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The Contribution of *MMP-7* Promoter Polymorphisms to Taiwan Lung Cancer Susceptibility

GUAN-LIANG CHEN[1,2,3], TE-CHUN SHEN[4], WEN-SHIN CHANG[4], CHIA-WEN TSAI[4], HSIN-TING LI[1,4], CHIH-LIANG CHUANG[2,3], YI-LIANG LAI[2,3], TE-CHENG YUEH[1,2,3], TE-CHUN HSIA[4*], SHOU-CHENG WANG[2,3*] and DA-TIAN BAU[1,4,5*]

[1]*Graduate Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan, R.O.C.;*
[2]*Taichung Armed Forces General Hospital, Taichung, Taiwan, R.O.C.;*
[3]*National Defense Medical Center, Taipei, Taiwan, R.O.C.;*
[4]*Terry Fox Cancer Research Laboratory, Translational Medicine Research Center, China Medical University Hospital, Taichung, Taiwan, R.O.C.;*
[5]*Department of Bioinformatics and Medical Engineering, Asia University, Taichung, Taiwan, R.O.C.*

Abstract. *Background/Aim: Matrix metalloproteinase-7 (MMP-7) plays an important role in metastasis behavior of cancer cells, and overexpression of MMP-7 has been associated with poor prognosis in non-small cell lung cancer. However, the contribution of various genotypes of MMP-7 has not yet been investigated in lung cancer in Taiwan. Therefore, this study aimed to investigate the association of MMP-7 genotypes with lung cancer risk among the Taiwanese. Materials and Methods: In this hospital-based case-control study, genotypes and distributions at two promoter sites of MMP-7, A-181G and C-153T, were determined, and their association with lung cancer risk in Taiwan was evaluated among 358 lung cancer patients and 716 age- and gender-matched healthy control individuals. In addition, the interaction of MMP-7 genotypes and smoking status were also examined. Results: The percentages of variant AG and GG at MMP-7 A-181G in the lung cancer group were similar to the control group (12.8% and 2.3% vs. 11.3% and 1.5%, respectively; p_{trend}=0.5294). The allelic frequency distribution analysis showed that the variant G allele at MMP-7 A-181G conferred non-significant elevated lung cancer risk compared to the wild-type A allele [odds ratio (OR)=1.18, 95% confidence interval (CI)=0.85-1.66, p=0.2289]. As for the genotypes of MMP-7 C-153T, all the studied Taiwanese population was of CC genotype. Furthermore, there was no obvious joint effect of MMP-7 A-181G genotype and smoking status on the lung cancer risk. No statistically significant correlation was observed between MMP-7 A-181G genotype distributions and gender. Conclusion: There was no evidence that the genotypes of MMP-7 A-181G may act as a biomarker in determining personal susceptibility to lung cancer in Taiwan.*

For many decades, lung cancer has been the most common and death-causing cancer worldwide, estimated to be responsible for about one in five of cancer deaths (1, 2). During the past years, despite the rapid development of precise medicine and personalized therapies, the overall 5-year survival rate for lung cancer patients remained less than 20% (3). Thus, searching and revealing of novel predictive and prognostic markers are still in urgent need, and should be validated in different populations with different genetic backgrounds.

Matrix metalloproteinases (MMPs), also named as matrixins, have been identified to play a central role in proteolysis of the extracellular matrix (ECM) molecules (4-6). In addition to be involved in embryonic development, reproduction, and tissue resorption and remodeling, MMPs are implicated in many tumorigenesis events, such as cell proliferation, differentiation, apoptosis, invasion, migration, metastasis, angiogenesis, and immune surveillance (7). From the viewpoint of cancer genomics, during the past years, several polymorphic genotypes of *MMP* family genes, especially those implicated in the regulation of gene expression, have been reported to be significantly associated with the inter-individual differences of susceptibility to several types of cancer (8-16), while some others have not

*These Authors contributed equally to this study.

