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ORIGINAL ARTICLE

Association of (−1,607) 1G/2G polymorphism of matrix metalloproteinase-1 gene with knee osteoarthritis in the Turkish population (knee osteoarthritis and MMPs gene polymorphisms)

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Abstract The aim of this study was to investigate whether functional polymorphisms in the promoter of matrix metalloproteinase-1 (MMP-1), MMP-2 and MMP-9 genes were associated with susceptibility to knee osteoarthritis in the Turkish population. The MMP-1 −1,607 1G/2G (rs1799750), MMP-2 −1,306 C/T (rs243865), and MMP-9 −1,562 C/T (rs3918242) polymorphisms were determined by polymerase chain reaction-restriction fragment length polymorphism assay in 157 patients diagnosed with knee osteoarthritis based on the criteria of American College of Rheumatology and in 84 controls in Mersin, Turkey. Genotype distributions and allele frequencies of MMP-1, MMP-2, and MMP-9 gene polymorphisms were compared between the patients and controls. There were significant differences between the groups regarding the genotype distribution of MMP-1 polymorphism ($P = 0.001$). The frequencies of 1G/1G and 1G/2G genotypes were significantly higher in the knee osteoarthritis than in the controls ($P = 0.002$, and $P = 0.006$, respectively). In addition, 1G allele frequency of MMP-1 gene was higher in the patients than in the control group ($P = 0.0001$). The genotype distributions and allele frequencies of MMP-2 and MMP-9 gene polymorphisms did not differ between the osteoarthritis and the control groups ($P > 0.05$). These findings suggest that the −1,607 1G/2G polymorphism in the MMP-1 gene may contribute to susceptibility to knee osteoarthritis in the Turkish population.

Keywords Knee osteoarthritis · MMP-1 · MMP-2 · MMP-9 · Gene polymorphism

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Introduction

Osteoarthritis (OA) is the most common joint disease and one of the most frequent causes of physical impairment [1]. The disease is generally characterized by a slowly progressive loss of articular cartilage, eburnation of subchondral bone and mild synovial inflammation. Failure of joint compartments is essential for the development of OA; however, marked changes have been reported to occur in the cartilage [2]. The articular cartilage consists of chondrocytes and extracellular matrix (ECM). The ECM of the normal cartilage is in a state of dynamic equilibrium, with a balance between synthesis and degradation of collagen and aggrecan. This balance is disrupted in OA in favor of proteolysis, which leads to pathologic cartilage destruction [3]. The matrix metalloproteinases (MMPs) from the chondrocytes have been considered the main enzymes responsible for this degradation [4].

About 20 identical MMPs are classified into different groups according to particular substrates they degrade, such as collagenases, stromelysins, gelatinases, matrilysins and the membrane-type MMPs (MT-MMPs) [5]. Several studies have shown that expression of MMPs is elevated in cartilage and synovial tissues of patients or of animal models with OA [6–9]. In a study by Tetlow et al. [10] all the OA specimens showed a greater frequency and distribution of

six MMPs (MMP-1, 2, 3, 8, 9, and 13) as compared with normal articular cartilage specimens. Similar to previous studies, a recent study has determined that levels of both MMP-2 and MMP-9 are significantly increased in OA cartilage [11].

The expression of MMPs has been shown to be affected by single nucleotide polymorphisms (SNPs) occurring in MMP gene promoters [12]. Over the last few years, some polymorphisms have been identified in the promoters of a number of MMP genes (MMP-1, 2, 3, 7, 9, 12, 13) [13]. These promoter polymorphisms have allele-specific effects on the regulation of MMP gene transcription and are associated with the development and/or progression of some common diseases (i.e., coronary heart disease, abdominal aortic aneurysm, rheumatoid arthritis, and cancers) [14–19]. The MMP-1 (−1,607 1G/2G), MMP-2 (−1,306 C/T) and MMP-9 (−1,562 C/T) polymorphisms are three of them and have been shown to be functionally important, and have increased transcriptional activity [13, 20].

