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

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Abstract

In addition to conventional genome-wide association studies (GWAS), a fine-mapping is increasingly used to identify the genetic function of variants associated with disease susceptibilities. Here, we used a fine-mapping approach to evaluate the casual variants based on a previous GWAS involving patients with intracranial aneurysm (IA). Fine-mapping analysis was conducted based on the chromosomal data provided by GWAS consisting 250 patients diagnosed with IA and 296 controls using posterior inclusion probability (PIP) and log10 transformed Bayes factor (log10BF). The narrow sense of heritability (h^2) explained by each casual variant was estimated. Subsequent gene expression and functional network analyses were used to calculate the transcripts per million (TPM) values. Twenty causal candidate single nucleotide polymorphisms (SNPs) surpassed a genome-wide significance threshold for creditable evidence (log10BF > 6.1). Four SNPs including rs75822236 (R535H, *GBA*; log10BF = 15.06), rs112859779 (G141S, *TCF24*; log10BF = 12.12), rs79134766 (A208T, *OLFML2A*; log10BF = 14.92), and rs371331393 (Q1932X, *ARHGAP32*; log10BF = 20.88) showed a completed PIP value in each chromosomal region, suggesting a high probability of variant causality associated with IA. Expression in *GBA* was highly enriched in the whole blood (TPM = 33.13), while *TCF24* were rarely expressed in all tissues and cells. No direct interaction was observed between the four casual genes; however, *PSAP* appeared to be particularly important via indirect correlation between other genes. Our results suggested that four mutations of *GBA*, *TCF24*, *OLFML2A*, and *ARHGAP32* were linked to IA susceptibility and pathogenesis. Our approach may promise more informative mutations in the following GWAS.

Introduction

Intracranial aneurysm (IA) refers to an abnormal focal dilatation of a cerebral artery due to a weakening of the intima of a blood vessel wall. The prevalence of IA in the general adult population has been reported to be nearly 6%¹. The incidence of unruptured intracranial aneurysms (UIAs) was 15.6 per 100,000 persons². The asymptomatic UIA can rupture suddenly resulting in subarachnoid hemorrhage (SAH), which is associated with a higher mortality rate exceeding 50% within one month after ictus^{3,4}. IA is a complex disease involving an interaction between clinical and genetic factors underlying its formation and growth². Important clinical risk factors for IA include female gender, hypertension and smoking. The risk of rupture is increased when the aneurysm is located between arterial branches or in the vertebrobasilar region, in addition to larger size at diagnosis, and the presence of a bleb or daughter sac⁵⁻⁷. Genetic studies have been performed to identify genes associated with IA via linkage analysis and single nucleotide polymorphisms (SNPs) of known candidate genes, strongly correlated genes or genome-wide association studies (GWAS) for screening multiple candidate genes. In particular, GWAS revealed large-scale genetic associations, which were primarily correlated with traits and diseases. GWAS technically compares allele frequencies in SNPs between cases and controls. However, complex traits of IA are not entirely attributed to a single gene, but are caused by the influence of multiple genes^{8,9}. Gene-gene and gene-environment interactions also affect the traits and diseases. Given the inherent features of the GWAS, genetic markers included in the same linkage disequilibrium exhibit similar correlation. Accordingly, even if a candidate gene is identified via GWAS, it could merely suggest a statistically significant difference rather than represent an etiological factor. Further, the precise location of the causative gene may differ in the same linkage disequilibrium (LD) block. Thus, it is important to reduce the errors via additional data processing to identify false-positive results obtained in GWAS.

Fine-mapping is one of the post-GWAS analyses used to narrow potential candidate variants directly affecting the trait¹⁰. This approach can be used to identify the regions associated with possible causal susceptibility based on the population of structures with LD⁹. It provides a complex correlation between the casual variants and the disease development using computational data without *in vivo* and *in vitro* molecular biology studies.^{10,11} Sekar *et al.*¹¹ showed that structurally diverse alleles of the complement component 4 genes contribute to schizophrenia via excessive complement activity, resulting in reduced numbers of synapses. Consequently, it can be used to assess the functional role of the risk allele, which is a challenge to investigate based on molecular mechanisms, despite the strong genetic association. Fine-mapping of complex traits has been increasingly performed in many diseases, especially cancer and stroke, but has yet to be reported in IA. Here, for the first time, we performed a fine-mapping analysis based on previous GWAS data sets to identify the causal candidate variants in an effort to identify the precise genetic variants associated with IA in a Korean adult cohort. We also performed a functional gene set enrichment analysis using the optimized candidate sets to analyze the biological relationship between candidate genes and IA.

