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Association of *Matrix Metalloproteinase-1* Promoter Polymorphisms With Asthma Risk

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Abstract. *Background/Aim: Matrix metalloproteinase-1 (MMP-1) expression has been documented as an influential contributor to the intricate milieu of allergic airway inflammation, tissue remodeling, and the exacerbation of asthma's severity. However, the genetic role underlying MMP-1 in the context of asthma has remained enigmatic, with its full implications yet to be unveiled. Considering this, our research was designed to investigate the association of MMP-1 -1607 rs1799750 and the propensity for asthma severity. Patients and Methods: As a case–control investigation, our study enrolled 198 individuals diagnosed with asthma and age- and sex-matched 453 non-asthmatic controls. The genotypes of MMP-1 rs1799750 were determined utilizing the polymerase chain reaction-restriction fragment length polymorphism methodology. Results: The frequency distributions of 2G/2G, 1G/2G and 1G/1G genotypes at MMP-1 rs1799750 were 49, 42.9, and 8.1%, respectively, among the patients with asthma. This pattern was not different from that of controls (43.7, 46.8, and 9.5%, respectively) (p for trend=0.4486). The allelic frequency pertaining to the variant 1G allele within the asthma group was 29.5%, with a non-significant disparity compared to the 32.9% in the control group (p=0.2596). Noticeably, there was a positive association between MMP-1 rs1799750 2G/1G and 1G/1G genotypes with asthma severity (p=0.0060). Conclusion: Our research indicated that the presence of MMP-1 rs1799750 1G allele might not be the sole arbiter of an individual's susceptibility to asthma, yet its potential to function as a discerning prognostic marker for the severity of asthma emerged as a noteworthy finding deserving attention and further exploration.*

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Asthma, an extensively prevalent chronic obstructive ailment characterized by intricate airway remodeling, commands global attention due to its substantial impact. The global burden of asthma is staggering, affecting approximately 300 million individuals worldwide, with its prevalence exhibiting an ongoing escalation (1, 2). At its core, asthma manifests with persistent airway inflammation, bronchial hyper-responsiveness (BHR), and variable airway obstruction. The hallmark of clinical presentation lies in the structural modifications occurring within the airways, collectively

referred to as airway remodeling, a phenomenon intricately linked to BHR, airflow obstruction, and the exacerbation of asthmatic symptomatology (3). In 2014, Temesi and his collaborators introduced a pivotal notion within the asthma landscape, proposing an involvement of nearly 200 genes in the etiological framework of asthma, as demonstrated through an animal asthma model (4). While epidemiological investigations have unveiled several genetic markers indicative of an individual's predisposition to asthma (5-8), the pursuit of tangible and pragmatic predictive markers for diagnostic and prognostic applications in the realm of asthma remains a paramount challenge encountered by translational scientists.

The matrix metalloproteinases (MMPs) constitute a diverse protein family responsible for the degradation of various extracellular matrix (ECM) components, including collagen, laminin, fibronectin, and others (9). Despite their significance, the intricate interplay among ECM deposition, MMP-1 expression, and airway function remains incompletely elucidated. The scientific literature has reported that MMP-1's involvement extends to the realm of airway ECM degradation and the maintenance of alveolar wall integrity. This interconnection, in turn, underscores its relevance to both benign and malignant chronic respiratory disorders, such as mycobacterium tuberculosis infection (10), chronic obstructive pulmonary disease (COPD) (11, 12), and emphysema (13, 14).

As far back as 1995, investigations revealed that the administration of collagenase exhibited the capacity to diminish passive tension while concurrently heightening muscle shortening effects within human bronchial smooth muscle strips (15). Correspondingly, collagenase treatment of lung slices was shown to precipitate spontaneous airway constriction (16), thereby culminating in an augmentation of bronchial hyper-responsiveness in an asthma guinea pig model (17). Furthermore, within the framework of airway contraction models, a corpus of research underscores the capacity of exogenously administered MMP-1 to potentiate airway contraction. Notably, the pro-contractile influences of interleukin-4 (IL-4) and interleukin-13 (IL-13) are found to intricately hinge on the expression levels of MMP-1 (18, 19). Intriguingly, MMP-1's presence within normal airways was observed to be at a relatively subdued level, in stark contrast to its pronounced expression within the airway smooth muscle bundles of individuals afflicted with asthma (20, 21). A noteworthy revelation from the preceding year (2022) elucidates the substantial elevation of MMP-1 expression levels within the serum of 25 patients with asthma compared to a cohort of 25 healthy controls in India (22). Collectively, the cumulative evidence underscores the potential pivotal role of MMP-1 in the trajectory of asthma development. Furthermore, the tantalizing possibility of genetic variations within *MMP-1* potentially influencing the etiological fabric of asthma remains an intriguing avenue of exploration. These collective insights converge to impel a deeper understanding of the intricate mechanisms underlying asthma, propelling the scientific community toward enhanced interventions and therapeutic strategies.

