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Familial Aggregation of Food Allergy and Sensitization to Food Allergens: A Family-Based Study

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Summary

Background—The increasing prevalence of food allergy (FA) is a growing clinical and public health problem. The contribution of genetic factors to FA remains largely unknown.

Objective—This study examined the pattern of familial aggregation and the degree to which genetic factors contribute to FA and sensitization to food allergens.

Methods—This study included 581 nuclear families (2,004 subjects) as part of an ongoing FA study in Chicago, IL, USA. FA was defined by a set of criteria including timing, clinical symptoms obtained via standardized questionnaire interview, and corroborative specific IgE cutoffs for >=95% positive predictive value (PPV) for food allergens measured by Phadia ImmunoCAP. Familial aggregation of FA as well as sensitization to food allergens were examined using generalized estimating equation (GEE) models, with adjustment for important covariates including age, gender, ethnicity and birth order. Heritability was estimated for food-specific IgE measurements.

Results—FA in the index child was a significant and independent predictor of FA in other siblings (OR=2.6, 95%CI:1.2–5.6, p=0.01). There were significant and positive associations among family members (father-offspring, mother-offspring, index-other siblings) for total IgE and

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specific IgE to all the 9 major food allergens tested in this sample (sesame, peanut, wheat, milk, egg white, soy, walnut, shrimp and cod fish). The estimated heritability of food-specific IgE ranged from 0.15 to 0.35 and was statistically significant for all the 9 tested food allergens.

Conclusion—This family-based study demonstrates strong familial aggregation of food allergy and sensitization to food allergens, especially, among siblings. The heritability estimates indicate that food-specific IgE is likely influenced by both genetic and environmental factors. Together, this study provides strong evidence that both host genetic susceptibilityand environmental factors determine the complex trait of IgE-mediated food allergy.

Keywords

familial aggregation; heritability; food allergy; sensitization to food allergens; IgE-mediated

Introduction

Food allergy, a condition caused by an immunoglobulin (Ig) E-mediated hypersensitivity reaction to food, is a growing clinical and public health problem in the United States and worldwide [1–3]. Like other atopic diseases, the prevalence of food allergy has risen substantially in the past decade [1,2,4]. Although accurate epidemiologic data are limited, food allergy affects approximately 5–8% of children and 1–4% of adults in the United States [5–7].

The etiology of food allergy is largely unknown. Like other complex human diseases such as asthma, food allergy is believed to be a complex trait influenced by both environmental and genetic factors and their interaction. In contrast to asthma, there are few published studies on genetics of food allergy and food-specific IgE, a major effector of food allergic responses and a commonly used clinical biomarker for IgE-mediated food allergy. The findings from previous genetic studies of food allergy were inconsistent [8–11]. In addition, these studies were of small sample size, ranging from 42 to 128 cases, and none of previous studies simultaneously examined all the most common food allergens in a single study.

Familial aggregation analysis and heritability estimation are useful approaches to determine the extent to which genetic factors influence complex traits such as food allergy. *Familial aggregation* is defined as the tendency of a trait or a disease to cluster in families. Evidence of familial aggregation of a trait or a disease indicates common genetic and/or shared environmental factors among family members [12,13]. *Heritability* is a measure used for estimating relative influence of genetic versus environmental factors on a trait or a disease, and is defined as the ratio of genetic variance to the total phenotypic variance in the population [14]. Since the genetic contribution to food allergy remains largely unknown, such information could help better understand the etiology of food allergy and elucidate the role of genetic factors in food allergy and its related traits such as food-specific IgE levels.

In this study, we included a total of 581 nuclear families enrolled in an ongoing food allergy study in Chicago. Clinical data, epidemiological data and a wide array of IgE assays (including 9 of the most common food allergens [6]) were collected for each subject. We first investigated familial aggregation of food allergy and sensitization to food allergens by examining the inter-relationship of these measurements among family members (father, mother, index child, and index child's sibling). We next estimated heritability of food-specific IgE levels using the family-based data. To our knowledge, this would be the largest family-based study of this kind to explore genetic influence on food allergy and on specific IgE to the most common food allergens.

