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# Multi-omics profiling approach in food allergy

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## ABSTRACT

The prevalence of food allergy (FA) among children is increasing, affecting nearly 8% of children, and FA is the most common cause of anaphylaxis and anaphylaxis-related emergency department visits in children. Importantly, FA is a complex, multi-system, multifactorial disease mediated by food-specific immunoglobulin E (IgE) and type 2 immune responses and involving environmental and genetic factors and gene-environment interactions. Early exposure to external and internal environmental factors largely influences the development of immune responses to allergens. Genetic factors and gene-environment interactions have established roles in the FA pathophysiology. To improve diagnosis and identification of FA therapeutic targets, high-throughput omics approaches have emerged and been applied over the past decades to screen for potential FA biomarkers, such as genes, transcripts, proteins, and metabolites. In this article, we provide an overview of the current status of FA omics studies, namely genomic, transcriptomic, epigenomic, proteomic, exposomic, and metabolomic. The current development of multi-omics integration of FA studies is also briefly discussed. As individual omics technologies only provide limited information on the multi-system biological processes of FA, integration of population-based multi-omics data and clinical data may lead to robust biomarker discovery that could translate into advances in disease management and clinical care and ultimately lead to precision medicine approaches.

**Keywords:** Food allergy, Genomics, Multi-omics, Skin prick test, Immunoglobulin E, Oral food challenge

## INTRODUCTION

Food allergy (FA) is a common condition affecting children and adults around the world. It is an adverse reaction to a food characterized by the acute onset of hives, swelling, difficulty breathing, and/or emesis after consumption of a food and is mediated by food-specific immunoglobulin E (IgE) and type 2 immune responses. The population prevalence of FA among children is increasing, affecting nearly 8% of children; FA is the most common cause of anaphylaxis in children, with anaphylaxis-related emergency department visits increasing by over 200% in the past decade.[1] In addition, FA severely impairs the quality of life of affected children, their family, and caregivers.[2,3]

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People of all races are affected by FA, but important differences are observed across ethnic populations in terms of FA triggers, presentation, and severity. Certain ethnic groups are more prone to particular FA than others; for example, African American children have a higher risk of FA to shellfish and finfish than do children of other races.[4]

FA is a complex, multi-system, multifactorial disease. Amounting clinical and research evidence support that diagnosis, monitoring, and management of allergic diseases requires a personalized approach.[5] As technology advances, so too does the scientific community's knowledge of this complex condition, and striking advances have been made over the past few decades in identifying the pathophysiology of IgE-mediated FA. However, increased efforts are needed to characterize distinct phenotypes, elucidate underlying mechanisms, and identify associated biomarkers of the clinical FA phenotype.[5] Although the clinical phenotype in FA is often clear, thorough FA endotyping has been limited by FA's multi-system involvement and by single immune cell or tissue characterizations not representing the much larger, more complex FA process.

Understanding genetic variation and how it contributes to FA development is critical to better define risk and explore new immune pathways that may be mechanistically implicated in FA. Although rare, single-gene defects leading to distinct disease states associated with FA have been identified (ie, *SPINK5* in Netherton syndrome, *DSG1* in SAM syndrome, *FOXP3* in immunodysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome),[6] the rapid increase in FA prevalence over the past 30 years supports that genetics alone cannot explain this phenomenon and that environmental influences are critical. Notably, environmental influences mediate their effects through epigenomic mechanisms that affect accessibility of endogenous genes, as well as microbial colonization and function.

In this review, we will examine studies that have been performed utilizing omics science in the context of FA. Integration of data acquired through omics studies as related to FA will be used to further our understanding of FA and to refine our approach to each individual patient. We will also discuss the advantages and challenges of integrating individual omics into multi-omics approaches using systems biology and machine learning technologies.[7]

## GENOMICS

FA is a multifactorial condition and its development and natural history are likely influenced by environmental and inherent, genetic factors. Genomics refers to the science of an organism's DNA or genetic content. Studies of heritability and family history of FA led to exploration for underlying genetic mechanisms that may be contributing to FA development.

