Supplemental Material

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I. Online Tables.

Online Table I. Deleterious effect of parenchymal hematoma in the discovery study subjects.

		In-hospital mortality (n=85)†			
	Total	**Absence**	**Presence**	**p**	**OR (95% CI)**
PH (%)	64 (5)	46 (3.9)	18 (21.2)	<0.001*	6.65 (3.65-12.1)
sICH (%)	18 (1.4)	7 (38.9)	11 (61.1)	<0.001*	25.02 (9.42-66.41)
non-sICH (%)	46 (3.7)	39 (3.3)	7 (9.5)	0.016*	3.05 (1.32-7.08)
		Mortality at 3-months (n=150)‡			
PH (%)	62 (5.1)	30 (2.8)	32 (21.3)	<0.001*	9.32 (5.47-15.89)
sICH (%)	18 (1.5)	4 (0.4)	14 (9.3)	<0.001*	27.20 (8.83-83.83)
non-sICH (%)	44 (3.7)	26 (2.5)	18 (13.2)	<0.001*	6.05 (3.22-11.36)
		Disability 3mRS >2 (n=541)‡			
PH (%)	62 (5.1)	8 (1.2)	54 (10)	<0.001*	9.17 (4.37-19.5)
sICH (%)	18 (1.5)	1 (0.1)	17 (3.1)	<0.001*	21.7 (2.88-163.62)
non-sICH (%)	44 (3.7)	7 (1)	37 (7.1)	<0.001*	7.19 (3.18-16.25)

*p-value <0.05. †In-hospital mortality was available in 1270 participants. ‡3-months modified Ranking Scale was available in 1211 patients. For categorical variables, frequencies as percentage were described.

PH: Parenchymal hematoma; sICH: Symptomatic intracerebral hemorrhage; OR: Odds-ratio. (95%CI): 95% Confidence Interval. 3mRS: 3-months modified Rankin Scale.

Online Table II. Logistic regression analysis of clinical variables regarding PH occurrence in the discovery cohort data. Only clinical variables with more than 10 cases and significantly associated in the univariate analysis were included in the logistic regression according to previous methodology of logistic regression (Perduzzi et al., 1996; Ortega Calvo et al., 2002). It is considered in logistic regression analysis that less than 10 cases in each of its possible values the estimates are not reliable (Perduzzi et al., 1996).

	Estimate	Standard Error	Z value	P value
Baseline NIHSS	-0.08	0.02	-4.19	2.75E-05
CE (No)	0.38	0.26	1.47	1.41E-01
DM (Yes)	-0.7	0.27	-2.63	8.52E-03

Online Table III. Summary statistics of the discovery, replication and meta-analysis stages.

SNP	CHR	POS	Location	Gene	EA / NEA	Absence	Presence	OR	p	p(GC)	Absence	Presence	OR	p	OR (95% CI)	p	Direction	p Het
rs77557904	2	1047076	intronic	*SNTG2*	G/C	0.05	0.15	6.56	8.62E-07	8.78E-07	0.06	0.09	2.01	0.1	3.82 (2.19-6.68)	2.43E-06	++	<0.05
rs62172138	2	77038345	intronic	*LRRTM4*	T/C	0.17	0.33	2.64	8.92E-06	9.08E-06	0.14	0.15	1.19	0.52	1.93 (1.38-2.70)	1.31E-04	++	<0.05
rs11687998	2	106384133	intronic	*NCK2*	T/C	0.20	0.37	2.76	2.48E-06	2.52E-06	0.19	0.21	0.98	0.92	1.77 (1.28-2.45)	5.15E-04	+-	<0.05
rs72824713	2	109986438	intronic	*SH3RF3*	A/G	0.07	0.15	5.38	5.68E-06	5.78E-06	0.1	0.07	0.62	0.16	1.66 (1.01-2.72)	4.55E-02	+-	<0.05
rs112541215	2	218916291	intronic	*RUFY4*	A/T	0.07	0.18	4.67	3.76E-06	3.83E-06	0.07	0.14	1.90	0.07	3.01 (1.88-4.84)	4.79E-06	++	0.06
rs35942239	3	16637561	intronic	*DAZL*	A/C	0.10	0.22	4.19	8.29E-07	8.44E-07	0.07	0.09	0.83	0.62	2.28 (1.45-3.59)	3.80E-04	+-	<0.05
rs72811500	5	160723914	intronic	*GABRB2*	A/G	0.05	0.15	5.36	3.46E-06	3.52E-06	0.09	0.11	1.34	0.41	2.62 (1.59-4.32)	1.50E-04	++	<0.05
rs980161	5	160725431	intronic	*GABRB2*	C/T	0.05	0.15	5.21	4.36E-06	4.44E-06	0.09	0.11	1.34	0.41	2.60 (1.58-4.27)	1.65E-04	++	<0.05
rs72811501	5	160725911	intronic	*GABRB2*	C/A	0.05	0.15	5.45	2.77E-06	2.82E-06	0.09	0.11	1.34	0.41	2.65 (1.61-4.36)	1.32E-04	++	<0.05
rs72813504	5	160728749	intronic	*GABRB2*	C/T	0.05	0.15	5.78	1.64E-06	1.67E-06	0.09	0.11	1.34	0.41	2.70 (1.63-4.46)	1.05E-04	++	<0.05
rs72813505	5	160730811	intronic	*GABRB2*	T/C	0.05	0.15	5.58	2.19E-06	2.23E-06	0.1	0.11	1.32	0.43	2.65 (1.61-4.37)	1.27E-04	++	<0.05
rs111707489	5	160734952	intronic	*GABRB2*	A/G	0.06	0.16	4.78	6.42E-06	6.54E-06	0.12	0.11	1.17	0.65	2.32 (1.44-3.74)	5.74E-04	++	<0.05
rs112594362	5	160737314	intronic	*GABRB2*	C/T	0.06	0.16	4.72	7.14E-06	7.27E-06	0.12	0.11	1.17	0.65	2.31 (1.43-3.72)	6.01E-04	++	<0.05
rs72813508	5	160740393	intronic	*GABRB2*	A/G	0.06	0.16	5.25	2.42E-06	2.46E-06	0.12	0.11	1.18	0.63	2.42 (1.49-3.92)	3.34E-04	++	<0.05
rs72813510	5	160741355	intronic	*GABRB2*	G/A	0.06	0.16	4.72	7.14E-06	7.27E-06	0.12	0.11	1.17	0.65	2.31 (1.43-3.72)	6.01E-04	++	<0.05
rs72813511	5	160741696	intronic	*GABRB2*	G/C	0.06	0.16	4.72	7.14E-06	7.27E-06	0.12	0.11	1.17	0.65	2.31 (1.43-3.72)	6.01E-04	++	<0.05
rs113801494	5	160743772	intronic	*GABRB2*	C/T	0.06	0.16	4.72	7.14E-06	7.27E-06	0.12	0.11	1.17	0.65	2.31 (1.43-3.72)	6.01E-04	++	<0.05
rs72813513	5	160745005	intronic	*GABRB2*	C/T	0.06	0.16	4.72	7.14E-06	7.27E-06	0.12	0.11	1.17	0.65	2.31 (1.43-3.72)	6.01E-04	++	<0.05
rs72813515	5	160748460	intronic	*GABRB2*	T/C	0.06	0.16	4.72	7.14E-06	7.27E-06	0.12	0.11	1.17	0.65	2.31 (1.43-3.72)	6.01E-04	++	<0.05
rs80343625	5	160752739	intronic	*GABRB2*	T/C	0.06	0.16	4.72	7.14E-06	7.27E-06	0.12	0.11	1.17	0.65	2.31 (1.43-3.72)	6.01E-04	++	<0.05
rs10068979	5	160755605	intronic	*GABRB2*	T/C	0.06	0.16	4.69	7.64E-06	7.78E-06	0.12	0.11	1.17	0.65	2.30 (1.43-3.71)	6.20E-04	++	<0.05
rs10052351	5	160757462	intronic	*GABRB2*	C/T	0.06	0.16	4.69	7.64E-06	7.78E-06	0.12	0.11	1.15	0.67	2.29 (1.42-3.68)	6.80E-04	++	<0.05

rs10060079	5	160759046	intronic	*GABRB2*	A/G	0.06	0.16	4.69	7.64E-06	7.78E-06	0.12	0.11	1.17	0.65	2.30 (1.43-3.71)	6.20E-04	++	<0.05
rs112795377	5	160759105	intronic	*GABRB2*	A/G	0.06	0.16	4.72	7.14E-06	7.27E-06	0.12	0.11	1.17	0.65	2.31 (1.43-3.72)	6.01E-04	++	<0.05
rs10060148	5	160759144	intronic	*GABRB2*	A/G	0.06	0.16	4.69	7.64E-06	7.78E-06	0.12	0.11	1.15	0.67	2.29 (1.42-3.68)	6.80E-04	++	<0.05
rs72817451	5	161164047	intergenic	*GABRA1*	G/A	0.05	0.15	4.97	9.57E-06	9.74E-06	0.11	0.12	1.56	0.19	2.67 (1.64-4.36)	8.10E-05	++	<0.05
rs72817454	5	161166243	intergenic	*GABRA1*	G/A	0.05	0.15	4.97	9.57E-06	9.74E-06	0.11	0.12	1.56	0.19	2.67 (1.64-4.36)	8.10E-05	++	<0.05
rs72817470	5	161219798	intergenic	*GABRA1*	T/C	0.05	0.13	5.58	9.48E-06	9.65E-06	0.11	0.13	1.75	0.1	2.90 (1.75-4.80)	3.83E-05	++	<0.05
rs6932387	6	4515915	intergenic	*CDYL*	A/G	0.27	0.44	2.64	1.67E-06	1.70E-06	0.34	0.25	0.69	0.08	1.40 (1.04-1.87)	2.50E-02	+-	<0.05
rs17209853	6	45374699	intronic	*RUNX2*	T/A	0.07	0.17	4.40	8.20E-06	8.35E-06	0.12	0.06	0.71	0.33	1.83 (1.14-2.93)	1.23E-02	+-	<0.05
rs78488630	6	45376859	intronic	*RUNX2*	C/T	0.07	0.17	4.40	8.20E-06	8.35E-06	0.12	0.06	0.71	0.33	1.83 (1.14-2.93)	1.23E-02	+-	<0.05
rs75864224	6	45377777	intronic	*RUNX2*	G/A	0.07	0.17	4.36	8.95E-06	9.11E-06	0.12	0.06	0.71	0.33	1.82 (1.14-2.92)	1.26E-02	+-	<0.05
rs75988681	6	45377848	intronic	*RUNX2*	T/C	0.07	0.17	4.40	8.20E-06	8.35E-06	0.12	0.06	0.71	0.33	1.83 (1.14-2.93)	1.23E-02	+-	<0.05
rs79359769	6	45378973	intronic	*RUNX2*	G/A	0.07	0.17	4.40	8.20E-06	8.35E-06	0.12	0.06	0.71	0.33	1.83 (1.14-2.93)	1.23E-02	+-	<0.05
rs113673672	6	45380647	intronic	*RUNX2*	G/T	0.07	0.17	4.40	8.20E-06	8.35E-06	0.12	0.06	0.71	0.33	1.83 (1.14-2.93)	1.23E-02	+-	<0.05
rs76954735	6	45381082	intronic	*RUNX2*	G/A	0.07	0.17	4.40	8.20E-06	8.35E-06	0.12	0.06	0.71	0.33	1.83 (1.14-2.93)	1.23E-02	+-	<0.05
rs4413614	6	45381328	intronic	*RUNX2*	C/T	0.07	0.17	4.36	8.95E-06	9.11E-06	0.12	0.06	0.71	0.33	1.82 (1.14-2.92)	1.26E-02	+-	<0.05
rs4370348	6	45381399	intronic	*RUNX2*	T/C	0.07	0.17	4.40	8.20E-06	8.35E-06	0.12	0.06	0.71	0.33	1.83 (1.14-2.93)	1.23E-02	+-	<0.05
rs17209874	6	45381584	intronic	*RUNX2*	A/G	0.07	0.17	4.40	8.20E-06	8.35E-06	0.12	0.06	0.71	0.33	1.83 (1.14-2.93)	1.23E-02	+-	<0.05
rs77252578	6	45381770	intronic	*RUNX2*	A/T	0.07	0.17	4.40	8.20E-06	8.35E-06	0.12	0.06	0.71	0.33	1.83 (1.14-2.93)	1.23E-02	+-	<0.05
rs1004130	6	45382093	intronic	*RUNX2*	T/C	0.07	0.17	4.40	8.20E-06	8.35E-06	0.12	0.06	0.71	0.33	1.83 (1.14-2.93)	1.23E-02	+-	<0.05
rs75205636	6	45384467	intronic	*RUNX2*	A/C	0.07	0.17	4.40	8.06E-06	8.21E-06	0.12	0.06	0.71	0.33	1.83 (1.14-2.94)	1.22E-02	+-	<0.05
rs7768466	6	45385439	intronic	*RUNX2*	T/C	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs7768666	6	45385607	intronic	*RUNX2*	C/A	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs17288397	6	45385742	intronic	*RUNX2*	A/G	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs77131077	6	45386096	intronic	*RUNX2*	T/C	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs74872917	6	45387663	intronic	*RUNX2*	A/G	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs7751427	6	45389234	intronic	*RUNX2*	G/A	0.07	0.17	4.53	6.08E-06	6.19E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.97)	1.11E-02	+-	<0.05
rs7771980	6	45389289	intronic	*RUNX2*	C/T	0.07	0.17	4.53	6.08E-06	6.19E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.97)	1.11E-02	+-	<0.05
rs6921145	6	45390511	Synonymous	*RUNX2*	A/G	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05

