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Genome-Wide Association Study of the Relationship Between Matrix Metalloproteinases and Intracranial Aneurysms

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Background and Purpose Matrix metalloproteinases (MMPs) are expected to play an important role in extracellular matrix (ECM) remodeling in response to hemodynamic stress. We investigated the association between MMPs and intracranial aneurysms (IAs) via a genome-wide association study (GWAS) of IAs.

Methods A GWAS data set of 250 IAs and 294 controls was used to analyze the genetic link between MMPs and IAs via single-nucleotide polymorphisms (SNPs), MMP gene families, and in silico functional analyses of gene ontology (GO) enrichment and protein–protein interaction (PPI).

Results Forty-eight SNPs and 1 indel out of 342 markers of MMP genes were related to IAs. The rs2425024 SNP located on MMP24 was the most strongly associated with IAs (OR=0.43, CI=0.30−0.61, $p=2.4\times10^{-6}$), suggesting a protective effect. The 16938619 SNP of MMP26 significantly increased the risk of an IA (OR=3.12, 95% CI=1.76−5.50, $p=8.85\times10^{-5}$). Five MMP genes (MMP24, MMP13, MMP2, MMP17, and MMP1) increased the susceptibility to an IA. MMP24 was the gene most closely related to IAs ($p=7.96\times10^{-7}$). GO analysis showed that collagen catabolism was the most-enhanced biological process. Further, metalloendopeptidase activity and ECM were predominantly detected in the cellular component and molecular function, respectively. PPI provided evidence that MMP2, TIMP2 (tissue inhibitor of metalloproteinase 2), and TIMP3 genes constitute a network for predicting IA formation.

Conclusions The present results provide comprehensive insight into the occurrence of IAs associated with MMPs.

Keywords matrix metalloproteinases; intracranial aneurysm; bioinformatics.

INTRODUCTION

Increased inflammation during extracellular matrix (ECM) remodeling in hemodynamic stress contributes to the development and growth of intracranial aneurysms (IAs).[1] Matrix metalloproteinases (MMPs) are a group of proteases that regulate the ECM via proteolysis, cell adhesion, and cytokines.[2] Accordingly, the effect of MMPs on IA pathogenesis has been widely investigated.[1,3] IA walls showed increased MMP9 expression with concomitant tissue inhibitor of metalloproteinase (TIMP) activity compared with the superficial temporal artery.[4] Aoki et al.[5] reported that increased levels of macrophage-derived MMP2 and MMP9 with gelatinase activity in the IA wall were closely linked to aneurysm progression. Unlike histopathological analyses, the possible effect of MMP gene polymorphisms on IAs has yet to be demonstrated.[6] Zhang et al.[7] reported that polymorphisms of MMP1, MMP3, MMP9, and MMP12 were not associated with IAs in the Caucasian population. However,

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the effects of MMP gene variations in IA formation vary with race.

Bioinformatics analyses are expected to provide new insights into the pathogenesis of various disease.[8] Case–control studies can reveal genes associated with disease occurrence, while bioinformatics provides additional information about gene interactions and their potential functions.[9] Krug et al.[10] reported that TTC7B was a risk factor for ischemic stroke based on gene expression profiling in peripheral blood mononuclear cells using a simple patient–control study. Bioinformatics analyses of original microarray data set revealed additional protective effects of ATF3 and EGR1 on ischemic stroke. Also, a functional analysis demonstrated an association between downregulation of the TP53 gene and poor neurological outcomes.[9] Early in 2019 we reported the first IA genome-wide association study (GWAS) in a Korean population, which revealed the presence of IA-associated single-nucleotide polymorphisms (SNPs) such as GBA, ARHGAP32, and MINK1 genes.[11] However, that study did not comprehensively investigate the association between MMP genes and IAs. Therefore, in the present study we investigated the role of genetic variants of MMPs in IAs using GWAS data sets, and determined whether individual MMP genes are associated with IAs. We also performed functional analyses to identify the specific enrichment domain and MMP-related interaction network involved in IA pathogenesis.

