

Molecular allergen sensitization of *Aspergillus fumigatus* in allergic bronchopulmonary aspergillosis in Guangzhou, Southern China

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Abstract

Background Few studies have assessed the sensitization of mycotic allergens and Aspergillus fumigatus molecular allergen. This study aimed to investigate the connection between A.fumigatus components and mycotic allergens between allergic bronchopulmonary aspergillosis (ABPA) patients and A. fumigatus (Af)-sensitized asthma.

Methods Serum Penicillium chrysogenum , Cladosporium herbarum , Mucor racemosus , Candida albicans , Alternaria alternata , Helminthosporium halodes and A.fumigatus allergen components (Asp f 1, Asp f 2, Asp f 3, Asp f 4, and Asp f 6) sIgE level were measured via ImmunoCAP assay in 18 ABPA patients and 54 Af-sensitized asthma patients in Guangzhou city.

Results 94.44% of ABPA patients and 87.04% of Af-sensitized asthma patients were co-sensitization to at least one another fungal allergen. The positivity rates of C. albicans ($P < 0.05$) and A.alternata ($P < 0.05$) were higher in ABPA than that in Af-sensitized asthma patients. The positive rates of Asp f 1 (88.89% vs 59.26%, $P < 0.05$), Asp f 2 (66.67% vs 33.33%, $P < 0.05$), Asp f 4 (61.11% vs 33.33%, $P < 0.05$), and Asp f 6 (66.67% vs 14.81%, $P < 0.001$) in ABPA were higher than those in Af-sensitized asthma patients. Patients with ABPA had higher IgE levels of Asp f 1 ($P < 0.05$), Asp f 4 ($P < 0.05$) and Asp f 6 ($P < 0.001$) than those of Af-sensitized asthma patients. A.fumigatus was strongly correlated with C.herbarum ($r_s = 0.688$) in ABPA and A.alternata ($r_s = 0.692$) in Af-sensitized asthma patients. Optimal scale analysis was show that ABPA was more relevant to Af-components. (Cronbach's alpha = 90.7%)

Conclusion The A.fumigatus components and it's connection with various mycotic allergens were different in ABPA and Af-sensitized asthma patients. This findings can expected to help local doctors in the diagnosis and immunotherapy of fungal allergies.

1.introduction

Fungi are the most common microorganisms in the human living environment, and it is not only easy to cause respiratory tract infection and induced inflammatory response, but also cause severe allergic reaction. Studies have shown that Aspergillus, Alternaria, Candida, Cladosporium and Epicoccum are considered major sources of allergens worldwide.^{1,2} During reproduction, fungi release large amounts of spores and hyphal fragments in the air, which may cause immunoglobulin E (IgE)-mediated respiratory allergic diseases,³ in particular Aspergillus fumigatus (Af)-sensitized asthma and allergic bronchopulmonary aspergillosis (ABPA).⁴

ABPA is a pulmonary disease caused by A.fumigatus, which pathogenesis is owing to allergic response against A.fumigatus colonising the airways rather than saprophytic or invasive of the fungi⁵⁻⁶. When patients with ABPA are exposed to fungi in the environment, they will show repeated wheezing, dyspnea, and even life-threatening in severe cases⁷. Due to the lack of effective clinical treatment, patients have heavy economic burden and poor quality of life. A European study shows that Af-sensitized asthma easy

to develop into ABPA⁸⁻⁹, which may induced by molecular allergen of *A.fumigatus*. There are five major molecular allergens of *A.fumigatus* (*Asp f 1*, *Asp f 2*, *Asp f 3*, *Asp f 4* and *Asp f 6*, respectively). Among them, *Asp f 1* is the most important protein of *A.fumigatus*. It secretes a lot after spore germination and early fungal invasived, which is related to fungal colonization and saprophytic. *Asp f 2* is a fibronectin, *Asp f 3* is an epitope of peroxidase membrane protein, *Asp f 4* is a glycosylated hydrolase and *Asp f 6* is a manganese superoxide dismutase¹⁰⁻¹¹. Our previous research shows that more than 18% asthmatic patients are sensitized to *Asp f 3*¹².

Although several studies have focused on the *A.fumigatus* sensitization in Southern China,^{13,14} the studies of the connection between various fungal allergens and *A.fumigatus* components was still lack, especially in Guangzhou, a beautiful and unique cultural city in southern China. In addition, various fungal allergens and *A.fumigatus* components maybe co-pathogenic and play an important role in ABPA or Af-sensitized asthma. Accordingly, in this study, we compared various fungal allergens and *A.fumigatus* major components between ABPA and Af-sensitized asthma patient, and expected to provide meaningful evidence for accurate diagnosis and for guiding disease treatment.

