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Predicting the development of early skin test sensitization in offspring of parents with asthma

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Abstract

Background The direct causal relationship between skin sensitization and asthma are controversial until now and remains to be further researched. Our aim is to analyse the role of parental asthma in the development of skin sensitization in offspring.

Materials and methods This study was performed among nuclear families (determined by index of asthma patients), and subjects included parents and offspring. Parents were subdivided into four phenotypes on the basis of skin sensitization (SPT+ or SPT–) and asthma status (AST+ or AST–) and offspring were subdivided into three age groups: 3–8, 9–14 and 15–20 years. The main tests included a standard questionnaire and skin prick tests.

Results Offspring's skin sensitization differed among parental phenotypes at all ages ($P < 0{\cdot}05$). In the SPT+/AST–, SPT–/AST+ and SPT+/AST+ groups, offspring were significantly more likely to be allergic than the ones in SPT–/AST– group at 3–8 years. Offspring with at least one parent with asthma were significantly more likely to have positive skin prick test response than those with non-asthmatic parents at age 3–8 years and 9–14 years, but not at 15–20 years among offspring with allergic parents. Results were independent of asthma in the children and of the characteristics of atopy in the parents.

Conclusion Parent asthma history is an independent risk factor for allergic sensitization in their offspring in a Chinese population.

Keywords Asthma, nuclear family, skin prick test.
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Introduction

The prevalence of asthma has increased worldwide, but asthma is less common in China than in countries with a Western lifestyle [1–3]. Furthermore, it is known widely that atopy and asthma are closely linked [4]. Many findings declared that atopic sensitization is linked to an increased prevalence of asthma, bronchial hyper-responsiveness, and a greater severity of respiratory symptoms [5]. However, less than 50% of asthma cases are attributable to atopy and areas with a high prevalence of atopy have an unexpectedly low rate of asthma [6,7]. In addition, cohort studies have declared that sensitization to asthma-related allergens that occurs early in life is much more strongly associated with asthma risk than late-onset sensitization [8,9]. These results show that a more complex relationship between allergic sensitization and asthma might exist and remain to be demonstrated.

Previous work has demonstrated the complex nature of the heritability of asthma and atopy and has suggested a significantly increased risk of asthma in children of parents with asthma and elevated total IgE levels [10,11]. The asthmatic condition itself might play a key role in determining a specific pattern of atopic sensitization [12,13]. In particular, a genetic predisposition to asthma might increase the subject's susceptibility to become sensitized to local aeroallergens [14,15]. The process of becoming sensitized to aeroallergens would either parallel or cause the development of asthma. Little is known, however, about the relationship between skin test reactivity to aeroallergens in offspring and parental asthma in mainland China. We were interested in examining our hypothesis that parental asthma might be an independent risk factor for the development of skin prick test sensitization in offspring.

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Patients and methods

Subjects

The diagnosis of asthma was made on the basis of the American Thoracic Society (ATS) criteria [16]. Physician-diagnosed asthma in our study was only used as a screening criteria and patients with physician-diagnosed asthma had to have a history of repeated onset of wheeze with dyspnoea but be asymptomatic between two events and have respiratory symptoms that were relieved by bronchodilator use. Asthma-index nuclear families were collected. The nuclear families of index cases were chosen based on the following criteria: (i) the presence of an index asthma patient who was at least 3 years of age; (ii) the existence of two or more siblings, at least 3 years of age; (iii) the availability of both parents; and (iv) the history of parental asthma in details. Furthermore, collection of data for all familial members mainly include completion of questionnaires and skin prick tests were performed, and written informed consent was obtained. The study was approved by the Institutional Review Board of Anhui Medical University.

Questionnaires

At the time of enrolment, parents completed a standardized questionnaire for themselves and their offspring, including questions on respiratory symptoms, respiratory health status, occupational history, tobacco use, home environment, breastfeeding, family history of asthma and their history of respiratory illness and other personal characteristics. If parents had ever had a physician-confirmed diagnosis of asthma, atopic dermatitis, or both, they were considered to have asthma, atopic dermatitis, or both.

