

Atopic Dermatitis Mediates the Association Between an *IL4RA* Variant and Food Allergy in School-Aged Children



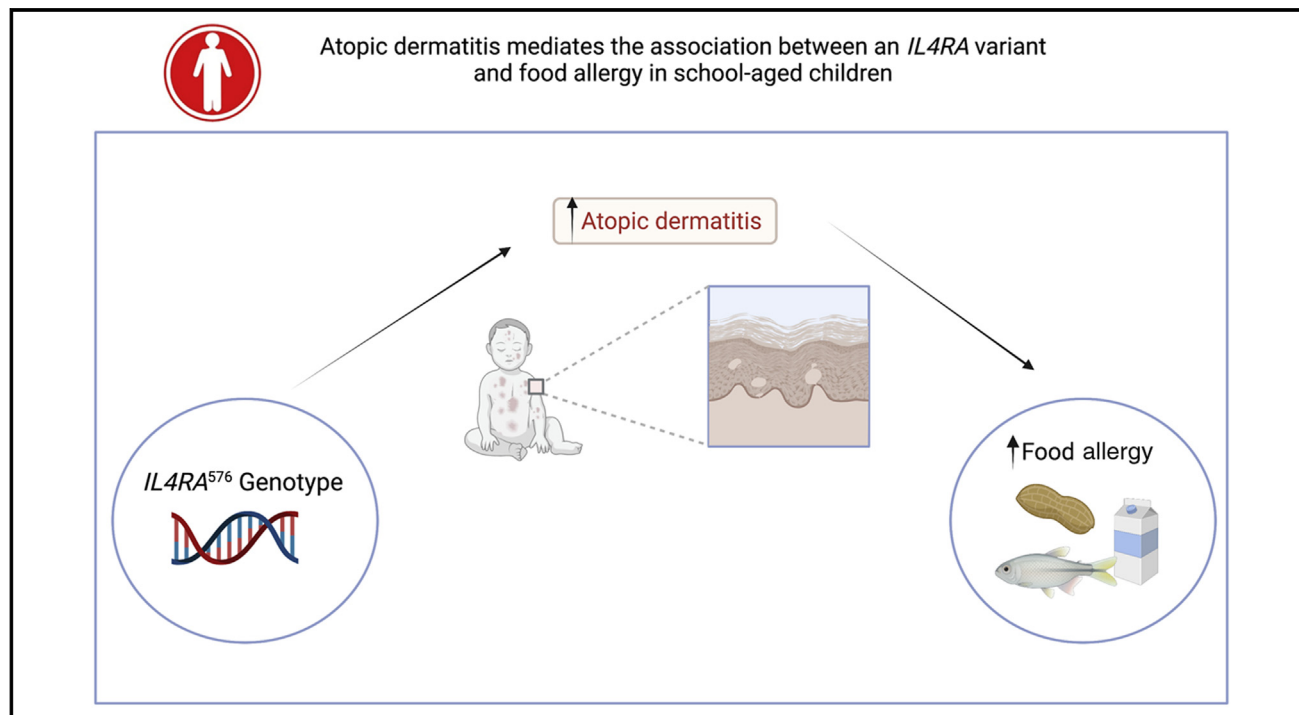
Tina M. Banzon, MD^{a,b,*}, Michael S. Kelly, MD^{b,c,*}, Lisa M. Bartnikas, MD^{a,b}, William J. Sheehan, MD^{d,e}, Amparito Cunningham, MD, MPH^a, Hani Harb, PhD^{a,b}, Elena Crestani, MD, MS^{a,b}, Linda Valeri, MSc, PhD^f, Kimberly F. Greco, MPH^g, Talal A. Chatila, MD, MSc^{a,b}, Wanda Phipatanakul, MD, MS^{a,b,g,†}, and Peggy S. Lai, MD, MPH^{b,h,i,†} Boston, Mass; Washington, DC; and New York, NY

What is already known about this topic? Atopic dermatitis and food allergy (FA) likely share genetic risk factors. The *IL4RA*^{R576} (human IL-4 receptor alpha chain gene) variant has been associated with increased risk and severity of allergic diseases such as asthma.

What does this article add to our knowledge? Atopic dermatitis is part of the causal pathway between a common *IL4RA* variant and FA. *IL4RA*^{R576} is also associated with a higher risk of severe FA reactions. These results support the epicutaneous exposure hypothesis in the development of FA and identify a vulnerable subgroup of children at risk for severe FA reactions.

How does this study impact current management guidelines? Disease-modifying treatments for AD may concurrently reduce the risk for future development of FA in children with genetic risk factors and warrant further investigation.

VISUAL SUMMARY



^aDivision of Allergy and Immunology, Boston Children's Hospital, Boston, Mass

^bHarvard Medical School, Boston, Mass

^cDepartment of Internal Medicine, Massachusetts General Hospital, Boston, Mass

^dDivision of Allergy and Immunology, Children's National Hospital, Washington, DC

^eGeorge Washington University School of Medicine and Health Sciences, Washington, DC

^fDepartment of Biostatistics, Columbia University Mailman School of Public Health, New York, NY

^gInstitutional Centers for Clinical and Translational Research, Boston Children's Hospital, Boston, Mass

Abbreviations used

AD- atopic dermatitis
 FA- food allergy
 IL4RA- human IL-4 receptor alpha chain gene
 IL4Rα- human IL-4 receptor alpha chain protein
 OR- odds ratio
 SICAS 1- School Inner-City Asthma Study
 SICAS 2- School Inner-City Asthma Intervention Study
 Treg- regulatory T

BACKGROUND: Atopic dermatitis (AD) and food allergy (FA) may share genetic risk factors. It is unknown whether genetic factors directly cause FA or are mediated through AD, as the dual-allergen hypothesis suggests.

OBJECTIVE: To test the hypothesis that AD mediates the relationship between an IL-4 receptor alpha chain gene (*IL4RA*) variant, the human IL-4 receptor alpha chain protein-R576 polymorphism, and FA.

METHODS: A total of 433 children with asthma enrolled in the School Inner-City Asthma Study underwent genotyping for the *IL4RA*⁵⁷⁶ allele. Surveys were administered to determine FA, AD, and associated allergic responses. Mediation analysis was performed adjusting for race and ethnicity, age, sex, and household income. Multivariate models were used to determine the association between genotype and FA severity.

