

The *Dermatophagoides pteronyssinus* Molecular Sensitization Profile of Allergic Rhinitis Patients in Central China

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Abstract

Background: House dust mites (HDMs) are the major aeroallergens in patients with rhinitis and/or asthma in China. However, the molecular sensitization of HDM is varied in different regions.

Objective: To investigate the *Dermatophagoides pteronyssinus* (Der p) molecular sensitization profile of allergic rhinitis (AR) patients in Central China.

Methods: AR patients with positive skin prick tests to Der p were enrolled in our study. Specific immunoglobulin E (sIgE) for Der p, *Dermatophagoides farinae* (Der f), *Acarus siro* (Aca s), *Blomia tropicalis* (Blo t), and Der p components Der p1, Der p2, and Der p10 were measured in all patients.

Results: A total of 130 patients were included. The overall prevalence of positive serum sIgE was 99.2% for Der p, 98.5% for Der f, 81.5% for Aca s, 83.1% for Blo t, 71.5% for Der p1, 64.6% for Der p2, and 11.5% for Der p10. HDM-AR patients with asthma displayed significantly higher concentrations of sIgE to Der p, Der f, Der p1, and Der p2 than did those without asthma ($P < .001$). The prevalence of asthma in HDM-AR patients was higher among the patients sensitized to both Der p1 and Der p2 (62.8%) than those sensitized to only 1 allergen (Der p1 26.7% or Der p2 16.7%; $P < .05$) or nonsensitized to Der p1 and Der p2 (19.4%; $P < .001$).

Conclusion: Der p has high cross-reactivity with other mite species. Der p1 and Der p2 are the major components to induce Der p sensitization among AR patients in Central China. Sensitization to both Der p1 and Der p2 may be a risk factor for developing asthma in HDM-AR patients.

Keywords

allergic rhinitis, asthma, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, Der p1, Der p2, molecular sensitization

Introduction

Exposure to indoor allergens, especially house dust mites (HDMs), and atopic sensitization are known to be major risk factors for asthma, allergic rhinitis (AR), and atopic dermatitis.¹ Self-reported AR in the Chinese population has significantly increased from 11.1% to 17.6% over a 6-year period, and 28% AR patients combine asthma, becoming the most prevalent chronic disorder in China.² Generally, diagnostic methods for HDM-related allergic diseases were primarily based on serum-specific immunoglobulin E (sIgE) measurements or skin prick tests (SPTs) with crude mite allergen extracts.³ Accordingly, crude allergen extracts contain varying concentrations of allergic and nonallergic components, and minor

allergens, such as panallergens, caused cross-reactivity that leads to inadequate accurate diagnosis.^{4,5} Molecular-based diagnosis is a method of choice for detection at the allergen components level and avoids problems associated with crude allergen extract tests.⁶ The availability of natural and recombinant allergens

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of *Dermatophagoides* species makes it possible to investigate the molecule sensitization profile in HDM-allergic individuals. Several meta-analyses found that the detection of *Der p1* or *Der p2* sIgE is a promising diagnostic tool in the diagnosis of *Dermatophagoides pteronyssinus* (*Der p*) IgE sensitization.^{7,8} However, previous studies found that the sensitization of HDM was different, Vidal et al. suggested that dual sensitization to both *Der p1* and *Der p2* in HDM-allergic patients was associated with asthma among HDM-allergic patients in their cross-sectional study.⁹ Wang et al. showed that *Der p1* sensitization was more important in children, while *Der p2* sensitization became more dominant in adults and after longer disease duration.¹⁰

Our previous study has found that HDMs, and *Der p* in particular, are the major aeroallergens among AR patients in Central China, with a sensitization rate of over 90%.¹¹ Therefore, the aim of this study was to investigate the *Der p* molecular sensitization profile and its association with clinical manifestations of HDM-AR patients in Central China.

Methods

Patients

The study was conducted from January 2017 to December 2017 in the Department of Allergy of Tongji Hospital, a tertiary university hospital in Central China. The study was approved by the Independent Ethical Committee of Tongji Hospital, and each participant or his or her statutory guardian signed the informed consent.

