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# The Phenotype of the Food-Allergic Patient



Amy A. Eapen, MD, MS\*, Haejin Kim, MD

## KEYWORDS

• Birth cohorts • Food allergy • Food sensitization • Atopic march

## KEY POINTS

- Food allergy presents with different phenotypes that are adjusted based on genetic risk, racial background, and environmental factors.
- Sensitization patterns exist in food allergy, and these patterns can give light to the phenotype of food allergy the child may have.
- Food allergy and sensitization is a risk factor for asthma, independent of whether the food allergy is outgrown.
- Assessing the food allergy phenotype of a child can allow physicians to provide the appropriate medical management of their food allergy as well as anticipatory guidance on the presence of other allergic diseases.

## BACKGROUND

The prevalence of food allergy among children has been steadily increasing over the past several decades. Published studies have reported a prevalence among children as high as 10%.<sup>1</sup> The National Health and Nutrition Examination, a population-based survey conducted in the United States, reported that self-reported food allergy among children in 2007 to 2010 was 6.53%, with the most common foods being reported as milk (1.94%), peanut (1.16%), and shellfish (0.87%).<sup>2,3</sup>

Among this group of food-allergic children, there is a wide range of phenotypes present. These phenotypes can be divided into several subcategories, not only by specific food but also by race and presence of other atopic manifestations. There is growing evidence that there are significant racial disparities present in food allergy, among other allergic diseases. There are also differences in the phenotype of food allergy among children who have coexistence of eczema, asthma, and allergic rhinitis compared with those who have food allergy alone. Investigating these phenotypes allow us to decipher the multiple risk factors that predispose children to have food

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allergy, as well as those that increase the risk for other allergic diseases. The purpose of this article is to detail the phenotypes of the food allergic patient, with emphasis on published data from significant longitudinal birth cohorts both here in the United States as well as across the globe.

## EVALUATION

### *Familial Inheritance*

Previous studies looking at familial aggregation and twin studies have found a strong genetic component in food allergy, with heritability rates ranging from 15% to 82%.<sup>4-7</sup> Two twin studies currently exist looking at these rates among monozygotic and dizygotic twin pairs. Sicherer and colleagues looked at the rates of peanut allergy among 58 twin pairs. Among the monozygotic twin pairs ( $n = 14$ ), there was a concordance rate of 64.3% ( $n = 9$ ) for peanut allergy compared with 6.8% ( $n = 3$ ) among dizygotic twins ( $n = 44$ ).<sup>8</sup> Second, a study looking at Chinese twins reported the sensitization rates for 9 foods and 5 aeroallergens among 472 monozygotic and 354 dizygotic twins aged 12 to 28 years. They found that there was a higher concordance rate for sensitization among monozygotic than dizygotic twins. However, there were differences in which allergens the twins were sensitized to, relaying a role of environmental factors in the allergic phenotype. Monozygotic twins sensitized to peanut and shellfish had the highest concordance rate at 58%.<sup>9,10</sup> These 2 studies demonstrate the strong genetic component in food allergy, specifically of peanut. There is a need for further twin studies to delineate the heritability patterns among other food allergens and the role of genetic risk with compounding environmental factors.

A common question in the office among parents with food allergy is how likely is their child to also develop food allergy? Liu and colleagues investigated the maternal genotypic and parent-of-origin effects among 588 Caucasian food allergy trios from the Chicago Food Allergy Study. They identified 1 single nucleotide polymorphism (rs423235) with significant maternal effect of any food allergy located in a noncoding RNA (LOC101927947). In addition, they identified 3 other loci with maternal genetic effects: 1 for any food allergy (rs976078 on 13q31.1) and 2 for egg allergy (rs1343795 and rs4572450 in *ZNF652* gene). Interestingly, they further demonstrated specific loci that showed significant parent-of-origin effects in boys only: 1 for peanut allergy (rs4896888 in the *ADGB* gene) and 2 for any food allergy (rs1036504 and rs2917750 in *IQCE* gene).<sup>4</sup> These findings support a strong parent-to-child inheritance pattern in the food allergy phenotype and a specific strong inheritance pattern from mother to child. Further investigations are needed to identify possible interventions that could protect an infant from these genetic patterns and prevent the onset of food allergy.

