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Laboratory Study

The rs522616 polymorphism in the matrix metalloproteinase-3 (*MMP-3*) gene is associated with sporadic brain arteriovenous malformation in a Chinese population

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ABSTRACT

In this study, we investigated the association between common variants in the matrix metalloproteinase-3 (*MMP-3*) gene and the risk of developing sporadic brain arteriovenous malformation (BAVM). We performed genotyping analyses for five single nucleotide polymorphisms (SNPs) in *MMP-3* in a case-control study involving 319 Chinese patients with BAVM and 333 Chinese controls. The association between *MMP-3* genotypes and the risk of developing BAVM was evaluated using logistic regression analyses. We found that the genotype frequencies were significantly different between patients and controls for the rs522616 A > G variant of *MMP-3* ($p = 0.02$). Logistic regression analysis revealed that the variant genotype of this polymorphism was associated with a significantly decreased risk of BAVM (adjusted odds ratio = 0.62, 95% confidence interval = 0.44–0.87, $p = 0.006$ for the AG compared with the AA genotype; adjusted odds ratio = 0.68, 95% confidence interval = 0.49–0.94, $p = 0.019$ for the AG + GG compared with the AA genotype). These findings indicate for the first time that the *MMP-3* rs522616 polymorphism may contribute to the etiology of sporadic BAVM in the Chinese population.

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1. Introduction

Patients with brain arteriovenous malformation (BAVM) have a 2–6% annual likelihood of experiencing a life-threatening intracranial hemorrhage (ICH).[1] Because of the long asymptomatic development period of BAVM, accurate detection at an early stage, followed by appropriate clinical management, would undoubtedly reduce the morbidity and mortality caused by this condition.

Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that degrade extracellular matrix (ECM) proteins, cell surface molecules, and other pericellular substances.[2] Excessive degradation of the vascular matrix by MMPs may result in the destabilization of vessels, which potentially leads to weakening of the vessel wall and passive dilation.[3,4] This is a critical step in angiogenesis and vascular remodelling.[5] However, it also appears to be important for the histological phenotype of BAVM, which is characterized by vessels that are structurally incomplete, consisting of enlarged feeding arteries, tangled masses of blood vessels and dilated arterialized veins.[6]

Previous studies have revealed that there is altered expression of MMPs and tissue inhibitors of metalloproteinases (TIMPs) in BAVM tissue. Compared with normal brain tissue, BAVM samples had higher levels of total MMP-9, active MMP-9, pro-MMP-9, TIMP-1 and TIMP-3.[7] MMP-3 is an activator of a number of pro-MMPs,[8] and though there is currently no evidence of abnormal expression of MMP-3 in BAVM tissue, *MMP-3* polymorphisms have been demonstrated to be associated with certain diseases that are characterized by the presence of an unstable extracellular scaffold.[9–12]

Based on this evidence, we hypothesized that polymorphisms in *MMP-3* might be associated with the risk of developing BAVM. To test this hypothesis, we conducted a case-control study in which we genotyped 319 Chinese patients with BAVM and 333 age- and sex-matched Chinese controls for five single nucleotide polymorphisms (SNPs) in *MMP-3*.

2. Materials and methods

2.1. Study population

All study subjects were genetically unrelated and of ethnic Han Chinese descent. Patients who had been newly diagnosed with

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Table 1
The five single nucleotide polymorphisms (SNPs) of matrix metalloproteinase-3 (*MMP-3*) examined in association with sporadic brain arteriovenous malformation in a Chinese population

SNP ID	Chromosome position[†]	Genetic location	Base change	Rationale for selection	MAF			Genotyping rate (%)
					NCBI[‡]	Case	Control	
rs569444	102212515	Intron 9	G >A	Tagging SNP	0.067	0.06	0.06	97.7
rs650108	102213997	Intron 8	A > G	Tagging SNP	0.389	0.39	0.37	98.6
rs522616	102220258	Promoter	A > G	Tagging SNP Promoter variant, modulates transcription	0.386	0.36	0.39	96
rs632478	102220891	Promoter	C > A	Promoter variant, modulates transcription	0.417	0.33	0.32	98.9
rs645419	102221531	Promoter	G > A	Promoter variant, modulates transcription	0.326	0.32	0.31	98

The *MMP-3* gene is located at locus 11q22.3, and is no. 185250 in the Online Mendelian Inheritance in Man database.
[†] SNP position in the online National Center for Biotechnology Information (NCBI) dbSNP database.
[‡] Minor allele frequency (MAF) for Chinese individuals in the NCBI dbSNPs database.[23]

incident BAVM (pathologically or angiographically) were consecutively recruited between January 2004 and December 2007 at Huashan Hospital, Fudan University, without placing restrictions on age or sex. Patients with a family history or diagnosis of hereditary hemorrhagic telangiectasia (HHT) were excluded. A total of 319 subjects consented to participate in the study and agreed to provide blood samples.

