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5

Potential Genetic and Environmental Determinants of Food Allergy Risk and Possible Prevention Strategies

The increase in food allergy has captured the attention of the medical and research communities and the general public. Although the extent of the increase and the most affected countries are not accurately known, there is little doubt that immunoglobulin E (IgE)-mediated food allergy and anaphylaxis were rarely reported 50 years ago but are now commonly described (see Chapter 3). The prevalence of allergenic reactions to foods might differ by region of the world in part because of differences in exposures to specific foods. However, the drivers for this modern day epidemic in food allergy are poorly understood. It is not clear whether this phenomenon is part of the global rise in all allergic diseases at the end of the 20th century, or is due to a new set of unique factors, or to a combination of both.

Like other complex diseases, food allergy is thought to be caused by a combination of genetic and environmental factors. This chapter describes the state of the scientific evidence related to what are currently thought to be the most relevant genetic and environmental risk factors as well as genome-environment (GxE) interactions. The chapter starts with a discussion of the application of the developmental/ecological model (see Chapter 1) to food allergy risk factors. To that effect, a brief summary of the parallel development of the immune system of the child is included. The concept of atopic march[1] is briefly introduced as potentially important when considering prevention strategies. Although other immune-related diseases, such as eczema

[1] The atopic march refers to the idea that atopic disorders progress over time from eczema (i.e., atopic dermatitis) to asthma (see Box 5-2 and Figure 5-1).

(also known as "atopic dermatitis"), are often components of the atopic march that includes food allergy, not all people with eczema develop food allergy. Consequently, preventing eczema might not always decrease the risk of developing food allergy. Therefore, the committee decided to focus only on the relevant literature directly linked to the development of food allergy and findings associated with eczema alone are not included in this report. Also, the chapter concentrates on food allergy as an outcome except for a few risk determinants for which there are no data on food allergies. In these cases, the committee explored food sensitization[2] as a potential surrogate outcome. Although food sensitization is on the causal pathway for IgE-mediated food allergy, care should be taken in interpreting these results because food sensitization may be a nonspecific marker predisposition to atopy in general, not to food allergy in particular.

To provide context for the current scientific evidence on risk determinants, the methodological limitations of studies to date are explained. The pre- and postnatal environmental risk factors that might explain the development of food allergies have been grouped into emerging hypotheses: (1) microbial hypotheses (hygiene and old friends); (2) allergen avoidance hypothesis; (3) dual allergen exposure hypothesis; (4) nutritional immunomodulation hypothesis; and (5) other hypotheses. Each section on a specific determinant factor ends with a conclusion statement about the evidence supporting the link between exposure to the considered determinant and food allergies. At the end of the chapter, the committee provides their overall conclusions, recommendations, and research needs about strategies for preventing food allergies.

FINDING PREVENTIVE MEASURES: A DEVELOPMENTAL/ECOLOGICAL APPROACH

As described in Chapter 1, the committee approached its task from a developmental/ecological perspective. From the developmental perspective, the committee emphasizes the importance of *developmental timing* for exposures and for safety. In considering the risk determinants for developing food allergies, the committee focused on the different developmental periods—prenatal, early childhood, primary school-age, adolescence, adulthood, and elder years. In the prenatal period and first year of life, a fetus and infant's gut goes through substantial microbiome and immune developmental changes (see Box 5-1). This key period presents a window of opportunity to modify health outcomes at a time when infants are ready to

[2] Sensitization is a condition where an individual produces detectable immunoglobulin E (IgE) to a particular allergen. It can precede a food allergy reaction, but not all individuals with detectable IgE to a food allergen will experience a food allergy reaction.

BOX 5-1
Highlights of Early Development: The Microbiome, the Immune System, and the Gastrointestinal Barrier

Humans acquire their genes from their parents and when infants are born, they acquire their microbiome primarily from their mothers but also from medical staff, family members, and others. After birth, microbes colonize every epithelial surface of the baby and the microbiome matures until adulthood. The gut has specific receptors that are required to be present in order for microbes to be able to colonize the human host and in that way the microbiome and the immune system co-develop; some microbes play a critical role in maturation of the immune system as they induce pro-inflammatory or anti-inflammatory responses to maintain homeostasis of the immune system.