rs3749864	6	45390733	intronic	*RUNX2*	C/G	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs11498195	6	45390949	intronic	*RUNX2*	C/G	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs3805811	6	45391654	intronic	*RUNX2*	C/G	0.07	0.17	4.54	5.93E-06	6.04E-06	0.12	0.06	0.69	0.29	1.80 (1.13-2.89)	1.41E-02	+-	<0.05
rs3792952	6	45391971	intronic	*RUNX2*	T/C	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs3828722	6	45392982	intronic	*RUNX2*	G/A	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs3828723	6	45393010	intronic	*RUNX2*	G/A	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs75870189	6	45394252	intronic	*RUNX2*	T/C	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs3805818	6	45395920	intronic	*RUNX2*	G/A	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs78645638	6	45396182	intronic	*RUNX2*	A/G	0.07	0.17	4.57	5.56E-06	5.66E-06	0.12	0.06	0.71	0.33	1.85 (1.15-2.98)	1.08E-02	+-	<0.05
rs59397804	6	45397695	intronic	*RUNX2*	A/G	0.07	0.17	4.53	5.90E-06	6.01E-06	0.12	0.06	0.73	0.36	1.87 (1.17-3.01)	9.51E-03	+-	<0.05
rs78417039	6	45399017	intronic	*RUNX2*	A/G	0.07	0.17	4.53	5.90E-06	6.01E-06	0.12	0.06	0.73	0.36	1.87 (1.17-3.01)	9.51E-03	+-	<0.05
rs17209881	6	45400146	intronic	*RUNX2*	G/A	0.07	0.17	4.53	5.90E-06	6.01E-06	0.12	0.06	0.73	0.36	1.87 (1.17-3.01)	9.51E-03	+-	<0.05
rs7750743	6	156867156	intergenic	*ARID1B*	T/G	0.05	0.13	6.19	9.38E-06	9.55E-06	0.07	0.04	0.63	0.29	2.06 (1.15-3.70)	1.56E-02	+-	<0.05
rs73179383	7	83803592	intronic	*SEMA3A*	C/T	0.06	0.17	5.05	1.95E-06	1.99E-06	0.07	0.12	2.19	**0.04**	**3.51 (2.12-5.81)**	**1.13E-06**	++	**0.11**
rs78128773	7	83805039	intronic	*SEMA3A*	A/C	0.06	0.17	5.05	1.95E-06	1.99E-06	0.07	0.12	2.19	**0.04**	**3.51 (2.12-5.81)**	**1.13E-06**	++	**0.11**
rs7808707	7	83805716	intronic	*SEMA3A*	C/T	0.06	0.17	5.05	1.95E-06	1.99E-06	0.07	0.12	2.19	**0.04**	**3.51 (2.12-5.81)**	**1.13E-06**	++	**0.11**
rs77933839	7	83808925	intronic	*SEMA3A*	A/T	0.06	0.17	5.05	1.95E-06	1.99E-06	0.07	0.12	2.19	**0.04**	**3.51 (2.12-5.81)**	**1.13E-06**	++	**0.11**
rs76623058	7	83809657	intronic	*SEMA3A*	G/T	0.06	0.17	5.05	1.95E-06	1.99E-06	0.07	0.12	2.19	**0.04**	**3.51 (2.12-5.81)**	**1.13E-06**	++	**0.11**
rs77423492	7	83810623	intronic	*SEMA3A*	C/T	0.06	0.17	5.05	1.95E-06	1.99E-06	0.07	0.12	2.19	**0.04**	**3.51 (2.12-5.81)**	**1.13E-06**	++	**0.11**
rs9642178	7	83814352	intronic	*SEMA3A*	C/T	0.06	0.17	5.05	1.95E-06	1.99E-06	0.07	0.12	2.19	**0.04**	**3.51 (2.12-5.81)**	**1.13E-06**	++	**0.11**
rs10256270	7	83821402	intronic	*SEMA3A*	G/A	0.06	0.17	5.05	1.95E-06	1.99E-06	0.07	0.12	2.19	**0.04**	**3.51 (2.12-5.81)**	**1.13E-06**	++	**0.11**
rs73179400	7	83827813	Upstream	*SEMA3A*	T/C	0.06	0.17	5.05	1.95E-06	1.99E-06	0.07	0.12	2.19	**0.04**	**3.51 (2.12-5.81)**	**1.13E-06**	++	**0.11**
rs73181306	7	83836989	intronic	*SEMA3A*	C/T	0.06	0.17	5.07	1.87E-06	1.90E-06	0.07	0.12	2.19	**0.04**	**3.51 (2.12-5.83)**	**1.10E-06**	++	**0.11**
rs7804323	7	83837045	intronic	*SEMA3A*	T/C	0.06	0.18	5.59	2.51E-07	2.56E-07	0.07	0.13	2.06	0.05	3.57 (2.19-5.83)	3.62E-07	++	<0.05
rs1962779	7	83837734	intronic	*SEMA3A*	C/G	0.17	0.32	2.94	2.77E-06	2.82E-06	0.2	0.34	2.00	**3.34E-03**	**2.43 (1.76-3.37)**	**7.85E-08**	++	**0.25**
rs73181369	7	83838055	intronic	*SEMA3A*	C/T	0.06	0.17	5.05	1.96E-06	2.00E-06	0.07	0.12	2.09	0.06	3.42 (2.07-5.65)	1.68E-06	++	0.09
rs73181375	7	83841037	intronic	*SEMA3A*	A/G	0.06	0.17	5.05	1.96E-06	2.00E-06	0.07	0.12	1.95	0.08	3.29 (2.00-5.42)	2.90E-06	++	0.06
rs12333631	7	83847574	intronic	*SEMA3A*	A/T	0.06	0.17	4.95	2.40E-06	2.44E-06	0.07	0.12	2.04	0.06	3.34 (2.03-5.50)	2.24E-06	++	0.08

rs7802925	7	83857204	intronic	*SEMA3A*	C/T	0.06	0.18	5.30	7.29E-07	7.42E-07	0.07	0.14	2.39	**0.02**	**3.69 (2.26-6.04)**	**1.94E-07**	++	**0.11**
rs73181392	7	83860527	intronic	*SEMA3A*	C/T	0.06	0.17	5.35	1.14E-06	1.16E-06	0.07	0.12	2.04	0.06	3.46 (2.09-5.72)	1.40E-06	++	0.06
rs10264700	7	83862435	intronic	*SEMA3A*	T/C	0.06	0.18	5.78	1.85E-07	1.88E-07	0.08	0.13	1.86	0.09	3.40 (2.09-5.53)	7.92E-07	++	<0.05
rs149766679	7	83870566	intronic	*SEMA3A*	T/C	0.06	0.17	5.42	1.00E-06	1.02E-06	0.07	0.12	2.04	0.06	3.48 (2.10-5.75)	1.28E-06	++	0.06
rs28884542	7	83873691	intronic	*SEMA3A*	A/G	0.06	0.17	5.42	1.00E-06	1.02E-06	0.07	0.12	2.04	0.06	3.48 (2.10-5.75)	1.28E-06	++	0.06
rs977752	7	83881990	intronic	*SEMA3A*	T/C	0.06	0.17	5.42	1.00E-06	1.02E-06	0.07	0.12	2.04	0.06	3.48 (2.10-5.75)	1.28E-06	++	0.06
rs73183125	7	83882827	intronic	*SEMA3A*	T/C	0.05	0.14	5.55	6.78E-06	6.90E-06	0.07	0.13	2.43	**0.02**	**3.68 (2.16-6.26)**	**1.68E-06**	**++**	**0.13**
rs1356804	7	83885441	intronic	*SEMA3A*	C/T	0.06	0.17	5.43	9.74E-07	9.92E-07	0.07	0.12	2.04	0.06	3.48 (2.10-5.76)	1.26E-06	++	0.06
rs73185111	7	83897777	intronic	*SEMA3A*	T/G	0.06	0.17	4.56	5.57E-06	5.67E-06	0.07	0.12	1.89	0.09	3.08 (1.88-5.03)	7.36E-06	++	0.08
rs28397702	7	83899831	intronic	*SEMA3A*	C/T	0.06	0.17	4.45	7.36E-06	7.49E-06	0.07	0.12	1.89	0.09	3.04 (1.86-4.96)	8.90E-06	++	0.09
rs10224865	7	83900221	intronic	*SEMA3A*	T/G	0.06	0.17	5.26	1.38E-06	1.40E-06	0.07	0.12	2.04	0.06	3.43 (2.07-5.67)	1.59E-06	++	0.07
rs58835109	7	83901404	intronic	*SEMA3A*	C/T	0.06	0.17	5.42	1.00E-06	1.02E-06	0.07	0.12	2.04	0.06	3.48 (2.10-5.75)	1.28E-06	++	0.06
rs73185120	7	83903085	intronic	*SEMA3A*	T/C	0.06	0.17	5.26	1.38E-06	1.40E-06	0.07	0.12	2.04	0.06	3.43 (2.07-5.67)	1.59E-06	++	0.07
rs76691117	7	83908179	intronic	*SEMA3A*	G/A	0.06	0.17	4.38	8.59E-06	8.74E-06	0.07	0.12	1.89	0.09	3.02 (1.85-4.92)	9.86E-06	++	0.09
rs73185127	7	83909859	intronic	*SEMA3A*	A/G	0.06	0.17	5.32	1.20E-06	1.22E-06	0.07	0.12	2.04	0.06	3.45 (2.08-5.70)	1.44E-06	++	0.06
rs1006795	7	83911148	intronic	*SEMA3A*	A/G	0.06	0.17	4.33	9.75E-06	9.93E-06	0.07	0.12	1.89	0.09	3.00 (1.84-4.89)	1.08E-05	++	0.10
rs6978737	7	83911749	intronic	*SEMA3A*	C/T	0.06	0.17	4.33	9.75E-06	9.93E-06	0.07	0.12	1.89	0.09	3.00 (1.84-4.89)	1.08E-05	++	0.10
rs73185135	7	83916111	intronic	*SEMA3A*	A/G	0.06	0.17	5.25	1.40E-06	1.43E-06	0.07	0.12	2.04	0.06	3.43 (2.07-5.66)	1.60E-06	++	0.07
rs6972377	7	83923643	intronic	*SEMA3A*	T/A	0.06	0.17	5.16	1.66E-06	1.69E-06	0.07	0.12	2.04	0.06	3.40 (2.06-5.62)	1.78E-06	++	0.07
rs6953184	7	83923740	intronic	*SEMA3A*	A/C	0.06	0.17	5.16	1.66E-06	1.69E-06	0.07	0.12	2.04	0.06	3.40 (2.06-5.62)	1.78E-06	++	0.07
rs149386527	7	83928114	intronic	*SEMA3A*	T/A	0.06	0.18	4.74	2.46E-06	2.50E-06	0.07	0.12	1.89	0.09	3.16 (1.94-5.15)	3.85E-06	++	0.07
rs10258884	7	83931034	intronic	*SEMA3A*	T/C	0.06	0.18	5.44	5.93E-07	6.04E-07	0.07	0.12	1.82	0.11	3.30 (2.01-5.42)	2.25E-06	++	<0.05
rs17158818	7	83931950	intronic	*SEMA3A*	A/G	0.06	0.18	5.53	4.97E-07	5.06E-07	0.07	0.12	2.04	0.06	3.54 (2.15-5.84)	7.15E-07	++	0.05
rs6949774	7	83934959	intronic	*SEMA3A*	T/C	0.06	0.18	5.53	4.97E-07	5.06E-07	0.07	0.12	2.04	0.06	3.54 (2.15-5.84)	7.15E-07	++	0.05
rs73189024	7	83942573	intronic	*SEMA3A*	T/C	0.06	0.17	5.02	2.34E-06	2.38E-06	0.07	0.12	2.04	0.06	3.35 (2.03-5.53)	2.27E-06	++	0.08
rs17158848	7	83950725	intronic	*SEMA3A*	A/T	0.06	0.16	4.60	8.84E-06	9.00E-06	0.07	0.12	2.04	0.06	3.19 (1.93-5.27)	6.19E-06	++	0.12
rs73189039	7	83953457	intronic	*SEMA3A*	A/G	0.06	0.16	4.69	7.23E-06	7.36E-06	0.07	0.12	2.12	0.05	3.28 (1.98-5.43)	4.09E-06	++	0.12
rs11786105	8	134786375	Downstream	*ST3GAL1*	C/T	0.37	0.54	2.26	9.20E-06	9.37E-06	0.38	0.35	0.83	0.36	1.43 (1.09-1.87)	8.80E-03	+-	<0.05

