

Familial Aggregation of Skin Sensitization to Aeroallergens in a Rural Area in China

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Key Words

Allergic sensitization • Skin prick test • Familial aggregation • Asthma index family

Abstract

Background: The prevalence of allergic sensitization has increased all over the world during last years and allergic sensitization may be related to genetic or environmental factors or to both. The objective of this study was to estimate the prevalence rates of allergic sensitization and assess the familial aggregation of allergic sensitization to aeroallergens in asthma index families. **Methods:** The skin prick test (SPT) reactivity to 8 aeroallergens and the SPT reactivity-related risk factors were evaluated. The allergic sensitization was based on SPT. Univariate and multivariate logistic regressive models were used to estimate the effect size (odds ratio, OR) of correlation within families with positive SPT. **Results:** Of 4,213 analyzed subjects in 1,006 asthma index families, 40.9% had at least one positive SPT, 42.3% in parents (father: 43.3%; mother: 42.3%), 43.9% in first offspring, and 36.0% in subsequent offspring. The most common allergens were *Dermaphagoides pteronyssinus* (DP), cockroach and *Dermatophagoides farinae* (DF). Allergic sensitization status of both parents and first offspring was related to the risk of allergic sensitiza-

tion for subsequent offspring. The OR for the positive (father)-positive (first offspring) group was 1.92 ($p < 0.01$), 3.26 ($p < 0.01$) for the positive (mother)-positive (first offspring) group, and 2.12 ($p < 0.01$) for the positive (father)-positive (mother) group, which were adjusted for age, sex, body mass index, history of asthma and smoking status. **Conclusions:** Our findings supported a significant familial aggregation of allergic sensitization in this Chinese population and highlighted the role of genetic factors in allergic sensitization.

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Introduction

The prevalence of diseases related to allergic sensitization has increased all over the world during recent decades, especially in western European countries [1], but also varied widely across different regions of the world [2, 3]. The prevalence of allergic diseases including asthma in the Chinese population has been reported to be lower than that in the west and the highest prevalence in schoolchildren was found in Hong Kong [2, 4]. The wide variation of allergic diseases and the recent increasing trend within populations were likely to be mainly explained by environmental factors, but genetic factors have also been

thought to be important in determining disease manifestations [5, 6].

Allergic sensitization is a well-known important risk factor for asthma in adults and children [3]. Sensitization to more than one indoor allergen is common for atopic children and puts young adults at high risk of bronchial hyperresponsiveness [7, 8]. Furthermore, high specific IgE is closely related to clinical allergy [9]. On the other hand, according to the definition of asthma, the asthma-related intermediate phenotypes can be related to skin prick tests (SPT) to aeroallergens [5]. However, although previous findings have shown that the history of parental asthma is an independent risk factor for allergic sensitization for children [10], the relative importance of different aeroallergens has rarely been assessed among populations in China, and the previously published results were considerably inconsistent [4].

In this study, we aim to evaluate the prevalence of allergic sensitization and estimate the effects of age and gender on allergic sensitization among relatives of nuclear families of asthma probands. Further aims were to assess the degree of familial clustering for allergic sensitization. To our knowledge, this is, thus far, the first study of familial aggregation for allergic sensitization in China.

The Ethical Committee of Anhui Medical University approved the study and written informed consent was obtained from each subject before the data were collected.

Materials and Methods

The selection of asthma probands and nuclear families and the methods used in this study have been reported in detail elsewhere [10]. In brief, physician-diagnosed asthma in our study was only used as a screening criterion, and the person first suffering from asthma was considered to be the proband for asthma in his/her family including the first-degree relatives, and therefore asthma index nuclear families were collected. The nuclear families of index cases were chosen based on the following criteria: (1) the presence of an index asthma patient who was at least 3 years of age, (2) the existence of two or more siblings, at least 3 years of age, (3) the availability of both parents, and (4) the detailed history of parental asthma. Further, data for all family members mainly including the completion of questionnaires and SPT were collected, and written informed consent was obtained.

At the time of enrollment, parents completed a standardized questionnaire for themselves and their offspring, including questions on respiratory symptoms and diseases, occupational history, tobacco use, home environment, breast-feeding and other personal characteristics. The data of all relatives in this study come from four categories: father, mother, first offspring, and subsequent offspring. A slightly modified version of the semiquantitative puncture method was used to perform SPT [11]. In addition to positive (histamine) and negative (saline) controls, the following antigens

were applied to the skin of the forearm: house dust, mixed trees, tobacco leaf, grass mix, *Dermatophagoides farinae* (DF), silk, *D. pteronyssinus* (DP) and cockroach. The sum of the longest and the mid-point orthogonal diameters divided by two was computed for each wheal after 15 min. Wheal size of 3 mm or greater, after subtraction of the negative control, was considered positive, and allergic sensitization was defined as at least one positive SPT.

