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Matrix Metalloproteinase 1, 3, and 9 Polymorphisms and Esophageal Squamous Cell Carcinoma Risk

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Background: Matrix metalloproteinases (MMPs) are multifunctional zinc-dependent proteinases that play a fundamental role in the pathogenesis of tumors. We have analyzed the association between 3 single-nucleotide polymorphisms (SNPs; *MMP1* -1607 1G/2G, *MMP3* -1612 5A/6A, and *MMP9* -1562 C/T) and the risk of esophageal squamous cell carcinoma (ESCC).

Material/Methods: We investigated these 3 SNPs in 132 patients and 132 controls using polymerase chain reaction-restriction fragment length polymorphism methods. The *MMP1* and *MMP3* genes are located on the same chromosome. Haplotype analysis was performed to study the combined effect of the linked *MMP* polymorphisms on ESCC risk.

Results: The *MMP1* and *MMP9* promoter polymorphisms were not associated with ESCC risk, while the *MMP3* -1612 5A/6A polymorphism was significantly associated with susceptibility to ESCC. Patients carrying the 5A allele had a significantly higher risk for developing ESCC compared with individuals carrying the 6A allele (OR=1.93; 95% CI 1.34–2.77; $p<0.01$). The 2G-5A and 1G-5A haplotypes were associated with a significantly increased risk of ESCC as compared with the 2G-6A haplotype (OR=2.04, 95% CI 1.37–3.04 and OR=3.65, 95% CI 1.26–10.55, respectively).

Conclusions: These findings implicate this *MMP3* polymorphism as a contributor to ESCC susceptibility.

MeSH Keywords: Esophageal Neoplasms • Genetic Association Studies • Matrix Metalloproteinase 1

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Background

Esophageal cancer is among the 10 most common cancers worldwide [1]. Given its anatomical location, esophageal neoplasia is associated with considerable morbidity, and typical symptoms include progressive dysphagia and weight loss. The 2 major pathological types of esophageal cancer are esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) [2].

China appears to have higher incidence of esophageal cancer than Western nations [3,4]. While the incidence of EAC in Western populations has recently risen and ESCC incidence has fallen [5], ESCC remains the major esophageal malignancy in China. Alcohol consumption and tobacco smoking represent the most significant risk factors for the development of esophageal cancer [6]. However, not all exposed individuals will develop neoplastic disease, suggesting that genetic factors may play key roles in esophageal cancer. Currently, single-nucleotide polymorphisms (SNPs) present in several genes have emerged as significant determinants of disease susceptibility.

Matrix metalloproteinases (MMPs) are a family of at least 20 proteolytic enzymes that play essential roles in cleaving extra cellular matrix (ECM) components. MMPs are classified into 6 subgroups (collagenases, stromelysins, gelatinizes, matrilysins membrane-type MMPs, and others,) on the basis of their structure and substrate specificity. *MMP1*, *MMP3*, and *MMP9*, represent different groups of MMPs: the collagenases, stromielysins, and gelatinases, respectively [7], Overexpression of *MMP1*, *MMP3*, or *MMP9* is closely related to the pathogenesis of tissue-destructive processes in a range of diseases, including ESCC [8–10].

Three polymorphisms have been identified at nucleotides -1607 1G/2G, -1612 5A/6A, and -1562 C/T in the promoter regions of the *MMP1*, *MMP3*, and *MMP9* genes, respectively, and these have been demonstrated to have functional effects on promoter activity and subsequent gene expression [11–13]. Multiple studies concerning the association of these polymorphisms with susceptibility to various malignancies have been conducted [14–17], but their findings are inconsistent. Until now, only a few [18,19] reports concerning the involvement of these 3 polymorphisms in ESCC have been published. Therefore, the aim of this current study was to ascertain whether SNPs in the promoters of the *MMP1*, *MMP3*, and *MMP9* genes are associated with the risk of developing ESCC in a Chinese population.