rs1361153	10	8458317	intergenic	*GATA3*	T/C	0.05	0.13	6.64	2.60E-06	2.65E-06	0.06	0.04	0.73	0.45	2.25 (1.28-3.98)	5.13E-03	+-	<0.05
rs77200798	10	8461766	intergenic	*GATA3*	G/A	0.06	0.13	5.72	9.07E-06	9.23E-06	0.06	0.04	0.73	0.45	2.14 (1.22-3.76)	7.84E-03	+-	<0.05
rs73631896	10	8461825	intergenic	*GATA3*	C/T	0.06	0.13	5.82	8.00E-06	8.14E-06	0.06	0.04	0.73	0.45	2.15 (1.23-3.78)	7.57E-03	+-	<0.05
rs113324753	11	108968987	intergenic	*C11orf87*	G/T	0.06	0.16	5.40	1.69E-06	1.72E-06	-	-	-	-	-	-	..	-
rs12365631	11	108971949	intergenic	*C11orf87*	G/C	0.06	0.16	4.94	4.20E-06	4.28E-06	-	-	-	-	-	-	..	-
rs80186307	11	108981862	intergenic	*C11orf87*	G/A	0.08	0.19	3.93	8.66E-06	8.82E-06	-	-	-	-	-	-	..	-
rs4356265	11	117301818	intronic	*DSCAML1*	T/C	0.11	0.22	3.92	1.89E-06	1.92E-06	0.11	0.17	1.87	**0.04**	**2.75 (1.83-4.15)**	**1.33E-06**	**++**	**0.08**
rs11220543	11	126443837	intronic	*KIRREL3*	T/C	0.44	0.61	2.23	7.95E-06	8.09E-06	0.43	0.43	0.92	0.7	1.51 (1.16-1.96)	2.35E-03	+-	<0.05
rs75224498	12	41527050	intergenic	*PDZRN4*	T/G	0.04	0.12	6.70	6.92E-06	7.04E-06	0.05	0.08	2.25	0.06	3.91 (2.16-7.09)	7.15E-06	++	0.07
rs11838259	12	41535464	intergenic	*PDZRN4*	T/G	0.04	0.13	7.16	2.34E-06	2.38E-06	0.05	0.09	2.04	0.08	3.79 (2.12-6.76)	6.44E-06	++	<0.05
rs7990716	13	74746182	intergenic	*KLF12*	C/T	0.10	0.21	3.66	7.63E-06	7.77E-06	0.09	0.11	0.89	0.72	1.95 (1.27-2.99)	2.17E-03	+-	<0.05
rs61964594	13	74746446	intergenic	*KLF12*	G/A	0.10	0.21	3.66	7.63E-06	7.77E-06	0.09	0.11	0.89	0.72	1.95 (1.27-2.99)	2.17E-03	+-	<0.05
rs726618	13	74747883	intergenic	*KLF12*	G/T	0.10	0.22	4.14	1.13E-06	1.15E-06	0.09	0.11	0.90	0.76	2.10 (1.37-3.23)	7.02E-04	+-	<0.05
rs1337043	13	74748926	intergenic	*KLF12*	C/T	0.11	0.23	3.58	5.81E-06	5.91E-06	0.09	0.11	0.87	0.67	1.93 (1.27-2.93)	2.01E-03	+-	<0.05
rs1337042	13	74749071	intergenic	*KLF12*	G/A	0.11	0.23	3.58	5.81E-06	5.91E-06	0.09	0.11	0.87	0.67	1.93 (1.27-2.93)	2.01E-03	+-	<0.05
rs1337041	13	74749179	intergenic	*KLF12*	C/A	0.11	0.23	3.54	6.83E-06	6.95E-06	0.09	0.11	0.87	0.67	1.92 (1.27-2.92)	2.17E-03	+-	<0.05
rs7999569	13	74750965	intergenic	*KLF12*	C/T	0.11	0.23	3.53	7.12E-06	7.25E-06	0.09	0.11	0.87	0.66	1.91 (1.26-2.90)	2.28E-03	+-	<0.05
rs2039629	13	74752497	intergenic	*KLF12*	G/T	0.11	0.23	3.53	7.12E-06	7.25E-06	0.09	0.11	0.87	0.66	1.91 (1.26-2.90)	2.28E-03	+-	<0.05
rs17062289	13	74758886	intergenic	*KLF12*	A/C	0.11	0.23	3.47	8.85E-06	9.01E-06	0.09	0.11	0.96	0.89	1.98 (1.31-3.00)	1.30E-03	+-	<0.05
rs12857591	13	74801272	Upstream	*LINC00402*	T/C	0.10	0.23	4.47	2.05E-07	2.09E-07	0.09	0.1	0.78	0.43	2.04 (1.34-3.12)	9.61E-04	+-	<0.05
rs2077879	13	74806116	intronic	*LINC00402*	T/G	0.10	0.24	4.53	1.19E-07	1.21E-07	0.09	0.1	0.77	0.42	2.07 (1.36-3.15)	7.34E-04	+-	<0.05
rs7989618	13	74806494	intronic	*LINC00402*	T/C	0.10	0.23	4.47	2.05E-07	2.09E-07	0.09	0.1	0.78	0.43	2.04 (1.34-3.12)	9.61E-04	+-	<0.05
rs2777656	13	74809900	intronic	*LINC00402*	T/C	0.10	0.24	4.53	1.19E-07	1.21E-07	0.09	0.1	0.77	0.42	2.07 (1.36-3.15)	7.34E-04	+-	<0.05
rs139082553	13	74813754	intronic	*LINC00402*	G/T	0.10	0.23	4.32	3.39E-07	3.45E-07	0.09	0.1	0.77	0.42	2.00 (1.31-3.05)	1.27E-03	+-	<0.05
rs61964624	13	74814176	intronic	*LINC00402*	T/C	0.10	0.23	4.47	2.05E-07	2.09E-07	0.09	0.1	0.78	0.43	2.04 (1.34-3.12)	9.61E-04	+-	<0.05
rs7332722	13	74815947	intronic	*LINC00402*	T/C	0.10	0.24	4.53	1.19E-07	1.21E-07	0.09	0.1	0.77	0.42	2.07 (1.36-3.15)	7.34E-04	+-	<0.05
rs7333089	13	74815990	intronic	*LINC00402*	C/G	0.10	0.24	4.53	1.19E-07	1.21E-07	0.09	0.1	0.77	0.42	2.07 (1.36-3.15)	7.34E-04	+-	<0.05
rs6562810	13	74816423	intronic	*LINC00402*	G/T	0.10	0.24	4.69	7.05E-08	7.18E-08	0.09	0.1	0.78	0.43	2.11 (1.38-3.21)	5.49E-04	+-	<0.05

rs17062427	13	74827332	intronic	*LINC00402*	T/C	0.11	0.23	3.64	3.58E-06	3.64E-06	0.1	0.11	0.75	0.33	1.75 (1.17-2.63)	6.63E-03	+-	<0.05
rs9543552	13	74844706	intergenic	*LINC00402*	T/C	0.19	0.33	2.69	7.35E-06	7.48E-06	0.25	0.19	0.68	0.1	1.37 (1.01-1.88)	4.53E-02	+-	<0.05
rs7993042	13	74854181	intergenic	*LINC00402*	G/A	0.18	0.32	2.73	8.30E-06	8.45E-06	0.24	0.18	0.69	0.1	1.38 (1.00-1.89)	4.85E-02	+-	<0.05
rs2340984	16	88799288	intronic	*PIEZO1*	A/G	0.17	0.30	2.87	7.75E-06	7.89E-06	0.22	0.21	1.14	0.59	1.81 (1.30-2.51)	4.47E-04	++	<0.05
rs112538348	17	60965309	intergenic	*MARCH10*	A/G	0.14	0.27	3.08	7.47E-06	7.60E-06	0.16	0.16	0.78	0.33	1.55 (1.09-2.20)	1.46E-02	+-	<0.05
rs76484331	20	62422504	intronic	*ZBTB46*	A/C	0.04	0.13	11.31	**2.49E-08**	**2.53E-08**	0.05	0.08	2.97	**0.01**	**5.84 (3.16-10.76)**	**1.61E-08**	++	**<0.05**
rs2180631	20	62426393	intronic	*ZBTB46*	T/C	0.05	0.13	5.98	7.21E-06	7.34E-06	0.05	0.09	2.76	**0.02**	**4.17 (2.34-7.41)**	**1.18E-06**	++	**0.19**
rs75004420	20	62427703	intronic	*ZBTB46*	A/G	0.05	0.13	7.82	6.13E-07	6.24E-07	0.05	0.09	2.55	**0.03**	**4.50 (2.52-8.04)**	**3.90E-07**	++	**0.06**
rs139848472	20	62430476	intronic	*ZBTB46*	A/C	0.05	0.13	7.82	6.13E-07	6.24E-07	0.05	0.09	2.55	**0.03**	**4.50 (2.52-8.04)**	**3.90E-07**	++	**0.06**
rs141335934	20	62437525	intronic	*ZBTB46*	T/C	0.06	0.14	5.61	6.05E-06	6.16E-06	0.07	0.09	1.43	0.33	2.76 (1.64-4.65)	1.41E-04	++	<0.05
rs6010663	20	62441298	intronic	*ZBTB46*	G/C	0.05	0.14	5.67	6.28E-06	6.39E-06	0.05	0.09	2.48	**0.03**	**3.88 (2.22-6.78)**	**1.96E-06**	++	**0.15**
rs6010665	20	62441600	intronic	*ZBTB46*	C/T	0.05	0.14	5.67	6.28E-06	6.39E-06	0.05	0.09	2.50	**0.03**	**3.89 (2.23-6.81)**	**1.86E-06**	++	**0.15**
rs113033986	20	62442559	intronic	*ZBTB46*	A/G	0.05	0.14	5.67	6.28E-06	6.39E-06	0.05	0.09	2.50	**0.03**	**3.89 (2.23-6.81)**	**1.86E-06**	++	**0.15**
rs1887407	20	62446569	intronic	*ZBTB46*	A/G	0.05	0.14	5.67	6.28E-06	6.39E-06	0.05	0.09	2.50	**0.03**	**3.89 (2.23-6.81)**	**1.86E-06**	++	**0.15**
rs117861539	20	62447063	intronic	*ZBTB46*	T/G	0.05	0.13	7.67	6.99E-07	7.12E-07	0.05	0.09	2.57	**0.03**	**4.49 (2.51-8.01)**	**3.94E-07**	++	**0.06**
rs4578911	20	62448938	intronic	*ZBTB46*	G/A	0.05	0.14	5.70	6.04E-06	6.15E-06	0.05	0.09	2.50	**0.03**	**3.90 (2.23-6.82)**	**1.81E-06**	++	**0.15**
rs6011153	20	62450502	intronic	*ZBTB46*	C/G	0.05	0.14	5.70	6.04E-06	6.15E-06	0.05	0.09	2.53	**0.03**	**3.92 (2.24-6.86)**	**1.68E-06**	++	**0.16**
rs61653788	20	62454706	intronic	*ZBTB46*	G/C	0.05	0.14	5.70	6.04E-06	6.15E-06	0.05	0.09	2.50	**0.03**	**3.90 (2.23-6.82)**	**1.81E-06**	++	**0.15**
rs116870978	20	62455923	intronic	*ZBTB46*	A/G	0.04	0.13	7.70	6.71E-07	6.83E-07	0.05	0.09	2.57	**0.03**	**4.50 (2.52-8.03)**	**3.84E-07**	++	**0.06**
rs73325349	20	62456913	intronic	*ZBTB46*	C/T	0.05	0.14	5.70	6.04E-06	6.15E-06	0.05	0.09	2.50	**0.03**	**3.90 (2.23-6.82)**	**1.81E-06**	++	**0.15**
rs6010673	20	62459863	intronic	*ZBTB46*	T/A	0.05	0.14	5.61	6.97E-06	7.10E-06	0.05	0.09	2.50	**0.03**	**3.87 (2.22-6.77)**	**2.00E-06**	++	**0.16**
rs6011174	20	62463347	Upstream	*ZBTB46*	G/A	0.05	0.14	5.70	6.04E-06	6.15E-06	0.05	0.09	2.50	**0.03**	**3.90 (2.23-6.82)**	**1.81E-06**	++	**0.15**
rs6011175	20	62463515	Upstream	*ZBTB46*	G/C	0.05	0.14	5.70	6.04E-06	6.15E-06	0.05	0.09	2.50	**0.03**	**3.90 (2.23-6.82)**	**1.81E-06**	++	**0.15**
rs6010674	20	62463591	Upstream	*ZBTB46*	T/C	0.05	0.14	5.70	6.04E-06	6.15E-06	0.05	0.09	2.50	**0.03**	**3.90 (2.23-6.82)**	**1.81E-06**	++	**0.15**
rs7344617	20	62463858	Upstream	*ZBTB46*	C/G	0.05	0.14	5.70	6.04E-06	6.15E-06	0.05	0.09	2.50	**0.03**	**3.90 (2.23-6.82)**	**1.81E-06**	++	**0.15**
rs6011176	20	62464735	Upstream	*ZBTB46*	C/G	0.05	0.14	5.70	6.04E-06	6.15E-06	0.05	0.09	2.50	**0.03**	**3.90 (2.23-6.82)**	**1.81E-06**	++	**0.15**
rs60022917	20	62465663	Upstream	*ZBTB46*	A/G	0.05	0.14	5.70	6.04E-06	6.15E-06	0.05	0.09	2.50	**0.03**	**3.90 (2.23-6.82)**	**1.81E-06**	++	**0.15**
rs6011178	20	62468374	Upstream	*ZBTB46*	G/C	0.05	0.14	5.70	6.04E-06	6.15E-06	0.05	0.09	2.50	**0.03**	**3.90 (2.23-6.82)**	**1.81E-06**	++	**0.15**

