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Association of *MMP7-181A/G* and *MMP13-77A/G* polymorphisms with colorectal cancer in a Mexican population

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ABSTRACT. Colorectal cancer (CRC) is characterized by enhanced expression and activity of several metalloproteinases (MMPs), including MMP13 and MMP7, which play an important role in tumor

invasion and metastasis. The objective of this study was to analyze the association of functional *MMP7-181A/G* and *MMP13-77A/G* promoter polymorphisms with susceptibility to CRC in a Mexican population. Genomic DNA samples were obtained from peripheral blood of 102 CRC patients and 125 blood donors who were included as the control group. Identification of polymorphisms was based on polymerase chain reaction-restriction fragment length polymorphism methodology. The association was estimated by the odds ratio (OR) test. The results showed that *MMP7-181A/G* and *MMP13-77A/G* variants were associated with CRC. For *MMP7-181A/G*, the AA (P = 0.02, OR = 3.38, 95% confidence interval (CI) = 1.16-9.84) and AG (P = 0.01, OR = 3.4, 95%CI = 1.17-9.83) genotypes were associated with an increased risk of CRC. For *MMP13-77A/G*, the AA and AG genotypes were associated with CRC (AA genotype: P = 0.04, OR = 3.2, 95%CI = 1.004-10.2; AG genotype: P = 0.01, OR = 4.08, 95%CI = 1.3-13.07). In conclusion, AA and AG genotype carriers for both polymorphisms are at a higher risk of developing CRC in this Mexican population.

Key words: MMP7; MMP13; Colorectal cancer; Polymorphisms; Mexican population

INTRODUCTION

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality in the western world (Berg and Søreide, 2011). The CRC incidence in Mexico is reported at 6.9 per 100,000 individuals (Ferlay et al., 2010). The etiology of CRC is complex and involves interactions between environmental and genetic factors. Further to the genetic factors in CRC, disease progression is regulated through interactions of genes involved in proliferation, migration, invasion, metastasis, and angiogenesis. These genes include the matrix metalloproteinase (MMP) genes, a family of 23 zinc-dependent endopeptidases involved in normal and pathological tissue remodeling and degrading components of the extracellular matrix (Jackson et al., 2010). Among the MMPs, MMP7 has been detected in normal tissues such as the endometrium and bronchial mucosa (Bister et al., 2004) and degrades elastin, laminin, proteoglycans, fibronectin, and type IV collagen (Remy et al., 2006). MMP13, also named collagenase, is involved in the degradation of collagen fibrillar types I, II, III, and VII and in fast extracellular matrix remodeling. CRC is characterized by the enhanced expression and activity of several MMPs including MMP7 and MMP13 (Leeman et al., 2002; Ghilardi et al., 2003; Cheng et al., 2007). Genes coding for both MMPs map at the limits of the 9 MMP cluster localized at chromosome 11q22.2, and are separated by an interval of approximately 412 kb (Rhead et al., 2010).

Some functional polymorphisms have been described in the promoter region of *MMP7* and *MMP13*. An A to G transition at position -181 (*MMP7-181A/G*) of *MMP7* was first described by Jormsjö et al. (2001), who demonstrated that the -181 G allele binds with higher affinity nuclear proteins, increases *in vitro* promoter activity, and creates a putative binding site for a heat shock transcription factor. In the *MMP13* promoter, Yoon et al. (2002) described a polymorphic variant as an A to G transition at position -77 (*MMP13-77A/G*) in the

consensus sequence for the transcription factor PEA3. Through its interaction with AP-1 sites, PEA3 confers responsiveness to oncoproteins such as H-ras (Gutman and Wasylyk, 1990). This polymorphism alters the consensus sequence of PEA3 (AGGAAG) and may modify its transcriptional activity and protein level (Yoon et al., 2002). In this study, we tested the contribution of functional *MMP7-181A/G* and *MMP13-77A/G* polymorphisms to CRC susceptibility in Mexican patients.

