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Association study between matrix metalloproteinase-3 gene (MMP3) polymorphisms and ankylosing spondylitis susceptibility

Yong Zhu[1*] | **Shunan Li**[2*] | **Zhi Huang**[1] | **Wenhua Xing**[1] | **Feng Li**[1] | **Yifeng Da**[3] | **Jianmin Xue**[3] | **Manglai Li**[3] | **Ke Sun**[3] | **Haiyu Jia**[4] | **Xuejun Yang**[1]

[1]The Second Affiliated Hospital of Inner, Mongolia Medical University, Hohhot, China

[2]The Hohhot First Hospital, Hohhot, China

[3]Inner Mongolia Medical University, Hohhot, China

[4]The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China

Correspondence
Xuejun Yang, #1 Yingfang Road, Inner Mongolia Medical University, Hohhot 010050, Inner Mongolia, China.
Email: yangxjhohhot@163.com
Haiyu Jia, #1 North Tongdao Road, Hohhot 010020, Inner Mongolia, China.
Email: nmjiahaiyu@qq.com

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Abstract

Background: Ankylosing spondylitis (AS) is the second most common cause of inflammatory arthritis worldwide affecting the axial skeleton. Single nucleotide polymorphisms (SNPs) of matrix metalloproteinase-3 (MMP3) in the development of AS has few been investigated in Chinese population.

Methods: A total of 362 patients with AS and 362 healthy controls were enrolled in the study. Five SNPs in MMP3 genotypes were identified by Agena MassARRAY. Chi-squared tests and genetic model were used to evaluate associations.

Results: rs522616 had a significant risk of AS development compared to those with the TT genotype ($p = 0.008$). By multiple logistic regression models analysis, in co-dominant model, rs522616 CT genotypes also had a 1.44-fold risk (95% CI = 1.06–1.96, $p = 0.008$) for AS development compared to those with TT genotypes. In recessive model, the CC genotypes was a significantly reduced AS risk for individuals with TT/CT genotype (OR = 0.64; 95% CI = 0.41–0.99, $p = 0.040$).

Conclusion: The present study suggests that MMP3 rs522616 polymorphism is associated with AS susceptibility and MMP3 might be a potential diagnostic biomarker for AS. Further independent studies with larger cohorts are warranted to validate our findings in different populations.

KEYWORDS

Ankylosing spondylitis (AS), Chinese population, matrix metalloproteinase3 (MMP3), Single nucleotide polymorphisms (SNPs)

1 | INTRODUCTION

Ankylosing spondylitis (AS) is the second most common cause of inflammatory arthritis worldwide affecting the axial skeleton (Campochiaro, 2016). It is characterized by inflammation of the spine and sacroiliac joint, resulting in initial erosion of the bone and joint and subsequent ankylosis. Arthritis affecting peripheral joints, particularly the hips, occurs in 40% of cases, and inflammation may also involve extraarticular sites such as the uvea, tendon insertions, aorta, lungs, and kidneys (Smith, 2015). Familial aggregation suggested the presence of shared susceptibility factors has been long observed, and studies of twin and family disease consistency indicate that susceptibility to disease is largely controlled by genetic factors (Reveille, 2001).

*Joint first authors.

Degradation of the extracellular matrix (ECM) components is the pathological feature of chronic arthritis. Previous studies have shown that matrix metalloproteinases (MMPs) play an important role in the degradation and remodeling of ECM (Matrisian, 1990; Singh, Srivastava, Chaudhuri, & Upadhyay, 2015). MMPs included a large family of zinc-dependent endoproteinases that are collectively capable of degrading all ECM components. MMPs are produced by fibroblasts, macrophages (Grillet, Dequeker, Paemen, Van Damme, & Opdenakker, 1997), synovial cells (Ahrens, Koch, Pope, Stein-Picarella, & Niedbala, 1996; Hembry, Bagga, Reynolds, & Hamblen, 1995; Okada, Takeuchi, Tomita, Nakanishi, & Nagase, 1989), endothelial cells, neutrophils, and chondrocytes (Malemud et al., 2016) in response to proinflammatory cytokines such as interleukin-1 and tumor necrosis factor-α (TNF-α) (Ito et al., 1996). Of the MMP family, MMP3 (stromelysin 1) hydrolyses a number of ECM components, activates several pro-MMPs, such as pro-MMP-1 and pro-MMP-9 (Nagase, 1997; Robichaud et al., 2015). MMP3 gene is localized in a MMP cluster of 400 kb at chromosome 11q21–23 that counts nine MMPs, which may activate other MMPs including collagenase, matrilysin, and gelatinase B (Nagase, Visse, & Murphy, 2006; Visse & Nagase, 2003). Together with other MMPs, it can synergistically degrade the major components of extracellular matrix (Johansson, Ahonen, & Kähäri, 2000) and is also capable of degrading proteoglycan, fibronectin, laminin and type IV collagen (Jin et al., 2005). There is less research on MMPs susceptibility to this disease. In this report, we investigated the role of MMP3 in AS susceptibility using a case-control study in Chinese Han population.

