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Original Article

Association between inflammatory cytokine gene polymorphisms and asthma susceptibility in Chinese Han children: a retrospective case-control study for potential diagnostic biomarkers

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Abstract: Objectives: This retrospective case-control study aimed to examine asthma prevalence and associated risk factors among the Han Chinese population, with particular emphasis on evaluating the interplay between inflammatory cytokine profiles and genetic polymorphisms in asthma pathogenesis. Methods: Conducted at Shanghai Seventh People's Hospital, the study recruited 480 pediatric asthma patients and 840 matched controls. Comprehensive data collection included standardized clinical evaluations and epidemiological questionnaires. Laboratory analyses comprised enzyme-linked immunosorbent assay (ELISA)-based quantification of interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-17 (IL-17), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) genotyping of relevant polymorphisms. Results: Asthma cases demonstrated markedly increased cytokine levels versus controls (P<0.05). Significant associations were found for IL-1β -511C/T (OR=1.88, 95% CI: 1.38-2.57, P<0.05), IL-10 -1082G/A (OR=1.65, 95% CI: 1.25-2.17, P<0.05), IFN-γ +2108 A/G (OR=2.36, 95% CI: 1.18-4.73, P<0.05), and TNF-α -308 G/A (OR=1.65, 95% CI: 1.25-2.17, P<0.05). Conclusions: Cytokine gene polymorphisms in IL-1B, IFN-γ, TNF-α, and IL1B are associated with altered inflammatory profiles in asthma, suggesting a genetic contribution to disease-related immune dysregulation. The findings establish that both cytokine dysregulation and specific genetic variants contribute to asthma susceptibility in the Chinese Han population. Our study suggests that these factors hold potential as biomarkers for the diagnosis and clinical prognosis of asthma.

Keywords: Asthma, inflammatory factors, gene expression, gene polymorphism

Introduction

Asthma, a prevalent chronic inflammatory disorder of the respiratory system, predominantly manifests in childhood and is characterized by recurrent symptoms including chest tightness, wheezing, dyspnea, and productive cough [1]. Epidemiological studies highlight its escalating global incidence, driven by modern lifestyle transitions and exacerbated environmental pollutants such as particulate matter (PM2.5) and nitrogen dioxide (NO_2). Pathophysiologically, aberrant immune responses-particularly eosinophilia inflammation and dysregulated type I/III interferon signaling - contribute to airway hyperresponsiveness and remodeling. While bronchodilators and inhaled corticosteroids remain first-line therapies, their limited efficacy in refractory cases underscores the need for novel biomarkers and targeted interventions. Emerging strategies, including modulation of mast cell-derived exosomes and glucocorticoid-responsive genes, demonstrate promise in improving diagnostic precision and therapeutic outcomes [2]. Addressing these multifaceted challenges requires integrating genetic, environmental, and immunological insights to mitigate disease recurrence and enhance long-term pulmonary function.

Asthma is increasingly recognized as a heterogeneous disease characterized by chronic airway inflammation, with cumulative inflammatory insults driving the development of airway

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hyperresponsiveness (AHR) over time. Clinical manifestations vary widely among patients, encompassing diverse etiologies, symptom profiles, treatment modalities, and therapeutic responses. This pathophysiological heterogeneity, compounded by multifactorial triggers - including genetic predisposition, environmental exposures, and dietary factors - contributes to the recurrent and refractory nature of asthma. Poorly controlled cases frequently exhibit unpredictable exacerbations, progressive declines in pulmonary function, and elevated risks of severe complications, such as respiratory failure, which substantially impair quality of life and long-term prognosis. Emerging evidence underscores the central role of dysregulated immune responses, particularly the imbalance between pro-inflammatory cytokines and anti-inflammatory mediators in perpetuating airway remodeling and treatment resistance. Consequently, sustained airway inflammation is now regarded as the pathogenic cornerstone of asthma initiation and progression. Asthma is a pervasive chronic inflammatory disorder of the airways, representing a significant and growing global health burden, particularly in pediatric populations. Its pathogenesis is characterized by a complex interplay of genetic predisposition and dysregulated immune responses. Central to this process is a network of inflammatory cytokines - including interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-17 (IL-17), interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) - which orchestrate airway inflammation, hyper-responsiveness, and remodeling. Genetic polymorphisms within the promoter or regulatory regions of these cytokine genes are critical determinants of interindividual variation in their expression, thereby influencing asthma susceptibility, severity, and therapeutic response. While contemporary asthma research has elucidated the role of inflammatory mediators in disease pathogenesis and diagnosis, their utility as predictive biomarkers for asthma control remains an understudied frontier with significant clinical implications. Current studies predominantly adopt a reductionist approach, focusing on isolated cytokines or single-nucleotide polymorphisms (SNPs) within individual genes, thereby overlooking the synergistic interplay of multifactorial inflammatory networks. In contrast, our study pioneers a comprehensive analysis of systemic cytokine profiles including IL-1β, IL-6, IL-17A, and TNF-α alongside their genetic regulators to unravel their collective impact on asthma severity and therapeutic responsiveness. Emerging evidence suggests that dynamic cytokine thresholds, rather than static elevations, may serve as predictive biomarkers for exacerbation risk and control stratification. By integrating longitudinal cytokine monitoring with genotype-phenotype correlations, this work advances a paradigm shift toward precision asthma management, bridging mechanistic insights with actionable clinical algorithms [3-11]. On the other hand, the results of gene polymorphism research are influenced by many factors. Different countries, regions, races and climatic environments can all lead to different results. Moreover, the results of previous studies have been inconsistent, and the sample size is relatively small. Despite the recognized importance, current research on inflammatory biomarkers in asthma faces notable limitations. Many studies adopt a reductionist approach, focusing on isolated cytokines or SNPs, which fail to capture the synergistic effects within the multifactorial inflammatory network. Furthermore, findings are often inconsistent due to inadequate sample sizes and population stratification, especially among Chinese Han children. There remains a significant gap in large-scale, systematic analyses that concurrently evaluate both systemic cytokine profiles and their genetic regulators to establish their combined utility as reliable diagnostic or prognostic tools.

