Clinical Rheumatology (2019) 38:223–228
https://doi.org/10.1007/s10067-018-4146-7

BRIEF REPORT

Genetic association analysis of Osteopontin and Matrix Gla Protein genes polymorphisms with primary knee osteoarthritis in Mexican population

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Received: 26 January 2018 / Revised: 7 May 2018 / Accepted: 10 May 2018 / Published online: 18 May 2018

Abstract

Primary osteoarthritis (OA) is a complex entity in which several loci related to different molecular pathways or classes of molecules are associated with its development as demonstrated through genetic association studies. Genes involved in bone formation and mineralization, such as osteopontin (*OPN*) and Matrix Gla protein (*MGP*), could also be related with OA. The aim of this study was to evaluate the association between the genetic variants of *OPN* and *MGP* with primary knee osteoarthritis in a Mexican population. A case-control study was conducted in 296 patients with primary knee osteoarthritis and in 354 control subjects. Study groups were assessed radiologically. The rs11730582 of *OPN* and rs1800802, rs1800801, and rs4236 of *MGP* were determined by TaqMan allele discrimination assays. The haplotypes of the polymorphisms of *MGP* were constructed. The association was tested through univariate and multivariate non-conditional logistic regression analyses. The polymorphisms of *MGP* complied with Hardy-Weinberg (HW) equilibrium. The polymorphisms of *OPN* and *MGP* were not significantly associated with primary knee osteoarthritis in the codominant, dominant, and recessive models ($p > 0.05$). Our study suggests that there are no associations between *OPN* and *MGP* polymorphisms with primary knee osteoarthritis in Mexican population.

Keywords Genetics · Knee · Matrix Gla protein · Osteoarthritis · Osteopontin · Polymorphism

Introduction

Osteoarthritis (OA) is the most common form of arthritis worldwide; approximately 10% of the world's population aged ≥ 60 years have symptomatic OA. Any joint can be affected, but the knee is the most common site involved and is one of the most common reasons for total joint replacement [1]. OA is classified as primary when no discernible cause is

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evident and as secondary when a triggering factor is apparent. Clinically, patients show chronic joint pain, joint stiffness, limitation of movement, and variable degrees of inflammation [2].

OA is characterized by progressive loss of articular cartilage, which is composed of chondrocytes and extracellular matrix (ECM). Chondrocytes are responsible for an equilibrium between the synthesis and degradation of ECM, which is formed mainly by collagen type II and aggrecan. Articular cartilage injuries lead chondrocytes to an over-expression of inflammatory cytokines, such as interleukin 1β (IL-1β) and Tumor Necrosis Factor alpha (TNF-α) [3]. These lead to a catabolic process and favor the production of collagenases and aggrecanases, including Matrix Metalloproteinases (MMP) and A Disintegrin and Metalloproteinase Thrombospondin Type I motifs (ADAMTS), resulting in progressive and irreversible cartilage destruction [4].

Primary OA is a multifactorial disease; however, several candidate genes studies have found numerous loci related to different molecular pathways or classes of molecules strongly associated with its development [5]. Genes involved in the regulation of bone formation could also be associated with primary knee OA. The Osteopontin (*OPN*) gene is located at 4q21-25, comprises seven exons, and codes for a phosphorylated acidic glycoprotein founded in several tissues and cells, and some polymorphic variants are located in the transcriptional-factor binding-site region that could affect the OPN protein function [6, 7]. OPN is a non-collagenous bone matrix protein produced by chondrocytes, osteoblasts, and synoviocytes and is a biochemical marker of OA severity [8, 9]. *OPN* expression is involved in bone remodeling and in cartilage-to-bone transitions in fracture repair [10], which suggest that could be involved in OA development. In Chinese population, the rs11730582 (-443 C>T) located in the promoter is associated with knee OA [11].