Early studies of twin pairs discordant or concordant for peanut allergy found that monozygotic twins had a much higher rate of peanut allergy concordance compared to dizygotic twins.[8,9] This suggested a strong genetic component to peanut allergy given the shared genetic composition between monozygotic twins and likely similar environmental influences.[8] Studies of siblings of children with peanut allergy have suggested increased risk, however, the estimates are variable likely due to the clear environmental influences on FA outcomes.[10–12] A large study of family history of atopy and risk of oral food challenge (OFC) confirmed FA showed that having 2 or more immediate family members (ie, mother, father, siblings) with allergic disease (ie, asthma, eczema, allergic rhinitis, or FA) was associated with increased risk for OFC proven FA.[13] Given this clear genetic signal, subsequent studies sought to uncover specific genotypes associated with FA.

Genome wide association studies (GWAS) are large-scale explorations of the entire genome seeking to identify genetic loci that may be associated with disease. While these studies do require subsequent follow-up studies to further decipher the implicated loci, they are powerful tools for identification of new variants related to FA (Table 1). The Chicago Family Cohort Food Allergy Study conducted a GWAS for common food allergies (defined based on clinical history and sensitization) and identified single nucleotide polymorphisms (SNPs) in between *HLA-DQB1* and *HLA-DQA2* and in *HLA-DRA* associated with

| First Author (Year of publication) | Sample size | | Main findings | Food allergy definition |
|---|---|---|---|---|
| | Discovery | Replication | | |
| Hong X (2015)[14] | 316 peanut allergy cases and 1891 controls | 86 peanut allergy cases and 127 controls | • PA: SNPs in *HLA-DR* and *-DQ* genes | Convincing clinical history and evidence of sensitization to food |
| Marenholz I (2017)[15] | 523 food allergy cases and 2682 controls | 380 food allergy cases and 986 controls; 671 food allergy cases and 1526 family-based controls | • FA: SNPs in *FLG-AS1*, *IL4/KIF3A*, *C11orf30/LRRC32*, and *SERPINB7*<br>• PA: SNP in *HLA-DQB1*<br>• EA: SNP in *SERPINB7/B2* | Majority oral food challenge; ~15% with history of an immediate, severe allergic reaction and evidence of sensitization to the food |
| Asai Y (2018)[17] | 850 peanut allergy cases and 926 controls<br>Meta-analysis for peanut allergy:<br>1582 peanut allergy cases and 5446 control subjects<br>Meta-analysis for food allergy:<br>7267 food allergy cases and 29,084 control subjects | | • PA: SNP in ITGA6<br>• FA & PA: SNPs in C11orf30 | Varied based on specific study (self-reported, convincing clinical history and evidence of sensitization, or oral food challenge) |
| Winters A (2019)[97] | 48 peanut allergic cases and 227 non-peanut allergic controls | Follow up on additional 267 study participants | • PA: SNPs in *MALT1* locus; Significant variants showed eQTL effects on *MALT1* expression | Oral food challenge diagnosed peanut allergy |
| Liu X (2018)[98] | 482 food allergy trios (child and both parents)<br>19 child-father<br>59 child-mother<br>28 food allergic child only | | • FA: SNP in *LOC101927947* with maternal effect; SNPs in *IQCE* with parent-of-origin effect in boys<br>• EA: SNPs in *ZNF652* gene with maternal effect<br>• PA: SNP in *ADGB* with parent-of-origin effect | Self-reported allergic reaction after food ingestion and evidence of sensitization to the food |
| Martino DJ (2017)[99] | 73 peanut allergy cases and 148 non-allergic controls | 117 cases and 380 controls | • PA: Variants in *HLA-DRB1* gene | Oral food challenge diagnosed peanut allergy |
| Asai Y (2018)[16] | 850 peanut allergy cases and 926 controls, 6 additional studies included in meta-analysis of HLA region | | • PA: SNPs in *HLA-DQB1* gene | Varied based on specific study (self-reported, convincing clinical history and evidence of |

