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*Original Article*

# Associations of polymorphisms in *MMP-7* and *MMP-8* with osteoarthritis risk in a Han Chinese population

Changxu Han[1,2], Yizhong Ren[2], Lingyue Kong[2], Tu Eerdun[2], Lunhao Bai[1]

*[1]Department of Orthopedic Surgery, Shengjing Hospital, China Medical University, Shenyang, Liaoning Province, China; [2]Department of Arthroscopy and Sports Medicine, The Second Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China*

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**Abstract:** Matrix metalloproteinases have proteolytic activity and are implicated in the degradation of extracellular matrix in cartilage. Studies have revealed the distribution of MMP-7 in human osteoarthritic synovial membrane and shown increased expression of MMP8 in human osteoarthritic cartilage. To investigate the potential association of *MMP-7* and *MMP-8* polymorphisms with osteoarthritis susceptibility, Sequenom MassARRAY method was performed to determine the genotypes of 416 osteoarthritis cases and 495 controls. The associations between the investigated SNPs and osteoarthritis risk were assessed under multiple inheritance models and haplotype analysis by multivariate logistic regression analysis with and without adjustments for age and gender. We found a risk allele for osteoarthritis in cases such as the allele "T" of rs12285347 in the *MMP-7* gene (OR = 1.23, 95% CI = 1.01-1.49, *P* = 0.036). When we analyzed the association under different inheritance models, we found *MMP-7* rs12285347 was associated with increased risk of developing osteoarthritis in an additive model with adjustment by age and gender (adjusted OR = 1.43, 95% CI = 1.04-1.95, *P* = 0.03) or without (OR = 1.24, 95% CI = 1.02-1.51, *P* = 0.03) and in a dominant model (adjusted OR = 1.55, 95% CI = 1.01-2.37, *P* = 0.04). Furthermore, *MMP-8* rs1892886 also correlated with increased risk of developing osteoarthritis in a recessive model (OR = 1.88, 95% CI = 1.07-3.31, *P* = 0.03). The present study provided evidence for a osteoarthritis susceptibility locus, *MMP-7* rs12285347 and *MMP-8* rs1892886, in a Chinese Han population from Northwest China. However, a significant association with other ethnicities and functional significance of these polymorphisms needs further confirmation.

**Keywords:** Osteoarthritis, *MMP-7*, *MMP-8*, polymorphisms, case-control study

## Introduction

Osteoarthritis (OA) is a major cause of severe arthralgia and physical disability in the elderly population across the world which brings considerable distress and inconvenience to patients [1]. The incidence of OA has been increasing in recent years and the health care cost has been a major challenge for the government finance. Multiple factors contribute to the development of this disease, such as age, joint trauma, and excess body weight [2, 3]. Moreover, genetic factors that lead to this illness have been gaining more attention for investigators. Studies have provided evidence for the effect of heritable components in the pathogenesis of OA [4-6]. Therefore, identificantion of more candidate genes or risk alleles that may responsible for OA pathogenesis can provide new directions for disease prevention in the early stage.

Single nucleotide polymorphisms (SNPs) are common genomic DNA variations within a particular population which can accelerate complex disease gene localization, such as hypertension, diabetes mellitus, and neoplasia [7, 8]. Several Genome-Wide Association Studies (GWAS) have identified gene polymorphisms involved in susceptibility to OA in North American Caucasians and Koreans [9, 10]. We also found relationships of many genetic locus with OA that differed depending on the ethnicity of subjects, such as *ADAM12*, *DVWA*, *IL1-R1* and *ESR1* after searching for susceptibility loci for this disease [11-14].

