

SUPPLEMENTARY MATERIAL

Vascular Endothelial Growth Factor and Ischemic Stroke Risk: A Mendelian Randomization Study

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Supplementary Table 1. Genetic variants for VEGF and each outcome (GIGASTROKE)

SNP	Outcome	EAF								N	GY	SE_GY	F
		chr	pos	a1	a2	GX	SE_GX	P					
rs10761741	LAS	10	65066186	T	G	0.4334	0.0800	0.0090	2.99E-19	1241207	0.0153	0.0211	79.01
rs114694170	LAS	5	88180196	C	T	0.0546	0.1500	0.0230	1.09E-11	1241207	0.0899	0.0515	42.53
rs1740073	LAS	6	43947398	T	C	0.3769	0.0900	0.0100	4.40E-17	1241207	-0.0012	0.0254	81.00
rs2375981	LAS	9	2692583	C	G	0.5365	0.2100	0.0100	9.49E-99	1241207	0.0021	0.0215	441.00
rs2639990	LAS	18	72915551	T	C	0.9209	0.1100	0.0180	5.85E-10	1241207	-0.0485	0.0431	37.35
rs4782371	LAS	16	88568831	G	T	0.3111	0.0700	0.0110	1.26E-09	1241207	-0.0313	0.0284	40.50
rs6921438	LAS	6	43925607	G	A	0.5273	0.6400	0.0080	1.00E-200	1241207	0.0012	0.0224	6399.99
rs6993770	LAS	8	106581528	A	T	0.7141	0.1600	0.0100	3.83E-55	1241207	0.0237	0.0233	256.00
rs7043199	LAS	9	2621145	T	A	0.7840	0.1000	0.0130	4.16E-14	1241207	0.0513	0.0294	59.17
rs10761741	AIS	10	65066186	T	G	0.4188	0.0800	0.0090	2.99E-19	1296908	0.0069	0.0070	79.01
rs114694170	AIS	5	88180196	C	T	0.0591	0.1500	0.0230	1.09E-11	1296908	0.0312	0.0156	42.53
rs1740073	AIS	6	43947398	T	C	0.3868	0.0900	0.0100	4.40E-17	1296908	0.0085	0.0080	81.00
rs2375981	AIS	9	2692583	C	G	0.5395	0.2100	0.0100	9.49E-99	1296908	0.0045	0.0071	441.00
rs2639990	AIS	18	72915551	T	C	0.9340	0.1100	0.0180	5.85E-10	1296908	-0.0131	0.0162	37.35
rs4782371	AIS	16	88568831	G	T	0.3015	0.0700	0.0110	1.26E-09	1296908	0.0052	0.0084	40.50
rs6921438	AIS	6	43925607	G	A	0.5187	0.6400	0.0080	1.00E-200	1296908	0.0006	0.0073	6399.99
rs6993770	AIS	8	106581528	A	T	0.7379	0.1600	0.0100	3.83E-55	1296908	0.0166	0.0080	256.00
rs7043199	AIS	9	2621145	T	A	0.7728	0.1000	0.0130	4.16E-14	1296908	-0.0080	0.0092	59.17
rs10761741	CES	10	65066186	T	G	0.4305	0.0800	0.0090	2.99E-19	1245612	0.0437	0.0166	79.01
rs114694170	CES	5	88180196	C	T	0.0604	0.1500	0.0230	1.09E-11	1245612	0.0341	0.0369	42.53
rs1740073	CES	6	43947398	T	C	0.3796	0.0900	0.0100	4.40E-17	1245612	-0.0032	0.0184	81.00
rs2375981	CES	9	2692583	C	G	0.5381	0.2100	0.0100	9.49E-99	1245612	0.0221	0.0163	441.00
rs2639990	CES	18	72915551	T	C	0.9274	0.1100	0.0180	5.85E-10	1245612	0.0054	0.0352	37.35
rs4782371	CES	16	88568831	G	T	0.3072	0.0700	0.0110	1.26E-09	1245612	0.0282	0.0196	40.50
rs6921438	CES	6	43925607	G	A	0.5229	0.6400	0.0080	1.00E-200	1245612	0.0265	0.0170	6399.99
rs6993770	CES	8	106581528	A	T	0.7278	0.1600	0.0100	3.83E-55	1245612	-0.0338	0.0180	256.00
rs7043199	CES	9	2621145	T	A	0.7748	0.1000	0.0130	4.16E-14	1245612	-0.0449	0.0212	59.17