Materials And Methods

GWAS-based summary statistics

The analysis was based on the summary statistics provided by the previous IA GWAS. In brief, the study included 250 adult patients with saccular aneurysm and 296 controls between March 2015 and December 2020^{12,13}. The AxiomTH Asian Precision Medicine Research Array (APMRA) (Thermo Fisher Scientific, MA, USA) were used for genotyping of the study subjects. High-quality plates were defined by a plate pass rate higher than 95% for samples. The average call rate of passing samples was greater than 99%. A total of 512,575 SNPs passed the quality control including genotyping call rate of 95% or higher, minor allele frequency of at least 1%, and Hardy-Weinberg equilibrium P -value $\geq 1 \times 10^{-612}$. GWAS-based summary statistics included allele types, minor allele frequencies, effect sizes, and p -values. The Institutional Review Board and Ethics Committee approved all protocols of the study (No. 2016-3, 2019-06-006).

Statistical Analysis

We performed a fine-mapping study to identify the role of casual candidate combinations in the susceptibility to IA using FINEMAP v.1.3.1¹⁴. Odds ratios (ORs) of individual SNPs were converted using the natural log-transformed formula (lnOR). Causality of each SNP or configuration was assessed using effect sizes, posterior inclusion probabilities (PIPs), and narrow sense of heritability (h^2), which was explained by casual SNPs. The log10-transformed Bayes factors (log10BF) for the individual casual SNPs and configurations were estimated via FINEMAP analysis. A log10BF value greater than 6.1 suggested significant genome-wide evidence. The fine-mapping approach requires the estimates of SNP correlations, and therefore LD matrices between SNPs were generated by PLINK v1.9 (<https://www.cog-genomics.org/plink/>)¹⁵. All the fine-mapping tests were conducted with individual chromosomes (chr1-22) due to the LD-based mapping procedure. Manhattan and regional association plots of fine-mapping results were obtained using the package of "qqman" in R v3.6.1 (<https://cran.r-project.org/web/packages/qqman>) and LocusZoom v1.3 written in the modified Python and R scripts¹⁶. Regional annotations and functional impact of SNPs were described using the ANNOVAR program including the PolyPhen-2 (<http://www.openbioinformatics.org/annovar/>)¹⁷.

Gene expression and functional network analyses

The expressions of causal candidate genes was evaluated in human blood, brain-specific tissues, or cells using the Genotype-Tissue Expression (GTEx) Portal (<https://gtexportal.org/home/>)¹⁸. Transcripts per million (TPM) values of a total of 56,200 genes were calculated in 13 brain tissues, 4 blood vessels (3 arterial tissues and 1 cell line of EBV-transformed lymphocytes), and a whole blood cell. Subsequent gene functional network analysis was conducted using the GeneMANIA program (<https://genemania.org/>)¹⁹.

