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The Association of *MMP-11* Promoter Polymorphisms With Susceptibility to Lung Cancer in Taiwan

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Abstract. *Background/Aim: Matrix metalloproteinases-11 (MMP-11) overexpression has been reported in various types of cancer including lung cancer. We aimed to examine the contribution of MMP-11 genotypes to lung cancer risk. Materials and Methods: In this case-control study, the MMP-11 rs738791, rs2267029, rs738792 and rs28382575 genotypes were determined among 358 lung cancer patients and 716 age- and gender-matched healthy control Taiwanese. Results: The percentages of rs738791 CT and TT were 50.6% and 9.2% in the case group, slightly higher than 48.5% and 8.1% in the control group (p for trend=0.5638). The allelic analysis showed that the rs738791 T allele did not confer lung cancer risk compared with the C allele. Similarly, there was no association between rs2267029, rs738792 or rs28382575 and lung cancer risk. There was no joint effect of MMP-11 genotypes among ever smokers or non-smokers. Conclusion: The genotypes of MMP-11 play a minor role in determining lung cancer risk in Taiwan.*

Lung cancer has been the most common and death causing cancer worldwide (1). Although there is a rapid development in precise and personalized therapies during the recent years, the overall 5-year survival rate for lung cancer patients remained less than 20% (2). Therefore, the search for clinically predictive and prognostic markers is still the main mission of cancer genomics and these novel markers should be validated as soon as possible in several populations with different genetic backgrounds and environments.

Matrix metalloproteinases (MMPs), also named matrixins, include 28 endopeptidases in charge of disruption of cellular basement membrane and extracellular matrix (ECM) contents (3-6). These MMPs play central roles in many tumorigenesis events, such as cell proliferation, differentiation, apoptosis, invasion, migration, metastasis, angiogenesis and immune surveillance, which makes them a very attractive target group for cancer therapeutic drug development (7, 8). During the past two decades, cancer genomics scientists have determined that some polymorphic genotypes of *MMPs*, especially those implicated in the regulation of gene expression, are significantly associated with the inter-individual differences in susceptibility to several types of tumors (9-17), while others do not (18-24). These biomarkers may be very useful in the detection and prediction of personalized cancer susceptibility, cancer therapy and prognosis after surgery. However, the literature about the contribution of *MMP-11* genotypes to cancer is extremely limited.

MMP-11, also named stromelysin-3 (25) and originally identified in invasive breast tumors (26), has been reported to be upregulated in the blood serum and solid tumor tissues of cancer patients, but almost absent in normal tissues. Over-expression of MMP-11 has been reported in many types of cancer including oral (27, 28), esophageal (29), pancreatic (30), colon cancer (31), ovarian carcinoma (32), and most important, non-small cell lung cancer (33). However, up to

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now, there have been no studies investigating the association of *MMP-11* genotypes with lung cancer risk. In light of the above, we, for the first time, conducted a hospital-based case-control study examining the genotypes of MMP-11 rs738791, rs2267029, rs738792 and rs28382575 among Taiwanese to reveal the contribution of *MMP-11* genotypes in lung cancer risk in Taiwanese.

Materials and Methods

Population collection methodologies. Three hundred and fifty-eight patients with histologically confirmed lung cancer were recruited at China Medical University Hospital as previously described with the approval of the Institutional Review Board (DMR100-IRB-284) (34). During the collection period, a double number of healthy volunteers were selected from the databank of Health Examination Cohort of China Medical University Hospital with more than 15,000 individuals as controls, matched for their age (no equal to or larger than 5 years), gender and smoking behavior. The exclusion criteria are concisely descripted as followed. As for the case group, any subject with history of any other malignancy and pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), pneumothorax and asthma was excluded. As for the control group, any subject with a previous malignancy, metastasized cancer from other known or unknown origin, and any genetic or familial diseases was also excluded. The finally included controls and cases are all Taiwanese and their demographic characteristics are summarized in Table I.