Material and Methods

Subjects

A total of 264 subjects were included in this study. Details of the case and control population have been described previously [20]. Briefly, this study recruited 132 patients with ESCC and 132 healthy controls. All subjects were unrelated ethnic Han Chinese. Patients were consecutively recruited from January 2005 to September 2007 at the People's Hospital of Suining, Sichuan, China. Diagnosis of ESCC was confirmed by histopathological examination. The ESCC patient group included 74 males and 58 females, with a mean age at diagnosis of 60 years. There were no significant differences in age, sex distribution, or cigarette smoking status between the case group and control group, suggesting that the matching of participants was adequate. The study was approved by the Ethics Committee of the Sichuan Cancer Institute. Written informed consent was obtained from all participants. All participants completed a questionnaire concerning their personal history and smoking history.

Genotyping

Genomic DNA used for the experiment was extracted from peripheral blood by proteinase K digestion and phenol/chloroform extraction. Polymorphism presence was determined using a polymerase chain reaction-restriction fragment length polymorphism method. PCR reactions were carried out in a total volume of 25 μL containing 30–40 ng of genomic DNA, 3.3 μL of

Table 1. Primer sequences and reaction conditions for MMP polymorphism detection.

Gene polymorphim	Primer sequence	Annealing temperature	Restriction enzyme	Product size (bp)
MMP1 -1607 1G/2G	F: TGACTTTTAAAACATAGTCTATGTTCA	51°C	AluI	2G: 269
	R: TCTTGGATTGATTTGAGATAAGTCATAGC			1G: 241 +28
MMP3 -1612 5A/6A	F: GGTTCTCCATTCCTTTGATGGGGGGAAAGA	65°C	TthIII	6A: 130
	R: CTTCCTGGAATTCACATCACTGCCACCACT			5A: 96 +34
MMP9 -1562C/T	F: ATGGCTCATGCCCGTAATC	62°C	SphI	C: 352
	R: TCACCTTCTTCAAAGCCCTATT			T: 208 +144

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Table 2. Characteristics of study subjects.

Group	Controls n=132 (%)	ESCC patients n=132 (%)	Significance
Age (years)	60.4 ±8.42	60.0 ±9.33	.55*
Gender			
Male	83 (62.88)	74 (56.06)	.26**
Female	49 (37.12)	58 (43.94)	
Smoking			
Smoker	56 (42.42)	63 (47.73)	.39**
Non-smoker	76 (57.58)	69 (52.27)	

* *p* value for t-test; ** Value for χ^2-test.

1 mol/l dNTP, 2.5 µL of 10 × PCR Buffer, 25 mM $MgCl_2$, 0.3 µL each 10 pM primer, and 0.3 µL 2.5 U/µL Taq polymerase, with the remaining volume DDH_2O. The details of primer sequences, annealing temperature, and restriction enzymes used are shown in Table 1. PCR products were digested overnight at 37°C with 0.5 U of the indicated restriction enzyme. Digestion products were then analyzed directly by vertical non-denaturing polyacrylamide gel electrophoresis and visualized by silver staining. To confirm the genotyping results, PCR-amplified DNA samples were examined with DNA sequencing. No differences were found in either quality controls and the results were 100% concordant.

Statistical analysis

Genotype and allele frequencies were compared between patients and controls using the χ^2 and Fisher's exact tests as appropriate. Tests of Hardy-Weinberg equilibrium were calculated with an observed genotype frequencies of fit χ^2 test with 1 degree of freedom. The odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the relative risk conferred by a particular allele and genotype. Statistical significance was set at $p<.05$. These analyses were performed using SPSS 15.0 software. Simultaneously, the *MMP1* -1607 1G/2G and *MMP3* -1612 5A/6A haplotype frequencies and linkage disequilibrium coefficient were estimated using the PHASE 2.0 program [21].

Results

Characteristics of the study subjects

The characteristics of the 132 ESCC patients and 132 control subjects included in this study are summarized in Table 2. No statistical differences in age and sex distribution were identified between ESCC patients and control individuals, suggesting that frequency-matching based on these variables was adequate. No family history of ESCC was reported among controls or cases.

