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The genetics of food allergy

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The term *food hypersensitivity* (allergy) refers to an adverse reaction mediated by specific immunologic responses to particular food proteins. Approximately 7% of children and 2% of adults suffer from food allergy [1]. The phenotypic expression of food allergy varies according to the foods involved, target organs, severity, chronicity, and underlying pathophysiology. The most common and best-characterized food allergy disorders are those mediated by food-specific IgE antibodies. This antibody also has a central pathophysiologic role in the disorders of the classical atopic triad: atopic dermatitis, asthma, and allergic rhinitis. When Coca and Cooke first coined the term *atopy* (“strange disease”) in 1923, the diseases under consideration did not include food allergy, but the current understanding suggests that food allergy also should be considered an atopic disorder. Food allergy most often is expressed in individuals and within families with other atopic diseases. Although much progress has been made on elucidating the genes responsible for asthma, immunoglobulin E (IgE) responsiveness, and atopic dermatitis [2,3], there has been relatively little progress on determining the genes that are responsible for food allergy.

Food allergy, like the other atopic disorders, is a complex trait with phenotypic expression that undoubtedly is based on multiple genes with major and minor influences. Like any human disease, the phenotype is influenced by gene–gene and gene–environment interactions. In approaching the genetics of complex traits such as food allergy, it is important to carefully define the specific phenotype under investigation. The success of linkage and association studies depends on numerous factors, most importantly the supposition that cases with the trait in question can be ascertained as cleanly and specifically as possible [4]. Once the disorder is defined appropriately, genetic dissection can proceed by first scouting for the impact of genetics on the expression of the disorder through genetic epidemiologic studies (eg, twin studies, relative risk assessment, segrega-

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tion analysis) and through DNA-based studies (eg, linkage and association). This article reviews the challenges in defining a food allergy phenotype, the progress in determining the genetic basis of food allergy, and the future directions for the investigation of the genes involved in this complex disease.

Food allergy phenotype

The basic immunopathology underlying food allergy can be divided broadly among disorders that are mediated by food-specific IgE antibodies (primarily manifested as acute reactions) and disorders that primarily are cell-mediated (resulting in chronic or subacute symptoms) [4–6]. A narrow definition of food allergy is complicated, because many disorders involve a variety of immunologic mechanisms. The food involved, target-organ reactivity, and other factors can modify the expression of the disorder [5]. Hypersensitivity to wheat serves as an excellent example of the myriad of manifestations of food allergy to a single trigger (Table 1).

Several authors have categorized food allergies by considering the pathophysiologic basis (IgE or not IgE-associated) and target organs affected [1,5,6]. Food-induced anaphylaxis is the prototypical IgE-mediated disorder and has a varied expression. Individuals can experience skin symptoms such as urticaria and angioedema; gastrointestinal symptoms such as vomiting, diarrhea and nausea; respiratory symptoms such as bronchospasm, laryngeal edema, and rhinitis; and cardiovascular symptoms such as shock. The question is whether the phenotype should be defined differently if an individual generally experiences only urticaria.

Several food allergy disorders occur without detectable IgE antibody (eg, transient gastrointestinal disorders in infancy and early childhood) [6]. Infantile proctocolitis is characterized by stools that contain mucous and bloody and localized eosinophilic inflammation of the rectum [7,8]. The disorder most often occurs in the context of the breast-fed infant whose mother ingests cow's milk protein. The symptoms resolve promptly following maternal dietary restriction, and the hypersensitivity generally resolves by age 1 to 2 years. A more severe form of non-IgE-mediated gastrointestinal food allergy that also presents in