Among OA associated genes, matrix metalloproteinases (*MMPs*) are a large gene family of extracellular zinc-dependent endopeptidases which are implicated in the degradation of extracellular matrix (ECM) [15]. Annu Nakki et al. showed that *MMP-8* variants have a sugges-

**Table 1.** Distributions of age and gender in OA cases and controls

| Variable | Cases (n = 416) | Controls (n = 495) | *P* value |
|---|---|---|---|
| Gender | | | <0.05 |
| Male | 271 (29.7%) | 180 (19.8%) | |
| Female | 145 (15.9%) | 315 (34.6%) | |
| Age, yr | 58.95 | 54.48 | <0.05 |

*P* values were calculated from Pearson Chi-square test.

tive association with OA susceptibility in the discovery cohort of Finnish [16]. However, association of *MMP-8* polymorphisms with OA risk in a Chinese Han population did not reach statistical significance [17]. Owing to the inconclusive results, we performed a comprehensive association analysis between OA and 9 susceptible SNPs in the *MMP-8* gene and *MMP-7* gene to assess whether these variants are associated with OA in a Chinese Han population from Northwest China.

## Materials and methods

### *Study participants*

This work was complied with the Helsinki Declaration and approved by the ethics committee of the Second Affiliated Hospital of Inner Mongolia Medical University. Each subject gave written informed consent after a full explanation for the genetic study. We recruited a total of 416 patients diagnosed with OA from 2013 to 2016 among Han Chinese in the Second Affiliated Hospital of Inner Mongolia Medical University. Inclusion criterias of OA cases were as follows: (1) All patients were native residents of Han Chinese in Northwest China, and all were genetically unrelated. (2) The diagnosis of OA was based on the criteria of the American College of Rheumatology. (3) Cases were recruited without age, sex, or occlusion site restriction. Controls were choosed from Physical Examination Center of the Second Affiliated Hospital of Inner Mongolia Medical University without OA medical history.

### *SNPs selection and genotyping*

Venous blood samples were collected from 911 subjects (416 cases and 495 controls) at the Orthopedics Department and Physical Examination Center. The GoldMag-Mini Purification Kit (GoldMag Co. Ltd. Xi'an, China) was used to extract genomic DNA from venous blood samples. DNA concentrations were determined using high performance liquid chromatography (NanoDrop2000; Thermo Fisher Scientific, Waltham, MA, USA). DNA samples were then stored at -20°C before genotyping.

We selected 9 SNPs in the *MMP-8* gene and *MMP-7* gene, each with a minor allele frequency greater than 5% in the HapMap Asian population. Sequenom MassARRAY Assay Design 3.0 Software was used to design the multiplexed SNP MassEXTENDED assay (Sequenom, Inc., San Diego, CA, USA). Subsequently, SNPs genotyping was performed using the Sequenom MassARRAY RS1000 recommended by the manufacturer. Data processing and analysis were performed with Sequenom Typer 4.0 Software [18].

### *Statistical analysis*

Microsoft Excel and SPSS 16.0 (SPSS, Chicago, IL, USA) were used to perform statistical analysis. Differences in age and gender between OA cases and controls were evaluated by Pearson Chi-square test. Allele frequencies of *MMP-8* and *MMP-7* SNPs in controls were evaluated by the exact test to determine whether these SNPs departed from Hardy-Weinberg equilibrium (HWE). The allele and genotype frequencies of these SNPs were compared in cases with controls using the Chi-square test/Fisher's exact test. Multiple inheritance models (dominant, recessive, and additive) were performed using PLINK software (http://pngu. mgh.harvard.edu/purcell/plink/) to estimate the correlation between each SNP and OA risk. The Haploview software package (version 4.2) and SHEsis software platform (http://www.nhgg.org/analysis/) were used for evaluate and visualize patterns of the pairwise linkage disequilibrium and haplotype construction [19-21]. ORs and 95% CIs calculated by unconditional logistic regression models with or without adjustment for gender and age were used to assess the associations between SNP and OA susceptibility, respectively. A two-sided $P \leq 0.05$ was regarded as statistically significant.

