.432	0.062
HLA- DRB5/HLA- DRB1 rs9271192 (C allele, MA)	0.663	0.691	0.796	0.721	0.653	0.789	0.469	0.292	0.992	0.728	0.411	0.533
MS4A4A- MS4A6A rs4938933 (C allele, MA)	0.491	0.598	0.992	0.572	0.936	0.844	0.748	0.784	0.739	0.582	0.784	0.496
MS4A4A- MS4A6A rs983392 (G allele, MA)	0.184	0.479	0.715	0.903	0.901	0.348	0.666	0.869	0.945	0.721	0.869	0.764
PICALM rs10792832 (A allele, MA)	0.366	0.532	0.392	0.706	0.737	0.863	0.764	0.922	0.318	0.778	0.179	0.809
PICALM rs3851179 (T allele, MA)	0.432	0.532	0.346	0.628	0.772	0.811	0.674	0.78	0.394	0.863	0.244	0.712
PTK2B rs28834970 (C allele, MA)	0.533	0.109	0.671	0.090	0.672	0.198	0.995	0.614	0.791	0.478	0.959	0.503
SORL1 rs11218343 (C allele, MA)	0.246	1.000	1.000	0.194	1	1	0.242	0.415	0.031	0.031	1.000	0.412
TREM1 rs6910730 (G allele, MA)	0.314	0.426	0.442	0.964	1	0.22	0.492	0.594	0.658	0.165	0.181	0.430
TREM2 rs75932628 (T allele, MA)	1.000	-	0.254	1.000	1	1	0.420	1	0.466	1.000	0.373	0.449
TREML2 rs3747742 (C allele, MA)	0.284	0.716	0.828	0.930	0.737	0.863	0.039	0.013	0.472	0.253	0.500	0.023
APOEε2	0.306	0.713	0.359	0.862	0.446	0.205	0.725	0.933	0.286	0.320	0.561	0.097

Supplementary Material

APOEε4	0.468	0.705	0.395	0.176	1	0.771	0.459	0.434	0.455	0.829	0.434	0.917
Total ApoJ (g/L)	0.282	0.571	0.888	0.620	0.608	0.820	0.711	0.953	0.364	0.432	0.107	0.858
VLDL ApoJ (μg/mmol chol)	0.815	1.000	0.064	0.712	0.388	0.033	0.367	0.302	0.624	0.664	0.827	0.269
LDL ApoJ (μg/mmol chol)	0.511	0.849	0.033	0.223	0.737	0.022	0.513	0.067	0.194	0.497	0.253	0.432
HDL ApoJ (μg/mmol chol)	0.615	0.285	0.104	0.181	0.374	0.306	0.419	0.648	0.244	0.484	0.031	0.872
Total ApoE (mg/L)	0.778	0.201	0.014	0.121	0.055	0.943	0.237	0.344	0.754	0.457	0.933	0.924
VLDL ApoE (μmol / mol chol)	0.506	0.338	0.598	0.211	0.891	0.759	0.481	0.790	0.756	0.083	0.562	0.701
LDL ApoE (μmol / mol chol)	0.833	0.003	0.408	0.178	0.334	0.631	0.407	0.403	0.816	0.689	0.756	0.785
HDL ApoE (μmol / mol chol)	0.537	0.256	0.044	0.096	0.087	0.654	0.703	0.898	0.413	0.586	0.498	0.508

ST2. Association of SNPs, circulating ApoE and ApoJ levels, and demographic variables with CAA-MRI common features. The data displayed are unadjusted p-values. cSS: cortical Superficial Siderosis; distr.: distribution; EPVS: Enlarged Perivascular Spaces; BG: Basal Ganglia; CSO: Centrum Semiovale; BG: Basal Ganglia; CMB: Cerebral Microbleedings; WMH: White Matter Hyperintensity; PV: periventricular. MA: Minor Allele

Supplemental Figure 1



SF1. Genotype frequency of the SNPs associated with the CAA-SVD burden score using the additive model. The genetic risk factor associated with a higher score is represented in darker grey, whereas the protective factor is represented in lighter grey. Genotype frequency is expressed as a percentage in each category of the score (0-6).