MATERIAL AND METHODS

Subjects

The study comprised 102 patients (53% females, 47% males; average age of 57 years, range = 20-96 years) diagnosed with colorectal adenocarcinoma according to clinicopathological criteria at civil hospitals in Guadalajara, Jalisco, Mexico. The control group comprised of 125 healthy people who were randomly selected from blood donors. All subjects were mestizos from Western Mexico and provided written informed consent before collection of blood samples. The Ethics and Research Committees of each participating institution approved the study (register numbers CI-14409 and 935/09).

Genotyping

DNA was extracted from peripheral blood samples of patients and control subjects by a modification of the CTAB-DTAB method (Gustincich et al., 1991). The polymorphisms *MMP7-181A/G* and *MMP13-77A/G* were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using the following primer pairs: *MMP7*-1: 5'-TGGTACCATAATGTCCTGAATG-3', *MMP7*-2: 5'-TCGTTATTGGCAGGAAGCACACA ATGAATT-3' (Lu et al., 2006) and *MMP13*-1: 5'-GATACGTTCTTACAGAAGGC-3', *MMP13*-2: 5'-GACAAATCATCTTCATCACC-3' (Yoon et al., 2002). PCR for *MMP7-181A/G* was performed for 35 cycles in a 25-µL volume containing 100 ng DNA, 10X buffer (500 mM KCl, 100 mM Tris-HCl, and 0.1% Triton™ X-100), 1.5 mM $MgCl_2$, 200 µM dNTPs, 10 pM of each primer, and 2 U Taq DNA Polymerase. Denaturation was carried out at 94°C, annealing at 65°C, and elongation at 72°C for 1 min each. Ten microliters of PCR product was digested with 10 U *Eco*RI, leading to fragments of 130 and 20 bp in the presence of the polymorphic G allele. The digested products were separated on 6% polyacrylamide gels. For *MMP13-77A/G*, PCR was similar to that for the *MMP7* polymorphism except that 3 mM $MgCl_2$ was used, and denaturing was for 30 s at 94°C, annealing was for 30 s at 66°C, and elongation was for 45 s at 72°C. Four units of *Bsr*I was used to digest 10 µL PCR product. Fragments observed by electrophoresis corresponded to 416 and 29 bp for the wild-type allele (A) and 249, 170, and 29 bp for the polymorphic allele (G). For quality control, genotyping was randomly repeated in 20% of the samples. Restriction digest of the Lambda bacteriophage vector was used as a digestion positive control.

Statistical analysis

Allele and genotype frequencies were estimated by direct counting in both groups. Hardy-Weinberg equilibrium (HWE) was assessed by the chi-squared test. Differences in allele

and genotype distributions between patients and controls were tested by the chi-squared test or the Fisher exact test, where appropriate. To measure the association of CRC with the presence of alleles or genotypes, the odds ratio (OR) and corresponding 95% confidence intervals (CI) were calculated. For *MMP7-181A/G* and *MMP13-77A/G*, the polymorphic GG genotypes were respectively used as reference. Since both polymorphisms are in *cis* conformation, an analysis of haplotypes and linkage disequilibrium was also carried out. The calculations were done using the Arlequin v3.11, SPSS v17.0 software package (SPSS, Inc., Chicago, IL, USA). For all statistical analysis, $P < 0.05$ was considered to be significant.

RESULTS

The control group and CRC patients were successfully genotyped for the *MMP7-181A/G* and *MMP13-77A/G* polymorphisms. Allele and genotype frequencies among controls were consistent with HWE. The variant alleles *MMP7-181G* and *MMP13-77G* were found in 37 and 32% of the control individuals, respectively (Table 1). The comparative analysis for both variants in controls and CRC patients showed significant differences as measured by the OR (Table 1). For *MMP7-181A/G,* the AA (P = 0.02, OR = 3.38, 95%CI = 1.16-9.84) and AG (P = 0.01, OR = 3.4, 95%CI = 1.17-9.83) genotypes were associated with an increased risk of CRC. Likewise, the AA and AG genotypes for *MMP13-77A/G* were associated with CRC (AA genotype: P = 0.04, OR = 3.2, 95%CI = 1.004-10.2; AG genotype: P = 0.01, OR = 4.08, 95%CI = 1.3-13.07). Furthermore, the genetic models tested confirmed that under a dominant model, the ORs for AA homozygotes and AG heterozygotes were nearly equal (*MMP7* variant: P = 0.01, OR = 3.4, 95%CI = 1.2-9.5; *MMP13* variant: P = 0.02, OR = 3.6, 95%CI = 1.16-11.12). Genotyping data of both polymorphisms in controls were also compared to the corresponding distributions in other populations (Table 2). Although haplotype analysis showed no statistical intergroup differences, all four possible haplotype combinations were observed with a frequency >5%, and the *MMP7-181A/MMP13-77A* haplotype was the most frequent in the control (46.5%) and CRC (55%) groups. The result was negative for linkage disequilibrium ($r^2 = 0.05$ in controls and $r^2 = 0.17$ in patients).

