

A Study on the Correlation between Polymorphisms of IL-13, IL-4, ADRB2 and FCER1B Genes and the Treatment of Childhood Asthma in Heilongjiang Region

Yuyang Men *, Si Chen, Jingbo Yu

Capital Medical University Affiliated Beijing Children's Hospital - Heilongjiang Hospital-Harbin Children's Hospital, Harbin, Heilongjiang, 150001, China

* Corresponding author: Yuyang Men

Abstract: Objective: To explore the distribution characteristics of polymorphisms of IL-13, IL-4, ADRB2 and FCER1B gene loci in children with asthma in Heilongjiang region, and to analyze their associations with baseline phenotypes (serum total IgE, FeNO, lung function) and maintenance inhaled corticosteroid (ICS) dose, so as to provide evidence for early identification of high-risk children and exploration of genetic susceptibility. Methods: A total of 100 children with newly diagnosed asthma were enrolled. The four loci were genotyped and children were stratified into high-risk (n=43) and low-risk (n=57) groups by genotype risk. All children received long-term stepwise treatment according to the Guidelines for the Diagnosis and Treatment of Childhood Bronchial Asthma (2025 edition) and were followed up at 3, 6 and 12 months. Results: The distributions of the four polymorphisms differed significantly between groups ($P < 0.001$). High FeNO values and greater severity of lung function obstruction were observed in the high-risk group ($P < 0.001$), while total IgE showed no significant inter-group difference ($P > 0.05$); FCER1B showed no significant difference between groups ($P = 0.482$). After guideline-based stepwise therapy, clinical symptoms improved from baseline in both groups; the inter-group differences in efficacy and relapse during follow-up were descriptive and confounded by baseline phenotypes. Conclusion: The four-locus polymorphisms are associated with baseline phenotypes of asthmatic children in Heilongjiang; genetic testing may serve as a reference for early identification of high-risk children. The benefit of genotype-guided therapy still requires validation by large-sample, prospective randomized studies.

Keywords: IL-13; IL-4; ADRB2; FCER1B; Gene Polymorphism; Asthma.

1. Introduction

Asthma, a common chronic airway disease, is recognized as a polygenic disorder in which genetic variations are closely implicated in its pathogenesis [1]. Both genetic and physical maps of DNA have substantially advanced our understanding of human diseases [2]. Single nucleotide polymorphisms (SNPs), the newer-generation genetic markers, refer to polymorphisms arising from single nucleotide variations in genomic deoxyribonucleic acid (DNA) sequences. Owing to their abundance and wide distribution across the human genome, SNPs have emerged as powerful tools for identifying susceptibility genes for various diseases and for screening high-risk populations [3]. Using a case-control design, Hua et al. established a predictive model for asthma susceptibility genes in Han Chinese children, demonstrating that a four-locus model comprising IL-13 R110Q, IL-4 590C-T, ADRB2 R16G, and FCER1B E237G achieved an accuracy of 80% [4]. Subsequent studies have indicated that these four loci serve as risk genes for wheezing in children under 5 years of age with a positive Asthma Predictive Index (API). Extensive research by both domestic and international investigators has been conducted on this model [5]. Given its highest reported accuracy, this model holds promise as an objective and effective tool for predicting the progression from preschool wheezing to childhood asthma in China, and is thus considered the optimal asthma predictive model. Notably, Heilongjiang Province features prolonged and severe winters, during which cold air stimulates the respiratory tract, inducing airway constriction and bronchospasm, thereby elevating the risk of asthma exacerbations. Concurrently, the

