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The Association of *MMP7* Promoter Polymorphisms With Gastric Cancer

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Abstract. *Background/Aim: Few studies have examined the genetic role of matrix metalloproteinases (MMPs) to early detection or prediction in gastric cancer development. In this study, the contribution of MMP7 promoter (A-181G and C-153T) polymorphic genotypes to gastric cancer risk in Taiwanese was investigated for the first time. Materials and Methods: A total of 121 cases and 363 controls were enrolled and their MMP7 genotypes at A-181G and C-153T were examined by polymerase chain reaction-restriction fragment length polymorphism methodology using genomic DNA from serum. Results: The GG genotype at MMP7 A-181G was found to represent a risk factor for gastric cancer, especially among smokers. No individual with variant genotype carrier at MMP7 C-153T was found among this Taiwanese population. Conclusion: The G allele of MMP7 A-181G may serve as an early predictor for gastric cancer risk in Taiwanese; other gastric cancer markers are still urgently needed.*

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Although there is a trend for a steady decline worldwide, gastric cancer is still the fourth most prevalent cancer and the second most common cause of cancer-related death worldwide (1, 2). It was estimated that about 783,000 deaths from gastric cancer occurred all over the world, and about half of the newly diagnosed gastric cancer cases were found in Eastern Asia, for instance, mainland Japan, China and Taiwan (2). The incidence and survival rates of patients with gastric cancer varies among different countries. For instance, the 5-year survival rate is extremely good only in Japan, where it reaches about 90% due to early diagnosis by endoscopic examinations and subsequent early tumor resection (3). On the contrary, 5-year survival rates vary from 10 to 30% among European countries (4). A combination of lifestyle, dietary and genomic factors contribute to the etiology of gastric cancer but a personalized genetic predictive strategy for gastric carcinogenesis remains largely unestablished. From the epidemiological viewpoint, dietary habits (5, 6), *Helicobacter pylori* infection status (7), alcohol consumption (8, 9), occupational exposures (10-12), obesity (13), and inherited genomic variations (14) may interact to play an important role in gastric cancer initiation and development but their contributions are largely unknown. In Taiwan, gastric cancer is the seventh most prevalent type of cancer (7^{th} in males and 10^{th} in females) and of death-causing cancer (15). There have been several gastric cancer genomic studies investigating the contribution of genomic factors to the etiology of gastric cancer in Taiwan (16-19).

It is a widely accepted concept that cancer is a multi-factorial and multi-stage disorder in which imbalance in the extracellular microenvironment is a prerequisite for cancer initiation and development (20). Hence, investigations have been focused on molecular alterations and may help to reveal the whole process of gastric carcinogenesis. Matrix metalloproteinases (MMPs), also known as interstitial collagenases, are in charge of the complex regulation of the extracellular microenvironment *via* their capacity to degrade its components, which may result in the initial step of tumorigenesis (21). MMPs are a family of proteins with individual capacities to degrade specific substrates, such as the collagens, elastins, and gelatins (22).

Alteration of expression of MMPs and imbalance of the extracellular microenvironment have frequently been found in many types of cancer, including gastric cancer. For instance, MMP2 and MMP9 were overexpressed in gastric cancer tissues compared with normal tissues (23). On the other hand, down-regulation of MMP3 and MMP13 was effective in suppressing the tumorigenic behavior of gastric cancer fibroblasts in both proliferation and migration (24, 25). Mounting evidence support the notion that MMPs may play an essential role in the progression of gastric cancer, and elucidating the potential markers, such as MMPs, for gastric cancer prediction may help in both prevention and therapy of gastric cancer. In literature, genetic alterations such as polymorphic genotypes of *MMPs* have been investigated for their contribution to personal susceptibility to specific types of cancer (26-29). However, few studies have investigated the role of polymorphisms of *MMPs* as risk determinates for gastric cancer, and those that have mainly investigated *MMP1* (30), *MMP2* (31) and *MMP9* (32-34).