METHODS

Processing of GWAS data

GWAS data sets from 250 adult patients with IAs and 296 control subjects obtained in a prospective multicenter study called "The First Korean Stroke Genetics Association Research" were used in the analysis.[11-13] There were 151 (60.4%) cases of ruptured aneurysms and 221 (88.4%) cases in the anterior circulation. Raw genetic data were generated using the Axiom™ Asia Precision Medicine Research Array (PMRA) Kit (Thermo Fisher Scientific, Waltham, MA, USA), which contains more than 750,000 SNPs encompassing East and South Asian populations based on human genome version 19 (build 37). The raw data were filtered as follows: 1) quality control test with a genotype call rate of ≥95%, 2) minor allele frequency ≥0.01, and 3) Hardy-Weinberg equilibrium ($p \geq 1\times10^{-6}$).[11] This study was approved by the institutional review boards (No. 2017-9, 2018-6, and 2019-6) of the participating hospitals, and informed consent was obtained from the patients or their relatives.

Bioinformatics analyses

A flow chart of the analyses is presented in Supplementary Fig. 1 (in the online-only Data Supplement). Analyses based on SNPs, MMP genes, and functions were carried out, and the results were integrated. Variant calling of SNPs/indels from the MMP gene families was performed to annotate the GWAS data. Manhattan plot and quantile–quantile (Q-Q) plots were constructed using MAGMA (version 1.6) implemented on the FUMA GWAS (Functional Mapping and Annotation of Genome-Wide Association Studies) platform (https://fuma.ctglab.nl/). The default settings were used, with the cutoff of significance defined by a p value of $0.05/23=2.17\times10^{-3}$ in a gene-based test. Regional plots were generated using the LocusZoom plot (http://csg.sph.umich.edu/locuszoom) focused to within 50 kilobases. Gene ontology (GO) analysis was performed using the Molecular Signatures Database (MSigDB C5) involving biological process (BP), cellular component (CC), and molecular function (MF) (http://www.broadinstitute.org/msigdb). A protein–protein interaction (PPI) network was identified using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING, version 11; http://string-db.org). The minimum required interaction score was set to a moderate confidence of 0.7.

RESULTS

SNP-based analysis

Forty-eight SNPs and 1 indel out of 342 genetic markers of MMP genes were associated with IAs ($p<0.05$) (Supplementary Table 1 in the online-only Data Supplement and Fig. 1A). The distribution of observed p values for the Q-Q plot was 1.01 (Fig. 1B). The top-20 SNP markers of MMPs associated with IAs are listed in Table 1. The intron variant of rs2425024 located on MMP24 was most strongly associated with IAs, suggesting a protective effect of the IA formation (OR=0.43, 95% CI=0.30–0.61, $p=2.4\times10^{-6}$). In particular, three of the top-five IA-related SNPs (i.e., rs2425024, rs6119593, and rs1555322) were located on MMP24. The rs16938619 SNP increased the risk of IAs significantly (OR=3.12, 95% CI=1.76–5.50, $p=8.85\times10^{-5}$). The G allele of this variant was rarely detected in the control group, in contrast to in the IA group.

Gene-based analysis of MMP gene families

Gene-based analysis was performed using MAGMA to improve the detection of the combined effects of multiple variants associated with each MMP gene (Fig. 1C).[14] MMP24 and MMP13 exceeded the genome-wide significance threshold ($p=0.0024$), with the association with IA associated being strongest for the MMP24 gene ($p=7.96\times10^{-7}$) (Table 2). The distribution of the observed p values was inflated ($p=1.01$). The following five MMP genes including represent IA-susceptibility genes: MMP24, MMP13, MMP2, MMP17, and

