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Genetic and Environmental Contributions to Allergen Sensitization in a Chinese Twin Study

Xin Liu, MD, PhD[1,‡], **Shanchun Zhang, MD, PhD**[1], **Hui-Ju Tsai, MPH, PhD**[1], **Xiumei Hong, PhD**[1], **Binyan Wang, MD, PhD**[1], **Yaping Fang, MD**[2], **Xue Liu, MD**[2], **Jacqueline A Pongracic, MD**[3], and **Xiaobin Wang, MD, MPH, ScD**[1]

[1] Mary Ann and J. Milburn Smith Child Health Research Program, Department of Pediatrics, Northwestern University Feinberg School of Medicine and Children's Memorial Hospital and Children's Memorial Research Center, Chicago, IL, USA.

[2] Institute for Biomedicine, Anhui Medical University, Hefei, China.

[3] Division of Allergy and Immunology, Department of Pediatrics, Northwestern University Feinberg School of Medicine and Children's Memorial Hospital, IL, USA.

Abstract

Background: Allergic disease is on the rise worldwide. Effective prevention of allergic disease requires comprehensive understanding of the factors that contribute to its intermediate phenotypes, such as sensitization to common allergens.

Objective: To estimate the degree of genetic and environmental contributions to sensitization to food or aeroallergens.

Methods: Sensitization was defined as a positive skin prick test to an allergen. We calculated the zygosity-specific concordance rates and odds ratios (ORs) for sensitization to food and aeroallergens in 826 Chinese twin pairs (472 MZ and 354 DZ) aged 12 to 28 years. We also applied structural equation modeling procedures to estimate genetic and environmental influences on sensitization.

Results: The concordance rates and risk of sensitization in one twin given the presence vs. the absence of sensitization in the other twin were higher in MZ twins than those in DZ twins. However, a large number of MZ twins were discordant in sensitization to common allergens. These observations suggest both genetic and environmental factors influence sensitization. Consistently, the estimated heritability and individual environmental components of the liability to sensitization ranged from 0.51 to 0.68 and 0.32 to 0.49, respectively, based on the best-fitted structural equation model. We also observed high phenotypic correlations between sensitization to two aeroallergens (cockroach and dust mite: 0.83) and two food allergens (peanut and shellfish: 0.58), but only moderate correlations for the pairs between sensitization to a food and an aeroallergen (0.31-0.46). The shared genetic and environmental factors between paired sensitizations contribute to the observed correlations.

Conclusion: We demonstrated that sensitization to common food and aeroallergens were influenced by both genetic and environmental factors. Moreover, we found that paired allergen sensitizations might share some common sets of genes and environmental factors. This study

[‡]Correspondence and reprint requests should be addressed to: Xin Liu, MD, PhD, Mary Ann and J. Milburn Smith Child Health Research Program, Children's Memorial Hospital and Children's Memorial Research Center; Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; telephone:312-573-7751, fax:312-573-7825, xnliu@childrensmemorial.org.

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underscores the need to further delineate unique and/or pleiotropic genetic and environmental factors for allergen sensitization.

Keywords

Twin; sensitization; positive SPT; structural equation modeling; heritability; environmental factors

INTRODUCTION

Allergic disease, including food allergy, allergic rhinitis (AR), atopic dermatitis (AD), and asthma, is one of the major causes of morbidity worldwide [1-3]. Its prevalence has been rising in many parts of the world and the global prevalence differences are lessening [1,3-6]. As such, the economic burden of these diseases is substantial in both developed and developing countries [7]. Currently, effective prevention strategies are limited because the genetic and environmental risk factors for allergic diseases and their intermediate or associated phenotypes are largely undefined.

Allergic diseases are a heterogeneous group of disorders, which share some common characteristics, including elevated immunoglublin E (IgE) concentration, increased TH2 cytokines, or eosinophilia [8-10]. There is compelling evidence that AR, AD, asthma, and their associated phenotypes are all so called complex traits that are influenced by environmental factors, genetic factors, and their interactions [11-14]. To date, only a few family and twin studies have evaluated genetic and environmental contributions to sensitization to specific allergens [15-21], a common allergic diseases-associated phenotype. However, none of these studies focused on sensitization to food allergens or quantified the extent to which the correlated sensitizations to allergens share common sets of genes and environmental factors. In addition, no study has estimated genetic and environment components of sensitization in a Chinese population, the largest population in the world which has a comparatively low prevalence of allergic diseases [22]. Of note, with the rapid increasing economic and cultural transitions that have occurred in recent decades, the prevalence of common diseases associated with the westernized lifestyle, such as type II diabetes and cardiovascular diseases, has been rising quickly. We predict that allergic diseases might become common in China in the near future.