(continued)

| First Author (Year of publication) | Sample size | | Main findings | Food allergy definition |
|---|---|---|---|---|
| | Discovery | Replication | | |
| | | | | sensitization, or oral food challenge) |
| Khor SS (2018)[100] | 11,011 Japanese women | | • Shrimp and peach allergy: SNPs in HLA-DR/DQ region | Self-reported food allergy |

**Table 1.** GWAS studies on FA

peanut allergy in children and young adults (aged 0–21 years).[14] A subsequent study of OFC proven FA in a German cohort of children detected 5 loci associated with FA and/or peanut allergy and replicated this association in additional FA cases from the same cohort and an independent cohort.[15] The loci identified include *SERPINB* gene cluster, *FLG*, cytokine gene cluster, *C11orf30/LRRC32* region, and HLA locus, with the HLA locus only associated with a peanut allergy phenotype.[15] A meta-analysis of 7 peanut allergy GWAS focused in on the HLA region and found *HLA-DQB1* to be the predominant region of interest.[16] A subsequent meta-analysis of 7 GWAS studies focused on FA and/or peanut allergy specifically identified several non-HLA regions associated with these phenotypes including *ITGA6*, *MMP12/MMP13*, *ANGPT4*, *C11orf30*, and *EXOC4*.[17]

While GWAS studies take a more unbiased, agnostic approach to identification of genomic regions implicated in FA, candidate gene studies often target a single gene known to play a role in the underlying pathophysiology of FA. Numerous candidate gene studies have been performed for the FA outcome and multiple recent and detailed reviews of the genetics of FA have been published in which these candidate genes are clearly outlined.[6,10]

Polymorphisms in genes encoding for various inflammatory and anti-inflammatory cytokines have been associated with FA.[10] These include *IL-10*, *IL-13*, *TGFβ*, and *IL28B*.[18–23] Polymorphisms in *IL-10* have also been associated with serum IL-10 levels in food allergic children and adults (diagnosed based on clinical history with exposure to the food and evidence of sensitization to the implicated food).[19,24] While *IL-13* is an attractive candidate gene given its role in sensitization development, it is not yet clear if polymorphisms in this gene are associated with clinical reactivity to a food versus food antigen sensitization alone in the pediatric population.[20,21]

Skin barrier dysfunction is implicated in food allergen sensitization and the FA phenotype. Atopic dermatitis is a significant risk factor for the development of FA. Filaggrin, encoded by the *FLG* gene, is a protein critical for skin barrier integrity, and loss of function mutations in this gene are associated with both atopic dermatitis, food allergen sensitization, and FA presence and persistence in children and adolescents.[25–27] In children with a *FLG* mutation, the association between *FLG* genotype and peanut allergy does appear to be modified by environmental peanut exposure, with increased environmental peanut exposure associated with increased risk.[28] *SPINK5*, a gene encoding a protease inhibitor protein in the skin epithelium, has also been associated with atopic dermatitis and FA in children.[29,30]

Additional genetic loci found to be associated with sensitization and FA in children and adults include *STAT6* and *CD14*.[10,31–33] *STAT6* polymorphisms were not only found to be associated with OFC proven FA but also higher serum specific IgE levels, and reaction severity in children.[34] *CD14* polymorphisms have also been shown to be associated with nonatopic asthma in a cohort of children and adults.[33]

## TRANSCRIPTOMICS

Transcriptomic studies of FA have been mainly conducted on blood cells, such as whole blood or peripheral blood mononuclear cells (PBMC), or

