

Fine-Mapping of Intracranial Aneurysm Susceptibility Based on a Genome-Wide Association Study

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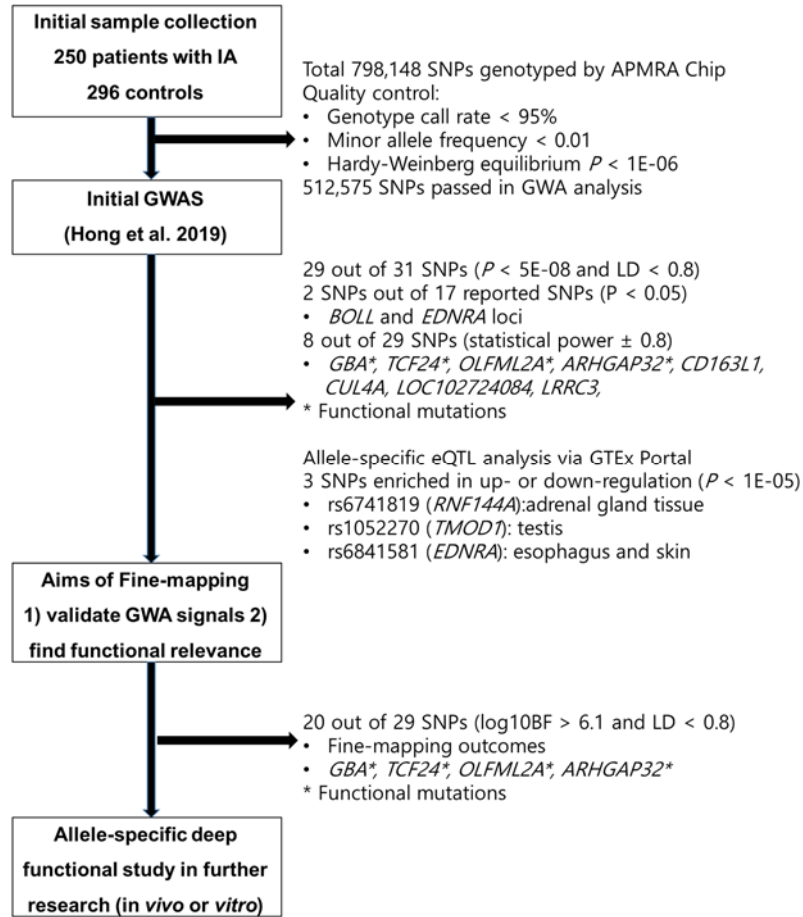
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SUPPLEMENTAL DATA

Supplementary Figure S1. Study workflow of genome-wide association study, fine-mapping, and further functional research. APMRA, AxiomTH Asian Precision Medicine Research Array; GWA, genome-wide association.



Supplementary Table S1. Comparison of genome-wide association study and FINEMAP results in intracranial aneurysm