The data were analyzed in two steps. First, the prevalence rates of allergic sensitization and the difference of allergic sensitization among relatives in asthma index families were analyzed. Second, trait correlation among family members indicates the familial clustering, which included the following relationships: first offspring-father, first offspring-mother, subsequent offspring-father, subsequent offspring-mother, and first offspring-subsequent offspring. A statistical software package (SAS, version 9.0) was used to analyze the data. Bivariate analyses and trend testing were performed by the χ^2 test and Fisher's exact test. $p < 0.05$ was considered statistically significant. The multiple logistic regression model was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for allergic sensitization.

Results

The study originally included 1,058 nuclear families and 4,506 relatives. Our analyses were limited to the 4,213 relatives in 1,006 nuclear families, who had complete data on skin test reactivity to aeroallergens. A comparison between the current study relatives and 287 relatives for whom data was missing was performed. Although the relatives lacking data were older and had more severe airway obstruction than those who had complete data, there were no significant differences between the two groups in sex, age, former/current cigarette smoking, and skin test reactivity to one allergen.

Our data were from 1,006 asthma index families which included a total of 4,213 participants. The characteristics of the study sample (table 1) showed that fathers, on average, were 3.2 years older than mothers, and smoking was much more frequent among fathers (78.9%) than mothers (2.1%). On average, the first offspring was 2.3 years older than subsequent offspring, and the percentage of male and female was nearly the same in these asthma index families (male: 50.5%; female: 49.5%). The difference in the level of education, smoking and breast-feeding rates between the first and subsequent offspring is not significant. Interestingly, no animals are kept as pets in rural China and, in general, farmers have no specific history of contact with animals.

Of 4,213 analyzed subjects, 40.9% had at least one positive SPT, 42.3% in parents (father: 43.3%; mother: 41.2%), 43.9% in the first offspring, and 36.0% in subsequent offspring. The difference was statistically significant be-

Table 1. Characteristics of the study sample

	Father (n = 1,006)	Mother (n = 1,006)	First offspring (n = 1,006)	Subsequent off- spring (n = 1,195)
Age, years	46.8 ± 10.6	43.6 ± 10.3	19.0 ± 10.3	16.7 ± 9.8
Height, m	1.66 ± 0.06	1.55 ± 0.05	1.54 ± 0.11	1.45 ± 0.13
Weight, kg	58.0 ± 6.9	51.13 ± 6.5	46.4 ± 10.7	32.2 ± 9.7
Female, %	–	–	53.8	48.5
Education, %				
Illiterate	12.3	49.7	5.3	6.4
Elementary	48.5	30.3	24.1	36.9
Middle	24.1	12.1	42.7	30.8
Higher	16.1	8.9	32.9	26.9
Smoking, %				
Never	20.0	97.2	100	100
Ever	14.5	0.3	0	0
Current	65.5	2.5	0	0
Breast-feeding, %	90.1	89.5	91.3	91.7

Table 2. Prevalence (%) of allergic sensitization of skin to aeroallergens in parents and offspring

Allergen	Parents (n = 2,012)			First offspring (n = 1,006)			Subsequent offspring (n = 1,195)			All members (n = 4,213)		
	father (n = 1,006)	mother (n = 1,006)	total	male (n = 579)	female (n = 427)	total	male (n = 456)	female (n = 739)	total	male (n = 2,041)	female (n = 2,172)	total
House dust	15.0	12.6	13.7	16.7	12.7	14.6	15.1	11.9	13.6	15.2**	12.0	13.6
Mixed trees	11.7	9.4	10.5	10.2*	6.5	8.3	7.1	4.8	5.9	10.3**	7.0	8.7
Tobacco leaves	12.0	9.4	10.6	10.4	10.5	10.4	9.1	7.7	8.4	10.9*	8.8	9.8
Grass mix	13.7**	8.6	10.9	10.6**	10.0	10.3	8.7	6.8	7.8	11.2**	7.9	9.5
DF	30.6*	26.2	28.2	29.9	29.0	29.5	25.4	21.9	23.7	29.1**	24.6	26.9
Silk	16.3**	12.0	14.0	13.0	11.8	12.4	10.8	10.9	10.8	13.4*	11.0	12.2
DP	35.8*	30.7	33.0	41.2**	30.8	35.9	31.6*	25.0	28.4	34.8**	27.6	31.2
Cockroach	36.3**	30.7	33.3	38.2**	32.7	35.4	29.2	24.3	26.9	33.2**	27.7	30.5
Any allergen	43.3	41.2	42.3	46.7*	40.2	43.9	43.1**	31.5	36.0	44.2**	37.8	40.9