2 | MATERIALS AND METHODS

2.1 | Subjects

Our study recruited 362 patients with AS from the HongHui Affiliated Hospital of Xi'an Jiaotong University College of Medicine Medical University Hospital and The Second Affiliated Hospital of Inner Mongolia Medical University. The study was approved by the Ethics Committee of The Second Affiliated Hospital of Inner Mongolia Medical University. All patients were diagnosed using the modified New York criteria. Patients were informed consent to participate. As a control group, healthy controls were matched 1:1 with AS patients by age and sex. A total of 362 potential controls were randomly selected from subjects with regular health examinations in the center, and they had no rheumatic Demographic characteristics and clinical features of patients with AS and healthy controls.

2.2 | Genotyping

The gene associated with AS were selected using UCSC (http://genome.ucsc.edu/) database. We found that MMP3 gene was associated with several diseases including AS. We then searched the SNPs in dbSNP database and 1,000 Genomes database (http://www.internationalgenome.org/) to obtain the genetic data of them. We selected five SNPs of the MMP3 gene based on the minor allele frequencies of all the selected SNPs were >5% in the 1,000 Genomes Project (http://www.internationalgenome.org/) Chinese population. All of the selected SNPs in the study were successfully genotyped with an average call rate of 99.38%. Blood samples were collected in tubes containing ethylene diaminetetraacetic acid (EDTA). DNA was extracted from whole blood using GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Co. Ltd. Xi'an City, China). We use NanoDrop 2000 (Thermo Scientific, Waltham, Massachusetts, USA) to measure DNA concentration. The design of SNP genotyping and data processing were performed by Agena MassARRAY platform Software (Agena Co. Ltd., San Diego, California, USA). Genotype calling was carried out with 3.0 version MassARRAY RT software and analyzed by 3.4 version MassARRAY Typer software (Gabriel, Ziaugra, & Tabbaa, 2009). Agena Typer 4.0 software was used for data management and analysis. We listed the primer in Table 1

TABLE 1 Primers used for this study

SNP_ID	2nd-PCRP	1st-PCRP	UEP_SEQ
rs520540	ACGTTGGATGCCAGCTCGTA CCTCATTTCC	ACGTTGGATGGCGAAAGGGCTT AACTGTTAT	CTCGTACCTCATTTCCTCTGAT
rs639752	ACGTTGGATGGGCTGCAATGC AGGGAAAAG	ACGTTGGATGCAGATAAATTCT CCACTTGC	tGGGAAGAAAGAAATAGGTGAT
rs646910	ACGTTGGATGGTTAAGCCC TTTCGCTTTAG	ACGTTGGATGCCACTGTAAGCT GGTGACTA	CGCTTTAGAAATACACTTTAGCATCT
rs679620	ACGTTGGATGAGAAATA TCTAGAAAACTAC	ACGTTGGATGAACAGGACCACT GTCCTTTC	tcTCTAGAAAACTACTACGACCTC
rs522616	ACGTTGGATGACAGAGA GAATTTCAGTCCG	ACGTTGGATGCGTAGCTGCTCC ATAAATAG	gaCGGTAAGCAATGTAATTCATTTCA