MMP7 is the smallest protein in the MMP family, in charge of the degradation of several subtracts such as fibronectin, vitronectin, elastin, collagen IV, aggrecan, and proteoglycans (35). MMP7 is also involved in inflammatory reactions via elevation of cell-surface processing for cytokines such as tumor necrosis factor-α (36). In 2019, a meta-analysis summarized eight studies from all over the world which investigated the contribution of *MMP7* A-181G genotype to gastric cancer risk (37). In that article, the authors suggested that the variant G allele of *MMP7* A-181G is associated with elevated gastric risk (1,545 patients with gastric cancer) (37). However, the summarized populations did not include Taiwanese, an extremely genetically conserved population with relatively high gastric cancer prevalence. Therefore, it is reasonable to hypothesize that the genotypes at *MMP7* promoter polymorphic sites may play a role in determining, the personal susceptibility to gastric cancer in Taiwanese *via* regulation of the expression of MMP7. Since promoter polymorphic sites of *MMP7* may control the expression level of MMP7, we aimed to evaluate the association not only of A-181G polymorphism, which has been frequently examined, but also of C-153T polymorphism, which has seldom been examined, with Taiwanese gastric cancer risk in the current study.

Materials and Methods

Recruitment of patients with gastric cancer and controls. One hundred and twenty-one patients with gastric cancer were recruited between 2005-2007 at the China Medical University Hospital. The mean age of these patients was 51.26 (SD=9.42) years, with a male/female ratio of 65/56. Well matched by both age and gender, a three-fold in the number of patients, that is to say, 363 healthy people without cancer were selectively recruited from the Health Examination Cohort of our Hospital with the great help of colleagues in the Department of Family Medicine. Our study design and protocol were approved by and under the supervision of the Institutional Review Board of our own Hospital (IRB number: DMR100-IRB-107). Written-informed consent was collected with the help of the Tissue Bank of China Medical University Hospital. Selected demographic characteristics of the two groups are summarized and evaluated in Table I.

Methodology for determination of MMP7 polymorphic genotype. Within 24 h after the blood collection, genomic DNA from each participant was extracted, aliquoted and stored by well-trained and IRB-approved research assistants as previously described (38, 39). The *MMP7* genotyping methodology was exactly the same as our recently published articles (26, 27, 40). The polymerase chain reaction (PCR) cycling conditions specifically for *MMP7* genotyping in My Cycler (Biorad, Hercules, CA, USA) were set as: a first step with one cycle at 94˚C for 5 min; a second step with 35 cycles of 94˚C for 30 s, 57˚C for 30 s, and 72˚C for 30 s; and a final step of extension at 72˚C for 10 min.

Statistical analysis methodology. Pearson's chi-square test without Yates' correction (when all investigated numbers were 5 or more in each cell compared) was applied to compare the distribution of the gender, *MMP7* genotypes and alleles between the case and control groups. The unpaired Student's *t*-test was applied for the comparison of distribution of the ages between the two groups. The associations between the *MMP7* polymorphisms and gastric cancer risk were computed with odds ratios (ORs) as well as their 95% confidence intervals (CIs) under unconditional logistic regression analysis after adjustment for confounding factors (including age, gender and behavioral indices in Table I). Any *p*-value less than 0.05 was taken as being significant in statistical analysis.

Results

Comparison of age and gender between the gastric cancer and cancer-free control groups. The demographic characteristics of the 121 patients with gastric cancer and the 363 controls are summarized and presented in Table I. Firstly, the data showed that the age and gender were well matched between the two groups (p=0.8918 and >0.99, respectively). Secondly, the average body mass index was not differentially distributed (p>0.05) between the two

Table I. *Selected characteristics of the control and gastric cancer patient groups.*

Character	Cases (n=121)	Controls (n=363)	*p*-Value[a]
Age, years			
Mean±SD	51.3±9.4	53.2±8.1	0.8918
Gender			
Female/male	56/65	168/195	>0.99
BMI, kg/m^2			
Mean±SD	27.1±5.8	26.7±6.6	0.9344
Alcohol consumer, n (%)			
Yes	39 (32.2)	84 (23.1)	0.0538
Heavy drinker[b]	12 (9.9)	11 (4.4)	**0.0049**
Cigarette consumer, n (%)			
Yes	42 (34.7)	71 (19.6)	**0.0012**
Heavy smoker[c]	13 (10.7)	6 (1.7)	**0.0001**
Helicobacter pylori infection, n (%)			
Yes	85 (70.2)	188 (51.8)	**0.0005**
Tumor location, n (%)			
Upper	17 (14.1)		
Middle	54 (44.6)		
Lower	50 (41.3)		