To address these gaps, we conducted a large-scale retrospective case-control study. Our investigation innovatively integrates the analysis of serum levels of six key cytokines with a comprehensive genotyping of their functionally relevant polymorphisms in a well-characterized cohort of Chinese Han children. This design allows for a holistic assessment of the genetic-immune interface in asthma. By employing multivariate regression and diagnostic efficiency analyses, we aim not only to identify significant associations but also to evaluate the potential of combined genetic and cytokine markers as a translational biomarker panel for improved asthma risk stratification and diagnosis. This study comprehensively investigated all the important loci of inflammatory factor-related genes through a large sample size, thereby comprehensively and rigorously analyzing the relationship between inflammatory factors and the onset of asthma.

Materials and methods

Study design and patient selection

This retrospective case-control study utilized data from the electronic medical record system and the biobank of Shanghai Seventh People's Hospital. The case group comprised 480 pediatric asthma patients admitted between January 2018 and December 2023. The control group consisted of 840 age- and sex-matched children who underwent routine health examinations during the same period. The study was approved by the Institutional Review Board (IRB No. 2024-7th-HIRB-107). All subjects and their families were aware of this study and voluntarily signed the informed consent. Inclusion criteria for cases: (1) Confirmed diagnosis of asthma according to the Global Initiative for Asthma (GINA) guidelines, with complete medical records; (2) Availability of a baseline serum sample in the hospital biobank collected at the time of diagnosis; (3) Han Chinese ethnicity. Exclusion criteria for cases: (1) Diagnosis of other chronic respiratory diseases; (2) Comorbid autoimmune, systemic inflammatory, or malignant diseases; (3) Incomplete clinical or laboratory data. Selection of Controls: Healthy controls were identified from the health examination database, matched for age (±1 year) and sex, with no history of asthma, allergic diseases, or other chronic inflammatory conditions. **Figure 1** shows the patient screening flowchart based on reporting STROBE guidelines.

Data extraction and variables

Data were independently extracted by two researchers using a standardized case report form. Any discrepancies were resolved by consensus or by consultation with a third investigator. The extracted data included: Demographics: Age, sex, body mass index (BMI). Clinical data: Asthma diagnosis, smoking exposure history. Laboratory Data: Serum levels of six inflammatory cytokines (IL-1β, IL-6, IL-10, IL-17A, IFN-γ, TNF-α) measured by enzyme-linked immunosorbent assay (ELISA) (Thermo Fisher Scientific, Waltham, MA, USA). Genetic data: Genotypes for pre-specified polymorphisms in the genes of the above cytokines (IL1B -511 C/T (rs16944), TNF -308 G/A (rs1800629)) determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) (Qiagen QIAamp DNA Blood Mini Kit, Hilden, Germany).

Outcome measures

The primary outcome was the association between specific cytokine gene polymorphisms and asthma susceptibility, measured by odds ratios (ORs) and 95% confidence intervals (CIs). Secondary outcomes included: (1) Differences in serum cytokine levels between asthma patients and controls; (2) The diagnostic performance of significant cytokines and/or genetic markers for asthma.

Statistical analysis

Statistical analyses were performed using SPSS 26.0 (IBM Corp.). Continuous variables were compared using independent t-tests or Mann-Whitney U tests. Categorical variables were compared using the χ^2 test or Fisher's exact test. Hardy-Weinberg equilibrium was assessed in the control group. The associations between genotypes and asthma risk were evaluated using unconditional logistic regression, calculating crude and adjusted ORs with 95% CIs. Multivariable logistic regression was used to adjust for potential confounders (age, sex, BMI). Multivariable logistic regression was used to adjust for potential confounders, including age (continuous), sex (categorical), and BMI (continuous). Correlation analyses were conducted using Spearman's rank correlation. The diagnostic performance of biomarkers was evaluated by generating receiver operating characteristic (ROC) curves. A two-tailed *p*-value <0.05 was considered statistically significant. Furthermore, it is necessary to emphasize that unconditional logistic regression analysis was performed to evaluate the associations between genotypes and asthma risk. Both crude (unadjusted) and adjusted ORs with 95% CIs were calculated. For multivariable analysis, we employed a forced entry (enter) method, wherein all pre-selected covariates-age, sex, and BMI-were entered into the model simultaneously. This approach was chosen based on a priori knowledge of these variables as potential confounders from previous literature, rather than using automated stepwise selection procedures (forward or backward). The 'enter' method ensures that adjustments are made for all specified confounders regardless of their individual statistical significance, provid-