## Results

### *Population characteristics*

In total, 911 subjects were genotyped (416 OA cases and 495 controls) for 9 SNPs. The distributions of age and gender of these OA cases and controls are listed in **Table 1**. The mean

**Table 2.** Basic information on candidate *MMP-7 and MMP-8* SNPs

| SNPs | Gene | Chromosome | Position | Allele | Minor allele frequency | | HWE *P* value | OR (95% CI) | *P*[a] |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Case | Control | | | |
| rs17352054 | MMP7 | 11q22.2 | 102393055 | A/C | 0.197 | 0.185 | 0.297 | 1.08 (0.86-1.37) | 0.507 |
| rs12285347 | MMP7 | 11q22.2 | 102396607 | C/T | 0.385 | 0.337 | 0.422 | 1.23 (1.01-1.49) | 0.036* |
| rs78978042 | MMP7 | 11q22.2 | 102398436 | T/C | 0.326 | 0.320 | 0.257 | 1.03 (0.84-1.25) | 0.802 |
| rs10502001 | MMP7 | 11q22.2 | 102398593 | T/C | 0.324 | 0.320 | 0.257 | 1.02 (0.83-1.24) | 0.875 |
| rs33927742 | MMP8 | 11q22.2 | 102584207 | A/G | 0.041 | 0.050 | 1.000 | 0.82 (0.52-1.28) | 0.374 |
| rs2509013 | MMP8 | 11q22.2 | 102584607 | T/C | 0.298 | 0.301 | 0.593 | 0.99 (0.81-1.21) | 0.899 |
| rs3740938 | MMP8 | 11q22.2 | 102587062 | G/A | 0.299 | 0.303 | 0.595 | 0.98 (0.80-1.20) | 0.844 |
| rs1892886 | MMP8 | 11q22.2 | 102591994 | A/T | 0.269 | 0.251 | 0.053 | 1.10 (0.89-1.36) | 0.363 |
| rs34546185 | MMP8 | 11q22.2 | 102594169 | A/T | 0.275 | 0.270 | 0.424 | 1.03 (0.84-1.26) | 0.791 |

HWE: Hardy-Weinberg equilibrium, OR: odds ratio, 95% CI: 95% confidence interval. *$p \leq 0.05$ indicates statistical significance.

**Table 3.** Association between *MMP-7* rs12285347 and *MMP-8* rs1892886 and OA risk under multiple inheritance models

| SNPs | Models | Genotype | Cases | Controls | Without adjustment | | With adjustment | |
|---|---|---|---|---|---|---|---|---|
| | | | | | OR (95% CI) | *P*[a] | OR (95% CI) | *P*[b] |
| rs12285347 (C>T) | Codominant | CC | 154 | 213 | 1.00 | | 1.00 | |
| | | TC | 204 | 230 | 1.23 (0.93-1.62) | 0.100 | 1.45 (0.93-2.27) | 0.083 |
| | | TT | 58 | 52 | 1.54 (1.01-2.37) | | 2.01 (1.02-3.96) | |
| | Dominant | CC | 154 | 213 | 1.00 | | 1.00 | |
| | | TT+TC | 262 | 282 | 1.29 (0.98-1.68) | 0.065 | 1.55 (1.01-2.37) | 0.044* |
| | Recessive | CC+TC | 358 | 443 | 1.00 | | 1.00 | |
| | | TT | 58 | 52 | 1.38 (0.93-2.06) | 0.110 | 1.63 (0.87-3.06) | 0.130 |
| | Additive | - | - | - | 1.24 (1.02-1.51) | 0.033* | 1.43 (1.04-1.95) | 0.026* |
| rs1892886 (A>T) | Codominant | AA | 224 | 268 | 1.00 | | 1.00 | |
| | | TA | 160 | 206 | 0.93 (0.71-1.22) | 0.075 | 1.37 (0.89-2.11) | 0.220 |
| | | TT | 32 | 21 | 1.82 (1.02-3.25) | | 1.77 (0.74-4.28) | |
| | Dominant | AA | 224 | 268 | 1.00 | | 1.00 | |
| | | TT+TA | 192 | 227 | 1.01 (0.78-1.31) | 0.930 | 1.41 (0.93-2.15) | 0.100 |
| | Recessive | AA+TA | 384 | 474 | 1.00 | | 1.00 | |
| | | TT | 32 | 21 | 1.88 (1.07-3.31) | 0.027* | 1.54 (0.66-3.63) | 0.320 |
| | Additive | - | - | - | 1.11 (0.89-1.37) | 0.350 | 1.35 (0.96-1.90) | 0.084 |