Materials and methods

Study population and data collection

This study is part of an ongoing family-based food allergy study in Chicago, IL. All the families were recruited from the Chicago area from August 2005 until May 2008. Family inclusion criteria consist of a child (age 0 to 21 years) with or without food allergy history and 2 or more family members including biological parents and/or siblings who were willing to participate in the study. Eligible families were defined as follows: 1.) families with both parents and at least one or more biological children (ages 0 to 21 years); 2.) families with one parent and at least two or more biological children (ages 0 to 21 years); or 3.) three or more biological siblings (ages 0 to 21 years). The index child in the current study is defined as the first child identified to be recruited into the study. Families with one or more food allergic child and those without a food allergic child are both included in this study. Epidemiological data such as home environment, diet, lifestyle, history of atopic diseases, and food allergy of each family member were collected through a questionnaire-based interview. Clinical data was obtained including type of symptoms and timing of symptom onset for those with food allergy. Other clinical data including height, weight, blood pressure and skin prick tests were collected on each family member. Venous blood samples were collected from each participating family member for IgE measurement and subsequent laboratory assays. Plasma samples were stored in −80°C freezers. The Institutional Review Board of Children's Memorial Hospital approved the study protocol. All study families gave written informed consent.

Total and specific IgE measurement

Total IgE, specific IgE for 9 food allergens (sesame, peanut, wheat, milk, egg white, soy, walnut, shrimp, cod fish) and specific IgE for 6 aeroallergens (two house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), cat dander, dog dander, cockroach and alternaria) were measured for each subject using Phadia ImmunoCAP. The reported range for total IgE was from 2.0 to 5,000 kU/L. The reported range for specific IgE was from 0.01 to 100 kUA/L. Total and specific IgE assays were performed by the Clinical Immunology Laboratory at Children's Memorial Hospital according to the manufacturer's prescribed protocol. For quality assurance and quality control, the total IgE assay was recalibrated every 28 days or as needed. Two curve controls were run to assess the validity of the current calibration curve. If these curve controls were out of range, recalibration was performed. In addition to the curve controls, a low, medium and high control supplied by Phadia were assayed. An internal pool control was also assayed every day.

Diagnosis of food allergy

Food allergy was defined as a subject who met all the criteria described below. 1.) Clinical symptom criteria – a previous reaction to a food with report of clear and objective findings consisting of any one of the following symptoms: **skin** symptoms with hives or angioedema; **respiratory tract** symptoms with trouble breathing, shortness of breath, repetitive coughing, wheezing, chest tightness; **throat** tightness, choking, or difficulty swallowing; **tongue** swelling; **cardiovascular** symptoms with fainting, dizziness, light-headedness, or decreased level of consciousness; **gastrointestinal** symptoms with vomiting; 2.) Timing of symptoms within 2 hours of ingestion; and 3.) Established specific IgE (sIgE) cutoffs – sIgE>=95% PPV for egg (7 kUA/L or for infants <=2 years, 2 kUA/L), milk (15 kUA/L or for infants <= 2 years, 5 kUA/L), peanut (14 kUA/L), fish (20 kUA/L), and sIgE>70%PPV for soy (30 kUA/L) and wheat (26 kUA/L) [15–18]. For other foods not listed above, we will use sIgE >= 3.5 IU/ml as cutoff, same as the ALEX study [19]. Of note, these criteria for defining food allergy are similar to what has been suggested in other studies which have evaluated the predictive value of sIgE when challenges were not carried out uniformly [20,21].

Statistical analyses

Familial aggregation analysis of food allergy—As several members from each family were included, generalized estimating equation (GEE) models were used to estimate the inter-relationship of clinical food allergy and other atopic diseases (such as eczema, asthma and seasonal allergy) among family members. The GEE approach accounts for the correlation between family members under the framework of regression analysis [22]. Food allergy and atopic diseases were coded as binary outcomes (yes/no). Covariates adjusted in the models included age (as continuous), sex, ethnicity (African Americans, Caucasians, Hispanic, and other) and birth order. Of note, ethnicity information of the index child and other siblings was defined as maternal ethnicity.

