Contribution of matrix metalloproteinases-1 genotypes to gastric cancer susceptibility in Taiwan

Mei-Due Yang1,2,†, Kuo-Cheng Lin1,†, Meng-Chun Lu1,*, Long-Bin Jeng2, Chieh-Lun Hsiao2,3, Te-Cheng Yueh2,3, Chun-Kai Fu2,3, Hsin-Ting Li2,3, Shiou-Ting Yen2,3, Chia-Wen Lin2, Cin-Wun Wu2,

Su-Yi Pang2, Da-Tian Bau2,3,*, Fuu-Jen Tsai4,*

1Department of Clinical Nutrition, China Medical University Hospital, Taichung 404, Taiwan
2Terry Fox Cancer Research Laboratory, China Medical University Hospital, Taichung 404, Taiwan
3Graduate Institute of Biomedical Sciences, China Medical University, Taichung 404, Taiwan
4Department of Medical Research, China Medical University Hospital, Taichung 404, Taiwan

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1. Introduction

Gastric cancer (GC) is the fourth most common cancer and the second most frequent cause of death from cancer worldwide [1, 2]. Globally, it was estimated that about 800,000 deaths occurred annually, and more than 70% of GC cases occurred in developed and developing countries and half of cases occurred in Eastern Asia, for instance, mainland China and Taiwan [2]. The incidence of GC varies among different countries as a result of genetic, epigenetic and environmental factors, which the accurate mechanisms for gastric carcinogenesis remained unknown. In addition to those known environmental factors such as unhealthy diets, infectious agents (e.g., Helicobacter pylori) and pre-existing conditions (e.g., pernicious anemia, atrophic gastritis, and intestinal polyps) [3, 4], the inherited genetic variations may play an important role in determining individual susceptibility to GC but are largely unrevealed, especially for the etiology of GC in Taiwan [5-12].

It is widely believed that GC carcinogenesis in a multicellular and multi-stage process in which the destruction of the extracellular microenvironment is a requisite for the transformation of normal tissues to tumors [13]. Hence, molecular investigations and understanding of the extracellular microenvironment and its deregulation during neoplasia is a key step to reveal the whole processes and mechanisms of malignancy. Matrix metalloproteinases (MMPs), also known as interstitial collagenses, are produced by both tumor and normal cells. MMPs may alter the microenvironment by degrading extracellular matrix, and subsequent cellular signals lead to the early stages of tumor formation [14]. Several of the MMPs have the unique activities to degrade the specific interstitial collagens (e.g., I, II, III, VII, VIII, X) and gelatin [15]. Among the various MMPs, MMP1 is the most ubiq-
uitously expressed one [16] and its overexpression is associated with several specific pathological status, including inflammation, tumor invasion and metastasis [17]. The upregulation of MMP1 mRNA has been found in the tissues from the patients of various types of cancer, such as colorectal cancer, esophageal cancer and GC [18-22]. In addition, overexpression of MMP1 protein is associated with poor prognosis of esophageal cancer and colorectal cancer [20, 21]. This MMP1 overexpression may be attributed to the juxtaposition of transcription factor binding sites and cooperativity among the factors that bind to these sites within the promoter region of the MMP1 gene [23].

The most famous polymorphic site in the promoter region of MMP1 is rs1799750, which contains a guanine insertion/deletion polymorphism (1G/2G polymorphism) at position -1607 which generates the sequence 5’-GGA-3’ which has a 2G allele. The presence of a 2G polymorphism could have higher transcriptional activity of endogenous MMP1 than that with only one G because the guanine insertion creates a binding site for a member of the Ets transcription factor family. Clinically, the 2G allele was found to contribute to increased invasiveness of endometrial carcinomas, and to the development of ovarian cancer, lung cancer, and colorectal cancer [24-31].