immune-related single cell lines derived from the blood, such as $CD4^+$ T cells or B cells. Transcriptomic profiling of purified $CD4^+$ T cells from 60 neonates, 30 of which developed FA by 12 months of age and 30 of which remained nonallergic, showed that suboptimal neonatal T cell activation pathways that signal through the NF-κB complex may increase the risk of FA.[35] FA was diagnosed on the basis of immediate clinical symptoms with oral exposure to egg, milk, or peanut and positive skin prick test (SPT) to the implicated allergen at 12 months of age. Among the FA group in the birth data set, a number of genes in T cell signaling pathways, including *RELB*, *NFKB2*, *LIF*, and *FAS*, were significantly downregulated. However, this study did not detect differentially expressed genes when assessed at 1 year of age.[35] Transcriptomic evaluation of PBMCs identified that TLR4-activated myeloid cell gene signatures were significantly associated with response to egg in PBMCs from children and adolescents with egg allergy.[36] The upregulated genes included several cytokines (*IL-9*, *IL-5*, and *TNFα*), $T_h2$-associated chemokines (*CCL22*, *CCL17*), and IgE receptor (*FcεRII*), whereas downregulated genes included genes encoding lysosomal and endosomal enzymes and scavenger receptors. Additionally, comparing cytokine expression between children and adolescents with and without egg allergy showed significant upregulation of 8 cytokines (*GM-CSF*, *IL-5*, *IL-7*, *IL-9*, *IL-21*, *IL-31*, *IFNα*, and *TNFα*).[36] A longitudinal study of the peripheral blood transcriptome of 19 children with peanut allergy before, during, and after an OFC to peanut identified 6 genes—*LTB4R*, *PADI4*, *IL1R2*, *PPP1R3D*, *KLHL2*, and *ECHDC3*—as key drivers of the acute response to peanut.[37] Two cell types, neutrophil and macrophage populations, were significantly increased during acute peanut-induced allergic reactions, whereas the naive $CD4^+$ T cell population was found be significantly decreased during that time.[37] Subsequent comparison between the patients who underwent peanut OFC with and without epinephrine treatment also showed increased fractions of macrophages and neutrophils, and a decreased fraction of naive $CD4^+$ T cells in patients who received epinephrine.[37] A similar transcriptomic study of 21 children with peanut allergy identified 245 upregulated and 77 downregulated differentially expressed genes (DEG) associated with allergic reaction severity as assessed during OFC; 2 of these genes, *NFKBIA* and *ARG1*, were identified as hub genes in the network analysis.[38] Gene Ontology (GO) enrichment analysis identified neutrophil-related functions, such as phagocytosis, neutrophil activation, and neutrophil degranulation, as significantly enriched biological processes for the upregulated genes.[38]

Whole blood RNA sequencing (RNAseq) has been performed to further characterize the immune response in FA and as an exploratory tool for biomarker identification.[39,40] Weighted gene co-expression network analysis on whole blood RNAseq data identified 3 significant gene modules associated with nut allergy in children (based on clinical history and sensitization or a failed OFC).[39] Two modules, one with the hub gene *IFIH1* and involved in the type 1 interferon signaling pathway, and the other module with hub gene *DRAM1* and involved in the regulation of cytokine secretion, were positively correlated. The third significant module with hub gene *ZNF512B* was negatively correlated with peanut allergy and involved in the positive regulation of humoral immune response.[39]

RNAseq of activated and resting $CD4^+$ T cells from patients with high- and low-threshold clinical reactivity to peanut (defined based on OFC) revealed differential expression of 31 genes in the peanut-activated cells of child and adult subjects with a high threshold versus low threshold.[41] When compared with resting T cells, peanut-activated T cells from both peanut allergy groups had strongly induced $T_h2$-associated genes, *IL4*, *IL13*, and *IL31*, and $T_h17$-related genes, *IL17A* and *IL17F*.[41] Several genes associated with pathogenic $T_h2$ cells (*IL5*, *IL9*, hematopoietic prostaglandin D synthase) and $T_h17$ cells (*IL22* and *IL26*) were expressed higher in patients with low thresholds than high thresholds.[41] In contrast, expression of several genes associated with regulatory T cells (*TNFRSF9*/*CD137*) and immune regulation (NFκB inhibitor delta, IL-1 receptor antagonist, vitamin D receptor, *CD200*) were increased in patients with high thresholds.[41]