rs79873740	20	62468531	Upstream	*ZBTB46*	T/C	0.05	0.14	5.49	8.40E-06	8.55E-06	0.05	0.09	2.50	**0.03**	**3.83 (2.20-6.69)**	**2.28E-06**	++	**0.17**
rs8115050	20	62469865	intergenic	*C20orf181*	A/G	0.05	0.14	5.62	6.86E-06	6.98E-06	0.05	0.09	2.52	**0.03**	**3.89 (2.22-6.80)**	**1.88E-06**	++	**0.16**
rs144908555	20	62469956	intergenic	*C20orf181*	A/G	0.04	0.13	10.43	5.26E-08	5.35E-08	0.05	0.09	3.13	**0.01**	**5.81 (3.15-10.68)**	**1.61E-08**	++	**0.05**
rs11905851	20	62470849	intergenic	*C20orf181*	T/C	0.05	0.13	6.08	6.27E-06	6.38E-06	0.05	0.09	3.05	**0.01**	**4.44 (2.48-7.97)**	**5.66E-07**	++	**0.25**
rs11908253	20	62470851	intergenic	*C20orf181*	C/T	0.05	0.13	6.08	6.27E-06	6.38E-06	0.05	0.09	3.05	**0.01**	**4.44 (2.48-7.97)**	**5.66E-07**	++	**0.25**
rs11905798	20	62471198	intergenic	*C20orf181*	A/G	0.05	0.13	6.08	6.27E-06	6.38E-06	0.05	0.09	2.90	**0.02**	**4.33 (2.42-7.75)**	**7.99E-07**	++	**0.21**
rs11905801	20	62471233	intergenic	*C20orf181*	A/G	0.05	0.13	6.08	6.27E-06	6.38E-06	0.05	0.09	2.90	**0.02**	**4.33 (2.42-7.75)**	**7.99E-07**	++	**0.21**
rs6011179	20	62471797	intergenic	*C20orf181*	A/T	0.05	0.14	5.61	6.91E-06	7.03E-06	0.05	0.09	2.59	**0.03**	**3.96 (2.26-6.96)**	**1.63E-06**	++	**0.18**
rs6011180	20	62471908	intergenic	*C20orf181*	A/C	0.05	0.14	5.61	6.91E-06	7.03E-06	0.05	0.09	2.59	**0.03**	**3.96 (2.26-6.96)**	**1.63E-06**	++	**0.18**
rs112821795	20	62473116	intergenic	*C20orf181*	C/T	0.05	0.14	5.61	6.91E-06	7.03E-06	0.05	0.09	2.59	**0.03**	**3.96 (2.26-6.96)**	**1.63E-06**	++	**0.18**
rs6010678	20	62473876	intergenic	*C20orf181*	C/G	0.05	0.14	5.61	6.91E-06	7.03E-06	0.05	0.09	2.59	**0.03**	**3.96 (2.26-6.96)**	**1.63E-06**	++	**0.18**
rs8121155	20	62474185	intergenic	*C20orf181*	C/T	0.05	0.14	5.61	6.91E-06	7.03E-06	0.05	0.09	2.59	**0.03**	**3.96 (2.26-6.96)**	**1.63E-06**	++	**0.18**
rs6010681	20	62474360	intergenic	*C20orf181*	A/G	0.05	0.14	5.61	6.91E-06	7.03E-06	0.05	0.09	2.59	**0.03**	**3.96 (2.26-6.96)**	**1.63E-06**	++	**0.18**
rs6011183	20	62474640	intergenic	*C20orf181*	T/C	0.05	0.14	5.61	6.91E-06	7.03E-06	0.05	0.09	2.59	**0.03**	**3.96 (2.26-6.96)**	**1.63E-06**	++	**0.18**
rs73325392	20	62475297	intergenic	*C20orf181*	C/A	0.05	0.14	5.61	6.91E-06	7.03E-06	0.05	0.09	2.59	**0.03**	**3.96 (2.26-6.96)**	**1.63E-06**	++	**0.18**
rs73325395	20	62475451	intergenic	*C20orf181*	A/G	0.05	0.14	5.61	6.91E-06	7.03E-06	0.05	0.09	2.59	**0.03**	**3.96 (2.26-6.96)**	**1.63E-06**	++	**0.18**
rs6010682	20	62476548	intergenic	*C20orf181*	G/A	0.05	0.14	5.61	6.91E-06	7.03E-06	0.05	0.09	2.59	**0.03**	**3.96 (2.26-6.96)**	**1.63E-06**	++	**0.18**
rs6010683	20	62476633	intergenic	*C20orf181*	T/C	0.05	0.14	5.91	4.34E-06	4.42E-06	0.05	0.09	2.35	**0.04**	**3.85 (2.20-6.75)**	**2.40E-06**	++	**0.11**
rs200210223	20	62478452	intergenic	*C20orf181*	C/G	0.05	0.13	7.33	1.05E-06	1.07E-06	0.05	0.09	3.10	**0.01**	**4.97 (2.74-9.04)**	**1.45E-07**	++	**0.16**
rs561090005	20	62478456	intergenic	*C20orf181*	G/C	0.05	0.13	7.33	1.05E-06	1.07E-06	0.05	0.09	3.10	**0.01**	**4.97 (2.74-9.04)**	**1.45E-07**	++	**0.16**
rs111874365	20	62478517	intergenic	*C20orf181*	G/A	0.05	0.14	5.81	5.04E-06	5.13E-06	0.05	0.09	2.59	**0.03**	**4.03 (2.29-7.09)**	**1.30E-06**	++	**0.16**

SNP: Single nucleotide polymorphism. CHR: Chromosome. bp: Base pair. EA: Effect allele. NEA: Non-effect allele. EAF: Effect allele frequency. OR: Odds-ratio. (95%CI): 95% Confidence Interval. GC: Genomic Control. Dir: Effect Direction. Het: Heterogeneity.

SNPs with p-value <1x10-5 in the discovery stage are presented. Alleles and chromosomal positions were identified on basis of 1000 Genome Project Phase 3. Location were described following ANNOVAR system.

Genetic variants: rs113324753, rs12365631, rs80186307 failed imputation quality controls in the replication cohort.

Online Table IV. Independent SNPs leading the most significant associations with PH in the meta-analysis. Extra columns for the complementary analysis including CE as covariate in the replication. SNP: Single nucleotide polymorphism. CHR: Chromosome. bp: Base pair. EA: Effect allele. NEA: Non-effect allele. EAF: Effect allele frequency. N. Variants: Number of variants reaching p>1x10-5, OR: Odds-ratio. (95%CI): 95% Confidence Interval. C.A.: Complementary Analysis adding CE as covariate.

SNP	CHR	Position (bp)	Gene	EA/NEA	EAF	Stage	OR (95%CI)	p	OR (95%CI) - C.A.	p - C.A.
						Meta-analysis	3.82 (2.19-6.68)	2.43x10-6	3.88 (2.21-6.80)	2.18x10-6
						Discovery	6.56 (3.10-13.89)	8.62x10-7	-	-
rs77557904	2	1047076	*SNTG2*	G/C	0.06	Replication	2.01 (0.88-4.59)	0.1	2.04 (0.88-4.71)	0.09
						Meta-analysis	3.01 (1.88-4.84)	4.79x10-6§	3.11 (1.92-5.04)	4.10x10-6
						Discovery	4.67 (2.43-8.96)	3.76x10-6	-	-
rs112541215	2	218916291	*RUFY4*	A/T	0.08	Replication	1.90 (0.96-3.74)	0.07	1.94 (0.96-3.95)	0.07
						Meta-analysis	2.43 (1.76-3.37)	7.85x10-8§	2.34 (1.69-3.25)	3.33x10-7
						Discovery	2.94 (1.87-4.61)	2.77x10-6	-	-
rs1962779	7	83837734	*SEMA3A*	C/G	0.19	Replication	2.00 (1.26-3.18)	3.34x10-3	1.84 (1.15-2.94)	0.01
						Meta-analysis	2.75 (1.83-4.15)	1.33x10-6§	2.62 (1.74-3.94)	4.30x10-6
						Discovery	3.92 (2.23-6.88)	1.89x10-6	-	-
rs4356265	11	117301818	*DSCAML1*	T/C	0.11	Replication	1.87 (1.03-3.38)	0.04	1.68 (0.93-3.04)	0.09
						Meta-analysis	4.23 (2.37-7.54)	1.03x10-6	4.08 (2.29-7.24)	1.67x10-6
						Discovery	9.89 (4.20-23.28)	1.56x10-7	-	-
rs564865745	12	41626444	*PDZRN4*	G/A	0.05	Replication	2.12 (0.97-4.62)	0.06	2.02 (0.93-4.35)	0.07
						Meta-analysis	**5.84 (3.16-10.76)**	**1.61x10-8***	**5.96 (3.22-11.05)**	**1.43x10-8**
						Discovery	**11.31 (4.82-26.55)**	**2.49x10-8***	-	-
rs76484331	**20**	**62422504**	***ZBTB46***	**A/C**	**0.1**	Replication	2.97 (1.24-7.09)	0.01	3.03 (1.25-7.34)	0.01

Online Table V. Genes associated with PH through a gene-set analysis.

CHR	Start	Stop	Gene	p	zstat
20	62472779	62477273	*C20orf181*	8.98E-07*	4.78
20	62524518	62569384	*DNAJC5*	1.79E-05	4.13
21	33041346	33106388	*SCAF4*	3.30E-05	3.99
9	123968072	124097121	*GSN*	5.67E-05	3.86
11	3846208	3864213	*RHOG*	7.45E-05	3.79
16	90069273	90088536	*DBNDD1*	1.64E-04	3.59
20	62494596	62524898	*TPD52L2*	2.22E-04	3.51
2	76972845	77822445	*LRRTM4*	2.36E-04	3.50
2	137521115	138437287	*THSD7B*	2.89E-04	3.44
16	58057470	58082805	*MMP15*	3.49E-04	3.39
13	23900965	24009841	*SACS*	3.51E-04	3.39
19	39831036	39878350	*SAMD4B*	3.67E-04	3.38
1	234038679	234462262	*SLC35F3*	5.53E-04	3.26
7	2391721	2422380	*EIF3B*	5.82E-04	3.25
11	33058963	33129489	*TCP11L1*	6.22E-04	3.23
11	68520088	68613878	*CPT1A*	6.39E-04	3.22
11	33035410	33057128	*DEPDC7*	6.99E-04	3.19
20	2819349	2849378	*VPS16*	7.21E-04	3.19
17	61970275	61976021	*CSH1*	7.59E-04	3.17
4	1339054	1383837	*UVSSA*	8.11E-04	3.15
16	88779751	88853619	*PIEZO1*	8.16E-04	3.15
4	1158720	1204750	*SPON2*	8.20E-04	3.15
17	61947372	61953126	*CSH2*	9.20E-04	3.12

CHR: Chromosome; Start/Stop: start and end position of the genomic region of interest (hg19); zstat: p-value converted to Z-value.
Only genes with a p-value <0.001 are shown
*p-value $<2.68 \times 10^{-6}$ (0.05/18647 protein coding genes)

Online Table VI. S-Multixcan results. N: Number of SNPs as eQTLs in GTEx. N indep: Number of independent SNPs considered by S-MultiXcan. sd: Standard deviation.

Gene	Gene Symbol	P-value	N	N indep	Z mean	Z sd
ENSG00000227088.1	*AC084149.2*	3.81E-05	6	4	-1.61	1.55
ENSG00000165966.14	*PDZRN4*	1.53E-04	46	8	0.02	1.36
ENSG00000235532.1	*LINC00402*	2.07E-04	9	3	2.9	1.49
ENSG00000173575.20	*CHD2*	2.14E-04	45	5	0.94	1.31
ENSG00000130584.10	***ZBTB46***	**3.16E-04**	29	6	-1.14	1.83
ENSG00000179862.6	*CITED4*	3.32E-04	42	8	0.44	1.86
ENSG00000156508.17	*EEF1A1*	4.61E-04	6	3	-0.29	2.75
ENSG00000156304.14	*SCAF4*	4.88E-04	47	1	3.37	0.61
ENSG00000178997.11	*EXD1*	4.96E-04	2	2	-2.99	0.69
ENSG00000204179.10	*PTPN20*	5.42E-04	13	5	0.22	1.12

Online Table VII. GNOVA genetic correlation results for ischemic stroke phenotypes, intracranial hemorrhage, and parenchymal hematoma. AIS: All Ischemic Stroke; LAS: Large Artery-Atherosclerosis Stroke; CES: Cardioembolic Stroke; SVS: Small Vessel Stroke; ICH: Intracranial Hemorrhage; WMHv: White matter hyperintensity volume.

Phenotype	Rho	SE	P value
AIS	-0.008	0.005	0.14
LAS	-0.009	0.006	0.11
CES	-0.004	0.006	0.45
SVS	-0.001	0.005	0.84
ICH	-0.042	0.045	0.34
deepICH	0.141	0.052	**6.7×10^{-3}**
lobarICH	-0.179	0.054	**8.6×10^{-4}**
WMHv	0.081	0.031	**9.2×10^{-3}**

Online Table VIII. Description of poor outcome phenotypes in the replication cohort.

	Replication cohort (n = 580)
Disabilitiy (%)	183 (40.9)
Mortality after 3 months (%)	61 (13.6)
In-Hospital mortality (%)	24 (5.4)

Online Table IX. Results of the PRS in the replication cohort. Welch Two Sample t-test of PRS best-fit threshold for disability after three months and Parenchymal Hematoma, Mortality after 3 months and In-Hospital mortality in the replication cohort.

	T-value	Standard Error	P-value
Disabilitiy after 3 months	4.89	4.13x10-4	1.51x10-6
Parechymal Hematoma	2.02	5.80x10-4	0.046
Mortality after 3 months	3.20	6.55x10-4	0.002
In-Hospital mortality	1.05	1.19x10-3	0.304

Online Table X. Multivariable logistic regression results for disability after three months.