The Matrix Gla protein (*MGP*) gene is located at 12p12.3, consists of four exons, and codes for a protein founded in cartilage, bone, and vascular smooth muscle [12]. The MGP protein is a developmentally regulated inhibitor of cartilage mineralization; it controls mineral quantity and plays a role in regulating chondrocyte maturation and ossification processes [13]. The polymorphic sites related to its function are widely distributed in different regions of *MGP*, and the evidence suggests that a nonsense mutation could produce a truncated protein that is unable to bind calcium, leading to abnormal cartilage calcification and to extensive vascular calcification [14]. Regarding this, *MGP* polymorphisms rs1800801, rs1800802 (located in the promoter region), and rs4236 (a nonsynonymous polymorphism located at exon 4, causing alanine to threonine amino acid change) have been associated with hand OA in Caucasian populations [15, 16]. These observations prompted us to investigate the possible association between *OPN* (rs11730582) and *MGP* (rs1800801, rs1800802, and rs4236) genes with primary knee OA in Mexican population.

Materials and methods

Study design and sample population

A case-control study was conducted whose protocol was approved by the Ethics and Investigation Committee of the Instituto Nacional de Rehabilitación. The study subjects were recruited at the Articular Rehabilitation Clinic and all were of Mexican mestizo origin (defined as a person born in Mexico, with a Spanish-derived surname and a family of Mexican ancestors back to the third generation). The cases were individuals aged > 40 years, with clinical diagnosis of primary knee OA according to American College of Rheumatology (ACR) classification criteria [17], a radiologic score of ≥ 2 for OA, body mass index (BMI, kg/m^2) of ≤ 27, with no history of severe injury or knee surgery, and with no other articular disease. The control group were subjects > 40 years of age, without clinical knee OA, a radiologic score of < 2, a BMI of ≤ 27, and no history of serious knee injury or joint diseases. Control individuals arrived at the clinic mainly due to orthopedic problems, nothing involving serious knee damage. Our main classification criterion was radiologic because this is the most standardized method for OA definition in association studies. Radiological classification was performed according to the Kellgren-Lawrence scale in weight-bearing anteroposterior and lateral radiographs by a sole experienced observer who was blinded to the patients' diagnoses [18]. All the participants were interviewed and responded to a questionnaire to collect demographic data, occupation, sports activities, possible knee injuries, clinical manifestations of OA, and other information to identify possible co-variables or confounders.

Genotyping

Only after obtaining written informed consent, a 5-ml sample of peripheral blood was collected. Genomic DNA was extracted by a salting-out method. The genotypes of *OPN* variant rs11730582 (-443 T/C) and *MGP* variants rs1800802 (-138 T/C, promoter region), rs1800801 (G/A, 5' UTR), and rs4236 (nonsynonymous polymorphism located on exon 4) were determined by TaqMan allele discrimination assays (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. Reactions were performed in 96-well plates and the 15-μl PCR mixture included 20 ng of genomic DNA, 100 nM of each probe, 900 nM of each primer, and 1× TaqMan PCR Master Mix (Applied Biosystems). PCR cycling conditions consisted of a 2-min pre-incubation period at 50 °C and an initial denaturation period of 10 min at

95 °C, followed by 40 cycles of denaturing at 95 °C for 15 s and annealing at 60 °C for 1 min. We employed the StepOnePlus™ Real-Time PCR System (Applied Biosystems) for data acquisition. The allelic discrimination software was used to analyze the PCR genotyping results.

Statistical analysis

Comparisons of continuous variables were carried out using the Student *t* test, and for categorical variables, we applied chi-squared statistics (x^2). Allelic and genotypic frequencies, as well as the Hardy-Weinberg equilibrium (HWE), were calculated for each polymorphism. The association between each polymorphism and primary knee OA was tested using codominant, dominant, and recessive models through univariate and multivariate non-conditional logistic regression analyses. For multivariate analysis, variables with a p value ≤ 0.15 in descriptive analysis were included and the most parsimonious models were reported. Additionally, haplotypes for *MGP* polymorphisms were constructed and their associations were also tested. Alpha level was 0.05, and STATA ver. 10.0 statistical software package and Haplo View ver. 4.0 were utilized for the calculations.

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

Results

A total of 650 subjects were evaluated; 296 comprised cases with primary knee OA and 354 were controls. Their clinical and demographic data are summarized in Table 1. Females were more frequent in both groups ($p = 0.4$). Mean age was 62.7 ± 11.2 years in cases and 55.8 ± 10.9 years in controls ($p < 0.05$). The presence of diabetes mellitus and arterial hypertension in cases was significantly higher than that of the control group ($p = 0.02$ and 0.0001, respectively).