Correspondence to: Da-Tian Bau, Terry Fox Cancer Research Laboratory, Translational Medicine Research Center, China Medical University Hospital, 2 Yuh-Der Road, Taichung, 404 Taiwan, ROC. Tel.: +886 422053366 (Ext. 5805), e-mail: datian@mail.cmuh.org.tw; artbau2@gmail.com

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

Characteristics	Controls (n=716)			Patients (n=358)			*p*-Value[a]
	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
Smoking status							
Ever smokers	563	78.6%		293	81.8%		
Non-smokers	153	21.4%		65	18.2%		0.2282
Histology							
Adenocarcinoma				218	60.9%		
SCC				106	29.6%		
Other				34	9.5%		

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

(17-19). The biomarkers are very helpful in early detection and prediction of personalized cancer susceptibility.

MMP-7 (also named as matrilysin, pump-1 protease) is the smallest member of the MMPs (28 kDa) in the human body. Constitutively, MMP-7 is produced by the epithelial cells of various tissues including mammary and parotid glands, pancreas, liver, prostate, and most important, the peribronchial glands of lung (20). It is involved of the proteolysis of various substrates in ECM including elastin, casein, type I, II, IV, and V gelatins, fibronectin, and proteoglycan (21-23). Activated MMP-7 may be involved in facilitating tumor invasion *via* cleaving the pro-peptides of pro-MMP-2 and pro-MMP-9 (24). MMP-7-deficient mice showed significantly reduced tumor multiplicity and body growth (25).

MMP-7 localized on human chromosome 11q21–q22 and two of its polymorphic sites, A-181G (rs11568818) and C-153T (rs11568819), were reported to exert allele-specific regulation of its expression. Briefly, the promoter assay showed that promoter constructs harboring the combination of the two variant alleles at *MMP-7* A-181G and C-153T were of higher expression than other constructs (26). Several association studies have investigated the association of the genotypes at *MMP-7* polymorphic sites with several types of cancer, including oral, breast, esophageal, gastric, colorectal, gallbladder, bladder, cervical cancer, astrocytoma, childhood leukemia, and renal cell carcinoma (16, 18, 27-37).

As for lung cancer, there were at least two important studies investigating the association of *MMP-7* genotypes with lung cancer risk (38, 39). In 2005, Zhang and his colleagues found that G allele at *MMP-7* A-181G was associated with significantly increased susceptibility to non-small cell lung carcinoma (NSCLC) (38). They also showed that smoking status did not significantly influence the association between the MMP-7-181A/G polymorphism and NSCLC (38). On the contrary, Sanli and his colleagues found that different *MMP-7* A-181G genotypes may not contribute to altered lung cancer risk in 2013 (39). The two papers were investigating Han and Caucasian populations, respectively, and it is very reasonable to explain the differences between their findings by the fact that there were differential influences of *MMP-7* genotypes on individual lung cancer risk among different racial populations/ethnicities. Thus, more investigations on different populations are needed to figure out the contribution of *MMP-7* genotypes to lung cancer risk. In light of the above, we conducted a hospital-based study to examine the genotypes of *MMP-7* among Taiwanese and reveal the contribution of *MMP-7* promoter genotypes to the Taiwanese lung cancer risk.

Materials and Methods

Patient collection. Three hundred and fifty-eight patients with lung cancer were histologically confirmed and recruited at the medical center in central Taiwan, as previously described, with the approval of the Institutional Review Board of China Medical University Hospital (DMR100-IRB-284) (19, 40, 41). Briefly, the exclusion criteria of the cases included history of any other malignancy and pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), pneumothorax, and asthma. During the same period, 760 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 (differences less than 5), gender, and smoking behavior. The exclusion criteria of the control group included previous malignancy, metastasized cancer from other known or unknown origin, and any genetic or familial diseases. The control and case individuals are all Taiwanese and their selected recorded characteristics are summarized in Table I.