Table 1
Examples of the clinical phenotypes of wheat allergy

Disorder	Organs affected	General pathophysiology
Anaphylaxis	Multiple	IgE
Food-associated, exercise-induced anaphylaxis	Multiple	IgE
Urticaria	Skin	IgE
Atopic dermatitis	Skin	IgE and cell mediated
Dermatitis herpetiformis	Skin	Cell mediated
Eosinophilic gastroenteritis	Gastrointestinal	IgE and cell mediated
Celiac disease	Gastrointestinal	Cell mediated
Baker's asthma	Lung	IgE

infancy is food protein-induced enterocolitis syndrome [9]. Symptoms include vomiting, diarrhea, and failure to thrive in infants who consume the causal food proteins, often cow's milk and soy and sometimes grains. Infants with this disorder become asymptomatic when the causal food protein is eliminated from the diet; however, re-exposure following complete avoidance results in a subacute onset of symptoms approximately 2 hours following ingestion. Symptoms include vomiting and diarrhea and sometimes progress to lethargy, dehydration, hypotension, acidemia, and methemoglobinemia [10]. This syndrome generally remits by age 2 or 3 years. Another infantile food allergy is food protein-induced enteropathy. These patients have a more indolent course without colitis and a lower incidence of emesis (30% versus 90%) than do patients with enterocolitis [11]. Some of these disorders can be confused (phenocopy) with IgE-mediated allergic reactions in which isolated gastrointestinal symptoms occur and can also represent a continuum of disorders with a similar underlying pathophysiology.

Several food allergy disorders do not fit into the categories of IgE or non-IgE mediated. A subset of indolent gastrointestinal disorders characterized by gut eosinophilia (eosinophilic gastroenteritis, eosinophilic esophagitis) is food-responsive. Some patients exhibit IgE antibody, whereas other patients do not; yet, subsets of each of these groups show resolution with dietary management [12]. Similarly, groups of patients with atopic dermatitis show either disease remission or exacerbation with dietary management, and subsets of each group either have or lack IgE antibody to potentially causal food proteins [13]. The role of food allergy in these disorders has been proven by using the gold standard of food allergy diagnosis: the double-blind, placebo-controlled, oral food challenge. Because only a subset of patients with these disorders has food allergy, these disorders represent phenocopies of food-allergic disease.

To complicate matters further, a number of additional features of food allergy disorders must be considered in defining particular phenotypes (Table 2). As mentioned earlier, one food may be responsible for multiple manifestations of food allergy, but conversely a single manifestation of food allergy can be

Table 2
Variables to consider in defining phenotypes of food allergy

Variable	Examples
Pathophysiology	IgE mediated, cell mediated Sensitization through gastrointestinal tract versus sensitization to homologous proteins in aeroallergens (pollen)
Severity	Single- versus multiple-organ involvement Respiratory and cardiovascular involvement Degree of end-organ response Dose of food-triggering reaction
Organ affected	Isolated versus multiorgan responses
Chronicity	Resolution of allergic response versus persistence Acute versus chronic symptoms
Foods involved	Type of food (eg, hen's egg, cow's milk) Number of foods

triggered by multiple foods. Environmental exposure is an obvious factor in terms of food-specific responses. A number of additional factors that may sway the phenotypic expression of food allergy have been proposed [14]. Assuming a given immunologic response (eg, IgE response to several proteins in milk), the reason that an individual may experience a variety of responses to ingestion of a food can be traced to variations in the absorption and deposition of the food protein and target-organ hyperreactivity. A clear example of this concept is the general positive correlation between reaction severity and amount of food ingested. A more elusive example is that the infant gut may be less capable of barring immunologically intact proteins from the blood stream compared with the mature gut (which may explain, in part, tolerance of certain foods as the child ages). The biochemical properties of food proteins also have a part in the phenotypic expression of allergy. The most common allergenic foods (egg, milk, peanut, tree nuts, fish, shellfish, soy, wheat) contain proteins that are resistant to degradation by heat and acid. Foods such as the peanut are particularly stable, but cooking methods can modify their allergenicities [15]. Once the food protein is circulating in the blood and can bind with IgE on mast cells and basophils, target-organ reactivity becomes key in directing the phenotypic expression. Individuals with underlying asthma are most likely to experience severe reactions that include a respiratory component [16].

