**Contribution of Matrix Metalloproteinase-1 Genotypes to Colorectal Cancer in Taiwan**

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**Abstract.** Background/Aim: Matrix metalloproteinase-1 is responsible for extracellular matrix regulation, and its genetic role in colorectal cancer (CRC) is unclear. The aim of the study was to investigate the contribution of Matrix metalloproteinase-1 genotypes to CRC risk in Taiwan. Materials and Methods: A total of 362 cases and 362 controls were included and their MMP-1 -1607 (rs1799705) genotypes were examined. The environmental factors and clinical-pathological records were also analyzed. Results: The genotypic frequency of MMP-1 rs1799750 were different between the CRC and control groups (p for trend=0.0083). 1G/2G and 1G/1G were associated with lower risk (p=0.0438 and 0.0030, adjusted OR=0.73 and 0.54, 95% CI=0.54-0.90 and 0.37-0.83). Among non-smokers, those with 1G/2G and 1G/1G genotypes were at 0.70- and 0.48-fold odds of having CRC. Among non-alcohol drinkers, people with 1G/2G and 1G/1G genotypes were at 0.71- and 0.54-fold odds. The 1G/1G genotype were statistically lower among CRC patients with lymph node metastasis (7.2%) than those without (19.0%). Conclusion: The genotypes at MMP-1 rs1799705 play a role in determining susceptibility to CRC risk in Taiwan.

Colorectal cancer (CRC), the second most common occurring cancer in females and the third most common cancer in males, it has over 1.8 million new cases in 2018 all over the world (1-3). The incidence and mortality rates of CRC vary by a factor of as high as ten (2-4). From the viewpoint of epidemiology, the environmental factors such as meat consumption, cigarette smoking, and exposure to carcinogens contribute to about 85% of CRC etiology (5, 6). At the same time, at least 15-20% of CRC etiology could be traced with familial cancer history (7, 8). In Taiwan, the incidence rate of CRC is on top of all types of cancer, while the mortality rate of CRC has been listed as the third among all types of cancer. With the efforts of some scientists, specific biomarkers for CRC have been reported within the decade (9-13). However, the interactions between genomic and environmental risk factors still need further investigation.

Matrix metalloproteinases (MMPs), is a family of proteins that degrade extracellular matrix proteins including collagen, laminin, and fibronectin, and so on (14). They also play a critical role in cell proliferation, differentiation, apoptosis, invasion, migration and immune responses (15, 16). In recent years, it has been shown that genotypic variants of MMPs were associated with the susceptibility of several types of cancer (17-20). Among these MMPs, MMP-1 is the first vertebrate collagenase to be purified and cloned, and is encoded by the MMP1 gene (21, 22). The most commonly studied MMP-1 polymorphism is rs1799750, which is located at -1607 of the promoter region. The variants may consist the "2G" insertion polymorphism, which has been reported to lead to higher levels of MMP-1 in the serum, potentially to higher levels of collagen breakdown than the 1G genotype (23). In a meta-analysis, it was concluded that people who have MMP-1 rs1799750 2G/2G genotypes may have a slightly higher metastasis rate (24). As far as CRC is

This article is freely accessible online.

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**Key Words:** Colorectal cancer, genotype, MMP-1, polymorphism, Taiwan.
Materials and Methods

Collection of 362 CRC cases and 362 controls. The investigated population has been recruited as described in our previous studies (9-12). Concisely, CRC cases have been recruited at the outpatient clinics of general surgery by well-trained colleagues. The pathological-clinical data of each participant were defined, graded and recorded by experienced doctors. We reselected some of the controls to match well the control and case group by age and gender. All the procedures were approved and supervised by the Institutional Review Board of the China Medical University Hospital (IRB project identification coding number: DMR99-IRB-108).

MMP-1 rs1799750 genotyping methodology. The genomic DNA from peripheral blood leukocytes of all participants were extracted and stored at −80°C as previously published (9, 10). The MMP-1 rs1799750 genotyping methodology is the same as previously reported (17, 19). The polymerase chain reaction (PCR) conditions set for MMP-1 rs1799750 genotyping were one cycle at 94°C for 5 min; 35 cycles at 94°C for 30 sec, one cycle at 57°C for 30 sec and one cycle at 72°C for 30 sec and a final extension at 72°C for 10 min.