Frequent asthma in offspring was defined as at least three asthma episodes in the previous year. Offspring were considered to have atopic dermatitis if a physician diagnosis was present and the child had used medications in the past year. The data of offspring for this study come from three age groups: 3–8 (6·6 ± 0·8), 9–14 (10·9 ± 0·7), and 15–20 (17·1 ± 0·4) years.

Skin prick tests and eosinophil levels

We used a slightly modified version of the semiquantiative puncture method to perform skin prick tests [17]. In addition to positive (histamine) and negative (saline) controls, the following antigens were applied to the skin of the forearm: house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), mixed trees and grasses, tobacco leaf, polyvalent molds, artemisia and silk. The sum of two perpendicular diameters was computed for each wheal after 15 min. Wheal sizes of 3 mm or greater, after subtraction of the negative control, were considered positive, and a positive skin prick test response was defined as atopy and a positive reaction to one or more allergens.

Total white blood cell counts were performed with by routine blood test counter. Blood smears from peripheral samples were stained (Wright–Giemsa stain) and evaluated under a microscope. A 200-count white blood cell differential was performed, and the percentages and absolute eosinophil counts were calculated accordingly. All samples were assayed in duplicates, and the means were computed.

Statistics strategy and data analysis

To explore role of a positive parental history of asthma, atopy, or both in the development of allergic sensitization in the offspring during the first 20 years of life, the relationship between parental phenotypes and skin prick test sensitization in the offspring was assessed in contingency tables, with χ^2-tests used to determine statistical significance. The Mantel–Haenszel test for homogeneity was used to compute odds ratios (OR) and 95% confidence intervals (CI) for skin prick test sensitization in the offspring associated with parental asthma after stratification by severity of allergic markers in the parents. With skin prick test sensitization in the offspring as a dependent variable, non-condition logistic regress model in SAS statistical software package (SAS Institute Inc., Cary, NC) was used in the multivariate analyses to adjust for potential confounding factors. ORs and 95% CIs were calculated as estimates of the relative risk for variables.

The results of skin prick test was used to define the atopy. Parents were subdivided into four groups of phenotypes as follows: SPT–/AST–; SPT–/AST+; SPT+/AST–; and SPT+/AST+. When conducting skin prick test, we considered the following variables of allergy: number of positive skin prick test responses, maximum wheal size, number of atopic parents (one or both), and eosinophil count. Maximum wheal size, number of positive skin prick test responses, and eosinophil count were calculated, and parents were divided into three groups according to these values. OR for the association between parental asthma and skin prick test sensitization in offspring were computed for all parents with difference skin prick test responses and for each group separately. When combining paternal and maternal information, we selected data regarding the parent with a positive skin prick test response, or in the case of two atopic parents, we chose the highest value. The statistical significance level is a two-sided α of 0·05 for all tests.

Results

The study originally included 1058 nuclear families and 4506 relatives. These analyses were limited to the 4213 relatives in 1006 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 were missing was performed. Although the relatives lacking data were older and had more severe airway obstruction than did those who had complete data, no significant differences between both groups in sex, age, previous/present cigarette smoking, skin test reactivity to one allergen.

Table 1 Characteristics of the nuclear families

	Offspring			
	Excluded	3–8 years	9–14 years	15–20 years
Number	106	768	701	732
Maternal asthma (%)	6·1	5·9	6·0	5·1
Maternal allergen sensitization (%)	40·5	42·4	41·8	43·0
Maternal smoking during pregnancy (%)	1·7	1·1	1·8	1·7
Maternal education (%, ≤ 9 y)	42·2	44·8	41·4	40·0
Paternal asthma (%)	5·6	5·3	5·8	5·2
Paternal allergen sensitization (%)	42·3	41·8	42·1	44·2
Breastfeeding (%)	90	89	90·1	91