Although the immune system begins to develop through transfer of maternal immunoglobulins across the placenta, data suggest that immune dysregulation can occur at birth (Zhang et al., 2016) and that immune responsiveness can be detected as early as 22 weeks of gestation (Jones et al., 1996; Prescott et al., 1998). Another method of transfer of bioactive compounds from the mother to the child is through consumption of breast milk. A multitude of hormones, growth factors, neuropeptides, and anti-inflammatory and immunomodulatory agents can influence gut colonization by microorganisms (Goldman, 2000). At the same time, the microbiome produces signaling molecules that interact with the host. The baby also produces antibodies.

Infant feeding practices (i.e., use of formula versus breast milk) influence the succession of microbiota colonization (Adlerberth and Wold, 2009). During their first year, infants transition to solid food, which happens concurrently with a number of factors, such as an increasing ability to chew. Over the same period, oral immune tolerance (a state of systemic immune unresponsiveness to ingested allergens) ordinarily is acquired (Pabst and Mowat, 2012). A substantial increase in oral immune tolerance to food has been hypothesized to occur at the time of weaning (Prescott et al., 2008), possibly in relation to changes in microbial constitution and developmental maturation of the mucosal immune system (i.e., gut-associated lymphoid tissues, or GALTs).

The largest interface between the environment and the individual is the intestinal epithelium. Molecules can either be absorbed or secreted through this barrier. In a healthy state, it is necessary for the host to develop immune homeostasis in order to balance the need to respond to pathogens while maintaining suppressed responses against commensal microbial antigens and food antigens. For example, the epithelium and dendritic cells in the GALT have receptors that recognize specific molecular patterns on pathogens. Also, tight junctions between cells lining the small intestine appear to play a significant role in regulating epithelial permeability and are dynamic, in that they are able to adapt to a variety of developmental, physiological, and pathological circumstances. This is likely controlled through the first year of life in response to dietary and developmental changes (Fasano, 2000) and also is facilitated by the commensal intestinal microbiota, which is essential for the normal development of the GALT and maintenance of immune homeostasis (Hansen et al., 2012; Sudo et al., 1997).

begin eating solid foods. Due to the importance of this period in establishing the onset of food allergies, the scientific literature on food allergy risk factors has focused more on these early life stages and less on those changes that may occur in older children, adolescents, or adults. Therefore, while the committee's conclusions and recommendations were crafted through a developmental lens, they are limited by the preponderance of scientific literature on these early ages.

Food Allergies and the Atopic March

Within the developmental perspective, the committee considered the concept of the atopic march (see Box 5-2) in their deliberations. The atopic march refers to the idea that atopic disorders progress over time from eczema to asthma (see Figure 5-1). In fact, in some publications, eczema is viewed as a proxy for food allergies because eczema frequently precedes the development of food allergies. In fact, eczema and food allergies are distinct conditions with different etiologies and it is not appropriate to assume that eczema is a surrogate for food allergy. Although the concept of the atopic march is generally accepted, the interplay of the various related immune conditions is still being studied and, therefore, it would be premature to adopt the general idea that strategies to prevent atopic disorders that typically occur earlier in a child's development necessarily would also prevent the onset of food allergy. Additional prospective cohort studies with the appropriate methodologies are needed, particularly to understand the relationship between other allergic disorders and food allergy. Thus, the committee did not include other allergic disorders (i.e., wheeze, asthma, eczema, or allergic rhinitis) or their risk factors in their review of the evidence of potential determinants of food allergy.

