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Genetics of Food Allergy

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Keywords

Food allergy; IgE-FA; genetics; epigenetics; human leukocyte antigen complex; filaggrin; ancestry; single nucleotide polymorphism (SNP); genome-wide association study (GWAS); multi-omics

"What is food to one is bitter poison to another." —*Lucretius (ca. 96 B.C.-55 B.C.), based on his observation of individual variations in adverse reactions caused by food allergy* [1]

Introduction

Food allergy (FA) is a complex disease of substantial public health concern; it affects ~8% of the pediatric population, and it is a common cause of anaphylaxis.[2] FA is the common cause of anaphylaxis in children, affecting up to 15 million people including 5 million children.[2–4] FA accounts for 3 million doctor visits, 125,000 to emergency room, 2,000 hospitalization and about150 deaths annually. The economic cost of food allergies is nearly $25 billion per year.[5] Food allergy (FA) is an adverse reaction to food (food hypersensitivity) occurring in susceptible individuals, which is mediated by a classical immune mechanism specific for the food itself. The best established mechanism in FA is due to the presence of IgE antibodies against the offending food. Food intolerance (FI) are all non-immune-mediated adverse reactions to food. The subgroups of FI are enzymatic (e.g. lactose intolerance due to lactase deficiency), pharmacological (reactions against biogenic amines, histamine intolerance), and undefined food intolerance (e.g. against some food additives). The diagnosis of an IgE-mediated FA (IgE-FA) is made by a carefully taken case history, supported by the demonstration of an IgE sensitization either by skin prick tests or by in vitro tests, and confirmed by positive oral provocation. For scientific purposes the only accepted test for the confirmation of FA/FI is a properly performed double-blind, placebo-controlled food challenge (DBPCFC). A panel of recombinant allergens, produced as single allergenic molecules, may in future improve the diagnosis of IgE-FA. Due to a lack of causal

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treatment possibilities, the elimination of the culprit <<food allergen>> from the diet is the only therapeutic option for patients with real food allergy. The basic immunopathology underlying food allergy can be divided into non-IgE-mediated (i.e. cell-mediated slow onset) and IgE-mediated (acute immediate reactions) FA.[6] The non-IgE-mediated food hypersensitivity encompasses non-immune mediated adverse reaction with delayed hypersensitivity whose mechanisms are less clear.[7] Such reactions include cell-mediated reactions that involve sensitized lymphocytes in tissues rather than antibodies.[8] The overall prevalence of cell-mediated reactions remains uncertain.[9,10] The most common non-IgE-mediated hypersensitivity reaction affecting all age groups of the population is celiac disease, also known as gluten-sensitive enteropathy, lactose intolerance due to histamine intolerance.[11] The IgE-mediated food allergy is the most common and life-threatening type of food allergic disorders.[12] It is also called immediate hypersensitivity reactions because of the short onset time between the ingestion of the offending food and the onset of symptoms.[3,8,13] Oral exposure to potential food allergens early in life is believed to promote tolerance, whereas cutaneous exposure through an impaired skin barrier promotes sensitization.[14] Tolerance is mediated by CD103+ dendritic cells in the gastrointestinal tract that bind to food allergens and migrate to mesenteric lymph nodes where regulatory T (Treg) cells are induced. In IgE-mediated food allergy, the induction and functioning of regulatory T (Treg) cells is believed to be compromised and the immune response is shifted towards the generation of T helper 2 (Th2) cells, leading to IgE class-switching in B cells.[15,16] The most common symptoms associated with IgE-mediated reactions involve the skin and may lead to anaphylaxis.[17,18] IgE-mediated mechanisms are also responsible for allergic reactions to pollens, mold spores, animal danders, insect venoms and other environmental stimuli.[19] Anaphylaxis is a severe and life-threatening systemic allergic reaction characterized by fall of blood pressure, upper airway obstruction, and difficulty breathing. IgE-mediated immunological reactions are the most important type of food allergy because these reactions involve a wide variety of different foods.[20]More than 170 foods are known to cause IgE-mediated food allergies. In the U.S., eight foods account for 90% of serious allergic reactions: milk, eggs, fish, shellfish, wheat, soy, peanuts, and tree nuts.[21,22] Hence, federal law requires food labels to clearly identify the food allergen source of all foods and ingredients that contain any protein derived from these common allergens (Food Allergen Labeling and Consumer Protection Act of 2004, Public L No. 108-282). To date, except strict avoidance, there are no effective curative treatments for IgE-mediated FAs.[23,24] This chapter primary addresses the genetics of IgE-mediated food allergy.

FA and the atopic march

The role of FA in the atopic march (progression of allergic diseases starting from infancy and typically includes atopic dermatitis, food allergy, allergic rhinitis, and asthma) is not well understood, but a strong association between FA and AD has been established.[25] Although the causal nature of this association has been debated, it is now generally accepted that cutaneous sensitization to food allergens is an important step in the development of FA, whereas exposure to food allergens through the oral route appear to promote tolerance.[26–28] Although FA sometimes precedes AD,[29] sensitization through an impaired non-lesional skin barrier before manifestation of AD has developed is likely a common route for food allergens. Indeed, skin barrier impairment at birth as measured by transepidermal water loss

predicts food allergy at age 2,[30] and one study found FLG genotype to be associated with sensitization to peanut allergen regardless of the presence of eczema.[31] Several rare monogenic disorders that are caused by genes involved in skin barrier formation and maintenance have been linked to FA. A well-known example is Netherton syndrome, caused by autosomal recessive mutations in the serine protease inhibitor Karzal type 5 (SPINK5).[32] The gene product of SPINK5, LEKTI, is involved in the regulation of desquamation. Netherton syndrome is characterized by defective cornification, chronic skin inflammation, impaired skin barrier, and multiple allergies, including FA.[33] Furthermore, the desmoglein 1 gene (DSG1) is involved in maintaining the structure of the epidermis, and loss-of-function mutations in this gene are the cause of severe dermatitis, multiple allergies, and metabolic wasting (SAM) syndrome. In addition to skin conditions such as severe psoriasiform dermatitis, ichthyosis and keratosis, elevated IgE levels and multiple food allergies have been observed in patients with SAM syndrome.[34,35]