Control subjects were volunteers from the health examination center of Huashan Hospital. The control subjects had no significant medical history nor experienced any chronic disease during the period in which the cases were recruited. An MRI scan was performed on each control subject to exclude asymptomatic BAVM. All controls were frequency-matched to patients based on age (±5 years), sex and area of residence (urban or rural).

After written informed consent was obtained, each participant was scheduled for an interview, and a structured questionnaire was administered by interviewers to collect information on demographic and clinical data. After the interviews, a single venous blood sample of approximately 3–5 mL was collected from each participant. The study was approved by the Human Subjects Review Committee of Huashan Hospital, Fudan University.

2.2. Polymorphism selection

Tagging SNPs (tSNPs)[13] or potentially functional polymorphisms in the promoter region (http://www.ncbi.nlm.nih.govSNP) of *MMP-3* were selected for analysis based on a literature review and sequence database searches. Three tSNPs of *MMP-3* with a minor allele frequency (MAF) greater than 0.05 in the HCB sample (45 unrelated Han Chinese from Beijing, China, representing one of the populations studied in the international HapMap project) were selected by using an r^2 threshold of 0.8 from the HapMap database using the Haploview program (Broad Institute; Cambridge, MA, USA). We also included in our analyses two potentially functional SNPs in the promoter region of *MMP-3* with MAF values of greater than 0.05 in the HCB sample or the CHN sample (24 individuals of Chinese descent from the Coriell Cell Repository, selected from the Han People of Los Angeles Panel of 100). The rationale for the selection of each polymorphism is shown in Table 1.

2.3. Genotyping

Genomic DNA was extracted from white blood cell fractions using the Qiagen Blood Kit (Qiagen; Chatsworth, CA, USA) and diluted to a stock concentration. Polymorphism-spanning gene fragments were amplified using polymerase chain reaction (PCR) and subsequently genotyped using the Sequenom MassARRAY SNP genotyping platform (Sequenom; San Diego, CA, USA). The sequences of the PCR primers and genotyping probes that we used are available upon request. Six no-template controls and four duplicate samples were included in each 384-well format for the purposes of quality control. The genotyping rate for the five SNPs ranged from 96.0% to 98.9%, and the consistency rate for duplicate samples was 100%.

2.4. Statistical analysis

Goodness-of-fit to the expectation of Hardy–Weinberg equilibrium (HWE) was assessed in control subjects using a χ^2 test for each SNP. Genotype frequencies in cases and controls were compared using a χ^2 test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression with adjustment for age and sex. Pairwise linkage disequilibrium (LD) among the five SNPs was measured using Lewontin's standardized coefficient D' and the LD coefficient r^2,[14] with haplotype blocks defined using Gabriel's[15] method and analyses carried out

Table 2
Demographics of the study population and genotype frequencies of selected single nucleotide polymorphisms (SNPs) of matrix metalloproteinase-3 (*MMP-3*) in a Chinese population

	Patients	%	Controls	%	*p*-value (χ^2 test)
Demographics					
Total number	319		333		
Sex					0.945
Male	185	58.0	194	58.3	
Female	134	42.0	139	41.7	
Mean age (years) ± SD	31.3 ± 14.7		32.4 ± 13.9		0.062
Genotype					
rs569444					
GG	276	88.8	289	87.6	0.48
GA	35	11.2	40	12.1	
AA	0	0	1	0.3	
rs650108					
AA	117	36.9	129	39.1	0.69
AG	152	47.9	158	47.9	
GG	48	15.1	43	13.0	
rs522616					
AA	132	43.4	113	34.7	0.02*
AG	124	40.8	169	51.8	
GG	48	15.8	44	13.5	
rs632478					
CC	139	44.1	143	43.3	0.34
CA	142	45.1	162	49.1	
AA	34	10.8	25	7.6	
rs645419					
GG	145	46.3	151	45.7	0.35
GA	137	43.8	155	47.0	
AA	31	9.9	24	7.3	

SD = standard deviation. Totals may not sum to 333 because of missing data.
* $p < 0.05$.

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