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Impacts of Matrix Metalloproteinase-9 Promoter Genotypes on Asthma Risk

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Abstract. *Background/Aim: The overexpression of matrix metalloproteinase-9 (MMP9) has been observed in asthmatic patients, yet the role of MMP9 genotype in determining asthma susceptibility remains unresolved. This study aimed to elucidate the contribution of MMP9 promoter rs3918242 genotype to asthma risk in Taiwan. Materials and Methods: A cohort comprising 453 non-asthmatic healthy controls and 198 asthmatic cases was assembled, and the MMP9 rs3918242 genotypes were determined using polymerase chain reaction-restriction fragment length polymorphism methodology. Results: Our findings indicated that people carrying the variant CT or TT genotype of MMP9 rs3918242 did not demonstrate an elevated risk of asthma compared to wild-type CC carriers (odds ratio=1.28 and 1.72, 95% confidence interval=0.87-1.87 and 0.72-4.13; p=0.2417 and 0.3201, respectively). Furthermore, individuals carrying the T allele at MMP9 rs3918242 did not exhibit a higher risk of asthma than those carrying the C allele (odds ratio=1.31, 95% confidence interval=0.96-1.79, p=0.0869). Interestingly, a positive association was observed between MMP9 rs3918242 CT or TT genotypes and the severity of asthma symptoms among asthmatic patients (p=0.0035). Conclusion: Although the T allele at MMP9 rs3918242 was not associated with asthma risk, it may serve as a predictor for asthma symptom severity. These findings warrant validation in larger and more diverse populations to further elucidate the significance of MMP9 in asthma etiology.*

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Asthma is a chronic respiratory inflammatory disease characterized by airway hyper-responsiveness, reversible airway obstruction, and airway wall remodeling, which involves significant thickening of the reticular basement membrane and deposition of extracellular matrix (ECM) components (1-3). In this context, matrix metalloproteinases (MMPs) have been identified as key players in ECM regulation and metabolism (4, 5). MMPs constitute a family of endoproteinases comprising more than 26 members (6, 7).

MMP9, also known as 92 kDa type IV collagenase, 92 kDa gelatinase, or gelatinase B, has been shown to play a crucial role in the development and progression of various human malignancies, including lung cancer (8), breast cancer (9, 10), osteosarcoma (11), pancreatic cancer (12), hepatocellular