### *Atopic March*

The atopic march has been used to signify the progression of allergic diseases through childhood with different ages of mean onset. This progression has identified atopic dermatitis as the predisposing ailment that can lead to other allergic diseases, including food allergy. Atopic dermatitis is thought to provide a break in the skin barrier, that allows sensitization to foods with progression to clinical allergy later on in childhood. However, food allergy can also follow atopic dermatitis, signifying the different endotypes and pathways of the disease. In general, atopic dermatitis has an earlier age of onset with a peak at 6 months,<sup>11</sup> and food sensitization starting shortly after.<sup>12</sup> Although atopic dermatitis can signify the start of a phenotype for food allergy, there is insufficient evidence to recommend routine panel food allergy testing to all infants with atopic dermatitis. Current guidelines do recommend testing

for specific foods, such as peanut, to risk stratify infants with specific risk factors and promote early introduction when appropriate.<sup>13</sup> A similar relationship is seen with the incidence of food allergy with asthma and allergic rhinitis. Several birth cohorts have identified these different “food allergic phenotypes,” signifying that the allergic disease progression may not truly be a “march” per se in being sequential, but instead dependent on key allergic disease risk factors and characteristics. **Table 1** details key highlights with respect to food allergy phenotypes from 4 specific birth cohorts: WHEALS, CCAAPS, HEALTHNUT, and PASTURE. The remainder of this article will go into details specific on these studies.

## LONGITUDINAL BIRTH COHORT DATA

### **Wayne County Health, Environment, Allergy and Asthma Longitudinal Study Cohort**

The Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS), a birth cohort from southeastern Michigan, recruited pregnant women between the ages of 21 and 49 years in predefined cluster of zip codes in Detroit and surrounding suburbs from August 2003 to November 2007.<sup>14</sup> Follow-up occurred at 1, 6, 12, 24, and 48 months after the child’s birth. Total immunoglobulin E (IgE) and serum-specific IgE was collected from children’s blood at 2 years of age for the following 10 allergens: *Der f*, dog, cat, Timothy grass, ragweed, *Alternaria alternata*, egg, peanut, cow’s milk, and German cockroach.

A latent class analysis was performed, which was described as “an unsupervised statistical method that simultaneously considers a number of variables to identify homogenous, mutually exclusive groups or classes within a heterogenous population”.<sup>15</sup> This analysis was used to determine if children could be grouped together based on their patterns of sensitization. The 594 of the 1258 women-children pairs (that had blood samples available) were clustered into 4 groups: class 1 (n = 457)—low to no sensitization, class 2 (n = 16)—highly sensitized, class 3 (n = 91)—milk and egg dominated, and class 4 (n = 30)—peanut and inhalant/no milk. Class 1 children were characterized as no sensitization (67.8%, n = 310) or monosensitized to either egg (17.2%, n = 23), *Alternaria* (16.4%, n = 22), *Der f* (7.5%, n = 10), dog (4.5%, n = 6), cat (1.5%, n = 2), or Timothy grass (0.8%, n = 1). Class 2 children were all sensitized to at least 4 of the following allergens: milk, egg, peanut, and Timothy grass.

In regard to food allergy, class 3 and 4 had the most striking patterns. Class 3 children predominated (94.5%, n = 86) with milk and egg sensitization; 27.9% of these children (n = 24) were sensitized to milk, egg, and peanut. Eighty percent of class 4 was sensitized to peanut (n = 24). Egg sensitization occurred in 43.3% of the individuals (n = 13).

This study also reported interesting findings regarding race. Class 3 (milk and egg dominated) was statistically significantly associated with the Black race, whereas classes 2 and 3 were associated but not statistically significant. In terms of the occurrence of wheezing, class 4 were 2.9 times more likely to have wheezed than those in class 1, but this pattern was not seen in the other 2 classes. Cord blood had also been collected in this cohort. Cord blood total IgE level was significantly higher ( $P < .01$ ) in both class 2 (highly sensitized) and class 3 (milk and egg dominated) but not in class 4 (peanut and inhalants).

This study demonstrated phenotypes of allergic disease based on allergen-specific IgE patterns. Although the atopic march refers to a stepwise direction in allergic disease onset, it does not address the possibility of different phenotypes in the allergic group.

