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Association of Matrix Metalloproteinase-7 Genotypes to the Risk of Oral Cancer in Taiwan

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Abstract. *Background/Aim: Matrix metalloproteinases (MMPs) play a critical role in inflammation and carcinogenesis, and the expression of mRNA MMP7 in oral squamous cell carcinoma tissues was higher than in the oral lichen planus or normal oral mucosa. However, the genotypic role of MMP7 has never been examined in oral cancer. Therefore, in the current study we aimed to examine the contribution of genotypic variants in the promoter region of MMP7 (A-181G and C-153T) to oral cancer risk in Taiwan. Materials and Methods: In this hospital-based case–control study, 788 patients with oral cancer and 956 gender-and age-matched healthy controls were genotyped for MMP7 A-181G and C-153T via polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methodology. Results: The distribution pattern of AA, AG and GG for MMP7 promoter A-181G genotype was 88.2, 10.4 and 1.4% in the oral cancer patient group and 89.0, 9.3 and 1.7% in the healthy control group, respectively (p for trend=0.6779), non-significantly differentially distributed between the two groups. There is no polymorphic genotype for MMP7 C-153T among Taiwanese. The comparisons in allelic frequency distribution also support the findings that G allele may not be the risk determinant allele for oral cancer. There is no interaction between the genotypes of MMP7 with age, gender, smoking, alcohol or betel quid consumption on oral cancer risk. Conclusion: Our results indicate that the MMP7 promoter genotypes only play an indirect role in determining the personal susceptibility to oral cancer in Taiwan.*

Oral cancer, the eighth most common cancer around the world, has the highest male incidence density in Taiwan (1, 2). It is believed that the regional variations of oral cancer around the world is dependent on the etiology and the risk factors involved (1). According to the official annual report of Taiwan, oral cancer is the fourth cause of cancer-related death among the males in Taiwan, and has been reported to be closely associated with betel nut, tobacco and alcohol consumption behaviors (3-5). In the recent decade, many genomic biomarkers for oral cancer in the Taiwanese population have been found (6-12). Also, overall revealing of cellular etiological investigations and the interactions among the genetic and lifestyle factors for each patient will contribute to further personalized cancer therapy.

The matrix metalloproteinases (MMPs, matrixins) are a family of endopeptidases which team up with their specific inhibitors, *e.g.* the tissue inhibitors of metalloproteinases (TIMPs), and play a key role in maintaining the homeostasis

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of extracellular matrix (ECM) components and the processes of inflammation, carcinogenesis and migration (13, 14). In early 1990's, the overexpression of MMPs in tumor and stromal cells in various cancers was reported to be associated with invasion and progression of tumorigenesis (15). In addition, MMPs released from distant organs, together with growth factors to tumor cells, can play a role in the initiation of metastasis (16, 17). In the human body, MMP7 has been shown to be constitutively produced by the mammary and parotid glands, pancreas, liver, prostate and peribronchial glands of the lung (18). In the past years, accumulating evidence indicated that the functional polymorphisms of MMPs may contribute to inter-individual differences in susceptibility to several types of cancer (19-27). In a promoter assay, the basal promoter activity was higher in promoter constructs harboring the combination of the two rare alleles of *MMP7* at A-181G (rs11568818) and C-153T (rs11568819) (28), and these two promoter polymorphisms were reported to be associated with coronary artery dimensions (28). In cancer genomic association studies, the genotypes of *MMP7* were investigated for their association with many types of cancer, including lung, breast, esophageal, gastric, colorectal, gallbladder, bladder, cervical cancer, astrocytoma, childhood leukemia and renal cell carcinoma (29-40), but seldom in oral cancer (41).

It is reported that the mRNA levels of MMP7 were significantly higher in oral squamous cell carcinoma than those in oral lichen planus and normal oral mucosa (42). In addition, Vairaktaris and colleagues found that the G allele carriers at *MMP7* A-181G were significantly higher in patients compared to controls, while this significant difference was more pronounced in patients with early stages of cancer and absent in those with advanced stages (41). Furthermore, it was reported that MMP7 was only expressed in oral squamous cell carcinoma but not in stroma cells and highly expressed MMP7 displayed a survival relevance, and can serve as a prognostic indicator (43). In light of the above, the purpose of the current study was to investigate the association of *MMP7* genotypes at the promoter region to the risk of oral cancer in a representative Taiwanese population.