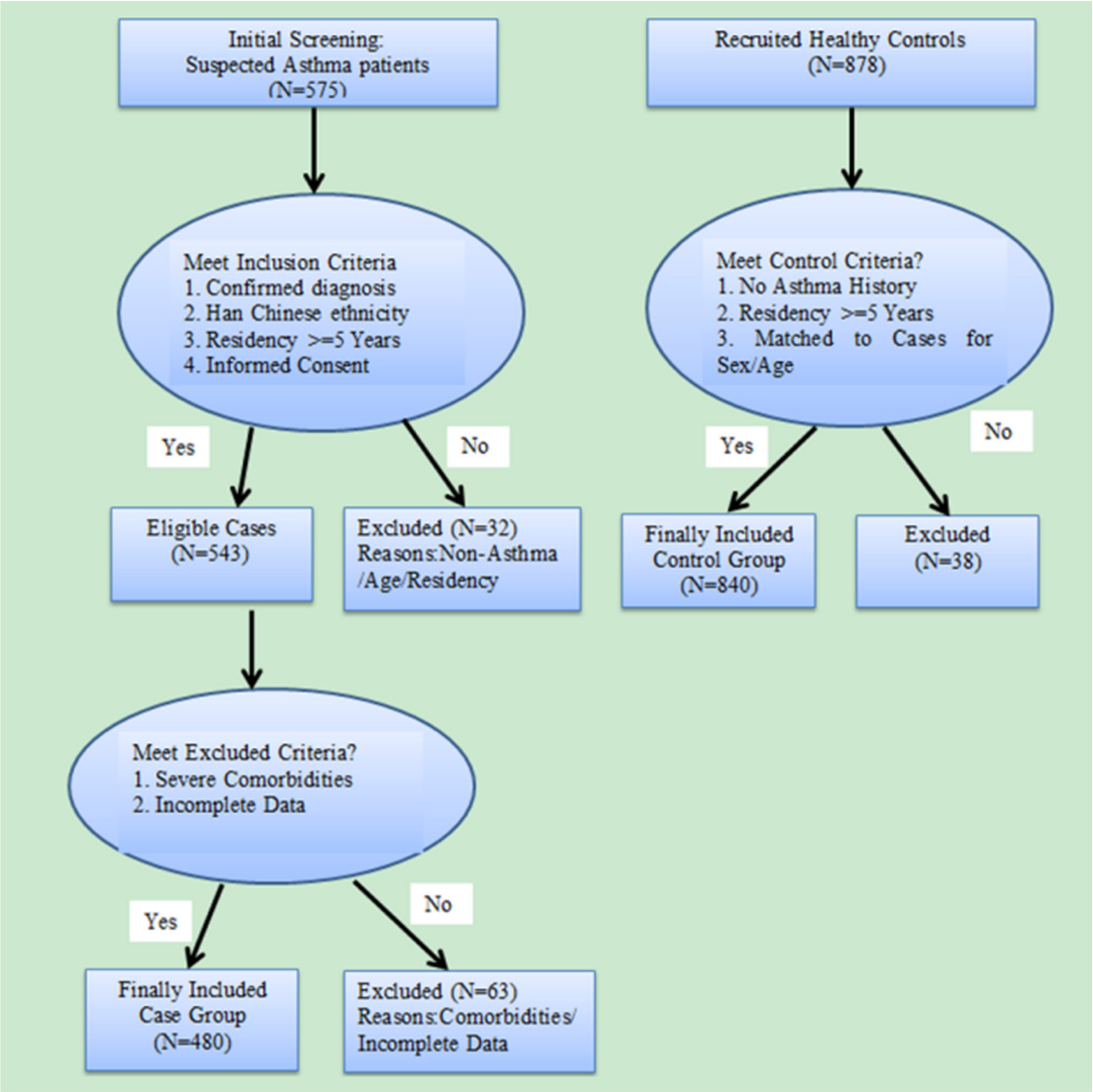

Figure 1. Patient screening flowchart based on reporting STROBE guidelines.

ing a more conservative and clinically interpretable estimate of the independent effect of each genotype. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Results

Comparison of demographic and baseline characteristics between groups

Demographic characteristics (gender, age, and weight) of the asthma and healthy control groups were analyzed using chi-square tests (for categorical variables) and independent t-tests (for continuous variables). No statistically significant differences were observed between the two groups, as indicated by *p*-values exceeding 0.05 for all comparisons (**Table 1**).

Hardy-Weinberg equilibrium (HWE) analysis

The genotype distributions of inflammatory factor loci in both the asthma and healthy control groups were evaluated for conformity to Hardy-Weinberg equilibrium (HWE). Observed and expected genotype frequencies were compared, with *p*-values >0.05 indicating compliance with HWE. All tested loci in this study satisfied HWE criteria (P>0.05), confirming the

Table 1. Participant characteristics of asthma

Characteristics	Asthma group (N=480)	Control group (N=840)	*p*
Age	8.6±2.2	8.2±2.1	>0.05
Men	306 (63.8%)	588 (70.0%)	>0.05
BMI	24.8±1.6	24.9±1.5	>0.05
Smokers	144 (30.3%)	255 (30.4%)	>0.05
Drinking history	81 (16.9%)	117 (13.9%)	>0.05
Diabetes mellitus	50 (10.4%)	86 (10.2%)	>0.05
Hypertension	306 (63.8%)	588 (70.0%)	>0.05

BMI, body mass index.