Gene	Chr	SNP	Position	Function	Major ^a	Minor ^a	MAF	HWE p	lnOR ^b	P in GWAS ^b	log10BF ^c	PIP ^c	<i>h</i> ^{2c}
<i>PRDM2</i>	1p36.21	rs61775135	14148407	intronic	C	A	0.285	0.626	-1.15	3.59E-13	9.48	2.61E-06	0.073
<i>GBA</i>	1q22	rs75822236	155204793	R535H	C	T	0.166	1	5.08	1.09E-19	15.06	1.0000	0.109
<i>FMO4</i>	1q24.3	rs3737926	171303565	F281F	C	T	0.264	0.079	-1.01	1.83E-10	7.10	1.10E-08	0.058
<i>RNF144A</i>	2p25.1	rs6741819	7147973	intronic	C	T	0.247	0.022	-1.38	4.05E-14	10.30	0.0905	0.079
<i>HDAC4,LOC150935</i>	2q37.3	rs59626274	240500249	intergenic	C	T	0.248	0.002	-1.34	5.78E-14	10.18	0.0679	0.078
<i>LINC01237</i>	2q37.3	rs78458145	242877035	ncRNA_intronic	G	A	0.285	0.007	-1.41	3.14E-15	11.27	0.8416	0.085
<i>SPCS3,VEGFC</i>	4q34.2	rs17688188	177471059	intergenic	G	A	0.222	0.030	-1.31	5.99E-13	9.29	0.9999	0.072
<i>TCF24</i>	8q13.1	rs112859779	67860369	G141S	C	T	0.216	2.02E-04	-1.69	3.33E-16	12.12	1.0000	0.090
<i>CCDC171,C9orf92</i>	9p22.3	rs12350582	16135142	intergenic	A	G	0.255	0.841	0.89	1.49E-08	5.44	3.34E-10	0.046
<i>LINGO2</i>	9p21.1	rs56942085	28518911	intronic	G	A	0.061	1	1.81	3.90E-08	5.07	1.42E-10	0.044
<i>TMOD1</i>	9q22.33	rs1052270	100275424	intronic	C	T	0.344	0.042	-0.89	2.71E-08	5.21	1.97E-10	0.045
<i>MIR3134</i>	9q31.3	rs79461840	114822158	ncRNA_intronic	T	C	0.076	0.003	1.93	1.40E-08	5.46	3.51E-10	0.046
<i>LOC101928775,LINC00474</i>	9q33.1	rs4979583	118571428	intergenic	C	T	0.325	0.874	0.90	4.61E-09	5.88	9.29E-10	0.049
<i>OLFML2A</i>	9q33.3	rs79134766	127561723	A208T	G	A	0.219	0.054	-1.97	1.70E-19	14.92	1.0000	0.107
<i>MYEOV,LINC01488</i>	11q13.3	rs76855873	69154455	intergenic	C	T	0.269	0.023	-1.11	1.23E-11	8.15	1.89E-13	0.064
<i>ARHGAP32</i>	11q24.3	rs371331393	128839272	stopgain	G	A	0.171	1	3.77	9.32E-27	20.88	1.0000	0.143
<i>CD163L1</i>	12p13.31	rs138525217	7528192	splicing	C	T	0.161	1	4.33	6.20E-23	17.77	1.0000	0.125
<i>SLC2A14</i>	12p13.31	rs118107419	7980394	intronic	C	A	0.262	0.012	-1.40	1.44E-14	10.71	8.60E-08	0.081
<i>DRAM1,CCDC53</i>	12q23.2	rs7964241	102338235	intergenic	A	G	0.278	0.166	0.91	1.95E-08	5.33	3.58E-13	0.045
<i>DRAM1,CCDC53</i>	12q23.2	rs56168082	102339295	intergenic	G	A	0.276	0.166	0.89	3.93E-08	5.07	1.97E-13	0.044
<i>CUL4A,LAMP1</i>	13q34	rs74115822	113931854	intergenic	G	A	0.112	0.001	1.83	1.12E-10	7.32	0.9960	0.058
<i>MIR365A,PARN</i>	16p13.12	rs11646803	14463359	intergenic	C	T	0.376	0.074	-0.79	4.76E-10	6.77	0.9422	0.055
<i>LOC102724084</i>	16q23.2	rs75861150	80193070	ncRNA_intronic	T	C	0.091	2.17E-04	-1.93	1.27E-08	5.51	0.0520	0.046
<i>SCARF1</i>	17p13.3	17_1538628	1538628	E639E	G	C	0.265	0.147	-0.94	6.02E-09	5.79	0.0008	0.048

<i>MINK1</i>	17p13.2	rs72835045	4780795	intronic	G	A	0.220	1.16E-06	-1.38	1.69E-12	8.92	0.9984	0.069
<i>SLC47A1</i>	17p11.2	rs2440154	19444987	intronic	G	A	0.204	0.791	0.98	1.42E-08	5.47	0.0004	0.046
<i>SLC47A1</i>	17p11.2	rs2289668	19454640	intronic	C	T	0.204	0.791	0.98	1.43E-08	5.46	0.0004	0.046
<i>NAPA-AS1</i>	19q13.32	rs55800589	47990889	ncRNA_intronic	G	C	0.364	2.37E-06	-0.96	3.35E-13	9.53	1.0000	0.073
<i>DSCAM</i>	21q22.2	rs727333	41702947	intronic	C	A	0.257	4.75E-04	-1.36	3.69E-14	10.38	0.1247	0.077
<i>LRRC3</i>	21q22.3	rs116969723	45876716	P63P	G	A	0.233	0.014	-1.45	3.83E-15	11.23	0.8753	0.083
<i>RFPL2,SLC5A4</i>	22q12.3	rs117398778	32609178	intergenic	T	C	0.138	1.56E-05	1.32	2.00E-09	6.24	0.9397	0.051

GWAS, genome-wide association study; HWE p, Hardy-Weinberg equilibrium (HWE) p-value; log10BF, log10 transformed Bayes factor; lnOR, natural log-transformed odds ratio; PIP, posterior probability; MAF, minor allele frequency.

