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Effect of *RAGE* polymorphisms on susceptibility to and severity of osteoarthritis in a Han Chinese population: a case-control study

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ABSTRACT. Recent studies have revealed that the inflammatory process plays a role in the pathogenesis of osteoarthritis (OA). The S100 family and receptor for advanced glycation end products (RAGE)

participate in regulating inflammation, even in the production of matrix metalloproteinases (MMPs). MMP-1 degrades cartilage, which may result in OA development. Moreover, polymorphisms in *RAGE*, *S100A8*, and *MMP-1* have a marked effect on ligand binding and transcription regulating. In this study, we investigated the potential genetic contribution of the *RAGE*, *S100A8*, and *MMP-1* genes to OA. We performed a matched case-control association study and genotyped OA patients and healthy controls, who were analyzed by polymerase chain reaction-restriction fragment length polymorphism assays. A total of 207 patients were diagnosed with knee OA and underwent total knee replacement. The control group included 207 individuals who had standard X-rays of the knee joints to confirm K/L < 2 and were matched by age and gender. Single-nucleotide polymorphisms in *RAGE* (-429T/C, -374T/A, and 557G/A), *S100A8* (rs3795391A/G), and *MMP-1* (-1607 1G/2G, -755G/T, and -519A/G) were evaluated. *RAGE* -374T/A, S100A8 rs3795391A/G, *MMP-1* -1607 1G/2G, -755G/T, and -519A/G showed no significant difference between OA patients and healthy controls. *RAGE* -429T/C and 557G/A showed a significant association between OA patients and healthy controls (P = 0.016 and 0.047, respectively). In haplotype analyses, no *RAGE* and *MMP-1* haplotypes showed associations with OA. Our results suggest that the investigated polymorphism in the *RAGE* gene play a role in OA in the Han Chinese population.

Key words: Matrix metalloprotease-1; Osteoarthritis; Polymorphism; Receptor for advanced glycation end products; S100A8

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease that causes progressive loss of joint function and is a leading cause of disability and impaired quality of life among the elderly in developed countries. OA is regarded as a multifactorial disease associated with a variety of risk factors, including genetic predisposition, aging, obesity, inflammation, and excessive mechanical loading (Zhang and Jordan, 2010). The increasing role of genetics in the pathogenesis of OA has been highlighted by epidemiological studies of family history and clustering, adoption studies, twin studies, and exploration of rare genetic disorders related to OA (Valdes and Spector, 2009). Several genome-wide association studies (Kerkhof et al., 2010; Zeggini et al., 2012; Pang et al., 2013) and candidate gene studies (Bratus et al., 2013; Gonzalez, 2013; Reynard and Loughlin, 2013) have suggested that polymorphisms in certain genes affects the pathogenesis of OA.

OA is a complex disease involving both biomechanical and metabolic factors that alter the tissue homeostasis of articular cartilage and subchondral bone (Sofat, 2009). Recent studies have revealed that the inflammatory process is involved in the pathogenesis of OA (Yuan et al., 2003). The small calcium-binding S100 protein family has been implicated in various inflammatory conditions. One member of the S100 family, S100A8, is predominant1y expressed in phagocytes and is strongly associated with pro-inflammatory functions (Soko-

love and Lepus, 2013). In addition, S100A8 has been identified in human articular cartilage, and its expression is upregulated in diseased tissue (Roth et al., 2001; van den Berg, 2011). The receptor for advanced glycation end products (RAGE) is a pattern-recognition receptor that binds to endogenous S100/calgranulins, amyloid-β-peptide, and high mobility group protein B1 (or amphoterin) to influence gene expression via activated signal transduction pathways (Reddy et al., 2006). RAGE participates in the regulation of inflammation (Hofmann et al., 1999). The interaction between S100A8 and RAGE increases matrix metalloproteinase (MMP) production and upregulates MMPs involved in mediating extracellular matrix destruction (Grogan and D'Lima, 2010). MMP-1 plays an important role in the degeneration of type II collagen, a primary extracellular matrix component. In OA cartilage, MMP-1 synthesis is increased (Martel-Pelletier and Pelletier, 1996).