RESULTS: AD was reported in 193 (45%) and FA in 80 children (19%). Each risk allele increased odds of AD 1.39-fold ([1.03-1.87], $P = .03$), and AD increased odds of FA 3.67-fold ([2.05-6.57], $P < .01$). There was an indirect effect of genotype, mediated by AD, predicting FA; each risk allele increased the odds of FA by 1.13 (odds ratio [95% CI], $Q/R = 1.13$ [1.02-1.24], $R/R = 1.28$ [1.04-1.51]; $P < .01$). Each risk allele increased the odds of severe FA symptoms 2.68-fold ([1.26-5.71], $P = .01$).

CONCLUSIONS: In a cohort of children with asthma, AD is part of the causal pathway between an *IL4RA* variant and FA. This variant is associated with increased risk of severe FA reactions. Addressing AD in children with an *IL4RA* polymorphism may modulate the risk of FA. © 2022 Published by Elsevier Inc. on behalf of the American Academy of

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Key words: Food allergy (FA); Atopic dermatitis (AD); *IL4RA*; Genetics; Asthma; Epicutaneous sensitization; Mediation analysis

INTRODUCTION

Atopic dermatitis (AD), a chronic inflammatory skin disease characterized by intense pruritus, eczematous lesions, and a relapsing disease course, is the first manifestation of the allergic march. Beginning with AD in the first few months of life, the allergic march continues with IgE-mediated food allergies (FAs) presenting between age 1 and 3 years and asthma appearing in early childhood.^{1,2} Early-onset AD has been linked with subsequent diagnosis of FA and asthma.³⁻⁵ The temporal relationship with AD preceding FA has raised questions about whether they are the result of a common risk factor or whether the development of AD itself increases the likelihood of FA.⁶

The dual-allergen exposure hypothesis proposes that allergic sensitization to food can occur through the skin, whereas early consumption of food proteins induces oral tolerance, protecting against the development of FAs.⁷ Several studies have described an increased risk of peanut sensitization and clinically confirmed peanut allergy due to epicutaneous exposure to peanut through an impaired skin barrier.⁸⁻¹⁰ The dual-allergen hypothesis posits that whether a child will develop allergy or tolerance hinges on the timing and balance of cutaneous versus oral exposure. Low-dose cutaneous exposure to environmental foods, such as on tabletops, dust, and hands, is thought to penetrate the skin barrier, where it is taken up by Langerhan's cells and leads to T_H2 responses and IgE production by B cells.^{11,12} Alternatively, it is proposed that tolerance is induced via early high-dose oral consumption, whereby T_H1 and regulatory T (Treg)-cell responses are believed to occur in gut-associated lymphoid tissue.^{11,12} However, only a fraction of children with AD go on to develop FA, raising questions of alternative explanations including shared genetic risk factors or environmental triggers.^{6,13}

AD, asthma, and FA may share genetic risk factors; however, it is unknown whether genetic risk alleles associated with FA are

^bDivision of Pulmonary and Critical Care, Massachusetts General Hospital, Boston, Mass

^cDepartment of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Mass

*Equal contribution and should be considered co-first authors; authorship order listed alphabetically.

[†]Equal contribution and should be considered co-last authors.

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Conflicts of interest: W. Phipatanakul reports consultancy fees from Genentech, Novartis, Regeneron, Sanofi, GlaxoSmithKline, and Astra Zeneca for therapeutics related to asthma, outside the submitted work. The rest of the authors declare that they have no relevant conflicts of interest.

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Corresponding author: Peggy S. Lai, MD, MPH, Bulfinch 148, 55 Fruit St, Boston, MA 02114. E-mail: PLAI@mgh.harvard.edu.

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mediated through concomitant AD diagnosis. A human IL-4 receptor alpha chain gene (*IL4RA*) variant, which results in a glutamine to arginine substitution at amino acid residue 576 (human IL-4 receptor alpha chain protein [IL4R α]-R576 polymorphism), has been identified as a possible locus of genetic predisposition for atopic disease.^{14,15} IL4R α -R576 results in a gain-of-function mutation at the IL-4 receptor, causing increased IL-4 pathway signaling.¹⁴ This IL4R α -R576 polymorphism has been associated with asthma diagnosis and severity.^{16,17} An anti-IL-4 mAb, dupilumab, has been shown to be effective in treating allergic diseases, including asthma and AD.^{18,19} However, less is known about the relationship between IL4R α -R576, AD, and FA.

We hypothesized that the *IL4RA* variant *IL4RA*^{R576} would be associated with increased risk of FA through AD as a mediator and associated with severe FA reactions.

METHODS

Study population and design

The School Inner-City Asthma Study (SICAS 1) and the School Inner-City Asthma Intervention Study (SICAS 2) were conducted between 2008 and 2013 in children (ages 5-17 years) with persistent asthma attending inner-city schools in a city in the northeast United States (see this article's Online Repository at www.jaci-inpractice.org).^{20,21} Full details of the methodology of selection of this cohort are published elsewhere.^{20,21} Inclusion criteria included physician diagnosis of asthma with either controller medication use or symptoms of exacerbation in the last year. Exclusion criteria included lung disease other than asthma and cardiovascular disease. All children from the SICAS cohorts who had genotyping for *IL4RA*⁵⁷⁶ performed were included in this study.

Outcome measures

Genotyping of the *IL4RA*^{Q576} and *IL4RA*^{R576} alleles was performed using the amplification resistance mutation screen PCR method on DNA extracted from either whole blood (GentraPuregene Blood Kit; Qiagen, Valencia, CA) or saliva (prepIT L2P; DNA Genotek, Ottawa, ON, Canada). In SICAS 1 and SICAS 2, parental surveys were administered at 3, 6, 9, and 12 months after enrollment.²⁰ Physician-diagnosed AD was reported by parents. Physician-diagnosed FA and FA symptoms occurring within 1 hour of food ingestion were reported by parents. IgE-mediated FA defined in our work was consistent with other studies,²² and included gastrointestinal (abdominal pain, vomiting, mouth/throat itching), respiratory (dyspnea, wheezing, throat tightness, cough), cardiovascular (syncope, hypotension), and cutaneous (urticaria, pruritis, edema) symptoms, which occurred within 1 hour of ingestion. FA diagnosis was independently assessed on the basis of history and reported symptoms by 2 study physicians (T.M.B. and L.M.B.). If ever there was disagreement between T.M.B. and L.M.B. on FA diagnosis, a blinded third study physician certified by the American Board of Allergy and Immunology (E.C.) adjudicated. Participants were not considered to have FA if reported symptoms after food ingestion were inconsistent with IgE-mediated FA. Severe FA symptoms were classified according to a grading system developed by Sampson,²³ and defined as the presence of any of the following symptoms (grade 3 anaphylaxis or above per Sampson anaphylaxis severity scoring system): throat tightness, difficulty breathing, coughing, wheezing, drop in blood pressure, or change in neurologic status (passing out).