Supplemental Table 3

		Total ApoJ (g/L) N=59	VLDL ApoJ ($\mu\text{g}/\text{mmol chol}$) N= 60	LDL ApoJ ($\mu\text{g}/\text{mmol chol}$) N=60	HDL ApoJ ($\mu\text{g}/\text{mmol chol}$) N=60
Sex	M	0.183 \pm 0.060	177.99 [113.78 – 217.36]	60.78 [4.34 – 93.81]	450.98 [0 – 881.95]
	F	0.198 \pm 0.062	198.21 [163.68 – 270.77]	88.96 [31.75 – 127.43]	756.79 [472.94 – 1048.78]
	<i>p</i>	0.369	0.070	0.104	0.127
HT	No	0.183 \pm 0.064	202.46 [136.30 – 271.21]	63.61 [10.38 – 131.55]	762.35 [472.29 – 1150.24]
	Yes	0.198 \pm 0.057	179.26 [145.10 – 230.58]	84.10 [52.14 – 118.75]	613.75 [57.84 – 901.28]
	<i>p</i>	0.363	0.247	0.680	0.145
DM	No	0.186 \pm 0.061	194.51 [143.29 – 252.64]	71.89 [25.95 – 127.25]	762.35 [239.62 – 1039.01]
	Yes	0.212 \pm 0.048	187.10 [117.76 – 252.07]	59.51 [1.01 – 111.45]	498.90 [0 – 852.09]
	<i>p</i>	0.288	0.645	0.202	0.240
DL	No	0.190 \pm 0.060	192.66 [138.30 – 235.21]	68.55 [15.77 – 119.17]	739.65 [0 – 1004.24]
	Yes	0.192 \pm 0.068	195.71 [166.46 – 292.48]	71.89 [3.85 – 141.09]	665.63 [238.65 – 971.54]
	<i>p</i>	0.876	0.405	0.633	0.887
Age	<i>r</i>	0.013	0.084	-0.183	- 0.073
	<i>p</i>	0.920	0.521	0.163	0.578

ST3. Association of demographic and clinical features with ApoJ levels. Total ApoJ is expressed as g/L and ApoJ in lipoprotein fractions is expressed as μg of ApoJ per mmol of cholesterol in each lipoprotein. A sample of total plasma with a null value was discarded. M: Male; F: Female; HT: Hypertension; DM: Diabetes Mellitus; DL: Dyslipidemia.

Supplemental Table 4

		Total ApoJ (g/L) N=59	VLDL ApoJ (µg/mmol chol) N= 60	LDL ApoJ (µg/mmol chol) N=60	HDL ApoJ (µg/mmol chol) N=60
rs11136000	C	0.189 ± 0.058	189.01 [146.14 – 260.64]	62.05 [11.04 – 125.20]	614.68 [0 – 950.47]
	T (MA)	0.200 ± 0.066	200.58 [139.71 – 268.94]	90.98 [58.70 – 123.61]	795.87 [586.48 – 1065.01]
	<i>p</i>	0.351	0.653	0.151	0.012 *
rs7012010	T	0.195 ± 0.061	190.81 [144.34 – 256.35]	78.11 [39.50 – 111.87]	751.23 [330.83 – 1028.20]
	C (MA)	0.188 ± 0.061	194.51 [144.05 – 292.48]	63.61 [9.72 – 129.29]	644.44 [0 – 971.54]
	<i>p</i>	0.554	0.551	0.657	0.241
rs9331888	C	0.195 ± 0.063	189.01 [142.53 – 267.55]	72.86 [13.57 – 127.08]	728.08 [238.65 – 977.89]
	G (MA)	0.185 ± 0.056	202.46 [161.32 – 266.45]	70.61 [42.22 – 109.06]	613.75 [13.22 – 995.16]
	<i>p</i>	0.456	0.496	0.907	0.558
rs9331896	T	0.187 ± 0.061	189.01 [145.10 – 264.09]	63.61 [12.31 – 126.14]	644.44 [13.22 – 961.01]
	C (MA)	0.203 ± 0.059	200.58 [142.53 – 267.55]	84.10 [46.50 – 122.02]	795.87 [549.54 – 1065.01]
	<i>p</i>	0.167	0.738	0.408	0.056 #