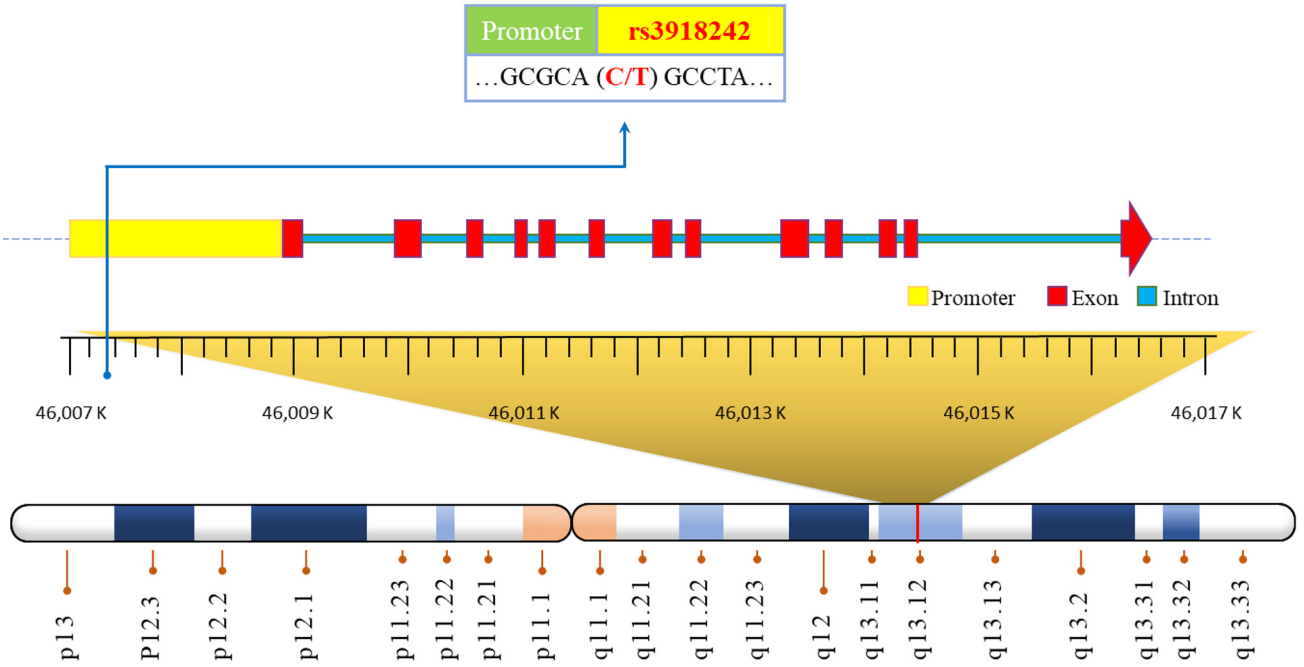

Figure 1. *The physical map for the matrix metalloproteinase-9 rs3918242 polymorphic site.*

carcinoma (13), cervical cancer (14, 15), and ovarian cancer (16). The ratio of MMP9 to its natural inhibitor (TIMP1) in bronchoalveolar lavage fluid was also found to be higher in children with symptomatic asthma compared to healthy controls (17-19). Additionally, MMP9 deficiency in mice leads to enhanced allergen-induced airway inflammation and increased numbers of eosinophils and levels of cytokines such as interleukins 4 and 13 (20-22). These accumulated data support the notion that MMP9 plays an important role in asthma pathogenesis.

Among the plethora of genetic variations linked to *MMP9*, extensive attention has been directed towards the *MMP9* rs3918242 polymorphism situated within the promoter region. The *MMP9* rs3918242 polymorphic genotypes have undergone thorough scrutiny for their potential correlation with diverse cancer forms, including breast cancer (23), gastric cancer (24), colorectal cancer (25, 26), prostate cancer (27), renal cell carcinoma (28), and childhood leukemia (29). Regarding asthma, several reports have examined the significant role of *MMP9* rs3918242 polymorphic genotypes (18, 30-34).

Based on the preceding information, the objective of this study was to assess the correlation between *MMP9* rs3918242 (depicted in Figure 1) and the susceptibility to asthma in Taiwan. Additionally, we also endeavor to provide an updated summary and discuss the highlighted findings and their limitations.

Materials and Methods

Enrollments of asthmatic cases and non-asthmatic controls. The research cohort consisted of 198 individuals diagnosed with asthma who were meticulously selected from China Medical University Hospital. The diagnosis of asthma was established based on the following criteria: (i) experiencing more than two or three episodes of wheezing and shortness of breath within the previous year; (ii) a confirmed diagnosis of asthma by pulmonologists, accompanied by spirometry evidence of reversible and variable airflow obstruction; (iii) the presence of relevant symptoms; and (iv) the prescription of asthma medications. Participants were all adults, with the youngest being 25 years old, and there were no restrictions based on sex. Furthermore, a control cohort comprising 453 non-asthmatic individuals, meticulously matched for sex and age (within ±5 years), was included, following the methodologies outlined in our previous publications (35, 36). Our study was approved and supervised by the Research Ethics Committee of China Medical University Hospital (CMUH106-REC1-004). To ensure the precision of evaluation, each asthmatic participant underwent thorough validation of the severity of their symptoms by a panel consisting of a minimum of two experienced pulmonary physicians, overseen by Dr. Hsia. This validation procedure adhered to the guidelines stipulated by the Global Initiative for Asthma (37). The clinical characteristics displayed by the asthmatic patients facilitated their classification into four distinct severity stages, meticulously defined, recorded, and closely monitored throughout the study duration.