To address these issues, we utilized an existing Chinese twin cohort to estimate the genetic and environmental influences on allergic sensitization to common food and aeroallergens. We also evaluated to what degree the inter-correlations among sensitization to multiple allergens are governed by genetic and environmental factors.

METHODS

Study Population

This study is nested within an existing prospective twin cohort of children and adolescents (~2,000 twin pairs) who were initially enrolled in 1998-2000 in the rural areas of Anqing and Luan, China, with an age range of 6-21 years (baseline study). Detailed information on recruitment at baseline has been reported previously [23]. Since 2005, twins who participated in the baseline study in Anqing area are being followed up to identify precursors of metabolic syndromes (follow-up study). They were invited to a central office to complete the questionnaire interview, anthropometric measurements, skin prick tests (SPT), and spirometry. Institutional Review Board approval was obtained from Children's Memorial Hospital in Chicago, IL and the Institute of Biomedicine, Anhui Medical University in Hefei, China. All the study subjects gave informed consent. In this report, we focus on 826

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twin pairs who have completed follow-up survey and zygosity determination and also have valid SPT tests as defined below.

Sensitization: Positive Skin Prick Test (SPT)

At the follow-up survey, SPT was performed on the volar aspect of the arms using Multi-Test II for 9 foods (cow milk, egg white, soybean, wheat, peanut, walnut, fish mix, shellfish mix, sesame seed) and 5 aeroallergens (*Alternaria tenius*, dust mite mix [*D. farinae* and *D. pteronyssinus*], cat hair, dog epithelia, cockroach mix [American and German]) with histamine and saline as positive and negative controls, respectively. The SPT results were read 15 minutes after application. Wheals were traced with a fine-tipped pen and transferred onto paper via a strip of transparent tape. The largest wheal diameter (a) and that orthogonal to it (b) were measured, and the mean wheal size ([a+b]/2) was calculated and recorded. A valid SPT was defined as wheal size for histamine >=3mm, wheal size for saline <3mm, and a difference between wheal size for histamine and saline of >=3mm. SPT was considered to be invalid if any one of above criteria is not fulfilled. We defined sensitization as a positive SPT with a meanwheal diameter 3 mm or greater than the saline control if SPT was valid. We defined sensitization score as the sum of positive SPT tests, which consists of four levels: 0=not sensitized, 1=sensitized to one allergen, 2=two allergens, 3=three and more allergens.

Zygosity Ascertainment

We determined twin zygosity, dizygotic (DZ) or monozygotic (MZ), by employing microsatellite probes, or ‘DNA finger-printing’. Specifically, ten autosomal microsatellite markers that have the highest heterozygosity information in the Chinese population were genotyped and scored, as described by Wang et al. [24].

Statistical Analysis

We presented the means of the anthropometric measures and the frequencies of epidemiological factors and sensitization by gender, and then compared the differences by fitting generalized estimating equations (GEE) to adjust the correlation within a twin pair. Probandwise concordance rates (PCR) were calculated for sensitization to the common allergens among MZ and DZ separately as $2a/(2a+b)$, where a is the number of twin pairs that both are sensitized and b is the number of twin pairs that only one is sensitized. In addition, we calculated zygosity-specific odds ratios (ORs), which can be interpreted as the risk of sensitization to an allergen in one twin given the presence vs. the absence of a sensitization to the same allergen in the other twin [25]. The significant ratios of MZ-specific OR and DZ-specific OR indicated that the tested phenotype is under the genetic control. These analyses were done using SAS, version 9.1 (SAS Institute, Cary, North Carolina).