2.materials And Methods

2.1 Study design

This study included 18 ABPA patients and 54 Af-sensitized asthma patients from 4,033 general population (9–79 year old) who had undergone *A.fumigatus* allergen sIgE tests during January 2016 to December 2017 in the Allergy Information Repository of the National Clinical Research Center for Respiratory Disease (AIR-NCRCRD, Guangzhou, Southern China).

The diagnosis of asthma was based on the Global Initiative for Asthma guidelines¹⁵, and the diagnostic criteria of ABPA was based on Agarwal et al.¹⁶ by respiratory specialist, the patients had undergone allergen-specific immunotherapy, parasitic infections, cancer and immunodeficiency was excluded. All patients provided written informed consent, and the study was approved by the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (GYYY-2016-73).

2.2 Serum allergen-specific IgE detection

In 18 patients with ABPA and 54 patients with Af-sensitized asthma, serum sIgE level of *Penicillium chrysogenum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Mucor racemosus*, *Candida albicans*, *Alternaria alternata*, *Helminthosporium halodes*, total IgE and *Aspergillus fumigatus* components including *Asp f 1*, *Asp f 2*, *Asp f 3*, *Asp f 4*, and *Asp f 6* sIgE were tested by PhadiaCAP 1000 (Thermo Fisher Scientific, Sweden). SIgE concentrations of 0.35 kUA/L or more were defined as positive or sensitization to the allergen. According to the sIgE levels, the reactivity was categorized quantitatively into six classes: Class 1 (≥ 0.35 kUA/L to < 0.70 kUA/L), Class 2 (≥ 0.70 kUA/L to < 3.50 kUA/L), Class 3 (\geq

3.50 kUA/L to < 17.50 kUA/L), Class 4 (\geq 17.50 kUA/L to < 50.00 kUA/L), Class 5 (\geq 50.00 kUA/L to < 100.00 kUA/L), and Class 6 (\geq 100.00 kUA/L).¹⁷

2.3 Statistical analysis

Data analyses were performed using the statistical software package SPSS 22.0 (IL, USA). Nonparametric quantitative data were described as medians (interquartile ranges), between-group comparisons of numerical data were performed using Mann-Whitney U tests or Kruskal-Wallis tests. Parametric quantitative data were depicted as means \pm standard deviations. To show the proportion of positive results, categorical data were reported as percentages. Chi-square (χ^2) tests or F-tests were used to demonstrate differences in proportions between groups. Correlation analyses among the groups were performed by calculating the Spearman correlation coefficient (r_s). The correlation between components was calculated with optimal scale analysis. Differences were regarded as statistically significant if the P value was lower than 0.05.

3.results

3.1 Totality

In AIR-NCRCRD, 7.30% of general population (295/4033) were sensitive to *A.fumigatus* in Guanzhou, sIgE level was 1.10 (0.54-3.79) kUA/L. The positive rate of *A.fumigatus* sIgE was significantly higher in adults than in children (10.50% vs. 2.20%, $P < 0.001$), but there were no differences between men and women. (**Table 1**). In 18 ABPA patients, there were 11 females, and the average age were 44.2 (range: 19 - 68) year old. In 54 patients with Af-sensitized asthma, there were 12 female, and the average age were 49.1 (range: 21 - 79) year old. There was no significant difference in age and gender between them.

3.2 Fungal sensitization between ABPA patients and Af-sensitized asthma patients

There was no significant difference of *A.fumigatus* sIgE levels between ABPA and Af-sensitized asthma patients ($P > 0.05$). In this study, 94.44% of ABPA patients and 87.04% of Af-sensitized asthma patients were sIgE-positive to at least one fungal allergen among the *P.chrysogenum*, *C.herbarum*, *M.racemosus*, *C.albicans*, *A.alternata*, and *H.halodes*. High positive rates to *P.chrysogenum* were found in 94.44% of ABPA patients and in 77.78% Af-sensitized asthma patients. The positivity rates of *C.herbarum* (88.89% vs 62.96%, $P < 0.05$) and *A.alternata* (72.22% vs 44.44%, $P < 0.05$) were higher in patients with ABPA than in Af-sensitized asthma patients (**Figure 1**). Although sIgE levels of *P.chrysogenum*, *C.herbarum*, *M.racemosus*, *C.albicans*, *A.alternata*, and *H.halodes* sIgE were higher in ABPA patients than in Af-sensitized asthma patients, there were no significant differences between two groups (**Figure 2a**).