OR: odds ratio, 95% CI: 95% confidence interval. [a]*p* values were calculated by unconditional logistic regression. [b]*p* values were calculated by unconditional logistic regression adjusted for age and gender. *$p \leq 0.05$ indicates statistical significance.

age of the OA cases was significantly greater than that of the controls (58.95 *vs*. 54.48 years, $P < 0.05$). Therefore, in the following steps, variables of age and gender were adjusted in multivariate unconditional logistic regression analysis to eliminate influences of residual confounding variables.

*Allele frequencies in cases and controls and odds ratio estimates for OA risk*

The basic information on *MMP-7* rs17352054, rs12285347, rs78978042 and rs10502001 and *MMP-8* rs33927742, rs2509013, rs3740938, rs1892886 and rs34546185 are listed in **Table 2**. None of these SNPs showed significant deviation from HWE among controls ($P > 0.05$). Using the Pearson Chi-square test, we found one polymorphism that was associated with increased risk of developing OA: rs12285347 in *MMP-7* (OR = 1.23, 95% CI = 1.01-1.49, $P = 0.036$; **Table 2**). The frequency of the T allele of *MMP-7* rs12285347 in cases was significantly greater than that of the controls (38.5% versus 33.7%).

**Table 4.** *MMP-7* and *MMP-8* haplotype frequencies and their associations with OA risk in cases and controls

| *MMP-7* Haplotype block | Haplotype frequencies | | Without adjustment | | With adjustment | |
|---|---|---|---|---|---|---|
| | Case | Control | OR (95% CI) | *P*[a] | OR (95% CI) | *P*[b] |
| TT | 0.674 | 0.68 | 1.00 | | 1.00 | |
| CC | 0.326 | 0.32 | 1.03 (0.84-1.25) | 0.80 | 0.85 (0.62-1.18) | 0.33 |
| *MMP-8* Haplotype block | Haplotype frequencies | | Without adjustment | | With adjustment | |
| | Case | Control | OR (95% CI) | *P*[a] | OR (95% CI) | *P*[b] |
| TG | 0.702 | 0.698 | 1.00 | | 1.00 | |
| CA | 0.298 | 0.302 | 0.98 (0.80-1.20) | 0.86 | 0.94 (0.68-1.29) | 0.69 |

OR: odds ratio, 95% CI: 95% confidence interval. [a]*p* values were calculated by unconditional logistic regression. [b]*p* values were calculated by unconditional logistic regression adjusted for age and gender.

*Association between rs12285347 and rs1892886 polymorphisms in MMP-7 and MMP-8, respectively, and OA risk under multiple inheritance models*

Genotype distribution of these SNPs between OA cases and controls showed no significant difference, no matter with or without adjustment by age and gender ($P > 0.05$). Next, we assumed the minor allele of each polymorphism was a risk allele, compared with the wild-type, and assessed the correlation between these SNPs and OA risk under multiple inheritance models. We found *MMP-7* rs12285347 was associated with increased risk of developing OA in additive model with adjustment by age and gender (adjusted OR = 1.43, 95% CI = 1.04-1.95, $P = 0.03$) or without (OR = 1.24, 95% CI = 1.02-1.51, $P = 0.03$) and in dominant model (adjusted OR = 1.55, 95% CI = 1.01-2.37, $P = 0.04$; **Table 3**). *MMP-8* rs1892886 was also correlated with increased risk of developing OA in recessive model (OR = 1.88, 95% CI = 1.07-3.31, $P = 0.03$; **Table 3**). But the significant association of rs1892886 was gone when the data was adjusted by age and gender.