region experiences relatively high environmental pollution, with elevated levels of airborne pollutants such as sulfur dioxide and nitrogen oxides, alongside increased particulates from smog, pollen, and dust mites. These agents can trigger airway inflammation and act as allergens or irritants that precipitate asthma. Therefore, determining whether the four-locus asthma-related genes can serve as a predictive tool to facilitate precise assessment of disease trajectories in pediatric patients carries substantial clinical significance and value. It has been observed that individual responses to glucocorticoids and β_2 -agonists in asthma therapy vary considerably, which may be attributable to differences in drug mechanisms and asthmatic pathways [6]. Consequently, polymorphisms in asthma susceptibility genes may modulate therapeutic efficacy. Moreover, given considerations of adherence and safety, and the fact that each child exhibits distinct responses, adverse effects, and compliance profiles to different medications, the selection of appropriate and effective agents remains a pivotal aspect of clinical management. In this study, we leverage the distribution of the four-locus genotype results in children with asthma, integrated with comprehensive clinical data, to analyze the associations between these polymorphisms and baseline asthma phenotypes—including total IgE, fractional exhaled nitric oxide (FeNO), and lung function—as well as the maintenance dosage of inhaled corticosteroids. Our objective is to enable early identification of high-risk children and to provide a reference for future pharmacogenetic investigations.

2. Materials and Methods

2.1. Study Population

A total of 100 children diagnosed with bronchial asthma at the Department of Respiratory Medicine, Harbin Children's Hospital, between January 2023 and December 2024 were enrolled as study subjects. Written informed consent was obtained from all parents or legal guardians. This study was approved by the Ethics Committee of Harbin Medical University.

2.1.1. Inclusion Criteria

(1) Diagnosis of asthma conforming to the Guidelines for the Diagnosis, Prevention, and Management of Childhood Bronchial Asthma (2025 edition);

(2) Newly diagnosed with bronchial asthma and without prior systematic treatment;

(3) Local residents of Heilongjiang Province;

(4) Informed consent signed by guardians.

2.1.2. Exclusion Criteria

(1) Incomplete clinical data;

(2) Wheezing attributable to congenital heart disease, primary immunodeficiency, congenital airway anomalies, congenital vascular ring malformations, neuromuscular weakness, tracheomalacia, foreign body aspiration, or gastroesophageal reflux disease.

2.2. Methods

Buccal mucosal exfoliated cells were collected from all participants, and genomic DNA was extracted. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) was employed to precisely genotype the rs1042713 locus of the ADRB2 gene, the rs2243250 locus of the IL4 gene, the rs569108 locus of the FCER1B gene, and the rs20541 locus of the IL13 gene, in order to analyze their polymorphic profiles. Participants carrying no homozygous risk alleles at any of the four loci served as the reference group; comparisons were made between various genotype combinations and this reference. Genotype combinations showing statistically significant differences ($P < 0.05$) with an odds ratio (OR) > 1 were classified as positive, i.e., the high-risk asthma group in this study, while the remainder were classified as negative, i.e., the low-risk asthma group (genotyping procedures were performed by Shanghai Decode Medical Laboratory Co., Ltd.). Concurrently, the genotypes of IL-13, IL-4, ADRB2, and FCER1B at the four loci were recorded as exploratory variables for each patient.

Following diagnosis, all children received long-term

stepwise therapy in accordance with the Guidelines for the Diagnosis, Prevention, and Management of Childhood Bronchial Asthma (2025 edition). Inhaled corticosteroids (ICS; budesonide, fluticasone propionate, or beclomethasone dipropionate) served as the cornerstone of maintenance therapy, with step 2–4 regimens selected based on the level of asthma control. Short-acting β_2 -agonists (SABA; salbutamol or terbutaline) were prescribed only as reliever medication on an as-needed basis, and during acute exacerbations, they were administered at guideline-recommended doses (2.5 mg for body weight ≤ 20 kg, 5 mg for > 20 kg, every 4–6 h, maximum 4 times daily) in combination with ICS. For patients with comorbid allergic rhinitis or ICS intolerance, a leukotriene receptor antagonist (montelukast) was added. Follow-up assessments for control levels and step-down/step-up adjustments were performed at 2–4 weeks, 1–3 months, 6 months, and 12 months of treatment. This study further explored the associations between the four-locus genotypes, baseline phenotypes, and the required ICS maintenance dosages.