Statistical analysis

Characteristics of the study participants were compared among the 3 genotype groups (*Q/Q*, *Q/R*, and *R/R*) using ANOVA for continuous variables and Pearson χ^2 statistic for categorical variables. In statistical models, the IL4R α -R576 polymorphism was primarily modeled as a continuous variable using the number of *R* alleles (0, 1, or 2), consistent with a gain-of-function mutation. Thus, all logistic regression output in which the number of risk alleles was used as a predictor is presented as odds ratio (OR) per *R* allele. As a sensitivity analysis, genotype was also modeled as a categorical variable by genotype (*Q/Q* vs *Q/R* vs *R/R*) or as a categorical variable with groupings based on presence or absence of a risk allele (*Q/Q* vs *Q/R* and *R/R*). Unless otherwise stated, *Q/Q* was used as the reference group. All multivariable regression models adjusted for possible confounding from age, sex, annual household income (above or below \$25,000), and race and ethnicity (White, non-Hispanic vs any other combination of races and ethnicities).

Logistic regression was used for models identifying the association between risk alleles and AD, risk alleles and FA, and AD and FA. All models adjusted for potential confounding by age, sex, income, and race and ethnicity as above. To investigate potential interaction and mediation effects of AD on the relationship between genotype and FA and test the hypothesis that AD is part of the causal pathway between risk alleles and FA, we performed a mediation analysis including a 4-way decomposition of the total effect using the CMAverse package in R.^{24,25} The purpose of the mediation analysis was to test the hypothesis that the effect of the risk genotypes on FA is mediated by AD. Although traditional mediation analyses are predicated on a significant total effect (ie, association between the *IL4RA*⁵⁷⁶ risk genotypes and FAs),²⁶ in the presence of an *a priori* hypothesized indirect effect (dual-allergen hypothesis), there is precedent for pursuing a mediation analysis.²⁷ The presence of an indirect effect, but not total effect, may be seen when the direct and indirect effects are in different directions. Under some models, the indirect effect may have greater power than the total effect; thus, using the total effect as a gatekeeper for deciding whether or not to continue with a mediation analysis may not always be the correct choice.^{27,28} For these reasons, *a priori* we decided to proceed with a mediation analysis regardless of the total effect. CIs for the indirect effects were based on 1000 bootstrapped replications, and multiple imputations of 10 iterations were used for missing income data (25% of study participants declined to answer questions on household income). A sensitivity analysis for unmeasured confounding in the mediation analysis was performed by estimating the E-value.²⁹ Logistic regression, using genotype as the predictor, was used to predict FA symptoms and specific food allergens in the subset of patients with FA. All statistical analysis was performed in R (R version 4.0.4; R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-tailed with alpha set at 0.05.

RESULTS

A total of 433 children from the SICAS cohorts consented to *IL4RA*⁵⁷⁶ genotyping and were included in the study (Table I). Sex, race, ethnicity, and income level were similar in genotyped participants compared with the overall SICAS 1 and SICAS 2 cohorts (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). However, genotyped patients were on average 0.5 years younger than the overall cohort (mean $\pm$ SD, 8.0 $\pm$ 1.9 vs 8.5 $\pm$ 1.9; $P < .001$). The reference genotype (*Q/Q*) was identified in 119 children (27%), whereas the heterozygous *Q/R*

TABLE I. Baseline characteristics of study population

Overall cohort	All (n = 433)	Q/Q (n = 119)	Q/R (n = 186)	R/R (n = 128)	P
Age (y), mean $\pm$ SD	8.0 $\pm$ 1.9	8.3 $\pm$ 1.9	7.9 $\pm$ 2.0	7.9 $\pm$ 1.8	.19
Sex: female, n (%)	203 (47)	58 (49)	81 (44)	64 (50)	.47
Race and ethnicity, n (%)					<.001
Black	130 (30)	15 (13)	55 (30)	60 (47)	
Hispanic/Latino	192 (44)	68 (57)	87 (47)	37 (29)	
Other/mixed	80 (18)	18 (15)	34 (18)	28 (22)	
White	31 (7)	18 (15)	10 (5)	3 (2)	
Income <\$25K,* n (%)	145 (44)	33 (35)	59 (43)	53 (52)	.05
AD,† n (%)	193 (45)	41 (35)	86 (47)	66 (52)	.02
FA,‡ n (%)	80 (19)	22 (20)	32 (18)	26 (21)	.73
Specific FAs, n (%)	All (n = 80)	Q/Q (n = 22)	Q/R (n = 32)	R/R (n = 26)	P
Peanut	39 (48.8)	8 (36.4)	19 (59.4)	12 (46.2)	.24
Fish	23 (28.7)	7 (31.8)	9 (28.1)	7 (26.9)	.93
Fruits	19 (23.8)	5 (22.7)	7 (21.9)	7 (26.9)	.90
Grains	16 (20)	5 (22.7)	8 (25)	3 (11.5)	.41
Soy	15 (18.8)	2 (9.1)	4 (12.5)	9 (34.6)	.04
Eggs	12 (15)	4 (18.2)	3 (9.4)	5 (19.2)	.51
Treenut	11 (13.8)	2 (9.1)	2 (6.2)	7 (26.9)	.06
Shellfish	8 (10)	3 (13.6)	2 (6.2)	3 (11.5)	.64
Vegetables	6 (7.5)	4 (18.2)	0 (0)	2 (7.7)	.05
Seeds	5 (6.2)	3 (13.6)	2 (6.2)	0 (0)	.15
Milk	5 (6.2)	1 (4.5)	2 (6.2)	2 (7.7)	.90
Meats	3 (3.8)	1 (4.5)	0 (0)	2 (7.7)	.30
Other	2 (2.5)	1 (4.5)	1 (3.1)	0 (0)	.58

Summary statistic presented as n (%) or mean $\pm$ SD.

*n = 101 missing as participant's caregiver declined to answer questions about household income.

†n = 4 missing.

‡n = 20 missing.

genotype was seen in 186 children (43%), and the homozygous *R/R* genotype was observed in 128 children (30%). Overall, 314 (73%) of the children genotyped were found to have at least 1 *R* allele (*Q/R* or *R/R* genotypes). Children with at least 1 *R* allele were more likely to identify as Black than other races and ethnicities (37% vs 12.6%). AD was reported in 193 children (45%); FA was reported in 80 children (19%). The most commonly reported FAs were peanut (39 of 80 [49%]), tree nuts (23 of 80 [29%]), and shellfish (19 of 80 [24%]; Table I). Hives (49 of 80 [61%]), skin redness (44 of 80 [55%]), and itchy mouth (41 of 80 [51%]) were the most prevalent FA symptoms reported. Severe FA reactions were reported in 47 participants (59%).