MMP-1, a pivotal enzyme, is encoded by the *MMP-1* gene and is localized to the genomic locus 11q22.3 (23, 24). Among the array of *MMP-1* polymorphisms, the most extensively scrutinized is rs1799750, positioned 1607 bases upstream from its promoter region. This polymorphism encompasses distinct variants, including the "2G" insertion polymorphism, associated with heightened MMP-1 serum levels in comparison to the "1G" genotype (25). While the scientific literature touches upon the exploration of *MMP-1* genotype-asthma associations, conclusive findings remain elusive (26, 27). Considering the preceding information, our current inquiry is poised to meticulously investigate the nexus between *MMP-1* genotypes and asthma within a population comprising 198 individuals diagnosed with asthma and 453 non-asthmatic controls. Moreover, our investigative curiosity extends to discerning the contributions of *MMP-1* genotypes to the clinical severity gradient stages among patients with asthma.

Patients and Methods

Selection of patients with asthma and non-asthmatic controls. The study population comprised 198 individuals diagnosed with asthma, meticulously selected from China Medical University Hospital. In tandem, a cohort of 453 non-asthmatic individuals was conscientiously chosen, with sex and age (within ±5 years) matching criteria, and included as controls in alignment with our previously published methodologies (7, 28). Ethical validation for the current investigation was secured from the Research Ethics Committee of China Medical University Hospital (CMUH106-REC1-004). To ensure the precision of the evaluation, the degree of symptom severity for each participant with asthma underwent rigorous validation by a panel of at least two seasoned pulmonary physicians, operating under the leadership of Dr. Hsia. This verification process was conducted in accordance with the guidelines stipulated by the Global Initiative for Asthma (GINA) (2). The clinical attributes exhibited by the patients with asthma enabled their categorization into four distinct severity stages, as meticulously delineated, recorded, and closely monitored over the course of the study.

Genotyping methodology for MMP-1 genotypes. Peripheral blood samples were meticulously collected from all participants, with subsequent genomic DNA extraction carried out within a 24-h post-blood collection, as per established procedures (29). The genotyping protocol for *MMP-1* rs1799750 was consistent with our previously detailed methodology (30). The polymerase chain reaction (PCR) conditions for *MMP-1* rs1799750 genotyping were initiated at 94˚C for 5 min, followed by 35 cycles of denaturation at 94˚C for 30 s, annealing at 57˚C for 30 s, extension at 72˚C for 30 s, and concluding with a final extension step at 72˚C for 10 min. Subsequently, the temperature was lowered to 25˚C.

Statistical methodology. To assess the adherence of the control group to Hardy-Weinberg equilibrium, the goodness-of-fit Chi-

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

Character	Controls (n=453)		Cases (n=198)		*p*-Value[a]
	n	%	n	%	
Age (years)					
25-40	285	63.4%	133	67.2%	
>40	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
Symptoms 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%: percent of predicted FEV1; [a]Chi-square with Yate's correction test or Student's t-test.

square test was implemented. Differential age distributions between the case and control groups were analyzed using the Student's *t*-test. The examination of diverse *MMP-1* genotype distributions was carried out through the Pearson's Chi-square test. To explore the potential interplay between *MMP-1* genotypes and symptom severity, a 2×4 Chi-square test was employed. In evaluating the influence of *MMP-1* genotypes on asthma risk, odds ratios (ORs) were computed alongside their corresponding 95% confidence intervals (CIs). A significance threshold of *p*-value greater than or equal to 0.05 was adopted to establish a non-statistical significance.