METHODOLOGICAL LIMITATIONS

Current evidence about the risk factors associated with food allergy or sensitization is derived primarily from epidemiological (observational or ecological) studies. In addition to potential limitations in any research study—such as lack of generalizability, small number of samples, and inaccurate outcomes measurements—epidemiological studies need to be interpreted appropriately, with particular consideration to potential confounding factors and their careful adjustment. For instance, being at high risk of allergic disease could be a confounder when exploring the effects of breastfeeding in food allergies because high-risk families are more likely to follow guidelines, which might inform them about the putative protective effects of breastfeeding. If researchers do not adjust their analysis for family history of allergy (the main risk of allergy development), breast-

BOX 5-2
The Atopic March

A food allergy can coexist with a variety of other allergic conditions that share the same signs and symptoms. A systematic review reported that in individuals with food allergy, 35 to 71 percent also had evidence of atopic dermatitis, 33 to 40 percent also had evidence of allergic rhinitis, and 34 to 49 percent had evidence of asthma (Boyce et al., 2010). A food allergy also can be part of the temporal pattern in which an individual develops multiple allergic disorders. This pattern, called the atopic march, describes a process in which atopic disorders progress over time from eczema (i.e., atopic dermatitis) to asthma (see Figure 5-1).

In the context of risk determinants and prevention strategies, understanding the mechanisms that underlie the atopic march from infancy to adulthood (including whether the allergic disorders have a cause-and-effect relationship or simply share similar environmental and genetic causes) would be important when considering prevention options or when identifying individuals at risk. For example, if eczema early in life (age 0 to 12 months) is a risk factor for developing peanut and milk allergy as a child, health care providers might consider this when designing effective prevention strategies.

One hypothesis that might explain the atopic march is the dual allergen exposure hypothesis. This hypothesis identifies the epithelium of the skin, airways, and digestive system as the primary location where both allergic sensitization and (later) allergic reactions are initiated. The hypothesis proposes that genetically determined or environmentally induced abnormalities affecting the epithelium could be a common factor in the development of allergic diseases. For example, certain mutations in the gene that codes for filaggrin, a protein essential in maintaining epidermal homeostasis in the skin, result in an impairment of epidermal barrier function that predisposes to allergic diseases not only in the skin (i.e., atopic dermatitis) but also to allergies affecting other anatomical sites, namely, allergic rhinitis, atopic asthma, food sensitization, and possibly food allergy.

Although the concept of atopic march is widely accepted, the questions about the nature of the relationships continue to be the subject of many investigations and much debate. For example, the authors of a systematic review on the causal relationship between eczema and subsequent allergic disorders concluded that atopic dermatitis might contribute to the development of allergic rhinitis. However, they could not reach a similar conclusion for the relationship between atopic dermatitis and food allergies (Dharmage et al., 2014). Also, a recent review of systematic reviews of birth cohort studies was not conclusive on whether early life food sensitization leads to eczema and other allergic disorders (i.e., wheeze, asthma, or allergic rhinitis) (Alduraywish et al., 2016). In the opinion of the authors of that report, the main reason for this was the lack of studies in which confounding factors (early life eczema and wheeze) had been considered.

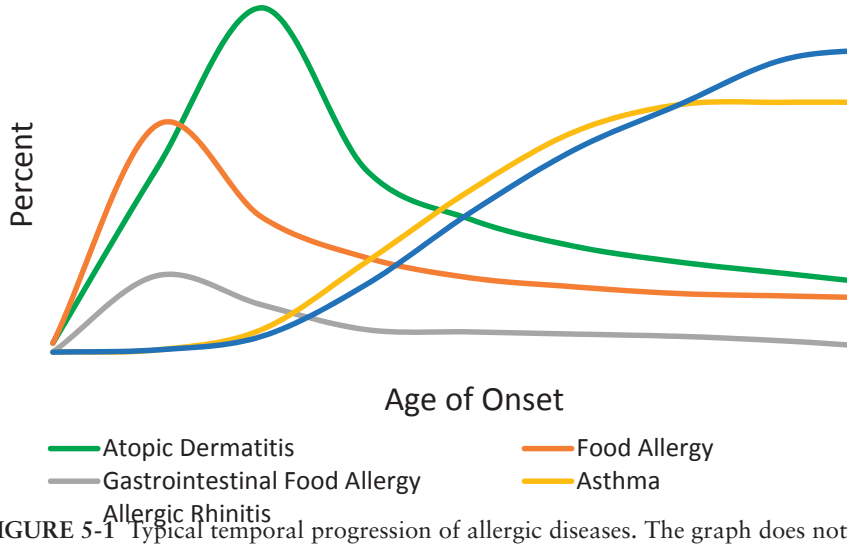

FIGURE 5-1 Typical temporal progression of allergic diseases. The graph does not include specific ages or percents on the x- and y-axis because it was not constructed from empirical data on the progression of immune-related diseases but from the concept of the atopic march, which needs to be studied further.