3.3 *A.fumigatus* component sensitization between ABPA patients and Af-sensitized asthma patients

The positive rates of Asp f 1 (88.89% vs 59.26%, $P < 0.05$), Asp f 2 (66.67% vs 33.33%, $P < 0.05$), Asp f 4 (61.11% vs 33.33%, $P < 0.05$) and Asp f 6 (66.67% vs 14.81%, $P < 0.001$) in ABPA patients were significantly higher than those in Af-sensitized asthma patients.

As shown in **Figure 2b**, sIgE levels of Asp f 1 [7.93 (1.40, 30.18) kUA/L vs. 0.18 (1.18, 10.65) kUA/L, $P < 0.05$], Asp f 4 [3.17 (0.10, 17.65) kUA/L vs. 0.03 (0.18, 5.07) kUA/L, $P < 0.05$] and Asp f 6 [1.22 (0.07, 5.70) kUA/L vs. 0.01 (0.05, 0.61) kUA/L, $P < 0.001$] in ABPA patients were higher than those in Af-sensitized asthma patients. The co-sensitization of five allergen components was shown in **Figure 3**, and there were 7 ABPA patients and 10 Af-sensitized asthma patients co-sensitization to Asp f 1, Asp f 2, Asp f 3, Asp f 4 and Asp f 6 at the same time. Interestingly, among them, there were 100% ABPA patients co-sensitization to *P.chrysogenum* and *C.albicans* (**Table 2**).

3.4 Correlation analysis between *A.fumigatus* components and various mycotic allergens in ABPA patients and Af-sensitized asthma patients

Spearman correlation analysis show that tlgE ($r_s = 0.586, P < 0.05$), *P.chrysogenum* ($r_s = 0.686, P < 0.05$), *C.herbarum* ($r_s = 0.688, P < 0.05$), *M.racemosus* ($r_s = 0.358, P < 0.05$), *C.albicans* ($r_s = 0.492, P < 0.05$), *A.alternata* ($r_s = 0.692, P < 0.05$), and *H.halodes* ($r_s = 0.585, P < 0.05$) had correlation with *A.fumigatus*. *A.fumigatus* component Asp f 1 ($r_s = 0.473, P < 0.05$), Asp f 2 ($r_s = 0.553, P < 0.05$), Asp f 3 ($r_s = 0.558, P < 0.05$), Asp f 4 ($r_s = 0.646, P < 0.05$) and Asp f 6 ($r_s = 0.730, P < 0.05$) was correlated with tlgE. In addition, Asp f 2 ($r_s = 0.653, P < 0.05$), Asp f 3 ($r_s = 0.478, P < 0.05$), Asp f 4 ($r_s = 0.540, P < 0.05$) and Asp f 6 ($r_s = 0.483, P < 0.05$) was correlated with *P.chrysogenum*, Asp f 2 ($r_s = 0.524, P < 0.05$) and Asp f 6 ($r_s = 0.537, P < 0.05$) was correlated with *M.racemosus*, Asp f 2 ($r_s = 0.568, P < 0.05$) and Asp f 3 ($r_s = 0.514, P < 0.05$) was correlated with *A.alternata*, other mycotic allergens hadn't significant correlation with *A.fumigatus* components. Interestingly, the correlation between *A.fumigatus* and it's component Asp f 2 was the strongest (ABPA: $r_s = 0.786$; Af-sensitized asthma: $r_s = 0.663$). Optimal scale analysis was show that ABPA was more relevant to Af-components (Cronbach`s alpha = 90.7%) (**Figure 4**).

4.discussion

Fungus is one of the important causes of respiratory diseases. Europe's investigations have shown that the incidence of fungus-induced respiratory tract allergies is as high as 20–30% in an atopic population, reaching 6% in the general population.^{18–20}

In our study, we found that 7.30% general population were sensitization to *A. fumigatus* in local. Guangzhou city is influenced by the East Asian monsoon season and has a humid and warm subtropical climate, with a relative air humidity of 68% and annual precipitation of more than 1,700 mm.²¹ This contribute greatly to the proliferation and growth of fungi, which prefer humid and warm environments. Therefore, a high concentration of mycotic spores in indoor and outdoor air is one of the most important causes of allergic respiratory tract diseases in Guangzhou.^{22,23} we also found that the positive rate of *A.fumigatus* was significantly higher in adult patients than in children. This suggested that sensitization to *A. fumigatus* allergens may be more common in adults and that adults with asthma should avoid contact with *A. fumigatus* allergens to prevent disease progression to ABPA²⁴.