To estimate heritability of these binary traits, we applied structural equation modeling procedures (Mx) using the maximum likelihood algorithm [26]. Specifically, we fitted a sex limitation model that allows for additive genetic (a^2), common/familial (c^2), and individual specific (e^2) environmental components of the liability to sensitization to a specific allergen for males (ACE model) and females (KLM model) separately. Of note, liability is a latent, normally distributed continuous variable with a threshold beyond which subjects will be defined as ‘affected’. We evaluated the following: 1) if the thresholds of liability are same across gender; 2) if the set of genes controlling sensitization is the same for males and females (i.e. male-female genetic correlation r_g is fixed as 0.5 for the opposite sex DZ (DZOS)); 3) if the variance component estimations are same for males and females (i.e. ACE=KLM); 4) if submodels (i.e. CE/LM, AE/KL, and AC/KL) where a^2, c^2, or e^2 were equated to zero provide similar fit as a saturate model (no restriction on any above

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parameters). Chi-square goodness of fit and Akaike Information Criteria (AIC) were used for model comparisons. We defined the best-fitted model as the one with the lowest AIC and not having a significant worse fit compared with the saturate model (i.e. Chi-square test is not statistically significant with p-value > 0.05). Finally, we fitted the Bivariate Cholesky decomposition models to calculate genetic (r_G) and environmental correlations (r_C and r_E) among paired sensitizations to multiple allergens. All the tests for estimating variance components and their correlations were conducted using Mx program.

RESULTS

This study includes 472 MZ and 354 DZ twin pairs aged 12 to 28 years at follow-up. The excess of males (931 males vs. 721 females) may reflect the gender composition in rural China. Table 1 shows the distribution of anthropometric measures, epidemiological factors, and sensitization stratified by gender. Males were taller and heavier, but had lower BMI than females. About 15% of males, but none of the females in 826 twin pairs actively smoke. There were no significant differences with regard to passive smoking, breastfeeding, and pets, mice, or cockroach at home by gender. The proportions of positive SPT were high for peanut, shellfish, dust mite, and cockroach (>10%), but were substantially different in males and females except for peanut. Males also have higher sensitization scores than females. The following concordance rates, zygosity-specific ORs, and heritability estimations only focused on the sensitization to these four allergens, any food allergen, any aeroallergen, and any allergen. For sensitization scores, we only estimated heritability.

Table 2 shows that concordant rates for sensitization are much higher in MZ twins than those in DZ twins, as are the risk of sensitization in one twin given the presence vs. the absence of the sensitization in the other twin ($OR_{MZ} > OR_{DZ}$). The ratios of OR_{MZ} and OR_{DZ} are statistically significant, suggesting genetic factors may be important contributors to sensitization. However, a quite large number of MZ and DZ twin pairs were discordant for sensitization to a specific allergen and any allergen, indicating that environmental factors, especially individual specific environmental factors also influence sensitization, given that twins share common familial factors in general.

Table 3 provides estimations on how a co-twin is concordant with their twin brother or sister (i.e. first twin in the table) with regard to sensitization to the same allergen. Among co-twins who were sensitized to any allergen, the proportion who were sensitized to peanut allergen as the first twin was significantly higher in MZ twins than DZ twins (53% vs. 29%, p=0.002). Of note, the concordant twin pairs contributed twice to the numerator and denominator for the proportion calculation, given that each twin can be considered as a co-twin of the other. This proportion calculation is similar to probandwise concordant rate except that discordant pairs were defined as sensitization to the different allergens. We also observed marginally different proportions of co-twins who were sensitized to shellfish among those who were sensitized to any allergens across zygosity (58% in MZ vs. 45% in DZ, p=0.08). These data indicated that there maybe a peanut-specific or shellfish-specific genetic influence on the corresponding sensitizations.

With structural equation modeling, we assessed goodness of fit of the models (Table 4). Model I is the saturated model with the estimations of 9 parameters (a^2, c^2, e^2, and liability thresholds for males and females separately, plus male-female genetic correlation in DZOS (r_g)). All the submodels below were compared with Model I. Model II is fitted to test if the liability thresholds are the same by gender. Model III is fitted to test if the same set of genes controlling the liability to sensitization for both males and females ($r_g = 0.5$ in contrast to free estimated r_g in model I). Model IV aims to test if the estimates of variance components are the same across gender (ACE=KLM). Model V consists of additive genetic and

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individual specific environmental components (AE model), which allows r_g to be estimated (Va), or r_g to be fixed at 0.5 (Vb), or r_g to be fixed at 0.5 and also the estimates for a^2 and e^2 to be the same by gender (Vc). Model VI allows for familial and specific environmental factors with different (VIa) or same (VIb) c^2 and e^2 by gender. Finally, model VIIs are models with additive genetic and familial environmental components only. The best-fitted model is Vc for all the sensitizations based on the lowest AIC and non-significant Chi-square test. As such, the results from model comparison indicated the followings for allergen sensitization: (1). different liability thresholds for males and females; (2). no statistical evidence for gender-specific genes; (3). no statistically significant common environmental component; (4). same additive genetic and individual environmental influence across gender.