Familial aggregation analysis of specific IgE—Since food-specific IgE is one of the major biomarkers of food allergy, we sought to examine familial aggregation of this phenotype as well. Because the distributions of total and specific IgE values were skewed towards higher values, a $\log_{10}$-transformation of total and specific IgE values was used to approximate a normal distribution. Transformed values were used for all the subsequent analyses. Of note, there were 0.4% of study subjects with total IgE > 5,000 kU/l and 1.2% of study subjects with specific IgE > 100 kUA/l. Thus, we recoded the subjects with total IgE > 5,000 kU/l as 5,001 kU/l, and the subjects with specific IgE > 100 kUA/l as 101 kUA/l.

We first examined correlation of total IgE, food-specific IgE and aeroallergen-specific IgE among family members. Spearman's rank correlation coefficients were used to estimate pairwise correlation between: (1) father-mother; (2) father-index child; (3) mother-index child; and (4) index child-other siblings.

Similar to food allergy, GEE models were used to estimate the inter-relationship of total IgE, food-specific IgE and aeroallergen-specific IgE among family members, and to account for the correlation between family members [22]. Two different GEE models were applied for continuous outcomes and binary outcomes, respectively. Log_{10}-transformed IgE values were treated as continuous outcomes. For binary outcomes, total IgE was recoded into two groups: top 25% (high) vs. lower 75% percentile (low). Specific IgE variables were recoded as detectable vs. non-detectable, using a cutoff value of 0.1 kUA/L. Likewise, covariates adjusted in the models included age, sex, ethnicity and birth order. All the above statistical analyses were performed using statistical packages R 2.6.1 (http://www.r-project.org) and Intercooled STATA 9.0 (College Station, TX).

Heritability Estimation—To determine the contribution of genetic factors to total IgE, food-specific IgE and aeroallergen-specific IgE, the narrow-sense heritability ($\hat{h}^2$) was estimated using variance component analysis implemented in the Sequential Oligogenic Linkage Analysis Routines software package (SOLAR) [23]. The *narrow-sense heritability* is defined as the ratio of total additive genetic variance over total phenotypic variance [14].

The formula for calculating $\hat{h}^2$ can be written as follow: $\hat{h}^2 = \sigma_a^2/(\sigma_G^2+\sigma_E^2)$, where σ_a^2 = additive genetic variance, σ_G^2 = additive + dominant genetic variance, and σ_E^2 = environmental variance.

Specifically, $\sigma_G^2+\sigma_E^2$ captures total phenotypic variance. Such heritability estimates can be used to evaluate the degree of genetic contribution to phenotypes of interest, for example, food-specific IgE levels. In detail, the variance was calculated using kinship matrix formulas employing the observed maximum likelihood parameter estimates of the polygenic model. The likelihood ratio test was used to test the null hypothesis of no genetic determination: $\hat{h}^2$

= 0 against the alternative hypothesis: $\hat{h}^2 \neq 0$. Likewise, age, sex and ethnicity were adjusted in heritability estimation.

Results

Description of demographic and clinical characteristics

Five hundred and eighty-one families (a total of 2,004 subjects) were included in this analysis. Table 1 presents demographic characteristics, food allergy and atopic diseases, and the distribution of IgE data in the study sample. The majority of the study subjects were Caucasian (~78%). The percentages of detectable food-specific and aeroallergen-specific IgE in index children were higher than those in parents and siblings. More than 45% of the participants had detectable IgE to one or more foods. Similarly, more than 50% of the participants had detectable IgE to one or more aeroallergens.

Correlation coefficients were calculated for total IgE, food-specific IgE and aeroallergen-specific IgE between father and mother, father and index child, mother and index child, and index child and other siblings (Supplemental table 1). The range of correlation coefficients for total IgE and specific IgE was from 0.01 to 0.23 between father and mother, from 0.08 to 0.27 between father and index child, from 0.10 to 0.29 between mother and index child and from 0.15 to 0.38 between index child and other siblings.