Several reports have recently identified polymorphisms in the *S100A8*, *RAGE* and *MMP-1* genes that may influence ligand binding or transcription regulation (Wicki et al., 1996; Ye, 2000; Hofmann et al., 2002).

MMP-1 polymorphism has been implicated in OA in a Turkish population, and RAGE polymorphism has been implicated in rheumatoid arthritis (RA) in Caucasians (Carroll et al., 2007; Barlas et al., 2009). However, no studies have analyzed the association between *RAGE*, *S100A8*, and *MMP-1* single-nucleotide polymorphisms (SNPs) and OA in the Han Chinese population. We hypothesized that genetic polymorphisms in the *RAGE*, *S100A8*, and *MMP-1* genes lead to altered biological activities of functional proteins. The purpose of this study was to determine whether *RAGE*, *S100A8*, and *MMP-1* gene polymorphisms are markers of susceptibility to OA or its severity in a Han Chinese population.

MATERIAL AND METHODS

Study population

This study was a 1:1 matched case-control study. Cases were matched to controls by gender and age (within 5 years). OA cases who had undergone total knee joint replacement (N = 207; 154 females and 53 males; age = 70.08 ± 7.41 years) for primary severe OA fulfilled the criteria of sufficiently severe signs and symptoms of OA to require joint replacement surgery. Other etiologies of knee joint OA, including inflammatory arthritis (i.e., rheumatoid, polyarthritic, or autoimmune disease), post-traumatic or post-septic arthritis, skeletal dysplasia, or developmental dysplasia, were excluded. Healthy control subjects (age, 71.03 ± 7.76 years) showed no signs or symptoms of joint disease (pain, swelling, tenderness, or restriction of movement), and standard X-rays of the knee joints confirmed the absence of OA. The ethics review committee of the Tri-Service General Hospital approved the study, and written informed consent was obtained from all participants (TSGH-100-05-023).

Selection and genotyping of polymorphisms

SNP genotype information was downloaded from the HapMap database (http://hapmap.ncbi.nlm.nih.gov/) and the National Center for Biotechnology Information dbSNP database (http://www.ncbi.nlm.nih.gov/snp). Tag SNPs were selected for *RAGE*, *S100A8*, and *MMP-1* genes using the criteria of minor allele frequency (MAF) > 5% and those in regulatory regions or reported by other investigators. Genomic DNA was extracted from peripheral blood

samples using a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The *RAGE* [-429 T/C (rs1800625), -374 T/A (rs1800624), and 557 G/A (rs2070600)], S100A8 (rs3795391), and MMP1 [-1607 2G/1G (rs1799750), -755 G/T (rs498186), and -519 A/G (rs1144393)] polymorphisms were screened using a thermocycler polymerase chain reaction (PCR) system 9700 (GeneAmp, Applied Biosystems, Foster City, CA, USA), followed by a restriction fragment length polymorphism assay. The PCR samples contained 10X buffer, 1.5 mM $MgCl_2$, 0.2 mM of each dNTP, and 1 U *Taq* DNA polymerase. PCR-grade water was added to a final volume of 50 μL. PCR products were digested with the respective restriction endonucleases (New England Biolabs, Inc., Ipswich, MA, USA), and the resulting fragments were separated on a 2.5% agarose gel containing 0.5 μg/mL ethidium bromide by electrophoresis at 100 V and visualized under UV light. Primer design was based on published sequences (Jurajda et al., 2002; Jin et al., 2005; Li et al., 2007; Checa et al., 2008; Kalousova et al., 2009; Daborg et al., 2010). The details of the primers, PCR conditions, restriction enzymes, and genotype configurations are shown in Table 1. Genotyping was performed by blinding of case and control status. To validate the genotyping results, at least 10% of samples were randomly selected for repeated genotyping.

Table 1. Oligonucleotides used in this study.