Interestingly, 94.44% of ABPA patients and 87.04% of Af-sensitized asthma patients were co-sensitization to at least one other fungal allergen. This is concurrent with previous reports by Chang et al. and Ezeamuzie et al. showing that *A.fumigatus*, *C.albicans*, and *P.chrysogenum* were fungal allergens with the highest co-sensitization rates among all allergenic fungi.^{3,5} SIgE sensitization to fungal species reflected well their phylogenetic relationship, since IgE reactivity correlated better in closely related molds than with phylogenetically distant molds.^{25,26} This phenomenon suggests that there may be a cross-react between allergies to *A.fumigatus* and other fungi.

In a study conducted in Sweden in 2010, Soeria-Atmadja et al. analyzed the associations among mycotic allergies in 688 patients who were allergic to fungi. They reported that *A.fumigatus* had extremely strong correlations with *P.chrysogenum* and *H.halodes* ($r_s = 0.85$ and 0.87 , respectively) and strong correlations with *C.herbarum*, *C.albicans*, and *A.alternata* ($0.60 \leq r_s < 0.80$).²⁶ However, in the present study, *A.fumigatus* was strongly correlated with *C.herbarum* ($r_s = 0.688$) in ABPA and *A.alternata* ($r_s = 0.692$) in Af-sensitized asthma patients but not correlated with *C.albicans* ($P > 0.05$).

The difference between fungal and nonfungal allergens is that fungal allergens are more complex. They contain proteases, glycosidases, and protein products, which can easily lead to cross-reactions.

Therefore, exposure to a single mycotic spore is equivalent to exposure to all fungal allergens.²⁷ For example, *P.chrysogenum* and *A.fumigatus* both belong to family Trichocomaceae.²⁵ Interaction between serum anti-*P.chrysogenum* antibodies in patients with ABPA can be greatly inhibited by *A.fumigatus*, probably owing to the high similarity between the primary allergenic components of *P.chrysogenum*, i.e., alkaline and vacuolar serine proteases, and their homologous allergenic components in *A.fumigatus* (Asp f 13 and Asp f 18).¹¹ Furthermore, the allergenic component in *A.alternata*, manganese-dependent superoxide dismutase (MnSOD), is the primary cause of the cross-reaction with Asp f 6.²⁸

In addition, ribosomal proteins are allergenic constituents of *A.fumigatus* components (Asp f 8 and Asp f 23), *A.alternata* components (Alt a 5 and Alt a 12), and *C.herbarum* components (Cla h 5 and Cla h 12).²⁹ Enolases are allergenic constituents of the *A.fumigatus* component Asp f 22, *A.alternata* component (Alt a 6), and *C.herbarum* component (Cla h 6).²⁹ Therefore, cross-reactivity among fungal allergens should be considered when diagnosing fungal allergies to determine the appropriate treatment regimen.

In addition, the positive rates of Asp f 1, Asp f 2, Asp f 4 and Asp f 6 in ABPA patients were significantly higher than those in Af-sensitized asthma patients in our study. Patients with ABPA were characterized by higher levels of IgE Abs to Asp f 1, Asp f 4 and Asp f 6 than those of Af-sensitized asthma patients. Some studies have shown that the combination of Asp f 1 and Asp f 2 can be considered a specific allergenic component in diagnosing *A.fumigatus* sensitization.¹² However, some other reports have shown that the sIgE levels for Asp f 2, Asp f 4, and Asp f 6 were highly specific markers for ABPA diagnosis. Their levels were significantly higher in the serum of patients with ABPA than in the serum of patients with Af-sensitized asthma patients.^{12,29} Therefore, in the presence of an *A.fumigatus* allergy, in-depth analysis of

A.fumigatus components could help to differentiate ABPA from Af-sensitized asthma patients. The insufficient sample size was the main defect of this paper, need to be supplemented by follow-up studies.

5. Conclusion

In summary, this study is the first study to demonstrate the complex relationship between *A.fumigatus* component and various mycotic allergens in ABPA and Af-sensitized asthma patients from Guangzhou, Southern China. Asp f 1, Asp f 2, Asp f 4 and Asp f 6 in ABPA patients were significantly higher than those in Af-sensitized asthma patients, and connection with various mycotic allergens. This findings can expected to help local doctors in the diagnosis of fungal allergies, particularly in distinguished diagnosis between ABPA and Af-sensitized asthma.

Declarations

Ethics approval and consent to participate

Approval was obtained from the ethic committee of The First Affiliated Hospital of Guangzhou Medical University (Reference number: GYFYY-2016-73). The use of human serum samples was in accordance with the legislation in China and the wishes of donors, their legal guardians or next of kin, where applicable, who had offered written informed consent to using the serum samples for future unspecified research purposes.