To our knowledge, no reports concerning the role of the MMPs promoter polymorphisms in knee OA have been reported as yet. We hypothesized that polymorphisms in MMP-1, MMP-2, and MMP-9 genes promoters may play an important role in the development of knee OA. We planned a study to determine whether the MMP-1 (−1,607) 1G/2G (rs1799750), MMP-2 (−1,306) C/T (rs243865), and MMP-9 (−1,562) C/T (rs3918242) polymorphisms were associated with susceptibility to knee OA in a Turkish population.

Materials and methods

We recruited 157 patients presenting with primary knee OA to the outpatient clinic of Physical Therapy and Rehabilitation Department of Mersin University Hospital, Mersin, Turkey. The diagnosis of OA in all patients was based on the criteria of the American College of Rheumatology, which include primary OA with any symptoms and signs of OA, and radiographic signs of OA according to the Kellgren–Lawrence grading. Patients with inflammatory arthritis (rheumatoid, polyarthritic, or autoimmune disease), posttraumatic or post-septic arthritis were excluded. No cases suggestive of skeletal dysplasia or developmental dysplasia were included.

The control group comprised a total of 84 individuals. They were selected from the subjects who were over 40 years of age and admitted to the outpatient clinic of Mersin University Hospital. The control group never had any signs or symptoms of OA, other arthritis or joint diseases (pain, swelling, tenderness, or restriction of movement) at any site based on their medical history and a thorough examination conducted by an experienced physiatrist. The control subjects had no relationship with the patients and no family history of OA.

All subjects were Caucasians from the southern part of Turkey. The study was approved by the ethical committee of the medical faculty of Mersin University and informed consent was obtained from all subjects.

DNA extraction and analysis

Venous blood samples were collected in ethylenediaminetetra acetic acid (EDTA) containing tubes. DNA was extracted from whole blood with the salting-out procedure [21].

Genotypic analyses of the MMP-1, MMP-2, MMP-9 genes polymorphisms

We used primer sets and the conditions of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay for identifying the MMP-1 promoter 1G/2G polymorphism at position −1,607 as described in the literature [18]. The 193-bp sequence of MMP-2 promoter region was amplified with PCR using the sense primer 5′-CTTCC TAGGCTGGTCCTTACTGA-3′ and antisense primer 5′-C TGAGACCTGAAGAGCTAAAGAGCT-3′. The reaction was conducted under the following conditions: an initial melting step of 2 min at 95°C, followed by 35 cycles of 45 s at 95°C, 60 s at 58°C, and 90 s at 72°C; and a final elongation of 7 min at 72°C. The PCR product was digested with Fsp I restriction endonuclease. The homozygous C/C alleles were represented by a DNA band size of 193 bp, whereas homozygous T/T alleles were 167 and 26 bp and heterozygotes (C/T) showed band sizes of 193, 167, and 26 bp respectively [22]. The MMP-9 C-1562T polymorphism was screened with restriction fragment length polymorphism (RFLP). The area surrounding the polymorphism was amplified with PCR using the oligonucleotide primers 5′-G CCTGGCACATAGTAGGCCC-3′ (forward) and 5′-CT TCCTAGCCAGCCGGCATC-3′ (reverse). The PCR product (436 bp) was digested with the restriction enzyme Bbu I (Pae I) (Fermentas). The CC homozygotes showed a single band of 436 bp and CT heterozygotes showed bands of 436, 242 and 194 bp, whereas TT homozygotes showed band sizes of 242 and 194 bp [23, 24].