Patients enrolled in our study were those who (1) were diagnosed with AR with or without allergic asthma based on the recommendations of the Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update¹² and Global Initiative for Asthma guidelines (<http://ginasthma.org/>), (2) showed positive SPTs to *Der p*, and (3) had allergic symptoms of rhinitis and/or asthma after exposure to *Der p*. The exclusion criteria were as follows: (1) with a history of specific allergen immunotherapy, (2) with upper respiratory infection or chronic rhinosinusitis, and (3) with concomitant medications (eg, antihistamines, intranasal corticosteroids) that could affect the AR symptoms 2 weeks before enrollment. The AR symptoms were assessed according to the ARIA guidelines,¹² and a visual analog scale (VAS) of 0 to 10 was used to evaluate the severity of disease symptoms: 0 for “no symptoms” and 10 for “very severe symptoms.”

Allergen sIgE and Components sIgE Test

Allergen serum sIgE was measured with the ImmunoCAP-250 system (Thermo Fisher Scientific) following the manufacturer's instructions. The tests included sIgE against *Dermatophagoides pteronyssinus* (*Der p*), *Dermatophagoides farinae* (*Der f*), *Acarus siro* (*Aca s*), *Blomia tropicalis* (*Blo t*), and *Der p* allergen components *Der p1*, *Der p2*, and *Der p10*. The concentration of allergen serum sIgE ranged from 0.10 to 100 kU_A/L. Any measurement above the upper limit of the measurement range was assigned a value of 100 kU_A/L; sIgE level over 0.35 kU_A/L was defined as positive. Positive IgE tests were categorized into 6 classes: class 1 (≥ 0.35 to < 0.70 kU_A/L), class 2 (≥ 0.70 to < 3.50 kU_A/L), class 3 (≥ 3.50 to < 17.50 kU_A/L), class 4 (≥ 17.50 to < 50.00 kU_A/L), class 5 (≥ 50.00 to < 100.00 kU_A/L), and class 6 (≥ 100.00 kU_A/L).

Statistical Analysis

Descriptive parameters, such as means and standard deviations for normally distributed continuous data, frequencies, and percentages for categorical data, were calculated. The abnormal distribution data were expressed as median and 25% to 75% interquartile ranges. The Pearson χ^2 test or Fisher's exact test was used to determine the association between categorical variables. The Mann-Whitney *U* test was used to compare numerical data between groups, and the Spearman rank test was used to assess correlations. The diagnostic value of sIgE concentrations was determined by calculating the area under the curve of the receiver operating characteristic (ROC) curve. $P < .05$ was considered statistically significant. Statistical Package for Social Sciences (SPSS version 19.0, IBM) was used for all statistical analyses.

Results

Demographic Characteristics and AR Severity of Participants

A total of 130 patients (57 women) with positive SPT to *Der p* were included. The mean age was 26.3 years. The AR patients enrolled in our study were mild intermittent (1.5%), mild persistent (8.5%), moderate-severe intermittent (11.5%), and moderate-severe persistent (78.5%) according to ARIA guidelines,¹² in which 60 (46.2%) patients had asthma. And the mean VAS scores of the symptoms were 5.06 ± 1.81 .

Prevalence of Sensitization and sIgE Levels of Mites and *Der p* Allergen Components

Among the patients, 129 (99.2%) showed positive for *Der p* in serum sIgE, and the *Der p*-negative patient

was sensitized to the *Der p1* and *Der f* (both in class 1). The overall prevalence of positive serum sIgE was 71.5% for *Der p1*, 64.6% for *Der p2*, 11.5% for *Der p10*, 98.5% for *Der f*, 81.5% for *Aca s*, and 83.1% for *Blo t*. Specifically, the proportion of *Der p* and *Der f* IgE levels was mainly of classes 4, 5, and 6. However, for *Aca s* and *Blo t*, the sIgE levels were mainly of class 2 and class 3 (81.1% and 73.1%, respectively). The sIgE levels for mites and *Der p* allergen components are summarized in Figure 1.