Association between genotype, FA, and AD

There was no significant difference in the proportion of children with reported FA across genotypes (Table I). In adjusted analysis, the number of *R* alleles was not associated with a statistically significant increase in odds of FA, although the effect size suggested increased risk (OR per *R* allele [95% CI], *P*; 1.11 [0.78-1.59], *P* = .56; see Table E2 in this article's Online Repository at www.jaci-inpractice.org). However, AD was more common in patients with at least 1 *R* allele (152 of 314 [48%] vs 41 of 119 [35%]), and adjusted analysis demonstrated increased risk of AD with each additional *R* allele (OR per *R* allele, 1.39 [1.03-1.87], *P* = .03). Furthermore, in adjusted analysis, AD was shown to increase the odds of FA (OR, 3.67 [2.05-6.57], *P* < .01). These results held in sensitivity analyses when comparing participants with no risk alleles (*Q/Q* genotype) and those with at least 1 risk allele (*Q/R* or *R/R* genotypes; Table E2).

This series of findings supported the possibility that the relationship between genotype and FA was influenced by AD. Specifically, our hypothesis was that there may be an indirect effect of genotype on FA that is mediated by the presence of AD, consistent with the dual-allergen hypothesis. To explore these findings further, causal mediation analysis was performed.

Causal mediation analysis allows the decomposition of the total effect of an exposure on an outcome, in the presence of a potential mediating factor, into a direct effect and an indirect effect. The indirect effect represents the portion of the total effect of the exposure on the outcome that is caused by the result of mediation from a third variable. In other words, the indirect effect determines the amount of the effect of the exposure on the outcome that is the result of the exposure making the mediating variable more likely and the mediator making the outcome more likely. In contrast, the direct effect represents the effect of the exposure on the outcome that is not the result of mediation through the hypothesized mediator variable (the portion of the effect of the exposure on the outcome after the effect of the mediated pathways has been accounted for). Mediation analysis was performed to determine the effect of number of risk alleles on FA, mediated by AD, modeling the outcome and the mediator, controlling for confounders of the exposure-outcome and exposure-mediator relationship (age, sex, income, and race and ethnicity).

Mediation analysis: IL4RA^{R576} allele increases odds of FA mediated via AD

Overall, the total effect of the number of risk alleles on the risk of FA was not statistically significant, although the effect size

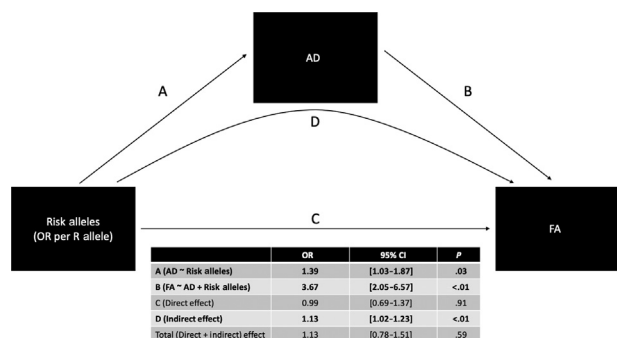


FIGURE 1. Mediation analysis predicting FA based on *IL4RA* genotype, mediated by AD. Mediation analysis performed using 2 logistic regression models: AD predicted from genotype (*Q/Q* vs *Q/R* or *R/R*), and FA predicted from AD and genotype. All genotype results are relative to the *Q/Q* genotype. Patients with at least 1 *R* allele were more likely to have AD; having AD was strongly associated with FA. Genotype was shown in increased odds of FA when mediated by AD (D, indirect effect; OR/risk allele, 1.13 [1.02-1.22], $P < .01$). Once the mediating effect of AD was removed, genotype was not shown to increase the odds of FA (C, direct effect; OR, 0.99 [0.78-1.51], $P = .59$). All models calculated using age, sex, income level (<\$25,000), and race and ethnicity as potential covariates. ORs and CIs calculated using 1000 bootstraps and missing data (income) addressed using multiple imputation using 10 imputations.

TABLE II. Mediation analysis of risk alleles predicting FA mediated by AD

Predictor = No. of R alleles (OR per R allele)			
Effect	OR	95% CI	P
Direct effects			
Pure natural direct effect	0.99	0.69-1.37	.91
Total natural direct effect	0.99	0.70-1.37	.91
Controlled direct effect	0.99	0.67-1.40	.91
Indirect (mediated) effects			
Pure natural indirect effect	1.13	1.02-1.24	<.01
Total natural indirect effect	1.13	1.02-1.23	<.01
Total effect	1.13	0.78-1.51	.59

All models controlled for possible confounding by age, sex, income, and race and ethnicity.

Proportion mediated represents the proportion of the total effect that is the result of the indirect (mediated) effect.

indicated a trend toward increased risk (total effect; OR, 1.13 [0.78-1.51]; $P = .59$). However, examining the direct and indirect effects of the mediation analysis further explains the mechanism by which genotype and AD may act on the risk of FA (Figure 1 and Table II). The indirect effect demonstrates that the number of *R* alleles increases the risk of FA along the pathway mediated by AD (OR per *R* allele, 1.13 [1.02-1.23], $P < .01$). It is along this indirect pathway (number of *R* alleles increasing the risk of AD, which in turn increases the risk of FA diagnosis) that a *Q/R* genotype had 1.13 times increased odds and a *R/R* genotype had 1.28 times increased odds of FA compared with a *Q/Q* genotype.