MMP-11 genotyping methodologies. After providing personal inform consents, all recruited subjects provided 3-5 ml of their blood and genomic DNA was extracted from peripheral blood leukocytes within the same day, diluted and aliquoted for genotyping as a temporary working stock at −20˚C as we routinely conducted (35); for long-term use the samples were stored at −80˚C or liquid nitrogen. The methodology for *MMP-11* genotype determination including the design of the specific primers and the selection of restriction enzymes was developed in our lab. Briefly, the polymerase chain reaction (PCR) cycling conditions were set as one cycle at 94˚C for 5 min; 35 cycles of 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 sequences of forward and reverse primers for *MMP-11* rs738791 were 5'-TCTAGGTCCAGCTCTTGCAT-3' and 5'-TTCCAAGTCCTTTCTGGCCT-3', respectively. The sequences of forward and reverse primers for *MMP-11* rs2267029 were 5'-CAGTGAGGCAGAATGTGTGT-3' and 5'-TGTAGCCTCTGGCACAGAAA-3', respectively. The sequences of forward and reverse primers for *MMP-11* rs738792 were 5'-TGATGCCTTGGAACAAGGTG-3' and 5'-AAGCACGAACCTCTTCTGTC-3', respectively. The sequences of forward and reverse primers for *MMP-11* rs28382575 were 5'-TCTTCTCAGGCTATGCCTAC-3' and 5'-TAGCCTGATATTCGTGGCCT-3', respectively. The obtained 423 bp PCR products for *MMP-11* rs2267029 were then digested with 1 unit of *HpyCH4V* resulting in 174 bp and 249 bp fragments when the A allele was present while remained intact when the G allele was present. The obtained 399 bp PCR products for *MMP-11* rs738792 were then digested with 1 unit of *Zua*I resulting in 189 bp and 210 bp fragments when the T allele was present while remained intact when the C allele was present. After amplification, the PCR products of *MMP-11* rs2267029 and rs738792 were subject to digestion and separation using 3% agarose gel electrophoresis. As for *MMP-11* rs738791 and rs28382575, direct sequencing PCR were conducted. All genotypes were determined by at least two expert researchers, listed in the acknowledgements section, independently and blindly, and the results were 100% concordant to each other. The success rate of PCR-restrictive fragment length polymorphism was 100%.

Statistical analysis. As for the comparison of age between the lung cancer and control groups, the unpaired Student's *t*-test was used. As for the comparisons of the distributions of the numbers among the subgroups, the Pearson's Chi-square or the Fisher's exact test (when any number was less than 5) was applied. Last, the associations between *MMP-11* genotypes and lung cancer risk were estimated by calculating the odds ratios (ORs) and their 95% confidence intervals (CIs) with logistic regression analysis methods. *p*-Value less than 0.05 was considered statistically significant.

Results

The frequency distributions of age, gender and smoking status of the investigated 358 cases of lung cancer and 716 healthy subjects are presented and compared in Table I. In addition, the histology of all the patients in the lung cancer group is also presented in Table I. Age and gender showed no difference between the control and case groups (p=0.5871 and 0.3642, respectively) (Table I, top part). These results confirmed the correctness of our age- and gender-matching strategy in selecting the control subjects in this case-control study. As for the histology of the lung cancer patients, about three-fifth of the cases (60.9%, 218 out of 358) were of adenocarcinoma type, while 29.6% (106 out of 358) were of squamous cell carcinoma type and 9.5% (34 out of 358) were of other types (Table I, bottom part).

The distribution of the four investigated *MMP-11* genotypes in the 358 lung cancer patients and the 716 non-cancer healthy subjects are presented and analyzed in Table II. First, the genotypes of MMP-11 did not show significantly different distribution between the two groups (p for trend=0.5638) (Table II top panel). In detail, the homozygous TT and heterozygous CT genotypes at *MMP-11* rs738791 were not associated with elevated lung cancer risk, compared with wild-type CC genotype (adjusted OR=1.30 and 1.17, 95%CI=0.82-2.08 and 0.83-1.53, p=0.3905 and 0.3818, respectively; Table II top panel). Furthermore, there was also no association between the CT+TT genotype of *MMP-11* rs738791 and lung cancer risk, compared with the CC wild-type genotype in the dominant analysis model, (adjusted OR=1.21, 95%CI=0.89-1.59, p=0.3152, Table II top panel). Similarly, no association was revealed by the co-dominant or dominant analysis model between *MMP-11* rs2267029, rs738792 or rs28382575 and lung cancer risk (Table II middle and bottom panels).