SNP: single nucleotide polymorphism; chr: chromosome number; pos: position of the lead SNP (GRCh37/hg19); EAF: effect allele frequency; a1: coding/effective allele; a2: the other allele; P: P-value, two-tailed and unadjusted (marginal z-test). GX: beta for the SNP-VEGF relationship; SE_GX: standard error of GX. GX: beta for the SNP-stroke relationship; SE_GY: standard error of GY. LAS: Large Artery Stroke; CES: Cardioembolic Stroke; SVS: Small-Vessel Ischemic Stroke (SVS); F-statistic: a measurement of instrument's strength, calculated by: $F\text{-statistic} = R^2 * (N - 2) / (1 - R^2)$ [1]. $\#R^2 = 2 * GX^2 * EAF * (1 - EAF) / [2 * GX^2 * EAF * (1 - EAF) + SE_GX^2 * 2 * N * EAF * (1 - EAF)]$ [2].

Supplementary Table 2. Genetic variants for VEGF and each outcome (MEGASTROKE)

SNP	Outcome	EAF								N	GY	SE_GY	F
		chr	pos	a1	a2	GX	SE_GX	P					Statistics
rs10761741	LAS	10	65066186	T	G	0.4292	0.0800	0.0090	2.99E-19	410484	0.0079	0.0244	79.01
rs114694170	LAS	5	88180196	C	T	0.0576	0.1500	0.0230	1.09E-11	410484	0.0971	0.0592	42.53
rs1740073	LAS	6	43947398	T	C	0.3742	0.0900	0.0100	4.40E-17	410484	0.0202	0.0263	81.00
rs2375981	LAS	9	2692583	C	G	0.5359	0.2100	0.0100	9.49E-99	410484	0.0145	0.0251	441.00
rs2639990	LAS	18	72915551	T	C	0.9248	0.1100	0.0180	5.85E-10	410484	-0.0593	0.0550	37.35
rs4782371	LAS	16	88568831	G	T	0.3094	0.0700	0.0110	1.26E-09	410484	-0.0332	0.0301	40.50
rs6921438	LAS	6	43925607	G	A	0.5221	0.6400	0.0080	1.00E-200	410484	0.0092	0.0258	6399.97
rs6993770	LAS	8	106581528	A	T	0.7217	0.1600	0.0100	3.83E-55	410484	0.0307	0.0277	256.00
rs7043199	LAS	9	2621145	T	A	0.7827	0.1000	0.0130	4.16E-14	410484	0.0600	0.0335	59.17
rs10761741	AIS	10	65066186	T	G	0.4280	0.0800	0.0090	2.99E-19	440328	-0.0019	0.0100	79.01
rs114694170	AIS	5	88180196	C	T	0.0603	0.1500	0.0230	1.09E-11	440328	0.0082	0.0232	42.53
rs1740073	AIS	6	43947398	T	C	0.3747	0.0900	0.0100	4.40E-17	440328	0.0083	0.0105	81.00
rs2375981	AIS	9	2692583	C	G	0.5389	0.2100	0.0100	9.49E-99	440328	0.0079	0.0103	441.00