Concise MMP-7 genotyping methodologies. After providing their inform consents, 3-5 ml of blood were collected from all the recruited individuals. On the same day, genomic DNA was extracted from peripheral blood leukocytes with the QIAamp Blood Mini Kit (Qiagen, Taipei, Taiwan), stored long-term at −80˚C, diluted and aliquoted for genotyping as a working stock at −20˚C (42-44). The methodology for *MMP-7* genotype determination including the design of specific primers and the selection of restriction enzymes for *MMP-7* A-181G (rs11568818) and C-153T (rs11568819) was exactly the same as our currently published papers (16, 18, 37, 45). 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 s, 59˚C for 30 s and 72˚C for 30 s, and a final extension cycle at 72˚C for 10 min. The sequences of forward and reverse primers for *MMP-7* A-181G were 5'-TGGTACCATAATGTCCTGAATG-3' and 5'-TCGTTATTGGCAGGAAGCACACAATGAATT-3', respectively. The obtained 150 bp PCR products were digested with 1 unit of *Eco*RI resulting in 120 bp and 30 bp fragments when the G allele was present, while remained intact when the A allele was present. After amplification, the PCR products were subject to digestion and separation using 3% agarose gel electrophoresis. As for *MMP-7* C-153T, direct sequencing PCR was conducted and double checked with the same primer pairs as for *MMP-7* A-181G. All the genotypic processing was independently and blindly repeated by at least two expert researchers listed in acknowledgement, and the results were 100% concordant to each other. The success rate of PCR-restrictive fragment length polymorphism was 100%.

Statistical analyses. The Student's *t*-test was applied for the comparison of age between the lung cancer and the control groups. Pearson's Chi-square or Fisher's exact test (when n<5) was applied to compare the distributions of the numbers among the subgroups. The associations between *MMP-7* genotypes and lung cancer risk were estimated by calculating the odds ratios (ORs) and their 95% confidence intervals (CIs) from logistic regression analysis. Statistically, any difference at $p<0.05$ was considered as significant.

Results

The frequency distributions of selected demographic characteristics, such as age and gender, for the 358 cases of lung cancer and 716 non-cancer healthy controls were compared and presented in Table I. As for the lung cancer group, the histology of all the patients was also recorded. Since frequency matching was applied in recruiting the non-cancer healthy individuals as the control group, the analysis results showed that there was no difference in respect to the distributions of age and gender between the control and case groups (p=0.5871 and 0.3642, respectively; Table I). About three-fifth of the lung cancer patients (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).

The distributions and frequencies of the *MMP-7* A-181G and C-153T genotypes of the 358 lung cancer patients (cases) and the 716 non-cancer healthy subjects (controls) were analyzed and presented in Table II. First, contrary to the Caucasian populations (46), the genotyping results showed that the genotype of *MMP-7* C-153T was the same in all the studied population with no variant detected (Table II). Second, the genotypes of *MMP-7* A-181G were not differently distributed between the two groups (p=0.5294; Table II). In detail, the *MMP-7* A-181G homozygous GG and heterozygous AG were not associated with elevated lung cancer risk (adjusted OR=1.49, 95% CI=0.88-1.74, p=0.3909 and adjusted OR=1.19, 95% CI=0.63-3.62, p=0.4371, respectively) compared to wild-type AA genotype (Table II). To confirm this finding, there was also no association between the AG+GG genotype of *MMP-7* A-181G and lung cancer risk, compared to AA wild-type genotype in the dominant analyzing model, (adjusted OR=1.23, 95% CI=0.88-1.74, p=0.3138; Table II).

Table II. *Distributions of matrix metalloproteinase-7 A-181G and C-153T genotype frequencies among lung cancer patients and healthy individuals*.

	Cases, n (%)	Controls, n (%)	Adjusted OR (95% CI)[a]	*p*-Value[b]
A-181G				
AA	304 (84.9)	624 (87.2)	1.00 (Reference)	
AG	46 (12.8)	81 (11.3)	1.19 (0.77-1.85)	0.4371
GG	8 (2.3)	11 (1.5)	1.49 (0.63-3.62)	0.3909
AG+GG	54 (15.1)	92 (12.8)	1.23 (0.88-1.74)	0.3138
p_{trend}				0.5294
C-153T				
CC	358 (100.0)	716 (100.0)	1.00 (Reference)	
CT	0 (0.0)	0 (0.0)	--	
TT	0 (0.0)	0 (0.0)	--	
p_{trend}				

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.