* p < 0.05, ** p < 0.01 vs. female in the same group.

tween males (44.2%) and females (37.8%; $p < 0.01$), first and subsequent offspring, but men were also significantly more sensitized to 8 allergens than women (table 2). DP, cockroach, and DF were the three most potent allergens in terms of frequency of reaction with 31.2, 30.5 and 26.9% prevalence in turn, followed by house dust (13.6%) and silk (12.2%), and the lowest was tobacco leaf (9.8%), grass mix (9.5%) and mixed trees (8.7%) (table 2). Furthermore, reactions to DP, cockroach, and DF as a group were significantly more common among all subjects. The prick test response to the mite and animal allergens were generally larger than to the botanic allergens. The two

largest wheal sizes for positive SPT to cockroach and DF were 42.0 and 40.0 mm, respectively, followed by 27.5 mm for mixed trees and 21.6 mm for DP. In addition to prevalence and wheal size, a positive SPT to one allergen increases markedly the likelihood that there will also be reactions to a second, third or other subsequent allergen. Reactions to those allergens were quite closely interrelated and their correlations were statistically significant (no data shown).

We used the multifactor logistic regression model to evaluate the relationship of the allergic sensitization status among the family members with adjustment made for

Table 3. Relationship of adjusted SPT positive among the family members by OR (95% CI)

	Mother	First offspring	Subsequent offspring
Father	0.79 (0.61–1.18)	1.29 (1.02–1.79)*	1.21 (0.96–1.50)
Mother	–	1.33 (1.10–1.91)*	1.30 (1.08–1.87)*
First offspring	–	–	2.24 (1.61–3.12)**

* $p < 0.05$; ** $p < 0.01$.

Table 4. OR of adjusted allergen sensitization of subsequent offspring in relation to adjusted allergen sensitization of other family members

	OR	95% CI	p value
Father	1.11	0.99–2.12	<0.05
Mother	1.20	1.02–2.76	<0.05
First offspring	2.22	1.51–3.60	<0.01

Each regression analysis included adjusted allergen sensitization for all family members adjusted for age, sex, BMI, history of asthma, and smoking status.

Table 5. Interaction of the allergic sensitization of father/mother and first offspring in allergic sensitization of subsequent offspring (OR and 95% CI)

SPT	Crude		Adjusted ¹	
	OR	95% CI	OR	95% CI
Father +				
1st offspring +	2.10*	1.22–3.28	1.92*	1.28–3.20
1st offspring –	0.94	0.68–1.53	0.91	0.73–1.59
Father –				
1st offspring +	1.85*	1.10–3.69	1.91*	1.19–3.81
1st offspring –	1.00	–	1.00	–
Mother +				
1st offspring +	3.20**	1.97–5.10	3.26**	2.11–6.06
1st offspring –	1.53	0.91–2.47	1.69*	1.04–3.50
Mother –				
1st offspring +	2.26*	1.30–4.00	2.13*	1.21–3.80
1st offspring –	1.00	–	1.00	–
Father +				
Mother +	2.00*	1.24–3.67	2.12**	1.63–3.71
Mother –	1.27	0.79–2.54	1.45	0.81–3.01
Father –				
Mother +	1.68	0.93–2.80	1.50	0.83–2.28
Mother –	1.00	–	1.00	–

* $p < 0.05$; ** $p < 0.01$.

¹ Adjusted for age, sex, BMI, history of asthma, and smoking status.

covariates. The first offspring's allergic sensitization was significantly related to the allergic sensitization of father (OR 1.29, $p < 0.05$), mother (OR 1.33, $p < 0.05$) and subsequent offspring (OR 2.24, $p < 0.01$). In addition, the mother's allergic sensitization might increase the risk of allergic sensitization of subsequent offspring (OR 1.30, $p < 0.05$) (table 3). Further, the independent association of the adjusted allergic sensitization status of father, mother, and first offspring with the OR of allergic sensitization of the subsequent offspring was examined separately (table 4). The allergic sensitization status of the parents and first offspring all appeared to be associated with elevated risks of allergic sensitization for subsequent offspring, and the effect was statistically significant (father OR = 1.11, mother OR = 1.20, first offspring OR = 2.22). In particular, it was obvious that the first and subsequent offspring were most closely correlated.