Correlation of sIgE Levels Between Mites and *Der p* Allergen Components

For sIgE, a significant high correlation was found between *Der p* and *Der f* ($\rho=0.981$, $P<.001$), *Der p1* and *Der p2* ($\rho=0.854$, $P<.001$), and *Der p1*, *Der p2*, and *Der p* ($\rho=0.929$ and $\rho=0.921$, respectively, $P<.001$). The correlation of sIgE between *Aca s*, *Blo t*, and *Der p* was moderate ($\rho=0.496$ and $\rho=0.518$, respectively, $P<.001$). In addition, the correlation between *Aca s* and *Blo t* was significantly high ($\rho=0.925$, $P<.001$; Figure 2). However, there was no significant correlation between *Der p10* and *Der p*, *Der f*, *Aca s*, *Blo t*, *Der p1*, and *Der p2*.

Concentrations of sIgE Levels to Mites and *Der p* Allergen Components in HDM-AR Patients With or Without Asthma

The median (interquartile range) sIgE levels were 14.15 kU_A/L (2.93–100.00 kU_A/L) for *Der p*, 17.65 kU_A/L (2.77–99.48 kU_A/L) for *Der f*, 1.68 kU_A/L (0.66–5.55 kU_A/L) for *Aca s*, and 2.09 kU_A/L (0.65–6.47 kU_A/L) for *Blo t*. The sIgE levels for *Der p* allergen components

were 4.58 kU_A/L (0.31–63.90 kU_A/L) for *Der p1*, 5.81 kU_A/L (0.02–77.95 kU_A/L) for *Der p2*, and 0.02 kU_A/L (0.01–0.07 kU_A/L) for *Der p10*. HDM-AR patients with asthma displayed significantly higher concentrations of sIgE to *Der p*, *Der f*, *Der p1*, and *Der p2* than those without asthma ($P<.001$; Figure 3). The ROC curve of sIgE concentrations showed that the area under the curve of *Der p* and *Der f* were 0.758 and 0.753, *Der p1* and *Der p2* were 0.761 and 0.767 ($P<.005$). The cut-off values for *Der p* and *Der f* were 25.95 kU_A/L and 33.65 kU_A/L (sensitivity 70.0%, specificity 81.4%), for *Der p1* was 8.35 kU_A/L (sensitivity 71.7%, specificity 80.0%), and for *Der p2* was 13.95 kU_A/L (sensitivity 71.7%, specificity 81.4%) (Figure 4). There was no significant correlation between the VAS scores of symptoms, and mites IgE levels in our study ($P>.05$).

Prevalence of Sensitization to *Der p* Allergen Components in *Der p*-positive AR Patients With or Without Asthma

Among the 129 *Der p*-positive patients, 68 (52.7%) showed positive IgE for *Der p1* and *Der p2*, while 28 (21.7%) patients showed negative IgE for *Der p1*, *Der p2*, and *Der p10*. Moreover, 23 (33.3%) patients in AR without asthma group and 45 (75.0%) patients in AR with asthma group showed positive IgE reactivity for *Der p*, *Der p1*, and *Der p2*. The prevalence of sensitization to *Der p* allergen components was the difference between the 2 groups ($P<.001$; Table 1).

The prevalence of asthma in HDM-AR patients was higher among the patients sensitized to both *Der p1* and *Der p2* (62.8%) than those sensitized to only 1 allergen (*Der p1* 26.7% or *Der p2* 16.7%; $P<.05$) or nonsensitized to *Der p1* and *Der p2* (19.4%; $P<.001$) (Figure 5).