2.3. Statistical Analysis

Statistical analyses were performed using SPSS version 27.0. Hardy–Weinberg equilibrium (HWE) for each genetic locus was tested using the exact test (Pearson's exact method) in the total sample ($n = 100$). The HWE P-values for all loci were > 0.05 (IL13: 0.225, IL4: 1.000, ADRB2: 0.843, FCER1B: 0.205), indicating that the genotype distributions conformed to HWE. Normality tests were conducted for all data. Categorical variables were expressed as frequencies and percentages (n, %) and analyzed using the chi-square test or rank-sum test as appropriate. Continuous variables were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$); between-group comparisons were performed using the independent-samples t-test after normality testing, and Welch's t-test was applied for samples with unequal variances. Correlations were examined using Pearson's correlation coefficient. A two-sided P-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics

A total of 100 children were enrolled, comprising 43 cases in the high-risk asthma group and 57 cases in the low-risk asthma group. No statistically significant differences were observed between the two groups in terms of sex or age distribution ($P > 0.05$), as shown in Table 1.

Table 1. Comparison of sex and age distribution between the two groups

Group	Number of cases	Sex	Age (years)
Low-risk group	57	Male 33(57.9%)	6.268 $\pm$ 2.615
		Female 24(42.1%)	
High-risk group	43	Male 31(72.1%)	5.66 $\pm$ 2.728
		Female 12(27.9%)	
χ^2/t		2.145	1.13
P		0.104	0.26

3.1.1. Genotype Distributions of the Four Loci

Significant differences in SNP genotypes were found between the two groups at the IL13 locus ($\chi^2 = 22.137$, $P < 0.001$), with the GG genotype being the most prevalent (86%) in the high-risk group. Significant intergroup differences were

also observed at the IL4 rs2243250 locus ($\chi^2 = 30.4$, $P < 0.001$), where the TT genotype predominated (90.7%) among high-risk children. At the ADRB2 rs1042713 locus, the genotype distribution differed significantly between groups ($\chi^2 = 12.516$, $P < 0.001$), with the AA genotype showing the

highest frequency (44.2%) in the high-risk group. In contrast, no significant difference was detected at the FcER1B rs569108 locus ($\chi^2 = 0.076$, $P = 0.482$), although the AA

genotype remained the most frequent (74.4%) in the high-risk group (see Table 2).

Table 2. Genotype distributions of IL13, IL4, ADRB2, and FCER1B loci between the two groups

Group		High-risk group	Low-risk group	χ^2	P
IL13	AA	3(7%)	8(14%)	22.137	<0.001
	AG	3(7%)	33(57.9%)		
	GG	37(86%)	16(28.1%)		
IL4	CC	0	5(8.8%)	30.402	<0.001
	CT	4(9.3%)	33(57.9%)		
	TT	39(90.7%)	19(33.3%)		
ADRB2	AA	19(44.2%)	7(12.3%)	12.516	<0.001
	AG	18(41.9%)	31(54.4%)		
	GG	6(14%)	19(33.3%)		
FCER1B	AA	32(74.4%)	41(71.9%)	0.076	0.482
	AG	11(25.6%)	16(28.1%)		
	GG	0	0		

3.1.2. Hardy–Weinberg Equilibrium Testing

The genotype distributions of all four loci were in Hardy–Weinberg equilibrium: the HWE P-values for IL13 rs20541, IL4 rs2243250, ADRB2 rs1042713, and FcER1B rs569108 were 0.225, 1.000, 0.843, and 0.205, respectively (all >0.05), confirming the reliability of the genotyping quality in this sample.

3.2. Serum Total IgE Levels

Serum total immunoglobulin E (IgE) levels were measured in all enrolled children. Although total IgE levels in the low-risk asthma group were lower than those in the high-risk group, the between-group difference did not reach statistical significance ($P > 0.05$), as presented in Table 3.