Table 5 shows the estimates from this best fitted model for the liability to sensitization of any food allergen, aeroallergen, any allergen, four specific allergens and sensitization score. Among all 826 twin pairs, the estimated heritability (h^2 in the table, equivalent to a^2) ranged from 0.51 to 0.68, and the rest of liability variance were explained by specific environmental components (e^2in the table). To explore if other covariates such as age and smoking may affect the estimate of genetic and environmental contributions, we performed stratified analyses by these covariates. There is no evidence that age and smoking status affected the estimates substantially (data not shown).

Table 6 shows the quantitative estimation of genetic ($\mathbf{C}_{GCP}$) and individual environmental contributions ($\mathbf{C}_{UCP}$) to the phenotypic (tetrachoric) correlation (r_{TP}) of the pairwise combinations of sensitization to four common allergens. The highest r_{TP} was observed for sensitization to two aeroallergens (cockroach and dust mite: 0.83), in which 71% (=0.59/0.83) and 29% (=0.24/0.83) were due to the shared genetic and environmental factors controlling for these two specific sensitizations, respectively. Similarly, 78% (=0.45/0.58) and 22% (=0.13/0.58) of phenotypic correlation between peanut and shellfish can be explained by genetic and environmental factors. Phenotypic correlations were moderate for the pairs between sensitization to a food and an aeroallergen (0.31-0.46), which again were accounted by shared genetic and environmental factors.

DISCUSSION

This is the first study to estimate genetic and environmental components of sensitization to food and aeroallergens in a Chinese rural population. We demonstrated that sensitization to common food and aeroallergens were influenced by both genetic and environmental factors. In addition, there are unique and common sets of genes and environmental risk factors underlying the immune response to four common allergens (e.g. peanut, shellfish, dust mite, and cockroach).

Sensitization to allergen is an important risk factor for the development of allergic diseases. However, only a few studies have been conducted in Western populations to estimate the genetic and environmental influences on immune response to common aeroallergens, measured either by serum specific IgE levels or by positive SPT. Concordance rates for positive serum specific IgE response to common aeroallergens, such as grass [21] and house dust mite [20], were higher in MZ twins than those in DZ twins. A family-based study also supported that specific IgE levels against house dust mite and Timothy grass were under genetic control with the estimated heritability in range of 33.8% to 57% [17,18]. However, two studies in Australian twins suggested that IgE reactivity to specific ryegrass pollen components [19] and house dust mite components [20] might be determined mainly by environmental factors based on similar concordance rates across zygosity. Similarly, previous studies of skin test to common aeroallergens were not quite consistent with each

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other. In 107 US twin pairs, Hopp et al. [16] observed significantly higher intrapair correlations for intradermal skin test scores in MZ twins than in DZ twins (0.82 vs. 0.46), with a heritability estimate of 73%. The heritability for positive SPT to house dust mite and for any positive SPT to more than 10 common indoor and outdoor allergens was less than 30% in 200 Dutch families with asthma [17]. In contrast, another US twin study suggested that positive SPT may be more influenced by environmental factors than genetic susceptibility, because the greater difference in concordance for skin tests between MZ and DZ twins was found when they were reared together (70% vs. 28%) than when they were reared apart (55% vs. 50%) [15]. To our knowledge, there is no twin study that has examined heritability for sensitization to food allergens. In a Western population (n=58 twin pairs), Sicherer et al [27] estimated heritability for peanut allergy ($h^2 = 0.82$) rather than sensitization to peanut. The prevalence of peanut allergy and other allergic diseases is low in China, however, allergen sensitization is quite common [28,29]. As such, the present study focused on sensitization to common food and aeroallergens.