TABLE 2 Genotype and allele frequency information of cases and controls

SNP	Chromosome	Position	Band	Alleles A/B	Gene(s)	MAF(control)	MAF(case)	OR	95%CI	*p*
rs639752	11	102,707,339	11q22.2	C/A	MMP3	0.334	0.324	1.050	0.85–1.30	0.676
rs520540	11	102,709,425	11q22.2	A/G	MMP3	0.334	0.324	1.050	0.85–1.30	0.676
rs646910	11	102,709,522	11q22.2	A/T	MMP3	0.084	0.097	0.850	0.60–1.22	0.378
rs679620	11	102,713,620	11q22.2	T/C	MMP3	0.341	0.327	1.070	0.86–1.32	0.559
rs522616	11	102,715,048	11q22.2	C/T	MMP3	0.374	0.372	1.010	0.82–1.24	0.920

Abbreviation: CI, Confidence interval; MAF, Minor allele frequency; OR, Odds ratio; SNPs, Single nucleotide polymorphisms.
p-value was calculated by Pearson's χ^2 test; $p < 0.05$ indicates statistical significance.

2.3 | Statistical analysis

Microsoft Excel (Microsoft, Redmond, WA) and SPSS Statistics (version 20.0, SPSS, Chicago, IL) were used for statistical analyses. SNP genotype frequencies in the case and control groups were calculated by Chi-square Test, and the Hardy–Weinberg equilibrium (HWE) was used to check the genotype frequency of the control group. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were tested using unconditional logistic regression analysis with adjustment for age and gender (Bland & Altman, 2000). Haploview version 4.2 was used to identify the linkage disequilibrium (LD) block and haplotypes (Barrett, Fry, Maller, & Daly, 2005). The significance level for all statistical analyses was 0.05.

3 | RESULTS

Tables 2 give the candidate SNP genotypes and allele frequency. These data conformed to the Hardy–Weinberg equilibrium (HWE) in that the allele frequencies ($p > 0.05$). By study design, there were no SNPs statistically significant. In Table 3 we displayed the genotype and AS risk. We found rs522616 had significant risk of AS development compared to those with the TT genotype ($p = 0.008$). To determine whether SNPs of MMP3 were associated with susceptibility to AS, multiple logistic regression analysis while adjusting for age and gender was conducted. Multiple logistic regression models (codominant models, dominant models, recessive models and additive model). As shown in Table 4, in codominant model, rs522616 CT genotypes also had a 1.44-fold risk (95% CI = 1.06–1.96, $p = 0.008$) for AS development compared to those with TT genotypes. In recessive model, the CC genotypes was a significantly reduced AS risk for individuals with TT/CT genotype (OR = 0.64; 95% CI = 0.41–0.99, $p = 0.040$). In contrast, the MMP3 other SNPs were not significantly associated with development of AS. In Table 5, five SNPs were analyzed for haplotypes, however, the results did not found any significantly ($p > 0.05$).

TABLE 3 MMP3 SNP genotypes and the risk of ankylosing spondylitis

SNP	Genotype	Control, *n*(%)	Case, *n*(%)	*p*
rs639752				
	A/A	287 (44%)	117 (43.7%)	0.707
	A/C	309 (47.3%)	123 (45.9%)	
	C/C	57 (8.7%)	28 (10.4%)	
rs520540				
	G/G	287 (44%)	117 (43.7%)	0.707
	A/G	309 (47.3%)	123 (45.9%)	
	A/A	57 (8.7%)	28 (10.4%)	
rs646910				
	T/T	534 (81.7%)	224 (83.6%)	0.516
	A/T	113 (17.3%)	43 (16%)	
	A/A	7 (1.1%)	1 (0.4%)	
rs679620				
	C/C	286 (43.9%)	112 (42%)	0.832
	C/T	306 (46.9%)	128 (47.9%)	
	T/T	60 (9.2%)	27 (10.1%)	
rs522616				
	T/T	270 (41.3%)	95 (35.7%)	0.008
	C/T	282 (43.1%)	143 (53.8%)	
	C/C	102 (15.6%)	28 (10.5%)	

Abbreviation: CI, Confidence interval; OR, Odds ratio; SNPs, Single nucleotide polymorphisms.
$p < 0.05$ indicates statistical significance.