The link between FA and monogenic inherited skin disorders further strengthens the case for cutaneous food sensitization through an impaired skin barrier as a causative event in the development of FA.[36] There are, however, also several monogenic diseases associated with FA that have been shown to be caused by mutations in genes involved in immune system responses. Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare disorder caused by mutations in the FOXP3 gene that leads to impaired development of CD4+CD25+ regulatory T cells. In addition to autoimmunity conditions, IPEX patients have a high risk of food allergies, AD, and elevated IgE levels.[37,38] Another example is the connective tissue disorder Loeys–Dietz syndrome, which is usually caused by mutations in TGFBR1 or TGFBR2. The resulting upregulation of TGFβ signaling appear to skew naïve CD4(+) T cells towards TH2 cytokine-producing cells, and patients have a strongly increased risk of all major allergic diseases, including FA.[39]

Food allergy and racial variation

Pediatric food allergy has increased tremendously over the past two decades and it is on the rise among all demographic groups.[40] However, its prevalence rates differ across ethnic groups.[41] Results from the NHANES indicated that the prevalence of FA is 4 times higher in African Americans (AA) than European Americans (EA).[42] AA children are reported to have an eightfold increase in the prevalence of peanut allergy as compared with the general U.S. pediatric population. AA individuals with FA have elevated levels of immunoglobulin E (IgE), peripheral eosinophilia, T helper 2 cytokines, and epithelial dysfunction as compared with EAs.[43–45] Recent studies showed that variants in several cytokine candidate genes that encode Th2-related molecules such as IL-4 and IL-13 show higher allele frequency in AA, suggesting that these alleles have been conserved to combat parasitic infections in Africans but not in Europeans.[46] This unique evolutionary trajectory might be the reason for high prevalence of allergic disorders in AAs.[47] Although AAs experience higher rates of FA prevalence and mortality than any other racial or ethnic group in America, few studies of FA have focused on this population, and almost all studies have predominantly employed EA samples. A PubMed search demonstrated that EAs are mentioned five times more often in various FA-related literature as compared with AAs. Bringing AA families into research will help to compare their results with those of other groups and to better understand the basis of

FA disparities.[48,49] It might help to unravel population-specific disease risk in the context of environmental exposure factors.[50]

Genetics and food allergy

Investigators study the genetics of food allergy for many reasons. First, some investigators study it to understand the evolutionary basis of our current population distribution of FA and its 'genetic architecture'. For others, such information provides insights into how malleable FA may be and what type of interventions may be most effective in altering population levels of FA. A second reason is the hope of identifying genes associated with increased risk of FA that can be used as prognostic factors to indicate who is likely to become allergic so that they can be given preventive therapy. A third reason is to identify genes that moderate the safety and/or efficacy of treatments. If we can identify such genes, then we are on our way to 'personalized medicine'.[51] Finally, among most biomedical researchers, the most common reason for wishing to identify genes that confer variations in FA is to identify physiologic 'pathways' through which FA develops so that such pathways can then be further studied and made targets for potential pharmaceutical intervention. Several experimental designs, including family, twin, and cohort studies, and analytic approaches, such as linkage analysis, candidate gene, genome-wide association, DNA methylation, and microbiome analysis have been used to study important questions such as: Why do some individuals develop FA and others do not? How do environmental and genetics factors interact to increase the risk of FA? A brief history of the search for genetic causes of FA are presented in Figure 1. Investigators screen the genome to locate regions contributing to variance (Box 1) in FA related outcomes.

Family-based studies

Family studies can address whether a disease aggregates in families. Such studies typically compare the prevalence of the disorder among first-degree relatives of affected cases to the prevalence in the population or among relatives of unaffected controls. A higher risk among relatives of cases indicates that the disease may be familial, but it does not necessarily mean that genes are involved; a disease may run in families for nongenetic reasons (i.e., a shared environment). Although environmental factors play a significant role in the onset of FA such as higher rate of food-related-health problems in lower-income children than higher income groups that might indicate the role of environmental exposure factors, the most widely used indicators of FA are familial aggregation and strong genetic component.[52–54].[54]

Twin-based studies

Twin studies compare the concordance rates of a disease between identical / monozygotic (MZ) twins (siblings who are essentially genetically identical) and fraternal /dizygotic (DZ) twins (who share on average half of their genes). Assuming that shared environmental influences on MZ twins are not different from environmental influences on DZ twins (the equal environments assumption), significantly higher concordance rates in MZ twins reflect the action of genes. Nevertheless, an MZ concordance rate less than 100% means that environmental factors influence the phenotype. The importance of genetic variants in FA stems from twin studies. A child with a parent or sibling with peanut allergy, one of the most common forms of FA, has a 7 times higher risk of having the condition than do children

without familial risk factors.[55] Twin studies have demonstrated that the concordance rate of 82% among monozygotic twins in developing peanut allergy far exceeds the concordance rate of 20% observed among di-zygotic twins .[56,57] In general, the heritability estimates for FA is as high as 81%.[58]

Association-based studies

Successful association studies require adequate sample sizes, and this can be difficult to achieve in GWAS studies in particular, where multiple testing corrections increases the number of participants required to reach significance. It is also important to have well characterized study populations with regard to demographics, and when recruiting from ethnically or racially heterogenous populations, this needs to be adjusted for in the statistical analyses using population stratification.