Results

Fine-mapping analyses

Fine mapping analyses entailed multiple SNP combinations by each autosome chromosome. A total of 20 causal candidate SNPs surpassed a genome-wide significance threshold for creditable evidence (log10BF > 6.1) (Fig. 1a). The log10BF values were strongly correlated with GWAS-based p -values (R^2 for correlation = 0.9861, $p < 0.0001$) (Fig. 1b). Among them, 13 SNPs showed a high PIP in each chromosomal region (PIP > 0.8) (Fig. 1c). The PIPs were slightly correlated with GWAS-driven p -values (R^2 for correlation = 0.0974, $p < 0.0001$) (Fig. 1d). Six out of 13 SNPs were located on exonic regions (Table 1). The rs371331393 (Q1932X), one SNP of *ARHGAP32* (11q24.3), exhibited a stop-gain function and was most significantly associated with increased IA risk (lnOR = 3.77, log10BF = 20.88). This variant showed the highest heritability (h^2 = 0.143). Three SNPs including rs75822236 (R535H, *GBA*; log10BF = 15.06), rs112859779 (G141S, *TCF24*; log10BF = 12.12), and rs79134766 (A208T, *OLFML2A*; log10BF = 14.92) were associated with amino acid substitutions, which may contribute to possible DNA sequence damage and increased association with IA. Eighteen SNPs, including *PRDM2*, *FMO4*, and *RNF144A*, which exceeded genome-wide significance level in GWAS ($p < 5 \times 10^{-8}$), were associated with low causality to IA formation ($1.89 \times 10^{-11} < \text{PIP} < 0.13$, log10BF > 5) (Supplementary Table 1). In summary, fine mapping annotated that *ARHGAP*, *GBA*, *TCF24*, and *OLFML2A* would be casual candidate genes.

Table 1
Significant causal susceptibility identified by fine-mapping after genome-wide association study

Gene	Chr	Function	SNP	M/m ^a	MAF	PIP ^b	log10BF ^b	<i>h</i> ^{2b}	lnOR	<i>P</i> in GWAS
<i>PRDM2</i>	1p36.21	intronic	rs61775135	C/A	0.285	2.61E-06	9.48	0.0733	-1.15	3.59E-13
<i>GBA</i>	1q22	R535H, exon11	rs75822236	C/T	0.166	1.0000	15.06	0.1088	5.08	1.09E-19
<i>FMO4</i>	1q24.3	F281F, exon8	rs3737926	C/T	0.264	1.10E-08	7.10	0.0577	-1.01	1.83E-10
<i>RNF144A</i>	2p25.1	intron	rs6741819	C/T	0.247	0.0905	10.30	0.0785	-1.38	4.05E-14
<i>HDAC4,LOC150935</i>	2q37.3	intergenic	rs59626274	C/T	0.248	0.0679	10.18	0.0777	-1.34	5.78E-14
<i>LINC01237</i>	2q37.3	ncRNA, intron	rs78458145	G/A	0.285	0.8416	11.27	0.0847	-1.41	3.14E-15
<i>SPCS3,VEGFC</i>	4q34.2	intergenic	rs17688188	G/A	0.222	0.9999	9.29	0.0718	-1.31	5.99E-13
<i>TCF24</i>	8q13.1	G141S, exon4	rs112859779	C/T	0.216	1.0000	12.12	0.0898	-1.69	3.33E-16
<i>OLFML2A</i>	9q33.3	A208T, exon4	rs79134766	G/A	0.219	1.0000	14.92	0.1072	-1.97	1.70E-19
<i>MYEOV,LINC01488</i>	11q13.3	intergenic	rs76855873	C/T	0.269	1.89E-13	8.15	0.0642	-1.11	1.23E-11
<i>ARHGAP32</i>	11q24.3	Q1932X, exon22	rs371331393	G/A	0.171	1.0000	20.88	0.1435	3.77	9.32E-27
<i>CD163L1</i>	12p13.31	splicing	rs138525217	C/T	0.161	1.0000	17.77	0.1248	4.33	6.20E-23
<i>SLC2A14</i>	12p13.31	intron	rs118107419	C/A	0.262	8.60E-08	10.71	0.0807	-1.40	1.44E-14
<i>CUL4A,LAMP1</i>	13q34	intergenic	rs74115822	G/A	0.112	0.9960	7.32	0.0584	1.83	1.12E-10
<i>MIR365A,PARN</i>	16p13.12	intergenic	rs11646803	C/T	0.376	0.9422	6.77	0.0548	-0.79	4.76E-10
<i>MINK1</i>	17p13.2	intron	rs72835045	G/A	0.220	0.9984	8.92	0.0688	-1.38	1.69E-12
<i>NAPA-AS1</i>	19q13.32	ncRNA, intron	rs55800589	G/C	0.364	1.0000	9.53	0.0726	-0.96	3.35E-13
<i>DSCAM</i>	21q22.2	intron	rs727333	C/A	0.257	0.1247	10.38	0.0773	-1.36	3.69E-14
<i>LRRC3</i>	21q22.3	P63P, exon2	rs116969723	G/A	0.233	0.8753	11.23	0.0827	-1.45	3.83E-15

GWAS, genome-wide association study; log10BF, log10 transformed Bayes factor; lnOR, natural log-transformed odds ratio; PIP, posterior inclusion probability; MAF, minor allele frequency.

