Contribution of Matrix Metalloproteinase-2 Promoter Genotypes to Nasopharyngeal Cancer Susceptibility and Metastasis in Taiwan

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Abstract. Background/Aim: Matrix metalloproteinase 2 (MMP2) is up-regulated in many cancers. However, the association of MMP2 genotype to nasopharyngeal cancer (NPC) susceptibility in Taiwan remains elusive. Materials and Methods: In this study, the role of MMP2 promoter C-1306T (rs243865) and C-735T (rs2285053) genotypes were investigated among 208 NPC patients and 416 healthy controls, and their role in NPC staging and TNM classifications were examined. Results: There was no differential distribution as for the genotypic or allelic frequencies at MMP2 promoter C-1306T or C-735T between the control and case groups. Noticeably, those with MMP2 C-1306T CT+TT genotypes had a lower metastatic risk than those with CC (p=0.0295). As for staging, T and N classifications, there was no differential distribution in C-1306T genotypes (p>0.05). Also, there was no differential distribution of C-735T genotypes according to different behavioral/clinicopathological characteristics. Conclusion: CT and TT genotypes at MMP2 C-1306T were associated with a significantly decreased risk of NPC metastasis.

From the viewpoint of epidemiology, nasopharyngeal cancer (NPC) is the 18th most commonly occurring cancer in men and the 22nd most commonly occurring cancer in women. There were 129,000 new cases in 2018 (1). NPC is a rapidly growing squamous cell carcinoma which features distant metastasis and affects both adults and children (2). Epstein-Barr virus (EBV) infection, cigarette smoking and alcohol consumption have been reported to be environmental risk factors for NPC (3, 4). Only a few people develop the disease in areas where NPC is endemic even though everyone is exposed to the same environment, suggesting that genetic differences such as single nucleotide polymorphisms (SNPs) may contribute to NPC carcinogenesis. However, the molecular mechanism of NPC induced by these factors is still unknown. Increasing knowledge of the genomics of NPC may lead to the discovery of novel biomarkers for the early detection and prediction of NPC susceptibility and also patients’ prognosis.

Extracellular matrix (ECM) structures play an important role in providing biochemical support of surrounding cells and in regulating micro-environmental remodeling during tumorigenesis (5). The matrix metalloproteinases (MMPs), also known as matrixins, are a family of calcium-dependent zinc-containing endopeptidases involved in ECM remodeling via controlling the degradation of the ECM components such as the connective tissue matrices (5, 6). In literature, MMPs, especially MMP2, were reported to be related to the regulation of NPC invasion and metastasis (7, 8).
Table I. Demographic characteristics of the investigated 208 nasopharyngeal carcinoma patients and 416 non-cancer healthy controls.

| Characteristics                | Controls (n=416) | Cases (n=208) | p-Value |
|--------------------------------|-----------------|---------------|---------|
| Age (y)                        |                 |               |         |
| Male                           | 304             | 152           | 0.7434b |
| Female                         | 112             | 56            | 1.0000a |
| Gender                         |                 |               |         |
| Behavioral habits              |                 |               |         |
| Cigarette smokers              | 157             | 87            | 0.3241a |
| Alcohol drinkers               | 130             | 73            | 0.3337b |
| Areca chewers                  | 118             | 64            | 0.5334a |
| Clinical stage, n, %           |                 |               |         |
| I and II                       | 88              | 42.3%         |         |
| III and IV                     | 120             | 57.7%         |         |
| Local tumor invasion (T classification) |           |               |         |
| I and II                       | 147             | 70.7%         |         |
| III and IV                     | 61              | 29.3%         |         |
| Lymph node involvement (N classification) |           |               |         |
| N0 and N1                      | 145             | 69.7%         |         |
| N2 and N3                      | 63              | 30.3%         |         |
| Distance metastasis (M classification) |           |               |         |
| M0                             | 177             | 85.1%         |         |
| M1                             | 31              | 14.9%         |         |

SD: Standard deviation; a Analyzed by Chi-square test; b Analyzed by unpaired Student’s t-test.

MMP2 gene is located on chromosome 16q21 and is composed of 12 introns and 13 exons (9). The MMP2 promoter C-1306T (rs243865) and C-735T (rs2285053) polymorphisms can affect expression of both mRNA and protein by altering its transcriptional activity, and eventually contributing to the development of several types of cancer, including breast, lung, esophageal and colon cancer (10-13). Also, MMP2 has been reported to be up-regulated in patients with oral squamous cell carcinoma, especially those with lymph node metastasis (14). In 2013, Huang and his colleagues reported that NPC cells had a higher rate of MMP2 expression in tumor metastases than in the primary cervical tumor (15). Thus, the present case-control genotyping study was performed to investigate the correlations of MMP2 promoter C-1306T (rs243865) and C-735T (rs2285053) polymorphisms with the susceptibility and metastatic potential of NPC in Taiwan.