Table 2 Comparison of risk for SKT+ in offsping at each group by parental phenotype

	Odds ratio and 95% confidence interval of offspring with SPT+		
Parental phenotype	3–8 years	9–14 years	15–20 years
SPT–/AST–	1·00	1·00	1·00
SPT–/AST+	1·45 (0·55–3·74)	1·36 (0·47–3·93)	1·58 (0·76–3·31)
SPT+/AST–	1·69* (1·06–2·69)	1·96** (1·27–3·02)	2·47 (1·63–3·75)
SPT+/AST+	3·28** (1·92–5·65)	3·11** (1·84–5·27)	3·11 (1·71–5·67)

Compared with the SPT–/AST– parental phenotype. $^{**}P < 0{\cdot}05$; $^{*}P < 0{\cdot}01$.

Furthermore, we totally analysed the data from 1006 eligible nuclear families, which had 4213 relatives including parents 2012 and offspring 2201. Of the 2201 offspring originally enrolled in our study, 768 offspring were assigned to the 3–8 years age group, 701 to 9–11 years age group, and 732 to 15–20 years age group. There are no significant differences between the offspring on whom complete and incomplete data (excluded) were available in terms of maternal smoking during pregnancy, maternal asthma, paternal asthma, breastfeeding, or lower respiratory tract infection in the first 3 years of life (Table 1).

The positive rates of atopy sensitivity were significant differences in 3–8, 9–14 and 15–20 years of age to 34·4% (264/768), 47·9% (336/701), 62·3% (456/731), respectively ($P < 0{\cdot}05$), and the percentage of offspring with positive skin prick test reactivity differed among parental phenotypes at all three groups. The ORs of positive skin prick test reactivity in offspring are listed in Table 2. Offspring of parents with positive skin prick test responses, either with or without asthma, were significantly more likely to have positive skin prick test reactivity than offsprings of SPT–/AST– parents at all ages. The OR of offspring with positive skin prick test reactivity in the SPT+/AST+ parental phenotype was significantly higher than that in the SPT+/AST– or SPT–/AST+ group at the 3–8, 9–14 and 15–20 years age groups. Furthermore, the risk of offspring with positive skin test responses is greater in the SKT+/AST+ than in the SKT+/AST– group parents, and there might exist synergic effect of parental SPT+ and AST+ on skin sensitization of offspring. In the SPT–/AST+ parental phenotype with few number of offspring, no meaningful comparison was possible at all groups of offspring. The differences were not found when analyses were performed for mothers and fathers separately.

In addition, SPT+/AST+ parents did show significantly higher values of maximum wheal size, number of eosinophils per cubic millimetre of blood and a significantly high proportion of subjects with more than three positive skin prick test reactivity compared with the SPT+/AST– group. Furthermore, parents were categorized into three groups by maximum wheal size, number of SPT+ and number of esosinophils per cubic millimetre to test the differences of offspring's skin prick test sensitization between SPT+/AST– and SPT+/AST+ phenotypes. The OR for the association between asthma in the parents and skin prick test sensitization in the offspring were given in Table 3. This proved that the association is specific to parental asthma rather than to a stronger allergic predisposition among asthmatic parents with positive skin prick test reactivity. Offspring of SPT+/AST+ parents were at greater risk to have positive skin prick test responses than the ones of SPT+/AST– parents, and they were also more frequently have asthma at all ages and have atopic dermatitis at 3–8 and 9–14 years of age (Table 4).