Accurate and consistent phenotyping of FA is essential to the success of gene association studies since differences in FA definitions and diagnostic methods can have a considerable impact on the results. FA prevalence vary widely depending on the diagnostic criteria, as demonstrated in a systematic review of European studies,[59] which found that the point prevalence of self-reported FA was 6-7 times higher than FA confirmed by oral food challenge (OFC). OFC in a clinical setting remains the gold standard for diagnosing FA, but while OFC is considered generally safe, it is not entirely risk-free, and can be associated with considerable discomfort for the patient.[60] A positive SPT and elevated specific IgE levels have low predictive value on their own but can confirm the IgE component of possible FA in the presence of a convincing clinical history. Greater SPT wheal size or higher specific IgE levels are associated with increased risk of FA, and a careful evaluation of clinical history together with a positive SPT wheal size or IgE levels above suggested cutoff levels may reduce or eliminate the need for OFC.[61]

Compared with the genetics of asthma, the genetics of FA is still a somewhat underexplored area. Studies with large and well phenotyped cohorts are needed to confirm results from earlier studies and to identify additional genetic associations, as well as to explore interactions with environmental factors. The results can help increase the understanding of the mechanisms behind the FA, and lead to the development of biomarkers for prediction and monitoring of FA.

Candidate-gene studies

Until recently, studies of FA-gene associations were mainly performed on specific candidate genes based on their known biological function. Hypothesis-driven studies of gene associations with food allergy have targeted well-known immune-related genes, some of which have previously been associated with other allergic diseases. A recent systematic review summarized results from both candidate gene association studies and genome-wide scans with different types of FA as outcomes.[62] Some of the genes that have been associated with FA in more than one study will be discussed. The human leukocyte antigen (HLA) system is important for the regulation the immune system and is encoded by a family of genes located in the major histocompatibility complex (MHC) gene complex on chromosome 6p21. Several HLAs belonging to the MHC class II (DP, DM, DO, DQ, and

DR), which present antigens from outside of the cell to T-lymphocytes, have been associated with various forms of asthma in a number of studies.[63] Several class II genotypes have also been shown to be associated with FA, and PA in particular. In a small study of based on peanut SPT and clinical history of peanut allergy, the genotypes DRB1*08, DRB1*08/12 tyr16, and DQB1*04 were found to be more frequent in peanut-allergic individual compared with controls.[64] The association between *HLA DQB1* and peanut allergy was also demonstrated in a Canadian study that found associations between it and DQB1*02 and DQB1*06:03P in a study population of European ancestry.

CD14 plays an important role in the innate immunity system as part of the protein complex that binds to lipopolysaccharide, a bacterial cell wall component. Several studies have examined CD14 as a candidate gene for FA. The CD14 SNP rs2569190 was associated with general FA in a racially mixed study population, and the association was found to be stronger when the analysis was restricted to white participants.[65] In a study of 53 children with peanut allergy and their peanut-tolerant siblings, rs2569190 was significantly associated with peanut allergy .[66] By contrast, the same SNP was not associated with FA in a Japanese study population.[67]

Interleukin-13 is a cytokine secreted by activated Th2 cells that plays a central role in allergic disease, and the association between the *IL-13* gene and asthma is well established. The association between *IL-13* and FA was explored in an Australian study of challenge-proven food allergic infants of European ancestry. The *IL-13* SNP rs1295686 was associated with FA in the discovery cohort as well as in an independent validation cohort and in a meta-analysis.[68] Moreover, the association appeared to be independent on the presence of eczema. Interestingly, no evidence that any of the variants tested increased the risk for FA when comparing food allergic cases to food-sensitized tolerant children, and there was an association with increased plasma IgE levels, which suggests that the association between *IL-13* and FA may be mediated by food sensitization. In a Japanese study of associations between FA and 26 loci previously linked to AD and EoE, an association between rs1295686 was seen regardless of eczema comorbidity.[69]

Several studies have found associations between FA and signal transducer and activator of transcription 6 (*STAT6*), a gene encoding a transcription factor that plays a role in IL4-mediated responses. *STAT6* genotype has been shown to be associated with general nut allergy in a study using participants of European ancestry,[70] and the association was later validated at the gene level in a Japanese population. The *STAT6* SNPs rs324015 and rs1059513 were found to be associated with challenge-proven FA as well as peanut allergy in a family study of 369 trios that included 262 children with FA. Both SNPs were also associated with more severe FA symptoms. In a recent case-control study of a West Bengal Indian population the *STAT6* SNP rs3024974 was not significantly associated with FA. There was, however, an association with food-specific IgE levels in individuals with childhood onset, but not adult onset, of FA.[71]

As discussed above, entry through an impaired skin barrier is believed to be a common route of sensitizing food allergens, and genes involved in maintenance of the skin barrier have been investigated for associations with FA. The barrier gene filaggrin (FLG),in particular,

has been investigated as a candidate gene and found to be significantly associated with peanut allergy[72] and general FA.[73] In the latter study, path analysis indicated that the effect of FLG-LOF mutations on FA risk was indirect and mediated by eczema and allergic sensitization to foods, suggesting that the association between FLG and FA can be explained by the increased risk of sensitization through a faulty skin barrier in individuals with FLG mutations. Similarly, in a study of peanut allergy, the association between FLG-LOF mutations and FA-sensitized but tolerant children was similar to the association between FLG-LOF mutations and food-sensitized children with FA, though the power to detect a difference was somewhat limited.[74]

As already mentioned, the gene product of SPINK5, LEKTI, is involved in the maintenance of the skin barrier, and several mutations in the SPINK5 gene have been associated with Netherton syndrome. In addition, the SPINK5 variant rs9325071 has been found to be associated with challenge-proven FA in an Australian candidate gene study of 12-month old infants, and the association was replicated in an independent study population.[75] Notably, the association remained in both study populations when the analysis was restricted to children without eczema.