Table III. *Allelic frequencies for matrix metalloproteinase-7 A-181G and C-153T polymorphisms among the lung cancer patients and healthy subjects*.

Allelic type	Cases, n (%) n=716	Controls, n (%) n=1432	Adjusted OR (95% CI)[a]	*p*-Value[b]
A-181G				
Allele A	654 (91.3)	1329 (92.8)	1.00 (Reference)	0.2289
Allele G	62 (8.7)	103 (7.2)	1.18 (0.85-1.66)	
C-153T				
Allele C	716 (100.0)	1432 (100.0)	1.00 (Reference)	
Allele T	0 (0.0)	0 (0.0)	--	

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.

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

Genotype	Non-smokers, n		OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value[c]	Smokers, n		OR (95% CI)[a]	aOR (95% CI)[b]	*p*-Value
	Controls	Cases				Controls	Cases			
AA	133	54	1.00 (ref)	1.00 (ref)		491	250	1.00 (ref)	1.00 (ref)	
AG	17	8	1.16 (0.47-2.84)	1.27 (0.56-3.28)	0.7472	64	38	1.17 (0.76-1.79)	1.14 (0.63-1.68)	0.4826
GG	3	3	2.46 (0.48-12.59)	3.05 (0.51-10.92)	0.2642	8	5	1.23 (0.40-3.79)	1.31 (0.50-3.82)	0.7212
p_{trend}					0.5210					0.7417
Total	153	65				563	293			

CI, Confidence interval; aOR, adjusted odds ratio.[a]By multivariate logistic regression analysis; [b]By multivariate logistic regression analysis after adjusted of age and gender status; [c]Based on Chi-square test without Yates' correction.

To further confirm the results for the genotype frequency distributions (Table II), analysis of allelic frequency distribution for the *MMP-7* A-181G and C-153T was also conducted and the results are shown in Table III. It was demonstrated that neither the genotype of *MMP-7* A-181G, nor that of C-153T was associated with lung cancer risk. In detail, the variant allele G was found at 8.7% of the lung cancer cases and at 7.2% of the control group (adjusted OR=1.18, 95% CI=0.85-1.66, p=0.2289; Table III). As for *MMP-7* C-153T, there was no variant T allele found in any of the examined individuals (Table III).

Since cigarette smoking behavior is one of the well-known risk factors for lung cancer in Taiwan (47), the possible interaction between the *MMP-7* A-181G genotype and personal smoking behavior was investigated, and the results are shown in Table IV. Among the non-smokers, there was no significant increased risk of lung cancer for AG and GG genotype carriers (OR=1.16, 95% CI=0.47-2.84, p=0.7472 and OR=2.46, 95% CI=0.48-12.59, p=0.2642, respectively, p_{trend}=0.5210) (Table IV, left part). Similarly, there was found no significant association between AG and GG genotypes and lung cancer risk among smokers (Table IV). After adjusting for age and gender, the results were all the same in both non-smoker and smoker groups with negative findings (Table IV). In addition, due to the high death rates of Taiwanese female non-small cell adenocarcinoma lung cancer patients (48), the potential differential contribution of *MMP-7* A-181G to males and females was investigated. However, there was no interaction between gender and *MMP-7* A-181G genotypes on lung cancer susceptibility in the Taiwan population (data not shown).