Materials and Methods

Investigated population. The current study was approved by the Institutional Review Board of the China Medical University Hospital (DMR101-IRB1-306) and written-informed consent has been obtained from all the participants. Totally, seven hundred and eighty-eight patients diagnosed with oral cancer were recruited at the China Medical University Hospital in central Taiwan. All patients voluntarily participated, completed a self-administered questionnaire and willingly provided 5 ml of their peripheral blood. The questionnaire administered to participants included questions on history and frequency of alcohol consumption, areca chewing and smoking habit. Self-reported alcohol consumption, areca chewing and smoking habits were evaluated and classified as categorical variables. Information on these factors was obtained as more than twice a week for years as ''ever''. A total of 956 non-cancer healthy individuals as controls were selected by matching for age and gender after initial random sampling from the Health Examination Cohort of the hospital. The male *versus* female ratio was 76% to 24% in each group. The mean age of the patients and the controls was 55.8 (SD=9.9) and 56.6 (SD=8.7) years, respectively. The selective demographic information for the participants is summarized in Table I.

MMP7 Genotyping methodology. Genomic DNA was extracted from peripheral blood leukocytes with a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan), stored long-term at –80˚C, diluted and aliquoted for genotyping as a working stock at –20˚C as we have frequently conducted (44). The *MMP7* genotyping methodology is the same as our recently published paper (40). Concisely, the polymerase chain reaction (PCR) cycling conditions were: one cycle at 94˚C for 5 min; 35 cycles at 94˚C for 30 sec, 59˚C for 30 sec and 72˚C for 30 sec, and a final extension at 72˚C for 10 min. The genotyping PCR for *MMP7* A-181G was conducted using the forward 5'-TGGTACCATAATGTCCTGAATG-3' and the reverse 5'-TCGTTATTGGCAGGAAGCACACAATGAATT-3' primer pairs. The obtained 150 bp PCR products were then digested with *Eco*RI and resulted in two fragments of 120 and 30 bp when the G allele was present. In the presence of the A allele, the 150 bp fragment remained intact. As for the *MMP7* C-153T, PCR was conducted with the same primers as for *MMP7* A-181G. After amplification, the PCR products were subjected to digestion and separation using 3% agarose gel electrophoresis. All the genotypic processing was repeated by two expert researchers independently and blindly, and their results were 100% concordant to each other. In addition, the success rate of PCR-restrictive fragment length polymorphism (RFLP) is 100%, and the genotypes of 5% of the participants in both the control and patient groups were analyzed by PCR direct sequencing (Genomics BioSci & Tech Co., Taipei, Taiwan). The concordance between direct sequencing and PCR-RFLP methods was 100%.

Statistical analyses. Those participants with complete genotypic and clinical data were subjects to final analysis. The descriptive statistics of patients and controls are presented as the mean and standard deviation (SD) or as percentages. The Student's *t*-test was used for the comparison of ages between the case and the control groups. The Pearson's chi-square test or Fisher's exact test (when any cell was less than five) was used to compare the distribution of the genotypes. Associations were evaluated and presented as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical data was deemed to be significant when the *p*-value was less than 0.05.

Results

Comparison of basic characteristics between the oral cancer patients and the healthy control groups. The frequency distributions of selected basic characteristics including age, gender, personal habits and primary tumor sites for the 788 patients with oral cancer and 956 non-cancer controls are summarized in Table I. Statistically, there was no difference in the distribution of age and gender

Table I. *Basic characteristics of the 788 patients with oral cancer and 956 controls investigated in this study.*