^a M/m indicates major/minor allele type, respectively.

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

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

Gene	Chr	Function	SNP	M/m ^a	MAF	PIP ^b	log10BF ^b	<i>h</i> ^{2b}	lnOR	<i>P</i> in GWAS
<i>RFPL2,SLC5A4</i>	22q12.3	intergenic	rs117398778	T/C	0.138	0.9397	6.24	0.0506	1.32	2.00E-09
GWAS, genome-wide association study; log10BF, log10 transformed Bayes factor; lnOR, natural log-transformed odds ratio; PIP, posterior inclusion probability; MAF, minor allele frequency.										
^a M/m indicates major/minor allele type, respectively.										
^b PIP, log10BF, and heritability (<i>h</i> ²) of individual variants were estimated via FINEMAP program to identify causal susceptibility to intracranial aneurysm (IA).										
^c lnOR and <i>P</i> -value were estimated by IA GWAS.										

Gene expression and functional network analyses

Gene expression and functional network analyses were performed using the four causal candidate genes (Fig. 2 and Supplementary Table 2). *GBA* was broadly enriched in all tissues and cell lines (6 < TPM < 34). In particular, it was highly expressed in the whole blood (TPM = 33.13). Conversely, *TCF24* was rarely expressed in all tissues and cells (TPM < 0.15). Expression in *OLFML2A* was moderate in all arteries (TPM = 2.37 to 9.54). *ARHGAP32* was rarely enriched in EBV-transformed lymphocytes and whole blood (TPM = 0.0667 and 0.2274, respectively), while it was enriched in the brain and blood vessels (TPM, between 3 and 24). No direct interaction was observed between the four casual genes (Fig. 3). However, these genes constitute a hub network interacting with neighbor genes, especially *PSAP*, *SCARB2*, and *ASAHI* (Fig. 3).

Discussion

Large-scale GWAS and meta-analyses have been widely used to identify and validate common or novel susceptible gene variants in various medical diseases over the past decade. However, given the overall genotype-phenotype analyses, disease-modifying functional mutations and direct biological relevance to disease have yet to be elucidated completely²⁰. In addition, the heritability of a specific trait cannot be fully explained by common SNPs of intronic or intergenic regions via GWASs that have been targeted to identify common variants in common complex diseases. Accordingly, even if a large number of susceptible loci were identified, a few cases showed their replication in an independent cohort. Thus, few disease-associated variants have been demonstrated in functional *in vitro* studies or used in treatment²¹. To overcome these limitations, an updated fine-mapping analysis was performed to identify the variant causality associated with human complex diseases and as a cost-effective genotyping strategy⁹. To date, many studies underscored the need for ‘feature selection’ to identify relevant “variables” using parametric or non-parametric models. However, feature selection is not a simple challenge and requires substantial genetic investigations. It is important to identify the causal or driver mutations linked to treatment of human complex diseases. The selection of genetic variants from GWAS is uncertain given the strongly correlated SNPs corresponding to a pairwise LD structure at the population level. A fine-mapping analysis facilitates the identification of creditable genetic variants to refine the selection bias such as false-positive variants based on the initial GWAS and to improve the findings of molecular functional studies⁹. Here, we performed a fine-mapping analysis based on the results of previous IA GWAS using the statistical method developed by Benner *et al.*¹⁴ Our findings may enable the identification of causal variants (true negative) and exclude potential false positives via statistically significant fine-mapping analysis of transformed GWAS results. Therefore, these analytical methods may enable the selection of functional candidate variants based on the molecular mechanisms associated with IA formation.