Single-cell RNAseq (scRNAseq) has been utilized to deeply phenotype cell populations

implicated in FA pathogenesis. ScRNAseq performed on peanut-activated $CD4^+$ T cells, polyclonally activated $CD4^+$ T cells, and regulatory T cells acquired from pediatric subjects with OFC proven peanut allergy found that the cells clustered into 3 states based on transcriptional similarity.[42] The peanut-activated $CD4^+$ T cells, regardless of the state, co-expressed *IL4*, *IL5*, *IL9*, *IL13*, and *IL17*RB.[42] Experimental approaches have been developed by which the variable region of the T cell receptor (TCR) can be sequenced, allowing for identification of cellular clones and elucidation of details surrounding TCR engagement.[43] The IgE $^+$ B cells of children with OFC proven peanut allergy have been phenotyped using scRNAseq and reveal a predominantly immature plasmablast phenotype marked by upregulation of several major histocompatibility complex (MHC) genes, *FCER2*, and *LAPTM5* and downregulation of *LGALS1* and *SKY*.[44]

Bulk sequencing of RNA extracted from the PBMC population during the course of egg oral immunotherapy (OIT) in egg allergic children showed dysregulation of a variety of genes which, upon pathway analysis, suggested decreased inflammation, acute phase responses, and $T_h2$ responses.[45] Genes involved in the signaling of TREM1, IL-6, and IL-17 are downregulated, and the production of inflammatory mediators was decreased.[45] The study further found that egg OIT enhanced innate immune and defense responses and attenuated various metabolic processes and responses to stimuli in PBMC of children with egg allergy.[45]

Longitudinal analysis of whole blood RNAseq data from adolescents undergoing peanut OIT identified dysregulated gene expression; however, the use of omalizumab with OIT did not seem to affect gene expression.[46] Single-cell exploration of specific cell types during the course of OIT for peanut has revealed gene expression changes that occur within the regulatory T cell population early in the course of OIT and quantitative and transcriptomic changes that occur within the peanut-activated $CD4^+$ T cell population while on OIT. Upregulation of particular markers in peanut-specific $CD4^+$ T cells, including *TGFβ*, has been shown in cases of successful desensitization.[47–49] Examining the skin transcriptome of children and adolescents with atopic dermatitis and FA compared to individuals with atopic dermatitis without FA identified increased dendritic cell activation and inflammation in the nonlesional skin of those with FA.[50]

## EPIGENOMICS

Epigenome-wide association studies performed on the whole blood of children with FA have revealed methylation changes in $T_h1$–$T_h2$ axis genes, including *IL1RL1*, *IL5RA*, *IL4*, *CCL18*, and association of *STAT4* with cow's milk allergy (CMA), defined by clinical history and evidence of sensitization.[51] Additionally, the study identified differentially methylated sites in the 3 CMA-associated gene loci, *NDFIP2*, *EVL*, and *TRAPPC9*.[51] Similarly, methylation changes in the promoter regions of $T_h1$ and $T_h2$ cytokine genes have been associated with the development of cow's milk tolerance among children with OFC proven CMA.[52] Compared to healthy children and children who outgrew a CMA, children with IgE-mediated CMA had significantly lower DNA methylation on *IL4* and *IL5* and higher DNA methylation on *IL10* and *INFy*.[52] A study of DNA methylation changes in the $CD4^+$ T cell compartment of infants with FA compared to age-matched, non-allergic control subjects at birth and 12 months of age showed longitudinally persistent differences in DNA methylation at genes in the MAP kinase signaling pathway in the subjects with OFC proven FA.[53] In the same study, differential methylation of genes (*HLA-DQB1*, *CD80*, and *TNFRSF17*) in the intestine immune network for the IgA production pathway were uniquely associated with FA at 12 months of age.[53] An epigenome-wide association study of purified B cells from adolescents with single FA to peanut, multiple FA including peanut, or a non-allergic clinical phenotype showed a differential methylation pattern of B cells.[54] The study further revealed variations in differential methylation of B cells when considering FA burden (single FA versus multiple FA).[54] FA was diagnosed based on a clinical history of a reaction and evidence of sensitization or a failed OFC.