With skin prick test reactivity in the offspring as the dependent variable and offspring's wheezing, parental asthma, parental atopic dermatitis, and characteristics of allergy in parents as independent variables, multivariate analyses were performed to further investigate the independent role of asthma in parents with positive skin prick test reactivity on the development of offspring's sensitization. The following variables were tested by the model: frequent wheezing for the offspring and physician-diagnosed asthma, maximum wheal size, number of positive skin prick test

Table 3 Odds ratio (OR) for skin test sensitization in offspring with parental asthma after stratification for the characteristics of atopy in only SPT+/AST– and SPT+/AST+ parents

Characteristics of atopy in parents	OR value	95% CI	*P*-value
Maximum wheal size			
10 mm	1·23	0·89–2·28	> 0·05
11–20 mm	1·60	1·19–3·40	< 0·05
> 20 mm	1·86	1·12–3·64	< 0·01
Number of SPT+			
1 or 4	1·89	0·91–3·03	> 0·05
4 or 6	2·09	1·28–4·16	< 0·01
> 6	1·34	0·82–2·97	> 0·05
Number of eosinophils			
< 100	2·02	0·96–3·88	> 0·05
101–200	2·36	1·64–3·65	< 0·01
> 200	1·97	0·97–3·02	> 0·05

reactivity, number of eosinophils, and number of parents with positive skin prick test reactivity for the parents.

Table 5 listed those variables that had a significant association with skin prick test reactivity in the offspring in the multivariate analyses. Although most variables tested were significantly associated with skin prick test sensitization in the offspring in univariate analysis, only parental asthma, asthma in the offspring, and the number of atopic parents showed statistical significance and their ORs were 1·91 (95% CI: 1·22–2·78, $P < 0·05$), 2·13 (95% CI: 1·54–2·96, $P < 0·01$), and 1·83 (95% CI: 1·42–2·99, $P < 0·05$), respectively. Parental asthma was a significant and independent risk factor for allergic sensitization in the offspring. The effect of parental asthma on the development of skin prick test sensitization in the offspring was independent of the offspring's asthma status and adjusted ORs were significant at 3–8 years (2·02; 95% CI = 1·58–3·01) and at 9–14 years age groups (1·85; 95% CI = 1·39–2·91) but not at 15–20 years age group (1·23; 95% CI = 0·82–2·54).

Discussion

Our data showed that both parental skin prick test reactivity and parental asthma are independent risk factors for the development of skin sensitization in early life of offspring and both could explain the greater prevalence of skin prick test sensitization in the offspring. It was noted that parental asthma was still a significant determinant of skin sensitization in the offspring after adjustment of maximum wheal size, number of positive skin prick test response and number of eosinophil. These results indicated that parental asthma might independently play an important role in the development of the asthmatic condition [18] and allergic sensitization [14] in offspring, respectively. Previous several studies

Table 4 Percentage of asthma and atopic dermatitis in offspring at each age group by parental phenotype*

	3–8 years, % (*n*)		9–14 years, % (*n*)		15–20 years, % (*n*)	
Parental phenotype	Frequent asthma	Atopic dermatitis	Frequent asthma	Atopic dermatitis	Frequent asthma	Atopic dermatitis
SPT–/AST–	3·8 (136)	16·7 (129)	2·6 (136)	12·1 (125)	3·3 (135)	16·2 (137)
SPT+/AST–	4·9 (451)	20·09 (450)	5·1 (467)	20·5 (454)	5·9 (458)	20·1 (462)
SPT+/AST+	9·2 (141)	32·6 (138)	10·7 (141)	31·0 (137)	8·7 (132)	28·5 (144)
P-value	< 0·01	< 0·01	< 0·01	< 0·05	< 0·05	> 0·05

P-value for the comparison between the SPT+/AST– and SPT+/AST+. *Not including the SPT–/AST+ parental families because there were few offspring in those families.