feeding can be misinterpreted as increasing the risk of allergic disease. This phenomenon is called "reverse causation" and is one of the reasons why randomized controlled trials (RCTs) are required to provide strong evidence that a factor is indeed causally related. Even with the best intentions, observational studies can be undermined by unmeasured confounders (i.e., residual confounding). High-quality data demonstrating causation should exist before recommendations are incorporated into public health guidelines. In most cases, this would mean RCTs. However, when evidence is not strong or trials are ethically difficult to mount (such as is the case for breastfeeding where randomization to a nonbreastfeeding arm would be unethical), clinicians need to interpret emerging or less robust evidence and provide carefully framed information to individual patients and their families to inform health decisions.

Until recently, food allergy has been less common than other allergic diseases. Therefore earlier allergy studies generally did not focus on food allergy as an outcome. It is only recently, as food allergy prevalence has increased, that attempts have been made to more precisely define and measure food allergy. Measurement methods have evolved from often inaccurate

self- or parent-reported data to better methods, such as the results of oral food challenges (OFCs). Recent literature, particularly after 2010, has more consistently reported food allergy outcomes using what is now regarded as the gold standard measurement—double-blind, placebo-controlled oral food challenge (DBPCOFC), in which the food is disguised so that neither parent nor health care professional knows whether the food or a placebo is being offered. Some experts have recommended that for children younger than 2 years, open OFC, in which foods in their natural state are offered (versus DBPCOFC) also can be included in the definition of gold standard because, in this age group, subjective symptoms do not complicate medical history and objective signs can be reliably used as endpoints.

Even DBPCOFC are limited by methodologic differences among studies (see Chapter 4). In addition, criteria for defining a positive oral challenge (i.e., a food allergic reaction) have not been formalized until recently (Koplin et al., 2012b; Sampson et al., 2012; see Chapter 4). Although most protocols state that a positive challenge is evidenced by an immediate reaction consistent with IgE-mediated food allergy, such as urticaria (hives), angioedema, or anaphylaxis, interpretation of more subjective symptoms, such as abdominal pain or nausea, or the more ubiquitous and less clearly defined sign of an eczema flare, remains difficult. Differences in criteria for defining a positive OFC across different studies and research centers hinders the ability to compare food allergy prevalence estimates among studies, to identify risk factors (because phenotypes might vary across different study cohorts), and to assess the success of different treatment strategies (including oral immunotherapy).

It should be noted, however, that performing large-scale OFCs is not always possible because of issues with compliance, risk to participants, and cost. As stated in Chapter 2, many population-based studies have relied on the detection of food-specific serum IgE (sIgE) antibodies as an indirect marker of food allergy, either alone or in conjunction with reported symptoms on ingestion of the food. These studies do provide insights into the temporal trend changes in food allergy prevalence, but should be viewed with caution when assessing risk factors for predicting food allergy owing to the high false positive rate and low specificity of this method. Self-reported measures tend to overreport food allergy due to the inability of individuals to distinguish between symptoms of food intolerance and food allergy. It is also not possible to employ reports from parents to determine allergic status to foods that have not yet been introduced into an infant's diet (see Chapters 3 and 4).

These methodological limitations, and specifically the outcome used to define the food allergy, and their implications for the interpretation of the studies reviewed herein, are noted in conjunction with the specific studies described in this chapter.

APPROACH TO LITERATURE REVIEW

Literature Search Strategy and Study Selection

Electronic literature searches of published systematic reviews (from 2010 to September 2015) and primary studies (from 2012 to September 2015) indexed in Medline, Cochrane Database of Systematic Reviews, EMBASE, and ISI Web of Science were conducted. The complete literature search and screening strategies, study selection flow, and study eligibility criteria are described in Appendix C. The committee based its literature search strategies on the systematic reviews by Marrs et al. and de Silva et al. and on selected individual papers published after those reviews (2012 and beyond) to develop its conclusions (de Silva et al., 2014; Marrs et al., 2013). Where appropriate, other systematic reviews also were considered.