Genome-wide association studies

The strength of genome-wide agnostic approaches is the ability to identify novel loci without an a *priori* biological hypothesis. Corrections for testing very high numbers of loci can, however, make it difficult to reach statistical significance, and necessitates large study populations. Recently, several GWAS of FA has confirmed some associations with genes previously identified using candidate-gene studies, and in addition, novel candidate loci have been discovered. The first GWAS to specifically investigate FA, as well as peanut, milk, and egg allergy, confirmed the association with HLA-DR and HLA-DQ in peanut allergy and identified specific loci in a region at 6p21.32 tagged by rs7192 and rs9275596.[76] These associations were replicated in individuals of European, but not non-European, ancestry. Interestingly, in a genome-wide scan of DNA methylation it was found that differential DNA methylation at 72 different loci were associated with one or both of rs7192 and rs9275596, and, furthermore, there was a difference in methylation levels between peanut allergy cases and controls at 18 of the differentially methylated positions. Further evidence of a role for HLA-DQ in peanut allergy came from a German GWAS of FA diagnosed by OFC in 497 cases and 2387 controls of European ancestry.[77] FA was stratified by food-specific allergy (egg, peanut, and milk), and it was found that loci centered on rs9273440 in the HLA-DQB untranslated 3'-region was specifically associated with peanut allergy. By contrast, loci in the epidermal differentiation near the filaggrin genes on 1q21.3 was associated with any FA unstratified for type, and the association was shown to be due to known LOF mutations in *FLG*. Loci in Serpin Family B Member 7 (SERPINB7), a region centered on rs11949166 between the interleukin 4 gene (IL4) and the kinesin family member 3a gene (KIF3A), and the locus were also associated with risk for any FA. All three loci have previously been implicated in allergic disease. Notably, the associations with FA was observed regardless of the presence of eczema in all 5 loci identified in the study except C11orf30/LRRC32.

To explore novel gene associations with peanut allergy, Asai et al. recently performed a GWAS on a Canadian group of patients as well as a meta-analysis of 7 studies from Canadian, American, Australian, German, and Dutch populations of varied ethnicity.[78,79] In the main GWAS analysis, only HLA SNPs and rs115218289, an imputed SNP located close to Integrin α6 (ITGA6), reached genome-wide significance. Conditioning on the top HLA SNP located upstream of HLA-DQB1, rs3134976, identified additional SNPs near the T cell adapter protein Src Kinase Associated Phosphoprotein 1 (SKAP1) and Catenin Alpha 3 (CTNNA3). In the meta-analysis of any FA, rs7936434 near *C11orf30* reached genome-wide significance. Loci that were suggestive of significance with both FA and peanut allergy in the meta-analyses included rs115218289, rs523865 in Angiopoietin-4 (ANGPT4), rs144897250 near Matrix metalloproteinase-12 (MMP12) and Matrix metalloproteinase-13 (MMP13), and rs78048444 near Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 3 (CHCHD3) and Exocyst complex component 4 (EXOC4). There were variations in phenotype definition ranging from self-report to food challenges among the studies included in the meta-analyses. Notably, the results differed between populations, and the association between FA and rs7936434 when the study using an FA definition based on self-report was excluded.

One genome-wide study of FA associations made use of copy number variations (CNVs), which are common genomic alterations, as molecular markers.[80] CNVs in the cell adhesion gene Catenin Alpha 3 (*CTNNA3*) were significantly associated FA in a discovery cohort of 357 cases with confirmed FA and 3980 controls, and the association was confirmed in an independent replication cohort. CNVs in Fox-1 homolog A (*RBFOX1*) were significantly associated FA in a meta-analysis of participants of European ancestry. Figure 2 lists variants and genes for which statistically significant (or suggestive) association has been found in several independent studies with food allergies, yet the truth of whether these studies are associated with, let alone cause, FA still remains questionable in most cases.

Epigenetics and contributions from the environment in FA

The dramatic rise in FA cases over the past 50 years is more likely due to alterations in the environment rather than to changes in the gene pool. Environmental factors such as the physical environment, the social environment, and the economic environment have all presumably contributed to an increase in the prevalence of FA. The association of putatively influential environment factors on FA has been demonstrated in studies on twins with a high genetic predisposition to FA. Further evidence of environmental effects has come from studies showing that emigrants to the United States usually showed marked differences in the incidence of allergy compared to their counterparts who remained in their native countries. These observations also show the relationship between our genes and the environment.