rs2639990	AIS	18	72915551	T	C	0.9290	0.1100	0.0180	5.85E-10	440328	-0.0157	0.0224	37.35
rs4782371	AIS	16	88568831	G	T	0.3085	0.0700	0.0110	1.26E-09	440328	0.0049	0.0122	40.50
rs6921438	AIS	6	43925607	G	A	0.5221	0.6400	0.0080	1.00E-200	440328	0.0031	0.0102	6399.97
rs6993770	AIS	8	106581528	A	T	0.7270	0.1600	0.0100	3.83E-55	440328	0.0213	0.0112	256.00
rs7043199	AIS	9	2621145	T	A	0.7790	0.1000	0.0130	4.16E-14	440328	0.0184	0.0129	59.17
rs10761741	SVS	10	65066186	T	G	0.4259	0.0800	0.0090	2.99E-19	198048	-0.0684	0.0227	79.01
rs114694170	SVS	5	88180196	C	T	0.0583	0.1500	0.0230	1.09E-11	198048	0.0668	0.0548	42.53
rs1740073	SVS	6	43947398	T	C	0.3750	0.0900	0.0100	4.40E-17	198048	0.0293	0.0247	81.00
rs2375981	SVS	9	2692583	C	G	0.5380	0.2100	0.0100	9.49E-99	198048	0.0177	0.0233	441.00
rs2639990	SVS	18	72915551	T	C	0.9271	0.1100	0.0180	5.85E-10	198048	-0.0085	0.0508	37.35
rs4782371	SVS	16	88568831	G	T	0.3059	0.0700	0.0110	1.26E-09	198048	0.0316	0.0278	40.50
rs6921438	SVS	6	43925607	G	A	0.5198	0.6400	0.0080	1.00E-200	198048	-0.0412	0.0237	6399.94
rs6993770	SVS	8	106581528	A	T	0.7217	0.1600	0.0100	3.83E-55	198048	-0.0009	0.0255	256.00
rs7043199	SVS	9	2621145	T	A	0.7799	0.1000	0.0130	4.16E-14	198048	0.0185	0.0306	59.17
rs10761741	CES	10	65066186	T	G	0.4291	0.0800	0.0090	2.99E-19	413304	0.0350	0.0203	79.01
rs114694170	CES	5	88180196	C	T	0.0622	0.1500	0.0230	1.09E-11	413304	0.0324	0.0467	42.53
rs1740073	CES	6	43947398	T	C	0.3729	0.0900	0.0100	4.40E-17	413304	0.0011	0.0204	81.00
rs2375981	CES	9	2692583	C	G	0.5366	0.2100	0.0100	9.49E-99	413304	0.0373	0.0196	441.00
rs2639990	CES	18	72915551	T	C	0.9253	0.1100	0.0180	5.85E-10	413304	-0.0431	0.0438	37.35
rs4782371	CES	16	88568831	G	T	0.3111	0.0700	0.0110	1.26E-09	413304	0.0410	0.0233	40.50
rs6921438	CES	6	43925607	G	A	0.5243	0.6400	0.0080	1.00E-200	413304	0.0022	0.0199	6399.97
rs6993770	CES	8	106581528	A	T	0.7251	0.1600	0.0100	3.83E-55	413304	-0.0241	0.0215	256.00
rs7043199	CES	9	2621145	T	A	0.7805	0.1000	0.0130	4.16E-14	413304	-0.0624	0.0250	59.17