BMI: Body mass index. [a]Based on chi-square test. [b]*i.e.* Not able to walk straight, respond to common questions properly more than twice weekly after drink, or drinking more than 100 ml per day for at least half year. [c]More than 1 pack per day for at least half a year. Significant *p*-values are shown in bold.

groups either. Thirdly, the percentages of alcohol users tended to be higher in the patient group (32.2%) than that in the control group (23.1%) (p=0.0538), while the percentage of heavy drinkers was significantly higher in the gastric cancer case group (9.9%) than that in the control group (4.4%) (p=0.0049). Regarding cigarette smoking status, the gastric cancer group had very significantly higher percentage of cigarette smokers, especially heavy smokers, than did the control group (34.7% *vs*. 19.6%, and 10.7% *vs*. 1.7%, p=0.0012 and 0.0001, respectively). As for *Helicobacter pylori* infection status, 70.2% of our Taiwanese gastric cancer cases were positive, significantly higher than that of 51.8% for the controls (p=0.0005). From the epidemiological viewpoint, the heavy consumption of alcohol and cigarettes, together with the infection by *H. pylori,* are the three major factors most likely to play an important role in gastric cancer etiology for Taiwanese.

Association analysis of MMP7 promoter genotypes at A-181G and C-153T with gastric cancer risk. The polymerase chain reaction-restriction fragment length polymorphism-based genotypic results for *MMP7* promotor A-181G and C-153T among the 121 gastric cancer cases and the 363 cancer-free controls are presented and compared in Table II. The genotypic frequency distributions for *MMP7* A-181G in the control group fit the Hardy–Weinberg equilibrium (p=0.3239). The genotypic frequency distributions for *MMP7* A-181G were statistically non-different between the gastric cancer and the cancer-free control groups (p for trend=0.1596) (Table II). *MMP7* A-181G heterozygous AG genotype seemed not to be associated with risk for gastric cancer among Taiwanese (p=0.2787). Interestingly, the homozygous GG genotype exhibited borderline association with gastric cancer risk for Taiwanese (adjusted OR=2.53, 95% CI=1.16-8.74; p=0.0908). We also compared those carrying the GG genotype with those with AA or AG genotype; the results showed that the GG genotype at *MMP7* A-181G conferred a 2.58-fold increased odds of gastric cancer, although not statistically significant (adjusted OR=2.58, 95% CI=1.21-8.56, p=0.1130) (Table II). Combining G allele-bearing genotypes to compare with the wild-type AA genotype showed that carrying AG/GG genotype at *MMP7* A-181G conferred a slightly increased risk for gastric cancer (adjusted OR=1.59, 95% CI=0.89-2.36; p=0.1447) (Table II). Finally, it should be noted that there was no individual with variant polymorphic genotype at *MMP7* C-153T among any of the examined Taiwanese participants (Table II). Overall, the *MMP7* A-181G but not C-153T genotype might play a role in determining personal susceptibility to gastric cancer among Taiwanese.

Association analysis of MMP7 allelic frequencies at A-181G and C-153T with gastric cancer risk. We further conducted allelic frequency analysis for *MMP7* promoter A-181G and C-153T association with gastric cancer risk to confirm the genotypic findings given in Table II, and the results are shown in Table III. There was a borderline difference in the distribution of alleles between the gastric cancer and control groups for the *MMP7* promoter A-181G (p=0.0734, Table III), with an adjusted OR for those carrying the variant G allele of 1.48 (95% CI=1.06-2.37) compared to those carrying the wild-type A allele (Table III). Thus, overall, the data supported that the G allele was associated with an elevated risk of gastric cancer. For the allelic frequency analysis, for *MMP7* C-153T, there was no association between the genotypes and gastric cancer since all those investigated carried the C allele (Table III).