Table 1. Comparison of allele and genotype frequency of *MMP7-181A/G* and *MMP13-77A/G* polymorphisms in the control group and CRC patients.

SNP	Genotype	Control group	CRC Patients	OR (95%CI)	P*
MMP7-181A/G		[N = 121 (%)]	[N = 102 (%)]		
	AA	49 (40)	46 (45)	3.38 (1.16-9.84)	0.02
	AG	54 (45)	51 (50)	3.4 (1.17-9.83)	0.01
	GG	18 (15)	5 (5)	1.0 (Reference)	
	A	152 (63)	143 (70)	1.38 (0.93-2.06)	0.10
	G	90 (37)	61 (30)	1.0 (Reference)	
	AG+AA	103 (85)	97 (95)	3.4 (1.2-9.5)	0.01
	GG	18 (15)	5 (5)	1.0 (Reference)	
MMP13-77A/G		[N = 125 (%)]	[N = 102 (%)]		
	AA	60 (48)	48 (47)	3.2 (1.004-10.2)	0.04
	AG	49 (39)	50 (49)	4.08 (1.3-13.07)	0.01
	GG	16 (13)	4 (4)	1.0 (Reference)	
	A	169 (68)	146 (72)	1.2 (0.80-1.8)	0.3
	G	81 (32)	58 (28)	1.0 (Reference)	
	AG+AA	109 (87)	89 (96)	3.6 (1.16-11.12)	0.02
	GG	16 (13)	4 (4)	1.0 (Reference)	

*Significance $P < 0.05$.

Table 2. Comparison of genotype distribution *MMP7-181A/G* and *MMP13-77A/G* polymorphisms in Mexican healthy people with other populations.

SNP	Population	N	AA (%)	AG (%)	GG (%)	P	Author/year
MMP7-181A/G	Chinese	350	90	9	1	0.00	Zhang et al., 2005
	Chinese	190	53	44	3	0.00	Wu et al., 2011
	Indian	195	32	47	21	0.17	Malik et al., 2011
	French	565	33	46	21	0.12	Liévre et al., 2006
	Mexican	121	41	44	15		This study
MMP13-77A/G	Belgian	265	51	39	10	0.70	Ogata et al., 2005
	Italian	423	40	46	14	0.23	Saracini et al., 2012
	Canadian	155	52	37	11	0.76	Ogata et al., 2005
	Japanese	60	30	45	25	0.03	Iwamoto et al., 2011
	Chinese	609	18	60	22	0.00	Zhang et al., 2006
	Mexican	124	48	39	13		This study

Significance at $P < 0.05$.

DISCUSSION

Association analysis

The present study showed that *MMP7-181A/G* and *MMP13-77A/G* promoter polymorphisms influence the genetic susceptibility to CRC in Mexican patients.