Table 5 Odds ratios (OD) (95% confidence intervals) with skin prick test reactivity for offspring in multivariate analysis*†

Variables	OR value	95% CI	*P*-value
Parental asthma	1·91	1·22–2·78	< 0·05
Offspring's asthma	2·13	1·54–2·96	< 0·01
Number of parents with positive skin test responses	1·83	1·42–2·99	< 0·05
Parental asthma at difference ages of offspring:			
3–8 years of age	2·02	1·58–3·01	< 0·01
9–14 years of age	1·85	1·39–2·91	< 0·05
15–20 years of age	1·23	0·82–2·54	> 0·05

*Only parents with positive skin prick test responses were included. †Variables included: physician-diagnosed atopic dermatitis in parents, number of positive skin prick test responses in parents, maximum wheal size in parents, parental eosinophils, and number of parents with positive skin prick test reactivity. Only those variables showed significant association with skin prick test reactivity in the offspring.

[14,19] indicated that maternal or paternal asthma was statistically a significant determinant of asthma in their offspring and were consistent with our study. A prospective birth-cohort study [20] suggested that the factors determining the development of skin prick test reactivity appear to be substantially different than those relationships with the development of offspring asthma. The relationship of sensitization to asthma reflects the susceptibility of individuals with asthma to become sensitized to those aeroallergens rather than an increased risk of asthma development among individuals exposed to those aeroallergens. These results might similarly proposed that there is a more complex relationship between allergic sensitization and the susceptibility to asthma than has been understood before and the mechanism certainly remains to study. We observed that offspring with a parental history of asthma were more likely to have allergic sensitization earlier in life than those without such a history. The effect of a familial predisposition for asthma was actually different among three age groups and decreasing with age. It is declared that factors other than parental asthma similarly play an important role in the development of allergic sensitization. Identification of factors that could predict the development of asthma in children is useful for early intervention, because atopic disorders usually manifest for the first time in childhood and often lead to chronic disease that may continue into adulthood [21]. Especially, it was suggested that various genetic mechanisms might exist underlying the pattern of skin sensitization developing at different ages.

Many studies have assessed parent-of-origin effects on the development of asthma and allergic susceptibility in offspring. There is a great deal of evidence that a maternal history of allergic disease has more influence than paternal history over subsequent allergic phenotypes in offspring [22], and the cohort study has demonstrated that maternal but not paternal history of asthma was an important predictor of subsequent wheeze in early childhood [23]. Maternal history of asthma also appears to change the effects of environmental factors that promote the development of asthma [24]. Given this great body of evidence that the maternal history of asthma predominates over paternal history as a determinant of asthma and atopy, our findings of no difference between influence of mother asthma history and influence of father asthma history on offspring may seem inconsistent. In contrast, Raby *et al.* [25] reported contradictory findings of a predominant paternal effect on the natural course of established airway hyper-responsiveness; therefore, the parent-of-origin effects on allergic sensibility still remain to be further studied. According to this and other studies, we consider that allergic sensitization is related to a genetic susceptibility for asthma and very low levels of aeroallergen exposure in early life might develop allergy. Our data suggested association of a genetic background for asthma and skin sensibility with development of asthma, airway hyper-responsiveness and change of lung function, and parental asthma history is an independent and important risk factor of positive skin prick test response in offspring.

Although our outcomes are supported by the epidemiologic and genetic data presented earlier, several important limitations of this study warrant consideration. Because this is a cross-sectional study and the time sequence between skin sensitization and asthma cannot be confirmed, our findings cannot be generalized to the entire population. A major issue in the present study is 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 also was reduced because of less misclassification of the probands based on information collected during this study. In addition, we used a physician diagnosis of asthma to minimize the risk of misclassifying as asthmatic those individuals, and did analysis only to those offspring having complete data of asthma and skin prick test sensitization in parents and offspring.

In conclusion, parental asthma is predictive of sensitization to perennial aeroallergens in offspring in families of asthmatic subjects in a rural area in China. The findings support the existence of a complex association between asthma and allergic sensitization. Although interactions between environmental changes and genetics may have led to the development of symptoms in large numbers of children who do have a strong genetic predisposition to asthma or atopy, future studies of the genetic influences on asthma and atopy need to take into consideration the potential phenotypic heterogeneity of these conditions and the effects of continuing changes in prevalence.

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