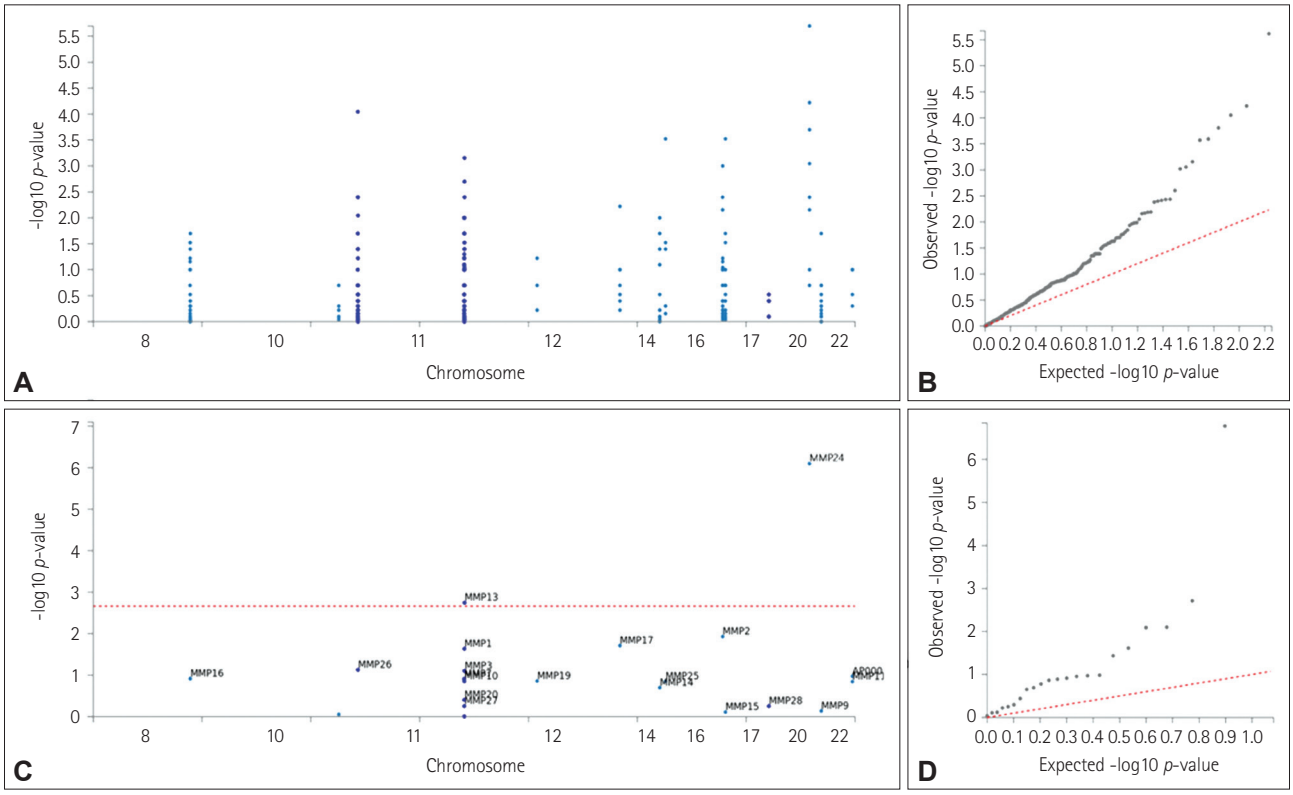

Fig. 1. Manhattan plots and quantile-quantile (QQ) plots of single variant associations (A, B) and gene-level associations (C, D) based on matrix metalloproteinase (MMP) families susceptible to intracranial aneurysms (IAs). The X- and Y-axes in panels A and C indicate the chromosome number and $-\log_{10}$10-transformed *p* value, respectively, and those in panels B and D indicate the $-\log_{10}$-transformed expected and observed *p* values, respectively. The points represent single-nucleotide polymorphisms (SNPs) or indels located on MMP gene families in panels A and B. Individual MMP genes are shown in panels C and D.