Gene	Polymorphism	Primer sequence (5'-3')	Annealing temperature; product size; Restriction enzyme; Products after digestion
RAGE	-429 T/C	F: GGGGCAGTTCTCTCCTCACT R: GGTTCAGGCCAGACTGTTGT	59.5°C; 250 bp; *Alu*I; 162+88 bp
RAGE	-374 T/A	F: GGGGCAGTTCTCTCCTCACT R: GGTTCAGGCCAGACTGTTGT	59.5°C; 250 bp; *Mfe*I; 215+35 bp
RAGE	557 G/A	F: GTAAGCGGGGCTCCTGTTGCA R: GGCCAAGGCTGGGGTTGAAGG	62°C; 397 bp; *Alu*I; 248+181+149+67 bp
S100A8	rs3795391 A/G	F: GTGTGCACATGTCTCTGTGTG R: CAACATGATGCCCACGGAACTTGC	60°C; 248 bp; *Tfi*I; 194+147+54+47 bp
MMP-1	-1607 2G/1G	F: TGACTTTTAAAACTGACTTTTAAAA CATAGTCTATGTTCA R: TCTTGGATTGATTTGAGATAAGTCATAGC	58°C; 269 bp; *Alu*I; 241+28 bp
MMP-1	-755 G/T	F: GATCCTCCCACCTCAGCCTCTTCCG R: CATGGTGAGACCCCATCTCT	67°C; 120 bp; *Msp*I; 97+23 bp
MMP-1	-519 A/G	F: CATGGTGCTATCGCAATAGGGT R: TGCTACAGGTTTCTCCACACAC	54°C; 200 bp; *Kpn*I; 176+24 bp

Statistical analysis

The demographics were evaluated using the Student *t*-test for continuous variables and reported as means ± standard deviation. For each SNP, deviation from Hardy-Weinberg equilibrium in the cases and controls was assessed using the standard χ^2 test. The allele and genotype frequencies of case and control groups were compared using χ^2 statistics or the Fisher exact test when the expected count was less than 5 in >33% of the input cells of the contingency table. Conditional logistic regression was used to estimate crude and adjusted (age, gender, and body mass index) odd ratios (ORs) and 95% confidence intervals (CIs) as a measure of association with the risk of OA. Linkage disequilibrium and haplotype analyses were performed using the Haploview software (http://www.broad.mit.edu/mpg/haploview/). Data were analyzed with the SPSS statistical software 18.0 (SPSS Inc., Chicago, IL, USA), and the results were considered to be statistically significant when the 2-tailed P value was <0.05.

RESULTS

Basic characteristics of the study population

Table 2 shows demographic and clinical characteristics of all subjects in the study. A significant difference in body mass index was observed between OA individuals and controls ($P < 0.01$). There was no significant difference in age or gender between the 2 groups.

Table 2. Characteristics of the study subjects.

	Cases	Controls	P value
Number	207	207	
Age (years)	70.08 ± 7.41	71.03 ± 7.76	0.204
Gender (male/female)	53/154	53/154	-
BMI (kg/m^2)	27.40 ± 3.58	24.12 ± 3.18	<0.001

Distributions of *RAGE*, *S100A8*, and *MMP-1* gene polymorphisms and their association with OA

The *RAGE* (-429 T/C, -374 T/A, and 557 G/A), *S100A8* (rs3795391 A/G), and *MMP-1* gene (-1607 2G/1G, -755 G/T, and -519 A/G) genotype distributions were all in Hardy-Weinberg equilibrium in cases and controls ($P > 0.05$), indicating that the study subjects were representative of the study field. The genotypic and allelic distributions of the 3 SNPs in RAGE and their associations with OA risk are shown in Table 3. The genotypic and allelic distributions of 557G/A in *RAGE* were significantly different between OA cases and healthy controls ($P < 0.05$). In *RAGE* 557G/A, when the GG genotype was used as the reference group, the AA genotype was associated with a higher risk of OA (adjusted OR = 2.78, 95%CI = 1.02-7.63, P = 0.047). The association between the *RAGE* -429 T/C polymorphism and risk of OA was significant, with the heterozygous carrier being at lower risk (adjusted OR = 0.42, 95%CI = 0.21-0.85, P = 0.016). The -374 T/A SNP in *RAGE* showed no significant genotypic and allelic association between the OA cases and healthy controls ($P > 0.05$). There was no significant difference in the genotype or allele frequencies of the *S100A8* gene (rs3795391 A/G) and *MMP-1* gene (-1607 2G/1G, -755 G/T, and -519 A/G) polymorphisms among any of the patient and control groups. SNPs in the dominant and recessive modes showed no significance (data not shown).