The distribution of *MGP* single nucleotide polymorphisms (SNP) rs1800801, rs1800802, and rs4236 was in agreement with the HWE ($p = 0.57$, 0.52, and 0.47, respectively); however, the rs11730582 polymorphism of the *OPN* gene showed a deviation from the HWE ($p = 0.015$). There was no association between the alleles of *OPN* and *MGP* variants and primary knee OA (OR ≈ 1.0; $p > 0.05$) (Table 2). The association testing between the *OPN* and *MGP* genotypes and knee OA under codominant, dominant, and recessive modes of inheritance did not show statistical significant differences or trend to association as indicated by the unadjusted and adjusted analyses (unadjusted and adjusted ORs ≈ 1.0; $p > 0.05$) (Table 3).

Table 1 General characteristics of the individuals studied

	Cases ($n = 296$)	Controls ($n = 354$)	p
Age (mean ± SD years)	62.7 ± 11.2	55.8 ± 10.9	0.00001
BMI (mean ± SD kg/m^2)	25.4 ± 2.4	25.1 ± 2.3	0.1
Gender, feminine (*n*, %)	228 (77.0)	262 (74.0)	0.4
Tobacco smoking (*n*, %)	80 (29.2)	105 (35.3)	0.1
Alcoholism (*n*, %)	92 (33.6)	116 (39.1)	0.2
Occupational activity (*n*, %)			
Current (*n*, %)	41 (13.8)	43 (12.1)	0.5
Previous (*n*, %)	27 (14.7)	50 (23.3)	0.03
Sports activity			
Current (*n*, %)	40 (13.5)	57 (16.1)	0.3
Previous (*n*, %)	122 (41.2)	173 (48.9)	0.05
Comorbidity			
Diabetes mellitus	64 (21.6)	51 (14.4)	0.02
Arterial hypertension	110 (37.9)	76 (21.7)	0.0001
Kellgren-Lawrence grading			
Grade 0, *n* (%)		202 (57.2)	
Grade 1, *n* (%)		151 (42.8)	
Grade 2, *n* (%)	112 (37.8)		
Grade 3, *n* (%)	129 (43.6)		
Grade 4, *n* (%)	55 (18.6)		

Four haplotypes were constructed by rs180081, rs1800802, and rs4236 *MGP* polymorphisms; the most frequent was the TCA haplotype in cases and controls (57.3 and 56.8%, respectively). There were no significant associations of the haplotypes with knee OA (OR ≈ 1.0; $p > 0.05$) (Table 4).

Table 2 Allelic association testing results of *OPN* and *MGP* polymorphisms in primary knee osteoarthritis and controls

SNP	Cases ($n = 296$) *n* (%)	Controls ($n = 354$) *n* (%)	OR (95% CI)[a]	p
rs11730582				
C	307 (52.0)	388 (55.0)	0.9 (0.7–1.1)	0.3
T	285 (48.0)	320 (45.0)	1.1 (0.9–1.4)	0.3
rs1800801				
T	188 (32.0)	231 (33.0)	0.9 (0.7–1.2)	0.7
C	404 (68.0)	477 (67.0)	1.0 (0.8–1.3)	0.7
rs1800802				
A	538 (91.0)	643 (91.0)	1.0 (0.7–1.5)	0.9
G	54 (9.0)	65 (9.0)	0.9 (0.7–1.5)	0.9
rs4236				
T	395 (67.0)	470 (66.0)	1.0 (0.8–1.3)	0.9
C	197 (33.0)	238 (34.0)	0.9 (0.8–1.2)	0.9

[a] Odds ratios (OR) and 95% confidence intervals (CI)

Table 3 Genotype association testing results of *OPN* and *MGP* polymorphisms in Mexican cases with primary knee osteoarthritis and controls