Table 1. Top-20 MMP polymorphisms associated with susceptibility to intracranial aneurysms

No.	Chr	BP	M	m	OR	*p*	mm/Mm/MM		rsID	Gene
							Case	Control		
1	20	33844938	A	C	0.43	2.4E-06	7/47/196	15/113/168	rs2425024	MMP24
2	20	33833729	C	A	0.39	5.9E-05	1/30/218	6/71/219	rs6119593	MMP24
3	11	4807548	A	G	3.12	8.8E-05	0/48/200	0/23/273	rs16938619	MMP26
4	20	33849179	G	A	0.37	1.6E-04	1/23/226	5/58/233	rs1555322	MMP24
5	16	3091695	A	G	0.43	2.6E-04	0/43/207	2/81/212	rs11642206	MMP25
6	16	58105677	T	C	2.05	2.7E-04	3/90/157	3/66/226	rs6499933	MMP15
7	11	102825635	T	C	1.55	7.0E-04	71/123/55	59/137/99	rs627363	MMP13
8	20	33859013	C	A	0.44	8.8E-04	2/23/223	5/58/233	rs2425041	MMP24
9	16	55534078	G	A	0.38	9.5E-04	1/15/232	5/47/244	rs80345658	MMP2
10	11	102811090	C	T	0.10	2.5E-03	0/2/247	0/19/277	rs150333315	MMP13
11	11	4835458	G	A	1.74	3.7E-03	6/73/171	6/53/235	rs7945484	MMP26
12	16	55427433	G	A	0.05	3.7E-03	0/1/249	1/18/276	rs74019045	MMP2
13	11	4909000	G	A	2.01	3.8E-03	0/58/192	2/35/259	rs2595982	MMP26
14	11	102835040	T	C	0.68	4.0E-03	34/104/112	53/150/92	rs72987535	MMP13
15	20	33834708	G	A	0.49	4.2E-03	0/33/217	0/69/227	rs3764733	MMP24
16	12	132333682	A	G	0.68	6.5E-03	26/88/133	29/153/112	rs79572159	MMP17
17	16	55502376	T	G	0.27	6.5E-03	0/6/243	1/21/274	rs11859163	MMP2
18	16	55436868	G	A	0.21	6.8E-03	0/4/246	1/17/278	rs142441049	MMP2
19	20	33828825	G	A	1.44	6.9E-03	57/132/61	53/139/104	rs6142338	MMP24
20	11	4961003	G	A	0.33	8.8E-03	0/9/239	0/27/269	rs36013257	MMP26

BP, base position; Chr, chromosome; M, major (reference allele); m, minor (risk allele); MMP, matrix metalloproteinase; OR, odds ratio.

Table 2. Results of gene-based analysis of MMP gene families associated with intracranial aneurysms

Gene	Chr	Start	Stop	NSNP	NPARAM	*p*
MMP24	20	33814457	33864801	7	3	7.96E-07
MMP13	11	102813724	102826463	3	2	1.79E-03
MMP2	16	55423612	55540603	23	13	0.01
MMP17	12	132312938	132336328	11	5	0.02
MMP1	11	102660651	102668891	2	1	0.02
MMP26	11	4726157	5013659	46	23	0.07
MMP3	11	102706532	102714534	6	1	0.08
MMP16	8	89044237	89340254	30	15	0.12
MMP7	11	102391239	102401484	5	3	0.12
MMP19	12	56229217	56236750	3	2	0.14
MMP25	16	3096682	3110727	5	2	0.14
MMP10	11	102641234	102651359	4	2	0.14
MMP11	22	24110413	24126503	5	2	0.14
MMP14	14	23305766	23318236	9	5	0.20
MMP20	11	102447566	102496063	13	5	0.39
MMP27	11	102562218	102576537	7	3	0.55
MMP28	17	34083268	34122711	6	2	0.56
MMP9	20	44637547	44645200	6	3	0.72
MMP15	16	58059470	58080805	4	1	0.77
MMP21	10	127455022	127464390	2	1	0.87
MMP8	11	102582526	102597781	5	2	0.98

MMP, matrix metalloproteinase; NPARAM, number of relevant parameters used in the model; NSNP, number of single-nucleotide polymorphisms annotated to the gene.