Among environmental factors implicated in FA are dietary habits, vitamin D intake, exposure to food allergens, pollution, and hygiene-related factors, including pet exposure.[60,81] The gut microbiota is part of the total exposome, and is influenced by components in the external environment, such as diet and the environmental microbiome. Early life dysbiosis has been associated with FA,[82] and further evidence of a role for the gut

microbiota in FA has been provided by studies in mice (40, 41, 42). Environmental factors can modify risk of disease in genetically predisposed individuals, and gene-environment (GxE) interactions are believed to be important for the risk of allergic disease (Figure 3). Although GxE interactions have been studied extensively in asthma,[83,84] the literature is more sparse for other allergic diseases, and very few studies on interactions between genes and environmental factors in FA have been published to date. The association between challenge-proven FA and low serum 25-hydroxyvitamin D_4 levels have been shown to be modified by a polymorphism in the vitamin D–binding protein (DBP) in such a way that the association was only found in the genotype associated with higher serum DBP levels.[85] Since high DBP levels decrease the vitamin D bioavailability, the results are consistent with vitamin D deficiency as a risk factor for FA. Another example of an interaction between genotype and an environmental variable is a study of peanut allergy which demonstrated a modifying effect of peanut allergen levels in dust on the association between FLG and both peanut sensitization and allergy.[86] Interestingly, the interaction was significant when adjusted for atopic dermatitis.

In recent years, evidence has accumulated indicating that environmentally induced epigenetic changes in the DNA of target genes is an important mechanism mediating GxE interactions. In particular, DNA methylation at loci of genetic variation can lead to a variable response to an environmental exposure depending on genotype. Although there are few demonstrated examples of associations between FA and genotypes being modified by environmental factors, several studies have linked DNA methylation to the risk of FA. As already mentioned above, two SNPs in the *HLA-DQ* and -*DR* genomic region significantly associated with peanut allergy in a GWAS were also found to be associated with differential methylation at multiple CpG sites.[76] In an epigenome-wide association study of methylation in CD4+ T-cells from 12 children with FA to egg or peanut and 12 age-matched controls, 153 CpG loci differentially methylated at birth and 179 differentially methylated at 12 months of age were identified.[87] A total of 136 loci were common to both time points. Of these, 44 loci were located within 10 base pairs of single nucleotide polymorphisms, and these loci were annotated to *HLA-DQB1*. Differentially methylated loci that were not associated with SNPs were annotated to 49 different genes. These were subjected to pathways enrichment analysis, which suggested enrichment of the KEGG pathway “MAPK signaling pathway”, a pro-inflammatory pathway with many different roles, including T cell development and differentiation.

A recent study explored transcriptomic and CD4+ T-cell epigenetic associations with reaction severity in 21 peanut-allergic children during double-blinded peanut challenges.[88] Among genes for which expression changes during challenge was significantly associated with reaction severity, 318 were replicated in an independent cohort of 19 peanut-allergic children. Gene ontology analysis on the 318 genes found them to be associated with regulation of nitric oxide processes, neutrophil activation, and macrophage activation, among other processes. Moreover, the association between reaction severity and 203 differentially methylated CpG sites were replicated in the independent cohort, and these CpG sites mapped to 197 unique genes. Four of the severity-associated CpG sites were located within 10Mb of a gene with severity-associated expression, and causal mediation analysis indicated that expression of PHACTR1 and ZNF121 mediates the association

between reaction severity and methylation of the associated CpGs. Interaction networks with the differentially expressed genes and the severity associated CpGs identified *NFKBIA* and *ARG1* as key hubs.

DNA methylation has been shown to be associated with immune tolerance in children undergoing oral immunotherapy for peanut allergy. In a study of 23 patients with peanut allergy undergoing oral immunotherapy and 20 controls with peanut allergy receiving standard of care and abstaining from peanut, participants who were immune tolerant to peanut 3 months after therapy withdrawal had decreased methylation of *FOXP3* CpG sites in antigen-induced regulatory T cells relative to the baseline before immunotheraphy.[89] No change in methylation was seen in controls or participants who remained non-tolerant after the treatment period. The changes in methylation in immune tolerant participants were accompanied by increased expression of *FOXP3* in antigen-induced regulatory T cells. The results add support to previous studies showing a role for regulatory T cells in the response to immunotherapy.[90]

Genome-wide DNA methylation profiling has also been used to develop signatures that can predict clinical outcomes of FA. Using DNA from peripheral blood mononuclear cells in whole blood, a signature of 96 CpG sites was found to predict response to oral food challenge better than skin prick testing and allergen-specific IgE levels in 58 food-sensitized children aged 11-15 months and 13 non-allergic controls.[91] The results were validated using CD4+ T cells from an independent cohort. Studies of epigenetic changes in FA can contribute to our understanding of the pathways involved in the development of FA, and the interplay between genes, epigenetics, and environmental factors. More studies are needed to validate and replicate earlier results, and to explore the role of environmental factors in triggering changes in methylation patterns and other epigenetic alterations.

Genomic information is measurable and well established while phenotyping and environmental exposures are less well standardized. As we move forward, deep phenotyping (e.g., oral food challenge (OFC)) will be limiting. In the future, multi-layer and longitudinal data, detailed measures of environmental exposures, detailed and standardized clinical information, combine genetic, race, clinical and environmental information as well as GxE interactions in risk prediction and leveraging big genomic data in racially diverse population could pave the way to personalized genomic medicine in cost effective way.[92] Precision medicine in FA requires precise inference of genetic ancestry.

FUTURE RESEARCH AND DIRECTIONS

Rapid progress in molecular genetics has increased our knowledge of the genomes of humans and other organisms and led to more detailed research into the genetic elements of allergy. Common human diseases such as FA are complicated by multiple factors (Box 1): phenocopies, genetic heterogeneity (both locus heterogeneity and allelic heterogeneity), trait heterogeneity, gene-gene interactions, gene-environment interactions, and factors such as admixture.[93–95] Future research into FA can be expected to include analyses of gene-gene and gene-environment interactions as well as transcriptome-wide expression studies that estimate the differences in the expression of genes under diverse environmental conditions.