Accordingly, we aimed at exploring whether the genotypes of MMP1 are associated with GC risk among Taiwanese. To test this hypothesis, we determined the genotypic frequency of three polymorphisms of the MMP1 gene at -1607 rs1799750 among a Taiwanese population, and analyzed its contribution to GC susceptibility and interactions with commonly known risk factors for GC, such as alcohol drinking, cigarette smoking, and Helicobacter pylori infection. To our knowledge, this is the first study carried out to evaluate the MMP1 genotypes in the high prevalence Taiwanese population.

2. Materials and methods

2.1. Study population and sample collection

One hundred and twenty one patients diagnosed with GC were recruited at the outpatient clinics of general surgery between 2005-2007 at the China Medical University Hospital, Taichung, Taiwan, Republic of China. The mean age of the gastric cancer patients were 51.26 (SD = 9.42) years. There were 56 females and 65 males. All patients voluntarily participated, completed a self-administered questionnaire and provided peripheral blood samples. Matched with age and gender, three hundreds and thirty non-cancer healthy people as controls were selected from the Health Examination Cohort of the hospital and the same questionnaires were recorded. Our study was approved by the Institutional Review Board of the China Medical University Hospital and written-informed consent was obtained from all participants with the help of Tissue Bank.

2.2. Genotyping assays

Genomic DNA was prepared from peripheral blood leucocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan). The forward and reverse primers for MMP1 promoter -1607 genotyping were 5’-TGACTTTTAAAAACATAGCTATGT-3' and 5’-GATTGATTTGAGATAATGCATAGC-3’, respectively. The polymerase chain reaction (PCR) cycling conditions were: one cycle at 94°C for 5 min; 35 cycles of 94°C for 30 s, 58°C for 30 s and 72°C for 30 s; and a final extension at 72°C for 10 min. After amplification, the PCR products were subject to digestion with Alu I restriction endonuclease for 2 h at 37°C and separation of 3% agarose gel electrophoresis. The genotypes were identified as homozygous 2G/2G (269 bp), heterozygous 1G/2G (269, 241 and 28 bp) and homozygous 1G/1G (241 and 28 bp). All the genotypic process was repeated by two researchers independently and blindly as previously performed, with results being 100% concordant. All the processes in MMP1 promoter -1607 genotyping are much similar to the previous papers we published [32, 33].

2.3. Statistical analyses

Student’s t-test was used for the comparison of ages between the case and the control groups. Pearson’s Chi-square test was used to compare the distribution of the MMP1 promoter -1607 genotypes among the subgroups. The associations between the MMP1 promoter -1607 genotypes and GC risk were estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) from logistic regression analysis. Any analyzing outcome with P < 0.05 was considered statistically significant.

3. Results

The selected characteristics of the GC patient group together with the control group are summarized in Table 1. The average BMI is of no difference (P > 0.05) between the control and GC patient groups. The percentage of alcohol consumers seemed to be higher in the GC patient group (32.2%) than that in the control group (23.1%), and the percentage of heavy drinkers are more than twice in the GC patient group (9.9%) than that in the control group (4.4%). As for the cigarette smoking habit analysis, there were significant trends that the GC patient group has higher percentage of cigarette consumers, especially heavy smokers, than the control group (34.7% vs. 19.6%, and 10.7% vs. 1.7%, respectively). As for the infection of Helicobacter pylori, 70.2% of the GC patients were positive, higher than 51.8% for the control subjects (P < 0.05). To sum up, the heavy consumption of alcohol and cigarette, in addition to the infection of Helicobacter pylori, are found to be the environmental factors contribute to increased GC risk in Taiwan.

The frequencies of the genotypes of MMP1 promoter -1607 polymorphisms in the GC patient and control groups are presented in Table 2. Compared with the 2G/2G genotype of MMP1 promoter -1607 as the reference group, there was no obvious increased risk in the 1G/2G or 1G/1G groups (OR = 0.88, 95% CI = 0.55-1.40, P = 0.5826; OR = 1.04, 95% CI = 0.60-1.79, P = 0.8970). The recessive and dominant models in the carrier comparison analysis showed a non-significant level for the variant 1G allele at MMP1 promoter -1607 to behave as a risk determinant for GC (Table 2). The frequencies of the alleles for the MMP1 promoter -1607 polymorphism between GC patient and control groups are presented in Table 3. Supporting the findings in Table 2, the variant 1G allele at XPD codon 312 was not significantly associated with increased GC cancer risk (OR = 1.01, 95% CI = 0.75-1.35, P = 0.9702) (Table 3).