MMP1. Linkage disequilibrium between the SNP of each MMP gene and an IA is presented in the Fig. 2. The top of each plot indicates the most-significant SNP in the region, and was rs2425024 in MMP24, rs627363 in MMP13, rs80345658 in MMP2, rs79572159 in MMP17, and rs2071232 in MMP1.

In silico functional analysis of MMP gene families

The most-enhanced BP function was collagen catabolism, followed by extracellular structure organization and ECM disassembly. For CC, metalloendopeptidase activity was the most enhanced in IA formation. For the MF cluster, ECM was the most enhanced, overlapping five IA-associated MMP genes (Fig. 3A, B, and C). The PPI network was drawn using the five IA-associated MMP genes with three regulators: TIMP1, TIMP2, and TIMP3. These findings provide evidence of a network based on MMP2, TIMP2, and TIMP3 genes for predicting IA formation (Fig. 3D).

DISCUSSION

Genetic studies of IAs commonly apply diverse methods, such as analyses of the SNPs of candidate genes, linkage analysis, microarray-based gene expression, GWAS, or whole-exome sequencing. Such studies focus on the primary genetic association based on frequency differences in a case–control study or the relationship between a specific locus and phenotype within families. Bioinformatics is now increasingly being used to identify the pathway and network associated with the pathogenesis of a disease, which cannot be determined using conventional genetic analyses. Most bioinformatics analyses of IAs have used microarray data obtained from small numbers of samples.[15] The present study investigated the associations between MMPs and IAs using GWAS data for the first time using a comprehensive approach based on SNPs, MMP gene families, and functional analyses. Our results indicated that rs2425024 was mostly associated with IAs. The two MMP24 and MMP13 genes showed associations with IAs that exceeded genome-wide significance.

The genetic influence of MMPs on IA formation remains controversial. Pannu et al.[16] reported that a polymorphism located at the 3' untranslated region of MMP9 (TT genotype)—but not MMP2 polymorphisms—significantly increased the risk of IAs (OR=1.91, p=0.005) in a Caucasian population. Conversely, the SNPs of the coding and the 3' untranslated region of MMP9 were not associated with IAs in direct gene sequencing.[17] Our study found that three SNPs of MMP24 were significantly associated with IAs, with it being particularly interesting that rs2425024, rs6119593, and rs1555322 exerted protective effects on IA formation. MMP24 is classified as a furin-activated MMP based on domain organization.[18]