Characteristic	Controls (n=956)			Cases (n=788)			*p*-Value
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			56.6 (8.7)			55.8 (9.9)	0.7951[a]
Gender							1.0000[b]
Male	727	76.0%		599	76.0%		
Female	229	24.0%		189	24.0%		
Personal habits							
Areca chewing	506	52.9%		661	83.9%		**<0.0001[b]***
Cigarette smoking	667	69.8%		595	75.5%		**0.0084[b]***
Alcohol drinking	641	67.1%		560	71.1%		0.0773[b]
Primary tumor site							
Tongue				325	41.2%		
Buccal mucosa				294	37.3%		
Mouth floor				30	3.8%		
Retromolar trigone				26	3.3%		
Alveolar ridge				18	2.3%		
Palate				18	2.3%		
Lip				39	4.9%		
Others				38	4.9%		

SD: Standard deviation; [a]based on Student's *t*-test; [b]based on Chi-square test. * and bolded: Statistically significant, $p<0.05$.

between the oral cancer patient and healthy control groups since we have applied the frequency matching approach in selecting the included non-cancer healthy controls (Table I). Among the investigated individuals, it was found that betel quid chewers and smokers were of higher percentages in the oral cancer patient group than in the control group (both $p<0.05$) (Table I, upper part). Indeed, smoking and betel quid chewing may be the risk behavioral factors for oral cancer for Taiwanese. From the clinical viewpoint, most of the primary tumors for the investigated oral cancer patients occurred in the tongue (41.2%) and buccal mucosa (37.3%) (Table I).

Association of MMP7 promoter genotypes and Taiwan oral cancer risk. The genotypic analysis for the MMP7 A-181G and C-153T among the healthy controls and the oral cancer patients are presented and compared in Table II. The data showed that there are no polymorphic genotypes among the investigated Taiwanese subjects at *MMP7* C-153T (Table II, lower panel). The genotypic frequency distributions for *MMP7* A-181G were non-significantly different between the oral cancer and the healthy control groups (p for trend=0.6779) (Table II, upper panel). In detail, the *MMP7* A-181G heterozygous AG and homozygous GG seemed not to be associated with any risk of oral cancer (p=0.4548 and 0.6625, adjusted OR=0.89 and 1.19, 95%CI=0.65-1.22 and 0.55-2.58, respectively; Table II, upper panel). After combination of the homozygotes and heterozygotes for the G allele (AG+GG), the analytic results still showed that the G allele at *MMP7* A-181G conferred unaltered risk for oral cancer (p=0.5917) (Table II). Overall, *MMP7* A-181G seems to play an indirect role in determining personal susceptibility to oral cancer among Taiwanese.

Table II. *Distributions of matrix metalloproteinase-7 A-181G and C-153T genotypic frequencies among the oral cancer patients and healthy controls.*

	Cases, n (%)	Controls, n (%)	Adjusted OR (95%CI)[a]	*p*-Value[b]
A-181G				
AA	695 (88.2)	851 (89.0)	1.00 (Reference)	
AG	82 (10.4)	89 (9.3)	0.89 (0.65-1.22)	0.4548
GG	11 (1.4)	16 (1.7)	1.19 (0.55-2.58)	0.6625
AG+GG	93 (11.8)	105 (11.0)	0.92 (0.69-1.24)	0.5917
p_{trend}				0.6779
C-153T				
CC	788 (100.0)	956 (100.0)	1.00 (Reference)	
CT	0 (0.0)	0 (0.0)	--	
TT	0 (0.0)	0 (0.0)	--	
p_{trend}				

OR: Odds ratio; CI: confidence interval. [a]Data have been adjusted for confounding factors age, gender, smoking, alcohol and betel quid consumption. [b]Based on Chi-square test without Yates' correction.

Table III. *Allelic frequencies for matrix metalloproteinase-7 A-181G and C-153T polymorphisms among the oral cancer patients and healthy controls.*

Allelic type	Cases, n (%) n=788	Controls, n (%) n=956	Adjusted OR (95%CI)[a]	*p*-Value[b]
A-181G				
Allele A	1472 (93.4)	1791 (93.7)	1.00 (Reference)	0.7462
Allele G	104 (6.6)	121 (6.3)	0.96 (0.72-1.25)	
C-153T				
Allele C	788 (100.0)	956 (100.0)	1.00 (Reference)	
Allele T	0 (0.0)	0 (0.0)	--	

OR: Odds ratio; CI: confidence interval. [a]Data have been adjusted for confounding factors age, gender, smoking, alcohol and betel quid consumption. [b]Based on Chi-square test without Yates' correction.