DNA extraction and storage. DNA extraction was performed on buffy coats obtained from peripheral blood samples of all participants within 24 h of collection using QIAamp Blood Mini Kit

Table I. *Distributions of baseline characteristics among the 198 asthmatic patients and 453 controls.*

Characteristic		Controls (n=453)		Cases (n=198)		*p*-Value[a]
		n	%	n	%	
Age	25-40 Years	285	63.4%	133	67.2%	
	>40 Years	168	36.6%	65	32.8%	0.2972
Sex	Male	190	41.9%	83	41.9%	
	Female	263	58.1%	115	58.1%	0.9956
Pulmonary functions, mean±SD	FEV1/FVC (%)	80.8±8.1		62.0±13.0		**<0.0001**
	FEV1%	92.9±5.8		69.1±12.9		**<0.0001**
Symptom severity	1 (Mildest)			60	30.3%	
	2			65	32.8%	
	3			34	17.2%	
	4 (Severest)			39	19.7%	

FEV1: Forced expiratory volume in first second; FVC: forced vital capacity; FEV1%: percentage of predicted FEV1; SD: standard deviation. [a]Chi-square with Yates' correction test or Student's *t*-test. Statistically significant *p*-values are shown in bold.

(38-40). The extracted DNA samples were stored at –80˚C for long-term preservation. Furthermore, DNA samples from both asthmatic patients and non-asthmatic controls were diluted, aliquoted, and prepared as a working stock collection, following previously established protocols (41, 42). The working stock DNA samples from asthmatic patients and non-asthmatic controls in 96-well plates were stored at –20˚C until further analysis.

Processes for the determination of MMP9 rs3918242 genotype. The *MMP9* rs3918242 genotype was determined following the methodology outlined in our previous publication (24, 43). Briefly, amplification of *MMP9* rs3918242 utilized the appropriate forward and reverse primer sequences. Then the DNA adducts were digested with *Sph* I (New England Biolabs, Taipei, Taiwan) before undergoing 3% DNA gel electrophoresis. The DNA fragments for *MMP9* rs3918242 CC, CT, and TT genotypes were determined to be 386 bp, 386+320+66 bp, and 320+66 bp, respectively.

Methodology of statistical analysis. The age distributions in the asthmatic and non-asthmatic groups were compared using unpaired Student's *t*-test. Genotype comparisons among subgroups were conducted using Pearson's chi-square test with Yates' correction. The assessment of associations between *MMP9* genotype and asthma risk involved the utilization of odds ratios (ORs) alongside their corresponding 95% confidence intervals (CIs) for each genotyping comparison. Statistical significance was identified as any statistical *p*-value less than 0.05.

Results

Analysis of demographic characteristics between the asthmatic and non-asthmatic groups. Table I provides a comprehensive summary of age, sex, and specific clinical attributes, including pulmonary function and symptom severity, for both the 198 asthmatics and the 453 non-asthmatic subjects. Due to the careful matching of age and sex between the two cohorts no statistically significant differences were observed regarding age and sex distributions (p=0.2972 and 0.9956, respectively). Regarding pulmonary functions, notable disparities were observed. Within the asthmatic group, both the mean ratio of forced expiratory volume in the first second to forced vital capacity (FEV1/FVC, %) and the percentage of predicted FEV1 (FEV1%) were observed to be lower when compared to the non-asthmatic group (both p<0.0001). Regarding symptom severity, among asthmatic patients, the distribution was as follows: 30.3% for stage 1, 32.8% for stage 2, 17.2% for stage 3, and 19.7% for stage 4 (Table I).