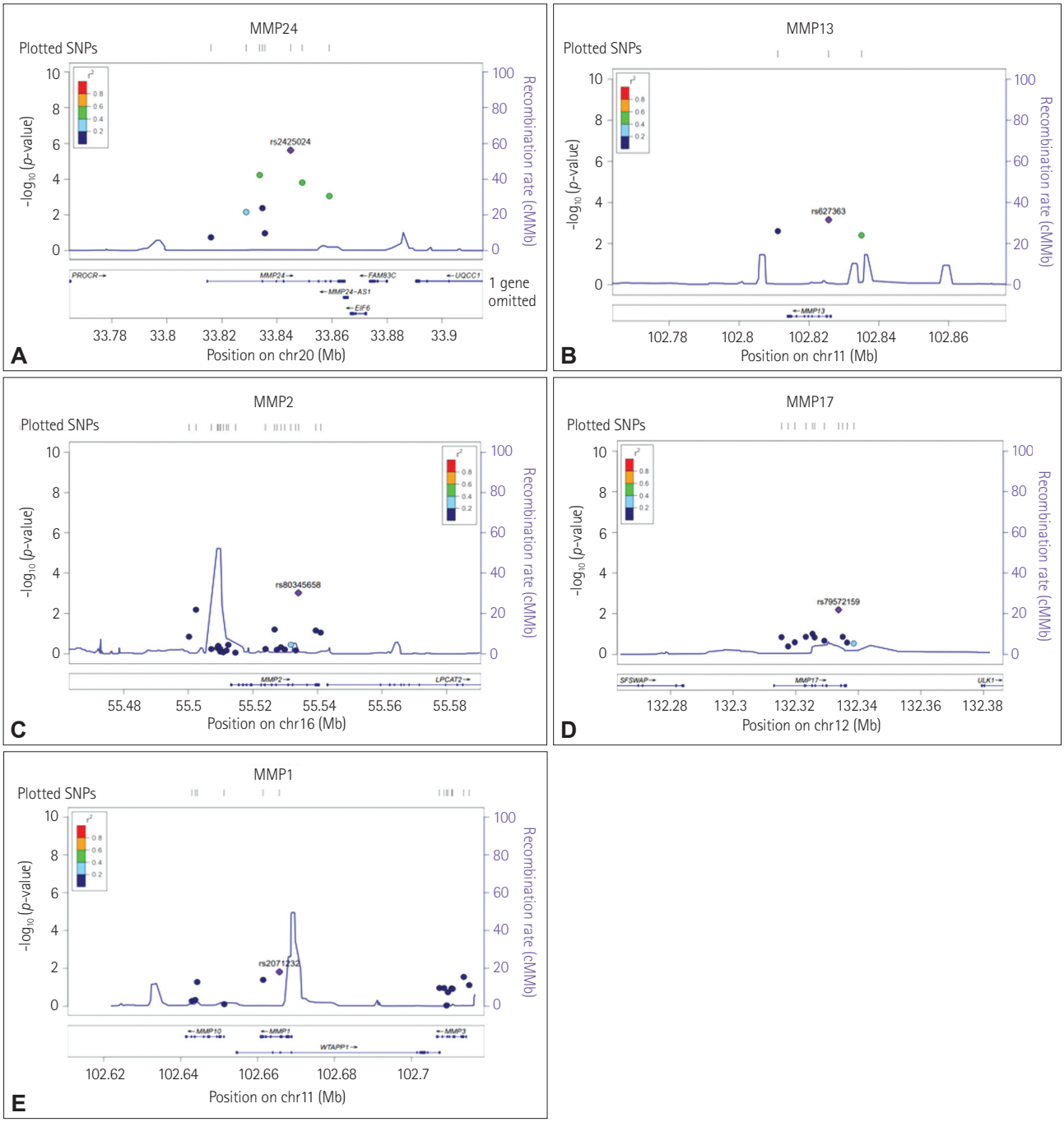

Fig. 2. Regional association plots obtained from a genome-wide association study of MMP SNPs for intracranial aneurysms. The most-significant SNPs in the genes, indicated by purple diamonds, were rs2425024 in MMP24 (A), rs627363 in MMP13 (B), rs80345658 in MMP2 (C), rs79572159 in MMP17 (D), and rs2071232 in MMP1 (E). The X- and Y-axes indicate the chromosomal position (megabases, Mb) and $-\log_{10}$-transformed *p* values. MMP, matrix metalloproteinase; SNP, single-nucleotide polymorphism.

Previous studies investigating MMP24 have mainly focused on its association with cancer. Sugimoto et al.[19] reported that MMP24 acted as a negative regulator of cancer progression by increasing the levels of YAP (yes-associated protein) and the resulting stiff ECM environment. These findings suggest the need for a further investigations, since MMP24 may interfere with IA formation by affecting ECM stiffness.