*Haplotype construction and analysis*

Partial candidate SNPs in *MMP-7* (rs78978042 and rs10502001) and *MMP-8* (rs2509013 and rs3740938) exhibited strong linkage. Four haplotypes with frequencies of more than 0.05 in OA cases and controls were chosen for further research (**Table 4**). However, we failed to find significant association in the *MMP-7* haplotype or the *MMP-8* haplotype with the risk of OA.

## Discussion

Single nucleotide polymorphisms are the most common type of human heritable variation which result in the occurrence of biodiversity among different geographic populations. Therefore, it is significant to explore the association between the ethnic and geographic distribution of polymorphisms and risk of diseases. In the present study, we found *MMP-7* rs12285347 and *MMP-8* rs1892886 were statistically significantly associated with an increased risk of OA in a Chinese Han population from Northwest China.

Matrix metalloproteinases are a large gene family of extracellular zinc-dependent endopeptidases which exhibit proteolytic activity implicated in the degradation of extracellular matrix in cartilage [15]. Among the MMP gene family members, MMP-7 has the highest activity against various ECM compositions that degrades type IV collagen, laminin-1, fibronectin, proteoglycan, type I gelatin, and insoluble elastin [22]. ECM degradation plays a central role during the destruction of articular cartilage in OA which finally leads to exposure of underlying subchondral bone. Friedrich and colleagues revealed distribution of MMP-7 in human osteoarthritic synovial membrane by immunohistochemistry [23]. Furthermore, biochemical study of human rectal carcinoma cells showed MMP-7 can activate the proMMP-1 and proMMP-9 which can also lead to cartilage destruction [22]. In the present study, we found *MMP-7* rs12285347 was associated with increased risk of OA according to both dominant and additive model analysis in current population, which indicates this polymorphism up-regulated the expression or function of MMP7.

*MMP-8*, a gene located in chromosome 11q22.2, has been reported to be involved in the pathogenesis of OA. MMP-8 plays several roles in inflammation, including degradation of extracellular matrix (ECM) components and regulation of cytokine activity [24]. Billinghurst et al. suggested that increased expression of MMP-8 is correlated with increased cleavage of type II collagen in human osteoarthritic cartilage [25]. Davidson and colleagues found the expression of MMP-8 in both cartilage and synovium from patients was higher than from controls [26]. The above conclusions support our current result for the association between *MMP-8* rs1892886 and OA susceptibility in a Chinese Han population from Northwest China. Compared with the findings by Su, a distinct difference in the relationship of *MMP-8* and OA risk was observed [17]. The following reasons may responsible for this difference. First, the two studies with the disparity of sample capacity which may be the source of different results. Second, we did not impose restrictions on occlusion site, such as hip, knee, and lumbar joints, which may also lead to the discrepancy of the two studies. Third, *MMP-8* rs1892886 was confirmed to be associated with OA risk in our study; however, which was not investigated by Su.

This case-control study has some potential limitations. First, body mass index is deeply connected to the pathogenesis of OA, which was not taken into analysis due to a lack of the corresponding clinical information. Second, the ethnicity of subjects was limited to the Chinese Han population. So, whether the current results are the same with other ethnicities is still unknown. Third, the selected SNPs were not large enough to fully clarify the association between *MMP-7* and *MMP-8* and OA susceptibility.

In summary, we have demonstrated that two genes of the *MMP* gene family (*MMP-7* and *MMP-8*) are associated with increased risk of OA in a Chinese Han population from Northwest China, which may provide new data for genetic screening of OA and a new direction for the investigation of pathogenic processes of OA.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Lunhao Bai, Department of Orthopedic Surgery, Shengjing Hospital, China Medical University, Shenyang 110000, Liaoning Province, China. E-mail: 364522490@qq.com

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