^a major/minor allele type.

^b lnOR and *P*-value were estimated by IA GWAS.

^c PIP, log10BF, and heritability (h^2) of individual variants were estimated via FINEMAP program to identify causal susceptibility to IA.

Supplementary Table S2. Expression of four causal candidate genes in 13 brain tissues, 4 blood vessels (3 artery tissues and EBV cells), and whole blood (transcripts per millions, TPM)

Tissue or cell types, TPM values	<i>GBA</i>	<i>TCF24</i>	<i>OLFML2A</i>	<i>ARHGAP32</i>
Artery-Aorta	26.6381	0.0000	2.3707	4.8536
Artery-Coronary	22.6014	0.0000	8.8402	4.3448
Artery-Tibial	18.5048	0.0000	9.5401	3.8799
Cells-EBV-transformed lymphocytes	13.2542	0.0000	0.4718	0.0667
Brain-Amygdala	6.4943	0.0758	1.0522	9.2092
Brain-Anteriorcingulatecortex(BA24)	8.5819	0.0529	0.9995	13.5215
Brain-Caudate(basalganglia)	9.8782	0.0782	1.2439	12.8529
Brain-CerebellarHemisphere	9.8881	0.0000	0.7039	4.8586
Brain-Cerebellum	9.5836	0.0166	1.0395	7.3319
Brain-Cortex	10.6011	0.0549	1.4575	19.6950
Brain-FrontalCortex(BA9)	13.1018	0.0508	1.1425	23.0975
Brain-Hippocampus	6.9035	0.0895	1.1693	6.8002
Brain-Hypothalamus	10.5743	0.1027	1.1759	6.1858
Brain-Nucleusaccumbens(basalganglia)	10.6235	0.0644	0.7168	12.7685
Brain-Putamen(basalganglia)	7.9459	0.0384	1.2849	9.1537
Brain-Spinalcord(cervicalc-1)	13.7758	0.1448	1.2204	4.5931
Brain-Substantianigra	8.7868	0.0567	1.3471	5.0176
WholeBlood	33.1310	0.0000	0.0980	0.2274

Supplementary Table S3. Associations of 29 SNPs in the previous GWAS (Hong et al. 2019) and replication stages.