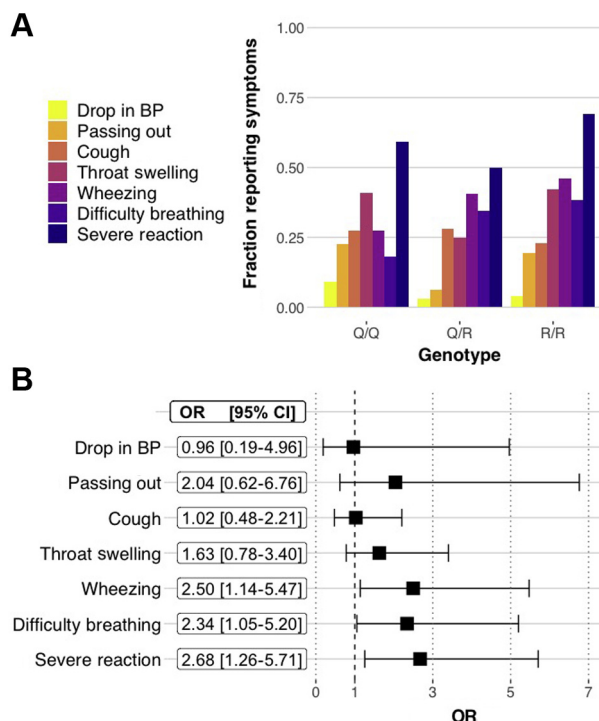


FIGURE 2. FA symptoms by *IL4RA* genotypes. (A) Unadjusted percent of patients with FA who report various FA symptoms stratified by number of *IL4RA*^{R576} alleles. Severe FA symptoms were defined as the presence of any of the following symptoms: throat tightness, difficulty breathing, coughing, wheezing, drop in blood pressure, or passing out. (B) The results of the multivariable logistic regression predicting FA symptoms based on presence of at least 1 risk allele (genotype *Q/Q* vs *Q/R* or *R/R*). All models are adjusted for age, sex, income level (<\$25,000), and race and ethnicity. BP, Blood pressure.

Sensitivity analysis for unmeasured confounding was performed on mediation analysis results (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). This analysis shows that for unmeasured confounding to nullify the results of the indirect effect, an unmeasured confounder would require a strength of association at least 1.35 times larger than the observed effect (E-value [95% CI lower limit], relative risk, 1.53 [1.17]). To further explore the possibility of interaction as well as mediation between genotype, AD, and FA, a 4-way decomposition of the mediation analysis was performed. This demonstrated no significant contribution of interaction or mediated interaction in explaining the total effect (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). Sensitivity analyses modeling the genotype using the presence or absence of at least 1 risk allele (*Q/Q* vs *Q/R* or *R/R*) demonstrated similar findings (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). Given concern that subjects with purely a vegetable or fruit allergy may have pollen FA syndrome, a sensitivity analysis was performed, reclassifying subjects with solely a vegetable or fruit allergy as not having FA. Reclassifying those with exclusively a vegetable or fruit allergy as not having FA changes the FA assignment of 8 patients ($n = 72$ from $n = 80$). This mediation analysis continued to demonstrate a significant

indirect effect of the number of risk alleles on FA mediated by AD (see Table E6 in this article's Online Repository at www.jaci-inpractice.org).

Patients with *IL4RA*^{R576} allele are more likely to report severe FA

Subject with FA symptoms, stratified by genotype, are presented in Table E7 in this article's Online Repository at www.jaci-inpractice.org. Children were more likely to report severe FA symptoms as the number of *R* alleles increased (Figure 2). Adjusting for age, sex, income, and race and ethnicity, each *R* allele increased the odds of severe FA symptoms 2.68-fold (1.26–5.71) ($P = .01$; Figure 2). Increasing *R* alleles also predicted increased likelihood to report respiratory symptoms of wheezing (OR per *R* allele, 2.50 [1.14–5.47], $P = .02$) and difficulty breathing (OR per *R* allele, 2.34 [1.05–5.20], $P = .04$; see Table E8 in this article's Online Repository at www.jaci-inpractice.org). Genotype did not show consistent associations with allergy to specific foods (see Table E9 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

In this study, we demonstrate that AD is part of the causal pathway between a common *IL4RA* polymorphism and FA. There was a dose-response relationship between the number of risk alleles and patient-reported severe FA reactions. The mediation analysis provided valuable insight into the relationship between genotype, AD, and how they may impact FA. AD mediated the relationship between the genotype and FA. Although genotype is immutable, identification of AD as part of the causal pathway between genotype and FA suggests that interventions targeted toward AD may influence FA diagnosis in children born with the risk allele. This observation also provides further support for the dual-allergen hypothesis.

Although the *IL4RA*-R576 polymorphism has been associated with increased risk for atopic diseases, our work did not demonstrate a statistically significant increased risk of FA based on genotype alone.¹⁴ In the case of our analysis, the indirect and direct effects are not in the same direction, which likely explains why the total effect is not statistically significant, but the indirect effect is. Larger cohorts will be required to further elucidate the effects of the *IL4RA* genotype on AD and atopic diseases independent of AD in the general population. Our results demonstrate that nearly all the excess risk for FA seen in those with at least 1 *IL4RA*^{R576} allele is attributable to the increased risk of AD in this population. Sensitivity analysis demonstrates that unmeasured confounding is unlikely to explain the results of this AD-mediated pathway. Furthermore, we demonstrate here that AD appears to act as a mediator in the link between genotype and risk for FA.

In addition to providing added support for the dual-allergen hypothesis, this work provides new insight into the *IL4RA* genotype as a risk factor for severity of FA reactions in a cohort of subjects with asthma. Previous work had shown that having at least 1 *IL4RA*^{R576} allele was associated with an increased risk of asthma and asthma severity, although the association of this gene with other atopic diseases has been less clear.^{16,17} Analogous to asthma, having at least 1 *IL4RA* risk allele was associated with severe FA symptoms, as well as respiratory FA symptoms. Consistent with a gain-of-function mutation, our work supports a dose-response relationship between the number of *IL4RA*^{R576}

alleles and increasing likelihood of AD-mediated FA and severe FA reactions. The mechanism leading to increased severity of FA reactions based on genotype in this cohort of children with asthma may be the same or similar to that of the previously noted increased asthma severity based on *IL4RA* genotype, and it remains unclear whether this result would also be found in patients without asthma.