Gene-gene interactions, also known as epistasis, refers to the expression of phenotypes only when specific alleles of two or more genes are present. Additionally, genomic studies have been expanded to include variations in DNA structure (Box 1).

Admixture mapping

It is well known that disease does not affect populations equally. This is because different populations are subject to distinct environmental exposure. Natural selection during the out-of-Africa expansion[96] may produce population-specific allele frequencies. Assessing variation in the rates of disease according to demographic factors, such as race or ethnicity, is the basis of epidemiologic research and affects clinical and public health practice.[97] The association between increased FA risk and African ancestry and the admixed nature of the African-American population suggests that admixture mapping might be an important FA gene-finding strategy to study directly genetically heterogeneous populations of African American nature.[98] Admixture mapping involves screening the genome of individuals of mixed ancestry who have a disease for chromosomal regions that have a greater percentage of alleles from the parental population with the higher disease risk.

Multi-omics approach

With the advent of omics-based big data-driven and unbiased approaches to define and characterize endotypes, including more accessible tools for human immunophenotyping, we can now gather detailed molecular information to de-convolute and identify patterns from the data, and gather further insights into the biology of diseases and health states of individual patients.[99,100] Statistical methods to integrate multi-omics data are emerging to provide important insights into disease pathophysiology of allergic diseases.[101] For example, machine learning approach uses computer algorithms to identify patterns from the systematically collected large molecular profile data, and along with clinical metadata, can assist personalized treatments for effective management of food allergies with similar molecular subtypes.[102,103] The increasing focus on multi-omics is expected to play an important role in the development of personalized medicine approaches that takes racial ancestry into account. It needs to be stressed, however, that any racial differences identified using proteomics, transcriptomics, or epigenetics can be expected to be modified or confounded by environmental factors associated with ancestry, given the profound influence of the environment on epigenetics and gene regulation.[104] Genomics can provide deep insights into the genetic drivers of food allergy, while transcriptomics sheds light on dysregulated gene regulation, and proteome provides deeper insight into what is going on at the molecular, tissue, and whole-body level.

Although racial disparities have been noted in the prevalence of FA, determining the relative contribution of ancestry-specific genetic risk factors from environmental factors has proved to be challenging because of the limited number of studies performed on African American and other minority populations.[105] The delineation and deconstruction of shared and unique biologic and genetic pathways among atopic disorders and ancestry-specific gene-environment interactions can help resolve the clinical complexity and better inform the development of novel therapies.

Future research should include deep phenotyping of diverse ancestral populations, better characterization of environmental determinants, and the application of new technologies utilizing "-omics" tools. These include next-generation sequencing, epigenetics, and eQTL approaches in appropriate tissues/cells along with publicly available bioinformatics and ancestry tools. Systematic integration of "big data" coming from providers (e.g., EMR), from omics (e.g., genomic, proteomic, epigenomic, metabolomic), and from multi-ethnic patients and non-providers (e.g., smart phone, monitoring tools for environmental triggers) can thus provide valuable insights to resolve the clinical complexity and ancestry-specific (or shared) etiology of food allergy.[106–109]

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Synopsis

The risk factors for food allergy (FA) include both genetic variants and environmental factors. Advances using both candidate-gene association studies and genome-wide approaches have led to the identification of FA-associated genes involved in immune responses and skin barrier functions. Epigenetic changes have also been associated with the risk of FA. Little is known about possible modifying effects of genetic variation on the associations between environmental factors and FA. In this chapter, we outline current understanding of the genetics, epigenetics and the interplay with environmental risk factors associated with FA. Future studies of gene-environment interactions, gene-gene interactions, and multi-omics integration may help shed light on the mechanisms of FA, and lead to improved diagnostic and treatment strategies.

Box 1.

Definitions of genetic and genetic related terminology.

Variance: a measure of statistical dispersion indicating how far values typically are from the distribution's mean

Genome: complete set of genetic information for an individual.

Epistatic variance: variance due to interaction among alleles at different loci (gene-gene interactions.

Heritability: the proportion of population variance in a trait attributable to segregation of a gene or genes (overall phenotypic variation/risk that is attributable to genetic factors).

Gene-gene interaction: when two or more DNA variations interact either directly (DNA–DNA or DNA–mRNA interactions), to change transcription or translation levels, or indirectly by way of their protein products, to alter disease risk separate from their independent effects.

Gene-environment interaction: when a DNA variation interacts with an environmental factor, such that their combined effect is distinct from their independent effects. An interaction is indicated when the presence of one factor (eg, diet) affects the influence of the second factor (eg, genetic) on disease risk.

Phenocopy: the presence of a disease phenotype that has a non-genetic (random or environmental) basis.

Trait heterogeneity: when a trait has been defined with insufficient specificity such that it represents at least two distinct underlying traits.

Genetic heterogeneity: the production of the same or similar phenotypes (observed biochemical, physiological, and morphological characteristics of a person determined by his/her genotype) by different underlying genetic mechanisms.

Race: group based on physical attributes, a social construct; no biological basis.

Ethnicity: group based on culture, language, physical attributes, religion, country of origin.

Ancestry: group based on DNA-- line of decent.

Admixture: interbreeding among different ancestry populations.

Candidate gene association studies: Targeted studies of association between selected genes of interest and a phenotype.

Genome- wide association studies: genetics research to associate specific genetic variations with particular trait.

Copy number variation: a sequence of bases within a genome differs in the number of copies among individuals or populations.

Population structure or population stratification: The presence of differences in allele frequencies between subpopulations in a population.