The dichotomy between IgE and non-IgE-mediated allergy is not complete, but there are other immunologic parameters that also impact the phenotypic expression of food allergy. Pattern of epitope recognition is one such variable. Individuals who direct an immune response to particular segments of food proteins may be more likely to manifest enduring allergy [17]. T-cell homing is another factor that seems to have a role in the phenotypic expression and food-induced atopic dermatitis. Studies in children and adults have shown an increased expression of the skin-homing molecule cutaneous lymphocyte antigen (CLA) during *in vitro* stimulation of peripheral lymphocytes with implicated foods (compared with food-allergic controls without atopic dermatitis) [18,19]. The up-regulation of this homing molecule may account for the skin manifestation. Another immunologic factor to consider in defining phenotypes is the concentration of the food-specific IgE antibody that is produced. The amount of specific IgE antibody correlates with the likelihood of exhibiting clinical response [20].

The route of sensitization may be an environmental factor that contributes to the type of reactions seen. Most labile proteins in fruits and vegetables are poor sensitizers when ingested; however, homologous proteins in pollens can sensitize by way of the respiratory tract and result in later symptoms on ingestion of foods with the shared protein structures (seen in oral allergy syndrome and pollen-related oral allergy syndrome).

Although one arbitrarily could elect to study the genetic basis of any food allergy phenotype, there are likely some types that are easier to narrowly define and more likely to result in fruitful gene searches. Several strategies in gene hunting highlight the usefulness of narrowing the phenotypic descriptions and using more severe types [4]. Until more defining features are available

to differentiate potential phenocopies of food-related gastrointestinal disorders and atopic dermatitis, these disorders will be more challenging to consider. IgE-mediated food allergy is easier to define than most other food allergies, but there are issues of clinical manifestations on ingestion. Not all patients with egg-specific IgE antibody have clinical reactions on ingestion of egg; however, there is a correlation between the amount of food-specific IgE that is produced and the likelihood of clinical reactions [20], and this can be used as a phenotypic characteristic. Strategies for genetic dissection of food allergy may benefit from selecting probands with clinical reactions and evidence of IgE antibody, particularly when the allergy is stable (albeit, the stability of the allergic phenotype may be, in part, dependent on features of the allergen in question).

Genetic epidemiology of food allergy

T_H2 -directed cellular responses and generation of IgE antibody are at the heart of atopic disorders. Although these disorders can occur together at a higher frequency than they occur by chance, they often do so at a different time period in life (Fig. 1) [21]. Numerous studies have shown that food allergy is a strong predictor of other atopic disease and that these conditions coexist at a higher rate than expected. This fact is illustrated in a study of a birth cohort of 1218 children from the Isle of Wight in the United Kingdom [21]. These children were followed for up to 4 years of age, at which time the cumulative prevalence of atopic disease was 27%. Family history of atopy was the best predictor of atopic disease. At 4 years of age, sensitization to aeroallergens was more common in those children who had egg allergy before 2 years of age (59.3% versus 18.2%; $P < 0.0001$). Egg allergy in infancy was associated with increased respiratory (asthma, rhinitis)

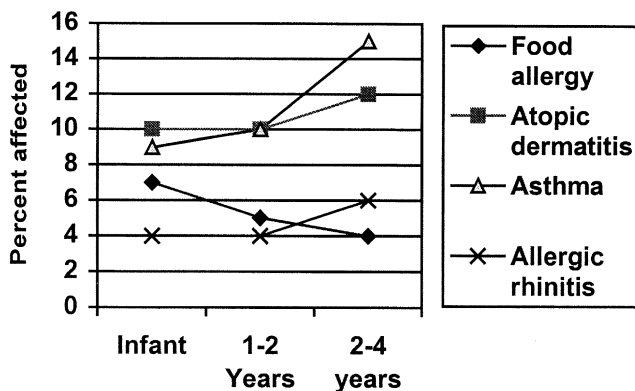


Fig.1. Manifestations of atopic disease in a birth cohort (1218) followed up to age 4 years (Isle of Wight, United Kingdom) [21]. Atopic disorders often coexist in individuals and among family members, but the age of onset and point prevalence vary according to age.

allergic disease (odds ratio [OR], 5.0; 95% confidence interval [CI], 1.1–22.3; $P < 0.05$) at 4 years of age, with a positive predictive value (PPV) of 55%. The addition of infantile eczema to egg allergy increased the PPV to 80%.