	Estimate	Standard Error	Z value	P value
(Intercept)	18.91	10.14	1.86	6.22E-02
PRS	68.56	27.46	2.50	1.25E-02
NIHSS	0.19	0.02	8.75	2.19E-18
Age	0.05	0.01	4.36	1.32E-05
Sex (Female)	0.21	0.24	0.87	3.83E-01

Online Table XI. Expression quantitative trait loci for rs76484331 over *ZBTB46* expression.

Tissue	p	Source
Blood	2.2E-06	eQTLGen Consortium
Esophagus – Mucosa	0.00003	GTEx Analysis Release V7
Artery - Tibial	0.029	GTEx Analysis Release V7
Artery - Aorta	0.088	GTEx Analysis Release V7
Brain - Amygdala	0.21	GTEx Analysis Release V7
Brain - Hippocampus	0.46	GTEx Analysis Release V7
Brain - Frontal Cortex	0.54	GTEx Analysis Release V7
Brain - Anterior cingulate cortex	0.61	GTEx Analysis Release V7
Brain - Hypothalamus	0.64	GTEx Analysis Release V7
Brain - Nucleus accumbens	0.66	GTEx Analysis Release V7
Artery - Coronary	0.66	GTEx Analysis Release V7
Whole Blood	0.68	GTEx Analysis Release V7
Brain - Substantia nigra	0.69	GTEx Analysis Release V7
Brain - Caudate (basal ganglia)	0.7	GTEx Analysis Release V7
Brain - Cerebellar Hemisphere	0.74	GTEx Analysis Release V7
Brain - Putamen (basal ganglia)	0.8	GTEx Analysis Release V7
Brain - Cerebellum	0.85	GTEx Analysis Release V7
Brain - Cortex	0.86	GTEx Analysis Release V7

Online Table XII. Histone modifications reported for rs76484331.

Location	Chromatin State	Tissue Group	Tissue
chr20:62422400..62423800	Enhancers	Heart	Right Ventricle
chr20:62414400..62429600	Quiescent/Low	Blood & T-cell	Primary mononuclear cells from peripheral blood
chr20:62414200..62431400	Quiescent/Low	Blood & T-cell	Primary T CD8+ memory cells from peripheral blood
chr20:62414200..62426800	Quiescent/Low	Blood & T-cell	Primary T CD8+ naive cells from peripheral blood
chr20:62414000..62455400	Quiescent/Low	Blood & T-cell	Primary T cells effector/memory enriched from peripheral blood
chr20:62414000..62425200	Quiescent/Low	Blood & T-cell	Primary T cells from cord blood
chr20:62414200..62433800	Quiescent/Low	Blood & T-cell	Primary T helper cells PMA-I stimulated
chr20:62417800..62427000	Quiescent/Low	Blood & T-cell	Primary T helper memory cells from peripheral blood 1
chr20:62417600..62452600	Quiescent/Low	Blood & T-cell	Primary T helper memory cells from peripheral blood 2
chr20:62414200..62432000	Quiescent/Low	Blood & T-cell	Primary T helper naive cells from peripheral blood
chr20:62414200..62424600	Quiescent/Low	Blood & T-cell	Primary T helper naive cells from peripheral blood
chr20:62418000..62435000	Quiescent/Low	ENCODE	GM12878 Lymphoblastoid Cell Line
chr20:62408600..62433800	Quiescent/Low	ENCODE	Monocytes-CD14+ RO01746 Primary Cells
chr20:62418600..62434200	Quiescent/Low	HSC & B-cell	Primary B cells from cord blood
chr20:62418000..62426000	Quiescent/Low	HSC & B-cell	Primary B cells from peripheral blood
chr20:62375800..62432400	Quiescent/Low	HSC & B-cell	Primary monocytes from peripheral blood
chr20:62414200..62434400	Quiescent/Low	HSC & B-cell	Primary Natural Killer cells from peripheral blood

Online Table VI (continued)

chr20:62419200..62423600	Repressed PolyComb	Blood & T-cell	Primary T cells from peripheral blood
chr20:62421000..62435000	Weak Repressed PolyComb	Blood & T-cell	Primary T helper 17 cells PMA-I stimulated
chr20:62415200..62437800	Weak Repressed PolyComb	Blood & T-cell	Primary T helper cells from peripheral blood
chr20:62417800..62432400	Weak Repressed PolyComb	Blood & T-cell	Primary T regulatory cells from peripheral blood
chr20:62421600..62427200	Weak Repressed PolyComb	HSC & B-cell	Primary neutrophils from peripheral blood
chr20:62422000..62442600	Weak transcription	Brain	Brain Angular Gyrus
chr20:62422400..62460000	Weak transcription	Brain	Brain Anterior Caudate
chr20:62422000..62457400	Weak transcription	Brain	Brain Cingulate Gyrus
chr20:62422000..62442800	Weak transcription	Brain	Brain Dorsolateral Prefrontal Cortex
chr20:62421600..62422600	Weak transcription	Brain	Brain Germinal Matrix
chr20:62421600..62452600	Weak transcription	Brain	Brain Hippocampus Middle
chr20:62421800..62423600	Weak transcription	Brain	Brain Inferior Temporal Lobe
chr20:62422200..62424000	Weak transcription	Brain	Brain Substantia Nigra
chr20:62422200..62424200	Weak transcription	ES-deriv	H1 Derived Neuronal Progenitor Cultured Cells
chr20:62422400..62426200	Weak transcription	ES-deriv	H9 Derived Neuron Cultured Cells
chr20:62422400..62423000	Weak transcription	ES-deriv	H9 Derived Neuronal Progenitor Cultured Cells
chr20:62422200..62440600	Weak transcription	Heart	Aorta
chr20:62421200..62423400	Weak transcription	Heart	Right Atrium
chr20:62407000..62434000	Weak transcription	HSC & B-cell	Primary hematopoietic stem cells

Online Table VI (continued)

chr20:62422000..62427200	Weak transcription	HSC & B-cell	Primary hematopoietic stem cells G-CSF-mobilized Female
chr20:62422200..62427200	Weak transcription	HSC & B-cell	Primary hematopoietic stem cells G-CSF-mobilized Male
chr20:62422000..62434200	Weak transcription	HSC & B-cell	Primary hematopoietic stem cells short term culture

Online Table XIII. Expression quantitative trait loci for rs76484331 and cis-genes.

Gene Symbol	Tissue	P	Source
ZGPAT	Blood	3.47E-52	eQTLGen Consortium
UCKL1	Blood	3.29E-39	eQTLGen Consortium
DNAJC5	Blood	1.46E-11	eQTLGen Consortium
SLC2A4RG	Blood	2.46E-10	eQTLGen Consortium
LIME1	Lung	1.30E-09	GTEx Analysis Release V7
LIME1	Thyroid	6.00E-09	GTEx Analysis Release V7
EEF1A2	Blood	2.39E-08	eQTLGen Consortium
LIME1	Artery - Tibial	3.10E-08	GTEx Analysis Release V7
LIME1	Nerve - Tibial	7.60E-08	GTEx Analysis Release V7
LIME1	Testis	2.40E-06	GTEx Analysis Release V7
LIME1	Pituitary	7.20E-06	GTEx Analysis Release V7
LIME1	Artery - Aorta	0.002	GTEx Analysis Release V7
LIME1	Brain - Cerebellum	0.0026	GTEx Analysis Release V7
LIME1	Whole Blood	0.05	GTEx Analysis Release V7

Only expression quantitative trait loci with p-value <0.05 are shown.

Online Table XIV. Phenotype associations of rs76484331.

Trait	P	Source
Impedance of arm right	1.61E-09	PhenoScanner - Neale-B_UKBB_EUR_2017
Impedance of arm left	1.31E-08	PhenoScanner - Neale-B_UKBB_EUR_2017
Impedance of whole body	3.18E-08	PhenoScanner - Neale-B_UKBB_EUR_2017
Primary / Intrinsic cardiomyopathies	4.59E-06	Cerebrovascular portal - UKBB
Systolic blood pressure	2.38E-05	PhenoScanner - Neale-B_UKBB_EUR_2017
Treatment with cetirizine 10mg tablet	3.16E-05	PhenoScanner - Neale-B_UKBB_EUR_2017
Cardiomyopathy	3.50E-05	PhenoScanner - Neale-B_UKBB_EUR_2017
Vascular or heart problems diagnosed by doctor: high blood pressure	3.64E-05	PhenoScanner - Neale-B_UKBB_EUR_2017
Treatment with enalapril	4.32E-05	PhenoScanner - Neale-B_UKBB_EUR_2017
Self-reported hypertension	4.41E-05	PhenoScanner - Neale-B_UKBB_EUR_2017
Trunk fat percentage	7.01E-05	PhenoScanner - Neale-B_UKBB_EUR_2017
Vascular or heart problems diagnosed by doctor: none of the above	9.20E-05	PhenoScanner - Neale-B_UKBB_EUR_2017
Cardiomyopathy	1.10E-05	Cerebrovascular portal - UKBB
Disease of lips	3.74E-04	Cerebrovascular portal - UKBB
Coronary atherosclerosis	5.97E-04	Cerebrovascular portal - UKBB
Excessive of frequent menstruation	8.58E-04	Cerebrovascular portal - UKBB
Body Mass Index	0.13	Cerebrovascular portal
Coronary artery disease	0.17	Cerebrovascular portal
Triglycerides	0.19	Cerebrovascular portal
Chronic kidney disease	0.19	Cerebrovascular portal
TOAST other undetermined	0.21	Cerebrovascular portal
Type 2 diabetes	0.27	Cerebrovascular portal

Non-lobar ICH	0.29	Cerebrovascular portal
TOAST small artery occlussion	0.31	Cerebrovascular portal
Type 2 diabetes adj BMI	0.35	Cerebrovascular portal
HDL cholesterol	0.36	Cerebrovascular portal
Cholesterol	0.43	Cerebrovascular portal
eGFR-creat (creatinina sérica)	0.47	Cerebrovascular portal
Waist-hip ratio	0.51	Cerebrovascular portal
TOAST large artery atherosclerosis	0.52	Cerebrovascular portal
LDL cholesterol	0.56	Cerebrovascular portal
Urinary albumin-to-creatinine ratio	0.57	Cerebrovascular portal
TOAST cardio-aortic embolism	0.58	Cerebrovascular portal
Microalbuminuria	0.59	Cerebrovascular portal
Cerebral white matter hyperintensities	0.64	Cerebrovascular portal
Lobar ICH	0.84	Cerebrovascular portal
Waist-hip ratio adj Body Mass Index	0.94	Cerebrovascular portal
Height	0.98	Cerebrovascular portal

Online Table XV. Associations of rs76484331 and clinical variants according to the additive model.

	RA	rs76484331			
	A	**CC**	**AC**	**AA**	**p**
Sex, male (%)		663 (55.1)	69 (58.5)	1 (33.3)	0.58
AF (%)		329 (27.4)	30 (25.4)	2 (66.7)	0.28
DM (%)		302 (25.1)	27 (22.9)	0 (0)	0.53
HTN (%)		786 (65.6)	80 (68.4)	1 (33.3)	0.41
ST (%)		334 (33.9)	40 (41.2)	0 (0)	0.16
TOAST (%)					
CE		504 (43.2)	49 (42.2)	3 (100)	0.14
LAA		204 (17.5)	15 (13.2)	0 (0)	0.37
Age (Years. IQR)		75 (65-82)	77 (64-82)	80 (72-85)	0.77
Baseline NIHSS (IQR)		12 (7-18)	12 (6-17)	10 (9-12)	0.71
Glucose (mg/dl. IQR)		120 (103-147)	117 (101-144)	142 (129-157)	0.30
OTT (min. IQR) †		130 (90-180)	120 (90-175)	100 (88-110)	0.50
SBP (mm Hg. IQR)		154 (138-172)	157 (143-170)	136 (127-159)	0.65
DBP (mm Hg. IQR)		82 (71-98)	81 (70-100)	58 (57-89)	0.37

† OTT was available in 788 participants.
For categorical variables, frequencies as percentage were described. For continuous variables, median values, interquartile range (IQR) were calculated.

RA: Risk allele; PH: Parenchymal hematoma; AF: Atrial Fibrillation; DM: Diabetes; HTN: Arterial hypertension; ST: Statins; TOAST: Trial of Org 1072 in Acute Stroke Treatment; CE: Cardioembolism; LAA: Large-artery atherosclerosis; NIHSS: National Institutes of Health Stroke Score; OTT: Time from onset to treatment; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Online Table XVI. Associations of rs76484331 and clinical variants according to the dominant-recessive model.