In this study, we found four causal genes that are potentially linked to IA such as *GBA*, *TCF24*, *OLFML2A*, and *ARHGAP32*. We speculated that these genetic variants may cause dysfunctional immune response and inflammation in DNA sequences damaged by amino acid substitution or gain- or loss-of-function mutations, which affects the IA formation. *GBA* located in the exonic regions of 1q22 (rs75822236) was significantly associated with IA¹². More specifically, GWAS revealed that the “T” allele of this variant increased the risk of IA.¹² In addition, a fine-mapping analysis also revealed a higher level of log10BF (15.06) and PIP (1.0), suggesting that this variant was a true positive for IA. The role of *GBA* was mainly investigated in Parkinson’s disease (PD) or Gaucher disease (GD), which is a recessive lysosomal storage disorder, and barely investigated in IA. Mata *et al.*²² reported that *GBA* mutations and E326K carrier were related to impaired working memory and executive function in patients with PD. In GD, null or severe homozygous mutations of *GBA* showed little or no human glucocerebrosidase activity²³. These findings suggested differences in phenotype due to the various *GBA*

mutations. Kleinloog *et al.*²⁴ reported enrichment of the lysosomal pathway in ruptured IA compared with UIA based on RNA sequencing analysis of aneurysm wall. Although the lysosomal pathway does not reflect an acute reaction to IA rupture²⁴, it is likely that it is induced by inflammation after bleeding.

OLFML2A and *TCF24* showed a protective effect against IA formation with log10BF levels greater than 12 and completed PIPs. However, the relationship between these two genes and IA is still unclear, even though it has been implicated in cardiovascular diseases. Conversely, *ARHGAP32* significantly increased the risk of IA with the highest log10BF (20.88) and completed PIP. *ARHGAP32* refers to Rho GTPase-activating protein 32 and mediates N-methyl D-aspartate receptor signaling¹². The role of *ARHGAP32* has been mainly investigated in the regulation of blood pressure. Rho-specific GTPase-activating protein *GRAF3* was highly expressed in smooth muscle cells (SMCs) and regulated blood pressure control by inhibiting the contractility of RhoA-mediated SMC²⁵. *GRAF3*-deficient mice also showed increased blood pressure in response to angiotensin II and endothelin 1²⁶. In actual clinical practice, many patients manifest both IA and hypertension. Inci *et al.*²⁷ reported that the rate of pre-existing hypertension was 43.5% in patients with IA, which was higher than 24.4% in the normal population. Hypertension may contribute to degeneration of the internal elastic lamina, weakening of the vessel wall, and IA formation²⁷. Nevertheless, it is unclear whether the role of *ARHGAP32* in IA is mediated indirectly via chronic hypertension or directly via change in vascular tone.

Functional network analyses showed that *PSAP* was an important gene in the development of IA. The role of *PSAP* gene was rarely investigated in IA and was mainly studied in PD. Oji *et al.*²⁸ reported that two SNPs of rs4747203 and rs885828, the intronic regions of the *PSAP* saposin D domain were linked to PD. *PSAP* mutation can also result in dopaminergic neurodegeneration and motor decline in mice. Although we did not include patients with PD, a fine-mapping analysis revealed that PD-related genes such as *GBA* and *PSAP* may contribute to IA. Lysosomal dysfunction and the resulting lysosomal storage disorder can contribute causally to PD. Putative damaging variants in at least one gene associated with lysosomal storage disorder were observed in most PD patients²⁹. However, lysosomal dysfunction can also be observed in the arterial wall. Lysosomal changes in the vascular SMCs were attributed to the accumulation of excessive substrate levels in the lysosomes of a primate model of atherosclerosis and hypertension³⁰. The excessive sterol accumulation in lysosomes can disrupt the lysosomal function³¹. Therefore, in this case, it is possible that lysosomal dysfunction may directly affect IA formation or may contribute to IA via atherosclerosis. Hokari *et al.*³² reported that atherosclerotic factors strongly increased the risk of middle cerebral artery aneurysm compared with paraclinoid aneurysm. After securing aneurysm, consistent statin therapy was significantly correlated with better prognosis.³³ Wu *et al.*³⁴ demonstrated that the autophagy–lysosomal pathway, which entails self-digestion of dysfunctional intracellular components by lysosomal enzymes, was an important pro-survival mechanism after SAH. However, the study investigated the role of the lysosome after SAH development, but not in IA development itself. Therefore, additional studies are needed to investigate the role of candidate variants in lysosomal dysfunction resulting in IA formation via abnormal ECM remodeling in response to hemodynamic stress.