Materials and Methods

Nasopharyngeal cancer patient and control groups collection. The current study was approved by the Institutional Review Board (DMR101-IRB1-306) of our Hospital. First, two hundred and eight patients diagnosed with NPC voluntarily provided 5 ml of their peripheral blood and completed a self-administered questionnaire. Then, for each case, two age- and gender-matched healthy controls, who had no NPC or other types of cancer, were selected from those attending the hospital for a health examination. Thus, a total of 416 non-cancer healthy individuals were selected as controls by matching for age and gender after initial random sampling from the Health Examination Cohort of the hospital. They contributed blood and completed the questionnaire. The questionnaire administered to each participant included questions on family history, 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 more than twice a week for many years. The male versus female ratio was 73.1% to 26.9% in each group, perfectly matched with each other. The recurrence and metastasis status of each patient was closely followed up at least twice per year after surgery. The mean age of the patients and the controls was 49.3 (SD=11.4) and 49.7 (SD=12.2) years, respectively, showing that the matching was successful causing a non-significant differential distribution between the case and control groups. More detailed information is summarized in Table I.

Genotyping processes. The genomic DNA from the peripheral blood leukocytes donated by each participant was prepared within 24 h after collection by using the QiAamp Blood Mini Kit (Blosom, Taipei, Taiwan), and stored at −80°C until processed, as per our previous articles (3-5). In this study, the genotypes at C-1306T and C-735T polymorphic sites in the MMP2 promoter region were determined for all the subjects in both the control and NPC patient groups. In brief, the polymorphic sites were genotyped by typical polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methodologies using the BioRad Mycycler (BioRad, Hercules, CA, USA) (16-20). Each PCR reaction consisted of a 5 min initial cycle at 94°C for 5 min; 40 cycles of 94°C for 30 sec, 55°C for 30 sec, and 72°C for 30 sec; and a final extension at 72°C for 10 min. After PCR, the SNP-containing DNA amplicons were subjected to individual overnight digestion by restriction
The frequency distributions of demographic indexes including age, gender, personal cigarette smoking, alcohol drinking and areca chewing habits for the 208 NPC and 416 non-cancer controls are summarized in Table I. Since frequency matching for age and gender was applied to recruit the non-cancer healthy controls, there was no difference in the distribution of age ($p=0.7434$) and a perfect match of gender was obtained ($p=1.0000$) between the control and case groups (Table I, top). For all the investigated individuals, a non-significant, higher percentage of cigarette smoking, alcohol drinking and areca chewing habits was found in the case group compared to the control group (all $p>0.05$) (Table I, top). The clinicopathological characteristics, including the clinical stages and TNM classifications, of the 208 NPC patients are presented in the bottom part of Table I.

The distributions of the MMP2 promoter C-1306T and C-735T genotypes among the non-cancer controls and the NPC patients are presented and statistically analyzed in Table II. The genotypes of MMP2 promoter C-1306T were non-differentially distributed between NPC and non-cancer control group ($p$ for trend=0.6152) (Table II, top). In detail, the MMP2 promoter C 1306T heterozygous CT and homozygous TT were not associated with altered NPC risk
Table IV. p-Values and odds ratios for matrix metalloproteinase-2 (MMP2) C-1306T genotypes stratified according to the clinical stages and TNM classifications.

| NPC patient status | MMP2 C-1306T genotype | p-Valuea |
|--------------------|------------------------|----------|
| Clinical stages    |                        |          |
| Stages I and II    | CC 64                  | CT+TT 24 |          |
| Stages III and IV  | CC 83                  | CT+TT 37 | 0.5773   |
| T classification   |                        |          |
| Stages I and II    | CC 99                  | CT+TT 48 |          |
| Stages III and IV  | CC 48                  | CT+TT 13 | 0.1019   |
| N classification   |                        |          |
| N0 and N1          | CC 98                  | CT+TT 47 |          |
| N2 and N3          | CC 49                  | CT+TT 14 | 0.1379   |
| M classification   |                        |          |
| M0                 | CC 120                 | CT+TT 57 |          |
| M1                 | CC 27                  | CT+TT 4  | 0.0295b  |

aThe p-values were calculated by the Chi-square test without Yates’ correction; bStatistically recognized as significant.