Haplotype analysis of *RAGE* and *MMP-1*

Haplotype analysis of the *RAGE* and *MMP-1* polymorphisms in OA patients and control subjects is shown in Table 4. Strong linkage disequilibrium was found among *RAGE* -429 T/C, -374 T/A, and 557 G/A ($r^2 > 0.70$, data not shown). In the *MMP-1* gene, -755 G/T and -519 A/G ($r^2 = 1.00$) also showed strong linkage disequilibrium (data not shown). Only 4 of the 8 possible haplotypes of *RAGE* were observed in both OA patients and control subjects, but no haplotypes showed an association with OA. The haplotypes of the *MMP-1* gene (-1607, 2G/1G, and -755 G/T) showed no significant difference.

Table 3. Association analyses of 7 tag SNPs with osteoarthritis.

SNP	Cases	Controls	Crude OR (95%CI)	P	Adjusted OR (95%CI)*	P
RAGE -429 T/C						
T/T	186	174	1		1	
C/T	18	31	0.54 (0.29-1.01)	0.052	0.42 (0.21-0.85)	0.016
C/C	3	2	1.40 (0.23-8.50)	0.712	1.25 (0.19-8.10)	0.813
C-allele	0.94	0.92	0.67 (0.39-1.14)	0.137	0.56 (0.31-1.02)	0.056
RAGE -374 T/A						
T/T	143	148	1		1	
A/T	56	52	1.12 (0.72-1.73)	0.630	1.05 (0.64-1.72)	0.841
A/A	8	7	1.18 (0.42-3.35)	0.752	1.28 (0.42-3.94)	0.662
A-allele	0.83	0.84	1.11 (0.77-1.60)	0.576	1.09 (0.73-1.63)	0.672
RAGE 557 G/A						
G/G	109	128	1		1	
A/G	84	71	1.39 (0.93-2.09)	0.113	1.38 (0.87-2.18)	0.169
A/A	14	8	2.06 (0.83-5.08)	0.119	2.78 (1.02-7.63)	0.047
A-allele	0.73	0.79	1.39 (1.01-1.92)	0.042	1.49 (1.04-2.13)	0.031
S100A8 rs3795391 A/G						
A/A	171	163	1		1	
A/G	36	43	0.80 (0.49-1.31)	0.369	0.89 (0.51-1.54)	0.674
G/G	0	1	-	-	-	-
G-allele	0.91	0.89	0.78 (0.49-1.24)	0.292	0.87 (0.52-1.45)	0.597
MMP1 -1607 2G/1G						
2G/2G	92	98	1		1	
2G/1G	88	89	0.73 (0.38-1.40)	0.347	0.91 (0.44-1.91)	0.811
1G/1G	27	20	0.70 (0.37-1.33)	0.269	0.82 (0.40-1.70)	0.591
1G-allele	0.34	0.31	0.87 (0.65-1.16)	0.336	0.90 (0.65-1.25)	0.531
MMP1 -755 T/G						
T/T	58	60	1		1	
T/G	116	104	1.45 (0.86-2.46)	0.163	1.11 (0.62-2.00)	0.719
G/G	33	43	1.26 (0.71-2.25)	0.435	0.93 (0.49-1.78)	0.827
G-allele	0.44	0.46	1.08 (0.82-1.42)	0.576	0.95 (0.70-1.30)	0.754
MMP1 -519 A/G						
A/A	179	173	1		1	
A/G	27	33	0.79 (0.46-1.37)	0.403	0.91 (0.50-1.66)	0.756
G/G	1	1	0.97 (0.06-15.6)	0.981	0.85 (0.05-13.9)	0.910
G-allele	0.93	0.92	0.82 (0.49-1.36)	0.436	0.91 (0.52-1.59)	0.747

*Adjusted for age, gender, and BMI.

Table 4. Haplotype frequencies in RAGE and MMP-1 between osteoarthritis patients and control subjects.