Our findings demonstrated that the AA homozygous and AG heterozygous genotypes of *MMP7-181A/G* were associated with CRC, but results of association reports for *MMP7-181A/G* with several diseases vary among populations. For example, the homozygous *MMP7 -181* AA genotype was associated with chronic obstructive pulmonary disease in Turkish patients (Mogulkoc et al., 2012) and with an increased risk for bronchiolitis obliterans syndrome in Dutch patients (Kastelijn et al., 2010). Regarding the GG genotype, it was associated with esophageal cell carcinoma, cardiogastric adenocarcinoma, or non-small cell lung cancer in Asian populations (Zhang et al., 2005). Likewise, a meta-analysis of 16 case-control studies involving 3099 cases and 4280 controls assessed the association between the *MMP7-181G* allele and cancer risk in East Asians (Yuan-Yuan et al., 2012). Ghilardi et al. (2003) also analyzed the polymorphism in 58 Italian CRC patients, but no direct association was found (OR = 2.41; 95%CI = 0.98-5.89). Because the frequency of the GG homozygous genotype was 7.5-fold higher (95%CI = 2.07-27.19) in metastasis-positive patients *vs* controls, the authors suggested that the *MMP7-181* GG genotype was only related to metastatic CRC.

The specific role for the *MMP7-181A/G* polymorphism has not yet been elucidated. This polymorphism was first identified by Jormsjö et al. (2001) in addition to the *MMP7-153C/T* variant. Based on promoter constructs, the authors tested all possible allele combinations for promoter activity in the differentiated human monocyte/macrophage cell line UB37, and found that combinations of *-181A/-153C* or *T* demonstrated higher MMP7 expression than did *-181G/-153C*, although the expression was less than that of *-181G/-153T.* The *MMP7-181A/G* operates in cis with the close polymorphism *MMP7-153T/C*, which was suggested by the increased basal transcription activity of *MMP7* resulting from specific allelic combinations (Jormsjö et al., 2001); therefore, the presence of a unique polymorphism in the *MMP7* promoter might not be enough to trigger protein overexpression. Moreover, although the *MMP7-181G* allele gave rise to a putative heat shock factor binding site based on computer analysis,

the specific transcription factor could not be identified by an electrophoresis mobility shift assay in UB37 cells (Jormsjö et al., 2001).

Although several CRC studies have described the overexpression of MMP7 (Akishima-Fukasawa et al., 2011; Karamitopoulou et al., 2011; Nastase et al., 2011; Bujanda et al., 2013), a relationship between the *MMP7-181A/G* polymorphism and MMP7 overexpression in CRC patients remains to be verified.

With respect to *MMP13-77A/G*, we found that individuals with the AA genotype had a 3-fold higher risk of developing CRC, whereas in AG patients, this risk increased to 4-fold. We also found that the dominant genetic model presented a risk for the wild-type A allele. These findings indicate that the risk is associated with the wild-type homozygous genotype but not with the polymorphic genotype. This suggests that the presence of the wild-type allele facilitates the interaction between the PEA3 site and the AP-1 site with consequently higher protein levels because the combination of these two sites confers responsiveness to oncogene products and growth factors (Gutman and Wasylyk, 1990); however, the polymorphic G allele could disrupt this interaction. In addition, the high sensitivity to growth factors conferred by the normal sequence could be affected when the G polymorphism is present (Yoon et al., 2002). In fact, using *in vitro* functional studies, Yoon et al. (2002) observed that the *MMP13-77A* allele had approximately twice the activity of the G polymorphic allele. This could explain why the AA and AG genotypes, which were also found to be associated with high CRC risk in our patients, could increase the expression of MMP13 and thus promote cancer development. Previous studies have documented the association of the *-77A/G* polymorphism with cancer. Li et al. (2009) showed that the AA genotype was associated with a certain pathological subtype and clinical stage of epithelial ovarian carcinoma in Chinese women. Vairaktaris et al. (2007) detected a significantly increased A allele frequency and a trend toward a statistical difference in the AA genotype in patients with oral cancer.

Population comparison

The genotype frequencies of the *MMP7-181A/G* and *MMP13-77A/G* polymorphisms in the reference group differed from those in Eastern but not European populations. These findings could be ascribed to the large European component in the Western Mexico population (Salazar-Flores et al., 2010). These results agree with an analysis of the genomic diversity in Mestizos from Central, North, and South Mexico that showed that the European component was larger than the Asian component in the whole Mexican population (Silva-Solezzi et al. 2009).

In this context, our study constitutes the first report of the association of *MMP7-181A/G* and *MMP13-77A/G* with CRC.

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