SNP: single nucleotide polymorphism; chr: chromosome number; pos: position of the lead SNP

(GRCh37/hg19); EAF: effect allele frequency; a1: coding/effective allele; a2: the other allele; P: P-value, two-tailed and unadjusted (marginal z-test). GX: beta for the SNP-VEGF relationship; SE_GX: standard error of GX. GX: beta for the SNP-stroke relationship; SE_GY: standard error of GY. LAS: Large Artery Stroke; CES: Cardioembolic Stroke; SVS: Small-Vessel Ischemic Stroke (SVS); F-statistic: a measurement of instrument's strength, calculated by: $F\text{-statistic} = R^2 * (N - 2) / (1 - R^2)$ [1]. $\#R^2 = 2 * GX^2 * EAF * (1 - EAF) / [2 * GX^2 * EAF * (1 - EAF) + SE_GX^2 * 2 * N * EAF * (1 - EAF)]$ [2].

Supplementary Table 3. Causal effects of single instrument between VEGF and each outcome

Outcome	Dataset	SNP	Beta	Se	P	OR(95% CIs)
LAS	GIGASTROKE	rs10761741	0.1913	0.2638	4.68E-01	1.21(0.72~2.03)
LAS	GIGASTROKE	rs114694170	0.5993	0.3433	8.09E-02	1.82(0.92~3.56)
LAS	GIGASTROKE	rs1740073	-0.0133	0.2822	9.62E-01	0.98(0.56~1.71)
LAS	GIGASTROKE	rs2375981	0.0100	0.1024	9.22E-01	1.01(0.82~1.23)
LAS	GIGASTROKE	rs2639990	-0.4409	0.3918	2.60E-01	0.64(0.29~1.38)
LAS	GIGASTROKE	rs4782371	-0.4471	0.4057	2.70E-01	0.63(0.28~1.41)
LAS	GIGASTROKE	rs6921438	0.0019	0.0350	9.57E-01	1.00(0.93~1.07)
LAS	GIGASTROKE	rs6993770	0.1481	0.1456	3.09E-01	1.15(0.87~1.54)
LAS	GIGASTROKE	rs7043199	0.5130	0.2940	8.10E-02	1.67(0.93~2.97)
CES	GIGASTROKE	rs10761741	0.5463	0.2075	8.48E-03	1.72(1.14~2.59)
CES	GIGASTROKE	rs114694170	0.2273	0.2460	3.55E-01	1.25(0.77~2.03)
CES	GIGASTROKE	rs1740073	-0.0356	0.2044	8.62E-01	0.96(0.64~1.44)
CES	GIGASTROKE	rs2375981	0.1052	0.0776	1.75E-01	1.11(0.95~1.29)
CES	GIGASTROKE	rs2639990	0.0491	0.3200	8.78E-01	1.05(0.56~1.96)
CES	GIGASTROKE	rs4782371	0.4029	0.2800	1.50E-01	1.49(0.86~2.58)
CES	GIGASTROKE	rs6921438	0.0414	0.0266	1.19E-01	1.04(0.98~1.09)
CES	GIGASTROKE	rs6993770	-0.2113	0.1125	6.04E-02	0.80(0.64~1.00)
CES	GIGASTROKE	rs7043199	-0.4490	0.2120	3.42E-02	0.63(0.42~0.96)
SVS	GIGASTROKE	rs10761741	-0.5450	0.2463	2.69E-02	0.57(0.35~0.93)
SVS	GIGASTROKE	rs114694170	0.1507	0.3193	6.37E-01	1.16(0.62~2.17)
SVS	GIGASTROKE	rs1740073	0.4089	0.2467	9.74E-02	1.50(0.92~2.44)
SVS	GIGASTROKE	rs2375981	0.1000	0.0957	2.96E-01	1.10(0.91~1.33)
SVS	GIGASTROKE	rs2639990	0.2173	0.3991	5.86E-01	1.24(0.56~2.71)
SVS	GIGASTROKE	rs4782371	0.0157	0.3529	9.64E-01	1.01(0.50~2.02)
SVS	GIGASTROKE	rs6921438	-0.0469	0.0323	1.47E-01	0.95(0.89~1.01)
SVS	GIGASTROKE	rs6993770	0.0294	0.1381	8.32E-01	1.02(0.78~1.34)
SVS	GIGASTROKE	rs7043199	0.1270	0.2690	6.37E-01	1.13(0.67~1.92)
AIS	GIGASTROKE	rs10761741	0.0863	0.0875	3.24E-01	1.09(0.91~1.29)
AIS	GIGASTROKE	rs114694170	0.2080	0.1040	4.55E-02	1.23(1.00~1.50)
AIS	GIGASTROKE	rs1740073	0.0944	0.0889	2.88E-01	1.09(0.92~1.30)
AIS	GIGASTROKE	rs2375981	0.0214	0.0338	5.26E-01	1.02(0.95~1.09)
AIS	GIGASTROKE	rs2639990	-0.1191	0.1473	4.19E-01	0.88(0.66~1.18)