Summary tables for all systematic reviews and studies conducted after 2012 are included in Appendix C. Ongoing trials of risk determinants of food allergy for which results were not available at the time of this publication are summarized in Table 5-1. Selected public health guidelines from various countries are listed in Table 5-2.

Grading the Evidence

For each factor described, the committee made a final conclusion statement considering the preponderance of the evidence collected, as described above. The committee used the approach taken by the 2015 Dietary Guidelines Advisory Committee to grade as strong, moderate, limited, or no grade (DGAC, 2015) (see Table 5-3).

GENETIC AND EPIGENETIC RISK FACTORS

The rise in the prevalence of allergic diseases has occurred more rapidly than can be accounted for by changes in genetic sequence (Tan et al., 2012b). Therefore, similar to other complex diseases, the rising prevalence of allergic diseases is likely due to environmental factors (i.e., the exposome).[3] In this way, the rise may be primarily occurring in those who are both genetically predisposed and exposed to the allergenic environment, as well as in those at risk through a heritable epigenetic mechanism from events that occurred when the parents of current children were in utero. Environmental exposures, including lifestyle and diet, interact[4] with genetic

[3] The exposome refers to all life course environmental exposures (including factors related to lifestyle, such as smoking or diet) from the prenatal period onward.

[4] An interaction is indicated when the simultaneous influence of two or more factors on a phenotype is not additive.

predisposition to modify the risk of disease. For example, the influence of the C-159 T polymorphism on the cluster of differentiation 14 (CD14) gene may be dependent on microbial stimulation from the environment (Lau et al., 2014), with individuals who carry the TT genotype demonstrating increased protection from eczema with exposure to dogs (Myers et al., 2010).

The concept of the epigenome,[5] which regulates gene expression and is largely established in utero, is relevant to early life origins of allergic disease. In contrast to deoxyribonucleic acid (DNA) sequences, which are relatively stable, the epigenome can be altered throughout the lifespan, but is particularly sensitive to environmental factors during early life periods (see Figure 5-2). Environmental factors that have often been considered in interaction with genetic risk factors include vitamin D (Koplin et al., 2016; Liu et al., 2011), smoking, air pollution, and microbial exposures (Tan et al., 2012b). Epigenetic considerations for other environmental factors, for which there is evidence of involvement in allergic diseases, have not yet been considered. It also would be useful to consider putative causative factors for food allergy, such as diet and food supplements, in relation to well-known genetic risks, such as filaggrin mutations.

A further consideration is the fact that these environmental risk factors may operate differentially based on the underlying risk category of the individual (i.e., genetic risk or family history, the more traditional form of risk stratification). As discussed below, evidence already exists of different responses to some environmental factors (e.g., vitamin D) based on a genetic risk factor (vitamin D receptor binding protein) (Koplin et al., 2016). In addition to biological variations, risk factors also may affect behavioral patterns, as has been described by Tey et al. (2014). The authors found that those with a family history of allergy were less likely to respond appropriately to guidelines revisions to introduce allergenic solids earlier in the diet of an infant. Future clinical practice guidelines and public health policy may need to take into account the way that a risk factor may differentially affect not only risk of disease, but also the behavior of the individual with a food allergy and/or their caregivers.

This section describes studies on the genetic and epigenetic factors that might affect food allergy outcomes.

[5] Epigenome refers to the chemical changes to the deoxyribonucleic acid and histone proteins (e.g., methylation) of an organism that occur through life and can result in changes to the structure of chromatin and to the function of the genome. These changes can be inherited through transgenerational epigenetic inheritance.