DNA methylation signatures have been explored as a potential diagnostic tool for clinically reactive FA. Martino et al. identified a 96-CpG

DNA methylation signature predictive of OFC outcome in a group of children with peanut and egg allergy.[55] This signature was found to perform more accurately than food-specific IgE levels and SPT wheal size.[55] Interestingly, the discovered 96-CpG DNA methylation signature overlapped with genes coding for proteins in the MAP kinase signaling pathway.[55] Targeted next-generation bisulfite sequencing has been used to analyze the DNA methylation signatures on PBMCs in 125 highly informative genomic regions containing 602 CpG sites on 70 immune-related genes from PBMCs, which subsequently identified significant differences in CpG methylation in regions for 12 genes in children with OFC proven peanut allergy compared to without peanut allergy.[56] Among the 12 genes, 3 genes (*IL4*, *IL12B*, and *IL2*) are associated with $T_h1/T_h2$ responses and 2 genes *(IL1B* and *IL6*) are associated with innate immune responses.[56] The DNA methylation signatures identified in this study were included in models for predicting peanut allergy and were found to perform more accurately than peanut sIgE.[56]

Forkhead box P3 (FoxP3), a transcription factor in regulatory T cells, has been shown to be differentially methylated in infants with active, OFC proven IgE-mediated CMA compared to those with oral tolerance of cow's milk and healthy controls.[57,58] Also, a higher rate of FoXP3 demethylation was observed among infants with CMA receiving extensively hydrolyzed casein formula supplemented with a probiotic compared to those receiving soy formula.[58] Similarly, the formula received was also associated with differential DNA methylation of *IL4*, *IL5*, *IL10*, and *IFN*γ in $CD4^+$ T cells.[58] This differential methylation in FOXP3, however, is not a consistent finding for IgE-mediated FA when considering allergens other than CMA.[59] A study of 64 children and adolescents with OFC-confirmed FA identified significant demethylation of promoter regions in the *HLA-G* gene and strong correlation of genetic variants and DNA methylation of the *HLA-DRB1* gene.[59]

Methylation of *FoxP3* does decrease during the course of OIT and is particularly prominent among individuals who continue to be tolerant of their allergen despite discontinuation of OIT.[60] During acute peanut-induced allergic reactions, peripheral blood RNAseq and DNA methylation assessment of $CD4^+$ T cells revealed 318 genes associated with reaction severity and 203 CpG sites within $CD4^+$ T cells associated with reaction severity, both of which were replicated in an independent cohort.[38] These findings offer a unique opportunity to improve our understanding of mechanisms underlying reaction severity.[61,62]

## PROTEOMICS

An exploratory study of multiplexed protein identification in plasma of 1-month-old infants found that a profile of 27 proteins together with history of exposure to a farming environment was predictive of allergy (including eczema, asthma, FA, or allergic rhinoconjunctivitis) versus non-allergy. This profile included IL-9, IL-17, GADD45A, MPO, MMP9, and CCR10.[63] In a large, European, population-based birth cohort, plasma proteomic multiplex assay was performed exploring inflammatory plasma proteins and associating these proteins with both asthma status and sensitization to peanut and tree nut storage proteins.[64] Although proteomics approaches have exciting potential for biomarker detection, proteomics in FA largely has been utilized for identifying and characterizing allergenic proteins within foods. These refined techniques allow for identification of the entire amino acid sequence of an allergenic food protein.[65] These techniques also allow for detection of IgE-binding epitopes.

## METABOLOMICS

In the investigation for biomarkers of FA disease activity and resolution, researchers have more recently initiated studies of the metabolome in FA. Studies of the serum metabolome in subjects with FA have identified alterations in specific metabolites and metabolic pathways exclusively associated with FA. These include decreases in sphingolipids, sphinomyelins, and ceramides in children with FA (defined based on clinical history and evidence of sensitization) compared to without FA/atopy and may be associated with multiple FA and/or anaphylactic clinical phenotypes.[66] This dysregulation of sphingolipid metabolism has been shown in other studies of children with FA, defined similarly.[67] Serum linoleic acid–to–total fatty acid ratio and serum phenylalanine are associated with OFC proven FA in 1-year-old subjects, and this FA association persists despite adjustment for age, sex, and

time to sample collection.[68] Furthermore, omega-3 metabolites and platelet-activating factor are metabolites that may have roles as biomarkers of FA resolution.[67]