Familial aggregation of food allergy and atopic diseases

To assess familial aggregation of food allergy and atopic diseases (such as eczema, asthma and seasonal allergy), GEE models were used with adjustment for age, sex, ethnicity and birth order. The inter-relationship of self-report food allergy and self-report atopic diseases were examined between father-offspring, mother-offspring and index child-other siblings (Table 2a). Significant positive associations between mother and offspring and between index child and other siblings were observed for food allergy and all examined atopic diseases before covariate adjustment (data not shown). Interestingly, all the positive associations remained significant after covariate adjustment (Table 2a). Significant association was only found on asthma between father and offspring.

We further examined familial aggregation of food allergy, which was defined by a set of criteria including timing, clinical symptoms obtained via standardized questionnaire interview, and corroborative specific IgE cutoffs for food allergens. Using similar criteria, allergy to egg white, milk and peanut were examined, individually. Importantly, significant associations were found between the index child and other siblings for food allergy (OR=2.6, 95%CI:1.2–5.6, p=0.01) and for allergy to egg white (OR=3.8, 95%CI:1.2–12.1, p=0.02) (Table 2b).

Familial aggregation of food-specific IgE

Likewise, GEE was applied to examine familial aggregation of food-specific IgE with adjustment for age, sex, ethnicityand birth order. Total IgE, food-specific IgE and aeroallergen-specific IgE were first treated as continuous outcome variables. The interrelationship of total IgE, food-specific IgE and aeroallergen-specific IgE between father-offspring, mother-offspring and index child-other siblings were examined separately. The results were shown in Table 3a. When treating total IgE and specific IgE as continuous outcome variables, significant positive associations between parents and offspring and between the index child and other siblings were observed for total IgE and specific IgE to all examined food allergens and aeroallergens (Table 3a).

Furthermore, total IgE (top 25% vs. lower 75%) and specific IgE (detectable vs. non-detectable) were treated as binary outcome variables to investigate familial aggregation. Similarly, there were significant positive associations for total IgE and most of the examined aero and food allergens between index child and other siblings, except for cod fish (Table 3b).

Heritability of total IgE and specific IgE

Heritability of total and specific IgE levels was estimated using variance components analysis implemented in the SOLAR program. The results in Table 4 demonstrated that the estimated heritability was significant for total IgE, food-specific IgE and aeroallergen-specific IgE, after adjusting for age, sex and ethnicity. The estimated heritability of total IgE was 0.49 ($p < 0.001$). The estimated heritability of food-specific IgE ranged from 0.15 to 0.35. The estimated heritability of aeroallergen-specific IgE ranged from 0.24 to 0.38.

Discussion

While a number of familial aggregation and genetic studies of asthma and atopy have been reported previously, few studies have specifically examined genetic influence on food allergy and food-specific IgE. This study is one of the first to investigate familial aggregation of food allergy and the most common food-specific IgE levels in a large family-based studyin the U.S. The results demonstrated significant familial aggregation for food allergy and sensitization to food allergens. In addition, this study is the first to estimate heritability for the most common food-specific IgE levels in a large family-based study in the U.S. We observed the estimated heritability of food-specific IgE ranging from 0.15 to 0.35, and the estimated heritability of aeroallergen-specific IgE ranging from 0.24 to 0.38, which were statistically significant after adjusting for major covariates. These findings suggested that a substantial variation of total IgE, food-specific IgE and aeroallergen-specific IgE, respectively, can be explained by genetic components. Our findings of familial aggregation of atopic diseases (including eczema, seasonal allergy and asthma), and heritability estimate of total IgE ($\hat{h}^2 = 0.49$) were comparable to previous studies. Previous studies documented familial aggregation and estimated heritability of total IgE between 0.45 and 0.80 [24–27]. The consistency of our findings with previous studies lent support that our study findings were unlikely due to chance.