Our study provides evidence that both genetic and individual specific environmental factors control for specific sensitization, by using simple association study of sensitization – an observed binary trait (Table 2 & 3) and complicated biometric modeling on the liability to sensitization – an unobserved normally distributed continuous trait (Tables 4 to 6). The heritability estimations for the variance in liability to sensitization to any aeroallergen and house dust mite were compatible with those estimated in Western populations [17,18]. In addition, we demonstrated that at least some common sets of genes and environmental factors contribute to the observed moderate to high correlations of pair-wised sensitizations to four common allergens (peanut, shell fish, cockroach, and house dust mite). Therefore, we anticipate that the genes within the linked regions identified from the genome-wide linkage studies on serum specific IgE and skin test to common aeroallergens [17,30-35] might also influence the sensitization to food allergens. Similarly, environmental risk factors of sensitization to aeroallergens, such as active or passive smoking [36], allergen exposure [37,38], and age of onset and number of episode for the respiratory infections [39,40], might play an important role on sensitization to food allergens. Importantly, our study also indicates that food antigen-specific genes controlling the corresponding sensitization might exist (Table 3). This needs to be further investigated in future studies.

This study has several strengths. First, twin design has a long-standing history of studying the magnitude of genetic and environmental influences on phenotypic traits. This is not possible using a general population. Second, unlike previous studies that tested sensitization to different allergens as one phenotype, we analyzed sensitization to any allergen, food allergen, aeroallergen, and also 4 common allergens separately. We demonstrated that sensitization to common allergens was influenced by different but also overlapping genetic and environmental factors. These findings provide not only statistical evidence on the clinical co-occurrence of sensitization to common allergens, but also the analytic guideline for future genetic epidemiological studies on this complex trait. For example, we can simultaneously test the associations between sensitization to different allergens with their common risk factors (e.g. genetic variants in genes *IL4*, *IL13*, and their receptors) using hierarchical modeling (HM). This approach can obtain more precise estimates with lower false positive rates compared with the conventional approach that analyze numerous correlated phenotypes one-by-one [41]. Third, we used a twin cohort with very low prevalence of allergic diseases [28], so that allergen sensitization is less likely to be affected by disease status and medication intakes (e.g. antihistamine). Fourth, since allergic diseases are expected to increase in the near future in China, understanding the genetic and environmental influence on sensitization to common food and aeroallergens will provide an important foundation for future genetic epidemiological study of allergic diseases in the Chinese population.

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Some limitations of this study should be considered. First, the studied samples were not quite comparable with those enrolled in Anqing area but excluded from this report either due to no follow-up or missing zygosity or missing or invalid SPT data, with regards to baseline characteristics. Specifically, the included twins were younger (years: 10.7±3.0 vs. 12.8±3.5) and had a lower BMI (kg/m2: 15.6±2.2 vs. 16.8±2.7) than those excluded twins. To what degree that these differences may affect the results is uncertain. However, it is unlikely substantial, given that these differences were similar for MZ and DZ twins and thereby may be canceled out. For example, included MZ twins were younger than excluded MZ twins (age: 10.8±3.0 vs. 12.5±3.6), and the same pattern was observed in DZ twins (age: 10.5±2.9 vs. 12.6±3.6). We will be better able to assess the impact of selection bias as we attempt to follow the remaining of the original cohort as many as possible in the coming year. Second, the estimates of common environment component for allergen sensitization are equal or very close to zero except for sensitization to cockroach (20%) and any sensitization (18%). Our current sample size has limited power to detect this component statistically (i.e. power estimate was less than 70% based on software TwinPower [42]. In addition, MZ twins experience more similar behavior (i.e. smoking) and indoor environment (i.e. pet, mice and cockroach at home) than DZ twins (data not shown), thus the heritability estimates from the best statistical model (Vc) might be inflated. Third, this study population consisted of children aged 12 or older, thus we could not adequately examine sensitization common in young children, such as sensitization to egg and milk. Finally, this is a cross-sectional analysis, and we did not evaluate the longitudinal change in sensitization. However, with the archived serum samples at baseline and follow-up, serum specific IgE to common food and aeroallergen will be measured and evaluated in our future studies.