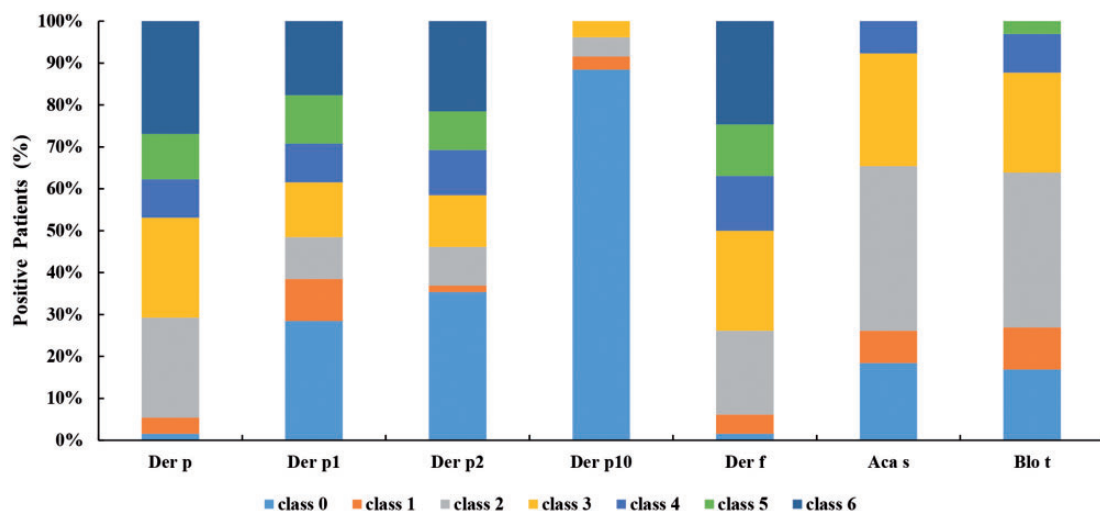


Figure 1. Prevalence of sensitization to mites and *Der p* allergen components in sIgE levels. *Der p*, *Dermatophagoides pteronyssinus*; *Der f*, *Dermatophagoides farinae*; *Aca s*, *Acarus siro*; *Blo t*, *Blomia tropicalis*.

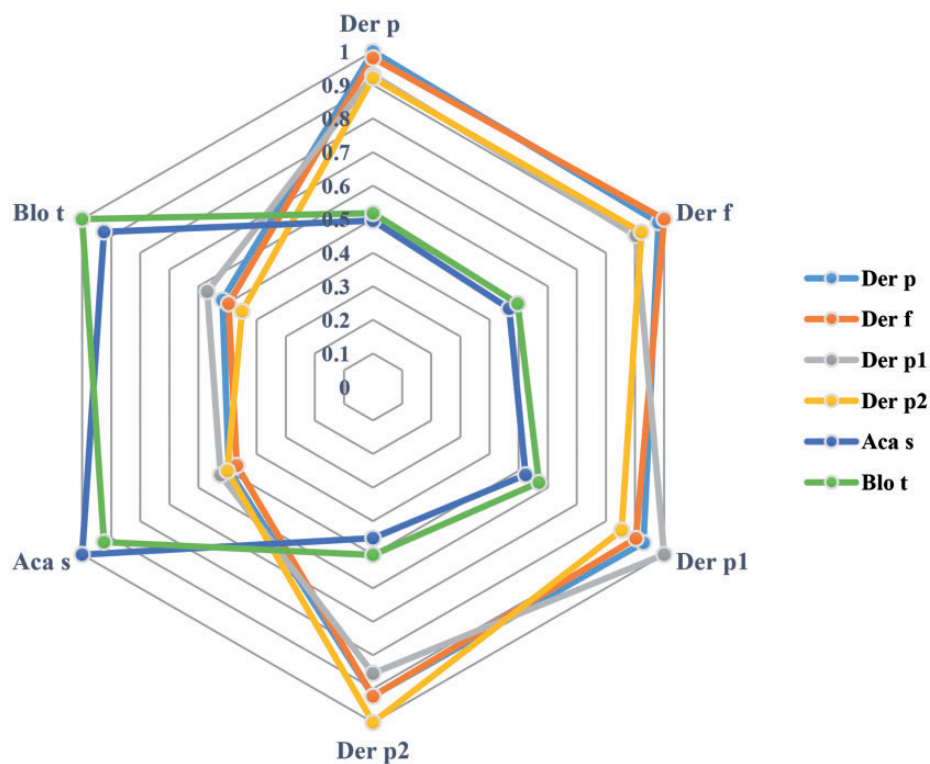


Figure 2. The Spearman correlation analysis between mites and *Der p* allergen components. *Der p*, *Dermatophagoides pteronyssinus*; *Der f*, *Dermatophagoides farinae*; *Aca s*, *Acarus siro*; *Blo t*, *Blomia tropicalis*.