Interaction analysis of the association of MMP7 A-181G genotypes and lifestyle factors with gastric cancer risk. The genetic–lifestyle interaction was of interest and therefore the interaction between *MMP7* A-181G and personal smoking habit on gastric cancer risk was analyzed (Table IV). The results showed that the distributions of genotypes at *MMP7* A-181G were significantly different between cancer and control groups among smokers (p=0.0217), but not among those who were non-smokers (p=0.9574) (Table IV). Consistent with the findings shown in Tables II and III, the

Table II. *Distribution of matrix metalloproteinase-7 A-181G and C-153T genotypic frequencies among the controls and patients with gastric cancer.*

Genotype	Cases (n=121)	Controls (n=363)	Adjusted OR (95% CI)[a]	*p*-Value[b]
A-181G				
AA	85 (70.3)	279 (76.9)	1.00 (Reference)	
AG	31 (25.6)	78 (21.5)	1.41 (0.88-2.03)	0.2787
GG	5 (4.1)	6 (1.6)	2.53 (1.16-8.74)	0.0908
p_{trend}				0.1596
Carrier comparison				
AA+AG	116 (95.9)	357 (98.4)	1.00 (Reference)	
GG	5 (4.1)	6 (1.6)	2.58 (1.21-8.56)	0.1130
AA	85 (70.3)	279 (76.9)	1.00 (Reference)	
AG+GG	36 (29.7)	84 (23.1)	1.59 (0.89-2.36)	0.1447
C-153T				
CC	121 (100.0)	363 (100.0)	1.00 (Reference)	

OR: Odds ratio; CI: confidence interval. [a]Adjusted for confounding factors age, gender, smoking, alcohol and *Helicobacter pylori* infection. [b]Based on chi-square test without Yates' correction.

Table III. *Allelic frequencies for matrix metalloproteinase-7 A-181G and C-153T in the control and gastric cancer patient groups.*

Allelic type	Cases (n=121*2)	Controls (n=363*2)	Adjusted OR (95% CI)[a]	*p*-Value[b]
A-181G				
Allele A	201 (83.1)	636 (87.6)	1.00 (Reference)	
Allele G	41 (16.9)	90 (12.4)	1.48 (1.06-2.37)	0.0734
C-153T				
Allele C	242 (100.0)	726 (100.0)	1.00 (Reference)	
Allele T	0 (0.0)	0 (0.0)	--	

OR: Odds ratio; CI: confidence interval. [a]Adjusted for confounding factors age, gender, smoking, alcohol and *Helicobacter pylori* infection. [b]Based on chi-square test without Yates' correction.

odds of developing gastric cancer for GG carriers was four-fold that for heterozygous AG carriers and nine-fold that of AA homozygotes (p=0.0210). There was no such difference observed for the non-smoker group. After adjusting for age, gender, alcohol drinking and *H. pylori* infection status, the results remained significant for smokers carrying AG and GG genotypes (Table IV). However, there was no interaction for alcohol drinking status or *H. pylori* infection status with *MMP7* A-181G genotype for gastric cancer susceptibility in this Taiwanese population (data not shown).

Discussion

As mentioned earlier, MMP7 degrades major ECM components such as casein, type I-V gelatins, fibronectins and proteoglycans and may alter the extracellular microenvironment (41). In previous literature, it was hypothesized that polymorphic genotypes at *MMP7* may determine personal risk for inflammatory processes, tumor initiation, invasion and metastasis (42). In 2000, a Japanese team first found that more than half of tumor tissues, 70 out of 136, from patients with gastric cancer overexpressed MMP7, and those patients with MMP7-positive tumor had significantly poorer survival and more frequently died of recurrence than did those with MMP7-negative tumors (43). In 2009, Okayama and colleagues further extended data on the importance of MMP7 showing that overexpression of MMP7, together with that of CD44v6 and negative expression of nuclear caudal type homeobox 2 may serve as powerful predictors of lymph node metastasis among patients with gastric cancer (44). Since then oncologists have started to reveal the detailed intracellular mechanisms and molecules involved in regulation of the expression of MMP7 (45, 46).