In summary, we provide strong evidence to support the important roles of both genetic factors and individual environmental factors on sensitization to food and aeroallergens in a large, population-based Chinese twin sample. Immune responses to different allergens might be influenced by some common sets of genetic and environmental factors, thus underscoring the importance to search for pleiotropic risk factors controlling sensitization.

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Table 1

Epidemiological Characteristics and Allergen Sensitization in Anqing Chinese Twin Study (N= 826 twin pairs).

Variables	Males (N=931)	Females (N=721)
	Mean ± SD	
Age (Yr)	17.5 ± 3.2	17.3 ± 2.9
Weight (kg) ***	49.5 ± 8.9	46.3 ± 6.7
Height (m) ***	1.6 ± 0.1	1.5 ± 0.1
BMI (kg/m^2) ***	19.1 ± 2.4	19.9 ± 2.4
	N (%) [a]	
Zygosity (MZ)	508 (55)	436 (60)
Current Smoking (yes)	135 (15)	0 (0)
Passive Smoking (yes)	664 (73)	491 (70)
Breastfeeding (yes)	542 (59)	428 (60)
Pet at home (Yes)	541 (58)	385 (53)
Mice at home		
No	273 (30)	215 (30)
Yes, Occasionally	436 (47)	354 (49)
Yes, Some or Many	215 (23)	152 (21)
Cockroach at home		
No	563 (61)	439 (61)
Yes, Occasionally	284 (31)	232 (32)
Yes, Some or Many	75 (8)	49 (7)
Allergen Sensitization [b]		
Any Food Allergen *	267 (29)	167 (23)
Peanut	131 (14)	90 (12)
Shellfish *	180 (19)	106 (15)
Sesame	26 (3)	17 (2)
Walnut	24 (3)	14 (2)
Soybean	50 (5)	37 (5)
Egg white	39 (4)	29 (4)
Fish	24 (3)	8 (1)
Milk	13 (1)	9 (1)
Wheat	15 (2)	6 (1)
Any Aeroallergen ***	428 (46)	253 (35)
Cockroach ***	299 (32)	161 (22)
Dust Mite **	337 (36)	208 (29)
Alternaria Tenius	77 (8)	58 (8)

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Variables	Males (N=931)	Females (N=721)
	Mean ± SD	
Cat	14 (2)	13 (2)
Dog	22 (2)	15 (2)
Any Allergen ***	512 (55)	312 (43)
Sensitization Score, sensitized to		
0 allergen	416 (45)	407 (57)
1 allergens	178 (19)	111 (16)
2 allergens	176 (19)	102 (14)
≥ 3 allergens ***	157 (17)	96 (13)

* p<0.05

** p<0.01

*** p<0.001

[a] N(%): number (percentage) of twins with regards to the specified variables. Percentage calculation was based on the number of twins with available information of the variable. For males, the number of twins with missing information on current smoking, passive smoking, breastfeeding, pet, mice, cockroach at home is: 13, 24, 10, 6, 7, and 9. The corresponding number for females is 14, 23, 4, 0, 0, and 1.

[b] Allergen sensitization was defined as a positive skin prick test to an allergen. The number of twins with missing information on sensitization to a specific allergen is ≤3.

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Table 2

Probandwise Concordance Rate (PCR %) and Odds Ratios [a] (ORs) by zygosity for allergen sensitization in Anqing Chinese twin study (N = 826 twin pairs).

	MZ (N=472 pairs)					DZ (N=354 pairs)					OR_{MZ} / OR_{DZ}
	+ +	+ −	− −	PCR	OR (95%CI)	+ +	+ −	− −	PCR	OR (95%CI)	OR (95%CI)
Any food allergen [b]	62	114	295	52.1	5.74 (3.62 – 9.11)	38	118	195	39.2	2.14 (1.29 – 3.53)	2.69 (1.36 – 5.31)
Peanut	23	75	374	38.0	6.14 (3.31 – 11.41)	10	80	262	20.0	1.66 (0.76 – 3.55)	3.73 (1.39 – 10.02)
Shellfish	33	91	348	42.0	5.75 (3.32 – 9.96)	20	88	245	31.3	2.54 (1.37 – 4.71)	2.27 (0.99 – 5.19)
Any Aeroallergen [c]	120	127	224	65.4	6.82 (4.50 – 10.33)	87	140	127	55.4	2.26 (1.47 – 3.47)	3.01 (1.66 – 5.49)
Cockroach	70	108	292	56.4	7.13 (4.50 – 11.31)	50	111	192	47.4	3.13 (1.93 – 5.09)	2.28 (1.17 – 4.45)
Dust mite	88	112	271	61.1	7.69 (4.94 – 11.99)	64	129	161	49.8	2.48 (1.58 – 3.89)	3.11 (1.65 – 5.84)
Any Allergen	163	125	182	72.3	7.74 (5.12 – 11.68)	121	128	102	65.4	3.05 (1.97 – 4.72)	2.54 (1.39 – 4.63)