Statistical analysis. Pearson’s Chi-square test without Yates’ correction was applied to compare the distribution of MMP-1 genotypic and allelic distributions between CRC and control groups. The associations between the MMP-1 genotypes and CRC risk were estimated by odds ratios (ORs) as well as their 95% confidence intervals (CIs) from logistic regression analysis.

Results

Basic indexes between CRC patient and control groups. The distribution of age and gender for the 362 CRC patients and 362 non-cancer healthy controls is shown and compared in Table I. There were 203 (56.1%) males and 159 (43.6%) females in the CRC group, and we matched the age and gender very well, so there was no significant difference between the two groups as for the frequencies of age or gender (both p>0.05) (Table I). As for the personal habits, 91 (25.1%) of the CRC group had smoking habits, while 44 (12.2%) had alcohol drinking habits. They were not significantly different from those of the control group (23.2% had smoking and 14.1% had alcohol drinking habit, respectively).}

| Characteristic                      | Controls (n=362) | Cases (n=362) | p-Valuea |
|-------------------------------------|-----------------|--------------|----------|
| Age (years)                         |                 |              |          |
| ≤60                                 | 95 (26.2%)      | 95 (26.2%)   | 1.0000   |
| >60                                 | 267 (73.8%)     | 267 (73.8%)  |          |
| Gender                              |                 |              |          |
| Male                                | 203 (56.1%)     | 203 (56.1%)  | 1.0000   |
| Female                              | 159 (43.6%)     | 159 (43.9%)  |          |
| Smoking habits                      |                 |              |          |
| Yes                                 | 84 (23.2%)      | 91 (25.1%)   | 0.5434   |
| No                                  | 278 (76.8%)     | 271 (74.9%)  |          |
| Alcohol drinking habits             |                 |              |          |
| Yes                                 | 51 (14.1%)      | 44 (12.2%)   | 0.4410   |
| No                                  | 311 (85.9%)     | 318 (87.8%)  |          |
| BMI                                 |                 |              |          |
| <24                                 | 175 (48.3%)     | 193 (53.3%)  | 0.1809   |
| ≥24                                 | 187 (51.7%)     | 169 (46.7%)  |          |
| Tumor size (cm)                     |                 |              |          |
| <5                                  | 195 (53.9%)     |              |          |
| ≥5                                  | 167 (46.1%)     |              |          |
| Location                            |                 |              |          |
| Colon                               | 257 (71.0%)     |              |          |
| Rectum                              | 105 (29.0%)     |              |          |
| Lymph node involvement              |                 |              |          |
| Negative                            | 210 (58.0%)     |              |          |
| Positive                            | 152 (42.0%)     |              |          |

SD, Standard deviation; BMI, body mass index. aBased on Chi-square test without Yates’ correction.
Association analysis of MMP-1 rs1799750 genotypes with CRC risk. The allelic frequency analysis of MMP-1 rs1799750 with CRC risk was performed and is presented in Table II. Consistent with the major finding in Table II, there is an obvious difference in the distribution of allelic frequencies between the CRC and healthy control groups regarding MMP-1 rs1799750 (Table III). In detail, those subjects carrying 1G allele at MMP-1 rs1799750 were lower in the CRC group (34.9%) than those in the control group (43.2%) (adjusted OR=0.73, 95%CI=0.52-0.81, p=0.0012) (Table III).

Interaction of personal habits with MMP-1 rs1799750 genotype on CRC risk. Since cigarette smoking and alcohol drinking habits serve as risk factors for CRC in Taiwan, we were interested to examine the interactions between the genotype of MMP-1 rs1799750 with personal cigarette smoking and alcohol drinking status. Firstly, among nonsmokers, those with MMP-1 rs1799750 1G/2G and 1G/1G genotypes were at 0.70- and 0.48-fold odds of having CRC (95%CI=0.48-1.01 and 0.29-0.78, p=0.0551 and 0.0027, respectively), while there was no synergistic or additive effect observed among the smokers (Table IV). After adjusting for age, gender, alcohol drinking and BMI status, the statistical significance still existed for the homozygous