Of note, the heritability estimate for a complex trait indicates genetic contribution to the variance of a phenotype and it is strictly relative. Within a given population, the heritability estimate will change if there is a change in the distribution of a relevant environmental exposure. Heritability estimate may also be influenced by population characteristics. Recruited from the Chicago area, the study population consisted of predominantly Caucasians (~78%) and included subjects from a wide range of socio-economic strata, from lower middle to upper class. Based on expected outdoor environmental exposures and context of living, this study is directly generalizable to Chicago urban and suburban populations. However, this study sample is over-represented by families with food allergy as 83% of families reported at least one family member with an allergic response to food. To address this issue, we performed separate analyses on familial aggregation and heritability among families with at least one food allergic member and among those without a food allergic member. We performed these analyses to investigate whether a difference exists between these two types of families. Interestingly, similar patterns of familial aggregation between mother-offspring and index child-other siblings were observed in these two groups of families (Supplement tables 2). Most familial aggregations between father-offspring were not significant among those without a food allergic member likely due to small sample size (N=99). Likewise, the estimated heritability of total and specific IgE in these two groups was comparable (Supplement table 3).

In addition to genetic contribution, shared environmental and lifestyle factors may also play a role in the observed familial aggregation of food allergy and food-sensitization. A number of longitudinal cohorts have observed an association between the development of atopy and epidemiologic factors which could be considered markers of less early life immune stimulation. These have included studies of: urban vs. rural lifestyle [28–30], absence vs. presence of pets in the home [31–33], birth order [34,35], and day care exposure [36,37]. Therefore, we applied a Mantel-Haenszel test statistics, which is also called Cochran's Q, to examine the differences in inter-relationships among parents, index child and other siblings. The data revealed some differences between father- or mother-offspring and index-child other siblings on self-reported food allergy. However, the differences were not significant using the stringent definition of food allergy used in this study (results not shown). The results support the interplay of genetic and environmental factors on food allergy.

There are several strengths in the present study. First, our study has utilized a well characterized family cohort, and a stringent phenotypic definition of food allergy. Second, to our knowledge, our study is one of the largest family-based studies to investigate genetic contribution to food allergy. Third, our study is one of the first studies to examine a broad array of the most common food allergen- and aeroallergen-specific IgE levels in a single study. Our findings have important clinical and research implications for food allergy. To date, family history is a predominant predictor of allergic diseases. No specific genetic factors have been identified for food allergy. Our findings suggest that genetic susceptibility influences the development of food allergy, and genetic factors should be an important aspect to consider in future investigation on the etiology of food allergy.

Some limitations of our study should also be considered. First, one of the major challenges in conducting large-scale epidemiologic and genetic studies of FA is how to define FA in a large population. The double-blind, placebo-controlled food challenge has been promoted as the gold standard for establishing diagnosis[38]. Such challenges are however, laborious, time-consuming and associated with risk of allergic reactions including anaphylaxis and are therefore not routinely performed in clinical practice or large research studies. Given the latter, we used a combination of timing, stringent clinical history, and established sIgE cutoffs to establish food allergy in this study. This approach has been suggested in previous reports when a double-blind placebo-controlled food challenge test is not available [15,20,21,39–42]. Of note, our definition of food allergy is more stringent than most published large-scale epidemiological studies of food allergy [8,9,43–45]. Importantly, our approach is similar to the ongoing National Institutes of Health (NIH) funded "Consortium of Food Allergy Research (CoFAR)". Specifically, inclusion criteria provided at http://clinicaltrials.gov/ct2/show/NCT00356174 state that children with egg or milk allergy will be enrolled based upon "Clinical history of allergy to cow's milk or egg and positive skin prick test (3 mm or larger) to cow's milk or egg OR moderate to severe atopic dermatitis and a positive prick skin test to cow's milk or egg OR positive oral food challenge (prior to study entry) to either cow's milk or egg and a positive skin prick test to cow's milk or egg" and during follow up study visits "Oral food challenges will occur at some visits, as clinically indicated." We have recognized the possibility that our definition of food allergy may miss some individuals who have FA but do not meet all the above criteria, thus underestimating the incidence rate of FA in this study sample and moreover may decrease our statistical power to detect such association. Second, we only observed familial aggregation of food allergy and allergy to egg white between siblings due to the available sample size. Since enrollment continues, when the sample size becomes large enough we will investigate whether the familial aggregation will be observed for other specific types of food allergy. In addition, a portion of recruited families had no paternal data. Our results on "father-offspring" association need to be interpreted with caution and remain to be confirmed in future studies. Third, we did not include parental smoking as a