Next- generation sequencing: an entire genome is sequenced from fragmented DNA, producing short (less than 300 bp) sequencing reads at high speed and low cost.

Single- nucleotide variants: a single base within a read or genome differs from the base found at the same position in other individuals or populations.

Meta-analysis: A routine approach to combining smaller GWAs using summary statistics/results to overcome the smaller sample sizes of individual studies.

Fine mapping: A set of statistical and laboratory approaches to determine the causal genetic variant for associated genetic loci.

Key Points

- Food allergy (FA) is a growing clinical and public health problem in the U.S. and worldwide.
- The development of FA likely results from complex interactions between multiple environmental and genetic factors.
- Although the genetics of FA are somewhat understudied, advances have been made in recent years using both candidate gene association studies and agnostic genome-wide approaches.
- Most genes found to be associated with FA are involved either in immune responses or in skin/epithelial barrier functioning, with filaggrin and genes in the human leukocyte antigen complex being among the most studied.

Clinics Care Points

- Food allergies are increasing and are a global health problem.
- IgE-mediated food allergies are the most common type of allergic reaction to food.
- Multiple studies suggest higher rate of food allergen sensitization in African American than European American children.
- Risk factors for the development of food allergy include parental history, atopic diseases particularly atopic dermatitis (AD), which can lead to the development of the atopic march through mechanisms of cutaneous sensitization.

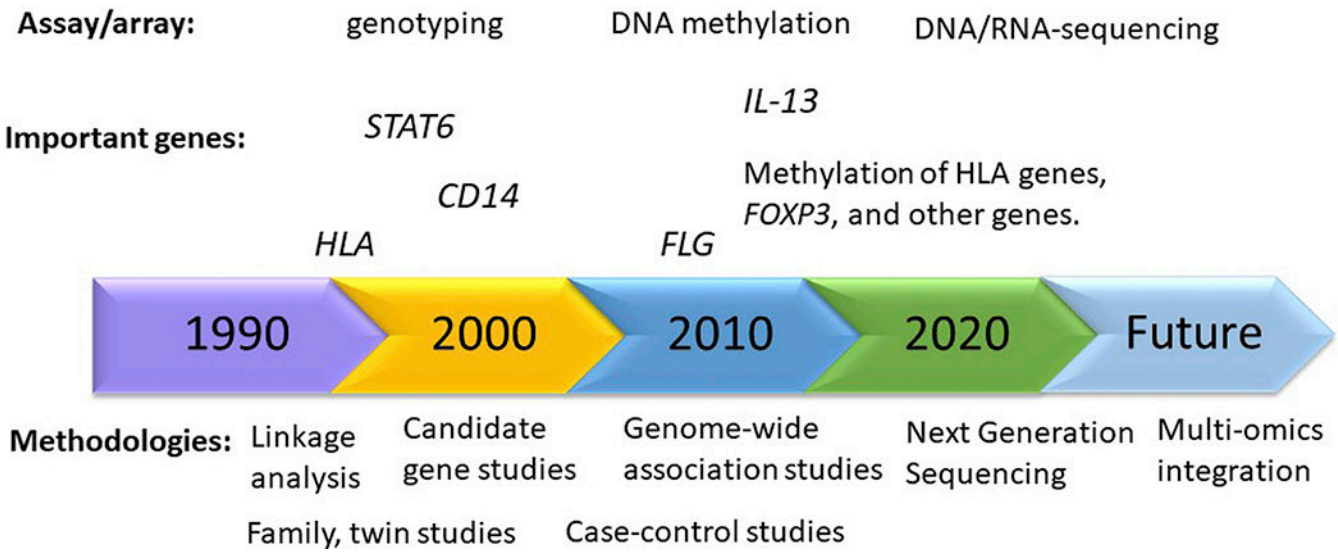

Figure 1.
A brief history of the search for genetic causes of food allergy (FA).