The genotype and allele frequencies of MMPs

The genotype distributions in the total sample were present in Hardy-Weinberg equilibrium. The genotype and allele frequencies of the 3 SNPs (*MMP1* -1607 1G/2G, *MMP3* -1612 5A/6A, and *MMP9* -1562 C/T) are summarized in Table 3. For *MMP3* -1612 5A/6A, there was a significant difference in the genotype and allele frequencies of this polymorphism between ESCC and control subjects. The 6A5A and 5A5A genotypes were associated with a significantly higher risk of ESCC as compared with the 6A6A genotype (OR=1.92; 95% CI 1.14–3.23; $p=.01$ and OR=5.42; 95% CI 2.01–14.63; $p<0.01$, respectively). Using the 6A allele as a reference, a significant correlation was detected between the presence of the 5A allele and a risk of developing ESCC (OR=1.93; 95% CI 1.34–2.77; $p<0.01$). However, genotype and allele frequencies of the *MMP1* -1607 1G/2G and *MMP9* -1562 C/T polymorphisms in ESCC patients were not significantly different from those in healthy controls ($p>.05$). Since the *MMP1* and *MMP3* genes are located in the same chromosome region (11q22.3), haplotype analysis was calculated and the estimated haplotype frequencies are summarized in Table 4. The results of 2LD analysis revealed that the *MMP1* -1607 1G/2G and the *MMP3* -1612 5A/6A polymorphisms displayed a linkage disequilibrium (D'=0.51) in healthy subjects. Haplotype analysis indicated that 2G-6A was the most common haplotype in healthy controls (39.6%), followed by the 2G-5A (37.3%), 1G-6A (18.0%), and 1G-5A (5.1%) haplotypes. The 2G-5A and 1G-5A haplotypes were associated with a significantly increased risk of ESCC as compared with the 2G-6A haplotype (OR = 2.04, 95% CI 1.37–3.04 and OR=3.65, 95% CI 1.26–10.55, respectively). Our study demonstrated 86% (*MMP1* -1607 1G/2G), 87% (*MMP3* -1612 5A/6A), and 88% (*MMP9*

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Table 3. Genotype and allele frequencies of three SNPs in the MMPs gene between ESCC patients and controls.

Polymorphisms	Controls n=132 (%)		ESCC patients n=132 (%)		OR (95% CI)		p
MMP1 -1607 1G/2G							
Genotypes							
2G2G	87	(65.91)	81	(61.36)	1.00	(Ref)	
2G1G	40	(30.30)	41	(31.06)	1.10	(0.65–1.87)	.72
1G1G	5	(3.9)	10	(7.58)	2.15	(0.70–6.55)	.17
Alleles							
2G	214	(84.47)	203	(76.89)	1.00	(Ref)	
1G	50	(15.53)	61	(23.11)	1.29	(0.85–1.96)	.24
MMP3 -1612 5A/6A							
Genotypes							
6A6A	65	(49.24)	40	(30.30)	1.00	(Ref)	
6A5A	61	(46.21)	72	(54.55)	1.92	(1.14–3.23)	.01
5A5A	6	(4.55)	20	(15.15)	5.42	(2.01–14.63)	<.001
Alleles							
6A	191	(72.35)	152	(57.58)	1.00	(Ref)	
5A	73	(27.65)	112	(42.42)	1.93	(1.34–2.77)	<.001
MMP9 -1562 C/T							
Genotypes							
CC	92	(69.70)	84	(63.64)	1.00	(Ref)	
CT	34	(37.98)	38	(28.79)	1.22	(0.71–2.12)	.47
TT	6	(4.01)	10	(7.58)	1.85	(0.64–5.24)	.26
Alleles							
C	218	(82.58)	206	(78.03)	1.00	(Ref)	
T	46	(17.42)	58	(21.97)	1.33	(0.87–2.05)	.19

Ref – reference category.

Table 4. Haplotype distribution in the patients with ESCC and controls.

Haplotype	Controls n=264 (%)		ESCC patients n=264 (%)		OR (95% CI)		p
2G-6A	146	(55.30)	104	(39.6)	1.00	(Ref)	
2G-5A	68	(25.80)	99	(37.30)	2.04	(1.37–3.04)	<.01
1G-6A	45	(17.10)	48	(18.00)	1.50	(0.98–2.42)	.01
1G-5A	5	(1.90)	13	(5.10)	3.65	(1.26–10.55)	.01

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-1562 C/T) power to detect an effect with an odds ratio of 2.2 in cases versus controls under a dominant genetic model.

Discussion

Our results appear to be in line with the well-documented functional relevance of the *MMP3* -1612 5A/6A SNP. Accordingly, this suggests that *MMP3* gene polymorphisms may be useful genetic susceptibility markers for ESCC.