[a] Odds ratio of sensitization in one twin given the presence vs. the absence of the sensitization in the other twin.

[b] Includes milk, egg, wheat, peanut, soybean, sesame, walnut, shellfish, fish.

[c] Includes cockroach, mite, cat, dog, *Alternaria Tenius* .

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Table 3

Concordance of sensitization to the same allergen in MZ and DZ twin pairs

	Monozygotic Twin Pairs (N) First Twin Sensitized to				**Dizygotic Twin Pairs (N) First Twin Sensitized to**			
Co-twin sensitized to	**Peanut**	**Shellfish**	**Cockroach**	**Dust Mite**	**Peanut**	**Shellfish**	**Cockroach**	**Dust Mite**
Same Allergen	23	33	70	88	10	20	50	64
Different Allergen from the first twin	41	48	49	43	50	48	39	47
Not sensitized to any allergen [a]	34	43	59	69	29	40	71	81
% co-twins sensitized to the same allergen, given co-twins sensitized to any allergen [b]								
	53% [c]	58%	74%	80%	**29%** [c]	45%	72%	73%

[a] Includes milk, egg, wheat, peanut, soybean, sesame, walnut, shellfish, fish, cockroach, mite, cat, dog, *Alternaria Tenius*.

[b] concordant pairs contribute twice to both numerator and denominator (e.g. 53%=[(23*2)/ ((23*2) + 41)]).

[c] P<0.01

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Table 4

Model-fitting results for allergen sensitization

Model *	Peanut		Shellfish		Cockroach		Dust Mite		Any Food Allergen		Any Aero Allergen		Any Allergen		Sensitization Score	
	χ^2	AIC	χ^2	AIC	χ^2	AIC	χ^2	AIC	χ^2	AIC	χ^2	AIC	χ^2	AIC	χ^2	AIC
I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
II	0.61	−1.39	5.19	3.19	14.63	12.63	7.41	5.41	5.20	3.20	14.55	12.55	17.07	15.07	17.63	15.63
III	0	−2.00	0.02	−1.98	0	−2.00	0	−2.00	0.05	−1.96	0	−2.00	0	−2.00	0.09	−1.92
IV	1.09	−6.91	3.38	−4.62	0.15	−7.86	2.42	−5.58	1.72	−6.28	1.17	−6.83	1.54	−6.46	2.40	−5.60
Va	0.14	−3.86	1.40	−2.60	1.43	−2.57	0.05	−3.95	0.17	−3.83	0	−4.00	1.19	−2.81	1.23	−2.77
Vb	0.14	−5.86	1.85	−4.15	1.43	−4.57	0.05	−5.95	1.44	−4.56	0	−6.00	1.19	−4.81	1.23	−4.77
Vc	1.09	**−8.91**	3.49	**−6.51**	1.43	**−8.57**	2.43	**−7.56**	1.72	**−8.28**	1.17	**−8.83**	2.78	**−7.23**	3.51	**−6.49**
VIa	5.16	−0.85	4.24	−1.76	4.75	−1.25	11.48	5.48	9.20	3.20	11.75	5.75	8.46	2.46	11.10	5.10
VIb	7.19	−2.81	6.71	−3.29	4.78	−5.22	13.73	3.73	9.42	−0.58	12.67	2.67	9.39	−0.61	13.04	3.04
VIIa	122	116	117	111	74	68	61	55	93	87	37	31	17	11	28.15	22.15
VIIb	122	112	118	108	74	64	61	51	94	84	37	27	17	7	30.61	20.61

Model II: same proportion of sensitization for males and females; r_g free for DZOS; ACE for males, KLM for females