The genetic-environment interaction of genotype of MMP1 promoter -1607 and alcohol consumption for the risk of GC is presented in Table 4. Among those non-alcohol drinkers, the variant 1G allele could not increase the risk of gastric cancer (OR = 0.80, 95% CI = 0.48-1.32, P = 0.3866). The contribution of alco-
hol consumption behavior to gastric cancer risk was at a slightly increased level for those people without 1G allele at MMP1 promoter -1607 polymorphic site (OR = 1.22, 95% CI = 0.51-2.89, \( P = 0.6593 \)), while for those with alcohol consumption behavior and 1G allele at MMP1 promoter -1607, no synergistically increased gastric cancer risk was found (OR = 1.44, 95% CI = 0.80-2.58, \( P \))

### Table 1 – Selected Characteristics of the control and gastric cancer patient groups.

| Character                  | Cases (n = 121) | Controls (n = 363) | \( P \)-value\(^a\) |
|----------------------------|-----------------|--------------------|---------------------|
| Age (SD)                   | 51.3 (9.4)      | 53.2 (8.1)         | 0.8918              |
| Gender (female/male)       | 56/65           | 168/195            | 1.0000              |
| BMI average (SD)           | 27.1 (5.8)      | 26.7 (6.6)         | 0.9344              |
| Alcohol consume            |                 |                    |                     |
| Number (%)                 | 39 (32.2)       | 84 (23.1)          | 0.0538              |
| Heavy drinker (%)\(^b\)    | 12 (9.9)        | 11 (4.4)           | 0.0049\(^*\)        |
| Cigarette consume          |                 |                    |                     |
| Number (%)                 | 42 (34.7)       | 71 (19.6)          | 0.0012\(^*\)        |
| Heavy smoker (%)\(^c\)     | 13 (10.7)       | 6 (1.7)            | 0.0001\(^*\)        |
| H. pylori infection        |                 |                    |                     |
| Number (%)                 | 85 (70.2)       | 188 (51.8)         | 0.0005\(^*\)        |
| Tumor location             |                 |                    |                     |
| Upper (%)                  | 17 (14.0)       |                    |                     |
| Middle (%)                 | 54 (44.6)       |                    |                     |
| Lower (%)                  | 50 (41.3)       |                    |                     |

\(^a\)\(P\)-value based on \( \chi^2 \) test.

\(^b\)Drunk more than twice weekly or more than 100 ml per day for at least half year.

\(^c\)More than 1 pack per day for at least half year.

### Table 2 – Distribution of matrix metalloproteinase-1 (MMP1) promoter -1607 genotypes among the controls and patients with gastric cancer.

| Genotype     | Cases (n = 121) | Controls (n = 363) | Odds Ratio (95% CI)\(^a\) | \( P \)-value\(^b\) |
|--------------|-----------------|--------------------|---------------------------|---------------------|
| MMP1 -1607   |                 |                    |                           |                     |
| 2G/2G        | 43 (35.5)       | 123 (33.9)         | 1.00 (reference)          |                     |
| 1G/2G        | 49 (40.5)       | 160 (44.1)         | 0.88 (0.55-1.40)          | 0.5826              |
| 1G/1G        | 29 (24.0)       | 80 (22.0)          | 1.04 (0.60-1.79)          | 0.8970              |
| \(P\)-value for trend |                 |                    |                           | 0.7821              |
| Carrier comparison |                      |                    |                           |                     |
| 2G/2G + 1G/2G| 92 (76.0)       | 283 (78.0)         | 1.00 (reference)          |                     |
| 1G/1G        | 29 (24.0)       | 80 (22.0)          | 1.12 (0.69-1.81)          | 0.6601              |
| 2G/2G + 1G/1G| 43 (35.5)       | 123 (33.9)         | 1.00 (reference)          |                     |
| 1G/1G + 1G/2G| 78 (64.5)       | 240 (66.1)         | 0.93 (0.60-1.43)          | 0.7401              |

\(^a\)CI, confidence interval; \(^b\)\(P\)-value based on \( \chi^2 \) test without Yate’s correction.