Previous literature suggests that polymorphisms in the *IL4R* can alter the risk of FA by impairing oral tolerance and promoting FA.^{30,31} Similar to our study's *IL4RA*^{R576} polymorphism, which results in a gain-of-function mutation at the *IL4R* causing increased *IL-4* pathway signaling, a well-characterized murine transgenic model of FA has been studied involving a gain-of-function *IL-4R* α chain polymorphism causing enhanced *IL-4* receptor signaling. In studies of these mice carrying inactivating mutation in the *IL-4R* α subunit's immunotyrosine inhibitory motif (*IL4ra*^{F709}), impaired generation and function of mucosal allergen-specific Treg cells was observed via a signal transducer and activator of transcription 6-dependent mechanism. This led to selective augmentation of *IL4R* signaling in Treg cells to induce their reprogramming into T_H2-like cells and FA susceptibility.³¹

Group 2 innate lymphoid cells, due to their secretion of *IL-4*, were also found to play a pivotal role in inducing FA in this murine model by increasing mucosal mast cell activation and hindering allergen-specific Treg-cell induction and suppressive functions.³⁰ Our study is consistent with observations made in these mechanistic models and suggests a role for immunomodulators, such as an anti-*IL-4R* antibody, as a possible therapy for FA. For children with risk alleles that result in increased *IL-4R* signaling, anti-*IL-4R* treatment may prove helpful in treating both AD and FA by resetting the circuit of impaired induction of allergen-specific Treg cells, which leads to T_H2-cell-type skewing.³⁰

Given that there is no current cure for FA, there has been increased interest exploring the use of biologic agents for FA. Dupilumab, a human mAb against the *IL4R* α subunit that acts as a dual inhibitor of *IL-4* and *IL-13* signaling, is currently approved for use for AD, asthma, and chronic rhinosinusitis with nasal polyposis.³² Given its T_H2-suppressive mechanism of action, dupilumab is also being investigated as a potential biologic treatment option for FA in several ongoing clinical trials evaluating its use either as an adjunct to oral immunotherapy for peanut allergy and milk allergy, or as monotherapy.^{33–35} Our findings support the impetus of the ongoing work that aims to translate the dual-allergen hypothesis into disease prevention by seeking to treat AD as an approach to prevent FA. Our work also supports ongoing trials using *IL-4* mAbs (such as dupilumab) as treatment for atopic diseases generally, but specifically for those with *IL4RA* polymorphisms and those with both AD and FA.^{36,37}

This study has several strengths. Our sample size included 433 children and represented a diverse group of subjects especially with regard to race and ethnicity. The number of *R* alleles was well distributed in our cohort, with an approximate 1:2:1 ratio of genotypes. Although this is unlikely the community prevalence of the risk allele, it did allow for higher power in detecting relationships between genotype, disease prevalence, and symptoms. We leveraged causal inference methods to identify mechanistic relationships between the genotype, AD, and FA.

There are some limitations worth noting. The study population consists of children with asthma, and thus is biased toward atopic diseases with a higher prevalence of AD, FA, and *IL4RA* polymorphisms than is reported in the general population.³⁸⁻⁴⁰ Our participants are reflective of an inner-city population with asthma; thus, generalizability to patients in other settings may be limited. Consistent with previous work, genotype and AD varied by race and ethnicity in our cohort, and although adjusted analysis treated race and ethnicity as a possible confounder, unmeasured confounding is possible.^{39,41} This study was retrospective, and performing an analysis not *a priori* specified for in the aims of the original studies. AD, FA diagnoses, and FA symptoms were reported by parents, and FA diagnosis was not confirmed by the criterion standard of double-blind placebo-controlled food challenge, although FA case determination was independently assessed by study physicians. FA cases met clinical criteria, including reported symptoms occurring within 1 hour that were consistent with IgE-mediated FA, and modeled from other studies to allow judicious diagnosis based on clinical algorithms.⁴²⁻⁴⁴

CONCLUSIONS

These results strengthen support for the dual-allergen hypothesis by demonstrating that AD is part of the causal pathway between the *IL4RA*-R576 polymorphism and FA in patients with asthma and provides further evidence for the use of biologics such as dupilumab in the blockade of IL-4-mediated pathways as a potential therapy in FA.

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ONLINE REPOSITORY

All tables and figures listed as online in the text are present here in the Online Repository.

In addition to online tables and figures, we have made available our data set and R code used for the analysis. The data

set is in comm separated values (.csv) format. The R code for the analysis is in R-markdown (.RMD) format, and the fully run output is also present as an HTML file. The R code used for the figures is in R (.R) format.

TABLE E1. Demographic comparison of overall SICAS 1 and SICAS 2 cohorts to study q576r- genotyped cohort

Characteristic	This study (n = 433)	Overall cohort (n = 625)	P
Age (y), mean $\pm$ SD	8.0 $\pm$ 1.9	8.5 $\pm$ 1.9	<.001
Sex: female, n (%)	203 (47)	300 (48)	.73
Race and ethnicity, n (%)			.41
Black	130 (30)	164 (27)	
Hispanic/Latino	192 (44)	286 (46)	
Other/mixed	80 (18)	110 (18)	
White	31 (7)	58 (9)	
Income <\$25K,* n (%)	145 (44)	195 (42)	.59

*Annual household income less than \$25,000/year.

TABLE E2. Univariate and multivariable regression modeling of genotype, AD, and FA

Predictor = No. of R alleles (OR per R allele)						
Outcome	Unadjusted OR	95% CI	P	Adjusted OR*	95% CI	P
AD	1.42	1.10-1.83	.01	1.39	1.03-1.87	.03
FA	1.06	0.77-1.47	.71	1.11	0.78-1.59	.56
Predictor = Genotype Q/Q vs Q/R or R/R						
Outcome	Unadjusted OR	95% CI	P	Adjusted OR*	95% CI	P
AD	1.80	1.16-2.79	<.01	1.74	1.05-2.88	.03
FA	0.99	0.57-1.71	.98	1.09	0.59-2.02	.76
Predictor = AD						
Outcome	Unadjusted OR	95% CI	P	Adjusted OR*	95% CI	P
FA	3.53	2.08-5.98	<.001	3.67	2.05-6.57	<.001

*Multivariable logistic regression model adjusting for age, sex, income, and race and ethnicity as covariates.

TABLE E3. Sensitivity analysis of mediation analysis genotype predicting FA, mediated by genotype

Predictor = No. of R alleles (OR per R allele)				
Effect	Relative risk	95% CI	E-value	E-value 95% CI
CDE	0.99	0.67-1.40	1.09	1.00- ∞
PNDE	0.99	0.69-1.37	1.09	1.00- ∞
TNDE	0.99	0.70-1.37	1.09	1.00- ∞
PNIE	1.13	1.02-1.24	1.53	1.17- ∞
TNIE	1.13	1.02-1.23	1.53	1.17- ∞
TE	1.13	0.78-1.51	1.50	1.00- ∞
Predictor = Genotype Q/Q vs Q/R or R/R				
Effect	Relative risk	95% CI	E-value	E-value 95% CI
CDE	0.84	0.49-1.56	1.66	1.00- ∞
PNDE	0.85	0.52-1.53	1.63	1.00- ∞
TNDE	0.85	0.52-1.53	1.63	1.00- ∞
PNIE	1.17	1.03-1.43	1.61	1.21- ∞
TNIE	1.17	1.03-1.43	1.61	1.20- ∞
TE	0.99	0.60-1.88	1.09	1.00- ∞

CDE, Controlled direct effect; PNDE, pure natural direct effect; PNIE, pure natural indirect effect; TE, total effect; TNDE, total natural direct effect; TNIE, total natural indirect effect.