Statistical analyses

The results of descriptive statistics were expressed in mean ± SD and frequencies (numbers and percentages) in tables. Multiple logistic regression models were used to

compare genotype distributions between cases and controls to determine the association between MMP1, 2 and 9 polymorphisms and knee OA. These two variables were incorporated into the model as covariates to adjust the groups for age and BMI, thus the relationship between genotypes and OA was corrected according to covariate effects. Odd ratios (ORs) for this model with the corresponding 95% confidence intervals (95% CIs) were also computed. Moreover, allele frequencies were assessed by counting alleles and calculating sample proportions. The Pearson Chi-squared test was used to compare the allelic frequency distribution between the control and the OA groups. An exact test was used to check deviations in the allele distribution from the Hardy–Weinberg equilibrium in each group. All statistical analyses were performed with SPSS software, version 12. $P < 0.05$ was considered significant.

Results

The demographic characteristics of the study population are shown in Table 1. The mean age of the patients and the control group was 61.7 ± 9.2 years (range: 41–86 years) and 52.3 ± 6.9 years (range: 41–75 years), respectively. The mean BMI was 30.0 ± 4.3 kg/m² in patients with knee OA and 27.3 ± 6.0 kg/m² in the control group. In addition, the male/female ratio was 36/121 in patients and 25/59 in controls. There were significant differences between the groups in age and BMI ($P = 0.0001$), but there was no significant difference in gender ($P = 0.218$). After the study population was adjusted for age (in years) and BMI (kg/m²) using multiple logistic regression model, the genotype distributions of MMP-1 (−1,607) 1G/2G, MMP-2 (−1,306) C/T, and MMP-9 (−1,562) C/T polymorphisms were compared between the patients and the control group. We also investigated whether there was an interaction between gender and all three polymorphisms. Since there was no interaction, the patient and the control groups were not subdivided based on genders. There were significant differences between the groups regarding the genotype distributions of MMP-1 (−1,607) 1G/2G polymorphism ($P = 0.001$) (Table 2). In the patients, the frequencies of 1G/1G and 1G/2G genotypes were higher than the frequency of 2G/2G genotype (r:8.05, $P = 0.002$, 95% CI:2.18–29.71 and r:3.2, $P = 0.006$, 95% CI:1.39–7.37, respectively). There was no significant difference between the patients and the controls regarding the genotype distributions of MMP-2 (−1,306) C/T and MMP-9 (−1,562) C/T polymorphisms ($P = 0.086$, $P = 0.515$, respectively) (Table 2).

Table 1 Characteristics of the study subjects

Characteristics	Patients (n:157)	Control (n:84)	P
Age (mean ± SD years)	61.7 ± 9.2	52.3 ± 6.9	0.0001
BMI (mean ± SD kg/m²)	30.0 ± 4.3	27.3 ± 6.0	0.0001
Female/male ratio (%)	77/23	69/31	0.218

The genotype distribution of the MMP-1 gene polymorphism was in the Hardy–Weinberg equilibrium in the control group ($\chi^2 = 0.9$, $P > 0.05$), but it was not so in the patients with knee OA ($\chi^2 = 7.98$, $P < 0.01$). The genotype distributions of MMP-2 and MMP-9 polymorphisms both in the patients and in the controls did not show deviations from the Hardy–Weinberg equilibrium ($P > 0.05$).

In addition, the allelic frequency of the MMP-1, MMP-2, and MMP-9 polymorphisms was analyzed in each group (Table 3). The MMP-1 −1,607 1G allele frequency was significantly higher in the patients than in the controls (38.1 vs. 21%, $P = 0.0001$). In contrast, the MMP-1 −1,607 2G allele frequency was significantly high in the controls as compared to the patients (79 vs. 61.9%, $P = 0.0001$), (Table 3). The allele frequencies of the MMP-2 and MMP-9 polymorphisms were not significantly different between

Table 2 Genotype distribution of MMP-1, MMP-2 and MMP-9 gene polymorphisms between groups