Table 3. Comparison of total IgE levels between the two groups by age subgroup

Group	<3 years, n	<3 years, IgE (IU/mL)	3–6 years, n	3–6 years, IgE (IU/mL)	>6 years, n	>6 years, IgE (IU/mL)
Low-risk asthma group	3	367.4±258.37	26	379.37±324.82	22	509.69±324.38
High-risk asthma group	5	632.22±448.31	21	475.69±398.84	23	521.94±375.1
t/z		-0.917		-1.21		-0.12
P		0.394		0.22		0.9

3.3. Fractional Exhaled Nitric Oxide (FeNO) Measurements

All participants underwent fractional exhaled nitric oxide (FeNO) testing. The reference standards for normal FeNO values in children were based on the 2011 American Thoracic

Society (ATS) clinical recommendations for FeNO interpretation [7, 8] (see Table 4). Comparative analysis revealed that the proportion of high FeNO values was significantly greater in the high-risk asthma group than in the low-risk group, with a statistically significant difference ($P < 0.001$), as shown in Table 5.

Table 4. Interpretation of fractional exhaled nitric oxide (FeNO) levels and corresponding type 2 airway inflammation status by age group (based on 2011 ATS recommendations)

Category	FeNO(ppb)		Type 2 airway inflammation
	Children >12 years	Children ≤12 years	
Low FeNO	<25	<20	Non-eosinophilic airway inflammation
Intermediate FeNO	25-50	20-35	Mixed airway inflammation
High FeNO	>50	>35	Eosinophilic airway inflammation

Table 5. Comparison of fractional exhaled nitric oxide (FeNO) values between the two groups

	FeNO value	
	Low FENO	Intermediate/high FENO
Low-risk group	44(77.2%)	13(22.8%)
High-risk group	9(20.9%)	34(79.1%)
χ^2	28.929	
P	<0.001	
z	-5.553	

3.4. Pulmonary Function Testing

In this study, pulmonary function testing was performed in all enrolled children with asthma. Given that the ability to cooperate with testing varies across different age groups,

age-appropriate methods were adopted. For children under 3 years of age, tidal breathing lung function testing was employed; for those aged 3–6 years, impulse oscillometry (IOS) was used; and for children aged 6 years and older, spirometry was performed. Based on the results, lung function

was categorized as normal, mild obstruction, and moderate-to-severe obstruction. All tests were conducted by trained technicians in the pulmonary function laboratory. The results showed that the proportion of moderate-to-severe

obstruction was significantly higher in the high-risk asthma group than in the low-risk group, with a statistically significant between-group difference ($P < 0.05$), as presented in Table 6.

Table 6. Comparison of pulmonary function obstruction severity between the two groups

Group	Pulmonary function			χ^2	P
	Normal	Mild obstruction	Moderate-to-severe obstruction		
Low-risk group	33(57.9%)	17(29.8%)	7(12.3%)	17.63	<0.001
High-risk group	6(14.1%)	23(53.3%)	14(32.6%)		

3.5. Treatment Response at 12 Months

After 12 months of stepwise therapy per the guidelines, all children showed clinical improvement relative to baseline. We further described the treatment responses in the two groups stratified by genetic risk: in the high-risk group, 5 cases (11.6%) showed no response, 17 (39.5%) showed partial remission, and 21 (48.8%) showed good response; in the low-risk group, 13 cases (22.8%) showed no response, 28 (49.1%) showed partial remission, and 16 (28.1%) showed

good response (see Table 7). The between-group distribution of therapeutic responses is presented as descriptive results only. Given that the high-risk group had more severe baseline phenotypes and the between-group comparisons were subject to confounding factors, these findings should not be interpreted as evidence for genotype-guided therapeutic superiority. (Note: The three-tier efficacy classification of "good response / partial remission / no response" used in this study was defined by the authors and is not a standard asthma control assessment tool recommended by the guidelines.)

Table 7. Comparison of therapeutic response between the two groups

Group	No response	Partial remission	Good response	χ^2	P
Low-risk group	13(22.8%)	28(49.1%)	16(28.1%)		
High-risk group	5(11.6%)	17(39.5%)	21(48.8%)	4.819	0.028

3.6. Wheezing Recurrence During Follow-up

Wheezing recurrence was recorded at the 3-, 6-, and 12-month follow-up visits. In the high-risk group, 8 cases experienced recurrence and 35 did not; in the low-risk group, 43 cases experienced recurrence and 14 did not (see Table 8). The between-group difference in recurrence rates is presented

as descriptive results only. Given the influence of baseline phenotypes, loss to follow-up, and the fact that both groups received guideline-recommended stepwise therapy, these findings should not be interpreted as demonstrating differential efficacy attributable to genotype-guided management.