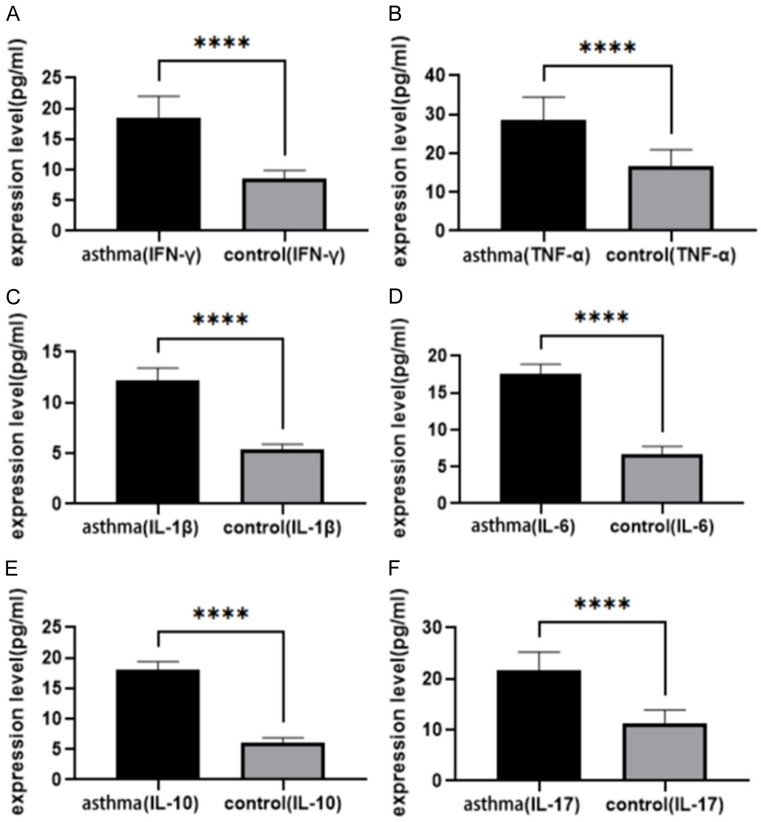

Figure 2. Comparison of inflammatory cytokine expression levels between asthma patients and healthy pregnant women. ****expression of all cytokine levels are significantly higher in the asthma group compared to the control group (P<0.05). A. IFN-γ; B. TNF-α; C. IL-1; D. IL-6; E. IL-10; F. IL-17. IL-1β, interleukin-1β; IL-6, interleukin-6; IL-10, interleukin-10; IL-17, interleukin-17; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α.

genetic representativeness of the sampled populations.

Expression levels of inflammatory cytokines

Expression levels of inflammatory cytokines (IL-1, IL-6, IL-10, IL-17, IFN-γ, and TNF-α) were visualized using bar graphs generated in GraphPad Prism software. Quantitative analysis revealed significantly elevated cytokine expression levels in the asthma group compared to the healthy control group (P<0.05 for all cytokines; **Figure 2**). Additionally, Spearman's rank correlation analysis was performed on the six cytokines (see **Figure 3**) to evaluate the interrelationships among various inflammatory mediators in both the asthma and control groups. Furthermore, the diagnostic potential of these cytokines was assessed using ROC curve analysis (**Figure 4**). The results demonstrated that IL-6 and TNF-α possessed high diagnostic efficiency, with AUC values of 0.817 and 0.813, respectively. IL-1β also showed moderate diagnostic value (AUC=0.761), while IL-10 exhibited relatively lower diagnostic performance (AUC=0.595).

Analysis of gene polymorphisms

All investigated gene polymorphism loci exhibited three distinct genotypes and two alleles. Significant associations with asthma susceptibility were identified for the following polymorphisms: *IL-1β* -511 C/T (rs16944), *IL-10* -1082 G/A (rs1800896), *IFN-γ* +2108 A/G (rs1861494), and *TNF-α* -308 G/A (rs1800629) (P<0.05). Remaining loci within these genes showed no statistically significant associations (P>0.05). Detailed genotype and allele frequency da ta are provided in **Tables 2**-**7**. Specifically, compared to the respective reference genotypes, carriers of the TC (adjusted OR= 2.45, 95% CI: 1.28-4.71, P=0.007) and TT (adjusted OR=2.89, 95% CI: 1.57-5.32, P<