### Table II. Distribution of matrix metalloproteinase-1 rs1799750 genotypic frequencies among the colorectal cancer patients and healthy controls.

| Genotype   | Cases, n (%) | Controls, n (%) | Adjusted OR (95%CI)a | p-Valueb |
|------------|--------------|-----------------|----------------------|----------|
| rs1799750  |              |                 |                      |          |
| 2G/2G      | 160 (44.2)   | 124 (34.3)      | 1.00 (Reference)     |          |
| 1G/2G      | 151 (41.7)   | 163 (45.0)      | 0.73 (0.54-0.90)     | 0.0438*  |
| 1G/1G      | 51 (14.1)    | 75 (20.7)       | 0.54 (0.37-0.83)     | 0.0083*  |

p_trend: p for trend. *Data have been adjusted for confounding factors age, gender, smoking, alcohol consumption and BMI status. bBased on Chi-square test without Yates’ correction. *Bold values indicate statistical significance.

### Table III. Allelic frequencies for matrix metalloproteinase-1 rs1799750 polymorphisms among colorectal cancer patients and healthy controls.

| Allelic type | Cases, n (%) | Controls, n (%) | Adjusted OR (95%CI)a | p-Valueb |
|--------------|--------------|-----------------|----------------------|----------|
| rs1799750    |              |                 |                      |          |
| Allele 2G    | 471 (65.1)   | 411 (56.8)      | 1.00 (Reference)     |          |
| Allele 1G    | 253 (34.9)   | 313 (43.2)      | 0.73 (0.52-0.81)     | 0.0012*  |

OR: Odds ratio; CI: confidence interval. aData have been adjusted for confounding factors age, gender, smoking, alcohol consumption and BMI status. bBased on Chi-square test without Yates’ correction. *Bold values indicate statistical significance.

respectively) (Table I). The control group had 51.7% people with BMI ≥24, while case group had 46.7% (p=0.1809) (Table I).
genotypic distributions and age, gender, BMI, tumor size or percentages of 1G/1G genotype of involvement (19.0%, location (all metastasis (7.2%) than those without lymph node correlation was observed between genotypes of MMP-1 rs1799750 and clinicopathological features among the 362 CRC patients were analyzed and the results are shown in Table VI. No statistically significant correlation was observed between A MMP-1 rs1799750 genotypic distributions and age, gender, BMI, tumor size or location (all p>0.05) (Table VI). Interestingly, the percentages of 1G/1G genotype of MMP-1 rs1799750 were statistically lower among the CRC patients with lymph node metastasis (7.2%) than those without lymph node involvement (19.0%, p=0.0052) (Table VI).

### Discussion

MMPs play a critical role in the metabolism of extracellular matrix components, and any imbalance of the extracellular microenvironment may be related to initiation and progression of cancer. MMP-1 specifically breaks down the interstitial collagens, type I, II, III, VI and X. It is such an essential protein that no knockout murine studies are available so far. Revealing the association of MMP-1 genotypes with CRC risk will not only advance our understanding of the mechanisms underlying tumorigenesis, but also facilitate the improvement of novel therapeutics.

The positive association of MMP-1 rs1799750 genotypes with CRC risk (Tables II and III) is consistent with previous reports in childhood leukemia (28), gastric cancer (29) nasopharyngeal carcinoma (30) and pterygium (19). In a meta-analysis investigating more than 38,000 subjects, the results also indicated that the genotypes of MMP-1 rs1799750 may be associated with colorectal, head and neck and renal cancer risk (31). However, in other types of cancers, the genotypes of MMP-1 rs1799750 may not directly contribute to susceptibility determination (17, 32-35), which indicated that the MMP-1 rs1799750 genotypes

### Table IV. Odds ratio for matrix metalloproteinase-1 rs1799750 genotype and colorectal cancer after stratification by smoking status.