Table 8. Comparison of wheezing recurrence during follow-up between the two groups

Group	No recurrence	Recurrence
Recurrence	14(24.6%)	43(75.4%)
High-risk group	35(81.4%)	8(18.6%)
χ^2	31.364	
P	<0.001	
z	-5.6	

3.7. Overall Management and Genotype-Phenotype Correlations

All children received long-term stepwise therapy in accordance with the Guidelines for the Diagnosis, Prevention, and Management of Childhood Bronchial Asthma (2025 edition). Inhaled corticosteroids (ICS; budesonide, fluticasone propionate, or beclomethasone dipropionate) served as the cornerstone of maintenance therapy, with step 2–4 regimens selected based on the level of asthma control. Short-acting β_2 -agonists (SABA; salbutamol or terbutaline) were prescribed only as reliever medication on an as-needed

basis, and during acute exacerbations, they were administered at guideline-recommended doses in combination with ICS. For patients with comorbid allergic rhinitis or ICS intolerance, montelukast was added. Follow-up assessments for control levels and step-down/step-up adjustments were performed at 2–4 weeks, 1–3 months, 6 months, and 12 months of treatment. Concurrently, the genotypes of IL-13, IL-4, ADRB2, and FcER1B at the four loci were recorded for each patient to analyze their associations with sex, age, total IgE, FeNO, changes in lung function, and genotype distributions. Clinical symptom and sign remission were compared between the two groups, and adverse events during treatment were documented (see Table 9).

Table 9. Comparison of adverse event rates between the two groups [n (%)]

Group	Muscle tremor	Palpitations	Facial flushing	Neuropsychiatric symptoms	Overall adverse event rate (%)
Low-risk asthma group	5(8.7)	1(1.7)	3(5.2)	2(3.5)	19.2
High-risk asthma group	4(9.3)	2(4.6)	3(6.9)	1(2.3)	23.2

4. Discussion

Bronchial asthma is fundamentally a Th2-type immune response of the airways triggered by various stimuli, including allergens, cold air, and viral infections, characterized by eosinophilic infiltration, mucus hypersecretion, and airway smooth muscle spasm. Among the numerous risk factors, the detrimental effects of environmental pollutants—particularly fine particulate matter (PM_{2.5})—on children's respiratory health are considerable. Under northern climatic conditions, these pollutants may exacerbate asthma symptoms and increase the risk of acute exacerbations and hospitalizations in affected children [9]. Although current guideline-recommended combination therapy with inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABA) achieves effective asthma control in the majority of pediatric patients, nearly 40% of children with asthma worldwide still fail to reach clinical remission.

Accumulating evidence indicates complex interactions among different genetic loci. The rs20541 locus of the *IL13* gene, the rs2243250 locus of the *IL4* gene, the rs1042713 locus of the *ADRB2* gene, and the rs569108 locus of the *FCER1B* gene have all been identified as susceptibility loci for childhood asthma. Alterations in the expression levels of these genes are significantly correlated with elevated IgE-related levels. IgE-mediated inflammatory responses constitute a critical step in the pathogenesis of allergic asthma. IL-4 and IL-13, as cytokines that play pivotal roles in immune responses, are involved in the regulation of Th2-type immune responses. On the surface of T cells, IL-4 and IL-13 bind to heterodimeric receptors composed of IL-4R α and IL-13R α 1. This binding promotes signal transduction along a shared pathway, ultimately facilitating immunoglobulin class switching from IgM to IgE—a key biological feature.

Among studies on the *IL-13* gene, the single nucleotide polymorphism (SNP) 2044A>G has been reported with the highest frequency. Variation at this SNP locus reduces the binding affinity between IL-13 and its receptor. The reduced receptor binding efficiency leads to elevated local IL-13 concentrations, which in turn enhances signal transduction following receptor engagement, ultimately contributing to severe asthma [10].