Consent for publication

Not applicable

Availability of data and material:

The data that support these findings are available on reasonable request from the corresponding author BQS. Data are not publicly available due to concerns regarding research participant privacy.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

Conceived and designed the experiments: BQS. Performed the experiments: NLW, HMH, PYZ, YL. Analyzed the data: WTL, ZHW. Wrote the paper: HSH, WTL. All authors read and approved the final manuscript.

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Tables

Table 1. *A.fumigatus* sensitization in the study population

<i>A. fumigatus</i> positive rate, % (n/N)	
Positive rates	7.3 (295/4033)
Sex	
Female	7.9 (184/2320)
Male	6.5 (111/1713)
Age	
≤ 14 years	2.2 (34/1552)
>14 years	10.5 (261/2481)
sIgE class	
Class 1	34.9 (103/295)
Class 2	38.0 (112/295)
Class 3	15.6 (46/295)
Class 4	9.8 (29/295)
Class 5	1.0 (3/295)
Class 6	0.7 (2/295)

The *A.fumigatus* allergen sIgE positivity rate was significantly higher in adults than in children (10.5% vs. 2.2%, $P < 0.001$).

Table.2 The sIgE level of *A.fumigatus* components and various mycotic allergens in ABPA patients which co-sensitization to Asp f 1, Asp f 2, Asp f 3, Asp f 4 and Asp f 6

NO.	<i>P.chrysogenum</i>	<i>C.herbarum</i>	<i>A.fumigatus</i>	<i>M.racemosus</i>	<i>C.albicans</i>	<i>A.alternata</i>	<i>H.halodes</i>	Asp f 1	Asp f 2	Asp f 3	Asp f 4	Asp f 6
1	28.80	5.28	35.30	1.74	7.86	7.72	13.5	23.90	4.52	30.60	60.80	6.39
2	9.28	2.46	15.90	0.80	8.23	5.07	2.28	6.03	6.89	28.20	5.58	13.80
3	10.40	1.08	6.30	1.46	1.72	2.72	1.27	0.75	4.71	4.98	0.75	0.39
4	100.00	1.49	12.40	4.86	5.38	2.56	1.61	1.58	8.53	0.30	27.70	5.48
5	44.10	1.09	27.60	3.13	8.62	2.18	2.49	100.00	10.90	12.80	100.00	6.34
6	5.93	1.95	40.60	0.21	1.00	2.15	0.50	42.40	16.80	11.10	80.10	4.12
7	2.76	0.16	8.61	0.09	0.46	0.11	0.31	8.94	0.42	6.73	8.43	3.98