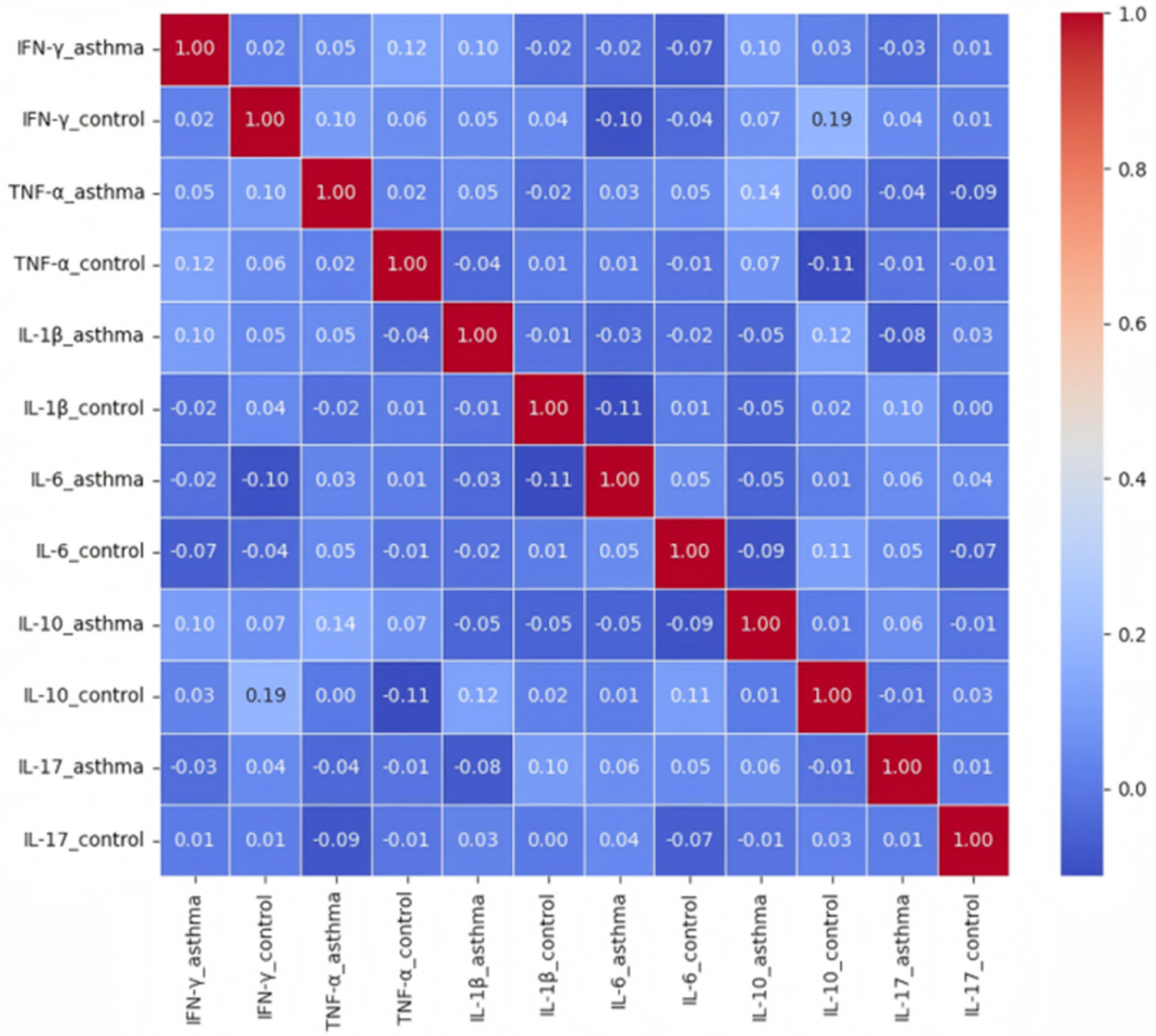

Figure 3. Spearman's rank correlation matrix heatmap for cytokine expression levels in asthma and control groups. Note: The values in the heatmap represent correlation coefficients; the color transition from blue to red indicates the progression from negative to positive correlation.

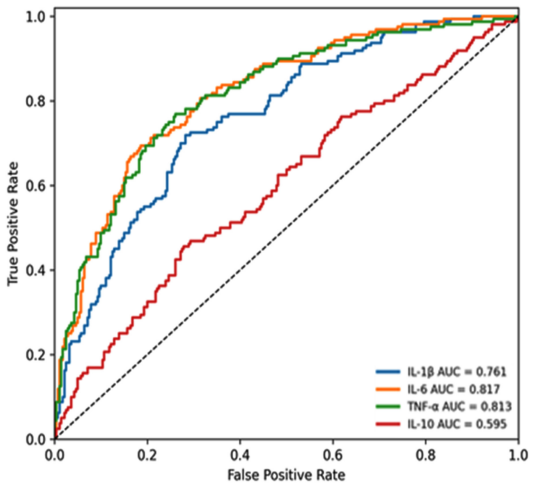

Figure 4. ROC curves of the degree of asthma. IL-1β, interleukin-1β; IL-6, interleukin-6; IL-10, interleukin-10; TNF-α, tumor necrosis factor-α.

0.001) genotypes of IL1B-511C/T (rs16944) had significantly higher asthma risk. For the IL10 -1082G/A (rs1800896) polymorphism, both the GA (adjusted OR=2.38, 95% CI: 1.44-3.92, P<0.001) and AA (adjusted OR=2.48, 95% CI: 1.42-4.32, P=0.001) genotypes were independent risk factors. Similarly, the GA (adjusted OR=1.79, 95% CI: 1.02-3.14, P=0.042) and AA (adjusted OR=1.72, 95% CI: 1.01-2.94, P=0.047) genotypes of TNF-308G/A (rs1800629) showed independent associations with asthma. In contrast, for IFNG +874A/T (rs2430561), only the TT genotype demonstrated an independent association (adjusted OR=2.21, 95% CI: 1.10-4.45, P=0.026), while the AT genotype did not (adjusted OR=1.01, 95% CI: 0.67-1.52, P=0.970). **Table 8** shows the SNP loci of independent risk factors for asthma.

Table 2. IL-1β genotype and allele frequency for patients with asthma

IL-1β loci	Control group (N=840)		Asthma group (N=480)		OR (95% CI)[a]	P[a]
	n	Percentage (%)	n	Percentage (%)		
-511 C/T						
CC	204	24.3	48	10.0	1.00[REF]	
TC	213	25.4	132	27.5	2.63 (1.36-5.11)	0.004
TT	423	50.3	300	62.5	3.01 (1.65-5.50)	<0.001
C	621	37.0	228	23.6	1.00[REF]	
T	1059	63.0	732	76.4	1.88 (1.38-2.57)	<0.001
+3954 C/T						
CC	435	51.8	240	50.0	1.00[REF]	
TC	336	40.0	198	41.3	1.07 (0.71-1.61)	0.752
TT	69	8.2	42	8.7	1.10 (1.54-2.26)	0.789
C	1206	71.8	678	70.6	1.00[REF]	
T	474	28.2	282	29.4	1.06 (0.78-1.43)	0.714
-31 C/T						
CC	453	53.9	267	55.6	1.00[REF]	
TC	336	40.0	180	37.5	1.91 (0.60-1.37)	0.647
TT	51	6.1	33	6.9	1.10 (0.49-2.45)	0.820
C	1242	73.9	714	74.4	1.00[REF]	
T	438	26.1	246	25.6	1.98 (0.71-1.34)	0.884

IL-1β, interleukin-1β; OR, odds ratio; CI, confidential index; [a]Adjusted for age, sex and BMI by logistic regression model.