ST4. Association of CLU SNPs with ApoJ levels. Total ApoJ is expressed as g/L and ApoJ in lipoprotein fractions is expressed as µg of ApoJ per mmol of cholesterol in each lipoprotein. A sample of total plasma with a null value was discarded. MA: Minor Allele. * $p < 0.05$; # $p < 0.1$.

Supplemental Table 5

		Total ApoJ (g/L) N=40	VLDL ApoJ (µg/mmol chol) N= 40	LDL ApoJ (µg/mmol chol) N=40	HDL ApoJ (µg/mmol chol) N=40
rs11136000	C	0.184 [0.149 – 0.242]	188.70 [144.05 – 233.51]	62.05 [8.27 – 105.83]	613.75 [0 – 971.54]
	T (MA)	0.213 [0.182 – 0.253]	195.71 [136.30 – 233.80]	90.98 [58.78 – 111.45]	849.37 [592.44 – 1065.01]
	<i>p</i>	0.136	0.944	0.180	0.020 *
rs7012010	T	0.205 [0.147 – 0.244]	187.90 [136.01 – 232.05]	71.89 [47.87 – 104.94]	775.89 [35.53 – 1013.02]
	C (MA)	0.190 [0.155 – 0.244]	189.82 [149.55 – 232.05]	65.35 [11.05 – 129.29]	698.44 [0 – 975.86]
	<i>p</i>	0.867	0.450	0.983	0.719
rs9331888	C	0.205 [0.155 – 0.247]	187.898 [136.01 – 219.95]	71.89 [22.54 – 111.45]	788.84 [25.61 – 1004.09]
	G (MA)	0.181 [0.147 – 0.236]	196.63 [151.11 – 258.50]	66.33 [37.35 – 104.94]	470.71 [3.30 – 1004.09]
	<i>p</i>	0.248	0.462	0.992	0.434
rs9331896	T	0.181 [0.149 – 0.243]	183.98 [144.05 – 233.51]	62.05 [29.54 – 104.94]	614.68 [0 – 966.28]
	C (MA)	0.216 [0.190 – 0.248]	195.71 [136.89 – 225.72]	87.02 [49.80 – 111.45]	850.73 [439.07 – 1065.01]
	<i>p</i>	0.111	0.872	0.343	0.045 *

ST5. Association of CLU SNPs with ApoJ levels in samples obtained >90 days after ICH. Total ApoJ is expressed as g/L and ApoJ in lipoprotein fractions is expressed as µg of ApoJ per mmol of cholesterol in each lipoprotein. MA: Minor Allele. * $p < 0.05$.

Supplemental Table 6

CAA		Total ApoE (mg/L) N=59	VLDL ApoE ($\mu\text{mol} / \text{mol}$ chol) N= 60	LDL ApoE ($\mu\text{mol} / \text{mol}$ chol) N= 60	HDL ApoE ($\mu\text{mol} / \text{mol}$ chol) N= 60
Sex	M	45.39 \pm 19.25	345.16 [162.16 – 691.93]	28.93 [12.20 – 43.99]	318.35 \pm 202.17
	F	46.33 \pm 15.51	274.69 [90.13 – 657.25]	46.12 [25.74 – 64.51]	354.98 \pm 225.31
	<i>p</i>	0.839	0.524	0.056	0.532
HT	No	42.75 \pm 11.30	366.44 [153.65 – 704.21]	39.99 [19.45 – 68.49]	353.13 \pm 223.92
	Yes	50.50 \pm 20.51	290.92 [159.67 – 634.64]	35.22 [19.88 – 56.65]	325.49 \pm 215.99
	<i>p</i>	0.086	0.950	0.732	0.634
DM	No	46.37 \pm 16.91	393.67 [163.38 – 704.21]	39.44 [21.69 – 65.46]	342.40 \pm 229.57
	Yes	48.03 \pm 20.21	183.82 [138.69 – 546.96]	30.32 [14.17 – 58.79]	347.32 \pm 161.28
	<i>p</i>	0.824	0.240	0.528	0.957
DL	No	46.78 \pm 15.36	380.06 [154.16 – 696.21]	39.01 [21.12 – 58.38]	336.31 \pm 241.43
	Yes	42.23 \pm 20.47	273.11 [163.90 – 697.77]	35.22 [14.99 – 85.01]	358.35 \pm 187.84
	<i>p</i>	0.363	0.677	0.965	0.731
Age	<i>r</i>	-0.028	-0.084	-0.243	0.048
	<i>p</i>	0.834	0.523	0.061	0.716