covariate in the final analyses since parental smoking was not statistically significant in our preliminary analysis. Additionally, previous studies did not observe consistent patterns for the effect of parental smoking on allergic sensitization in children [46].

The rapid advancements in human genetics have made it possible to conduct large-scale candidate gene studies and genome-wide scans in food allergy. We anticipate that we will enter an exciting era to better understand the genetics of food allergy. Major challenges in future genetic studies of food allergy will be to achieve a large enough study sample and to carefully phenotype study subjects with and without food allergy. At present, well-defined comprehensive phenotypic definitions are lacking in the literature and are necessary for conducting large-scale population or genetic studies. The phenotypic definition applied in this study can serve as a practical approach in a population setting.

In summary, this study documents strong evidence of familial aggregation of food allergy and sensitization to food allergens, as well as significant heritability of food-specific IgE. The findings indicate that genetic factors may play an important role in the pathogenesis of food allergy. Identification of susceptibility genes related to food-specific IgE and the development of clinical food allergy may facilitate better understanding of the causes and biological mechanisms of food allergy and ultimately lead to improved preventive and therapeutic strategies for food allergy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and IgE data in the examined family-based food allergy cohort.

	Father (328)	Mother (567)	Index child (580)	Other siblings (529)
Age (mean; SD), yr	40 (6)	38 (6)	7 (4)	6 (4)
Sex, % male	--	--	60	50
Ethnicity, % *				
African American	3	6	7	6
Caucasian	84	76	76	78
Hispanics	7	9	9	8
History of food allergy, % yes	18	21	78	17
History of asthma, % yes	18	23	38	20
History of eczema, % yes	15	20	64	32
History of seasonal allergy, % yes	34	39	38	20
Total IgE (mean; SD), kU/L	113 (250)	81 (150)	426 (1089)	131 (261)
Specific IgE, % detectable				
Egg white	11	11	66	39
Sesame	35	25	70	35
Peanut	16	14	67	24
Soy	12	9	57	23
Milk	17	16	67	43
Shrimp	17	12	25	12
Walnut	9	6	46	16
Cod fish	2	1	14	3
Wheat	30	22	65	38
D pteronyssinus	44	34	43	22
D farinae	45	36	53	25
Cat	36	34	52	27
Dog	38	36	68	33
Cockroach	23	16	45	16
Alternaria	36	29	57	32
Number of positive food-specific IgE, %				
0	47	55	13	37
1	16	19	8	17
2 or more	37	27	79	47
Number of positive aeroallergen-specific IgE, %				
0	30	40	17	47
1	21	19	15	17
2 or more	49	41	69	35

* Note: Ethnicity information of index child and other siblings is the same as maternal ethnicity information

Table 2

Table 2a. Inter-relationship of self-reported atopic diseases among parents, index child and other siblings.						
Disease	**Father-Offspring[a, b]**		**Mother-Offspring[a,c]**		**Index-Other siblings[a,d]**	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
History of food allergy[#]	0.8 (0.8–1.8)	0.49	1.5 (1.1–2.1)	0.005	6.8 (2.6–17.8)	< 0.001
History of eczema	0.6 (0.6–1.4)	0.60	1.9 (1.4–2.5)	< 0.001	3.0 (1.9 –4.7)	< 0.001
History of asthma	1.3 (1.3–3.0)	0.002	2.1 (1.5–2.8)	< 0.001	2.4 (1.5–3.7)	< 0.001
History of seasonal allergy	0.7 (0.7–1.5)	0.99	2.9 (2.2–3.7)	< 0.001	3.5 (2.2–5.7)	< 0.001