Genotypes	Patients (%)	Controls (%)	P values	OR	95% CI
MMP-1					
2G/2G[a]	68 (43.6)	52 (64.2)	1.000	1	(–)
1G/1G	31 (19.9)	5 (6.2)	0.002	8.05	2.18–29.71
1G/2G	57 (36.5)	24 (29.6)	0.006	3.20	1.39–7.37
MMP-2					
CC[a]	100 (63.7)	52 (61.9)	1.000	1	(–)
CT	51 (32.5)	26 (31.0)	0.089	2.05	0.89–4.66
TT	6 (3.8)	6 (7.1)	0.235	0.36	0.07–1.93
MMP-9					
CC[a]	115 (73.2)	57 (67.9)	1.000	1	(–)
CT	39 (24.8)	26 (31.0)	0.266	0.62	0.27–1.43
TT	3 (1.9)	1 (1.2)	0.682	0.59	0.05–7.29

OR, odd ratio; 95% CI, 95% confidence interval

[a] Reference genotype

Table 3 Allelic frequency distribution of MMP-1, MMP-2 and MMP-9 gene polymorphisms between groups

Alleles	Patients (%)	Controls (%)	*P* values
MMP-1			
1G	119 (38.1)	34 (21)	0.0001
2G	193 (61.9)	128 (79)	
MMP-2			
C	251 (79.9)	130 (77.4)	0.511
T	63 (20.1)	38 (22.6)	
MMP-9			
C	269 (85.7)	140 (83.3)	0.496
T	45 (14.3)	28 (16.7)	

the patients and the controls ($P = 0.511$ and $P = 0.496$, respectively).

Discussion

The matrix metalloproteinase family comprises more than 20 enzymes that are associated with degradation of the extracellular matrix [4, 5]. The activity of these enzymes is regulated at several levels, including regulation of transcription, activation of latent MMPs, and inhibition of MMPs activity by specific tissue inhibitor metalloproteinases (TIMPs) [25]. It appears that for most MMPs, the key step is transcriptional regulation because most MMP genes are expressed only when active physiological or pathological tissue remodeling takes place [13, 26].

In recent years, some functional polymorphisms of MMPs, including MMP-1 (−1,607) 1G/2G, MMP-2 (−1,306) C/T and MMP-9 (−1,562) C/T polymorphisms, have been detected. [13]. These polymorphisms influence MMPs gene expression and are associated with the development and/or progression of some common diseases such as coronary heart disease, abdominal aortic aneurysm, chronic periodontitis, rheumatoid arthritis, and cancers [14–19].

In this study, we firstly examined the role of genetic variants at MMP-1, MMP-2, and MMP-9 gene promoters in susceptibility to knee OA. We observed significant differences in genotype distributions and allele frequencies between knee OA and control groups for the −1,607 1G/2G polymorphism of MMP-1 gene promoter. It seemed that individuals with 1G/1G genotype were eight times and individuals with 1G/2G genotype were three times more likely to develop knee OA than individuals who are 2G/2G homozygous. In addition, the frequency of 1G allele was higher in the patients with knee OA than healthy controls. Overall, we suggest that MMP-1 −1,607 1G/2G polymorphism may be a genetic marker of susceptibility to knee OA in the Turkish population.

The (−1,607) 1G/2G polymorphism of MMP-1 gene promoter was first described by Rutter at al. in 1998. The two alleles (1G and 2G) are formed by an insertion/deletion of a guanine at position −1,607. The presence of 2G creates the sequence 5′ AAGGAT 3′, which is the consensus sequence for the Ets family of transcription factors. Thus, the 2G allele results in an increased transcriptional activity and MMP-1 expression [12].

