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ORIGINAL RESEARCH

The Relationship Between *MMP17* Variants and Ischemic Stroke Risk in the Population from Shaanxi Province in China

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Background: Ischemic stroke (IS) was a multifactorial disease, which was the main cause of death and adult disability. Genetic factors cannot be ignored.

Objective: The present study discussed the relationship between *MMP17* variants and the susceptibility of IS.

Methods: Based on the Agena MassARRAY platform, we genotyped single nucleotide polymorphisms (SNPs) on the *MMP17* gene in 1345 participants (670 controls and 675 cases). We used logistic regression analysis to analyze the association of *MMP17* SNPs with the risk of IS in the Chinese population, with odds ratio (OR) and 95% confidence intervals (CIs). False-positive report probability (FPRP) detected false positives on the significant results. Besides, we detected the SNP–SNP interaction to predict IS risk by multifactor dimensionality reduction (MDR) analysis.

Results: In the total analysis, *MMP17* rs7975920 conferred an increased susceptibility to IS. After a stratified analysis by age and gender, the significant association between rs7975920 and IS risk was displayed in the subjects aged >55 years old and females. After stratified analysis by smoking and drinking, *MMP17* rs6598163 was related to the risk of IS in smokers and rs7975920 was associated with the risk of IS in smokers and was in correlation with IS risk in drinkers.

Conclusion: In short, we first observed that *MMP17* rs7975920 and rs6598163 were related to the risk of IS. The above results provided a theoretical basis for the elaboration of the role of MMP17 in IS in the Chinese population.

Keywords: ischemic stroke, MMP17, single nucleotide polymorphisms, population

Introduction

Stroke is a multifactorial disease that is considered to be the leading cause of adult death and disability in many countries. About 85% of stroke patients are due to ischemia.[1] In the United States, it is one of the fifth deadliest diseases. According to the statistics of stroke data in 2016, from 2009 to 2012, the number of people over 20 years old reached 6.6 million.[2] The prevalence of the disease increases with age. In the latest report on the American Heart Association in 2020, that number was expected to reach 7 million.[3] In China, the incidence rate of this disease is also increasing year by year, which has caused a certain degree of economic and mental burden to the country and the patients' family. In 2013, some researchers conducted a survey in 155 urban regions and rural centers in 31 provinces, with a total of 480,687 adults aged ≥20 years old.[4] Of these, 7672 people (4217 males and 3455 females) were diagnosed with mild stroke (1596/100,000) and 1643 people (903 males and 740 females) with sudden stroke (345.1/100,000). Areas with high incidence of IS were most prominent in the northern and central regions. Therefore, it is urgent to explore the pathogenic factors of IS. The prevalence of overweight, smoking, hypertension and diabetes has been found to increase the risk of IS.[5–9] But most importantly, genetic factors played an important role in the exploration of stroke risk, especially IS.

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Matrix metalloproteinases (MMPs) are calcium-dependent zinc endopeptidases of the metzincin superfamily. It is usually expressed as an inactive proenzyme with a propeptide domain. Propeptides are cleaved during exocrine secretion to activate MMP enzymes. Currently, human MMP homologues have been reported, which are divided into six subfamilies: collagenase, gelatinase, matrix hemolysin, membrane metalloproteinases and other MMPs.[10,11] MMPs played a role in the physiological processes of neuroinflammatory response[12] and angiogenesis.[13] MMPs were also involved in many physiological and pathological processes of the brain and blood–brain barrier.[14] Gelatinases MMP2[15] and MMP9[16] were the most studied in the destruction of blood–brain barrier (BBB) after IS. Also, in an article reported by Takeuchi et al,[17] altering MMP9 activity reduced BBB damage. However, the function of *MMP17* has not been reported in the physiological process of IS.

In the study, we selected variants of *MMP17* (rs6598163, rs34515698 and rs7975920) on the basis of the 1000-genome project. Based on Agena MassARRAY platform, we designed amplification primers and extension primers for these sites. Later, we analyzed the genotype distribution of *MMP17* polymorphisms in cases and controls and their correlation with the risk of IS population from Shaanxi province in China, so as to provide insights into the pathogenesis of IS.