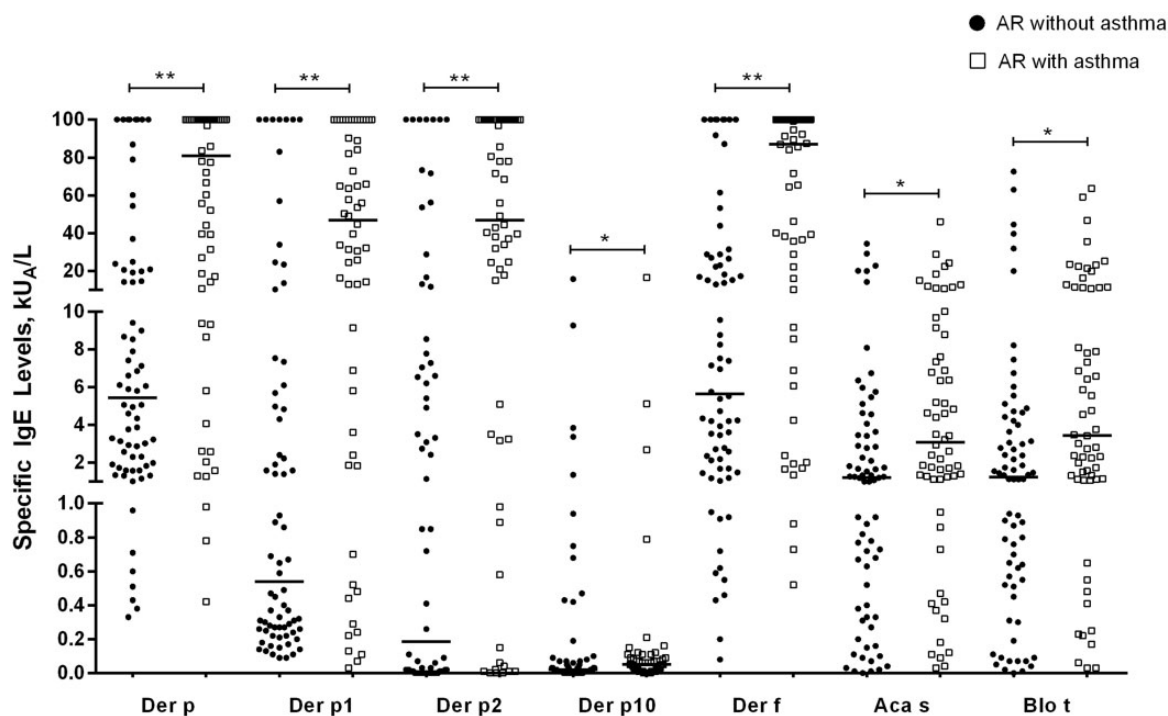


Figure 3. sIgE levels to mites and *Der p* allergen components in HDM-AR individuals with or without asthma. ** $P < .001$; * $P < .05$. AR, allergic rhinitis; IgE, immunoglobulin E; *Der p*, *Dermatophagoides pteronyssinus*; *Der f*, *Dermatophagoides farinae*; *Aca s*, *Acarus siro*; *Blo t*, *Blomia tropicalis*.

Discussion

HDMs are the most prevalent allergens in patients with asthma and/or rhinitis in China.¹³ However, sensitization and allergy are not always fully comparable. Molecular-based diagnosis or component-resolved diagnosis provide us with a useful tool to improve the allergy diagnosis and investigate the molecule sensitization profile and selection of patients for immunotherapy.⁴ So far, more than 20 different allergen components of *Dermatophagoides* have been described.¹⁴ *Der p1*, *Der p2*, and *Der p10* are the commercially and easily available *Der p* allergen components. *Der p1*'s cysteine protease activity may cause airway epithelial cell desquamation, cytokine release, mucosal barrier destroyed, and promotion of allergen molecules crossing the epidermal cells.¹⁵ Although *Der p2* has structural homology with myeloid

differentiation factor 2, a lipopolysaccharide coreceptor for toll-like receptor 4, tends to be targeted by adaptive immune responses.¹⁶ The knowledge of the allergen molecular structural features provides important contributions to the understanding of cross-reaction processes and to the improvement of personality diagnosis and immunotherapy and reduces the cost for the patients and the society.¹⁷