Model III: different proportions of sensitization for males and females; r_g = 0.5 for DZOS; ACE for males, KLM for females

Model IV: different proportions of sensitization for males and females; r_g = 0.5 for DZOS; ACE = KLM

Model Va: different proportions of sensitization for males and females; r_g free for DZOS; AE for males, KM for females

Model Vb: different proportions of sensitization for males and females; r_g = 0.5 for DZOS; AE for males, KM for females

Model Vc: different proportions of sensitization for males and females; r_g = 0.5 for DZOS; AE = KM

Model Via: different proportions of sensitization for males and females; r_g = 0.5 for DZOS; CE for males, LM for females

Model VIb: different proportions of sensitization for males and females; r_g = 0.5 for DZOS; CE = LM

Model VIIa: different proportions of sensitization for males and females; r_g = 0.5 for DZOS; AC for males, KL for females

Model VIIb: different proportions of sensitization for males and females; r_g = 0.5 for DZOS; AC = KL.

r_g:male-female genetic correlation; ACE and KLM models allows for additive genetic, common, and specific environmental components in males and females, respectively.

*Model I: Different proportions of sensitization for males and females; r_g free for DZOS; ACE for males, KLM for females

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Table 5

Heritability estimates [a] of allergen sensitization in Anqing Chinese twin study (N=826 twin pairs).

	h^2 (95%CI)	e^2 (95%CI)
Any food allergen [b]	0.56(0.44 - 0.67)	0.44(0.33 – 0.56)
Peanut	0.51(0.34 – 0.66)	0.49(0.34 – 0.66)
Shellfish	0.54(0.39 – 0.67)	0.46(0.33 – 0.61)
Any Aeroallergen [c]	0.63(0.52 – 0.72)	0.37(0.28 – 0.48)
Cockroach	0.64(0.53 – 0.73)	0.36(0.27 – 0.47)
Dust mite	0.66(0.55 – 0.75)	0.34(0.25 – 0.45)
Any Allergen	0.68(0.58 – 0.76)	0.32(0.24 – 0.42)
Sensitization Score	0.60(0.52 – 0.67)	0.40(0.33 – 0.48)

[a] Maximum likelihood estimation of the best fitted model from table 4. h^2 and e^2 represent genetic and specific environment components, respectively.

[b] Includes milk, egg, wheat, peanut, soybean, sesame, walnut, shellfish, fish.

[c] Includes cockroach, mite, cat, dog, *Alternaria Tenius*.

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Table 6

Genetic and environmental contributions to phenotypic correlations among sensitization to four common allergens in 826 Chinese Twin Pairs.

Paired-variables	Variance components correlations [a]		Genetic and environmental contributions to phenotypic correlations [b]		
	r_G	r_E	r_{TP}	C_{GCP}	C_{ECP}
Peanut_Shellfish	0.87 (0.72 – 1.00)	0.27 (0.05 – 0.48)	0.58	0.45	0.13
Peanut_Cockroach	0.17 (−0.04 – 0.37)	0.51 (0.29 – 0.70)	0.31	0.10	0.21
Peanut_Dust Mite	0.39 (0.20 – 0.57)	0.25 (0.02 – 0.47)	0.33	0.23	0.10
Shellfish_Cockroach	0.39 (0.21 – 0.56)	0.34 (0.11 – 0.55)	0.37	0.23	0.14
Shellfish_Dust Mite	0.56 (0.40 – 0.72)	0.33 (0.11 – 0.52)	0.46	0.33	0.13
Cockroach_Dust Mite	0.92 (0.84 – 1.00)	0.66 (0.50 – 0.78)	0.83	0.59	0.24

$r_{TP} = C_{GCP} + C_{UCP}$, $C_{GCP} = r_{G^*}\sqrt{h_1^2 * h_2^2}$, $C_{UCP} = r_{E^*}\sqrt{e_1^2 * e_2^2}$ where h^2s and e^2s estimated from Bivariate Cholesky decomposition models were very similar to those in table 5 (± 0.01).

[a] r_G, Genetic correlation between paired sensitizations; r_E, individual specific environmental correlation between paired sensitizations.

[b] r_{TP}, phenotypic correlation between paired sensitizations; C_{GCP}, Genetic contribution to r_{TP}; C_{UCP}, unique environmental contribution to r_{TP}.