Table 3. IL-6 genotype and allele frequency for patients with asthma

IL-6 loci	Control group (N=840)		Asthma group (N=480)		OR (95% CI)[a]	P[a]
	n	Percentage (%)	n	Percentage (%)		
-174 G/C						
GG	414	49.3	246	51.3	1.00[REF]	
GC	276	32.9	144	30.0	1.88 (0.47-1.64)	0.804
CC	150	17.8	90	18.7	1.01 (0.48-2.13)	0.869
G	1104	65.7	636	66.3	1.00[REF]	
C	576	34.3	324	33.7	0.98 (0.65-1.47)	0.992
-1363 G/T						
GG	390	46.4	234	48.7	1.00[REF]	
GT	354	42.2	144	30.0	1.68 (0.37-1.26)	0.281
TT	96	11.4	78	16.3	1.35 (0.59-3.11)	0.617
G	1134	67.5	612	63.8	1.00[REF]	
T	546	32.5	300	36.2	1.02 (0.67-1.55)	0.981
-1363 C/G						
CC	486	57.8	300	62.5	1.00[REF]	
GC	330	39.3	162	33.8	1.80 (0.45-1.42)	0.530
GG	24	2.9	18	3.7	1.22 (0.26-5.66)	0.881
C	1302	77.5	762	79.4	1.00[REF]	
G	378	22.5	198	20.6	1.90 (0.56-1.44)	0.735

IL-6, interleukin-6; OR, odds ratio; CI, confidential index; [a]Adjusted for age, sex and BMI by logistic regression model.

Discussion

Asthma currently affects approximately 334 million individuals globally, with reported incidence rates ranging from 13% to 20% and demonstrating a persistent upward trajectory. Epidemiological analyses reveal significant geographical disparities: developed nations ex-

Table 4. IL-10 genotype and allele frequency for patients with asthma

IL-10 loci	Control group (N=840)		Asthma group (N=480)		OR (95% CI)[a]	P[a]
	n	Percentage (%)	n	Percentage (%)		
-592 C/A						
CC	234	27.9	114	23.8	1.00[REF]	
CA	336	40.0	228	47.5	1.39 (0.86-2.37)	0.180
AA	270	32.1	138	28.7	0.91 (0.53-1.56)	0.738
C	804	47.9	456	47.5	1.00[REF]	
A	876	52.1	504	52.5	1.01 (0.77-1.34)	0.919
-1082 G/A						
GG	306	36.4	90	18.8	1.00[REF]	
GA	342	40.7	246	51.2	2.45 (1.49-4.02)	<0.001
AA	192	22.9	144	30.0	2.55 (1.47-4.43)	<0.001
G	954	56.8	426	44.4	1.00[REF]	
A	726	43.2	534	55.6	1.65 (1.25-2.17)	<0.001
-819 T/C						
TT	456	54.3	282	58.8	1.00[REF]	
TC	276	32.8	150	31.2	1.88 (0.48-1.61)	0.793
CC	108	12.9	48	10.0	0.72 (0.29-1.78)	0.624
T	1188	70.7	714	74.4	1.00[REF]	
C	492	29.3	246	25.6	0.83 (0.54-1.29)	0.476

IL-10, interleukin-10; OR, odds ratio; CI, confidential index; [a]Adjusted for age, sex and BMI by logistic regression model.

Table 5. IL-17 genotype and allele frequency for patients with asthma

IL-17 loci	Control group (N=840)		Asthma group (N=480)		OR (95% CI)[a]	P[a]
	n	Percentage (%)	n	Percentage (%)		
rs2275913						
GG	435	51.8	240	50.0	1.00[REF]	
GA	336	40.0	198	41.3	1.07 (0.71-1.61)	0.752
AA	69	8.2	42	8.7	1.10 (1.54-2.26)	0.789
G	1206	71.8	678	70.6	1.00[REF]	
A	474	28.2	282	29.4	1.06 (0.78-1.43)	0.714
rs763780						
TT	453	53.9	267	55.6	1.00[REF]	
TC	336	40.0	180	37.5	1.91 (0.60-1.37)	0.647
CC	51	6.1	33	6.9	1.10 (0.49-2.45)	0.820
T	1242	73.9	714	74.4	1.00[REF]	
C	438	26.1	246	25.6	1.98 (0.71-1.34)	0.884

IL-17, interleukin-17; OR, odds ratio; CI, confidential index; [a]Adjusted for age, sex and BMI by logistic regression model.

hibit higher prevalence rates compared to developing countries, while temperate climatic zones show elevated disease burden relative to colder regions [12]. The global proportion of children with asthma symptoms is 14.2%, and the mortality rate is 0-0.7 per 100,000 people, which is higher than that of adults [13]. The lifetime prevalence of asthma in children is as high as 14% [13], and the heritability of single nucleotide polymorphisms in children is about 3 times that of adults. Studies have shown that before adolescence, the incidence of childhood asthma is higher in males than in females; after puberty, the prevalence is higher in female children [12]. At present, the proportion of children suffering from bronchial asthma is about 1%-4%, which is significantly higher than the incidence of adult asthma in China. The high