Results

Demographic characteristics of patients with asthma and non-asthmatic participants. Table I presents a comprehensive overview of the age, sex, and certain clinical attributes, including pulmonary functions and symptom severity, concerning the 198 individuals diagnosed with asthma and the 453 non-asthmatic controls. Due to our meticulous matching of age and sex between the two cohorts of patients with asthma and controls, no significant distinctions emerged in terms of age and sex (p=0.2972 and 0.9956, respectively). Turning to the realm of pulmonary functions, noteworthy disparities were evident. The mean ratio of forced expiratory volume (FEV) in the first second to forced vital capacity (FEV1/FVC, %) and the percentage of predicted FEV1 (FEV1%) both exhibited lower values within the asthma group compared to the control group (both p<0.0001). In terms of symptom severity, the distribution among patients with asthma 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 between MMP-1 rs1799750 polymorphisms and asthma risk. The distribution frequencies of *MMP-1* rs1799750 genotypes within the cohort of 198 patients with asthma and 453 non-asthmatic healthy controls are meticulously detailed in Table II. To begin with, the frequencies of *MMP-1* rs1799750 genotypes within the control group demonstrated adherence to the Hardy-Weinberg equilibrium (p=0.2009). Subsequently, upon scrutinizing the differential frequencies of *MMP-1* rs1799750 genotypes, no statistically significant distinctions emerged between the patients with asthma and the non-asthmatic healthy controls (p for trend=0.4486, Table II). A more granular assessment revealed that both the 2G/1G and 1G/1G genotypes of *MMP1* exhibited non-significant distribution patterns when comparing patients with asthma to non-asthmatic controls (OR=0.82 and 0.76, 95%CI=0.58-1.16 and 0.41-1.42, p=0.3009 and 0.4753, respectively; Table II). Moreover, the findings stemming from comparisons between the combined 2G/2G+2G/1G genotypes and the 1G/1G genotype (OR=0.84, 95%CI=0.46-1.53, p=0.6681), as well as between the 2G/2G genotype and the 2G/1G+1G/1G genotypes (OR=0.81, 95%CI=0.58-1.13, p=0.2462), collectively indicated that individuals harboring the variant genotypes exhibited an unaltered risk of asthma compared to those with the wild-type genotype within the studied population (Table II).

Association of MMP-1 rs1799750 variant allelic 1G with asthma risk. Table III comprehensively presents the allelic frequencies of *MMP-1* rs1799750 polymorphisms within the cohort of patients with asthma and non-asthmatic healthy

Table II. *Distributions of MMP-1 rs1799750 genotypes among patients with asthma and non-asthmatic controls.*

Genotype	Asthmatic cases, n (%)	Non-asthmatic controls, n (%)	OR (95%CI)	*p*-Value[a]
rs1799750				
2G/2G	97 (49.0)	198 (43.7)	1.00 (Reference)	
2G/1G	85 (42.9)	212 (46.8)	0.82 (0.58-1.16)	0.3009
1G/1G	16 (8.1)	43 (9.5)	0.76 (0.41-1.42)	0.4753
p_{trend}				0.4486
p_{HWE}				0.2009
Carrier analysis				
2G/2G+2G/1G	182 (91.9)	410 (90.5)	1.00 (Reference)	
1G/1G	16 (8.1)	43 (9.5)	0.84 (0.46-1.53)	0.6681
2G/2G	97 (49.0)	198 (43.7)	1.00 (Reference)	
2G/1G+1G/1G	101 (51.0)	255 (56.3)	0.81 (0.58-1.13)	0.2462

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

Table III. *Distribution of MMP-1 rs1799750 allelic frequencies among patients with asthma and non-asthmatic controls.*

Allelic type	Asthmatic cases, n (%)	Non-asthmatic controls, n (%)	OR (95%CI)	*p*-Value[a]
rs1799750				
Allele 2G	279 (70.5)	608 (67.1)	1.00 (Reference)	
Allele 1G	117 (29.5)	298 (32.9)	0.86 (0.66-1.11)	0.2596

OR: Odds ratio; CI: confidence interval. [a]Based on Chi-square test with Yates' correction.

controls. In alignment with the observations detailed in Table II, individuals possessing the 1G allele at *MMP-1* rs1799750 exhibited no discernible alteration in asthma risk in comparison to those harboring the 2G allele (OR=0.86, 95%CI=0.66-1.11, *p*=0.2596) (Table III).

Correlation between MMP-1 rs1799750 genotypes and asthmatic symptom severity. Our investigative focus extended to the intricate interplay between *MMP-1* genotypes and the severity of asthma symptoms within a clinical context. In pursuit of this exploration, patients with asthma underwent stratification based on their *MMP-1* rs1799750 genotypes and corresponding symptom severity profiles. The outcomes of this analysis are meticulously outlined in Table IV. Evidently, the outcomes delineated in Table IV underscore that individuals harboring variant genotypes (2G/1G or 1G/1G carriers) at *MMP-1* rs1799750 were confronted with an elevated susceptibility to grapple with severe symptom severity, in contrast to their wild-type (2G/2G) counterparts (*p*=0.0060) (Table IV). In a more nuanced examination, the distribution percentages of wild-type carriers within the first (mildest), second, third, and fourth (most severe) stages of patients with asthma stood at 45.5%, 31.7%, 12.9%, and 9.9%, respectively. Notably, a substantial disparity emerged: the percentages of wild-type carriers were distinctly higher among patients in the first stage, and conversely lower among those in the fourth stage. In stark contrast, a reverse trend was observed for variant genotype carriers, where distributions diverged in an opposing trajectory (Table IV).