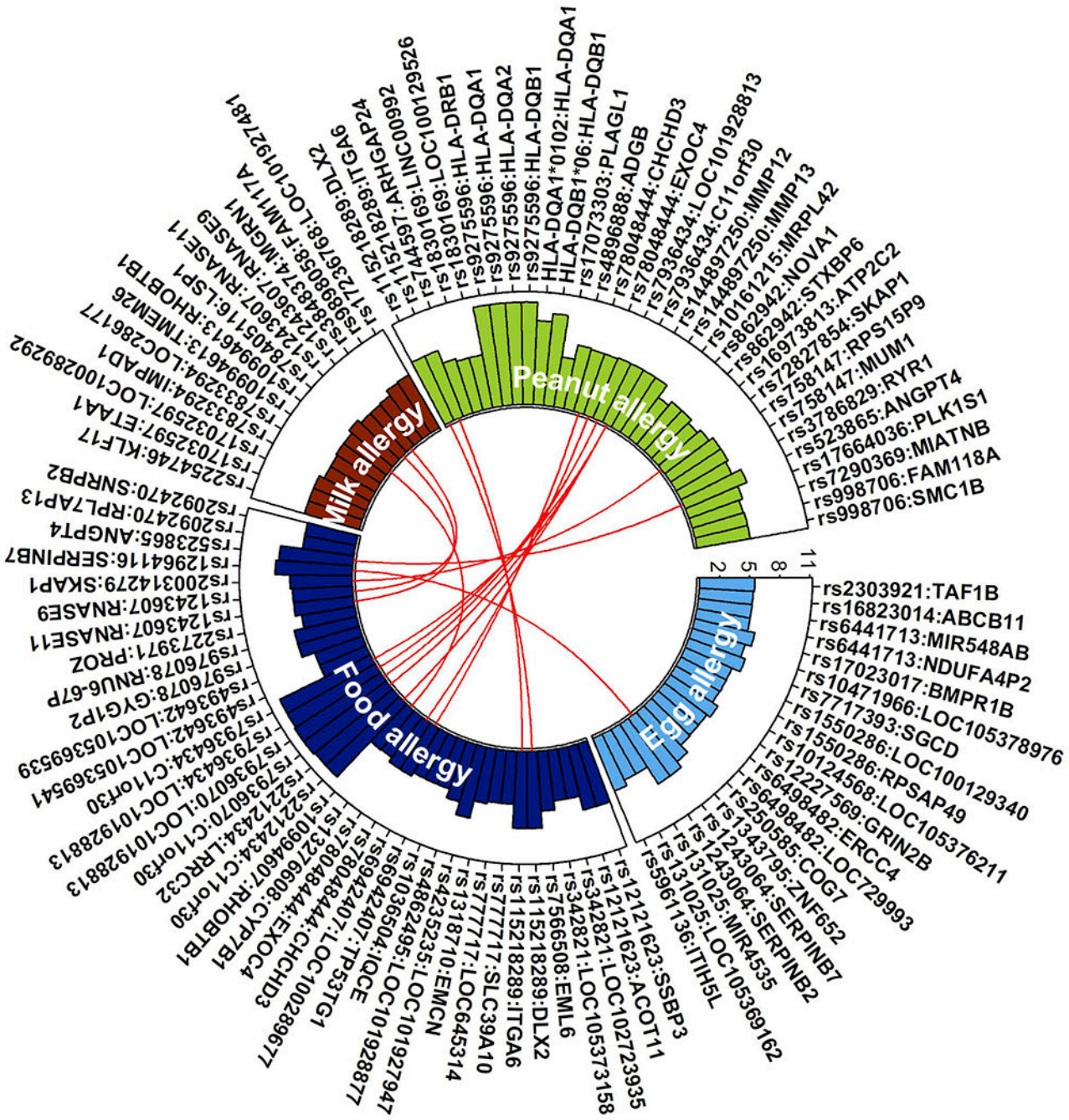

Figure 2.

Variants associated with food allergies. Circle plot based on NHGRI-EBI Catalog shows genome-wide association studies (GWAS) variants associated with food allergies. SNPs and the corresponding mapped genes are shown along the outer circle. The rectangles show the log transformed p-value from the SNP-trait association. Y-axis is the −log10(p-value), X-axis is the SNP-gene pair for each disease. Red lines connect the shared gene (regardless of SNP) between traits.

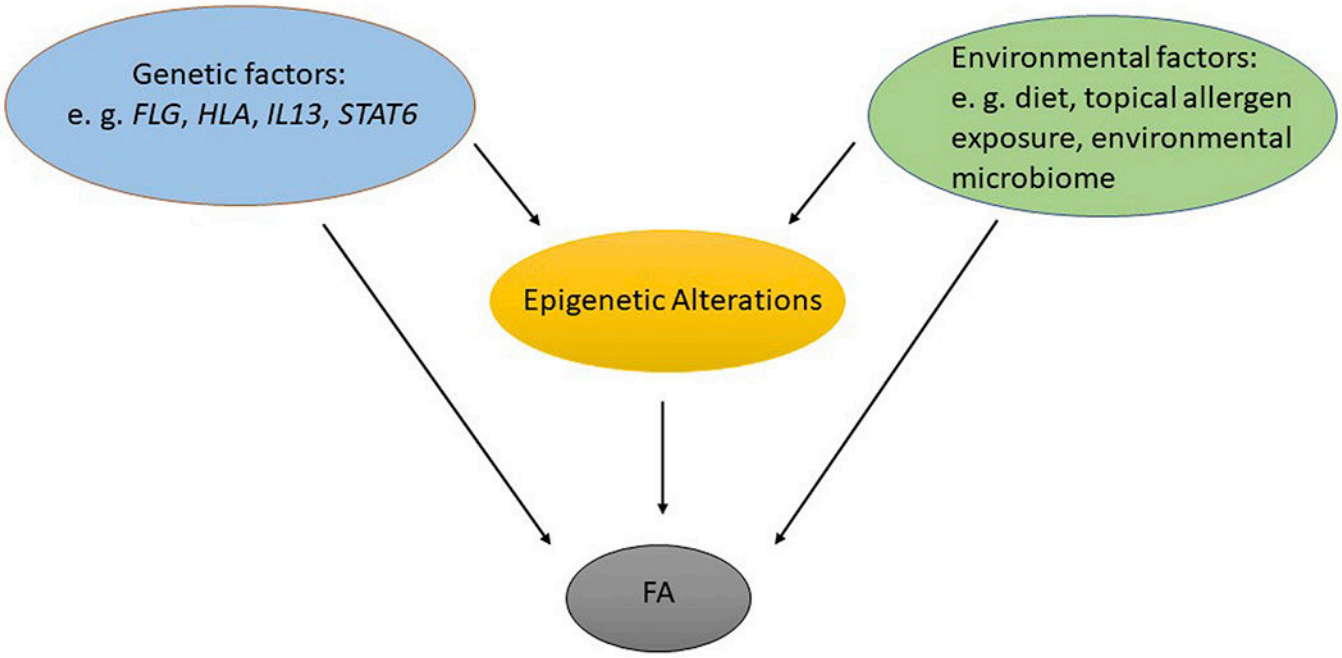

Figure 3.
Overview of possible pathways to food allergy (FA), based on genetic and environmental risk factors.