Thereafter, several clinical researchers have indicated that the 2G allele may contribute to increased invasiveness of colorectal tumors and to the development of ovarian cancer and also of lung cancer [27–29]. Our results were not consistent with the above studies because we determined that 1G allele and 1G genotypes of MMP-1 polymorphism were associated with susceptibility to knee OA. Recently, there have been a few studies with comparable results to this study. One study has shown a significant increase in 1G/1G or 1G/2G genotypes in sarcoidosis patients with ocular or more organs involvement [30]. A recent study by Kuo et al. has revealed a similar trend of 1G genotypes associated with endobronchial tuberculosis (TB). Their results revealed that the frequency of 1G genotypes of MMP-1 polymorphism was higher in patients with endobronchial TB than in patients with pulmonary TB who did not develop endobronchial TB. The endobronchial TB patients with 1G genotypes of MMP-1 polymorphism were more vulnerable to subsequent tracheobronchial stenosis after completion of chemotherapy [31]. In another study, there is a 100% association of the MMP-1 1G allele with primary sclerosing cholangitis (PSC) accompanied by cholangiocarcinoma as compared to only 72% association of the MMP-1 1G allele with PSC alone [32].

The −1,306 C to T transition is located in a core recognition sequence of Sp1 (CCACC box), which abolishes the Sp1-binding site and consequently diminishes promoter activity. The gene expression driven by the C allelic MMP-2 promoter is significantly greater than that of T allelic counterpart both in epithelial cells and macrophages, indicating the functional significance of this polymorphism [33]. Moreover, a recent study has demonstrated that the promoter activity of the −1,306C/−735C haplotype is stronger than that of the −1,306T/−735T haplotype, suggesting a synergistic effect of these two polymorphisms [34].

The single nucleotide polymorphism in the MMP-9 gene at position −1,562 is due to a C–T substitution. In vitro studies have shown that the C–T substitution results in the loss of binding of a nuclear protein to this region of the MMP-9 gene promoter, and an increase in transcriptional activity in macrophages [14].

Although several studies have demonstrated that MMP-2 −1,306 C/T or MMP-9 −1,562 C/T polymorphisms are associated with coronary atherosclerosis, chronic periodontitis, and cancers (i.e., lung, gastric, oral and endometrial

cancers) [14, 35–39], in the presented study, we determined no significant differences between the patients and the control subjects regarding genotype and allele frequencies of these polymorphisms.

We found no association between MMP-2 and MMP-9 polymorphisms and knee osteoarthritis. This may simply indicate that these polymorphisms have a minor or no role in the susceptibility to knee osteoarthritis. There are also different SNPs in the MMP-2 and MMP-9 promoter region. The −1,306 C/T polymorphism in MMP-2 gene and the −1,562 C/T polymorphism in MMP-9 gene are only two of them [22]. Another possibility is that these polymorphisms in the MMP-2 and MMP-9 genes may be responsible for the pathogenesis of osteoarthritis, but this influence might have been too small to be detected in the present study sample and a larger sample size or haplotype analyses may be required. Alternatively, a possible association may have been weakened by disease heterogeneity, environmental factors or gene-environment interactions.

However, the expression of MMPs is, to a large extent, also regulated at the transcriptional level by various cytokines such as tumor necrosis factor-α and interleukin-1 and growth factors. These cytokines affect MMP expression through the binding of transcription factors such as AP-1 and NFκB to the promoters of the MMP genes [14].

Our study has some potential limitations. Firstly, the size of the study population is relatively small, so the possibility of type I or type II errors could not be excluded. Our findings need to be confirmed in larger samples and in different ethnic groups. Secondly, our study population was not homogeneous in terms of age and BMI, but we adjusted both groups for age and BMI using multiple logistic regression method.

In summary, this is the first report to show that 1G/1G or 1G/2G genotypes and 1G allele of MMP-1 promoter polymorphism are associated with a greater risk for susceptibility to knee OA. Identifying the underlying genetic factors could enhance our understanding of the pathogenesis of this complex disorder, which could eventually lead to improved prevention and treatment of this common disease. There is a need for further studies in large cohorts of knee OA patients including the polymorphisms of other MMPs (i.e., MMP-3, MMP-8, MMP-13) or others polymorphisms of the MMP-2 and MMP-9 with haplotype analyses or the transcription factors (i.e., AP-1, NFκB).

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