Discussion

MMP-1 plays a pivotal role in the degradation of various collagen types, including I, II, III, VI, and X (31). The indispensability of MMP-1 is underscored by the lack of available knockout murine models for further investigation. Assessing the influence of *MMP-1* polymorphisms on asthma susceptibility not only deepens our insights into the intricate mechanisms governing asthma origins, but also lays the groundwork for the advancement of novel therapeutic strategies.

In the present hospital-based case-control study, the potential impact of *MMP-1* rs1799750 polymorphism on asthma susceptibility was meticulously investigated, encompassing a cohort of 198 individuals with asthma and 453 carefully matched controls in terms of age and sex (Table I). Notably, this study stands out as the most expansive epidemiological inquiry centered on the role of

Table IV. *Association of MMP-1 rs1799750 polymorphisms with the symptom's severity among patients with asthma.*

Genotype	Symptom severity, n (%)				*p*-Value[a]
	1 (mildest)	2	3	4 (severest)	
rs1799750					
Wild-type 2G/2G genotype	46 (45.5)	32 (31.7)	13 (12.9)	10 (9.9)	
Variant 2G/1G or 1G/1G genotypes	23 (23.7)	35 (36.1)	18 (18.6)	21 (21.6)	**0.0060**

[a]Chi-square with Yate's correction test; The significant *p*-value is bolded.

MMP-1 in asthma etiology, representing a substantial advancement in scale compared to previous endeavors (control:case ratio of 453:198 in this study *versus* 88:43 in the earlier study by Huang and his colleagues) (26). They pioneered research into the subject by reporting that the 1G allele at *MMP-1* rs1799750 exhibited a link to persistent airway obstruction among individuals with asthma (26). While the current investigation did not yield statistically significant disparities, there appears to be a propensity for higher occurrences of the variant 2G/1G and 1G/1G genotypes within the asthma group in comparison to the control group (Table II and Table III). An intriguing observation is that both Huang's study and our own focus on Taiwanese populations. Nonetheless, in order to draw definitive conclusions, further studies encompassing diverse populations and larger sample sizes are imperative.

A noteworthy focal point of the present investigation lies in the correlation observed between the genotypes of *MMP-1* rs1799750 and the severity of symptoms within the cohort of patients with asthma (Table IV). Notably, there appears to be an inclination suggesting that individuals carrying the 1G/1G or 2G/1G genotypes may be more prone to experiencing more pronounced symptom severity when compared to those harboring the wild-type 2G/2G genotype (Table IV).

The presence of MMP-1 within the airways of individuals with asthma has been reported, and its activation within airway smooth muscle cells has been linked to mast cell-derived tryptases (32). A myriad of factors has been identified as capable of enhancing MMP-1 expression in lung tissues, including cigarette smoking (33-35). Overexpression of MMP-1 has been observed in airway epithelial cells, inflammatory cells, and notably airway smooth muscle cells of individuals with asthma (36, 37), with a particularly heightened presence in the outer wall of small airways in fatal asthma cases (38). MMP-1 expression closely aligns with bronchial repair capacity (39), and is intricately connected to the proliferation of airway smooth muscle (32). Transient surges in MMP-1 activity during asthma exacerbations have been associated with the severity of such exacerbations (32). The alterations in ECM orchestrated by MMP-1 within the context of airway remodeling could contribute to an environment that fosters increased airway constriction and exacerbation of asthma symptoms. Of particular note is the potential for interrupting interactions between mast cells and airway smooth muscle cells to serve as a potential countermeasure for mitigating airway remodeling in asthma.

In summary, our study outcomes propose that while the 1G/1G genotype of *MMP-1* rs1799750 may not exhibit a direct correlation with an increased asthma risk, individuals carrying the variant 1G allele appear to experience more severe asthma symptoms. The manipulation of MMP-1 expression could potentially serve as a therapeutic approach for averting the onset and/or mitigating the progression of asthma severity.

Conflicts of Interest

All the Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Research design: Chen LH, Li CH, Bau DT; Questionnaire summary: Chen LH, Li CH, Wang SC, Chiu KL, Wu MF, Hsia TC; Experiment performance: Yang JS, Tsai CW, Chang WS; Statistical analysis and confirmation: Wang SC, Tsai CW, Hsia TC; Manuscript writing: Chen LH, Li CH, Bau DT; Polishing and correction: Wang SC, Hsia TC, Bau DT.

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