MMP13 is classified as an archetypal MMP containing collagenase.[18] A few studies investigating the role of MMP13 in IAs (e.g., Mao et al.[20]) have found the expression level of MMP13 to be higher in abdominal aortic aneurysms than in the atherosclerotic aorta, and localized to the medial smooth-

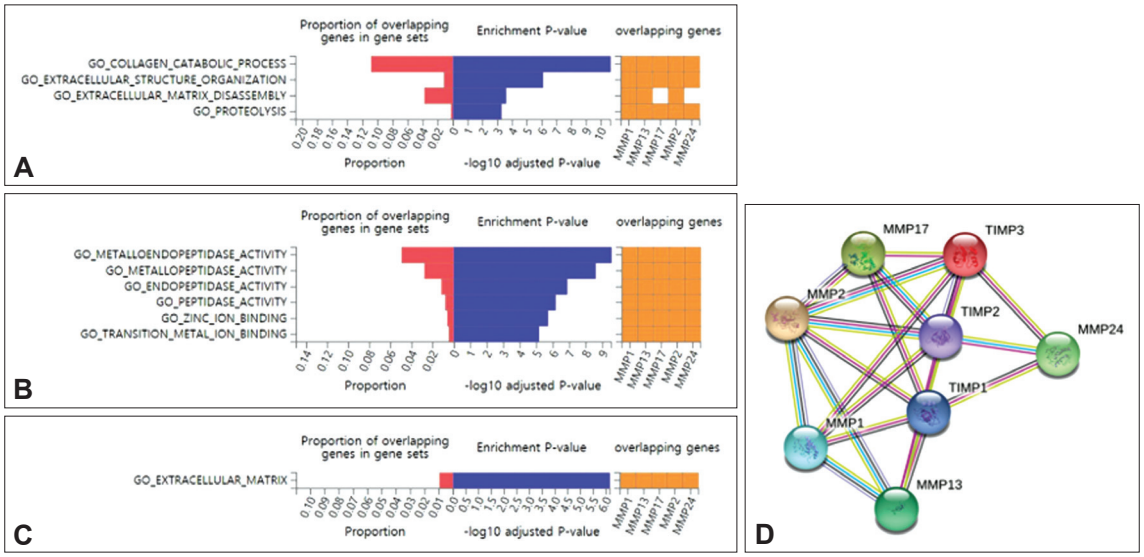

Fig. 3. Results from gene enrichment analyses of five IA-associated MMP genes for the biological process (A), cellular component (B), and molecular function (C). (D) Protein–protein interaction network based on the five IA-associated MMP genes with three regulators: TIMP1, TIMP2, and TIMP3. Individual lines represent the associations between MMP and TIMP genes. IA, intracranial aneurysm; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase.

muscle cells. Ma et al.[21] reported that MMP13 deficiency in mice significantly reduced the number of newborn neuroblasts in the cortical peri-infarct area. Accordingly, MMP13 may play critical roles in angiogenesis and neurogenesis during recovery after ischemic stroke. Our study found that MMP13 was closely associated with IAs, but it was not clear whether it promotes or inhibits IA formation. The analysis of MMP13 SNPs revealed that the rs627363 SNP increased the risk of an IA (OR=1.55), whereas rs150333315 (OR=0.098) and rs72987535 (OR=0.676) inhibited IA formation. Thus, additional investigations are needed to determine the cumulative effect of the different SNPs of MMP13 on IAs.

A histopathological study revealed focal areas of gelatin lysis in the IA wall characterized by increased MMP2 expression.[22] However, the impact of MMP2 variations on IAs is disputed. Low et al.[23] reported that two MMP SNPs (rs243847 [p=0.00086] and rs243865 [p=0.0009]) were associated with IAs in a Japanese population. Alg et al.[24] similarly reported that the rs243865 T allele was associated with ruptured IAs in a Caucasian population in the UK. However, other investigators have found no association between MMP2 and IA occurrence.[16] It is particularly interesting that the 3 MMP2 SNPs in the top-20 SNPs of IAs associated with MMPs showed a protective effect on IA formation. In addition, MMP2 was the MMP that was most strongly associated with IAs. MMP2 is highly expressed in blood vessels, the brain, and blood (Supplementary Fig. 2 in the online-only Data Supplement). Therefore, it is necessary to investigate multigene interactions in the pathogenesis of IAs.