A number of other studies illustrate the link between food allergy and other atopic disease. A study subsample from the German Multi-Center allergy birth cohort study was evaluated to determine risk factors for aeroallergen sensitization at age 5 years. Sensitization to at least one of four food allergens in the first year of life had a PPV of 71% for later aeroallergen sensitization [22]. Children with persistent sensitization to foods (age, >1 year) produced significantly higher total IgE and specific IgE levels than did children who were only transiently food-sensitized by 2 years of age. Children who were persistently sensitized to food had a 3.4-fold higher risk for developing allergic rhinitis and a 5.5-fold higher risk for developing asthma than did children who were only transiently food-sensitized [23]. In another study, among 5149 individuals with peanut or tree nut allergy (median age, 5 years), the reported point prevalence of asthma was 46%, atopic dermatitis was 50%, and allergic rhinitis was 27% [24]. The strong association of food allergy and atopic dermatitis is illustrated by a study of children with atopic dermatitis that used blinded oral food challenges to determine the rate of food allergy [25]. The prevalence of food allergy in these children was 37%. It is clear that these various atopic disorders are associated.

Considering the coexistence of these atopic disorders within individuals and families, it can be surmised that many of the genes linked to the phenotypes for asthma and atopic dermatitis are also responsible for food allergy. The myriad of genes that were identified in linkage and association studies of asthma and atopic traits (eg, total and specific IgE) [2,3], are undoubtedly active in food allergy. Genes that are involved in the inflammatory response (eg, cytokines, chemokines, MHC cluster, Fc Epsilon R1- β , T-cell receptor α , T-cell receptor δ) as opposed to genes that are more organ-specific (eg, β -adrenergic receptor polymorphisms in asthma) likely are involved. Molecules that are active in the gastrointestinal processing of antigens and in modulating gastrointestinal immune responses may be unique candidate genes for food hypersensitivity.

Genetic basis of peanut allergy

Peanut hypersensitivity is a potentially useful food allergy phenotype in gene hunting. Whereas allergy to foods such as milk, egg, and soy resolve in early childhood, peanut hypersensitivity generally persists [26]. The stability of the phenotype is particularly secure once children are beyond age 2 or 3 years, because before those ages the allergy may remit in about 20% [27]. Still, compared with the 85% remission rates by age 3 for milk, egg, wheat, and soy allergy, peanut allergy represents a stable phenotype. Peanut allergy generally accounts for a narrow range of clinical symptoms. Unlike milk or wheat allergy, peanut hypersensitivity usually is manifested as acute, and often severe, anaphylactic reactions. Tests supporting its diagnosis are easy to perform, and at some

degree of high positive values of IgE, reactivity becomes likely. Peanut-specific IgE levels over 15 kU/L is highly predictive (>95%) of reactions [20], as is a large diameter in a prick skin test wheal [28]. Like other food allergies, however, there may be sensitization without clinical reactivity on ingestion of the food. Another concern about studying the genetics of food allergy is the influence of environmental exposure. Because peanut protein is common in the diet [29], can be passed in breast milk [30], and is a hidden ingredient in a number of processed foods [31–33], exposure essentially is guaranteed. In a study of 185 children, 50% of the children were exposed to peanut by age 12 months and 100% were exposed by age 24 months [34]. Overall, the narrow phenotype expression, stability of the allergy, ubiquity of environmental exposure, and ease of diagnosis make peanut allergy attractive for genetic studies.