Method

Study Subjects

Of the study, 1345 subjects (670 controls and 675 cases) were randomly recruited from Xi'an No.3 Hospital. The cases were confirmed by computed tomography (CT) scans and/or magnetic resonance imaging (MRI). The exclusion criteria for IS patients were to exclude patients who have suffered from systemic inflammatory disease, coronary artery disease, cerebral hemorrhage, and so on. The healthy people were determined by the annual health assessment from the physical examination center of the hospital and they had no history of cerebrovascular disease or myocardial infarction, hypertension and so on. The study was conducted in accordance with the ethical guidelines of declaration of Helsinki in 1975. And the study was approved by the ethics Committee of Xi'an No.3 Hospital, each participant had written informed consent.

Clinical Data Collection

In the study, we collected data on age, gender, family history, smoking and drinking from the participants' medical records. Based on the physical examination report of subjects, some biochemical parameters, such as alanine aminotransferase, aspartate aminotransferase, platelet count, platelet-specific volume, albumin, total bilirubin, leukocyte count, triglyceride, percentage of monocytes, basophil count, red blood cell count, mean hemoglobin concentration, etc. were collected. All indicators were tested by professional technicians according to standard operating methods.

DNA Extraction, SNPs Selection, and Genotyping

In the fasting state, 3 mL blood sample was collected from each participant by a professional and stored with an anticoagulant tube of EDTA. Genomic DNA was then extracted from the participants' blood samples by GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Co. Ltd., Xi′an, China) as the amplification template. The concentration and purity of genomic DNA were determined by Nanodrop 2000. Based on the 1000-genome project (https://www.internationalgenome.org/), we chose loci with minor allele frequencies (MAFs) >5% and Hardy-Weinberg equilibrium (HWE) >0.01 in the global population. Primers (amplification and extension) design were complete by Agena MassARRAY Assay Designer 3.1 (shown in the Supplementary Table 1). Based on Agena MassARRAY platform, genotyping of *MMP17* SNPs were fulfilled. The sequencing data were sorted and analyzed by Agena Bioscience TYPER, version 4.0.

Statistical Analyses

All statistical analyses were carried out using SPSS 19.0 and Microsoft Excel 22.0. The continuous variables were expressed as mean ± standard error (SE) and compared by Student's *t*-test. The expected genotype frequencies of SNPs were compared with the actual genotype frequencies in the control group with the chi-square test assay to detect

whether these sites were consistent with HWE. The allele and genotype frequencies of the selected SNPs were analyzed with chi-squared tests. Then, based on PLINK software, version 1.07, the odds ratios (OR) and 95% confidence intervals (CIs) were calculated by logistic regression analysis to assess the association between *MMP17* polymorphisms and IS risk. Significant results were tested by FPRP analysis (power OR = 2.0 and prior probability level of "0.25, 0.1, 0.01, 0.001, 0.0001"). MDR software observed the interaction (synergy or antagonism) among SNPs to predict its relationship with IS risk. $P < 0.05$ indicated statistical significance.

Results

The Basic Information of Study Subjects and Variants

In total, 670 controls (440 males and 230 females) and 675 cases (455 males and 220 females) were randomly recruited (Supplementary Table 2). The basic information of subjects' characteristics was shown in the table The mean age of 670 controls and 675 cases were 55.61±0.35 years old and 54.91±0.26 years old, respectively. By calculation, the two groups were matched by age ($p = 0.107$) and gender ($p = 0.500$). Moreover, smokers and drinkers were evenly distributed in the two groups ($p = 0.608$, $p = 0.684$). Additionally, we collected some clinical parameters of the participants (not shown).

In Table 1, the basic information of the selected SNPs in *MMP17* gene, including chromosome, position, alleles, minor allele frequency (MAF) in cases and controls, consequence and HWE *p*-value. In the allele model, subjects with rs7975920-C were more likely to develop IS (OR: 1.25, $p = 0.010$).