Figures

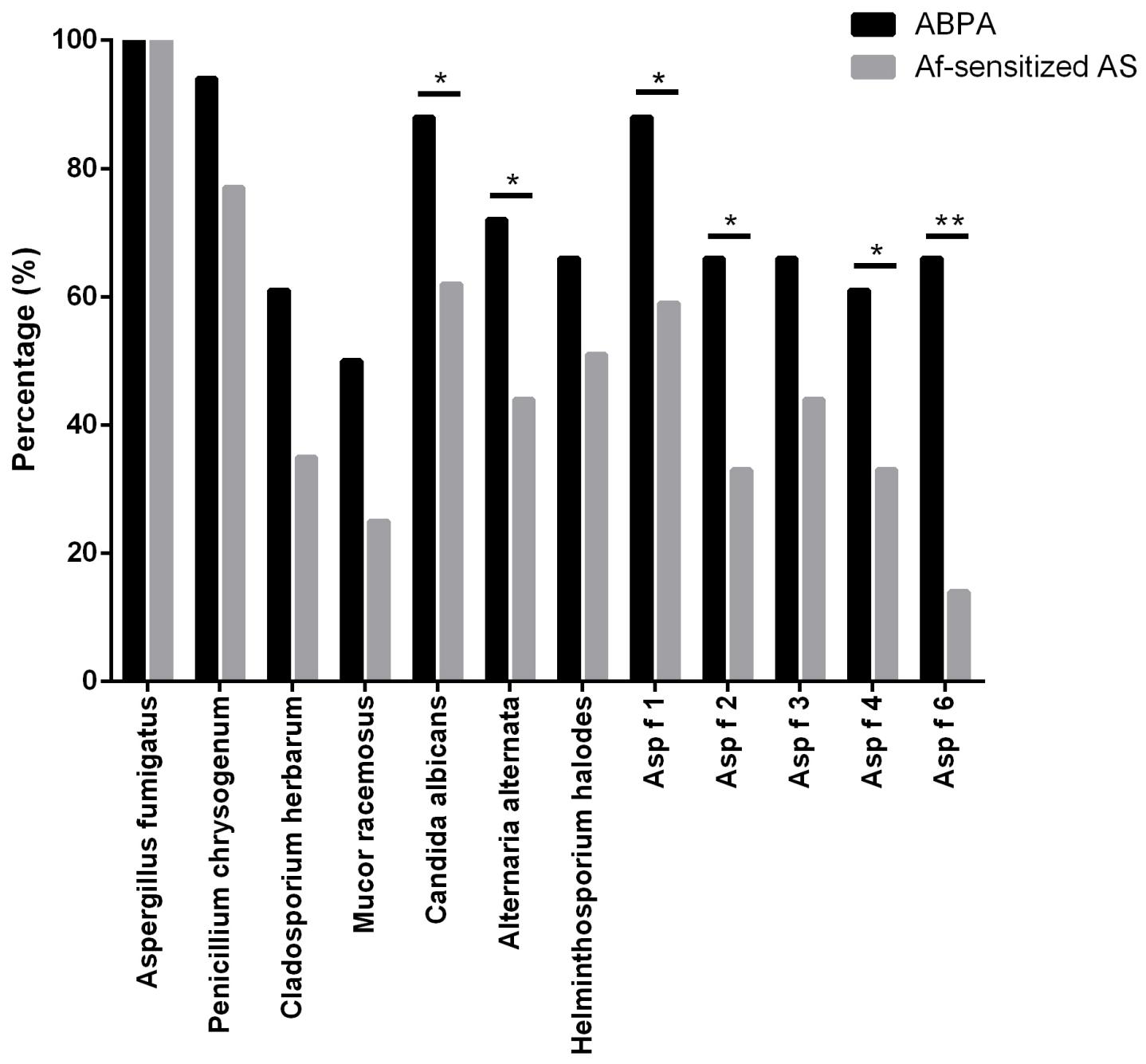


Figure 1

The positive rate of fungal allergens and *A. fumigatus* components between ABPA and *A. fumigatus* sensitized asthma patients
 ABPA: allergic bronchopulmonary aspergillosis; Af-sensitized AS: *A. fumigatus* sensitized asthma patients