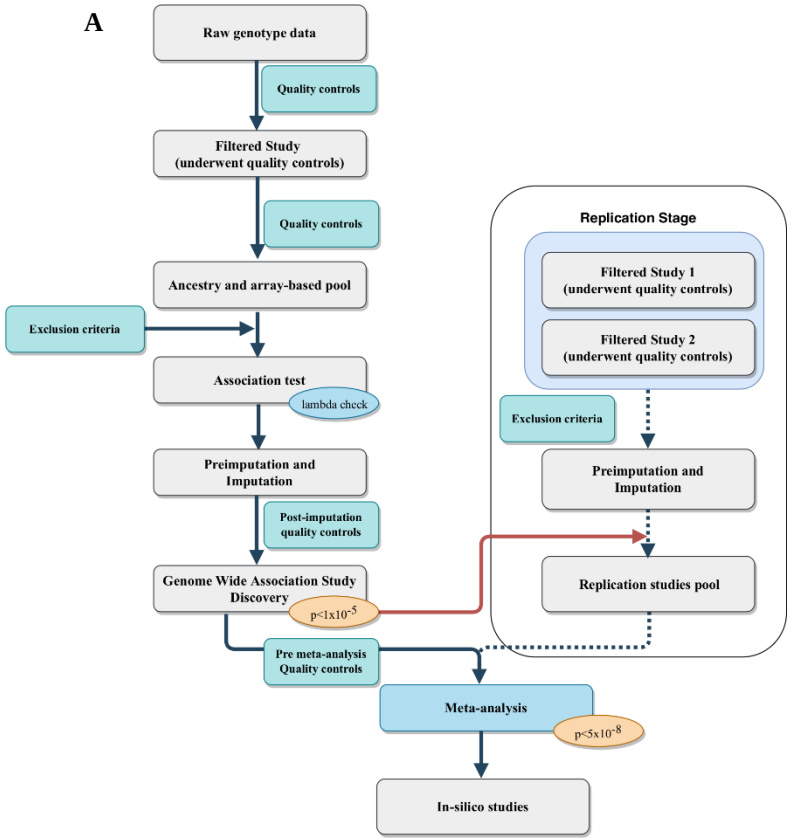
	RA	Genotype rs76484331		
	A	CC	AC + AA	p
Sex, male (%)		663 (55.1)	70 (57.9)	0.56
AF (%)		329 (27.4)	32 (26.4)	0.81
DM (%)		302 (25.1)	27 (22.3)	0.50
HTN (%)		786 (65.6)	81 (67.5)	0.68
ST (%)		334 (33.9)	40 (40)	0.23
TOAST (%)				
CE		504 (43.2)	52 (43.7)	0.91
LAA		204 (17.5)	15 (12.8)	0.20
Age (Years. IQR)		75 (65-82)	77 (64-82)	0.80
Baseline NIHSS (IQR)		12 (7-18)	12 (7-17)	0.46
Glucose (mg/dl. IQR)		120 (103-147)	118 (101-144)	0.33
OTT (min. IQR) †		130 (90-180)	120 (88-173)	0.58
SBP (mm Hg. IQR)		154 (138-172)	157 (140-170)	0.61
DBP (mm Hg. IQR)		82 (71-98)	81 (70-100)	0.29

† OTT was available in 788 participants.
For categorical variables, frequencies as percentage were described. For continuous variables, median values, interquartile range (IQR) were calculated.

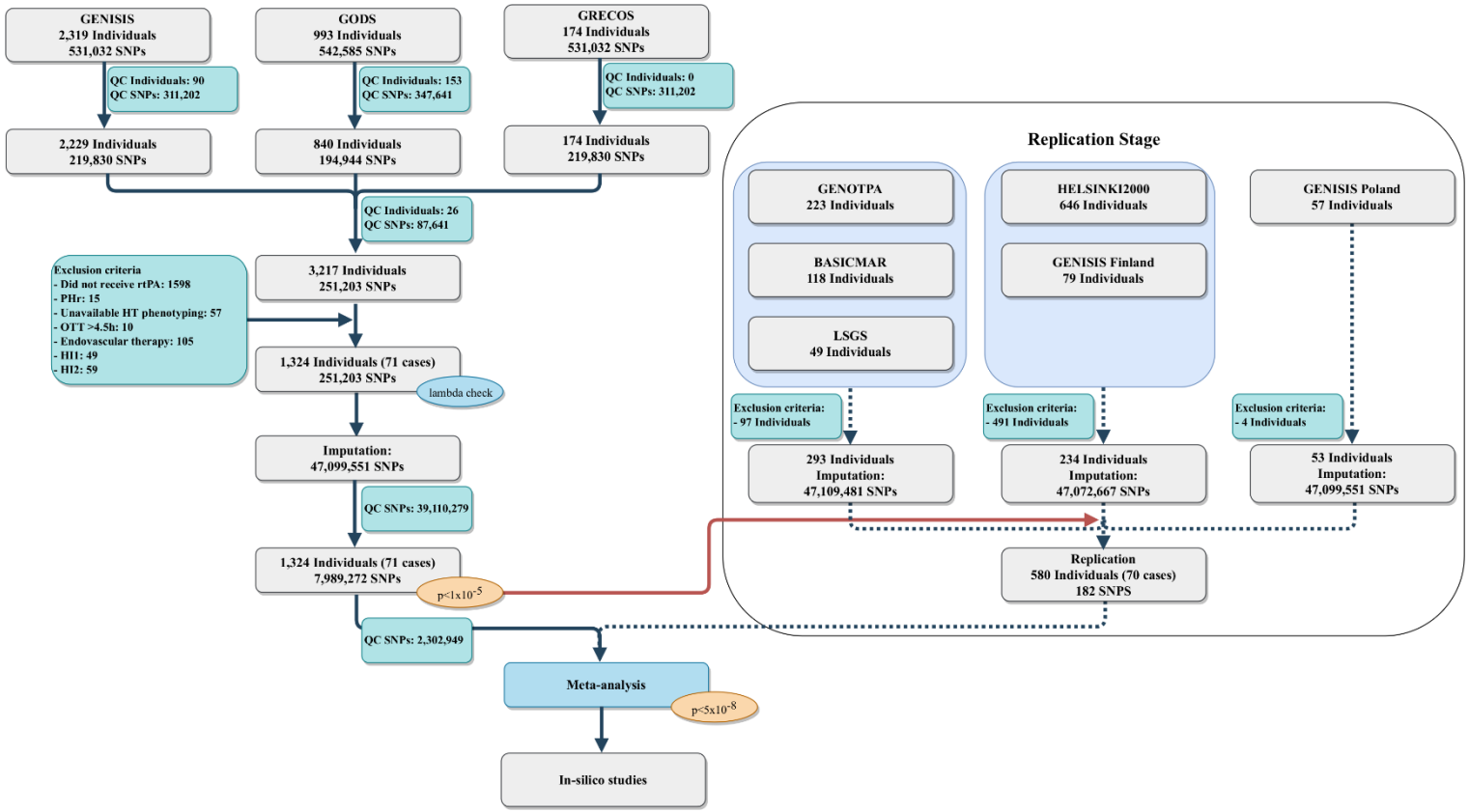
RA: Risk allele; PH: Parenchymal hematoma; AF: Atrial Fibrillation; DM: Diabetes; HTN: Arterial hypertension; ST: Statins; TOAST: Trial of Org 1072 in Acute Stroke Treatment; CE: Cardioembolism; LAA: Large-artery atherosclerosis; NIHSS: National Institutes of Health Stroke Score; OTT: Time from onset to treatment; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

II. Online Figures.

Online Figure I. Analysis overview.

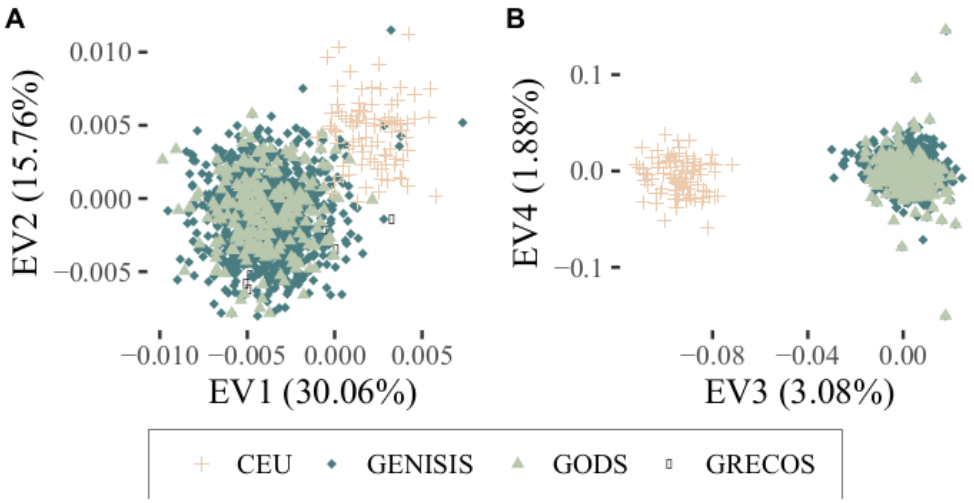


B



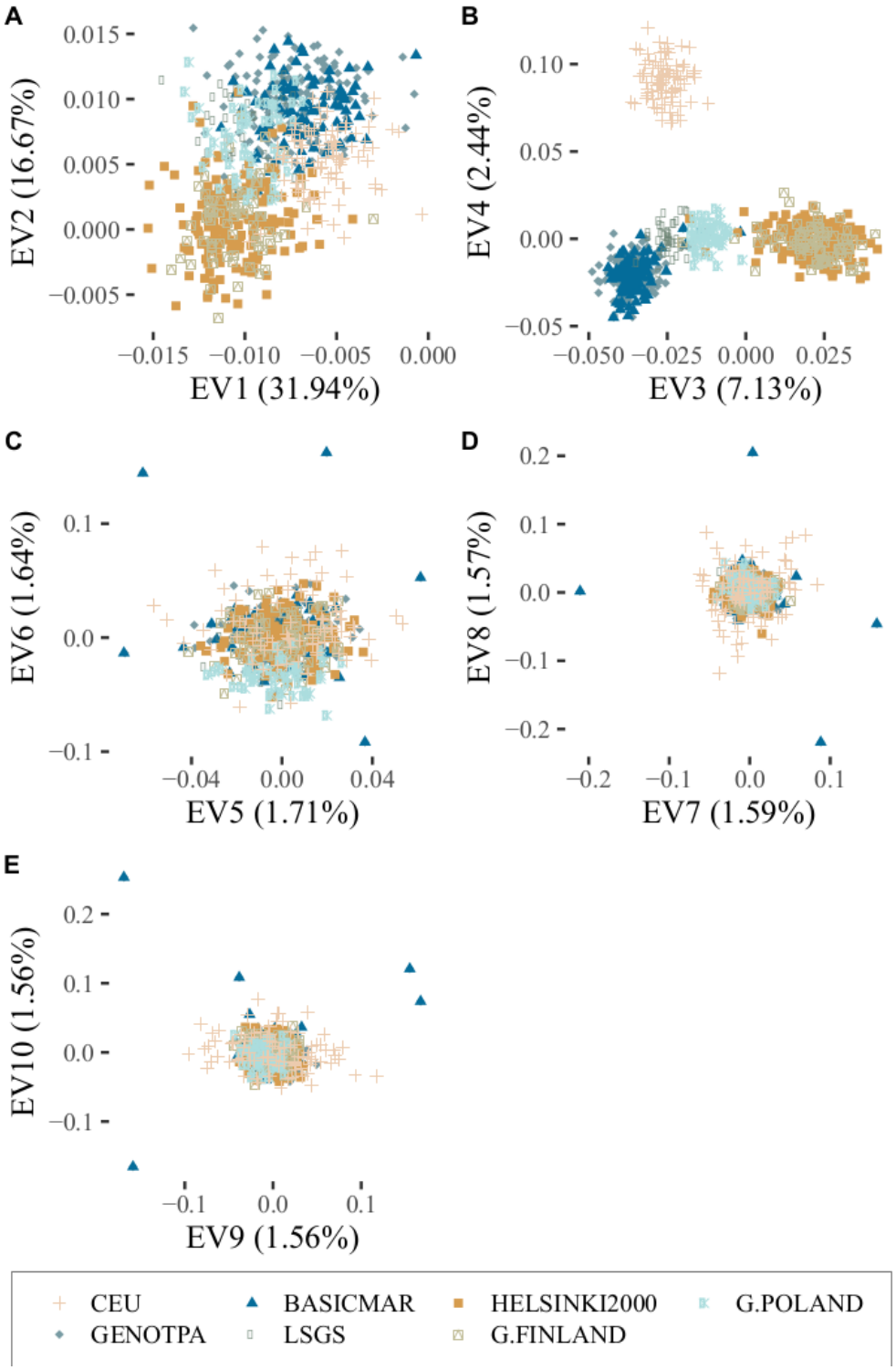
A. Workflow of the analysis. **B.** Workflow of samples and SNPs of the discovery and replication stage.
Red line represents the selection of SNPs that achieved nominally significance (p<1x10-5) that were selected for replication stage.

Online Figure II. Principal components included in the discovery stage.