The Association Between *MMP17* Polymorphisms and Ischemic Stroke Risk

We introduced four genetic models (codominant, dominant, recessive and log-additive) to further study the effect of these loci on the risk of IS (Table 2). Rs7975920 conferred an increased susceptibility to IS (Heterozygous G/C: OR: 1.27, $p_{adj} = 0.035$; Homozygous C/C: OR: 1.57, $p_{adj} = 0.044$; log-additive: OR: 1.26, $p_{adj} = 0.009$). Also, we used FPRP analysis to verify the significant results in the allele model (Power = 0.983, FPRP values = 0.029, 0.081), the heterozygous model (Power = 0.921,

Table 1 The Basic Information of Selected Variants in *MMP17*

SNP-ID	Gene	Chr: Position	Consequence	Allele (A/B)	MAF		HWE	OR (95% CI)	*p*-value
					Case	Control	*p*-value		
rs6598163	MMP17	12:131840694	Missense	A>G	0.516	0.495	0.440	1.09(0.94–1.27)	0.264
rs34515698	MMP17	12:131840695	Synonymous	T>C	0.021	0.028	0.417	0.73(0.44–1.19)	0.202
rs7975920	MMP17	12:131840696	Synonymous	G>C	0.299	0.254	0.610	1.25(1.06–1.48)	**0.010**

Notes: *p*-value was calculated from Person's chi-square test. Bold values indicated that the *p*-value was statistically significant.
Abbreviations: SNP, single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; A, minor alleles; B, major alleles.

Table 2 The Association Between *MMP17* Polymorphisms and Ischemic Stroke Risk

SNP-ID	Model	Genotype	Frequency		With Adjustment	
			Case	Control	OR (95% CI)	*p*-value
rs7975920	Codominant	G/G	55	40	1	
		G/C	290	260	1.27(1.02–1.60)	**0.035**
		C/C	325	370	1.57(1.01–2.42)	**0.044**
	Dominant	G/G	55	40	1	
		G/C-C/C	615	630	0.92(0.74–1.15)	0.014
	Recessive	G/G-G/C	345	300	1	
		C/C	325	370	0.24(0.07–0.84)	0.116
	Log-additive	–	–	–	1.26(1.06–1.50)	**0.009**

Notes: *p*-value was calculated by logistic regression analysis with adjustments for age and gender. Bold values indicated that the *p*-value was statistically significant.
Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

FPRP values = 0.122, 0.294) and the homozygous model (Power = 0.418, FPRP values = 0.227, 0.469) at the prior probability of 0.25 and 0.1 (Table 3).

Besides, we assessed the relationship between genotypes at different loci and clinical parameters (alanine aminotransferase, aspartate aminotransferase, platelet count, platelet-specific volume, albumin, total bilirubin, leukocyte count, triglyceride, percentage of monocytes, basophil count, red blood cell count, mean hemoglobin concentration, etc.) shown in Supplementary Table 3. We observed that patients with different genotypes (A/A, G/A and G/G) of rs6598163 had significantly different clinical parameters (alanine aminotransferase, aspartate aminotransferase, platelet-specific volume, albumin, total bilirubin) in cases. Healthy people with different genotypes (A/A, G/A and G/G) of rs6598163 had significantly different clinical parameters (alanine aminotransferase, aspartate aminotransferase, platelet count, platelet-specific volume) in controls. In addition, carriers of rs7975920 genotypes (G/G, G/C and C/C) in controls and cases had different clinical parameters (leukocyte count, triglyceride, percentage of monocytes, basophil count, platelet-specific volume, red blood cell count and mean hemoglobin concentration).

Association Between *MMP17* Polymorphisms and Ischemic Stroke Risk Stratified by Age and Gender

Age and gender stratification analysis was also done in the assessment of the association between *MMP17* polymorphisms and IS stroke risk (Table 4). In the subjects aged >55 years old, the significant association between rs7975920 and IS risk was displayed in the allele (OR: 1.43, p_{adj} = 0.005), heterozygous (OR: 1.51, p_{adj} = 0.013), dominant (OR: 1.54, p_{adj} = 0.007) and log-additive (OR: 1.42, p_{adj} = 0.008) models. In females, the locus was closely associated with IS risk in the allele (OR: 1.47, p_{adj} = 0.008), heterozygous (OR: 1.77, p_{adj} = 0.006),

Table 3 Results of FPRP Analysis for Significant Findings

Model	OR (95% CI)	Power	Prior Probability				
			0.25	0.1	0.01	0.001	0.0001
rs7975920							
G vs C	1.25(1.06–1.48)	0.983	**0.029**	**0.081**	0.492	0.907	0.990
G/G vs G/C	1.27(1.02–1.60)	0.921	**0.122**	0.294	0.821	0.979	0.998
G/G vs C/C	1.57(1.01–2.42)	0.418	0.227	0.469	0.907	0.990	0.999

Notes: The level of false-positive report probability threshold was set at 0.2. Bold values indicated that the FPRP value is less than 0.2.
Abbreviation: FPRP, false positive report probability.