Genetic epidemiology of population studies of peanut allergy

There has been a significant rise in the prevalence of atopic conditions in Westernized countries over the past 2 decades. There is an impression that peanut allergy also has increased, a fact that reflects the environmental aspects influencing the disorder. To estimate the influence of genetics on the expression of peanut allergy, it is helpful to estimate the relative risk (λ_R) for the disorder. Relative risk is defined as the recurrence risk for a relative of an affected person divided by the risk for the general population. The author undertook a prevalence study of peanut allergy in the United States by administering a random-digit dialing telephone survey [35]. Among 4374 households representing 12,032 individuals, the prevalence of peanut allergy was 0.6% (0.7% in adults and 0.4% for children under 18 years). Although the study was not designed to determine prevalence in relatives, 8.6% of probands had an affected first-degree relative living in the home (the total number of affected first-degree relatives was underestimated, because relatives outside of the home were not tallied). The prevalence of peanut allergy also was investigated in a survey in Great Britain. Similar to the US data, 0.4% of adults and 0.6% of children reported the allergy [36]. There was a high rate of additional relatives with the allergy in the same household (3.2%), and these were first-degree relatives in 90% of the homes. Allergy among relatives not residing in the same home as the proband was not determined. The rate of peanut allergy also was determined to be 0.5% in a birth cohort of children followed up to age 4 years on the Isle of Wight in the United Kingdom [37]. According to these population-based studies, the population risk for peanut allergy is 0.5%, and the relative risk is approximately 6.4 to 17.8.

Relative risk among siblings (λ_S) may be a better estimate of genetic impact, because generational environmental influences are reduced. Hourihane and colleagues investigated 622 subjects with peanut allergy in the United Kingdom [38]. It was determined that 0.1% of grandparents, 0.6% of aunts and uncles, 1.6% of parents, and 7.0% of siblings had peanut allergy. Assuming that the rate of peanut allergy is 0.5% in the general population, the relative risk among siblings is 14. The

estimated relative risk among siblings for peanut allergy is not as high as that seen in Mendelian traits (eg, $\lambda_S = 500$ for cystic fibrosis) but is relatively high for a complex trait (>10 is favorable for successful gene identification) [4]. In comparison, type I diabetes mellitus, which is considered an attractive target for complex trait analysis, has a similar relative risk among siblings.

Genetic epidemiology of peanut allergy: a twin study

Relative risk assessment is subject to the influences of environmental factors. One method to control for this confounding effect is to estimate heritability (variance in a phenotype that is genetically determined) by studying the frequency of shared disease between monozygotic and dizygotic twin pairs. Twin pairs are an advantageous study group because they generally are exposed to a similar environment, allowing the estimation of genetic and environmental causes of familial resemblance without a strong influence from the environment [39]. The procedure is predicated on the fact that monozygotic twins have all their genes in common, whereas dizygotic twins share, on average, only half of their genes. Under the assumptions of equal environment for both twin types, random mating, and no genotype–environment correlation or interaction, a greater similarity between identical versus fraternal twins is attributed to accumulated effects of several genes (additive genetic effects). Heritability of 100% indicates complete genetic influence and no environmental influence on a trait, and heritability of 0% indicates solely an environmental influence. Previous twin studies have estimated a high degree of heritability in atopic diseases, including asthma (87%) [40], atopic dermatitis (74%) [41], and allergic rhinitis (74%–82%) [41,42].

Through advertisements of the Food Allergy and Anaphylaxis Network, the author ascertained twin pairs in which at least one member had peanut allergy [43]. Individuals with peanut allergy, or parental surrogates, were interviewed by telephone. A full atopic history was obtained, and peanut allergy and zygosity were determined using previously validated questionnaires. Heritability of peanut allergy was determined using univariate genetic-model fitting by maximum likelihood with the Mx software package. Fifty-eight twin pairs were recruited in which there were members who had a convincing diagnoses of peanut allergy. Table 3 shows the number of twin pairs concordant and discordant for peanut allergy. Heritability of peanut allergy was estimated at 81.6% (95% CI, 41.6%–99.7%), with model fitting using a population prevalence of 0.4%. This result

Table 3
Concordance rate for peanut allergy among twins

Twin type	Concordant	Discordant	Concordance rate (%) ^a
Monozygotic	9	5	64.3
Dizygotic	3	41	6.8

^a $P < 0.0001$

was similar to that found in other atopic disorders and shows a strong genetic influence on peanut allergy.