TABLE 5-1 Registered Randomized Controlled Clinical Trials and Observational Studies on Prevention

Study	Study Design, Country	Population	N	Age When Outcome Is Ascertained	Food Allergy Outcome Definition	Exposure	Question to Answer
BEAT (Beating Egg Allergy)	RCT, Australia	Infants with high risk of atopy, 4-6 mo		8 and 12 mo	Egg allergy assessment	Egg introduction versus placebo	What is the effect of early introduction of egg into the diet of infants at high risk of atopy and subsequent egg allergy?
CoFAR2	Observational, US	Children with egg and/or milk allergy, 3-15 mo	515	After 3 years of age	Peanut allergy		What is the development of peanut allergy in infants (3 to 15 months in age) with known milk or egg allergy?
EAT (Enquiring about Tolerance)	RCT, UK	Infants 3 mo	1,306	3 years		Early introduction of 6 allergenic foods together with breastfeeding versus standard introduction (6 months)	Does introducing certain foods early in a child's diet along with continued breastfeeding stop infants from developing food allergy?
STEP (Starting Time for Egg Protein)	RCT, Australia	Infants 4-6 mo without eczema but atopic mothers	1,500			Egg introduction versus placebo	

HEAP	Germany	Infants 4-6 mo	800	12 mo	Egg allergy	Egg introduction versus placebo	
PreventADALL (Preventing Atopic Dermatitis and Allergies in Children)	RCT, Norway	Infants		6, 12, 36, and 48 mo	Early food introduction by 3-4 mo	Food allergy to any intervention allergen (cow milk, peanut, wheat, egg)	Is primary prevention of allergic diseases possible by skin care and early food introduction?
PIFA (Pertussis Immunisation and Food Allergy)	Observational (case-control), Australia	Children 14-18 years		14-18 years	History of consistent clinical symptoms following ingestion of an implicated food and evidence of sensitization to that food by laboratory testing	Whole cell versus acellular pertussis vaccine	What is the possible food allergy-preventive benefit of using whole cell pertussis vaccination compared with acelluar pertussis vaccine for whooping cough vaccination in childhood?
VITALITY	RCT, Australia	Infants 6-8 weeks		12 months	Challenge-proven food allergy in study participants with positive SPT	Vitamin D (400 IU/day) versus placebo for 10 months	Can vitamin D supplementation in infants prevent food allergy in the first year of life?

continued

TABLE 5-1 Continued

Study	Study Design, Country	Population	N	Age When Outcome Is Ascertained	Food Allergy Outcome Definition	Exposure	Question to Answer
Early Life Origins of the Food Allergy Epidemic	Observational, Canada	Peanut-sensitized children, 4-10 years		5 years	DBPCOFC to peanut	Eating versus avoiding peanut	Does avoidance of peanut by children with positive SPT to peanut in the first 5 years of life increase the likelihood of developing a persistent peanut allergy by age 5 years?
The Cork BASELINE Birth Cohort Study (BASELINE)	Observational, Ireland	Infants		2 years		Incidence and prevalence of food allergy	What are the early life factors, including parental allergy, genetic susceptibility measured using fillagrin mutational status, skin barrier function, and vitamin D status and their effect on risk of eczema and food allergy in the first 2 years of life?

Probiotic Supplementation in Breastfed Newborn Infants	RCT, US	Infants, 1-7 days old, with intent to be exclusively breastfed for a minimum of 6 months	First 78 weeks of life	Levels of serum FABPs and glutathione-S-transferase (alpha-GST) will be measured as markers of GI permeability and potential food allergy; parental report of feeding intolerance	Probiotic supplementation versus placebo	What is the dose of a probiotic supplement (Bifidobacterium longum subsp. infantis) required to achieve predominant gut colonization in healthy newborn, breastfed infants? Does supplementation with this probiotic reduce the chance of developing eczema and food allergies in enrolled infants?
PROOM-3	RCT, Sweden	Pregnant women with at least one parent or a sibling with clinical symptoms or history of allergic disease and their newborn infants	6 and 12 months	IgE-associated disease measured by SPT (milk, egg, wheat, peanut)	Dietary supplementation with L. reuteri and omega-3 PUFA during pregnancy and postnatally versus placebo	Can supplementation with Lactobacillus reuteri and omega-3 fatty acids during pregnancy and lactation reduce the risk of allergic disease in infancy?