**Table 1**  
**Longitudinal birth cohorts and food allergy**

<b>Birth Cohort</b>	<b>WHEALS</b>	<b>CCAPS</b>	<b>HEALTHNUTS</b>	<b>PASTURE</b>
Geographic location	Southeast Michigan, USA	Greater Cincinnati area, Ohio, USA	Melbourne, Australia	Rural areas of 5 European nations: Austria, Finland, France, Germany, and Switzerland
Unique characteristics of cohort	Racially diverse with 62% Black race	Higher risk cohort with at least one atopic parent	Used challenge-proven outcomes to assess the role of infantile food allergy in development of asthma	Assessed role of farm animals on allergic disease presence
Times of follow-up postnatally	1, 6, 12, 24, and 48-months of age	1, 2, 3, 4, and 7 y	11 or 15 mo, 1 y, 4 y	1, 4, and 6 y
Total recruited	1258	762	5276	1133
Food allergens tested	Egg, peanut, cow's milk	Cow's milk, egg	Egg, peanut, sesame, and cow's milk or shrimp	Cow's milk, hen's egg, cow's milk, peanut, hazelnut, carrot, and wheat
Key food allergy phenotype finding	Black race was a significant risk factor for milk and egg allergy	Food sensitization in the presence of <i>KIF3A</i> mutations poses a significant risk for asthma, independent of aeroallergen sensitization	Asthma at 4 years of age is twice as common in children with food allergy, irrespective of whether child outgrows allergy	Farm exposure can alter sensitization patterns
PMIDs for key food allergy articles	24636082	30830718, 19759553	29153880, 20608942	28531273

### Key highlights

- The “highly sensitized” group class 2 was the most likely to ever have atopic dermatitis and more likely to ever have wheeze and doctor diagnosis of asthma than the “low to no sensitization” class 1.
- Associations between class and asthma diagnosis were similar in class 3 and class 4, suggesting that food allergens are not as strongly associated with asthma as being highly sensitized.
- There seems to be a cosensitization pattern, with peanut sensitization being equally likely to be paired with at least 1 inhalant sensitization as with 2 other food sensitizations.
- Milk and egg cosensitization was the most common pairing, with this pairing consistently associated with the lowest rate of allergic disease outcomes among the 3 higher risk groups (Class 2, 3, 4).
- There are racial differences in which allergic diseases predominate in the Black race, with milk and egg food allergies having a statistically significant association.
- Race was the most obvious risk factor across the classes. The investigators propose that the racial differences observed could play a role in the racial disparities seen in asthma if early life food allergen sensitization is more strongly associated with asthma than with other types of sensitizations.

### Cincinnati Childhood Allergy and Air Pollution Study Cohort

The Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS) is a birth cohort of 762 infants born to atopic parents between 2001 and 2003.<sup>16</sup> Follow-up evaluations occurred at 1, 2, 3, 4, and 7 years of age where skin prick testing (SPT) to milk, egg, and 15 aeroallergens was performed. Because only 2 food allergens were tested, they did not examine the pattern of cosensitization of foods but did examine the presence of food sensitization and timing of asthma and eczema onset compared with aeroallergen sensitization. As previous data had shown, of the children who had food and aeroallergen sensitization, 70% were food sensitized by their first birthday, and food sensitization preceded aeroallergen sensitization in 52% of cosensitized children. In the presence of early eczema, the odds of having food sensitization (OR = 3) compared with aeroallergen sensitization (OR = 1.9) was higher in the food-sensitized group. Forty-three percent of their food-sensitized children did not have eczema compared with 58% of the aeroallergen group, which signifies that eczema or atopic dermatitis is not a mandatory precursor to food sensitization.

In regard to presence of asthma risk compared with sensitization patterns, a multivariate model revealed that aeroallergen sensitization load, but not food sensitization load, was associated with asthma among children without a history of early eczema.<sup>17</sup> Among those with early eczema, neither aeroallergen sensitization nor food sensitization was significantly associated with asthma risk. However, being African American was associated with asthma risk among children without early eczema but not among those with early eczema.

This study revealed significant genotype patterns with other allergic disease as well. They specifically looked at the role of a coding subunit of the kinesin-2 motor complex, *KIF3A*, which plays a role in the formation and/or function of primary and motile cilia.<sup>18</sup> In children with early eczema, genotype *KIF3A rs12186803* and food sensitization interacted to significantly increase the risk of asthma at 7 years of age, whereas neither variable on its own was associated with asthma risk. This pattern did not depend on the presence of early aeroallergen sensitization. This signified the role of food

sensitization in altering the allergic disease progression to asthma in specific genotypes of children with early eczema onset.

Another analysis focused on the Caucasian children in the group (76.6%, 583) demonstrated food sensitization to be the highest risk factor for development of eczema by age 1 to 3 years.<sup>19</sup> They reported that children with positive SPT (this included foods and/or aeroallergens) by age 3 years were 3 times more likely to have a specific genotype in *CD14* and *IL4 $\alpha$*  compared with children without eczema who had negative SPT. This further portrayed the role of genetic susceptibility to allergic disease, such as food allergy and eczema.