Table 6. IFN-γ genotype and allele frequency for patients with asthma

IFN-γ loci	Control group (N=840)		Asthma group (N=480)		OR (95% CI)[a]	P[a]
	n	Percentage (%)	n	Percentage (%)		
+874 A/T						
AA	453	53.9	237	49.4	1.00[REF]	
AT	336	40.0	180	37.5	1.02 (0.68-1.55)	0.911
TT	51	6.1	63	13.1	2.36 (1.18-4.73)	0.014
A	1242	73.9	654	68.1	1.00[REF]	
T	438	26.1	306	31.9	1.33 (0.98-1.79)	0.066
+2108 A/G						
AA	429	51.1	240	50.0	1.00[REF]	
AG	336	40.0	198	41.3	1.05 (0.70-1.59)	0.803
GG	75	8.9	42	8.7	1.00 (0.49-2.03)	0.998
A	1194	71.1	678	70.6	1.00[REF]	
G	486	28.9	282	29.4	1.02 (0.76-1.38)	0.888

IFN-γ, interferon-γ; OR, odds ratio; CI, confidential index; [a]Adjusted for age, sex and BMI by logistic regression model.

Table 7. TNF-α genotype and allele frequency for patients with asthma

TNF-α loci	Control group (N=840)		Asthma group (N=480)		OR (95% CI)[a]	P[a]
	n	Percentage (%)	n	Percentage (%)		
-308 G/A						
GG	303	36.1	114	23.8	1.00[REF]	
GA	342	40.7	237	49.4	1.84 (1.05-2.95)	0.011
AA	195	23.2	129	26.8	1.76 (1.03-3.01)	0.038
G	948	56.4	465	48.4	1.00[REF]	
A	732	43.6	495	51.6	1.65 (1.25-2.17)	<0.001
-376 G/A	0					
GG	420	50.0	228	47.5	1.00[REF]	
GA	336	40.0	198	41.3	1.09 (0.61-1.95)	0.899
AA	84	10.0	54	11.2	1.18 (1.47-2.99)	0.905
G	1176	70.0	654	68.1	1.00[REF]	
A	504	30.0	306	31.9	1.09 (0.72-1.66)	0.762
-863 C/A	0					
CC	390	46.4	234	48.7	1.00[REF]	
CA	354	42.2	144	30.0	1.68 (0.37-1.26)	0.281
AA	96	11.4	78	16.3	1.35 (0.59-3.11)	0.617
C	1134	67.5	612	63.8	1.00[REF]	
A	546	32.5	300	36.2	1.02 (0.67-1.55)	0.981

TNF-α, tumor necrosis factor-α; OR, odds ratio; CI, confidential index; [a]Adjusted for age, sex and BMI by logistic regression model.

incidence of childhood asthma not only affects the growth of children but also affects the quality of life of children's families.

Asthma is a chronic respiratory disorder characterized by complex multifactorial pathogenesis. As the disease progresses, patients typically experience symptoms such as cough, chest tightness, and dyspnea, which profoundly impair quality of life and functional capacity. Globally, asthma ranks among the most prevalent airway diseases in adults, affecting approximately 216 million individuals annually [14]. Despite advancements in clinical care, its prevalence persists unabated, imposing substantial socioeconomic burdens. The China

Table 8. The SNP loci of independent risk factors for asthma

Gene (SNP)	Genotype	Adjusted OR (95% CI)[a]	*P* value
IL-1β -511 C/T	CC	1.00 (Reference)	
	TC	2.45 (1.28-4.71)	0.007
	TT	2.89 (1.57-5.32)	<0.001
IL-10 -1082 G/A	GG	1.00 (Reference)	
	GA	2.38 (1.44-3.92)	<0.001
	AA	2.48 (1.42-4.32)	0.001
TNF-α -308 G/A	GG	1.00 (Reference)	
	GA	1.79 (1.02-3.14)	0.042
	AA	1.72 (1.01-2.94)	0.047
IFN-γ +874 A/T	AA	1.00 (Reference)	
	AT	1.01 (0.67-1.52)	0.970
	TT	2.21 (1.10-4.45)	0.026

IL-1β, interleukin-1β; IL-10, interleukin-10; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; OR, odds ratio; CI, confidence interval; SNP, single nucleotide polymorphism. [a]Adjusted for age, sex and BMI by logistic regression model.

Pulmonary Health (CPH) study revealed an adult asthma prevalence exceeding 4%, corresponding to nearly 50 million cases nationwide [15]. Asthma-related morbidity remains alarmingly high, with 450,000 annual deaths and a global economic burden surpassing US $50 billion, disproportionately affecting low-income populations and patients with suboptimal disease control [16]. In China, asthma management remains suboptimal, with urban control rates below 30% and even lower rates in rural regions, lagging behind global standards. Poorly controlled asthma precipitates recurrent exacerbations - marked by acute wheezing, chest discomfort, and respiratory distress - which contribute to persistent physical and psychological sequelae, increased mortality, and elevated healthcare utilization. Frequent hospitalizations exacerbate financial burdens on families and healthcare systems, particularly in resource-limited settings. Given the chronic, progressive nature of asthma, enhancing disease control and reducing exacerbation frequency represent urgent public health priorities.