MMPs are a pivotal family of zinc-dependent enzymes that are involved in all stages of cancer progression. MMPs are considered to be particularly important for the invasion and metastasis processes of cancer cells, as these require proteolysis of the ECM and basement membrane. However, recent studies have reported that MMPs are involved in regulating tumor cell growth, apoptosis, invasion, cell adhesion, metastasis, angiogenesis, cell signaling, and immune surveillance [22,23]. In normal tissues, MMP levels are usually low. Accordingly, overexpression of *MMP1*, *MMP3*, or *MMP9* may contribute to the pathogenesis of tissue-destructive processes in ESCC. Functional studies indicate that the -1607 1G/2G, -1612 5A/6A, and -1562 C/T polymorphisms affect *MMP1*, *MMP3*, and *MMP9* promoter activities, respectively.

MMP9, also called gelatinase B and 92-kDa type IV collagenase, is involved in the breakdown of gelatin, collagens and elastin [24]. To our knowledge, a link between the *MMP9* -1562 C/T polymorphism and ESCC has not previously been established. Zhang et al. [13] first reported that the *MMP9* -1562 C/T polymorphism created a binding site for a transcriptional repressor protein. We therefore suspected that this functional polymorphism could be involved with ESCC pathogenesis. However, we did not find any link between the *MMP9* -1562 C/T polymorphism and ESCC in this study.

The *MMP1* gene promoter carries a common deletion/insertion polymorphism at position -1607. The 2G allele, as opposed to the 1G allele, is associated with the creation of a new 5'-GGA-3' core recognition sequence for the Ets family of transcription factors [11]. Our finding was consistent with the findings of a previous report that found no association between the *MMP1* polymorphism and ESCC risk.

The *MMP1* (human collagenase-1) and *MMP3* (human stromelysin-1) genes are located in the same chromosome region (11q22.3). Both are produced by macrophages, stromal fibroblasts, and epithelial cells and *MMP3* exhibits proteolytic activity on numerous extracellular matrix proteins [25]. Additionally, *MMP3* is capable of activating several other MMPs, including *MMP1* and *MMP9*. Moreover, *MMP3* can influence the secretion of some cell-surface molecules, including E-cadherin, and promote tumor formation and progression [26]. The *MMP3* gene promoter has a dimorphism at position -1172, where either 5 (5A allele) or 6 (6A allele) adenosine residues are found. Deletion of an adenosine (5A) leads to increased *MMP3* transcription compared with the 6A allele *in vitro* [27]. Therefore, the presence of the *MMP3* -1612 5A/6A polymorphism is associated with an increased risk of developing a range of cancers, including colorectal adenoma [28], hepatocellular carcinoma [29], and lung cancer [30]. This study identified a higher frequency of the 5A allele in ESCC patients (OR 1.53; p=.035) when compared with controls. The frequency of the *MMP3* 5A allele among control Chinese individuals was 0.276, which was significantly lower than that reported in Austria (0.470) [31], Italy (0.440) [14], Czech Republic (0.483) [32], and Sweden (0.536) [32]. Zhang et al. [33] indicated that the *MMP3* 5A allele was a significant risk factor for ESCC only in current or ex-smokers, suggesting that the effect of the *MMP3* -1612 5A/6A polymorphism on ESCC might be influenced by cigarette smoking. In the current study, we found no evidence to support this.

There are several limitations to our study. Firstly, this was a hospital-based case-control study. Secondly, the subjects were not adjusted in our logistic regression models because of the lack of detailed information about their diet, alcohol consumption, and environmental data. Finally, we selected common SNPs within the same haplotype structure instead of haplotype tagging SNPs, and the selection criteria for the candidate polymorphisms were based on evidence of putative functional change. This strategy may lead to inherited error in the analysis, and further studies with larger samples are needed to explore this further.

In summary, our research provides evidence that the *MMP3* -1612 5A/6A polymorphism is a genetic susceptibility factor for the development of ESCC in a Chinese population. Additionally, the 2G-5A and 1G-5A haplotypes are associated with a higher risk of ESCC. Further studies in diverse ethnic populations are needed to verify our results, and an evaluation of gene-environment interactions on the risk of ESCC development would also be of great value.

Conclusions

These findings implicate this *MMP3* polymorphism as a contributor to ESCC susceptibility.

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Disclosure statement

No competing financial interests exist.

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