Gene	Chr	SNP	M	m	MAF	HWE p	Stage 1 ^a		Stage 2 ^b		Stage 3 ^c	
							lnOR ^e	P ^e	ln(OR) ^e	P ^e	ln(OR) ^d	P ^d
<i>PRDM2</i>	1p36.21	rs61775135	C	A	0.285	0.626	-1.15	3.59E-13	4.00	0.7495	NA	NA
<i>GBA</i>	1q22	rs75822236	C	T	0.166	1	5.08	1.09E-19	NA	NA	NA	NA
<i>FMO4</i>	1q24.3	rs3737926	C	T	0.264	0.079	-1.01	1.83E-10	0.24	0.7801	NA	NA
<i>RNF144A</i>	2p25.1	rs6741819	C	T	0.247	0.022	-1.38	4.05E-14	-1.57	0.06768	NA	NA
<i>HDAC4, LOC150935</i>	2q37.3	rs59626274	C	T	0.248	0.002	-1.34	5.78E-14	1.17	0.4364	-0.59	0.2636
<i>LINC01237</i>	2q37.3	rs78458145	G	A	0.285	0.007	-1.41	3.14E-15	-1.13	0.09543	NA	NA
<i>SPCS3, VEGFC</i>	4q34.2	rs17688188	G	A	0.222	0.03	-1.31	5.99E-13	1.33	0.04135	NA	NA
<i>TCF24</i>	8q13.1	rs112859779	C	T	0.216	2.02E-04	-1.69	3.33E-16	0.19	0.8588	NA	NA
<i>CCDC171, C9orf92</i>	9p22.3	rs12350582	A	G	0.255	0.841	0.89	1.49E-08	-0.01	0.9763	0.31	0.1932
<i>LINGO2</i>	9p21.1	rs56942085	G	A	0.061	1	1.81	3.90E-08	0.86	0.2593	0.78	0.03301
<i>TMOD1</i>	9q22.33	rs1052270	C	T	0.344	0.042	-0.89	2.71E-08	-0.76	0.107	-0.47	0.05375
<i>MIR3134</i>	9q31.3	rs79461840	T	C	0.076	0.003	1.93	1.40E-08	2.17	0.00245	NA	NA
<i>LOC101928775, LINC00474</i>	9q33.1	rs4979583	C	T	0.325	0.874	0.9	4.61E-09	0.78	0.03896	NA	NA
<i>OLFML2A</i>	9q33.3	9_127561723	G	A	0.219	0.054	-1.97	1.70E-19	NA	NA	NA	NA
<i>MYEOV, LINC01488</i>	11q13.3	rs76855873	C	T	0.269	0.023	-1.11	1.23E-11	0.76	0.308	NA	NA
<i>ARHGAP32</i>	11q24.3	rs371331393	G	A	0.171	1	3.77	9.32E-27	NA	NA	NA	NA
<i>CDI63L1</i>	12p13.31	rs138525217	C	T	0.161	1	4.33	6.20E-23	NA	NA	NA	NA
<i>SLC2A14</i>	12p13.31	rs118107419	C	A	0.262	0.012	-1.4	1.44E-14	0.58	0.5324	0.60	0.05648
<i>DRAM1, CCDC53</i>	12q23.2	rs7964241	A	G	0.278	0.166	0.91	1.95E-08	0.95	0.0465	0.32	0.1598
<i>CUL4A, LAMP1</i>	13q34	rs74115822	G	A	0.112	0.001	1.83	1.12E-10	-1.80	0.154	NA	NA
<i>MIR365A, PARN</i>	16p13.12	rs11646803	C	T	0.376	0.074	-0.79	4.76E-10	-0.02	0.971	NA	NA
<i>LOC102724084</i>	16q23.2	rs75861150	T	C	0.091	2.17E-04	-1.93	1.27E-08	-16.60	0.9906	NA	NA
<i>SCARF1</i>	17p13.3	17_1538628	G	C	0.265	0.147	-0.94	6.02E-09	1.16	0.1904	1.10	1.17E-04
<i>MINK1</i>	17p13.2	rs72835045	G	A	0.22	1.16E-06	-1.38	1.69E-12	1.83	0.1472	NA	NA

<i>SLC47A1</i>	17p11.2	rs2440154	G	A	0.204	0.791	0.98	1.42E-08	0.97	0.03906	0.56	0.01104
<i>NAPA-ASI</i>	19q13.32	rs55800589	G	C	0.364	2.37E-06	-0.96	3.35E-13	NA	NA	NA	NA
<i>DSCAM</i>	21q22.2	rs727333	C	A	0.257	4.75E-04	-1.36	3.69E-14	-0.39	0.5288	NA	NA
<i>LRRC3</i>	21q22.3	rs116969723	G	A	0.233	0.014	-1.45	3.83E-15	-1.11	0.4892	NA	NA
<i>RFPL2, SLC5A4</i>	22q12.3	rs117398778	T	C	0.138	1.56E-05	1.32	2.00E-09	1.69	0.01276	NA	NA

HWE p, Hardy-Weinberg equilibrium p-value; M, major allele; m, minor allele; MAF, minor allele frequency.

^a The estimation of stage 1 has been reported in the previous GWAS composed of 250 patients with IA and 296 controls (Hong et al. 2019 J Clin Med).

^b Stage 2 shows replication results of 29 genome-wide significant signals in a hospital-based independent study composed of 50 patients with IA and 46 controls.

^c Stage 3 shows replication results of 29 genome-wide significant signals in an independent study composed 50 hospital-based patients and 575 healthy controls without underlying diseases. Controls were extracted from 8,105 subjects the Rural and Mid-size City cohort in Korean Genome Epidemiology Study.

^d Natural log-transformed odds ratio (ln(OR)) and p-values were estimated by multivariate logistic regression analysis adjusting for gender, age, hypertension, diabetes mellitus, hyperlipidemia, smoking status, and four principal component values.