In contrast to MMP24, MMP13, and MMP2, there was no genome-wide significant association of MMP17 and MMP1 with IAs in our study. MMP17 is known to be essential for the maturation of vascular smooth-muscle cells.[25] Martín-Alonso et al.[25] reported that deficiency of MMP17 increased the susceptibility to an angiotensin-II–induced thoracic aortic aneurysm by altering the ECM in the arterial wall. In addition, during the development of the aorta wall, osteopontin cleavage mediated by MMP17 regulates the maturation of vascular smooth-muscle cells via the c-Jun N-terminal kinase signaling pathway. Our study also showed that the rs79572159 SNP of MMP17 exerted a protective effect on IA formation. Nevertheless, few studies have investigated the effects of MMP17 on IAs, and so further research is needed. MMP1 has been mainly studied for the occurrence of IAs in patients with autosomal dominant polycystic kidney disease (ADPKD).[26] Ameku et al.[26] compared vascular cell differentiation of induced pluripotent stem cells between ADPKD patients with and without IAs based on altered calcium entry and gene expression profiles. They found that ADPKD patients with an IA had a higher expression level of MMP1 than did those without an IA. However, ADPKD is an autosomal dominant inherited disorder caused by mutation of either the PKD1 or PKD2 gene. In addition, a prevalence rate of IAs in patients with ADPKD of approximately 8% has been reported,[26,27] suggesting that another genetic predisposition plays a role in sporadic IAs. Accordingly, additional in vivo studies into the role of MMP1 in IAs are also needed.

The activity of an MMP is controlled through its interaction with TIMP.[28,29] Aoki et al.[29] reported increased mRNA levels of TIMP1 and TIMP2 in the early stage of IA formation,

but not in the late stage. Conversely, mRNA expression levels of MMP2 and MMP9 were significantly increased in the late state of IA formation. After an IA ruptures, increased TIMP1 exerts a protective effect on cerebral vasospasm.[30] Therefore, an imbalance between MMPs and TIMPs is thought to be related to IA formation and vasospasm by altering ECM remodeling. We drew PPI networks using the five MMP genes and three TIMP genes, and analyses of the interconnectivity between the genes revealed that MMP2, TIMP2, and TIMP3 constituted a network with the strongest correlation with IAs. These results warrant future research focusing on IA formation and growth through the interactions of MMP2 with TIMP1 and TIMP2.

This study had a few limitations. First, the relatively small number of original GWAS data sets (with 250 IAs and 294 controls) is of concern; however, this is the first study integrating the results of the association between MMPs and IAs. It is necessary to corroborate the present findings using a large cohort of IA patients and elucidate the relationship between MMPs and IA formation via biological verification of the results both in vivo and in vitro. Second, we used PMRA chips based on Asian genetic variants. Most previous GWAS studies used SNP arrays designed using genetic variants of Caucasian populations, and the influence of MMPs on IAs may vary with race.[11,31] Third, we performed bioinformatics analyses of IA GWAS data derived from blood samples, rather than from IA tissues. The strength and direction of any correlation between the expression of an MMP and IAs depend on the sample origin. Thus, further studies are needed to determine the expression levels of MMPs in IA tissues and their circulating levels.

In conclusion, the present bioinformatics analyses have provided comprehensive insight into the occurrence of IAs associated with MMPs. More-specific studies based on the characteristics of each MMP are needed in the future that include suppressing or enhancing the expression of each SNP in order to maximize the therapeutic effect.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.2.163.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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