			Frequency		OR (95%CI)	P value
			Case	Control		
	RAGE					
-429 T/C	-374 T/A	557 G/A				
T	T	G	0.515	0.551	0.86 (0.66-1.14)	0.296
T	T	A	0.253	0.205	1.32 (0.95-1.82)	0.098
T	A	G	0.160	0.155	1.04 (0.71-1.51)	0.838
C	T	G	0.054	0.084	0.64 (0.36-1.09)	0.096
	MMP-1					
-1607 2G/1G	-755 G/T	-519 A/G				
2G	G	A	0.369	0.403	0.87 (0.65-1.14)	0.309
2G	T	A	0.276	0.271	1.02 (0.76-1.40)	0.861
1G	T	A	0.214	0.186	1.20 (0.85-1.68)	0.307
1G	T	G	0.058	0.070	0.82 (0.47-1.43)	0.477
1G	G	A	0.071	0.056	1.29 (0.73-2.26)	0.372
2G	T	G	0.012	0.015	0.83 (0.25-2.75)	0.764

DISCUSSION

We investigated the association between *RAGE*, *S100A8*, and *MMP-1* gene polymorphisms and OA and identified significant associations for *RAGE* -429 T/C and 557 G/A. No associations with gene polymorphisms at *RAGE* -374 T/A or *S100A8* rs3795391 A/G or with *MMP-1* -1607 2G/1G, -755 T/G, and -519 A/G were identified.

RAGE has been shown to play a role in OA (Loeser et al., 2005). Animal model studies have described a possible role of *RAGE* in the onset and severity of arthritis (Hofmann et al., 2002; Kokkola et al., 2003). Relatively few studies have investigated the association between *RAGE* polymorphisms and arthritis. Hofmann et al. (2002) reported that the *RAGE* 557 G/A polymorphism was correlated with the susceptibility to RA. A study of 233 patients in a Han Chinese population found that polymorphisms in *RAGE* at 577 G/A were associated with OA. Their results also indicated that 557G/A was positively associated with obesity (Han et al., 2012). However, no interaction was found between obesity and *RAGE* polymorphisms in the current study (data not shown). In the present study, the *RAGE* -374T/A polymorphism showed no association with OA, but the *RAGE* -429T/C and 577 G/A polymorphisms were found to be associated with OA. The -429T/C and -374T/A polymorphisms exerted a marked effect on transcriptional activity, and the 577 G/A (G82S) polymorphism promotes glycosylation of *RAGE* at asp81 and is associated with enhanced ligand binding and consequent receptor signaling (Li and Schmidt, 1997; Hudson et al., 2001). The *RAGE* SNPs may affect the susceptibility to OA by altering transcriptional activity.

Thus far, no associations between polymorphisms in the *S100A8* gene and OA have been reported. We observed no difference in the frequencies of the *S100A8* rs3795391A/G genotype and allele between OA patients and controls. *S100A8* rs3795391A/G may have a very small an effect on the susceptibility to OA.

We also identified the haplotypes in *RAGE* and *MMP-1*, but none were associated with OA. A previous study found a weak association between a *RAGE* gene promoter haplotype and ischemic stroke in men (Zee et al., 2006), and another study showed that the *MMP-1* haplotype is associated with OA (Abd-Allah et al., 2012). Our results are inconsistent with these results. Further studies are required to confirm the reported association between the *RAGE* and *MMP-1* haplotypes and genetic susceptibility to OA. These findings suggest that a weak association exists between *RAGE* gene polymorphisms and OA susceptibility.

Our study had some limitations. First, the results apply to the Han Chinese population and may not generalize to other ethnic groups. Our sample size was relatively small, limiting its statistical power to detect existing associations. Second, the complicated process of *RAGE* gene expression and activity *in vivo* is unclear, possibly because of modulation by other genes. The continued accumulation in databases of SNP data for other genes will improve such studies.

The investigated polymorphism in the *RAGE* gene may play a role in OA in the Han Chinese population. Definitive confirmation of the correlations between *RAGE* gene polymorphism and OA should be further studied in a larger population size.

Conflicts of interest

The authors declare that they have no competing interests.

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