Airway inflammation, driven by elevated inflammatory mediators (cytokines, leukotrienes), constitutes the pathological cornerstone of asthma [2]. This inflammatory cascade intensifies with disease severity, underscoring the therapeutic imperative to modulate inflammatory pathways. Prior genetic studies have predominantly focused on isolated loci within single inflammatory factor-related genes (IL-4, TNF-α), yielding inconsistent findings due to methodological limitations such as small sample sizes, population stratification, and environmental confounders (ethnicity, climate).

To address these gaps, this study employs a large-scale design to systematically evaluate polymorphisms across all critical loci of inflammatory factor-related genes. By harmonizing data from diverse cohorts, we aim to clarify the genetic architecture of asthma susceptibility, enhance reproducibility, and identify biomarkers for early diagnosis. This approach not only mitigates biases inherent in fragmented studies but also facilitates the development of personalized anti-inflammatory therapies, which may reduce exacerbation and long-term disability.

Our findings on the association between specific cytokine gene polymorphisms and asthma susceptibility are largely consistent with, yet extend beyond, previous literature, thereby validating and refining the current genetic landscape of asthma. Mechanistically, the A allele of this promoter polymorphism is believed to enhance transcriptional activity, leading to increased TNF-α production, which can exacerbate airway inflammation and hyperresponsiveness - a central pathway in asthma pathogenesis. Similarly, our observed association for IL-1β -511C/T aligns with a prior meta-analysis [17], supporting the role of this pro-inflammatory cytokine in early immune activation in the airways. However, our study also reveals nuanced differences. While we confirmed the association of IL-10 -1082G/A (rs1800896), we did not find a significant role for the IL-6 -174G/C polymorphism, in contrast to some reports [9, 18]. These discrepancies may be attributed to several factors. First, population stratification is a key determinant; our study focused exclusively on Han Chinese children, whose genetic background and linkage disequilibrium patterns may differ from Caucasian or other ethnic cohorts studied previ-

ously. Second, differences in asthma phenotypes and severity across study populations could influence genetic associations, as certain polymorphisms might be more relevant to specific endotypes. Third, environmental interactions, which were not comprehensively adjusted for in this retrospective design, might modulate genetic effects. Lastly, statistical power varies; our larger sample size provides robust power to detect modest genetic effects, which might have been underpowered in smaller studies reporting negative results. The integration of cytokine level measurements with genotyping offers mechanistic insights. The concurrent elevation of serum TNF-α, IL-1β, and IL-6 levels in our asthma cohort, alongside the genetic associations for TNF-α and IL-1β, suggests that these polymorphisms may contribute to disease susceptibility partly through a quantitative trait effect, influencing the systemic inflammatory milieu. The lack of association for certain polymorphisms despite elevated cytokine levels implies that other regulatory mechanisms may be predominant drivers of IL-6 dysregulation in our specific cohort.

Our study represents the largest investigation to date exploring the association between asthma and inflammatory factors, incorporating >1,300 samples to ensure robust statistical power. The results demonstrate that IL-1, IL-6, IL-10, IL-17, IFN-γ, and TNF-α are critically implicated in asthma pathogenesis, aligning with prior evidence linking cytokine dysregulation to airway inflammation and hyperresponsiveness. These inflammatory mediators exhibit significant potential as diagnostic and prognostic biomarkers, enabling early identification of high-risk populations and personalized therapeutic strategies. The large cohort size enhances generalizability and reduces type II errors, addressing limitations of earlier fragmented studies with smaller samples. By systematically analyzing multiple inflammatory pathways, this work clarifies their synergistic roles in asthma progression, corroborating findings from RSV bronchiolitis studies where IL-4, IL-10, and IL-17 were similarly elevated.

Despite its contributions, our study has several limitations that warrant consideration. First, the retrospective, single-center design may introduce selection bias and limit the generalizability of our findings to broader populations or different healthcare settings. Second, while we analyzed a panel of key cytokines and polymorphisms, our approach was hypothesis-driven rather than exploratory; thus, other important inflammatory mediators or genetic variants outside our selected panel might have been overlooked. Third, the measurement of serum cytokines represents a static snapshot at diagnosis, which may not fully capture the dynamic nature of inflammation over the disease course or in response to treatment. Fourth, although we adjusted for major confounders, unmeasured or residual confounding factors, such as detailed environmental exposures, medication use prior to sample collection, or microbiome data, could influence both cytokine levels and asthma risk. Future research should aim to address these limitations through prospective, multicenter cohort studies that enroll incident asthma cases and follow them longitudinally. Incorporating high-throughput omics approaches could unbiasedly identify novel biomarkers and pathways. It is also crucial to investigate the functional consequences of the identified polymorphisms using in vitro or in vivo models to establish causal links. Finally, integrating clinical data with deep phenotyping and environmental data will be essential for developing personalized predictive models that can guide early intervention and targeted therapy in asthma management. While our design controlled for common variables, unmeasured confounders-such as environmental triggers or genetic polymorphisms-may influence outcomes. Incorporating transcriptomic or proteomic profiling could unravel gene-environment interactions, as exemplified by recent RNA interference therapies targeting lipoprotein (a). Pooling data from diverse cohorts would strengthen causal inferences; a strategy successfully employed in multinational anaphylaxis studies [19-37].

This study underscores the centrality of inflammatory dysregulation in asthma and provides actionable biomarkers for clinical practice. Future research should integrate advanced computational frameworks and longitudinal designs to address residual gaps.

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Disclosure of conflict of interest

None.

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