The β_2 -adrenergic receptor encoded by *ADRB2* is highly expressed on airway smooth muscle upon allergen stimulation. Binding of the receptor to β_2 -adrenergic agonists activates specific G proteins, generating cyclic adenosine monophosphate (cAMP), which induces bronchodilation and reduces wheezing symptoms. Beyond its role in airway relaxation and inflammatory modulation, *ADRB2* may also promote IgE synthesis through other pathways, thereby linking it closely to the pathophysiology of asthma [11]. Zhang et al. reported that polymorphisms in the regulatory regions of *ADRB2* are associated with response to short-acting β_2 -agonists (SABA) during acute exacerbations in children with asthma; patients carrying the T allele at rs2895795, rs11168070, and rs12654778 showed greater improvements in lung function, and those with the TT genotype at rs2895795 exhibited better responses to SABA treatment. Conversely, the AA genotype has been associated with poorer responses to salbutamol or salmeterol, and the use of long-acting β_2 -agonists may increase the risk of asthma deterioration [12].

Numerous studies, both domestic and international, have

confirmed that polymorphisms at the E237G locus of the *FCER1B* gene exacerbate wheezing symptoms in children and significantly increase the likelihood of abnormal pulmonary function [13, 14]. The proposed mechanism by which *FCER1B* polymorphisms contribute to the onset and progression of childhood wheezing involves increased secretion of cytokines, which disrupts the Th17/Treg balance [15,16]. When allergens cross-link IgE bound to FCER1 on mast cell surfaces, FCER1B enhances signal transduction through FCER1, leading to the release of various inflammatory mediators and the initiation of allergic responses, with a consequent marked increase in serum IgE levels that perpetuates IgE-mediated inflammation. Children with asthma carrying the AA genotype of *FCER1B* may demonstrate more favorable responses to ICS therapy compared with those carrying other genotypes, potentially due to effects on signaling pathways or receptor expression related to corticosteroid action. In contrast, patients with the GG or AG genotype exhibit poorer responses to budesonide, generally modest therapeutic effects, and a higher risk of asthma deterioration, and these variants have also been linked to pulmonary function outcomes in children with asthma [17, 18]. Ramirez-Falcon et al. reported that children carrying the GG genotype face a higher risk of asthma deterioration with long-term corticosteroid use [19]. Other studies have shown that patients with the GLCCI1 S01040037 GG genotype or the CRHR1 S01039318 CC genotype respond poorly to ICS (budesonide and fluticasone propionate) [20].

In summary, IL-13, IL-4, *ADRB2*, and *FCER1B* exert their effects through distinct pathways in IgE-mediated inflammatory responses, and gene–gene interactions exist among them. With the rapid advancement of pharmacogenomics, mounting evidence underscores the close relationship between genetic factors and therapeutic efficacy. For children presenting with wheezing episodes, the four-locus asthma-related gene panel may also serve as one of the risk assessment tools for identifying severe asthma in pediatric patients.

5. Summary

By comparing the distribution of the four-locus genotypes and comprehensive clinical data among the enrolled children, this study found that the polymorphisms of these four loci exhibit a specific distribution pattern in children with asthma in Heilongjiang Province. Genetic testing may serve as one of the reference indicators for early identification of children at high risk for asthma. However, several limitations should be acknowledged. First, this was a single-center, observational study with a relatively small sample size ($n = 100$). The high-risk and low-risk groups were stratified based on genotype risk rather than randomized allocation, and the high-risk group had more severe baseline phenotypes. Consequently, the between-group comparisons are subject to confounding factors, and no causal conclusion can be drawn that genotype-guided therapy is superior to standard care. Second, the follow-up duration of 12 months is insufficient to assess long-term recurrence and outcomes after treatment discontinuation. Third, the lack of significant between-group difference at the *FCER1B* locus ($P = 0.482$) suggests that the applicability of the four-locus model across different age groups and ethnicities warrants further validation. Fourth, pharmacogenomics-guided drug selection for asthma remains at an exploratory stage and has not yet been incorporated into

routine recommendations in major domestic or international guidelines; this study serves only as an exploratory association analysis. The potential benefits of genotype-guided therapy still require confirmation through large-scale, prospective, randomized trials.

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