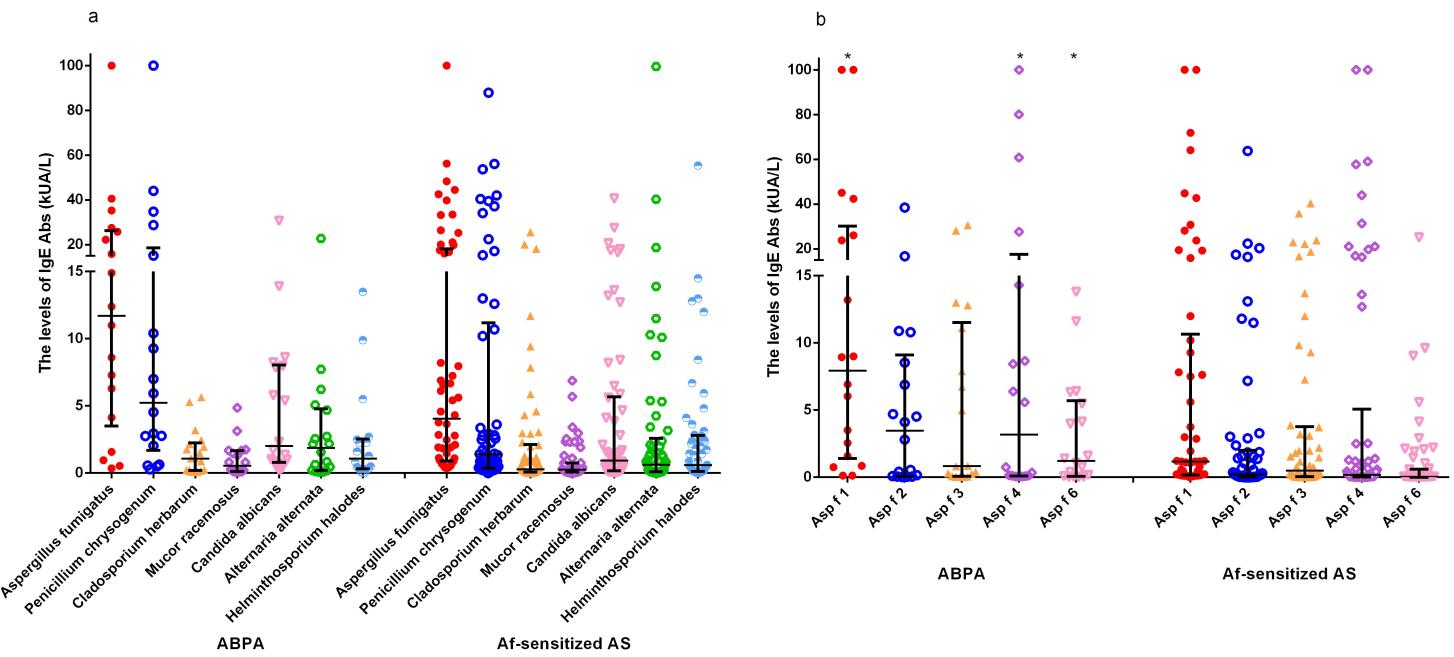


Figure 2

The sIgE levels of fungal allergens and *A. fumigatus* components between ABPA and *A. fumigatus* sensitized asthma patients (a) fungal allergens; (b) *A. fumigatus* components ABPA: allergic bronchopulmonary aspergillosis; Af-sensitized AS: *A. fumigatus* sensitized asthma patients.

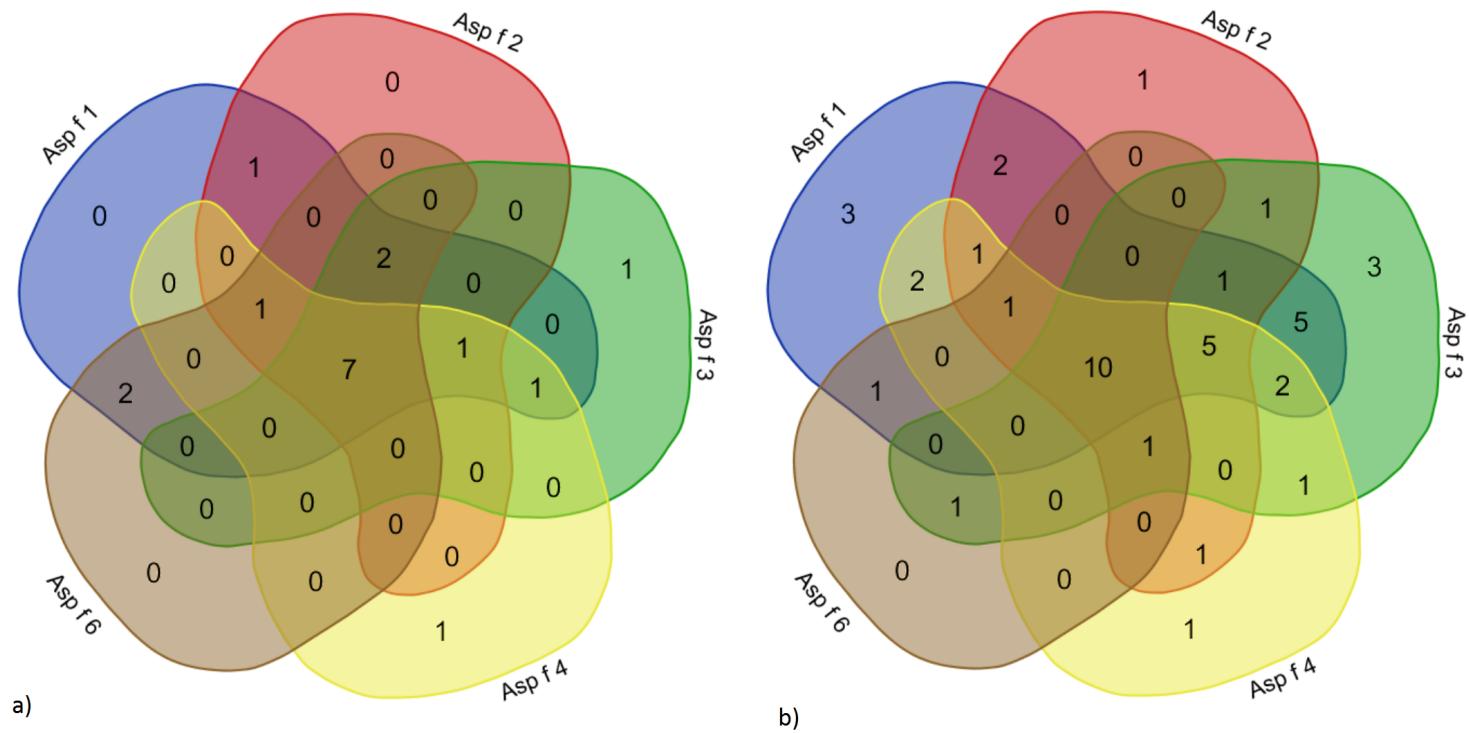


Figure 3

Co-sensitization of *A. fumigatus*-components. (a) Allergic bronchopulmonary aspergillosis; (b) *A. fumigatus* sensitized asthma patients