Association of MMP9 rs3918242 genotypes with asthma risk in Taiwanese. Table II presents the genotypic distributions of *MMP9* rs3918242 among the 453 non-asthmatic controls and the 198 asthmatic patients. Firstly, the genotypic frequencies of *MMP9* rs3918242 among non-asthmatic controls were in accordance with the Hardy-Weinberg equilibrium (p=0.2757). Secondly, the genotypic frequencies of *MMP9* rs3918242 did not display any statistically significant distinction between the asthmatic case and non-asthmatic groups (p for trend=0.2484). Specifically, neither the heterozygous CT nor the homozygous variant TT genotypes of *MMP9* rs3918242 were associated with asthma susceptibility (OR=1.28 and 1.72, 95% CI=0.87-1.87 and 0.72-4.13, p=0.2417 and 0.3201, respectively). Thirdly, in a recessive model contrasting individuals bearing the TT genotype with those bearing the CC or CT genotype, the OR for asthma was 1.61 (95% CI=0.68-3.83, p=0.3938). Lastly, in a dominant model comparing individuals carrying the CT or TT genotype with those carrying the CC genotype, there was a non-significantly increased asthma risk in the former (OR=1.33, 95% CI=0.92-1.90; p=0.1511, Table II).

Table II. *Distribution of matrix metalloproteinase-9 rs3918242 variant genotypes among the 198 asthmatic patients and 453 controls.*

	Frequency, n (%)			
Genotype	Cases (n=198)	Controls (n=453)	OR (95%CI)	*p*-Value[a]
rs3918242				
CC	133 (67.2)	331 (73.1)	1.00 (Reference)	
CT	56 (28.3)	109 (24.1)	1.28 (0.87-1.87)	0.2417
TT	9 (4.5)	13 (2.8)	1.72 (0.72-4.13)	0.3201
p_{trend}				0.2484
p_{HWE}				0.2757
Carrier comparison				
CC+CT	189 (95.5)	440 (97.2)	1.00 (Reference)	
TT	9 (4.5)	13 (2.8)	1.61 (0.68-3.83)	0.3938
CC	133 (67.2)	331 (73.1)	1.00 (Reference)	
CT+TT	65 (32.8)	122 (26.9)	1.33 (0.92-1.90)	0.1511

CI: Confidence interval; OR: odds ratio. [a]Based on chi-square test with Yates' correction. p_{trend}, *p*-Value for trend analysis. p_{HWE}, *p*-Value for Hardy-Weinberg equilibrium.

Table III. *Allelic frequencies for matrix metalloproteinase-9 rs3918242 in the control and asthmatic patient groups.*

	Allelic frequency, n (%)			
Allelic type	Cases (n=396)	Controls (n=906)	OR (95%CI)	*p*-Value[a]
C	322 (81.3)	771 (85.1)	1.00 (Reference)	
T	74 (18.7)	135 (14.9)	1.31 (0.96-1.79)	0.0869

CI: Confidence interval; OR: odds ratio. [a]Based on chi-square test with Yates' correction.

Association of MMP9 rs3918242 allelic frequencies with asthma risk in Taiwanese. To further corroborate the findings in Table II, an analysis for allelic frequency was conducted to assess the involvement of *MMP9* rs3918242 in asthma risk in Taiwanese, as illustrated in Table III. The data indicated that the presence of variant T alleles at *MMP9* rs3918242 did not significantly differ between the asthmatic case and non-asthmatic control groups (p=0.0869). Individuals harboring the variant T allele at *MMP9* rs3918242 demonstrated a 1.31-fold odds ratio (95% CI=0.96-1.79) for asthma susceptibility compared to those carrying the wild-type C allele (Table III). Thus, the findings from the allelic frequency analysis suggest that the *MMP9* rs3918242 variant CT or TT genotype may not be a major determinant for elevated risk of asthma in Taiwanese.

Stratified analysis of MMP9 rs3918242 genotypes according to severity of asthmatic symptoms. While *MMP9* rs3918242 genotypes may not serve as practical predictors for asthma risk, we are intrigued by the intricate interplay between *MMP9* genotypes and the severity of asthmatic symptoms within the clinical context. To explore these further, asthmatic patients were stratified based on their *MMP9* rs3918242 genotypes and corresponding symptom severity profiles. The results of this analysis are detailed in Table IV. We combined the variant genotypes (CT and TT) due to their minor proportions compared to the wild-type CC genotype at *MMP9* rs3918242. The results presented in Table IV emphasize that individuals carrying variant genotypes (CT or TT) at *MMP9* rs3918242 were more prone to experiencing severe symptomatology compared to their wild-type (CC) counterparts (p=0.0035) (Table IV). Upon detailed examination, the distribution of wild-type carriers across the first (mildest), second, third, and fourth (most severe) stages among asthmatic patients was 36.9%, 30.0%, 19.6%, and 13.5%, respectively. Remarkably, a notable discrepancy was observed: the percentage of wild-type CC carriers was significantly higher among patients in the mildest stage (36.9% *versus* 16.9%), while conversely it was lower among those in the most severe stage (13.5% *versus* 32.3%) (p=0.0035). Conversely, the opposite pattern was evident for carriers of the variant genotypes CT or TT at *MMP9* rs3918242, with distributions diverging in an opposite direction (Table IV).