TABLE E4. Mediations analysis of genotype predicting FA mediated by AD including the interaction term

Predictor = No. of R alleles (OR per R allele)			
Mediation analysis	OR	95% CI	P
Controlled direct effect	1.19	0.68 to 2.16	.56
Pure natural direct effect	0.98	0.71 to 1.34	.93
Total natural direct effect	0.96	0.69 to 1.31	.82
Pure natural indirect effect	1.14	1.02 to 1.31	.02
Total natural indirect effect	1.11	1.02 to 1.25	.02
Total effect	1.09	0.78 to 1.51	.62
Four-way decomposition Excess relative risk 95% CI P			
Controlled direct effect	0.09	−0.19 to 0.35	.56
Interaction effect	−0.10	−0.32 to 0.14	.44
Mediated interaction effect	−0.03	−0.11 to 0.04	.44
Pure natural indirect effect	0.14	0.02 to 0.31	.02
Predictor = Genotype Q/Q vs Q/R or R/R			
Mediation analysis	OR	95% CI	P
Controlled direct effect	1.34	0.56 to 4.01	.58
Pure natural direct effect	0.88	0.53 to 1.56	.65
Total natural direct effect	0.8	0.48 to 1.47	.48
Pure natural indirect effect	1.29	1.04 to 1.62	.02
Total natural indirect effect	1.17	1.03 to 1.37	.02
Total effect	1.03	0.62 to 1.95	.92
Four-way decomposition Excess relative risk 95% CI P			
Controlled direct effect	0.14	−0.26 to 0.72	.58
Interaction effect	−0.26	−0.52 to 0.20	.25
Mediated interaction effect	−0.14	−0.40 to 0.09	.25
Pure natural indirect effect	0.29	0.04 to 0.62	.02

All models controlled for possible confounding by age, sex, income, and race and ethnicity.

TABLE E5. Mediation analysis of risk alleles predicting FA mediated by AD

Predictor = Genotype Q/Q vs Q/R or R/R			
Effect	OR	95% CI	P
Direct effects			
Pure natural direct effect	0.85	0.49-1.53	.63
Total natural direct effect	0.85	0.52-1.53	.63
Controlled direct effect	0.84	0.52-1.53	.63
Indirect (mediated) effects			
Pure natural indirect effect	1.17	1.03-1.43	.01
Total natural indirect effect	1.17	1.03-1.43	.01
Total effect	0.99	0.61-1.88	.89

Genotype modeled as Q/R or R/R vs Q/Q. All models controlled for possible confounding by age, sex, income, and race and ethnicity. Proportion mediated represents the proportion of the total effect that is the result of the indirect (mediated) effect.

TABLE E6. Sensitivity analysis of mediation analysis genotype predicting FA, mediated by genotype, recoding those with presumed pollen FA syndrome as nonallergic

Predictor = No. of R alleles (OR per R allele)			
Effect	OR	95% CI	P
Direct effects			
Pure natural direct effect	1.13	0.80-1.67	.47
Total natural direct effect	1.13	0.80-1.67	.47
Controlled direct effect	1.13	0.79-1.71	.47
Indirect (mediated) effects			
Pure natural indirect effect	1.10	1.02-1.20	.01
Total natural indirect effect	1.10	1.02-1.20	.01
Total effect	1.24	0.88-1.78	.21
Predictor = Genotype Q/Q vs Q/R or R/R			
Effect	OR	95% CI	P
Direct effects			
Pure natural direct effect	1.14	0.66-2.17	.64
Total natural direct effect	1.14	0.66-2.17	.64
Controlled direct effect	1.14	0.64-2.22	.64
Indirect (mediated) effects			
Pure natural indirect effect	1.16	1.03-1.37	.01
Total natural indirect effect	1.16	1.03-1.37	.01
Total effect	1.32	0.75-2.54	.30

All models controlled for possible confounding by age, sex, income, and race and ethnicity.

Proportion mediated represents the proportion of the total effect that is the result of the indirect (mediated) effect.

TABLE E7. Severe FA symptoms and specific food allergens by genotype

FA symptoms, n (%)	Q/Q (n = 22)	Q/R (n = 32)	R/R (n = 26)	P
Skin*	19 (86)	22 (69)	21 (81)	.28
Gastrointestinal†	15 (68)	22 (69)	20 (77)	.74
Respiratory‡	13 (59)	16 (50)	17 (65)	.49
Cardiovascular§	2 (9)	1 (3)	1 (4)	.58
Neurologic	5 (23)	2 (6)	5 (19)	.19
Throat tightness	9 (41)	8 (25)	11 (42)	.31
Coughing	6 (27)	9 (28)	6 (23)	.90
Wheezing	6 (27)	13 (41)	12 (46)	.39
Difficulty breathing	4 (18)	11 (34)	10 (39)	.28
Drop in blood pressure	2 (9)	1 (3)	1 (4)	.58
Passing out	5 (23)	2 (6)	5 (19)	.19
Severe reaction¶	13 (59)	16 (50)	18 (69)	.33

*Defined as hives, redness of the skin, or swelling.

†Defined as gastrointestinal pain, vomiting, diarrhea, or itchy mouth.

‡Defined as rhinorrhea, coughing, wheezing, or difficulty breathing.

§Defined as blood pressure drop.

||Defined as passing out.

¶Defined as at least 1 of the following: throat tightness, trouble breathing, drop of blood pressure, or passing out.