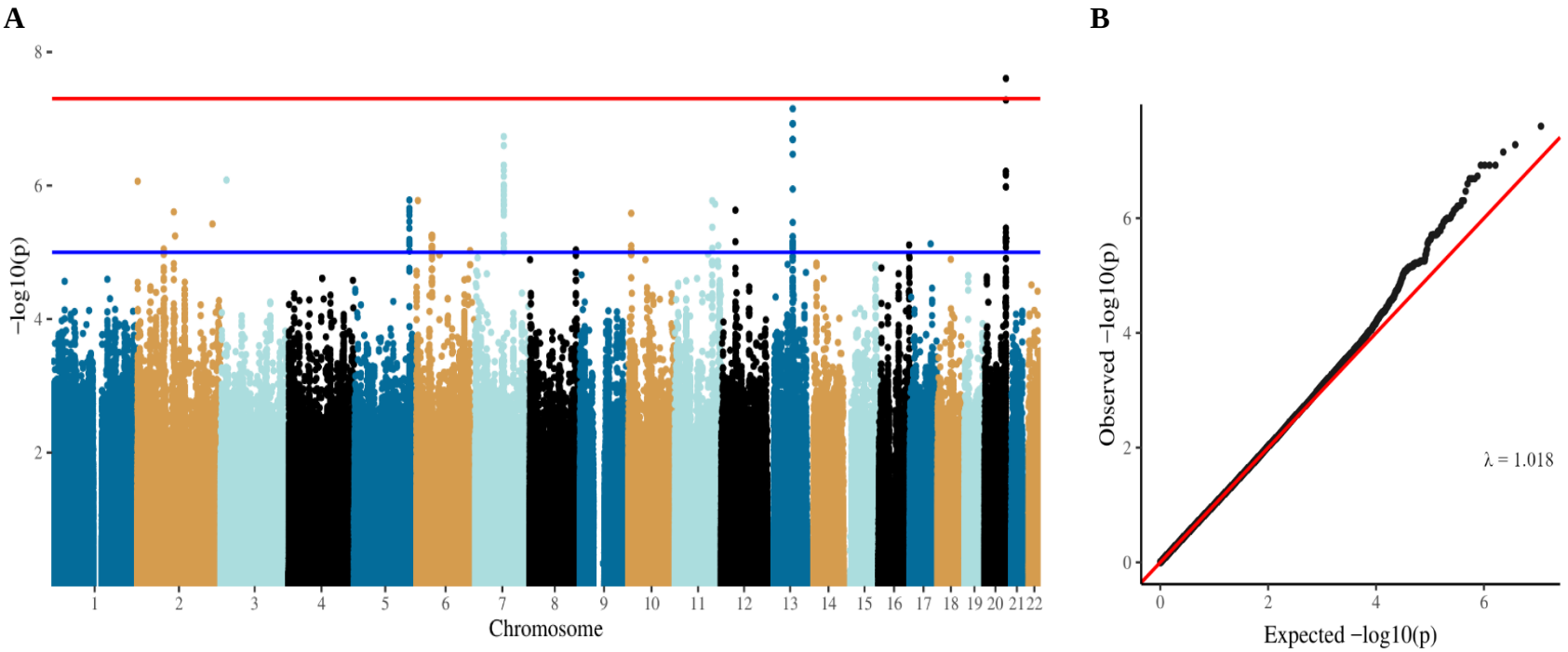
EV: Eigenvector; CEU: Central European ancestry population; GENISIS, Genetics of Early Neurological Instability after Ischemic Stroke project; GODS, Genetic contribution to functional Outcome and Disability after Stroke project; GRECOS, Genotyping Recurrence Risk of Stroke. Axis labels indicate the percentage of variance explained by the eigenvector. Central European ancestry population belongs to The HapMap 3 project.

Online Figure III. Principal components included in the replication stage.



EV: Eigenvector; CEU: Central European ancestry population; GenoTPA, Genetic study in ischemic stroke patients treated with t-PA; BASICMAR, Base de Datos de Ictus del Hospital del Mar; LSGS, Leuven Stroke Genetics Study; HELSINKI2000, Helsinki 2000 Ischemic Stroke Genetics Study; G.FINLAND: GENISIS Finland. G.POLAND: GENISIS Poland. Axis labels indicate the percentage of variance explained by the eigenvector. Central European ancestry population belongs to The HapMap 3 project.

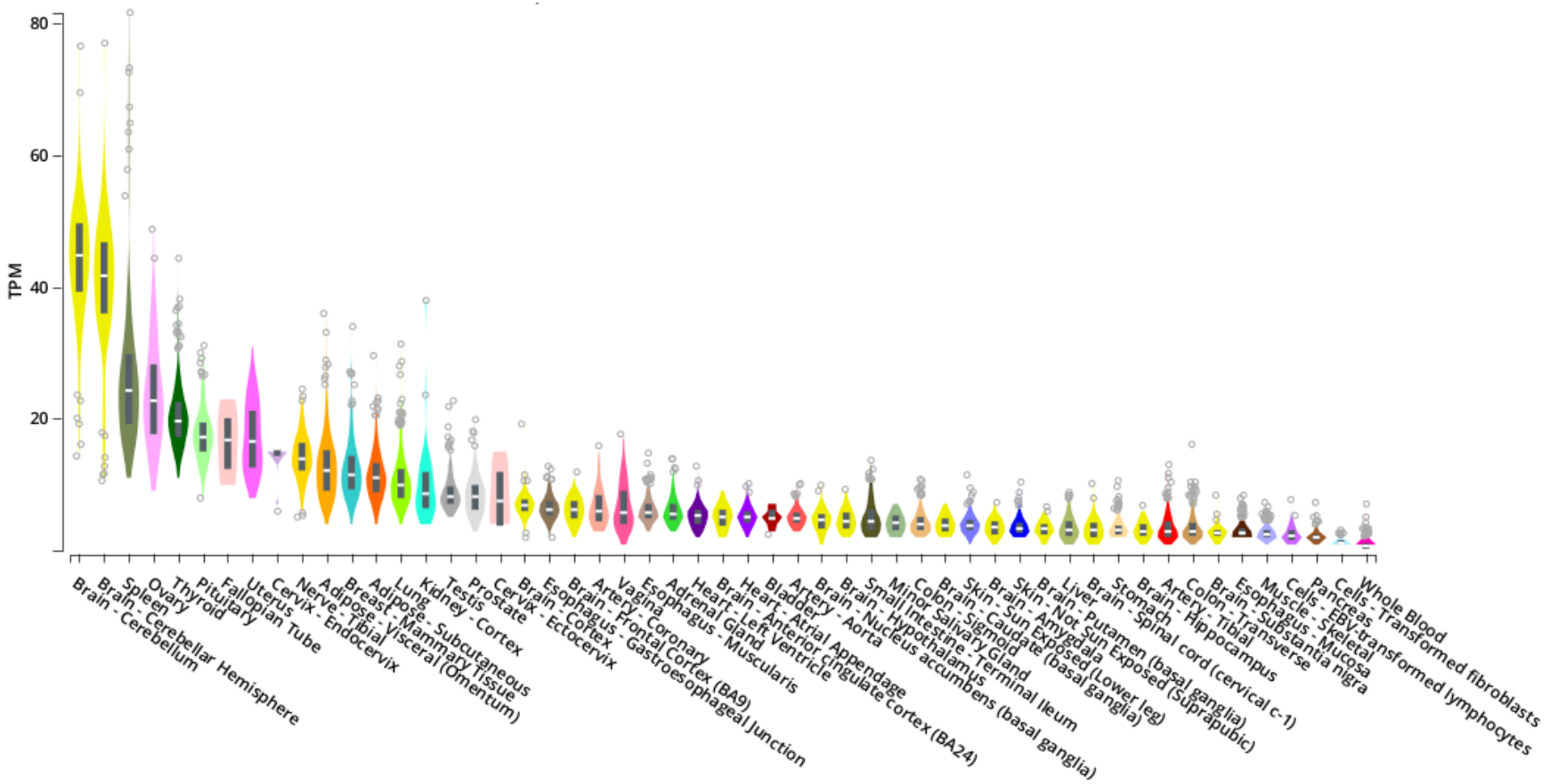
Online Figure IV. Manhattan plot and QQ plot of the discovery phase.



A. Manhattan plot of genome-wide association discovery-study. SNPs were represented by dots and plotted based on their genome-wide association study p-values. Redline shows genome-wide significance ($p < 5\times10^{-8}$) and blue line represents the suggestive association significance threshold ($p<1x10^{-5}$). Results were adjusted for age, sex, baseline NIH Stroke Scale score, diabetes, and three principal components.

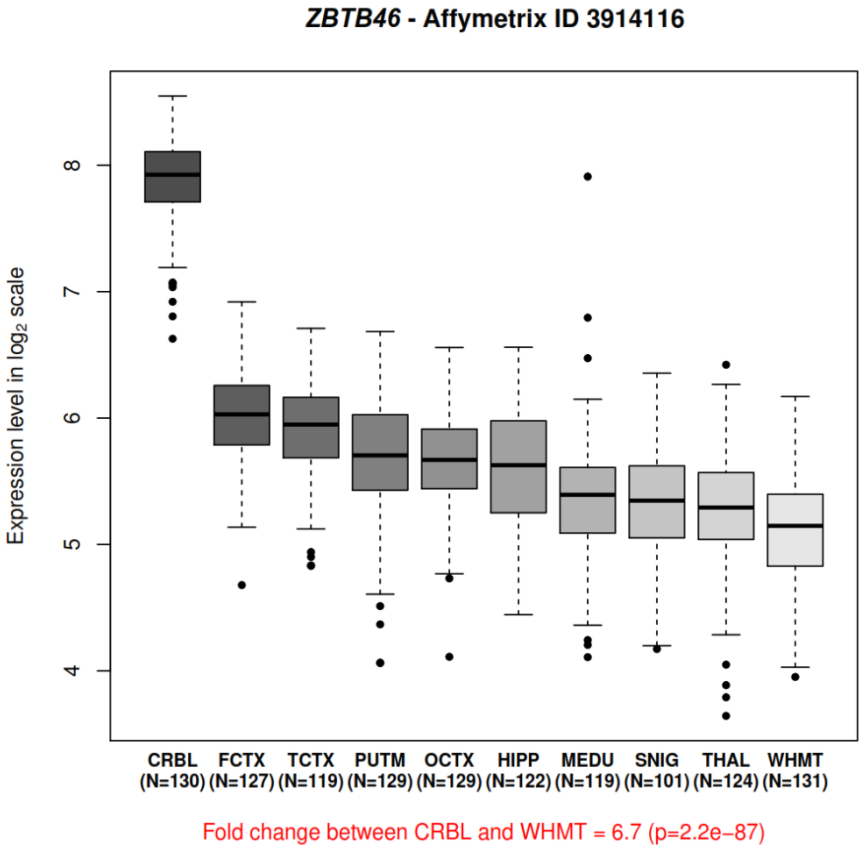
B. Quantile-quantile plot of the p-values obtained after the association testing. The *x*-axis represents the expected $-\log_{10}$ p-value under the null hypothesis and lambda is the median of the resulting chi-squared test statistics divided by the expected median of the chi-squared distribution under the null hypothesis.

Online Figure V. Gene expression of *ZBTB46* in human tissues.

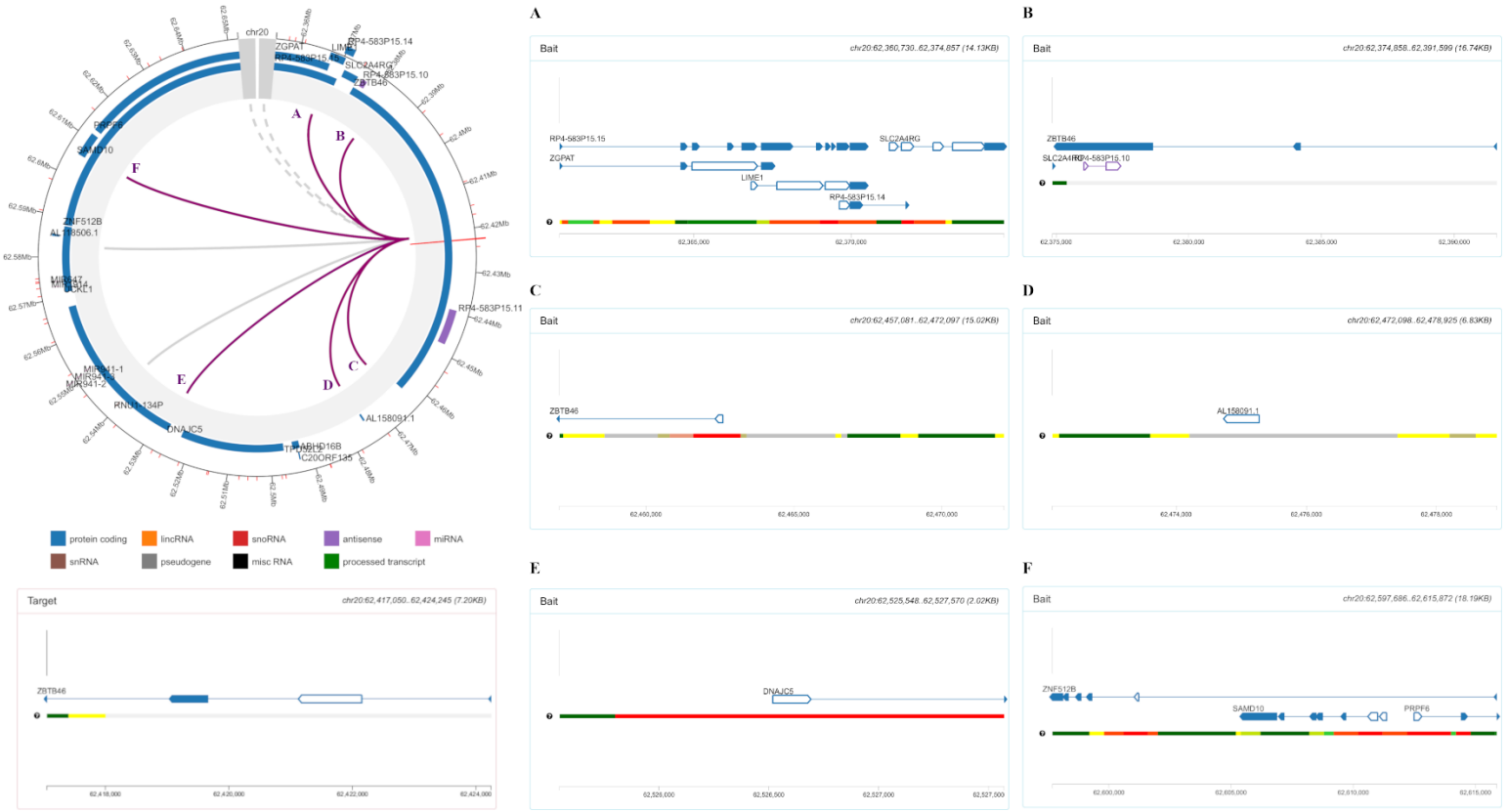


Gene expression for *ZBTB46* (ENSG00000130584.6) was represented by Transcripts per Million (TPM). Data were extracted from GTEx portal on 06/20/2019

Online Figure VI. Expression of *ZBTB46* transcript across brain tissues from BRAINEAC (Braineac.org) database, web server for data from the UK Brain Expression Consortium (UKBEC). The UKBEC dataset consists of 134 individuals in ten CNS regions including the cerebellum (CRBL), n = 130; frontal cortex (FCTX), n = 127; temporal cortex (TCTX), n = 119; putamen (PUTM), n = 129; occipital cortex (OCTX), n = 129; hippocampus (HIPP), n = 122; medulla (MEDU), n = 119; substantia nigra (SNIG), n = 101; thalamus (THAL), n = 124; and white matter (WHMT), n = 131.