(p=0.5332 and 0.4853, OR=0.89 and 1.46, 95%CI=0.61-1.29 and 0.50-4.30, respectively; Table II, top). Similarly, the genotypes of MMP2 promoter C-735T were not differentially distributed between oral cancer and non-cancer control groups (p for trend=0.7509) (Table II, bottom). In detail, the MMP2 promoter C 735T heterozygous CT and homozygous TT were not associated with altered NPC risk (p=0.5283 and 0.7424, OR=1.12 and 0.87, 95%CI=0.78-1.62 and 0.37-2.03, respectively; Table II, bottom). The observed distributions of the genotypes C 1306T and C-735T of the MMP2 promoter were in Hardy-Weinberg equilibrium in both control and case groups (all p>0.05).

To confirm the findings in Table II, allelic frequency distribution analysis of the MMP2 promoter C-1306T and C-735T was also conducted and the results are summarized in Table III. In accordance with the finding that CT or TT genotype of MMP2 promoter C-1306T was not associated with NPC risk, the variant allele T was found in 16.1% in the case group, not significantly different from the 16.5% in the control group (p=0.8710, OR=0.97, 95%CI=0.71-1.34). It was also validated that there was no significant differential distribution (p=0.7989, OR=1.04, 95%CI=0.77-1.40) as for the allelic frequencies of MMP2 promoter C-735T (Table IV, bottom). To sum up, there was no significant difference in the allelic frequencies of MMP2 promoter C-1306T or C-735T between the control and NPC groups (Table III).

Next, we examined whether the MMP2 promoter C-1306T and C-735T genotypes could serve as markers of the clinical stages or TNM classification of the investigated Taiwanese NPC patients. Noticeably, the NPC patients carrying the genotypes CT+TT at the MMP2 promoter C-1306T had a lower risk of metastasis (p=0.0295) than patients carrying the wild-type CC genotype at MMP2 promoter C-1306T (Table IV, bottom). On the contrary, there was no differential distribution of the MMP2 promoter C-1306T genotype among NPC patients of different clinical stages (p=0.5773), T classifications (p=0.1019) or N classifications (p=0.1379) (Table IV, top). MMP2 promoter C-735T genotype was not associated with clinical stage, T, N or M classification in these NPC patients (Table V).

Discussion

In the current case–control association study, the contribution of MMP2 promoter C-1306T and C-735T genotypes to NPC risk was firstly evaluated in 208 Taiwanese NPC patients and 416 age- and gender-matched healthy control subjects. Variations in the two SNP loci, C-1306T and C-735T, both located upstream of the MMP2 transcriptional start site, might destroy the binding site of Sp1, resulting in a decrease in transcription, and eventually a decrease in MMP2 protein expression levels (21). In literature, there are already two case-control studies investigating the contribution of MMP2 genotypes to head and neck (HNC) cancer (22, 23). In 2004, Lin and his colleagues reported that the CC genotype frequency at MMP2 C-1306T was significantly higher in oral squamous cell carcinoma (OSCC) cases than in controls (p=0.04) (22). Consistently, O-Charoenrat and colleagues have found that the T allele frequencies were significantly lower in the patient compared to the control group (6.9%
validated in more populations. Moreover, they have also found that MMP2 expression in HNC cells containing the CC genotype was significantly higher than that in cells with the CT genotype (23). In 2018, our team found that the variant T allele at MMP2 C-1306T conferred lower oral cancer susceptibility than the wild-type C allele (24). Although sample size (control:case=288/242 and 496/478, 956/788, respectively) was similar to the one in the current study focused on the investigation of NPC, our conclusion should be validated with more studies. The current study showed that although the genotypes at MMP2 C-1306 or C-735T cannot serve as predictors of NPC risk in Taiwan (Tables II and III), the variant CT and TT genotypes at MMP2 C-1306T were associated with significantly decreased risk of NPC metastasis (Table IV).

The MMP2 protein, also named gelatinase, plays a significant role in the degradation of various substrates, such as fibrillar collagen, elastin, endothelin, fibroblast growth factor, MMP-9, MMP-13, plasminogen, and TGF-β (25). The degradation of ECM by MMP2 is an important step in the invasion and metastasis processes (26, 27). Overexpressed and activated MMP2 is observed and reported to be associated with poor prognosis of many types of cancer including melanoma, colorectal, breast, ovarian, lung and prostate cancer (28).

Overall, the C allele at MMP2 C-1306T contributes to higher mRNA and protein levels of MMP2 compared to the T allele. Moreover, elevated levels of active MMP2 is thought to promote epithelial-mesenchymal transition (EMT) and enhances angiogenesis

Conflict of Interest

The Authors declare no conflicts of interest in regard to this study.

Authors’ Contributions

Research Design: Hsu SW and Gong CL; Patient and Questionnaire Summarize: Hsu SW and Shih LC; Experiment Performance: Hsu HM, Wang YC and Chang WS; Statistical Analysis: Chao CC, Tsai YT; Manuscript Writing: Tsai CW and Bau DT; Reviewing and Revising: Bau DT, Chang WS and Tsai CW.

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