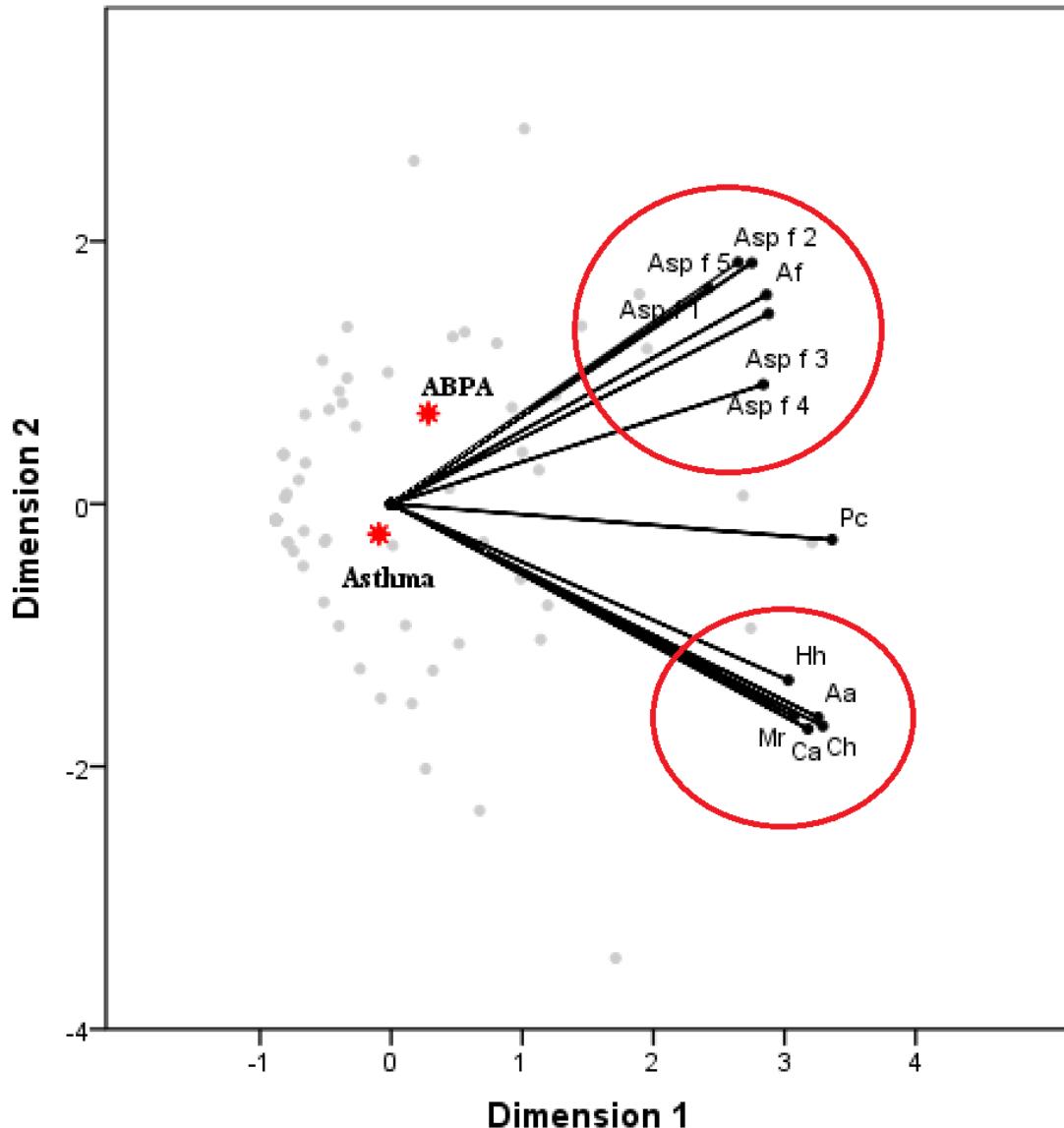


Figure 4

The optimal scale analysis of fungal allergens and *A. fumigatus* components. The closer the distance between points, the closer the relationship is. Contrast to Af-sensitized asthma patients, ABPA was more relevant to Af-components. (Cronbach's alpha = 90.7%). Pc: *P.chrysogenum*; Ch: *C.herbarum*; Af: *A.fumigatus*; Mr: *M.racemosus*; Ca: *C.albicans*; Aa: *A.alternata*; Hh: *H.halodes*