### Table 3 – Allele frequencies for matrix metalloproteinase-1 (MMP1) promoter -1607 in the control and gastric cancer patient groups.

| Allele    | Cases (n = 242) | Controls (n = 726) | Odds Ratio (95% CI)\(^a\) | \( P \)-value\(^b\) |
|-----------|-----------------|--------------------|---------------------------|---------------------|
| MMP1 -1607|                 |                    |                           |                     |
| 2G        | 135 (55.8)      | 406 (55.9)         | 1.00 (reference)          | 0.9702              |
| 1G        | 107 (44.2)      | 320 (44.1)         | 1.01 (0.75-1.35)          |                     |

\(^a\)CI, confidence interval; \(^b\)\(P\)-value based on \( \chi^2 \) test without Yate’s correction.
The genetic-environment interaction of genotype of MMP1 promoter -1607 and cigarette consumption for the risk of gastric cancer is presented in Table 5. Among those non-cigarette smokers, the variant 1G allele could slightly decrease the risk of gastric cancer (OR = 0.80, 95% CI = 0.48-1.33, P = 0.3911). The contribution of cigarette consumption behavior to gastric cancer risk was 1.77- and 1.96-fold for those people without (95% CI = 0.77-4.08, P = 0.1770) or with 1G allele at MMP1 promoter -1607 (95% CI = 1.08-3.55, P = 0.2223) (Table 5).

Among people not infected with *Helicobacter pylori*, the carriage of MMP1 promoter -1607 allele 1G was not associated with an decreased risk of gastric cancer (OR = 0.84, 95% CI = 0.41-1.73, P = 0.6387). On the contrary, *Helicobacter pylori* infection was associated with an increased risk of gastric cancer among those without variant 1G allele of MMP1 promoter -1607 (OR = 2.58, 95% CI = 1.27-5.26, P = 0.0078). At the same time, *Helicobacter pylori*-infected individuals who were carriers of MMP1 promoter -1607 allele 1G also exhibited an increased risk of gastric cancer (OR = 1.84, 95% CI = 1.02-3.33, P = 0.0423). In summary, the results in Table 4, 5 and 6 indicated a synergistic interaction of MMP1 promoter -1607 allele 1G with cigarette smoking and *Helicobacter pylori* infection, but not with alcohol drinking, in the development of gastric cancer.

### 4. Discussion

In the present study, we have investigated the association of MMP1 promoter -1607 genotypes, with gastric cancer susceptibility in Taiwan. The results demonstrated that the MMP1 promoter -1607 genotypes were not significantly associated with risk of developing gastric cancer in Taiwan (Tables 2, 3). To the best of our knowledge, this is the first epidemiology study based on molecular genetics to find the significant association between MMP1 genotypes and the susceptibility to gastric cancer with the analysis of the gene-environment interaction in Taiwan. Interestingly, a synergistic interaction of MMP1 promoter -1607 allele 1G with cigarette smoking (Table 5) and *Helicobacter pylori* infection (Table 6), but not with alcohol drinking (Table 4), in the development of gastric cancer. In 2004, Matsumura and his coworkers firstly examined the contribution of MMP1 genotypes to GC risk [34], but findings that the genotypes were neither associated with the GC risk nor the prognosis such as lymph node metastasis and clinical stages. From that time, a few reports focused on investigating the associations of three common MMP1 polymorphism, promoter -1607, with GC risk among different ethnicities, but with conflicting and inclusive results [35-38]. We have summarized the characteristics of each of the literature in the last Table of this article, in addition to our current findings (Table 7).