Table 2b. Inter-relationship of food allergy among parents, index child and other siblings.						
Traits	**Father-Offspring[a, b]**		**Mother-Offspring[c]**		**Index-Other siblings[d]**	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Allergic to any food [*]	0.6 (0.6–4.0)	0.37	1.4 (0.8–2.6)	0.22	2.6 (1.2–5.6)	0.01
Egg white	NA		NA		3.8 (1.2–12.1)	0.02
Milk	0.1 (0.1–6.0)	0.70	7.4 (1.8–30.9)	0.006	1.9 (0.9–4.1)	0.12
Peanut	NA		5.1 (1.7–15.0)	0.003	7.2 (0.8–61.9)	0.07

[#]Note: Food allergy was defined based on self-reported history.

[*]Food allergy was defined by clinical symptoms, timing of symptoms within 2 hours of ingestion, and established specific IgE cutoffs.

[a]Logistic regression was performed with adjusting covariates: age, sex, ethnicity and birth order.

[b]Offspring's disease history is outcome variable as father's disease history is predictor.

[c]Offspring's disease history is outcome variable as mother's disease history is predictor.

[d]Other sibling's disease history is outcome variable as index child's disease history is predictor.

Table 3

Table 3a. Inter-relationship of total IgE and specific IgE among parents, index child, and other siblings

Allergen	Father-Offspring[a,b]			Mother-Offspring[c]			Index-Other siblings[d]		
	β	se	*p*	β	se	*p*	β	se	*p*
Total IgE	0.35	0.05	< 0.001	0.24	0.03	< 0.001	0.33	0.04	< 0.001
Food-specific IgE									
Sesame	0.38	0.08	< 0.001	0.24	0.07	< 0.001	0.42	0.06	< 0.001
Peanut	0.19	0.07	0.009	0.22	0.06	< 0.001	0.21	0.06	< 0.001
Wheat	0.37	0.07	< 0.001	0.36	0.05	< 0.001	0.30	0.05	< 0.001
Milk	0.34	0.08	< 0.001	0.19	0.07	0.006	0.14	0.05	0.008
Egg white	0.36	0.08	< 0.001	0.29	0.07	< 0.001	0.19	0.05	0.001
Soy	0.36	0.07	< 0.001	0.36	0.05	< 0.001	0.29	0.05	< 0.001
Walnut	0.19	0.07	0.005	0.28	0.06	< 0.001	0.41	0.06	< 0.001
Shrimp	0.15	0.05	0.002	0.21	0.04	< 0.001	0.25	0.06	< 0.001
Cod fish	0.17	0.07	0.02	0.43	0.09	< 0.001	0.23	0.07	0.002
Aeroallergen-specific IgE									
D pteronyssinus	0.19	0.04	< 0.001	0.10	0.03	< 0.001	0.26	0.05	< 0.001
D farinae	0.21	0.04	< 0.001	0.10	0.03	0.001	0.24	0.05	< 0.001
Cat	0.24	0.05	< 0.001	0.16	0.03	< 0.001	0.32	0.05	< 0.001
Dog	0.31	0.06	< 0.001	0.20	0.04	< 0.001	0.29	0.05	< 0.001
Cockroach	0.26	0.05	< 0.001	0.23	0.04	< 0.001	0.26	0.05	< 0.001
Alternaria	0.20	0.05	0.001	0.24	0.04	< 0.001	0.40	0.05	< 0.001

Table 3b. Inter-relationship of detectable total IgE and specific IgE among parents, index child, and other siblings

Allergen	Father-Offspring[a, b]		Mother-Offspring[c]		Index-Other siblings[d]	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Total IgE	1.9 (1.2–3.1)	0.008	2.0 (1.4–3.0)	< 0.001	4.9 (2.8–8.6)	< 0.001
Food-specific IgE						
Sesame	1.5 (1.1–2.2)	0.02	1.8 (1.4–2.5)	< 0.001	3.6 (2.2–6.1)	< 0.001
Peanut	1.4 (0.9–2.2)	0.14	1.8 (1.3–2.6)	0.002	3.0 (1.7–5.3)	< 0.001