Association of MMP7 promoter allelic frequencies and Taiwanese oral cancer risk. The distributions of allelic frequencies for *MMP7* A-181G and C-153T polymorphisms among the oral cancer patients and the healthy controls are shown in Table III. Supporting the findings in Table II, G allele at *MMP7* A-181G was not significantly associated with oral cancer risk (p=0.7462 and adjusted OR=0.96) (Table III). In detail, the percentages of minor allele frequencies in the oral cancer patient and the healthy control groups were 6.6% and 6.3%, respectively (Table III). Consistent with the findings in Table II, all the investigated subjects carried a C allele at *MMP7* C-153T among Taiwanese (Table III). We have also performed stratification analysis for the *MMP7* A-181G genotypes according to age, gender, smoking, alcohol and betel quid consumption status, however, no significant association was found in the stratification analysis between any subgroups (data not shown).

Discussion

In the current study, we firstly examined the contribution of *MMP7* genotypes to oral cancer susceptibility in Taiwan, where the highest oral cancer incidence around the world exists. In normal condition, MMP7 is commonly expressed in ductal epithelium of exocrine glands in skin, salivary glands, pancreas, glandular epithelium of intestine and reproductive organ, liver, and breast. Since MMP7 is in charge of degrading ECM macromolecules such as casein, type I~V gelatins, fibronectins and proteoglycans (45), it is very possible that hereditary genomic variations may determine personal risk for inflammation processes, tumor initiation, invasion and metastasis (46). The supporting evidence comes from several ways: a) MMP7 is found to be highly expressed in the luminal surface of dysplastic glands in human colorectal cancers (45); b) In clinical practice, MMP7 inhibitors can potentially be applied to control the invasive capacity of cancers (46); c) MMP7 was found to be highly expressed in advanced colorectal adenomas and involved in converting colorectal adenomas into a malignant state and facilitating cancer growth (47).

In literature, the A-181G genotype of *MMP7* was studied about its association with many types of cancer, including breast, esophageal, gastric, colorectal, gallbladder, bladder, cervical cancer, childhood leukemia and renal cell carcinoma (31-40). However, little is known about the contribution of *MMP7* genotypes to oral cancer, except the research reported by Vairaktaris and his colleagues (41). In that investigation, the authors found that the detected carrier frequency of the G allele at *MMP7* A-181G was significantly higher in patients compared to controls (74.8% *versus* 61.7%, p=0.0257). The individuals in that study were 95 Greeks and 184 Germans, consisting of 159 patients with oral cancer and 120 healthy controls (41).

In the current study, we found that the G allele of *MMP7* A-181G were non-significantly associated with altered risk to oral cancer (Tables II and III). As far as we are aware, the current study is the first to reveal the genotypic contribution of *MMP7* promoter genotypes to oral cancer in Taiwan, with an inconsistent finding to theirs. Compared with the investigated subjects, our samples are more genetically conserved (all Chinese) and representative (788 oral cancer patients and 956 healthy controls). The inconsistent findings between ours and theirs about the associations may come from different genetic background since the G allele of *MMP7* A-181G is common (about 40-43%) in Caucasians and rare (2.5-5%) in East Asians (28-30, 48-50). The presence of the G allele at *MMP7* A-181G was associated with 2- to 3-fold higher transcriptional activity than that with the A allele, because it reportedly facilitated the binding of nuclear activating proteins in the promoter of *MMP-7* (28). It is very possible that the G allele of MMP7 A-181G played a more important role in determining the susceptibility to oral cancer for Caucasians (such as Germans and Greeks) than for East Asians (such as Taiwanese), and further phenotypic investigations are needed to reveal the detail mechanisms.

In conclusion, this study examined the genotypic patterns of *MMP7* A-181G and C-153T among Taiwanese. The genotypes of neither *MMP7* A-181G nor C-153T contributed to an alteration of susceptibility for Taiwanese to oral cancer. In addition, age, gender, smoking, alcohol or betel quid consumption did not interact with the *MMP7* A-181G genotype in determining oral cancer susceptibility.

Conflicts of Interest

The Authors declare no conflicts of interest with any person or company.

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