To further confirm the results in Table II, we also analyzed the distributions allelic frequency for each of the investigated

Table I. *Distribution of selected demographic data of the 358 patients with lung cancer and the 716 matched controls.*

Characteristics	Controls (n=716)			Patients (n=358)			*p*-Value
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			64.8 (6.8)			64.0 (6.9)	0.5871
Gender							
Male	488	68.1%		254	70.9%		
Female	228	31.9%		104	29.1%		0.3642[a]
Smoking status							
Ever smokers	563	78.6%		293	81.8%		
Non-smokers	153	21.4%		65	18.2%		0.2282[a]
Histology							
Adenocarcinoma				218	60.9%		
SCC				106	29.6%		
Other				34	9.5%		

[a]Based on Chi-square test; SCC: Squamous cell carcinoma; SD: standard deviation.

MMP-11 polymorphic sites. The results are presented in Table III. This analysis showed that neither the C nor the T allele of *MMP-11* rs738791 was associated with lung cancer risk. In detail, the variant allele T was found at 34.5% of patients in the lung cancer group, not significantly different from the control group that was 32.3% (adjusted OR=1.11 95%CI=0.92-1.34, p=0.3147 (Table III top panel). Similarly, there was no difference in the distribution of the allelic frequencies of *MMP-11* rs2267029, rs738792 or rs28382575 between the case and control groups (Table III middle and bottom panels).

Discussion

In the current study, we examined the contribution of *MMP-11* genotypes to lung cancer risk with relatively large numbers of patients and controls. The data showed that *MMP-11* rs738791, rs2267029, rs738792 and rs28382575 were not the major determinants of lung cancer risk for Taiwan citizens (Tables II and III). As far as we know, this is the first study to investigate the contribution of *MMP-11* genotypes to lung cancer worldwide.

In the literature, the studies investigating the contribution of the genotypes of *MMP-11* to human diseases are very limited. In 2010, the contribution of the *MMP-11* rs738792 to Kawasaki disease was examined in a Korean population containing 101 cases and 306 controls (36). The CC genotype at *MMP-11* rs738792 was at higher level in the Kawasaki disease group (14.3%) than the control group (4.5%) (36). The change from T to C at *MMP-11* rs738792 results in the replacement of Val with Ala, which may greatly affect the functions of encoded protein. In 2012, the genotypes of *MMP-11* together with other *MMPs* were investigated of their association with myopia in an Australian population containing 269 myopes and 274 controls (37). None of the investigated polymorphic genotypes of *MMPs*, including rs738791 of *MMP-11*, was found to be associated with myopia after the correction for multiple testing (37). In 2015, the association of genotypes of *MMP-11* with oral cancer was investigated in a Taiwan population containing 595 oral cancer patients and 561 controls (38). Although the genotype of *MMP-11* rs738792, together with rs738791, rs2267029 and rs28382575, was not found to be a predictor of oral cancer susceptibility, it can serve as a predictor for lymph node metastasis, and synergistically interacts with betel quid chewing and smoking habits to increase the risk of oral cancer (38). In 2018 and 2019, the same group extend the case-control association study to hepatoma and uterine cervical cancer (39, 40). They found that the CT+TT genotypes of *MMP-11* rs738791 can enhance the risk of hepatoma compared with the wild-type CC genotype. The *MMP-11* rs738791, similar to rs2267029, is an intronic polymorphic site. Thus, it is possible that the different genotypes of *MMP-11* rs738791 may affect the efficiency of alternative splicing or the stability of the mRNA, leading to differential regulation of *MMP-11* expression during tumorigenesis. The detailed mechanisms and the contributions of the variant genotypes of *MMP-11* rs738791 to cancer development need further investigation.

Cigarette smoking is closely related to various types of cancer worldwide, and the 126-country worldwide efforts have suppressed smoking prevalence from 24.73% in 2005 to 22.18% in 2015 (41). In Taiwan, although cigarette smoking behaviors are prohibited in public areas and cigarettes are charged with extremely high tax, there are still many smokers. From the epidemiological viewpoint, smoking is a risk factor for lung cancer and the percentage of smokers in our case group was as high as 81.8%. We have matched the control

Table II. *Distributions of matrix metalloproteinas-11 genotypic frequencies among lung cancer patients and healthy subjects.*