Table 3b. Inter-relationship of detectable total IgE and specific IgE among parents, index child, and other siblings

Allergen	Father-Offspring[a, b]		Mother-Offspring[c]		Index-Other siblings[d]	
Wheat	1.9 (1.3–2.7)	0.001	2.3 (1.6–3.2)	< 0.001	3.9 (2.4–6.3)	< 0.001
Milk	2.2 (1.3–3.6)	0.002	1.3 (0.9–1.9)	0.12	1.8 (1.2–2.7)	0.009
Egg white	1.9 (1.0–3.4)	0.04	2.1 (1.4–3.2)	0.001	1.7 (1.1–2.7)	0.02
Soy	2.4 (1.4–4.2)	0.002	1.6 (1.0–2.5)	0.04	2.9 (1.8–4.9)	< 0.001
Walnut	1.3 (0.7–2.3)	0.40	1.4 (0.8–2.5)	0.19	4.6 (2.6–8.1)	< 0.001
Shrimp	2.5 (1.4–4.3)	0.001	1.6 (1.0–2.5)	0.05	2.2 (1.2–4.0)	0.009
Cod fish	2.0 (0.4–9.4)	0.40	5.0 (0.3–83.5)	0.27	0.9 (0.2–4.4)	0.93
Aeroallergen-specific IgE						
D pteronyssinus	2.1 (1.4–3.1)	< 0.001	1.6 (1.2–2.1)	0.002	1.7 (1.1–2.7)	0.02
D farinae	2.1 (1.5–3.0)	< 0.001	1.7 (1.3–2.3)	< 0.001	2.0 (1.3–3.1)	0.003
Cat	1.6 (1.1–2.3)	0.007	1.7 (1.3–2.3)	< 0.001	2.8 (1.8–4.5)	< 0.001
Dog	1.9 (1.4–2.8)	< 0.001	1.6 (1.2–2.1)	< 0.001	2.8 (1.7–4.5)	< 0.001
Cockroach	1.8 (1.2–2.8)	0.005	1.6 (1.1–2.2)	0.01	2.1 (1.2–3.5)	0.008
Alternaria	1.8 (1.3–2.6)	0.001	2.6 (1.9–3.4)	< 0.001	3.3 (2.1–5.3)	< 0.001

[a] Note Linear regression was performed for Table 3a; logistic regression was performed for Table 3b; adjusted covariates: age, sex, ethnicity and birth order.

[b] Offspring's IgE is outcome variable as father's IgE is predictor

[c] Offspring's IgE is outcome variable as mother's IgE is predictor

[d] Other sibling's IgE is outcome variable as index child's IgE is predictor

Table 4

Heritability estimates for total IgE and specific IgE [a]

	$\hat{h}^2$ (SE)	*P*
Total IgE	0.49 (0.05)	< 0.001
Food-specific IgE		
Sesame	0.27 (0.04)	< 0.001
Peanut	0.15 (0.04)	< 0.001
Wheat	0.35 (0.04)	< 0.001
Milk	0.15 (0.04)	< 0.001
Egg white	0.20 (0.04)	< 0.001
Soy	0.34 (0.05)	< 0.001
Walnut	0.26 (0.05)	< 0.001
Shrimp	0.29 (0.05)	< 0.001
Cod fish	0.19 (0.05)	< 0.001
Aeroallergen-specific IgE		
D pteronyssinus	0.24 (0.05)	< 0.001
D farinae	0.25 (0.05)	< 0.001
Cat	0.33 (0.05)	< 0.001
Dog	0.32 (0.05)	< 0.001
Cockroach	0.35 (0.05)	< 0.001
Alternaria	0.38 (0.05)	< 0.001

[a]Note: Variance component analysis was performed with adjusting covariates: age, sex and ethnicity.