SNP	Cases ($n = 296$) n (%)	Controls ($n = 354$) n (%)	OR (95% CI)[a]	p	OR (95% CI)[b]	p	OR (95% CI)[c]	p
rs11730582								
Codominant								
TT	70 (23.6)	61 (17.2)	1.3 (0.8–2.1)	0.2	1.2 (0.8–2.0)	0.4	1.3 (0.8–2.0)	0.3
TC	145 (48.9)	198 (55.9)	0.8 (0.6–1.2)		0.9 (0.6–1.3)		0.8 (0.6–1.2)	
CC	81 (27.4)	95 (26.8)	1.0		1.0		1.0	
Dominant								
TT/TC vs CC	215 (72.6)	259 (73.2)	0.9 (0.7–1.4)	0.9	0.9 (0.7–1.4)	0.9	0.9 (0.7–1.4)	0.8
Recessive								
TT vs CC/TC	70 (23.6)	61 (17.2)	1.5 (1.01–2.2)	0.04	1.3 (0.9–2.0)	0.1	1.4 (0.9–2.1)	0.06
rs1800801								
Codominant								
TT	28 (9.5)	40 (11.3)	0.8 (0.5–1.4)	0.8	0.9 (0.5–1.6)	0.8	0.8 (0.5–1.5)	0.6
TC	132 (44.6)	151 (42.7)	1.0 (0.7–1.4)		1.1 (0.8–1.6)		1.1 (0.8–1.5	
CC	136 (45.9)	163 (46.1)	1.0		1.0		1.0	
Dominant								
TT/TC vs CC	160 (54.1)	191 (53.9)	1.0 (0.7–1.4)	0.9	1.1 (0.8–1.5)	0.6	1.0 (0.7–1.4)	0.8
Recessive								
TT vs TC/CC	28 (9.5)	40 (11.3)	0.8 (0.5–1.4)	0.4	0.9 (0.5–1.5)	0.6	0.8 (0.5–1.4)	0.5
rs1800802								
Codominant								
GG	4 (1.4)	4 (1.1)	1.2 (0.3–4.8)	0.8	0.8 (0.2–3.8)	0.9	0.9 (0.2–3.8)	0.8
GA	46 (15.5)	57 (16.1)	0.9 (0.6–1.5)	0.8	1.0 (0.6–1.6)	0.9	0.9 (0.6–1.5)	0.8
AA	246 (83.1)	293 (82.8)	1.0		1.0		1.0	
Dominant								
GG/GA vs AA	50 (16.9)	61 (17.2)	0.9 (0.6–1 .5)	0.9	1.0 (0.6–1.5)	0.9	0.9 (0.6–1.4)	0.8
Recessive								
GG vs GA/AA	4 (1.4)	4 (1.1)	1.2 (0.2–6.5)	0.8	0.8 (0.2–3.7)	0.8	0.9 (0.2–3.8)	0.9
rs4236								
Codominant								
CC	29 (9.8)	43 (12.2)	0.8 (0.5–1.4)	0.5	0.9 (0.5–1.6)	0.8	0.9 (0.5–1.5)	0.6
CT	139 (47)	152 (42.9)	1.1 (0.8–1.6)		1.2 (0.8–1.7)		1.2 (0.8–1.7)	
TT	128 (43.2)	159 (44.9)	1.0		1.0		1.0	
Dominant								
CC/CT vs TT	168 (56.8)	195 (55.1)	1.1 (0.8–1.5)	0.7	1.2 (0.8–1.6)	0.3	1.1 (0.8–1.5)	0.5
Recessive								
CC vs CT/TT	29 (9.8)	43 (12.2)	0.8 (0.4–1.3)	0.3	0.8 (0.5–1.4)	0.5	0.8 (0.5–1.3)	0.4

[a] Unadjusted odds ratios and 95% confidence intervals [OR (95% CI)]

[b] Adjusted by gender, age, BMI

[c] Adjusted by previous sport activities, diabetes mellitus, arterial hypertension

Discussion

The polymorphisms of *OPN* and *MGP* genes have been used as genetic markers for studying several diseases, including OA [6, 14, 19]. We investigated the association of *OPN* and *MGP* polymorphisms with primary knee OA in Mexican mestizo population and the results revealed lack of genetic influence of those polymorphisms in primary knee OA in our population sample. To the best of our knowledge, this is the first study to examine such an association in Mexico, or even in Latin America.