HLA class II genes: candidate genes for peanut allergy

The HLA genes have a major role in regulating the immune response, and particular polymorphisms of these loci have a well-known role in predisposition to a large number of immunologically mediated diseases. In terms of allergic diseases, particular HLA class II alleles have been shown to influence specific IgE responses to several airborne pollens, mold spores, domestic animals, and house dust mite [44–50]. The most consistent associations have been determined when low-molecular-weight determinants are considered [51,52]. Only a few studies have considered immunologic responses to foods. The role of HLA class II molecules in celiac disease has been partially defined [53,54], and a role in milk allergy has been suggested [55].

Two studies have addressed the role of HLA in peanut allergy. A case report describing a single atopic, multiplex family in which four of five children had peanut allergy [56] found no linkage to T-cell receptor alleles, but peanut allergy segregated with paternal HLA. Another study determined the HLA class II genetic polymorphisms in individuals from 37 families in which at least one member had peanut allergy [57]. Fifty peanut-allergic individuals were compared with controls (34 nonpeanut-allergic siblings and 293 population controls). When the families with peanut allergy were considered as a whole and compared with population controls, there were significant associations with six alleles; when only the peanut-allergic individuals were compared with population controls, three of the associations remained. When peanut-allergic individuals were compared with sibling controls, only one allele (DBR1 *03) was associated weakly ($P=0.03$). The study offered some support for the association of HLA genotypes to peanut allergy, but the associations were weak and were not relevant in the analysis of affected siblings.

Future directions

It is clear that HLA class II specificities alone do not determine the phenotype of peanut allergy or any other particular food allergies. The biologic processes that result in food allergy likely involve genes that regulate antigen processing in the gut, the development of allergic immune responses, particular characteristics of target organs involved in the allergic response, and numerous other potential candidates. One candidate gene recently investigated is N-acetyltransferase 2 (NAT2) [58]. Polymorphisms in this gene are associated with fast and slow acetylator phenotypes, which are associated with variations in drug metabolism that impact drug efficacy and side effects. One hundred and thirty-six children with IgE-mediated food allergy were compared with 123 healthy children. The NAT2 alleles (*4, *5, *6, *7) were determined by polymerase chain reaction-

restriction fragment length polymorphism methods. A statistically significant increase in the proportion of homozygous slow acetylators (76.5%) was found among patients with food allergy compared with that in healthy subjects (53.7%; $P < 0.001$). The risk for development of IgE-mediated food allergy was 2.8 times greater (95% CI, 1.6–4.9) in slow acetylators. Unfortunately, atopic, nonfood-allergic controls were not evaluated, so the specificity of the association for food allergy is not proven. Nonetheless, the results were intriguing, because there were no homozygous fast acetylators within a subset of children with severe food allergy. This genotype may be an important factor in individual susceptibility to IgE-mediated food allergy.

The number of genes identified that have a role in atopic diseases continues to grow. Many of the same genes are responsible for food allergy, but there are likely to be additional genes at work, particularly genes associated with gastrointestinal immune responses. Improved allergy diagnostic methods and an expanded understanding of the molecular mechanisms of food allergy will improve identification of specific food allergy phenotypes for study and candidate genes to explore. These advances, in concert with improved methods for gene discovery and the completion of the Human Genome Project, likely will enable identification of the genes responsible for this group of disorders. Once the genes are identified, improved measures for food allergy diagnosis, prevention, and treatment can follow.

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