In our study, 71.5% and 64.6% of AR patients showed positive IgE for *Der p1* and *Der p2*, respectively. Fifteen patients (11.7%) were sensitized to *Der p10* in *Der p*-positive patients. The sensitization rates of *Der p1* and *Der p2* in HDM-AR patients were lower compared with the rates reported by Zeng et al. in southern China (89% and 83.5%)¹⁸ and by Wang et al. in east China (95% and 93%).¹⁰ The prevalence of IgE responses to *Der p1*

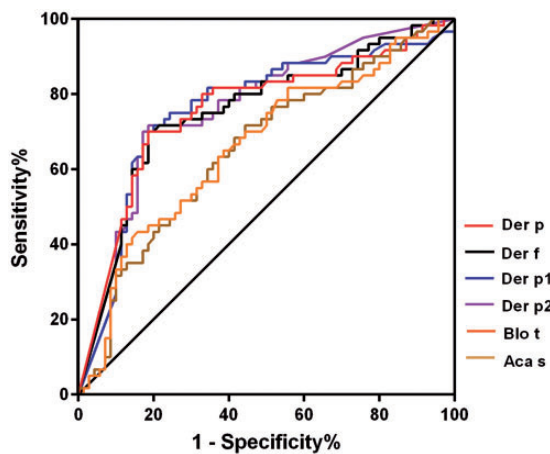


Figure 4. The ROC curve of mites and *Der p* allergen components sIgE concentrations in HDM-AR patients with or without asthma.

Der p, *Dermatophagoides pteronyssinus*; *Der f*, *Dermatophagoides farinae*; *Aca s*, *Acarus siro*; *Blo t*, *Blomia tropicalis*.

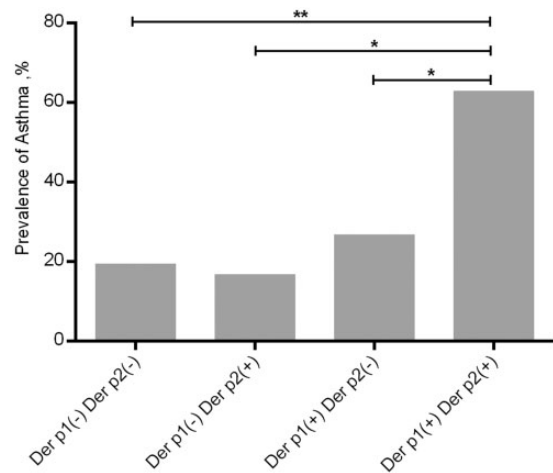


Figure 5. Prevalence of asthma in HDM-AR patients in relation to positively or negatively of specific IgE to *Der p1* and *Der p2*. +, positive, sIgE ≥ 0.35 kU_A/L; -, negative, sIgE < 0.35 kU_A/L; ** $P < .001$; * $P < .05$.

Der p, *Dermatophagoides pteronyssinus*.

Table 1. Prevalence of Sensitization to *Der p* Allergen Components in *Der p*-Positive AR Patients With or Without Asthma.

<i>Der p</i> Components				AR Without Asthma	AR With Asthma	Total
<i>Der p</i>	<i>Der p1</i>	<i>Der p2</i>	<i>Der p10</i>	N (%)	N (%)	N (%)
+	+	+	-	23 (33.3)	45 (75.0)	68 (52.7)
+	-	-	-	22 (31.9)	6 (10.0)	28 (21.7)
+	+	-	-	9 (13.0)	4 (6.7)	13 (10.1)
+	+	+	+	6 (8.7)	4 (6.7)	10 (7.8)
+	-	+	-	4 (5.8)	1 (1.7)	5 (3.9)
+	-	-	+	3 (4.3)	0 (0)	3 (2.3)
+	-	+	+	1 (1.4)	0 (0)	1 (0.8)
+	+	-	+	1 (1.4)	0 (0)	1 (0.8)
				69	60	129

Abbreviations: AR, allergic rhinitis; -, negative—sIgE < 0.35 kU_A/L; +, positive—sIgE ≥ 0.35 kU_A/L.