In literature, there were a few studies providing evidence for the increased risk of GC among cigarette smokers [9, 39-43], but some others were not [44, 45]. In the current study from the epidemiologic viewpoint, we have also found that cigarette smoking may also contribute to the risk of GC (P = 0.0012), especially for those heavy smokers (P = 0.0001) (Table 1). Similarly, we have found that cigarette consumption behavior among those carrying the 1G allele at MMP1 promoter -1607 were of 1.96-fold (95% CI = 1.08-3.55, P = 0.0265) increased risk of developing GC. In 2012, Smyth and his colleagues have investigated the contribution of tobacco usage history to their 5-year survival status, finding that smoking was a risk factor of gastric cancer and associated with worse 5-year survival [46]. For those who smoked less than 20 pack-years (defined as light smokers) and equal to or more than 20 pack-years (defined as heavy smokers), their GC disease-specific survival, 5-year disease-free survival and overall survival rates were less than the non-smokers [46]. To sum up, the behavior of cigarette smoking may not only contribute to individual GC risk, but to overall death rates after the undergoing of surgical resection. The detail interaction of MMP1 genotype with smoking

### Table 4 – Combined analysis of MMP1 promoter -1607 genotype and alcohol consumption for gastric cancer risk.

| XPD codon 312 allele A carrier | Alcohol consumption | Controls/Cases | Odds Ratio (95% CI)* | P-valuea |
|--------------------------------|---------------------|---------------|---------------------|----------|
| (−)                           | (−)                 | 101/34        | 1.0 (reference)     |          |
| (+)                           | (−)                 | 178/48        | 0.80 (0.48-1.32)    | 0.3866   |
| (−)                           | (+)                 | 22/9          | 1.22 (0.51-2.89)    | 0.6593   |
| (+)                           | (+)                 | 62/30         | 1.44 (0.80-2.58)    | 0.2223   |

*a*, CI, confidence interval; bP-value based on χ² test.

### Table 5 – Combined analysis of MMP1 promoter -1607 genotype and cigarette consumption for gastric cancer risk.

| XPD codon 312 allele A carrier | Cigarette consumption | Controls/Cases | Odds Ratio (95% CI)* | P-valuea |
|--------------------------------|-----------------------|---------------|---------------------|----------|
| (−)                           | (−)                   | 103/32        | 1.0 (reference)     |          |
| (+)                           | (−)                   | 189/47        | 0.80 (0.48-1.33)    | 0.3911   |
| (−)                           | (+)                   | 20/11         | 1.77 (0.77-4.08)    | 0.1770   |
| (+)                           | (+)                   | 51/31         | 1.96 (1.08-3.55)*   | 0.0265*  |

*a*, CI, confidence interval; bP-value based on χ² test.
behavior on GC etiology needs further investigations.

As for *Helicobacter pylori* infection, the data in Table 1 showed that about half (51.8%) of the Taiwanese people were infected, which were significantly lower than 70.2% in the gastric cancer patients (*P* = 0.0005) (Table 1). The stratified analysis showed that among those people without the 1G allele at MMP1 promoter -1607, the status of *Helicobacter pylori* infection has caused a significant higher risk of GC to them (OR = 2.58, 95% CI = 1.27-5.26, *P* = 0.0078) (Table 6). The *Helicobacter pylori* infection would perform an increase of GC risk for those people with the 1G allele at MMP1 promoter -1607 (OR = 1.84, 95% CI = 1.02-3.33, *P* = 0.0423) from those people without *Helicobacter pylori* infection (*P* = 0.6387).

Thus, the MMP1 may cause an alteration of extracellular matrix, interact with the consequence of *Helicobacter pylori* infection, and determine the GC initiation and development. The detail mechanism needs further investigations.

These results suggested that genetic variants of MMP1 promoter -1607 may play a critical role in GC etiology indirectly via the alteration of extracellular matrix components, and *Helicobacter pylori* infection status. In conclusion, our findings suggest that although the MMP1 promoter -1607 genotype itself was not associated with risk to GC, the 1G allele of MMP1 promoter -1607 is still an useful marker combined with cigarette smoking, and *Helicobacter pylori* infection status, for individualized early detection, prevention and anticancer intervention.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

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