TABLE E8. Univariate and multivariable regression modeling using genotype to predict FA symptoms

Predictor = No. of R alleles (OR per R allele)						
Symptom	Unadjusted OR	95% CI	P	Adjusted OR*	95% CI	P
Hives	1.05	0.59-1.88	.87	1.24	0.63-2.44	.54
Redness of the skin	0.98	0.56-1.74	.95	1.00	0.51-1.96	>.99
Swelling	1.08	0.61-1.91	.78	1.54	0.78-3.05	.22
Vomiting	1.01	0.52-1.96	.99	0.97	0.46-2.06	.94
Gastrointestinal pain	1.08	0.58-2.01	.80	1.04	0.51-2.16	.91
Diarrhea	0.91	0.41-2.00	.81	0.83	0.32-2.18	.70
Rhinorrhea	0.67	0.32-1.44	.31	0.73	0.30-1.76	.48
Itchy mouth	1.82	1.01-3.29	.05	2.84	1.33-6.06	.01
Throat swelling	1.06	0.58-1.92	.86	1.63	0.78-3.40	.20
Coughing	0.89	0.47-1.70	.73	1.02	0.48-2.21	.95
Wheezing	1.49	0.82-2.70	0.19	2.50	1.14-5.47	.02
Difficulty breathing	1.61	0.85-3.03	.14	2.34	1.05-5.20	.04
Blood pressure drop	0.58	0.15-2.25	.43	0.96	0.19-4.96	.97
Passing out	0.91	0.41-2.00	.81	2.04	0.62-6.76	.24
Skin symptoms†	0.88	0.44-1.73	.70	1.03	0.48-2.23	.94
Gastrointestinal symptoms‡	1.25	0.66-2.34	.49	1.50	0.69-3.27	.30
Respiratory symptoms§	1.16	0.65-2.06	.62	1.98	0.97-4.02	.06
Cardiovascular symptoms	0.58	0.15-2.25	.43	0.96	0.19-4.96	.97
Neurologic symptoms¶	0.91	0.41-2.00	.81	2.04	0.62-6.76	.24
Severe reaction#	1.26	0.71-2.24	.44	2.68	1.26-5.71	.01
Predictor = Genotype Q/Q vs Q/R or R/R						
Symptom	Unadjusted OR	95% CI	P	Adjusted OR*	95% CI	P
Hives	0.87	0.31-2.40	.79	0.93	0.27-3.16	.90
Redness of the skin	0.61	0.22-1.68	.34	0.49	0.13-1.81	.29
Swelling	0.83	0.31-2.23	.72	1.53	0.45-5.16	.49
Vomiting	0.77	0.25-2.37	.65	0.61	0.17-2.25	.46
Gastrointestinal pain	0.89	0.31-2.57	.83	0.72	0.20-2.59	.62
Diarrhea	0.72	0.19-2.68	.62	0.58	0.12-2.89	.50
Rhinorrhea	0.62	0.18-2.12	.45	0.67	0.15-3.04	.60
Itchy mouth	2.31	0.84-6.36	.10	4.21	1.12-15.9	.03
Throat swelling	0.7	0.26-1.93	.50	1.38	0.37-5.15	.63
Coughing	0.93	0.31-2.81	.90	1.37	0.32-5.89	.67
Wheezing	2.02	0.69-5.90	.20	5.25	1.02-26.9	.05
Difficulty breathing	2.55	0.76-8.55	.13	8.36	1.00-70.0	.05
Blood pressure drop	0.36	0.05-2.71	.32	0.92	0.05-16.4	.95
Passing out	0.47	0.13-1.67	.24	0.85	0.13-5.75	.87
Skin symptoms†	0.45	0.12-1.75	.25	0.44	0.08-2.24	.32
Gastrointestinal symptoms‡	1.23	0.42-3.56	.71	1.15	0.29-4.52	.84
Respiratory symptoms§	0.91	0.34-2.47	.86	1.94	0.57-6.60	.29
Cardiovascular symptoms	0.36	0.05-2.71	.32	0.92	0.05-16.4	.95
Neurologic symptoms¶	0.47	0.13-1.67	.24	0.85	0.13-5.75	.87
Severe reaction#	0.98	0.36-2.66	.97	3.07	0.86-10.9	.08

*Multivariable logistic regression model adjusting for age, sex, income, and race and ethnicity as covariates.

†Defined as hives, redness of the skin, or swelling.

‡Defined as gastrointestinal pain, vomiting, diarrhea, or itchy mouth.

§Defined as rhinorrhea, coughing, wheezing, or difficulty breathing.

||Defined as blood pressure drop.

¶Defined as passing out.

#Defined as at least 1 of the following: throat tightness, trouble breathing, drop of blood pressure, or passing out.

TABLE E9. Univariate and multivariable regression modeling using genotype to predict specific FAs

Predictor = No. of <i>R</i> alleles (OR per <i>R</i> allele)						
FA	Unadjusted OR	95% CI	<i>P</i>	Adjusted OR*	95% CI	<i>P</i>
Peanut	1.19	0.67-2.10	.55	1.53	0.77-3.07	.23
Fish	0.91	0.35-2.34	.85	0.83	0.26-2.68	.76
Fruits	1.07	0.48-2.37	.87	1.37	0.51-3.69	.53
Grains	1.68	0.34-8.23	.52	1.51	0.27-8.47	.64
Soy	2.37	0.93-6.07	.07	2.33	0.84-6.51	.10
Eggs	2.59	1.12-6.00	.03	3.03	0.96-9.56	.06
Treenut	0.89	0.48-1.66	.71	0.88	0.40-1.94	.76
Shellfish	1.13	0.58-2.21	.72	1.28	0.57-2.88	.55
Vegetables	0.49	0.15-1.54	.22	0.65	0.16-2.63	.54
Seeds	0.26	0.06-1.17	.08	0.21	0.04-1.12	.07
Milk	0.69	0.34-1.42	.31	0.29	0.09-0.97	.05
Meats	0.35	0.04-2.98	.34	0.31	0.02-3.92	.36
Other	1.31	0.40-4.34	.66	1.06	0.26-4.30	.94

Predictor = Genotype Q/Q vs Q/R or R/R						
FA	Unadjusted OR	95% CI	<i>P</i>	Adjusted OR*	95% CI	<i>P</i>
Peanut	2.01	0.73-5.52	.18	4.75	1.13-20.0	.03
Fish	0.60	0.13-2.74	.51	0.64	0.09-4.61	.66
Fruits	0.72	0.19-2.68	.62	0.94	0.17-5.20	.94
Grains	0.75	0.06-8.71	.82	0.68	0.04-10.3	.78
Soy	1.84	0.36-9.26	.46	1.56	0.27-9.13	.62
Eggs	2.89	0.60-14.0	.19	3.53	0.37-33.6	.27
Treenut	0.82	0.28-2.37	.71	0.93	0.23-3.77	.91
Shellfish	1.08	0.34-3.47	.89	1.47	0.32-6.84	.62
Vegetables	0.16	0.03-0.95	.04	0.18	0.02-1.57	.12
Seeds	0.23	0.04-1.46	.12	0.2	0.02-2.01	.17
Milk	0.80	0.24-2.63	.71	0.28	0.05-1.60	.15
Meats	0.37	0.02-6.16	.49	0.36	0.01-12.2	.57
Other	1.56	0.16-14.7	.70	0.8	0.07-9.19	.85

*Multivariable logistic regression model adjusting for age, sex, income, and race and ethnicity as covariates.