Discussion

Chronic asthma is characterized by abnormal remodeling and altered airway function, partly attributed to changes in ECM deposition, potentially influenced by MMP9 imbalance (44,

Table IV. *Association of matrix metalloproteinase-9 rs3918242 genotypes with the symptom severity among asthmatic patients.*

	Symptom severity, n (%)				
Genotype	1 (Mildest)	2	3	4 (Severest)	*p*-Value[a]
rs3918242					
Wild-type CC genotype	49 (36.9)	40 (30.0)	26 (19.6)	18 (13.5)	
Variant CT or TT genotypes	11 (16.9)	25 (38.5)	8 (12.3)	21 (32.3)	**0.0035**

[a]4×2 Comparison was conducted with chi-square with Yates' correction test. Statistically significant *p*-values are shown in bold.

Table V. *Literature reported the genotypes of matrix metalloproteinase-9 rs3918242 among asthmatic patients.*

			CC:CT:TT genotype, n			
First author	Year	Cohort ehnicity	Controls	Cases	Highlights of the study	Reference
Chiu	2024	Taiwan	331:109:13	133:56:9	No genotype significantly contributed to altered asthma risk (p=0.2484); CT/TT genotypes contributed to severe asthma symptoms (**p=0.0035**)	Current study
Jimenez-Morales	2013	Mexican	Total 426	Total 403	No genotype significantly contributed to altered asthma risk (p>0.05)	34
Hong	2012	China	50:17:1	44:19:2	No genotype significantly contributed to altered asthma risk (p=0.6838)	18
Ganter	2005	German	208:54:7	171:56:4	No genotype significantly contributed to altered asthma risk (p=0.4521)	32
Lose	2005	Australian	290:94:8	365:134:15	No genotype significantly contributed to altered asthma risk (p=0.5138)	31
Holla	2000	Czechoslovakian	60:16:3	44:13:2	No genotype significantly contributed to altered asthma risk (p=0.9632)	30

Statistically significant *p*-values are shown in bold.

45). Elevated levels of MMP9 in airways or alveolar macrophages may indicate chronic airway inflammation in patients with asthma (46). Studies have reported associations between a higher MMP9 level and reduced lung function (47), as well as an elevated serum MMP9 level in children with asthma compared to healthy controls (48). The current study aimed to investigate the association between *MMP9* rs3918242 genotypes and asthma in a Taiwanese population consisting of individuals distributed across different stages of asthma and in non-asthmatic controls (Table I). The results indicate that CC, CT, or TT genotypes at *MMP9* rs3918242 are not determinants of asthma susceptibility (Table II and Table III). However, variant CT or TT genotypes at *MMP9* rs3918242 may predict severe asthma severity (Table IV). Although previous research has shown that the *MMP9* rs3918242 genotype can lead to increased MMP9 expression (48, 49), we did not provide direct evidence of this in this study.