ST6. Association of demographic and clinical features with ApoE levels. Total ApoE is expressed as mg/L and ApoE in lipoprotein fractions is expressed as μmol of ApoE per mol of cholesterol in each lipoprotein. A sample of total plasma with a null value was discarded. HT: Hypertension; DM: Diabetes Mellitus; DL: Dyslipidemia.

Supplemental Table 7

CAA		Total ApoE (mg/L) N=59	VLDL ApoE (μ mol / mol chol) N= 60	LDL ApoE (μ mol / mol chol) N= 60	HDL ApoE (μ mol / mol chol) N= 60
APOE ϵ 2	No	43.16 \pm 14.02	287.58 [143.76 – 634.64]	35.07 [17.64 – 51.61]	323.57 \pm 211.25
	Yes	67.04 \pm 21.56	407.84 [200.08 – 908.61]	67.48 [58.79 – 171.32]	477.68 \pm 219.04
	<i>p</i>	<0.001 ***	0.377	0.001 **	0.076 #
APOE ϵ 4	No	48.59 \pm 17.17	363.52 [151.26 – 697.77]	38.57 [20.21 – 67.48]	355.04 \pm 228.17
	Yes	36.82 \pm 11.73	284.09 [120.15 – 504.03]	36.76 [20.33 – 46.34]	292.80 \pm 163.54
	<i>p</i>	0.024 *	0.641	0.484	0.363

ST7. Association of ApoE genotype with ApoE levels. Total ApoE is expressed as mg/L and ApoE in lipoprotein fractions is expressed as μ mol of ApoE per mol of cholesterol in each lipoprotein. A sample of total plasma with a null value was discarded. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; # $p < 0.1$.

Supplemental Table 8

CAA		Total ApoE (mg/L) N=40	VLDL ApoE (μ mol / mol chol) N= 40	LDL ApoE (μ mol / mol chol) N= 40	HDL ApoE (μ mol / mol chol) N= 40
APOE ϵ 2	No	44.80 [33.50 – 53.80]	246.47 [149.22 – 616.76]	32.43 [20.04 – 64.51]	333.69 \pm 210.54
	Yes	61.50 [50.83 – 81.40]	580.46 [233.83 – 911.02]	93.13 [56.72 – 176.51]	491.43 \pm 236.61
	<i>p</i>	0.012 *	0.271	0.005 **	0.104
APOE ϵ 4	No	47.10 [38.28 – 59.70]	327.22 [149.22 – 719.94]	39.28 [22.93 – 91.08]	382.93 \pm 225.26
	Yes	34.30 [29.73 – 37.63]	266.97 [151.45 – 432.72]	35.41 [19.25 – 46.00]	212.39 \pm 96.62
	<i>p</i>	0.007 **	0.493	0.447	0.007 **

ST8. Association of ApoE genotype with ApoE levels in chronically obtained samples (>90 days after ICH). Total ApoE is expressed as mg/L and ApoE in lipoprotein fractions is expressed as μ mol of ApoE per mol of cholesterol in each lipoprotein. * $p < 0.05$; ** $p < 0.01$.