4 | DISCUSSION

rs522616 polymorphisms in the MMP3 gene were identified. This report confirmed the MMPs significant association of AS risk. One of the main features of ankylosing spondylitis (AS) is bone loss due to an imbalance between bone formation and resorption. MMPs are important in this context, particularly MMP3. The level of this proteolytic enzyme is high in the serum of AS patients, suggesting a relationship with the bone degradation typical of this disease. Matrix

TABLE 4 Association between MMP3 polymorphism and risk of ankylosing spondylitis under genetics model

	Model	Genotype	Control	Case	OR (95% CI)	*p*-value	AIC	BIC
rs639752	Codominant	A/A	287 (44%)	117 (43.7%)	1	0.71	1,116.1	1,130.6
		A/C	309 (47.3%)	123 (45.9%)	0.98 (0.72–1.32)			
		C/C	57 (8.7%)	28 (10.4%)	1.20 (0.73–1.99)			
	Dominant	A/A	287 (44%)	117 (43.7%)	1	0.93	1,114.8	1,124.4
		A/C-C/C	366 (56%)	151 (56.3%)	1.01 (0.76–1.35)			
	Recessive	A/A-A/C	596 (91.3%)	240 (89.5%)	1	0.42	1,114.1	1,123.8
		C/C	57 (8.7%)	28 (10.4%)	1.22 (0.76–1.96)			
	Log-additive	—	—	—	1.05 (0.84–1.31)	0.67	1,114.6	1,124.3
rs520540	Codominant	G/G	287 (44%)	117 (43.7%)	1	0.71	1,116.1	1,130.6
		A/G	309 (47.3%)	123 (45.9%)	0.98 (0.72–1.32)			
		A/A	57 (8.7%)	28 (10.4%)	1.20 (0.73–1.99)			
	Dominant	G/G	287 (44%)	117 (43.7%)	1	0.93	1,114.8	1,124.4
		A/G-A/A	366 (56%)	151 (56.3%)	1.01 (0.76–1.35)			
	Recessive	G/G-A/G	596 (91.3%)	240 (89.5%)	1	0.42	1,114.1	1,123.8
		A/A	57 (8.7%)	28 (10.4%)	1.22 (0.76–1.96)			
	Log-additive	—	—	—	1.05 (0.84–1.31)	0.67	1,114.6	1,124.3
rs646910	Codominant	T/T	534 (81.7%)	224 (83.6%)	1	0.47	1,116	1,130.4
		A/T	113 (17.3%)	43 (16%)	0.91 (0.62–1.33)			
		A/A	7 (1.1%)	1 (0.4%)	0.34 (0.04–2.78)			
	Dominant	T/T	534 (81.7%)	224 (83.6%)	1	0.48	1,115	1,124.6
		A/T-A/A	120 (18.4%)	44 (16.4%)	0.87 (0.60–1.28)			
	Recessive	T/T-A/T	647 (98.9%)	267 (99.6%)	1	0.26	1,114.2	1,123.9
		A/A	7 (1.1%)	1 (0.4%)	0.35 (0.04–2.83)			
	Log-additive	—	—	—	0.85 (0.60–1.22)	0.37	1,114.7	1,124.3
rs679620	Codominant	C/C	286 (43.9%)	112 (42%)	1	0.83	1,113.3	1,127.7
		C/T	306 (46.9%)	128 (47.9%)	1.07 (0.79–1.44)			
		T/T	60 (9.2%)	27 (10.1%)	1.15 (0.69–1.90)			
	Dominant	C/C	286 (43.9%)	112 (42%)	1	0.59	1,111.3	1,121
		C/T-T/T	366 (56.1%)	155 (58%)	1.08 (0.81–1.44)			
	Recessive	C/C-C/T	592 (90.8%)	240 (89.9%)	1	0.67	1,111.5	1,121.1
		T/T	60 (9.2%)	27 (10.1%)	1.11 (0.69–1.79)			
	Log-additive	—	—	—	1.07 (0.86–1.33)	0.55	1,111.3	1,120.9
rs522616	Codominant	T/T	270 (41.3%)	95 (35.7%)	1	0.008	1,102.9	1,117.3
		C/T	282 (43.1%)	143 (53.8%)	1.44 (1.06–1.96)			
		C/C	102 (15.6%)	28 (10.5%)	0.78 (0.48–1.26)			
	Dominant	T/T	270 (41.3%)	95 (35.7%)	1	0.12	1,108.1	1,117.7
		C/T-C/C	384 (58.7%)	171 (64.3%)	1.27 (0.94–1.70)			
	Recessive	T/T-C/T	552 (84.4%)	238 (89.5%)	1	0.04	1,106.3	1,116
		C/C	102 (15.6%)	28 (10.5%)	0.64 (0.41–0.99)			
	Log-additive	—	—	—	1.01 (0.82–1.24)	0.92	1,110.5	1,120.2