	Cases, n (%)	Controls, n (%)	Adjusted OR (95%CI)[a]	*p*-Value[b]
rs738791				
CC	144 (40.2)	311 (43.4)	1.00 (Reference)	
CT	181 (50.6)	347 (48.5)	1.17 (0.83-1.53)	0.3818
TT	33 (9.2)	58 (8.1)	1.30 (0.82-2.08)	0.3905
CT+TT	214 (59.8)	405 (56.6)	1.21 (0.89-1.59)	0.3152
p_{trend}				0.5638
rs2267029				
GG	201 (56.2)	411 (57.4)	1.00 (Reference)	
AG	129 (36.0)	257 (35.9)	1.04 (0.80-1.37)	0.8504
AA	28 (7.8)	48 (6.7)	1.27 (0.79-1.97)	0.4853
AG+AA	157 (43.8)	305 (42.6)	1.07 (0.83-1.38)	0.6949
p_{trend}				0.7833
rs738792				
TT	186 (52.0)	392 (54.7)	1.00 (Reference)	
CT	144 (40.2)	271 (37.9)	1.13 (0.87-1.48)	0.4059
CC	28 (7.8)	53 (7.4)	1.15 (0.71-1.87)	0.6673
CT+CC	172 (48.0)	324 (45.3)	1.13 (0.88-1.46)	0.3867
p_{trend}				0.6874
rs28382575				
TT	339 (94.7)	685 (95.7)	1.00 (Reference)	
CT	18 (5.0)	29 (4.0)	1.25 (0.69-2.03)	0.4603
CC	1 (0.3)	2 (0.3)	1.05 (0.13-8.62)	1.0000
CT+CC	19 (5.3)	31 (4.3)	1.21 (0.77-2.42)	0.4734
p_{trend}				0.7614

OR: Odds ratio; CI: confidence interval. [a]Data have been adjusted for confounding factors age, gender and smoking. [b]Based on Chi-square test without Yates' correction or Fisher's exact test when any number is less than 5.

Table III. *Allelic frequencies for matrix metalloproteinas-11 polymorphisms among the lung cancer patients and healthy subjects.*

Allelic type	Cases, n (%)	Controls, n (%)	Adjusted OR (95%CI)[a]	*p*-Value[b]
rs738791				
Allele C	469 (65.5)	969 (67.7)	1.00 (Reference)	
Allele T	247 (34.5)	463 (32.3)	1.11 (0.92-1.34)	0.3147
rs2267029				
Allele G	531 (74.2)	1079 (75.3)	1.00 (Reference)	
Allele A	185 (25.8)	353 (24.7)	1.08 (0.88-1.34)	0.5494
rs738792				
Allele T	516 (72.1)	1055 (73.7)	1.00 (Reference)	
Allele C	200 (27.9)	377 (26.3)	1.10 (0.90-1.34)	0.4285
rs28382575				
Allele T	696 (97.2)	1399 (97.7)	1.00 (Reference)	
Allele C	20 (2.8)	33 (2.3)	1.34 (0.78-2.32)	0.4912

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

group with the case group according to age, gender and smoking status during our selection of control subjects, therefore, the percentage of smokers in the control group was as high as 78.6%, not significantly different from the case group (p=0.2282) (Table I). As a matter of fact, Taiwan government has teamed up with the citizens to lower smoking behavior from 32.5% in 1990 to 15.3% in 2016. Theoretically, the harmful consequences of smoking on lung cancer prevalence should have been lowered. However, instead, the elevation in thermal power generation and fine particulate matter (PM 2.5) contamination in the air may serve as a new environmental risk contributor for keeping lung cancer in the

throne of death-causing cancers in Taiwan (42). We also stratified cases and controls according to their smoking status and found that the four polymorphic genotypes were not predictors for lung cancer risk in smokers or non-smokers (data not shown).

In conclusion, this is the first study that investigated the contribution of genotypes of *MMP-11* in determining personal susceptibility to lung cancer and the results showed that the genotypes at rs738791, rs2267029, rs738792 and rs28382575 may not serve as useful biomarkers for early detection or prediction of lung cancer risk among the Taiwanese.

Conflicts of Interest

All the Authors declare no conflict of interest regarding this study.

Authors' Contributions

Research Design: Chen GL, Wang SC and Huang WC; Patient and Questionnaire Summarize: Shen TC and Hsia TC; Experiment Performance: Li HT and Chang WS; Statistical Analysis: Chen GL and Shen TC; Manuscript Writing: Tsai CW and Bau DT; Reviewing and Revising: Chang WS, Tsai CW and Bau DT.

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