Table 4 Association Between *MMP17* Polymorphisms and Ischemic Stroke Risk Stratified by Age and Gender

SNP	Model	Genotype	> 55		≤55		Female		Male	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
rs7975920	Allele	G	1		1		1		1	
		C	1.43(1.11–1.83)	**0.005**	1.15(0.91–1.46)	0.236	1.47(1.10–1.95)	**0.008**	1.16(0.93–1.43)	0.181
	Codominant	G/G	1		1		1		1	
		G/C	1.51(1.09–2.09)	**0.013**	1.08(0.78–1.51)	0.628	1.77(1.18–2.66)	**0.006**	1.07(0.81–1.42)	0.622
		C/C	1.75(0.88–3.47)	0.112	1.79(1.00–3.23)	0.052	1.97(0.97–3.99)	0.062	1.47(0.83–2.60)	0.185
	Dominant	G/G	1		1		1		1	
		G/C-C/C	1.54(1.13–2.10)	**0.007**	1.18(0.86–1.61)	0.304	1.80(1.22–2.66)	**0.003**	1.12(0.86–1.47)	0.407
	Recessive	G/G-G/C	1		1		1		1	
		C/C	1.47(0.75–2.88)	0.265	1.73(0.98–3.06)	0.060	1.48(0.75–2.92)	0.258	1.43(0.82–2.50)	0.211
	Log-additive	–	1.42(1.10–1.84)	**0.008**	1.22(0.96–1.56)	0.106	1.54(1.14–2.09)	**0.005**	1.14(0.92–1.42)	0.241

Notes: *p*-value was calculated by logistic regression analysis with adjustments for age and gender. Bold values indicated that the *p*-value was statistically significant.
Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

dominant (OR: 1.80, p_{adj} = 0.003) and log-additive (OR: 1.54, p_{adj} = 0.005) models. A non-significant association was observed between the variant and IS risk in people aged ≤55 years old and males.

Association Between *MMP17* Polymorphisms and Ischemic Stroke Risk Stratified by Smoking and Drinking

Smoking and drinking stratification analysis was also done in assessing the relationship between *MMP17* variants and IS risk (Table 5). The results indicated that rs6598163 was related to the risk of IS (allele G: OR: 1.36, p_{adj} = 0.006; Heterozygous G/A: OR: 1.60, p_{adj} = 0.016; Homozygous G/G: OR: 1.77, p_{adj} = 0.013; dominant G/A-G/G: OR: 1.65, p_{adj} = 0.006; log-additive: OR: 1.34, p_{adj} = 0.011) in smokers. Rs7975920 was associated with the risk of IS (allele C: OR: 1.35, p_{adj} = 0.017; Heterozygous G/C: OR: 1.41, p_{adj} = 0.044 dominant G/C-C/C: OR: 1.42, p_{adj} = 0.033; log-additive: OR: 1.30, p_{adj} = 0.046) in smoker and was in correlation with IS risk (allele C: OR: 1.33, p_{adj} = 0.022; log-additive: OR: 1.31, p_{adj} = 0.037) in drinkers. However, the two variants were not found to be associated with IS risk in non-smokers and non-drinkers.

SNP-SNP Interaction Analyzed by the MDR Software Was Used to Predict Ischemic Stroke Risk

Then, we used MDR software to analyze the impact of potential SNP–SNP interaction on IS risk (Table 6). The two-locus model containing *MMP17* variants (rs34515698 and rs7975920) was considered to be the best model for the effect of SNP–SNP interaction on IS risk (cross-validation consistency = 10/10, testing balanced accuracy = 53.6%, OR: 1.37, 95% CI = 1.11–1.71, p = 0.004). We displayed the interaction between each site with the dendrogram (In Figure 1A) and circle graph (Figure 1B). In Figure 1B, the interaction between rs34515698 and rs7975920 was antagonistic, with the information gain value −0.42%.