Table 5 showed that the father's sensitization was not important if stratified by the sibling's sensitization, whereas the mother's sensitization had an additive effect to the sibling's sensitization. In the asthma index families, the OR for positive (father)-positive (first offspring) group was 1.92 ($p < 0.01$), 0.91 ($p > 0.05$) for the positive-negative group, and 1.91 ($p < 0.01$) for the negative-positive group. The OR for the positive (mother)-positive (first offspring) group was 3.26 ($p < 0.01$), 1.69 ($p < 0.05$) for the positive-negative group, and 2.13 ($p < 0.05$) for the negative-positive group. Finally, we also found that the OR for the positive (father)-positive (mother) group was 2.12 ($p < 0.01$), that for the positive-negative group was 1.45 ($p > 0.05$), and that for the negative-positive group was 1.50 ($p > 0.05$). In short, the risk estimates for positive-negative and negative-positive groups were lower than those for positive-positive groups.

Discussion

The present study assessed the overall prevalence of allergic sensitization, the distribution of sensitization to multiple aeroallergens relevant in asthma index families, and family clustering of positive SPT. The prevalence rates of SPT reactivity to common airborne allergens among the relatives of families with asthma was similar to the findings in western developed countries ranging from 21 to 46% [12], but was more common in our study than the ECRHS results from Sweden among subjects aged 20–44 years (36%) and in Tallinn, Estonia (39.3%) in a study of the general population [1]. In our study of asthma index families, the most common allergens were DP,

cockroach and DF, whereas the most common ones in Finland were dog and cat, and in Russia mugwort and cockroach [13].

SPT was an important intermediate phenotype of atopic disease and the SPT reaction, appearing within minutes after the introduction of the allergen, has been a diagnostic tool of clinical allergy for many years. However, the International Study of Asthma and Allergies in Childhood showed that there was marked difference in the global prevalence of atopic disease [14]. This variation occurs not only between countries but also regionally within countries, with the highest prevalence being in westernized, industrialized countries [15]. It is unclear how allergic sensitization and allergen exposure differ between these countries. Those factors influencing the study outcome may include the number and concentration of allergen extracts, SPT method and procedure, regional differences, allergen exposure, and sample size. On the other hand, atopic disease has a strong hereditary component: if both parents are affected by atopic disease (or one parent and a sibling) 40% of offspring will be affected [15]. It is likely that children inheriting the 'atopy gene(s)' are more likely to become susceptible and to develop allergic inflammation when exposed to the specific environmental influences [16, 17]; i.e., if both of parents are affected by allergic sensitization, their offspring are more likely to carry the gene related to allergic sensitization and to suffer from positive SPT or allergic sensitization.

Early in 1984, Hopp et al. [18] reported that skin test reactivity is determined by genetic and environmental factors with a greater genetic influence as reflected in the higher correlation in monozygous twins, but similar epidemiological studies concerning the association between genetic and SPT reactivity have been rare afterward. Nevertheless, several SPT-related gene loci have been found and may further determine the interrelation of SPT to multifactor of genetic [5, 19, 20]. Therefore, it is reasonable to consider the possibility that genes also play a pivotal role in SPT reactivity. If such a genetic effect does exist, then allergic sensitization status will tend to be correlated within families. We conducted the current investigation in asthma index families and found a significant familial clustering (table 3). Further, the additive or multiplicative effect may exist between the effects of mother-first offspring and father-mother pairs on the positive SPT of the subsequent offspring (for adjustment of known confounders). The OR estimated for all types of relative pairs and the greater risk with parent-offspring and offspring-offspring pairs than father-mother pairs also proposed that genetic factors may play an important role. However, the

familial aggregation of positive SPT found in this study may result from either genetic factors or shared household environmental factors, or both. The extent of the genetic contribution is difficult to estimate accurately because familial aggregation may be attributable to variations of multiple genes [21, 22]. A striking finding of this study is that the father's sensitization was not important if stratified by the sibling's sensitization, whereas the mother's sensitization had an additive effect with the sibling's sensitization (table 4). A non-Mendelian mode of transmission referred to as genomic imprinting may also be used to explain the genetic modifications, as in other diseases [23]. Genomic imprinting refers to an epigenetic effect that causes a differential expression of a gene, depending on the sex of the transmitting parent. The imprinting process, exemplified by the Prader-Willi syndrome [24], allows gene expression from only the maternally or paternally derived chromosome. However, this process remains to be further confirmed. The major limitation of the study is that all subjects came from asthma index families and were exclusively Chinese, limiting its generalizability to the general population and to other ethnic populations. A major issue in the present study was the use of highly selected probands as the basis for the study of families. This limited the size of the population available for study, but the potential for bias was also reduced because of the controlled misclassification of the probands based on information collected during this study. In addition, the prevalence rates of allergic sensitization may be overestimated for the general population in China.

In conclusion, our findings support a significant familial aggregation of allergic sensitization in the Chinese population studied, which highlighted a role of genetic factors in allergic sensitization.

Acknowledgments

The authors are grateful to the study members and their parents for their support. This work was supported by Natural Science Foundation of the Anhui Education Department grant No. 2003kj172.

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