and *Der p2* was similar to that reported for Australia (74%–77%)¹⁹ and Singapore (63%),²⁰ which may be accounted for the geographical, age, clinical status-related differences, and different IgE measurement techniques. Furthermore, the serum IgE for *Der p1* and *Der p2* and the serum IgE for *Der p* showed a good correlation. Our study suggested that for the detection of *Der p1* or *Der p2* sIgE may be suitable tools of sufficient diagnostic accuracy for use in the diagnosis of *Der p* IgE sensitization. We did not find a significant correlation between the levels of *Der p10* and *Der p*, *Der p1*, and *Der p2*. A number of studies have confirmed that *Der p10* was the minor mite allergen, and the cross-reactivity was extremely frequent between *Der p10* and shrimp, and high level *Der p10* sIgE reactivity was usually associated with seafood-induced symptoms.^{19,21,22}

Our study found that the HDM-AR patients with asthma displayed higher concentrations of sIgE to *Der p*, *Der f*, *Der p1*, and *Der p2* than those without asthma, in accordance with the study which found that the IgE levels and sensitivity to HDMs in the AR-asthma comorbidity group were significantly higher than AR-only group.²³ Resch et al. found that asthmatic children had an expanded IgE repertoire with more recognized allergen components (*Der p1*, *Der p2*, *Der p5*, and *Der p7*), and the risk of being asthmatic was more than 2-fold higher in patients with IgE reactivity to *Der p2*,¹ whereas Zeng et al. showed that the levels of *Der p* and *Der p1* (but not *Der p2*) were higher in patients with either asthma alone or AR with asthma than in those with AR alone in southern China.¹⁸ However, Bronnert et al. did not find any association between *Der p1* or *Der p2* IgE levels and the occurrence of a clinical condition such as asthma or rhinitis in their study.²¹ In our study, the ROC curve of *Der p*, *Der f*, *Der p1*, and *Der p2* sIgE concentrations presented a medium sensitivity and specificity in AR with or without asthma group, which indicated that the utility of sIgE concentration of *Der p*, *Der f*, *Der p1*, and *Der p2* to distinguish AR with or without asthma is still under controversy. From the perspective of qualitative analysis, compared with AR patients, the sIgE levels, both positive to *Der p1* and *Der p2*, were higher in asthmatic patients, which were in accordance with Vidal et al. in Spain⁹ and indicated that sensitization to both *Der p1* and *Der p2* may be a risk factor for asthma in HDM-AR patients. *Der p1* and *Der p2* may play a role jointly in HDM-AR patients with their different biochemical functions. Further studies are needed to investigate the components role in rhinitis and asthma pathogenesis.

In our study, we also found that the sIgE prevalence was 83.1% for *Blo t* in Wuhan, a humid subtropical climate region, which was similar to Hainan (85.8%), a tropical zone.²⁴ *Blo t* is the most prominent mite species in the tropical and subtropical regions of the world.²⁵

Zheng et al. did not find *Blo t* samples in Wuhan in their study.²⁶ A possible explanation for this might be that the HDM and *Blo t* had similar allergen molecular structural features, and the positive rates may be associated with cross-reactivity. Several studies have reported the cross-reactivity among mite species, and the sequence alignment of *Blo t* and *Der p* allergens showed 35.5% to 94.4% homology.^{25,27,28} The results in our study implied that the molecular-based diagnosis was important in HDM-AR patients. Further research should be undertaken to investigate *Aca s* and *Blo t* and to evaluate the functional role in allergen sensitization and pathogenesis of allergic diseases.

In conclusion, *Der p* has high cross-reactivity with other mite species. *Der p1* and *Der p2* are the major components to induce *Der p* sensitization among AR patients in Central China. Sensitization to both *Der p1* and *Der p2* may be a risk factor for developing asthma in HDM-AR patients.

Author Contributions

Yongshi Yang involved in data collection, statistical analysis, and paper writing. Rongfei Zhu involved in data collection and paper writing. Nan Huang, Wenjing Li, and Yin Wang involved in data collection. Wei Zhang involved in laboratory test. Lin Yang contributed to data collection, paper writing, and revising the manuscript.

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Declaration of Conflicting Interests

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