| Genotype | Non-smokers, n | OR (95% CI)a | aOR (95% CI)b | p-Value | Smokers, n | OR (95% CI)a | aOR (95% CI)b | p-Value |
|----------|----------------|--------------|--------------|---------|------------|--------------|--------------|---------|
|          | Controls       | Cases        | Controls     | Cases   |            | Controls     | Cases        |         |
| 2G/2G    | 94             | 122          | 1.00 (ref)   | 1.00 (ref) | 30         | 38           | 1.00 (ref)   | 1.00 (ref) |
| 1G/2G    | 124            | 112          | 0.70 (0.48-1.01) | 0.68 (0.45-1.01) | 0.0551   | 39           | 39           | 0.79 (0.41-1.52) | 0.72 (0.38-1.47) | 0.4776 |
| 1G/1G    | 60             | 37           | 0.48 (0.29-0.78) | 0.45 (0.27-0.75) | 0.0027* | 15           | 14           | 0.74 (0.31-1.76) | 0.71 (0.30-1.68) | 0.4916 |
| Total    | 278            | 271          |              |         | 84         | 91           |              |         |

CI, Confidence interval; aOR, adjusted odds ratio. aBy multivariate logistic regression analysis; bby multivariate logistic regression analysis after adjusted for confounding factors age, gender, alcohol consumption and BMI status; *Bold values indicate statistical significance.

### Table V. Odds ratios for matrix metalloproteinase-1 rs1799750 genotype and colorectal cancer after stratification by alcohol drinking status.

| Genotype | Non-drinkers, n | OR (95% CI)a | aOR (95% CI)b | p-Value | Drinkers, n | OR (95% CI)a | aOR (95% CI)b | p-Value |
|----------|-----------------|--------------|--------------|---------|-------------|--------------|--------------|---------|
|          | Controls        | Cases        | Controls     | Cases   |          | Controls     | Cases        |         |
| 2G/2G    | 105             | 139          | 1.00 (ref)   | 1.00 (ref) | 19         | 21           | 1.00 (ref)   | 1.00 (ref) |
| 1G/2G    | 143             | 134          | 0.71 (0.50-1.00) | 0.69 (0.46-1.02) | 0.0501   | 20           | 17           | 0.77 (0.31-1.88) | 0.75 (0.33-1.90) | 0.5655 |
| 1G/1G    | 63              | 45           | 0.54 (0.34-0.85) | 0.51 (0.31-0.81) | 0.0080* | 12           | 6            | 0.45 (0.14-1.44) | 0.49 (0.19-1.53) | 0.1758 |
| Total    | 311             | 318          |              |         | 51         | 44           |              |         |

CI, Confidence interval; aOR, adjusted odds ratio. aBy multivariate logistic regression analysis; bby multivariate logistic regression analysis after adjusted for confounding factors age, gender, smoking and BMI status; *Bold values indicate statistical significance.

| Genotype | Non-smokers, n | OR (95% CI)a | aOR (95% CI)b | p-Value | Smokers, n | OR (95% CI)a | aOR (95% CI)b | p-Value |
|----------|----------------|--------------|--------------|---------|------------|--------------|--------------|---------|
| 1G/1G (adjusted OR=0.45, 95%CI=0.27-0.75) (Table IV). Secondly, among non-alcohol drinkers, people with MMP-1 rs1799750 1G/2G and 1G/1G genotypes were at 0.71- and 0.54-fold odds of having CRC (95%CI=0.50-1.00 and 0.34-0.85, p=0.0501 and 0.0080, respectively), while there was no synergistic or additive effect observed among alcohol drinkers (Table V). After adjusting for age, gender, cigarette smoking and BMI status, the statistical significance still existed for the homozygous 1G/1G (adjusted OR=0.51, 95%CI=0.31-0.81, Table V).

**Correlation between genotypes of MMP-1 rs1799750 and clinicopathological features.** The correlations between genotypes of MMP-1 rs1799750 and clinicopathological features among the 362 CRC patients were analyzed and the results are shown in Table VI. No statistically significant correlation was observed between A MMP-1 rs1799750 genotypic distributions and age, gender, BMI, tumor size or location (all p>0.05) (Table VI). Interestingly, the percentages of 1G/1G genotype of MMP-1 rs1799750 were statistically lower among the CRC patients with lymph node metastasis (7.2%) than those without lymph node involvement (19.0%, p=0.0052) (Table VI).
may be indirectly involved in carcinogenesis. The detailed mechanisms of how MMP-1 rs1799750 genotypes interact with other molecules leading to CRC need further investigation. One possible explanation is that MMP-1 rs1799750 2G/2G genotype may elevate the transcriptional activity of MMP-1, leading to a higher expression of MMP-1 in the tissue, which activates the breakdown of collagens (23). The possible mechanism make sense that the 1G/1G genotype at MMP-1 rs1799750 may be associated with a lower risk of local lymph node metastasis (Table VI).