### **Key highlights**

- Although eczema predisposes a child to food sensitization, there is a significant number of children (47% in this cohort) who have food sensitization in the absence of eczema.
- Food sensitization in the presence of early eczema posed a significant increase in asthma risk for those with genotype *KIF3A rs12186803*, independent of the presence of early aeroallergen sensitization.
- Food sensitization in Caucasian children were found to be the highest risk factor for development of eczema by age 1 to 3 years.

### **HEALTHNUTS Cohort**

The HEALTHNUTS cohort is a longitudinal population-based cohort study of allergic disease in Melbourne, Australia.<sup>20</sup> Five thousand two hundred seventy-six infants between 11 and 15 months were recruited from immunization clinics around Melbourne with a 74% participation rate. These participants underwent SPT to egg, peanut, sesame, cow's milk, or shrimp and were examined for eczema. If the SPT was positive to egg, peanut, or sesame, the child was invited for an oral food challenge (OFC) to that food. At 4 years of age, the parents were given a questionnaire about their allergic outcomes (asthma, eczema, and allergic rhinitis). The aim of this study was to determine the relationship between the presence and number of food allergies at age 1 years and asthma at age 4 years.

They reported that asthma at 4 years of age was twice as common in those with challenge-proven food allergy. Egg allergy alone was associated with higher risk of asthma, but peanut allergy alone was not. Children with 2 or more food allergies and coexistent eczema were almost 3 times more likely to develop asthma compared with children without food allergy and those with a single food allergy.<sup>21</sup> Interestingly, asymptomatic food sensitization and OFC-proven food allergy in infancy were associated with an increased risk of asthma by 4 years of age. Furthermore, the increased risk of asthma was similarly high among food allergic infants who outgrew and did not outgrow their food allergy. This study further demonstrates the risk that sensitization to foods in addition to challenge-proven food allergy contributes to childhood asthma and defining the food allergy phenotypes.

They performed a latent class analysis, similar to the WHEALS cohort, to identify phenotypes of food allergy.<sup>22</sup> From their analysis, they defined 5 classes: class 1—no allergic disease (70%); class 2—non-food-sensitized eczema (16%); class 3—single egg allergy (9%); class 4—multiple food allergies, predominately peanut (3%); and class 5—multiple food allergies, predominately egg (2%).

They further investigated the risk factors for the different phenotypes. For all phenotypes, males were at increased risk of belonging to non-food-sensitized eczema and multiple food allergy phenotypes (classes 2, 4, and 5). As far as environmental risk factors are concerned, exposure to pet dogs in the home was associated with reduced

risk of membership in non-food-sensitized eczema and multiple food allergies—peanut phenotypes but the difference was not statistically significant. Presence of siblings reduced the risk of single egg allergy and non-food-sensitized eczema but not multiple food allergies.

They also noted that filaggrin gene mutations were associated with a higher risk for the non-food-sensitized eczema and egg allergy phenotypes, with an odds ratio of 2.37 but interestingly was not associated with either multiple food allergy phenotypes. There has also been research investigating the role of vitamin D insufficiency in the risk of food allergy. The HEALTHNUTS study group found that the association between vitamin D insufficiency and allergy phenotypes was modified by parent's country of birth. Vitamin D insufficiency was a risk factor for the 3 food allergy phenotypes (class 3–5) only among those infants with both parents born in Australia.

Similar to WHEALS, HEALTHNUTS also identified race as a risk factor for food allergy phenotypes. HEALTHNUTS reported that infants with one or both parents born in Asia, compared with those with both parents born in Australia, were at an increased risk of all 3 food allergy phenotypes. This further emphasizes the role of race and genetic background in the different phenotypes of food allergy. Together, this cohort further identified different food allergy phenotypes and risk factors associated with these classes. It emphasizes that a “one-size-fits-all” approach in both preventive medicine in averting food allergy as well as treatment options would not address the needs and risk factors for each phenotype.

### **Key highlights**

- Asthma at 4 years of age was twice as common in those with challenge-proven food allergy, irrespective of whether the child outgrew the food allergy.
- Those with 2 or more food allergies and coexistent eczema were almost 3 times more likely to develop asthma compared with those children without food allergy and those with a single food allergy.
- Vitamin D insufficiency was a risk factor for the 3 food allergy phenotypes (class 3–5) only among those infants with both parents born in Australia.
- Infants with one or both parents born in Asia, compared with those with both parents born in Australia, were at an increased risk of all 3 food allergy phenotypes.