In this study, we concluded that the GG genotype (*versus* AA) of *MMP7* A-181G is significantly associated with increased risk of gastric cancer for Taiwanese smokers (Table IV), and this finding is consistent with the meta-analysis finding (37). As far as we are concerned, the present study is the first to reveal the genotypic contribution of *MMP7* promoter genotype to gastric cancer with a representative population from Taiwan, where

Table IV. *Odds ratios for association of matrix metalloproteinase-7 A-181G genotype and gastric cancer after stratification by smoking status.*

	Non-smokers, n					Smokers, n				
Genotype	Controls	Cases	OR (95% CI)[a]	Adjusted OR (95% CI)[b]	*p*-Value[c]	Controls	Cases	OR (95% CI)[a]	Adjusted OR (95% CI)[b]	*p*-Value
AA	223	61	1.00 (Reference)	1.00 (Reference)		56	24	1.00 (Reference)	1.00 (Reference)	
AG	64	17	0.97 (0.53-1.78)	0.98 (0.59-1.64)	0.9242	14	14	2.33 (0.97-5.63)	2.24 (1.23-3.68)	0.0565
GG	5	1	0.73 (0.08-6.38)	0.85 (0.21-5.92)	0.7760	1	4	9.33 (0.99-87.93)	8.31 (1.25-43.57)	**0.0210**
P_{trend}					0.9574					**0.0217**
Total	292	79				71	42			

CI: Confidence interval; OR: odds ratio. [a]Multivariate logistic regression analysis; [b]multivariate logistic regression analysis after adjustment for age, gender, alcohol drinking and *Helicobacter pylori* infection status; [c]based on chi-square test without Yates' correction. Significant *p*-values are shown in bold.

gastric cancer is very prevalent and causes many deaths. In literature, *MMP7* A-181G genotype has been examined for its association with a panel of cancer types including oral, esophageal, breast, colorectal, gallbladder, bladder, cervical cancer, renal cell carcinoma, leukemia, and most of all gastric cancer (26, 27, 29, 40, 47-58). The association of *MMP7* genotype with gastric cancer in the current study is very meaningful, but its significance was borderline from simply the genotype viewpoint. Its significance in those people with risky behavioral habits, smoking and alcohol drinking, was much higher. Negative findings for *MMP7* polymorphic effects in bladder cancer (48), renal cell carcinoma (57), oral cancer (40), colorectal cancer (27), and lung cancer (26) in Taiwanese indicate that *MMP7* may influence Taiwanese susceptibility to these diseases *via* other mechanisms such as regulation of translation or protein–protein interaction, and not simply from regulation at the transcriptional level *via* polymorphic variations in the promoter region.

There are several directions for further investigation of the role of *MMP7* in gastric cancer etiology. Our significant findings might be validated with more samples. Moreover, similarly designed studies in East-Asian countries with similar genetic backgrounds to Taiwanese may be pooled together for further meta-analyses. Insufficiency of primary cultured cells also restricts advancement. *MMP7* genotype–phenotype correlation might be revealed after phenotypic determination in aspects of its transcripts, protein level and activity in primary cultures of cells from tumoral and non-tumoral sites of patients with gastric cancer. In pilot experiments by our team, the culture of these primary cells is relatively more difficult than that of other types of cancer, such as oral and breast cancer. Similarly to the study here of behavioral risk factors, the contribution of *MMP7* genotype and phenotype to gastric cancer can also be further understood in the stratification of the gastric cancer population into several subgroups according to their clinical characters, such as gastric cancer stage and tumor location. A complete understanding of the *MMP7* genotype–phenotype in joint effects with diet and behavior of patients would be very helpful in understanding the role of *MMP7* in the etiology and development of gastric cancer.

In conclusion, to our knowledge, this is the first study which has provided evidence examining the association of polymorphisms at *MMP7* promoter sites A-181G and C-153T with gastric cancer risk in Taiwan. Our results suggest that the variant GG genotype of the promoter A-181G but not C-153T of *MMP7* significantly affects personal susceptibility to gastric cancer, especially for Taiwanese smokers.

Conflicts of Interest

All the Authors have declared no conflicts of interest in regard to this study.

Authors' Contributions

Research design: Fu CK, Chien YC and Chung HY; patient and questionnaire summaries: Fu CK and Yang MD; experimental work: Wang YC and Chang WS; statistical analysis: Chen JC, Hwang JJ and Yu CC; article writing: Tsai CW and Bau DT; review and revision: Chang WS, Tsai CW and Bau DT.

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