There were so many environmental or clinical factors involved in CRC risk, such as age, gender, familial CRC history, diet, alcohol consumption, and obesity, tumor site, size, grade, histologic type, TNM stage, and carcinoembryonic antigen (CEA) level, and they all have been reported to affect the overall survival of CRC patients (36-39). But the study is conducted with non-smoking (Table IV) and non-alcohol drinking habits to influence the CRC risk needs further investigation.

In conclusion, we provided evidence for the association of polymorphisms at MMP-1 rs1799750 with CRC risk. Our results suggest that the 1G/2G and 1G/1G genotypes of the rs1799750 confer personal susceptibility to risk among Taiwanese. These polymorphisms may also serve as predictors for better prognosis, such as lower rate of metastasis.

Conflicts of Interest

The Authors have declared no conflicts of interest regarding this study.

Authors’ Contributions

Research design: Wu MH, Yueh TC and Chang WS; patient and questionnaire summaries: Wu MH, Yueh TC and Yang MD; experimental work: Chang WS and Tsai CW; statistical analysis: Fu CK and Yu CC; article writing: Tsai CW and Bau DT; review and revision: Bau DT.

Acknowledgements

The Authors are grateful to Yu-Chen Hsiau, Yu-Ting Chin and Tai-Lin Huang for their excellent technical assistance. All the participants including those who were not selected into the control group of the study are appreciated. This study was supported mainly by Taichung Armed Forces General Hospital (grant number: TCAFGH-D-109018). The funders had no role in study design, data collection, statistical analysis, or decision to publish or preparation of the manuscript.

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Table VI. Correlation between matrix metalloproteinase-1 rs1799750 genotypes and clinicopathological properties of 362 colorectal cancer patients.

| Characteristics               | Case number | Genotypes | p-Value* |
|-------------------------------|-------------|-----------|----------|
|                               | 2G/2G (%)   | 2G/1G (%) | 1G/1G (%) |< 0.05 |
| Age (years)                   |             |           |          |
| ≥60                           | 95          | 36 (37.9) | 40 (42.1) | 19 (20.0) | 0.1131 |
| >60                           | 267         | 124 (46.4)| 111 (41.6)| 32 (12.0) |          |
| Gender                        |             |           |          |
| Male                          | 203         | 85 (41.9) | 88 (43.3) | 30 (14.8) | 0.6007 |
| Female                        | 159         | 75 (47.2) | 63 (39.6) | 21 (13.2) |          |
| BMI                           |             |           |          |
| <24                           | 193         | 86 (44.6) | 77 (39.9) | 30 (15.5) | 0.6185 |
| ≥24                           | 169         | 74 (43.8) | 74 (43.8) | 21 (12.4) |          |
| Tumor size                    |             |           |          |
| <5 cm                         | 195         | 86 (44.1) | 78 (40.0) | 31 (15.9) | 0.5273 |
| ≥5 cm                         | 167         | 74 (44.3) | 73 (43.7) | 20 (12.0) |          |
| Location                      |             |           |          |
| Colon                         | 257         | 111 (43.2)| 107 (41.6)| 39 (15.2) | 0.6226 |
| Rectum                        | 105         | 49 (46.7) | 44 (41.9) | 12 (11.4) |          |
| Lymph node involvement        |             |           |          |
| Negative                      | 210         | 90 (42.9) | 80 (38.1) | 40 (19.0) |          |
| Positive                      | 152         | 70 (46.1) | 71 (46.7) | 11 (7.2)  | 0.0052* |

*aBased on Chi-square test without Yates’s correction; *Bold value indicates statistical significance.
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Received January 19, 2021
Revised February 4, 2021
Accepted February 15, 2021