In 2000, Holla and colleagues conducted the first investigation into the association of *MMP9* rs3918242 polymorphism with asthma risk in a Czechoslovakian population, but found no significant association (30). In 2005, Lose and colleagues similarly found no association between *MMP9* rs3918242 and asthma or asthma severity in an Australian population (31). In the same year, Ganter and colleagues reported another negative association among German children (32). In 2006, Nakashima and colleagues reported similar results but revealed a significant association between *MMP9* rs2274755, which was in complete linkage disequilibrium with *MMP9* rs3918242, and childhood asthma risk (33). In 2010, Pinto and colleagues found that another *MMP9* polymorphism, rs2664538 at exon 6, significantly increased the risk of non-atopic asthma (50). In 2012, Hong and colleagues examined the contribution of *MMP9* rs3918242 genotype to childhood asthma and found no association in a small Chinese pediatric population (18). In 2013, Jimenez-Morales and colleagues investigated the role of other polymorphisms at *MMP9* in childhood asthma in a Mexican population. They proposed a haplotype of rs2274755, rs17577, and rs3918249 of *MMP9* as being associated with asthma risk, but found no association with *MMP9* rs3918242 genotype (34). We have summarized the authors, ethnicities, sample sizes, and key findings of all literature focused on *MMP9* rs3918242 and asthma risk for a comprehensive understanding of the role of *MMP9* in asthma (Table V).

The genotypic distribution for *MMP9* rs3918242 in our control group adheres well to the Hardy-Weinberg equilibrium (p=0.2757). Information obtained from the results of 3,120 East Asian samples indicates that C and T alleles constitute 86.54% and 13.43%, respectively. Among the non-asthmatic controls in our study, C and T alleles were represented at frequencies of 85.10% and 14.90%, respectively. This concordance suggests that our cohort's genotyping accurately represents the entire Taiwanese population, with allelic frequencies aligning closely with those of East Asians (51). The current study reveals that the *MMP9* rs3918242 polymorphism was not associated with asthma risk in this Taiwanese population. Additionally, we found no significant associations among subgroups stratified by age or sex (data not shown). Several plausible explanations exist for this lack of functional association. Firstly, elevated MMP9 levels are observed not only in asthma but also in other inflammatory diseases, such as acute respiratory tract diseases and chronic obstructive pulmonary disease (52). Thus, elevated MMP9 levels may be attributed to other factors rather than the *MMP9* rs3918242 polymorphism. Secondly, the T allele at *MMP9* rs3918242 may have minor effects but is closely linked to other potentially functional polymorphisms within *MMP9* or other genes involved in the inflammatory response (53), which may play more fundamental roles in asthma.

An important finding of this current study is the correlation detected between *MMP9* rs3918242 genotypes and the severity of symptoms among the asthmatic patient cohort (Table IV). Particularly noteworthy is the trend suggesting that individuals with the variant CT or TT genotypes of *MMP9* rs3918242 may be more prone to experiencing heightened symptom severity compared to those with the wild-type CC genotype (Table IV). Our findings may underscore the potential of the *MMP9* rs3918242 T allele as a practical predictor of severe asthma symptoms in Taiwanese. This finding contrasts with the report by Lose and colleagues, which indicated no association between *MMP9* rs3918242 genotype and asthma severity in an Australian population (31). This discrepancy might be attributed to differences in investigated populations, sampling criteria, sample sizes, and definitions of symptom severity.

In summary, our study provides evidence indicating that the T allele of the *MMP9* promoter rs3918242 polymorphism may have a minor role in predicting adult asthma susceptibility in Taiwanese. Conversely, our results indicate that the *MMP9* rs3918242 T allele has an exacerbating effect on the severity of symptoms among asthmatic patients, potentially serving as a predictor for asthma symptom severity. Overall, these preliminary findings warrant validation with larger sample sizes and/or diverse ethnicities. Further studies are urgently needed to deepen our understanding of the involvement of *MMP9* genotype/phenotype in asthma etiology.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Research design: Chiu KL, Chen GL, Bau DT, and Hsia TC; patient and questionnaire summaries: Chiu KL, Chen GL, Shen TC, Chen LH and Hsia TC; experimental work: He JL, Chang WS and Tsai CW; data clearance and identification: He JL, Chen JC and Hsia TC; statistical analysis: Chen JC, Chang WS and Tsai CW; article writing: Chiu KL, Hsia TC and Bau DT; review and revision: Tsai CW, Chang WS, Hsia TC and Bau DT.

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