Table 5 Association Between *MMP17* Polymorphisms and Ischemic Stroke Risk Stratified by Smoking and Drinking

SNP	Model	Genotype	Smokers		Non-Smokers		Drinkers		Non-Drinkers	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
rs6598163	Allele	A	1		1		1		1	
		G	1.36(1.09–1.69)	**0.006**	1.13(0.92–1.40)	0.247	1.11(0.90–1.38)	0.324	0.94(0.76–1.16)	0.563
	Codominant	A/A	1		1		1		1	
		G/A	1.60(1.09–2.35)	**0.016**	1.07(0.75–1.54)	0.706	1.07(0.73–1.56)	0.732	1.02(0.70–1.47)	0.930
		G/G	1.77(1.13–2.78)	**0.013**	1.31(0.85–2.02)	0.216	1.13(0.72–1.75)	0.597	0.83(0.54–1.29)	0.411
	Dominant	A/A	1		1		1		1	
		G/A-G/G	1.65(1.15–2.38)	**0.006**	1.14(0.81–1.61)	0.443	1.09(0.76–1.55)	0.645	0.95(0.67–1.35)	0.791
	Recessive	A/A-G/A	1		1		1		1	
		G/G	1.31(0.90–1.89)	0.161	1.26(0.87–1.81)	0.219	1.08(0.75–1.55)	0.685	0.82(0.57–1.19)	0.298
	Log-additive	–	1.34(1.07–1.68)	**0.011**	1.14(0.92–1.42)	0.225	1.06(0.85–1.32)	0.596	0.92(0.74–1.14)	0.430
rs7975920	Allele	G	1		1		1		1	
		C	1.35(1.06–1.72)	**0.017**	1.17(0.92–1.48)	0.194	1.33(1.04–1.70)	**0.022**	1.18(0.93–1.50)	0.167
	Codominant	G/G	1		1		1		1	
		G/C	1.41(1.01–1.96)	**0.044**	1.08(0.78–1.48)	0.649	1.26(0.90–1.76)	0.173	1.22(0.89–1.69)	0.218
		C/C	1.45(0.78–2.72)	0.242	1.72(0.91–3.26)	0.094	1.81(0.97–3.37)	0.062	1.49(0.78–2.82)	0.227
	Dominant	G/G	1		1		1		1	
		G/C-C/C	1.42(1.03–1.95)	**0.033**	1.15(0.85–1.56)	0.373	1.33(0.97–1.83)	0.073	1.26(0.92–1.71)	0.151
	Recessive	G/G-G/C	1		1		1		1	
		C/C	1.25(0.68–2.30)	0.472	1.67(0.9–3.11)	0.106	1.64(0.89–3.01)	0.110	1.35(0.72–2.52)	0.347
	Log-additive	–	1.30(1.01–1.67)	**0.046**	1.19(0.93–1.53)	0.168	1.31(1.02–1.68)	**0.037**	1.22(0.95–1.57)	0.121

Notes: *p*-value was calculated by logistic regression analysis with adjustments for age and gender. Bold values indicated that the *p*-value was statistically significant.
Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval.

Table 6 SNP–SNP Interaction of MMP17 Gene Were Analyzed by the MDR Method

Model	Training Bal. Acc.	Testing Bal. Acc.	CVC	OR (95% CI)	*p*
rs7975920	0.535	0.535	10/10	1.33(1.07–1.64)	**0.010**
rs34515698, rs7975920	0.540	0.536	10/10	1.37(1.11–1.71)	**0.004**
rs6598163, rs34515698, rs7975920	0.542	0.531	10/10	1.39(1.12–1.72)	**0.003**

Notes: Bold values indicate that the *p*-value was statistically significant. *p*-values were calculated using χ^2 tests.
Abbreviations: MDR, multi-factor dimensionality reduction; Bal. Acc, balanced accuracy; CVC, cross-validation consistency; OR, odds ratio; 95% CI, 95% confidence interval.

Discussion

Globally, IS is one of the most important causes of morbidity and mortality. It may be the result of multiple factors, among which genetic factors are the least negligible. In the present research, *MMP17* rs7975920 conferred an increased susceptibility to IS. In subjects aged >55 years old and females, there was a significant association between rs7975920 and IS risk. Also, the results indicated that *MMP17* rs6598163 was related to the risk of IS in smokers. In addition, rs7975920 was associated with the risk of IS in smokers and drinkers. We hope that the results of this study will lay a foundation for the role of *MMP17* gene in the pathogenesis of IS, and also provide theoretical clues for the pathogenesis of IS.