Discussion

In the current paper, the contribution of *MMP-7* genotypes to lung cancer risk was investigated in Taiwan, where the lung cancer is the highest death-causing cancer according to the national statistics (48). The promoter polymorphisms at *MMP-7* have been reported to affect its expression (26), and herein, it was shown that neither the wild-type A nor the variant G allele at the MMP7 A-181G were associated with increased risk of lung cancer in Taiwanese (Tables II and III). Interestingly, no variant genotypes of *MMP-7* C-153T were detected among the studied population (Tables II and III). As far as we know, this is the first paper to investigate the contribution of *MMP-7* genotypes to lung cancer risk in Taiwanese population. In 2010, the same polymorphic *MMP-7* sites (C-153T and A-181G) were examined among 349 Caucasian lung cancer patients, about their role in prediction of chemotherapy outcome, including response after the second cycle, progression-free survival (PFS), and overall survival (OS) (46). Although their findings in associating the genotypes of *MMP-1*, -2, -3, -7, -9 or -12 with lung cancer prognosis were all negative, the group reported that the combined variant alleles, which lead to an enhanced expression of *MMP-7* in the plasma (26), were associated with a longer lifetime of lung cancer patients with squamous carcinoma after starting chemotherapy, compared to lung cancer patients carrying other *MMP-7* genotypes (46). In the present study, we have collected a number of lung cancer patients, and a nearly double number of healthy individuals as controls, in Taiwan. However, the predictive and prognostic potential of *MMP-7* genotypes in lung cancer patients was not investigated, neither the expression level of MMP-7 in the plasma nor the genotype-phenotype correlation of MMP-7 were evaluated in our population.

MMP-7 has also been implicated in lung cancer invasion metastasis. More specifically, it has been shown that down-regulation fibulin-5, a metastatic suppressor for lung cancer, can activate MMP-7 *via* ERK pathway and subsequently promote lung cancer cell invasion (49). Thus, MMP-7 genotypes may be a novel biomarker for early prediction of poor disease prognosis in addition to lung cancer risk. However, the genotypes at *MMP-7* promoter region (C-153T and A-181G) were not predictive of either lung cancer

susceptibility or prognosis (46). The two MMP-7 promoter SNPs were not proved to be predictive biomarkers for oral cancer (50), childhood leukemia (37), or breast cancer in Taiwan either (16). The above findings suggest that studies should focus on the predictive capacity of *MMP* genes, except *MMP-7*, in lung cancer risk or prognosis, taking into account their involvement in multiple pathways and networks. The genotypes of *MMP-7* may play a minor role in determination of lung cancer susceptibility. In 2017, Jung and his colleagues examined the feasibility and accuracy of lung cancer detection using a 7-protein biomarker panel. They reported that EGFR1, MMP7, CA6, KIT, CRP, C9, and SERPINA3 served well in study cohort of 100 Korean lung cancer patients and 100 control individuals (51).

The smoking behaviors are risk factors for various types of cancer worldwide, and the efforts from the WHO Framework Convention on Tobacco Control have suppressed the smoking prevalence for 126 countries from 24.73% in 2005 to 22.18% in 2015, with an average decrease in prevalence of 2.55 percentage points worldwide (52). In our population, obviously smoking status was a risk factor for lung cancer, since the percentages of smokers in the case group was as high as 81.8%. However, the case group was matched to the control group not only by age and gender, but also by smoking status; therefore, the percentage of smokers in the control group was also very high (78.6%) (Table I). In fact, the government has prohibited the smoking behavior in public since 1997 and the percentages of ever smokers in Taiwan have been significantly lowered from 32.5% in 1990 to 15.3% in 2016. Therefore, it is expected that the prevalence of smoking and associated consequences, such as lung cancer risk, may be reduced in Taiwan in the near future. However, the elevation in thermal power generation and the air pollution with particulate matter less than 2.5 m may serve as a new risk factor for lung cancer in Taiwan (53).

The biological function of MMPs apparently is more complex than their proved involvement in the control of tumor cell proliferation and metastasis (54, 55). In 2007, the mRNA expression level of MMP-7 was found to be higher in NSCLC tissues than normal controls; however, the expression levels of MMP-7 protein were not studied (56). Correlation of patient status, genotype, and phenotype would be very helpful to reveal the role of MMPs, especially MMP-7, in lung cancer progress and prognosis. Although power analysis was performed for the current study and representativeness was examined as well, a larger number of cases would be necessary to further examine the contributions of specific genotypes in lung cancer risk and prognosis, according to patient characteristics, such as gender and smoking status.

In conclusion, the genotypes A-181G and C-153T at *MMP-7* promoter region were not shown to serve as useful biomarker for lung cancer risk prediction in the studied Taiwanese population. In addition, no joint effects of *MMP-7* genotypes and smoking status on lung cancer susceptibility were observed.

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