Online Figure VII. Capture Hi-C interactions of rs76484331 in GM12878 cells.



The left diagram shows the location of the variant rs76484331 (red line across all the tracks) and its interactions with DNA regulatory elements (purple arcs A-F), the diagram was restricted to a window of 300 Kb. The red panel presented the target (rs76484331), whether blue panels (A-F) represent the chromatin fragments identified as baits. The panels illustrate canonical genes transcripts, where exons with a white are those containing transcriptional start sites. Each bait region is identified by colors: yellow – enhancers; dark green – weak transcription; light green – transcription at gene 5′ and 3′; red – flanking active transcription start sites.Data were extracted from GTEx portal on 10/29/2019.

III. Online Methods.

I. Description of the cohorts used the discovery stage.

Genetics of Early Neurological Instability after Ischemic Stroke (GENISIS)

GENISIS is an international project which aim is to capture the variety of mechanisms related to brain injury and early recovery. The study consisted in ischemic stroke patients, with neurological evaluation (NIHSS)[1] within 6 hours from onset of symptoms and 24-hours follow-up. The stroke diagnosis was performed by trained neurologists and confirmed by neuroimaging. Participants had to be over the age of 18 years, have provided informed consent, and do not underwent endovascular thrombectomy. Local Institutional Review Boards approved the enrolling and the data collection in each site[2].

Patients treated with rtPA and information of hemorrhagic transformation were selected from Spain recruitment sites: Vall d'Hebron University Hospital, Hospital Universitari Germans Trias I Pujol, Hospital Universitari del Mar, Hospital de la Santa Creu i Sant Pau, Mutua de Terrassa University Hospital, Hospital Universitario de Albacete, Hospital Clínico Universitario Valladolid, Hospital Clínico Universitario de Santiago, Hospital Virgen del Rocío y Virgen de la Macarena, Hospital Universitari Son Espases, Hospital Clinic. Meanwhile for replication stage, participants from Finland (Helsinki University Central Hospital) and Poland (Jagiellonian University Hospital) were included.

Genetic contribution to functional Outcome and Disability after Stroke (GODS)

Subjects with diagnosis of acute ischemic stroke, baseline NIHSS[1] assessment >4, and functional outcome[3] at 90 days were selected from the Spanish Stroke Genetics Consortium (GeneStroke). Diagnosis of ischemic stroke was based on neurological symptoms and neuroimaging. Subjects were excluded whether aged <18 years old, concomitant pathology or recurrent stroke during the 3 months follow-up occurs, and posterior vascular territory infarction or lacunar stroke were detected. Each one of the Ethics Committees of the participating centers approved the study, and all patients or relatives signed the informed consent[4].

Acute ischemic stroke participants were recruited at Spanish centers: Hospital Universitari del Mar (Barcelona), Hospital Universitari Son Espases (Mallorca), Vall d' Hebron University Hospital (Barcelona), Hospital Clínic (Barcelona), Hospital Universitari de Girona Doctor Josep Trueta (Girona), Hospital de la Santa Creu i Sant Pau (Barcelona), Hospital Universitari Germans Trias I Pujol (Can Ruti) and Hospital de Basurto (Bilbao). All the selected patients received intravenous thrombolytic therapy.

Genotyping Recurrence Risk of Stroke (GRECOS)

Consecutive Caucasian patients, aged >18 years old, with a first ischemic stroke that were admitted to the emergency department of 23 Spanish Hospitals were recruited. Stroke diagnosis was performed by trained neurologists, according to the World Health Organization definition[5] and confirmed by neuroimaging. For the present study, we selected patients treated with rtPA, who were enrolled at the Vall d' Hebron University Hospital.

Patients with modified Rankin Scale (mRS)[3] at discharge ≥4, with a life expectancy lower than one year at the time of inclusion, and patients participating in a clinical trial of secondary

prevention of stroke were excluded. On basis of their experience and information provided by other physicians, the neurologists decided whether to include or exclude each patient from the study. Risk factors, clinical evolution and radiological data were collected from the clinical records during hospitalization. One-year follow-up were performed to record the occurrence of ischemic stroke recurrence or global vascular recurrences. Moreover, each participant received a phone call and standard questionnaires to capture follow-up clinical and demographic every 3 months. The study was approved by the ethics committee, and all patients or their relatives gave informed written consent.[6] PH cases were selected and then matched with controls. The balance was at least 1:1 and we considered hospital of recruitment, age (±10 years) sex and TOAST.

II. Description of the cohorts for the replication stage.

PH cases were selected and then matched with controls. The balance was at least 1:1 and we considered hospital of recruitment, age (±10 years) sex and TOAST.

The Genetic study in ischemic stroke patients treated with tPA (GenoTPA)

We recruited consecutive Caucasian patients with acute ischemic stroke who were admitted to the emergency room and received rtPA within 4.5 hours of onset of symptoms. Patients were enrrolled at Spanish hospitals (Vall d'Hebron University Hospital, Hospital Clinic, Hospital Universitari de Girona Doctor Josep Trueta, Hospital de la Santa Creu i Sant Pau, Hospital Universitari Germans Trias I Pujol, Hospital Universitari del Mar, Hospital de Basurto) between 2002 to 2012. The study protocol was approved by the Ethics Committee of each center, all patients or relatives signed the informed consent.

Patients were identified by medical evaluation at emergency room arrival; stroke diagnosis was performed by trained neurologists and confirmed by neuroimaging. There were no exclusion criteria regarding age, sex or ethnicity. Follow-up CT scan at 24 hours after onset of symptoms or if neurological worsening occurred were performed and was classified according to European Cooperative Acute Stroke Study (ECASS)[7].

BASe de datos de ICtus del hospital del Mar (BASICMAR)

The Stroke database from Hospital del Mar (BASICMAR) is an ongoing prospective study of all acute strokes assessed since 2005 at the IMIM-Hospital Universitari del Mar (Barcelona, Spain). The hospital serves three of the ten districts in Barcelona, Spain providing medical care for a population of 339,196. Patients with first-ever and recurrent stroke are included. There are no exclusion criteria regarding age, sex or ethnicity. All participants provided written consent. Clinical evaluation and neuroimaging were assessed by trained neurologist. Patients with acute infarct confirmed radiographically and treated with thrombolysis therapy were selected[8].

Leuven Stroke Genetics Study (LSGS)

Patients admitted to the Stroke Unit of the University Hospitals at Leuven, Belgium between 2005 and 2009 were enrolled. Subjects were European descent, aged 18 years or older with acute cerebral ischemia, defined as a clinical stroke with imaging confirmation. All participants underwent brain imaging and a standardized protocol including lab examination, carotid ultrasound, and cardiac examination[8]. Those who received rtPA and with 24 hours follow-up CT scan were select. Hemorrhagic transformation subtype was determining following the European

Cooperative Acute Stroke Study (ECASS)[7]. Written informed consent was obtained from all subjects.

Helsinki 2000 Ischemic Stroke Genetics Study (HELSINKI2000).

The study was designed for investigating genetic factors underlying ischemic stroke in a Finnish population and in the long-term to be incorporated to multicenter multinational similar datasets. This study received approval from local ethics committee (October 27, 2010; and Amended June 27, 2016). All ischemic stroke cases in this study were recruited from the Helsinki University Central Hospital, which is the only neurological emergency unit for a population of 1.5 million inhabitants[9]. Only patients with positive neuroimaging findings for a new-onset brain infarction were recruited following written informed consent. All included subjects are of Finnish Caucasian origin.

III. Clinical risk factors definitions.

Atrial fibrillation (AF), the subject carries a pre-existing diagnosis of AF, and may or may not be anticoagulated; or the subject has an EKG in the EMR showing AF.

Diabetes mellitus (DM), when a pre-existing diagnosis of diabetes is present and is taking diabetic medication (oral and/or insulin). A pre-existing diagnosis of diabetes is not taking diabetic medication and has an elevated blood sugar at the time of acute evaluation.

Arterial hypertension (HTN), when the subject carries a pre-existing diagnosis of arterial hypertension; and may or may not be treated by antihypertensive medication.

Statins (ST), whether the subject (or family member) confirms that they are regularly taking a medication within the statin family and/or a medication within the statin family is listed on the medication reconciliation at admission.

Stroke etiologic subtypes (TOAST), the ischemic stroke (IS) subtypes were classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST)[10]:

> Cardioembolism (CE), IS resulted from an embolism originating in the heart.
>
> Large Artery Atherosclerosis (LAA), IS resulted from occlusion of a large, major named vessel of the brain or neck.
>
> Small Vessel Occlusion (SVO), lacunar syndrome with or without evidence of ischemic lesion less than 1.5 cm in diameter in the brain stem or subcortical white matter.
>
> Other Etiology (OT), rare causes such as non-atherosclerotic vasculopathies, hematologic disorders, or hypercoagulable states.
>
> Undetermined Etiology (UND) includes: two or more causes, a negative evaluation (unknown etiology), or incomplete evaluation.

Baseline NIHSS, National Institutes of Health Stroke Scale[1] (0-42 points) assessed at the initial clinical evaluation.

Glucose, a measurement of the blood glucose level in mg/dl obtained in the acute setting during the initial clinical evaluation or before rtPA bolus.

Time from onset to treatment (OTT), was calculated using the time when the patient was last known seen without neurologically symptoms and the time of rtPA bolus administration. Whether the patient was sleeping and wakes up with symptoms, the last time the patient was known to have been alert and oriented.

Blood pressure (SBP / DBP), was measured in mmHg at the time of admission to the emergency department, prior to rtPA bolus.

IV. Genome-Wide Association Studies and meta-analysis quality controls.

Pre-imputation quality controls were applied using PLINK v1.9. Briefly, samples filters included sex discordance, duplicate or kinship (Pihat >0.18), missing data rate (>5%) and batch effects. As well, ethnic outliers from European ancestry were discarded (>6 SDs from mean) by a projection of principal components (PC) onto HapMap3 data. Genetic variants were removed based on genotyping call rate (<97%), minor allele frequency (MAF <1%) and significantly out Hardy Weinberg equilibrium ($p=1x10^{-6}$)[11]. Further, A/T and C/G SNPs were discarded to avoid unreliable strand orientation; then polymorphisms were aligned with the 1000 Genome Project (1000G) Phase 3 reference panel[12].

Later than imputation, genetic variants with R-square imputation accuracy lower than 0.3, allele frequency value of 1%, and concordance difference by more than ±0.2 among studied and the reference population allele frequencies were excluded.

Prior meta-analysis, the discovery and replication studies underwent harmonization and quality controls[13], consisting of MAF (<0.03), imputation accuracy (<0.5) and extreme effect values (beta ≥4 or ≤−4).

V. Independent genomic loci and functional annotation.

Independent SNPs were selected based on genome-wide significance and r2<0.6 within a 250 Kb gene window size, the lead SNP was identified using 1000G Phase 3. Functional annotation was performed through the Annotate Variation (ANNOVAR) system[14] and the Functional Mapping and Annotation of Genome-wide Association Studies (FUMA)[15].

VI. Poligenic Risk Score generation.

We performed the best-fit function of PRSice-2, which runs logistic regressions to determine the p-threshold with the largest variance explained by the PRS, assessed as the increment in Nagelkerke's pseudo-R2. The best-fit for the PRS estimation of disability after three months was observed for a threshold of p=0.00530005, pseudo-R2= 0.0684721, and composed by 3,506 SNPs.

Welch Two Sample t-test was performed to further study this PRS against PH, mortality after 3 months and in-hospital mortality in the replication cohort. Significant association was observed with PH and mortality after 3 months, but we did not find an association with in-hospital mortality (Online Table IX). Interestingly in a multivariable logistic regression for disability after three months the PRS remained significant in the logistic regression after inclusion of clinical variables: NIHSS, sex and age (Online Table X).

VII. URL.

Cerebrovascular Portal: https://cerebrovascularportal.org/
Capture HiC Plotter: https://www.-chicp.org/
eQTL consortium: https://www.eqtlgen.org/
FUMA: https://fuma.ctglab.nl/
GTEX: https://gtexportal.org/home/
METAL: https://genome.sph.umich.edu/wiki/METAL;
Michigan Imputation Server: https://imputationserver.sph.umich.edu/index.html#!;
PhenoScanner: http://www.phenoscanner.medschl.cam.ac.uk/
PLINK: http://www.cog-genomics.org/plink2/
RegulomeDB: http://www.regulomedb.org/
SHAPEIT: https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html
Single-nuclei Brain RNA-seq expression browser: http://ngi.pub/snuclRNA-seq/
SMR & HEIDI: http://cnsgenomics.com/software/smr/#Overview
SNPTEST: https://mathgen.stats.ox.ac.uk/genetics_software/snptest/snptest.html

IV. Online References.

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