continued

TABLE 5-1 Continued

Study	Study Design, Country	Population	N	Age When Outcome Is Ascertained	Food Allergy Outcome Definition	Exposure	Question to Answer
Mis-BAIR (Melbourne Infant Study-BCG for Allergy and Infection Reduction)	RCT, Australia	Infants, younger than 10 days old		1 year	SPT and challenge-proven food allergy	BCG immunization for TB versus no immunization	Does BCG immunization at birth, compared to no BCG immunization, lead to a reduction in measures of allergy and infection in the first 12 months of life?
Molecular Basis of Food Allergy	Observational, US	Food allergic individuals ages 4 months to 75 years		Various			What is the molecular basis of food allergy? What are the genetic factors that lead to the development of food allergy?

NOTE: AU = Australia; DBPCOFC = double-blind, placebo-controlled oral food challenge; FABP = fatty acid binding protein; GI = gastrointestinal; IgE = immunoglobulin E; sIgE = food-specific serum IgE; SPT = skin prick test; TB = tuberculosis; UK = United Kingdom; US = United States.

Genetics

The role of genetics in food allergies was initially supported by its familial aggregation (Tsai et al., 2009) and heritability estimates derived from twin studies (Liu et al., 2009; Sicherer et al., 2000). Later, the ability to explore the genome opened the possibility to examine the involvement of specific candidate genes. More recently the potential for discovery of new loci has expanded with the use of genome-wide association studies (GWASs)[6] (Hong et al., 2015). However, unlike other diseases and phenotypes, for which hundreds of loci have been identified, the number of loci that have been tentatively associated with food allergies is still rather small.

As expected, most of these candidate genes encode products influencing immune mechanisms, including antigen presentation or a shift of the immune system toward a Th2 response. The hypothesis is that genetic predispositions may result in dysregulation of the immune system and, in the context of specific environmental factors, lead to food allergy. However, the association studies performed to date that have aimed to uncover the genetic architecture of food allergies have faced similar challenges as for other complex human diseases to date. Specifically, the identified loci can explain only a very small fraction of the phenotypic variance and few of the loci examined have provided conclusive and consistent findings across populations (see Table 5-4).

Only one GWAS has been reported in relation to food allergies (peanut, milk, and egg) (Hong et al., 2015). Two single nucleotide polymorphisms (SNPs) showed an association with peanut allergy that was above the GWAS threshold for significance, both of them in the human leucocyte antigen (HLA)[7] system. The first one, rs7192, is in the HLA-DR region and the second one, rs9275596, is located in the HLA-DQ region. Most interesting, both loci are also associated with differential DNA methylation. Therefore, these results support the relevance of the HLA system as well as epigenetic modifications in the predisposition to peanut allergy. In this study, though, the food allergy outcome was defined based on a convincing history of clinical allergic reaction on ingestion of a specified food and evidence of

[6] Genome-wide association studies (GWASs) examine many common genetic variants in different individuals to see if any variant is associated with a trait. GWASs typically focus on associations between single-nucleotide polymorphisms (SNPs) and traits like major diseases (Gottgens, 2012).

[7] The human leukocyte antigen (HLA) system is a gene complex located in chromosome 6p21 that encodes the major histocompatibility complex (MHC) proteins, which are cell proteins responsible for the regulation of the immune system. MHC class I, II, and III have different functions. MCH class I present peptides from inside the cell, MHC class II present antigens from outside of the cell to T-lymphocytes and stimulate the multiplication of T-helper cells. MHC class III are components of the complement system.