### ***Protection Against Allergy Study in Rural Environments Study***

The Protection Against Allergy Study in Rural Environments (PASTURE) birth cohort included children from rural areas in 5 European countries: Austria, Finland, France, Germany, and Switzerland.<sup>23</sup> It was designed to evaluate risk and preventive factors for atopic diseases. Pregnant women recruited between 2001 and 2005 were divided into 2 groups: those living on family-run farms where livestock was kept (farm group) and those not living on a farm from those same rural areas (reference group). Altogether, 1133 children were included.

A latent class analysis was performed on 1038 of the children.<sup>24</sup> Consistent with other birth cohorts, they identified that early phenotypes of atopic dermatitis (onset before age 2 years) were strongly associated with food allergy, but late phenotypes were not. They also assessed IgE sensitization patterns within the first 12 months of life and maternal and environmental influences. Sensitization to foods was assessed by cord blood (infancy) and peripheral blood (ages 1, 4, and 6 years) to 6 foods. Food sensitization was more common in the farm group only at lower specific IgE levels. This study portrayed the influence of environmental factors on sensitization patterns and the possible alterations due to a modified immune response on production of specific IgE.<sup>25</sup>

### Key highlights

- Environmental factors, such as being on a farm, can alter food sensitization patterns through a modified immune response.

### DISCUSSION

Food allergy presents in different phenotypes in children, with each phenotype carrying varying risks for future allergic diseases. There are several birth cohorts that have tried to delineate these risks, including those risk factors predisposing infants to become allergic to begin with (Fig. 1). In this article, the authors detail 4 studies that highlight a portion of identified food allergy phenotypes. Each cohort is unique and significant in the field of allergy in its own way, contributing to different aspects from racial background to genetic risks and environmental factors. Together, they identify that food allergy and sensitization poses a risk for future allergic diseases but that it may not be in the pattern of the traditional atopic march as previously described.

A meta-analysis and systemic review aimed to assess the association of food sensitization and subsequent allergic diseases in birth cohort studies.<sup>26</sup> Their search



**Fig. 1.** Food allergy phenotypes/determinants. Figure details phenotypes detailed by allergy birth cohort data from 4 cohorts: WEHALS, CCAPS, HEALTHNUTS, and PASTURE. FA, food allergy.

revealed 13 cohorts across the globe. A common theme among these cohorts was that food sensitization in the first 2 years of life was related to eczema in late infancy, wheeze/asthma, eczema, or allergic rhinitis in childhood and asthma in young adults. Identifying sensitization patterns such as foods sensitized to, as well as predisposing factors such as family atopy, racial background, and living conditions can allow physicians to assess the predisposing factors for each patient and allow more personalized management of each child's food allergy. It can also allow physicians to provide anticipatory guidance to families on the possibilities of other allergic diseases such as asthma that may appear in their child.

Additional birth cohorts are needed to further detail these risks and possible role of interventions in preventing allergy in not only different ethnicities and genetic backgrounds but also varying living conditions to tie in the role of environmental factors with genetics. Overall, food allergy changes quality of life in and of itself and, with the addition of other allergic diseases, poses different risks in different groups of children.<sup>27</sup> It is imperative that physicians assess the role of food allergy in each infant and the different phenotypes in which it may present as to properly counsel each patient.

## SUMMARY

Longitudinal birth cohorts have identified previously undescribed food allergy phenotypes that pose different risks for future allergic diseases in children. They characterize different factors that place infant at risk for food allergies. Identifying these phenotypes allows physicians to risk assess each child who comes into the allergy office and also provide a management plan that is best fit for each different phenotype.

## CLINICS CARE POINTS

- Food allergy has several different phenotypes; identifying these phenotypes can allow physicians to provide better patient-focused care.
- Food sensitization patterns can identify which infants are at risk for future allergic disease, even in children who outgrow their clinical food allergy.
- Food allergy and sensitization is a strong risk factor for asthma, and physicians should consider counseling both groups of this risk.
- Racial disparities occur in food allergy, and it is important to consider a patient's racial background when assessing management protocols for not only their food allergy but also other allergic diseases.
- Identifying infants early on with risk factors such as food sensitization and atopic dermatitis can help give anticipatory guidance to parents on management of their child's care.
- Determining single food versus multiple food sensitizations can lead to better counseling for parents.

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## DISCLOSURE

The authors have nothing to disclose.

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