AIS	GIGASTROKE	rs4782371	0.0743	0.1200	5.36E-01	1.07(0.85~1.36)
AIS	GIGASTROKE	rs6921438	0.0009	0.0114	9.34E-01	1.00(0.97~1.02)
AIS	GIGASTROKE	rs6993770	0.1038	0.0500	3.80E-02	1.10(1.00~1.22)
AIS	GIGASTROKE	rs7043199	-0.0800	0.0920	3.85E-01	0.92(0.77~1.10)
LAS	MEGASTROKE	rs10761741	0.0988	0.3050	7.46E-01	1.10(0.60~2.00)
LAS	MEGASTROKE	rs114694170	0.6473	0.3947	1.01E-01	1.91(0.88~4.14)
LAS	MEGASTROKE	rs1740073	0.2244	0.2922	4.42E-01	1.25(0.70~2.21)
LAS	MEGASTROKE	rs2375981	0.0690	0.1195	5.63E-01	1.07(0.84~1.35)
LAS	MEGASTROKE	rs2639990	-0.5391	0.5000	2.81E-01	0.58(0.21~1.55)
LAS	MEGASTROKE	rs4782371	-0.4743	0.4300	2.70E-01	0.62(0.26~1.44)
LAS	MEGASTROKE	rs6921438	0.0144	0.0403	7.21E-01	1.01(0.93~1.09)
LAS	MEGASTROKE	rs6993770	0.1919	0.1731	2.68E-01	1.21(0.86~1.70)
LAS	MEGASTROKE	rs7043199	0.6000	0.3350	7.33E-02	1.82(0.94~3.51)
AIS	MEGASTROKE	rs10761741	-0.0238	0.1250	8.49E-01	0.97(0.76~1.24)
AIS	MEGASTROKE	rs114694170	0.0547	0.1547	7.24E-01	1.05(0.77~1.43)
AIS	MEGASTROKE	rs1740073	0.0922	0.1167	4.29E-01	1.09(0.87~1.37)
AIS	MEGASTROKE	rs2375981	0.0376	0.0490	4.43E-01	1.03(0.94~1.14)
AIS	MEGASTROKE	rs2639990	-0.1427	0.2036	4.83E-01	0.86(0.58~1.29)
AIS	MEGASTROKE	rs4782371	0.0700	0.1743	6.88E-01	1.07(0.76~1.50)
AIS	MEGASTROKE	rs6921438	0.0048	0.0159	7.61E-01	1.00(0.97~1.03)
AIS	MEGASTROKE	rs6993770	0.1331	0.0700	5.72E-02	1.14(0.99~1.31)
AIS	MEGASTROKE	rs7043199	0.1840	0.1290	1.54E-01	1.20(0.93~1.54)
SVS	MEGASTROKE	rs10761741	-0.8550	0.2838	2.58E-03	0.42(0.24~0.74)
SVS	MEGASTROKE	rs114694170	0.4453	0.3653	2.23E-01	1.56(0.76~3.19)
SVS	MEGASTROKE	rs1740073	0.3256	0.2744	2.36E-01	1.38(0.80~2.37)
SVS	MEGASTROKE	rs2375981	0.0843	0.1110	4.47E-01	1.08(0.87~1.35)
SVS	MEGASTROKE	rs2639990	-0.0773	0.4618	8.67E-01	0.92(0.37~2.28)
SVS	MEGASTROKE	rs4782371	0.4514	0.3971	2.56E-01	1.57(0.72~3.42)
SVS	MEGASTROKE	rs6921438	-0.0644	0.0370	8.21E-02	0.93(0.87~1.00)
SVS	MEGASTROKE	rs6993770	-0.0056	0.1594	9.72E-01	0.99(0.72~1.35)
SVS	MEGASTROKE	rs7043199	0.1850	0.3060	5.45E-01	1.20(0.66~2.19)
CAS	MEGASTROKE	rs10761741	0.4375	0.2538	8.47E-02	1.54(0.94~2.54)
CAS	MEGASTROKE	rs114694170	0.2160	0.3113	4.88E-01	1.24(0.67~2.28)
CAS	MEGASTROKE	rs1740073	0.0122	0.2267	9.57E-01	1.01(0.64~1.57)
CAS	MEGASTROKE	rs2375981	0.1776	0.0933	5.70E-02	1.19(0.99~1.43)
CAS	MEGASTROKE	rs2639990	-0.3918	0.3982	3.25E-01	0.67(0.30~1.47)
CAS	MEGASTROKE	rs4782371	0.5857	0.3329	7.85E-02	1.79(0.93~3.44)
CAS	MEGASTROKE	rs6921438	0.0034	0.0311	9.12E-01	1.00(0.94~1.06)
CAS	MEGASTROKE	rs6993770	-0.1506	0.1344	2.62E-01	0.86(0.66~1.11)
CAS	MEGASTROKE	rs7043199	-0.6240	0.2500	1.26E-02	0.53(0.32~0.87)

SNP: single nucleotide polymorphism; Beta: estimate of SNP effect size; Se: estimate of standard error; P: P-value, two-tailed and unadjusted (marginal z-test). OR: odds ratio; CIs: confidence intervals; LAS: Large Artery Stroke; CES: Cardioembolic Stroke; SVS: Small-Vessel Ischemic Stroke (SVS);

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