MMPs are a family of proteolytic enzymes that played a key role in extracellular matrix (ECM) degradation, as well as in mediating intercellular adhesion and cytokine signaling.[18] Except MMP-28, all MMPs are widely expressed in mammals. In general, the expression level of MMP was low, but MMP-2 and MT1-MMP were constitutively expressed in precursor and activated forms in the brain.[19] On the contrary, TIMPs (tissue inhibitors of metalloproteinases), an inhibitor of MMP-mediated proteolytic activity, can inactivate MMP activity by combining with MMP,[20,21] which can prevent excessive tissue degradation and damage under physiological conditions. In other conditions, MMPs can also be activated by reactive oxygen species and other influencing factors.[22]

Recent reports indicated that MMP-related factors played an important role in cerebrovascular diseases, such as IS.[23,24] *MMP17*, a member of membrane metalloproteinases, has been involved in the studies of intracranial aneurysm (IA) and thoracic aortic aneurysm. In an article published by Kim et al,[25] they comprehensively investigated the relationship between MMP variants and IA susceptibility using GWAS. The results indicated that MMPs genes, including *MMP17* gene, increased susceptibility to IA. In a separate paper reported by Martín-Alonso et al, *MMP17* was crucial for the maturity of vascular smooth muscle cells (VSMCs) and played an important role in the function of arterial walls.[26] Not only that, in mice, loss of Mmp17 leaded to dysfunction of VSMCs and changes in the extracellular matrix (ECM) of vascular wall. Mmp17 deficiency also increased susceptibility to angiotensin II–induced aortic thoracic aneurysms by altering the ECM in arterial walls.[26] In addition, Kim et al found that *MMP17* rs79572159 had a protective against IA formation.[25] However, so far, the possible role of *MMP17* SNPs in IS has not been reported. The present report first showed that *MMP17* rs7975920 and rs6598163 were related to the risk of IS, especially in smokers and drinkers. The above results revealed the importance of smoking and drinking for IS-related studies.

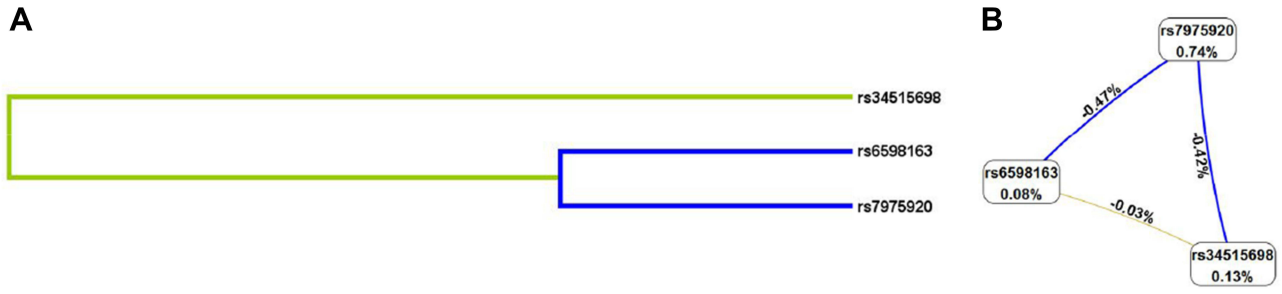

Figure 1 MDR software was used to analyze the impact of potential SNP-SNP interaction on IS risk. From the (**A**) dendrogram and (**B**) circle graph, the two-locus model containing rs34515698 and rs7975920 was considered to be the best model.

In conclusion, we first observed that *MMP17* rs7975920 and rs6598163 were related to the risk of IS. The above results provided a theoretical basis for the elaboration of the role of *MMP17* in IS in the population from Shaanxi province in China.

Data Sharing Statement

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

Ethics Approval and Informed Consent

This study was approved by the ethics Committee of Xi′an No.3 Hospital (Ethical approval No.: SYXSLL-2019-034), and all participants provided written informed consent.

Consent for Publication

All authors agree to publicize the paper.

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Disclosure

The authors report no conflicts of interest in this work.

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