Abbreviation: AIC, Akaike information criterion; BIC, Bayesian Information Criterions; CI, Confidence interval; OR, Odds ratio; SNPs, Single nucleotide polymorphisms.

$p < 0.05$ indicates statistical significance.

TABLE 5 MMP3 haplotype frequencies and the association with the risk of ankylosing spondylitis

Haplotype	rs639752	rs520540	rs646910	rs679620	rs522616	Freq	OR (95% CI)	*p*-value
1	A	G	T	C	C	0.37	1.00	—
2	C	A	T	T	T	0.32	0.98 (0.71–1.35)	0.91
3	A	G	T	C	T	0.20	1.13 (0.79–1.64)	0.50
4	A	G	A	C	T	0.09	0.82 (0.50–1.36)	0.45
Rare	*	*	*	*	*	0.02	2.80 (0.89–8.81)	0.08

Note: 95% CI, 95% confidence interval; OR, odds ratio.

metalloproteinase-3 (MMP3, also known as human fibroblast stromelysin) is a secreted metalloprotease produced predominantly by connective tissue cells (Lièvre et al., 2006). Together with other MMPs, it can synergistically degrade the major components of the extracellular matrix (Johansson et al., 2000) and is also capable of degrading proteoglycan, fibronectin, laminin and type IVcollagen (Jin et al., 2005). The exact biological mechanisms are unknown, but tissue degradation of biochemical mediators, especially MMPs, has been identified as an important factor (Zade, Gosavi, Hazarey, & Ganvir, 2017). Recent studies have shown that it plays an important role in AS.

Serum MMP3 levels were significantly higher in patients than in healthy subjects, and to a greater extent in patients with high disease activity (Chen et al., 2006). In addition to digesting components of ECM, MMP3 activates a number of pro-MMPs and is critical in the full generation of active MMPs (Nagase, 1997; Visse & Nagase, 2003). It plays a key role in cartilage damage and joint destruction. Serum MMP3, originating directly from inflamed joints, can be specific markers of inflammation in joint activity (Vandooren, Kruithof, & Yu, 2004).

At present, there are few studies on MMP3 polymorphism. We found rs522616(MMP3) was associated with AS risk, as far as we know, no other studies have been reported the SNP associated with AS risk. In addition, we demonstrated that the CC genotype of rs522616, which is located in the promoter region of MMP3, was associated with a lower risk of developing AS. It is possible that a variant in the promoter region of MMP3 could affect the production of proteolytic enzymes. Meanwhile, it may have an effect on the risk of AS occurrence. It may be the reason that the transcription factor can bind to rs522616 C allele of the MMP3 promoter, activate its transcription, and lead to a higher expression of this gene.

Although AS is thought to be caused by a complex interaction of environmental and genetic factors, the polymorphisms identified in this study might be useful for predicting the susceptibility to the disease. In conclusion, the present study suggests that MMP3 rs522616 polymorphism is associated with AS susceptibility and MMP3 might be a potential diagnostic biomarker for AS. Further independent studies with larger cohorts are warranted to validate our findings in different populations.

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CONFLICTS OF INTEREST

The authors have declared that they have no conflict of interest.

ORCID

Yong Zhu https://orcid.org/0000-0002-8840-686X
Xuejun Yang https://orcid.org/0000-0003-2713-7237

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