Table 4 Haplotypes of rs180081, rs1800802, and rs4236 *MGP* polymorphisms

Haplotype	Case, control frequencies	OR (95% CI)	*p*
TCA	0.573, 0.568	1.0 (0.8–1.3)	0.8
CTA	0.314, 0.322	0.9 (0.7–1.2)	0.7
TCG	0.091, 0.092	0.9 (0.7–1.5)	0.9
CCA	0.019, 0.014	1.3 (0.5–3.5)	0.5

There is a relationship between OPN and MGP with OA. It has been observed that *OPN* messenger RNA (mRNA) levels are significantly elevated in OA [20], and high OPN levels in plasma, synovial fluid, and articular cartilage have been closely associated with OA severity [8, 10]. OPN play an important role in advanced stages of OA by regulating the expression of several inflammatory cytokines, such as interleukin-6 and interleukin-8 and inhibiting the expression of MMP and ADAMTS [21, 22]. On the other hand, mineralization of ECM is key in the development and function of skeletal tissues, and the expression of MGP within the mammalian growth plate is required for normal chondrocyte differentiation [13]. In *Mgp*-deficient mice, there is inappropriate cartilage calcification of the growth plate [23]. In OA, the levels of uncarboxylated MGP protein are significantly lower than in controls in synovial fluid, which suggests a role in the pathogenesis of the disease [24].

Our results indicate that the genetic variants studied are unlikely to play a role in the development of the disease; however, an association between polymorphisms of *OPN* and *MGP* and OA has been found in Chinese and in Caucasian populations. Jiang et al. reported that the rs11730582 of *OPN* affected thrombin-cleaved *OPN* levels in the synovial fluid of subjects with knee OA and was significantly associated with radiographic severity [11]. The association of *MGP* with hand OA has been studied in Caucasian population. The rs4764133 was associated with an increased risk of hand OA [16], and the rs1800802 and rs4236 were associated with a reduced prevalence of OA, joint-space narrowing, and osteophytosis [15]. Several factors could explain the differences among the results, including differences in age of the individuals studied, the rate of OA progression, and ethnic differences, since complex interactions between several genetic and environmental factors inherent in each population may be involved in OA development.

The present study could entertain some limitations, including selection bias, sample size, and ethnicity. In that hospital-based case-control study, there is a possibility of incurring in selection bias; however, we assessed only primary knee OA as closely as possible, and other modifiers or potential confounders strongly associated with secondary OA were rigorously controlled during study subject recruitment or were controlled through multivariate statistical analysis. Therefore, we consider that our study groups are accurately selected and that the possibility of selection bias in our sample is quite low. Regarding sample size, when compared with other studies, we have a lesser number of patients; however, as we already stated, we consider that individuals included in our study were properly selected; thus, we have an accurate internal validity.

There is genetic heterogeneity among Mexican mestizos regarding their Amerindian and European contributions, which could affect our results. Northern Mexicans possess a higher European ancestral contribution and central-coastal Mexican subpopulations have a higher Amerindian ancestry [25]; however, it is important to consider that the Instituto Nacional de Rehabilitación is a tertiary care referral center in Mexico City that receives patients residing in nearly all regions of the country. Therefore, the source population from among which controls were sampled did not differ from that of the cases, since both groups were from the same geographic regions of the country.

In general, the majority of genetic association studies conducted on OA have been developed in Asian and Caucasian populations; to the best of our knowledge, this is the first study in which the *OPN* and *MGP* polymorphisms have been investigated in a Latin-American population. Our study suggests no significant associations between these polymorphisms and OA of the knee; however, further investigation is needed to achieve a better understanding of the relationship between *OPN* and *MGP* polymorphisms and the development of knee OA.

Compliance with ethical standards

All procedures performed in participants were in accordance with the ethical standards of the Ethics and Investigation Committee of the Instituto Nacional de Rehabilitación and with the 1964 Helsinki declaration and its later amendments. Written Informed consent was obtained from all individuals participating included in the study.

Disclosures None.

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