A fine-mapping analysis may enable the detection of mutations involving the candidate genes and thereby contribute to treatment based on genome-based precision medicine. Identifying the causal variants beyond GWAS provides a crucial blueprint in predicting disease risk and preventing IA as well as metabolic diseases and stroke³⁵. To the best of our knowledge, this was the first fine-mapping analysis based on the results of a GWAS of IA. Nevertheless, the interpretation of the results may have some limitations. First, the sample size was relatively somehow small to discover more functional mutations to achieve a sufficient statistical power, even though four common mutations have been detected in our study. Second, variables regarding aneurysm location and size were not considered in the analysis. Microscopic analysis of the aneurysm during actual surgery often reveals atherosclerotic changes in the aneurysm wall, especially in elderly patients with larger aneurysm. Accordingly, GWAS and subsequent fine-mapping analysis should be performed together given the metabolic status of a large number of patients with IA.

In summary, fine-mapping analysis robustly identified four functional mutations of causal candidate genes, such as *GBA*, *TCF24*, *OLFML2A*, and *ARHGAP32* that have associated with IA. Mutations in these genes show play roles in immune and inflammatory systems according to our literature review and functional annotations. Their mutations suggest a possible polygenic inheritance of IA formation. Finally, our study will provide more informative and replicable causal susceptibilities to IA including four mutations in the second stage GWAS.

Declarations

Data and resource availability

The data that support the findings of this study was submitted as online supplemental material, and further detailed information is available upon request to the corresponding author. All genotype and phenotype resources are managed by “The First Korean Stroke Genetics Association Research” study constructed from the Sacred Heart Hospital Stroke Database.

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Author contributions

E.P.H. and J.P.J. designed and managed this study. Analysis was done by E.P.H. and B.J.K. Sample preparation and data collection were done by D.H.Y., B.J.K., E.P.H. and J.P.J. Drafting and reviewing of manuscript were done by E.P.H., D.H.Y., B.J.K., J.H.A., J.J.P., J.K.R. and J.P.J.

Competing interests

The authors declare no competing interests.

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Figures

Figure 1

(a and c) Manhattan plots show $\log_{10}$ -transformed Bayes factors ($\log_{10}\text{BF}$) and posterior inclusion probability (PIP) of variant causality estimations based on the summary statistics of a genome-wide association study (GWAS) of intracranial aneurysm (IA). (b and d) Plots compare the significance of IA GWAS, $\log_{10}\text{BF}$, and PIP. A red dash line indicates a genome-wide significance and a strong PIP of IA formation in the panels A and C, respectively ($\log_{10}\text{BF} = 6.1$ and $\text{PIP} = 0.8$). R-square (R^2) indicates the correlation between IA GWA p-value ($-\log_{10}$ transformed) and $\log_{10}\text{BF}$ in panel B and PIP in panel D: P-value for R^2 .

Figure 2

A heatmap of multiple gene expression involving GBA, TCF24, OLFML2A, and ARHGAP32 in human cells and tissues including artery, brain, and whole blood is presented. Gene expression was estimated as transcripts per million (TPM). Genes and types of cells or tissues were ordered via agglomerative hierarchical clustering.

Figure 3

Susceptibility to intracranial aneurysm (Homo sapiens) based on multiple protein interactions between proteins coded by four causal hub genes including GBA, TCF24, OLFML2A, and ARHGAP32. The network included neighboring genes correlated with four hub genes. The width of individual lines indicates the intensity of the interaction between proteins. The colors in each line indicate multiple functions including physical interaction, co-expression, prediction, co-localization, genetic interaction, pathways, and shared protein domains.

Supplementary Files

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