TABLE 5-2 Current Guidelines on Food Allergy Prevention

Guideline (reference)	Year	Country	Breastfeeding
Interim Guidance Regarding Peanut Introduction from the American Academy of Pediatrics; American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma & Immunology; and others[a] (Fleischer et al., 2015)	2015	US, Australia, Japan, European Union (EU)	

Early Introduction of Foods	Infant Formula	Diet of Mother	Prebiotics or Probiotics
Introduce peanut-containing products into the diets of "high-risk" infants early on in life (between 4 and 11 months of age) in countries where peanut allergy is prevalent. Infants with early-onset atopic disease, such as severe eczema, or egg allergy in the first 4 to 6 months of life (LEAP criteria) might benefit from evaluation by an allergist or physician to diagnose any food allergy and assist in implementing these suggestions of early peanut introduction.			

continued

TABLE 5-2 Continued

Guideline (reference)	Year	Country	Breastfeeding
NIAID/NIH-supported Guidelines (Boyce et al., 2010)	2010	US	Recommends that all infants be exclusively breastfed until 4 to 6 months of age, unless breastfeeding is contraindicated for medical reasons.
2016 Addendum to the NIAID/NIH-supported Guidelines (Togias et al., 2017)	2016	US	
World Health Organization and World Allergy Organization (WHO, 2003)	2003	Worldwide	Breastfeed exclusively until 6 months.

Early Introduction of Foods	Infant Formula	Diet of Mother	Prebiotics or Probiotics
	Does *not* recommend using soy infant formula instead of cow milk infant formula as a strategy for preventing the development of food allergy or modifying its clinical course in at-risk infants. Suggests that the use of hydrolyzed infant formulas, as opposed to cow milk formula, may be considered as a strategy for preventing the development of food allergy in at-risk infants who are not exclusively breastfed.	Does *not* recommend restricting maternal diet during pregnancy or lactation as a strategy for preventing the development or clinical course of food allergy.	
Suggests that the introduction of solid foods should *not* be delayed beyond 4 to 6 months of age. Potentially allergenic foods may be introduced at this time as well.			
	Infants with cow milk allergy should avoid cow milk proteins; if a supplement is needed, use hypoallergenic formula, if available, and affordable to improve symptom control.	No special diet for the lactating mother.	

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TABLE 5-2 Continued

Guideline (reference)	Year	Country	Breastfeeding
American Academy of Allergy, Asthma & Immunology (Fleischer et al., 2013)	2013	US	Exclusive breastfeeding for at least 4 and up to 6 months is endorsed.
European Academy of Allergy & Clinical Immunology Guidelines (Muraro et al., 2014)	2014	EU	Exclusive breastfeeding for at least the first 4-6 months of life is recommended.

Early Introduction of Foods	Infant Formula	Diet of Mother	Prebiotics or Probiotics
Complementary foods can be introduced between 4 and 6 months of age. Highly allergenic foods can be given as complementary foods once a few complementary foods have been tolerated first and should initially be given at home first rather than at day care or a restaurant.	For high-risk infants who cannot be exclusively breastfed, hydrolyzed formula appears to offer advantages to prevent allergic disease and cow milk allergy.	Avoidance diets during pregnancy and lactation are not recommended at this time, but more research is necessary for peanut. This recommendation does not apply to infants who manifest signs of allergic disease shortly after birth, because treatment may, in some cases, involve dietary interventions during lactation.	
Introduction of complementary foods after the age of 4 months according to normal standard weaning practices and nutrition recommendations, for all children irrespective of atopic heredity.	For high-risk infants: If a supplement is needed during the first 4 months, a documented hypoallergenic formula is recommended.	No special diet during pregnancy or for the lactating mother.	

continued

TABLE 5-2 Continued

Guideline (reference)	Year	Country	Breastfeeding
European Society of Pediatric Allergy and Clinical Immunology and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition (Agostoni et al., 2008)	2008	Europe	Exclusive or full breastfeeding for about 6 months is a desirable goal.

Early Introduction of Foods	Infant Formula	Diet of Mother	Prebiotics or Probiotics
There is no convincing scientific evidence that avoidance or delayed introduction of potentially allergenic foods, such as fish and eggs, reduces allergies, either in infants considered at increased risk for the development of allergy or in those not considered to be at increased risk. Complementary foods should not be introduced before 17 weeks and foods should be added one at a time to allow detection of reactions to individual components. It is prudent to avoid both early (<4 months) and late (>7 months) introduction of gluten and to introduce gluten gradually while the infant is still breastfed because this may reduce the risk of wheat allergy.			

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