Importantly, fecal and serum metabolites are affected by a number of different factors, including dietary diversity, age, activity, exposures, and the microbiome.[69,70] A study of the maternal and cord blood metabolome, specifically lipidome, and FA outcome (defined using clinical history and evidence of sensitization) in offspring has identified that elevated cord blood triacylglycerols are associated with a decreased risk of FA, despite controlling for maternal atopic history, race/ethnicity, sex, and infant feeding.[71] However, these findings are not consistent and warrant further study.[72] Assessing the fecal metabolome in healthy and allergic twin subjects (children and adults) found differentially represented metabolites enriched for the diacylglycerol pathway in healthy twin pairs and differentially represented metabolites enriched for a food component/plant subpathway, including secoisolariciresinol, in twin pairs with allergy.[73] Lower levels of fecal short-chain fatty acids (SCFA) are reported in children with FA compared to without FA, and higher levels of fecal SCFA early in life may be protective of atopy outcomes, including FA, in later childhood.[69,74] After identification of urinary metabolites in murine models of FA that were thought to be specific to the disease and reflective of severity, urinary tetranor-PGDM and –PGEM levels were assessed in humans. These levels were found to be significantly higher in the urine of individuals with FA (defined based on OFC or sensitization) compared to healthy control subjects and other individuals with atopy.[75] In a group of children and adolescents, these levels were also found to be increased at 4 h after a positive OFC, and the levels were associated with reaction severity.[76] Further studies of the metabolome of FA individuals is critical to advance our understanding of the role of the metabolome in FA pathophysiology and management.

## MICROBIOME

Multiple studies support the conclusion that the fecal microbiome is different among children with FA compared to their healthy counterparts. The unique comparison of the fecal microbiome of twin pairs (children and adults) who are healthy versus who have FA showed an abundance of bacteria from the Clostridia class in the healthy twin pairs, including *R. bromii* and *P. faecium*.[73] In a mouse model of FA, mice with FA who receive a fecal transplantation from a healthy infant show some degree of protection from anaphylaxis when compared to mice with FA who receive a fecal transplantation from an infant with FA.[77,78] Similarly, mice with FA who were fed a mixture of *Clostridiales* bacteria strains were protected against anaphylaxis.[77] These studies of the microbiome and FA outcomes in humans and murine models reveal a likely consequential role of disturbance of the microbiome in FA.

The fecal microbiome is influenced by diet. A clinical trial of infants with CMA fed extensively hydrolyzed formula without lactose followed by the same extensively hydrolyzed formula containing lactose found increased populations of fecal *Bifidobacteria* and *Lactobacilli* and decreased populations of *Bacteroides*, *Prevotella*, and *Clostridia* when the infants with CMA were receiving the lactose-containing formula.[79]

The microbiome may have a role in tolerance acquisition or natural resolution of FA. More infants with CMA placed on extensively hydrolyzed formula supplemented with *Lactobacillus rhamnosus* GG acquired tolerance when compared to infants with CMA who did not receive this supplementation.[80] Although the study was small, differences in bacterial enrichment, diversity, and fecal metabolites that are the products of particular bacterial strains were detected between infants with tolerance and FA.[80] A similar observational study of infants with FA found enrichment of *Firmicutes* and *Clostridia* in the fecal microbiome of infants with CMA at 3–6 months of age who developed natural tolerance of cow's milk by 8 years of age.[81] Interestingly, in an independent study, these groups of microbes were also found to be prominent in the feces of children with FA compared to siblings without FA and healthy control subjects.[82]

Exploration of the oral or salivary microbiome of children and adolescents with peanut allergy compared to similarly aged healthy control subjects showed detection of increased *Neisseria* spp in

patients with peanut allergy and *Lactobacillales*, *Bacteroidales*, *Bacillales*, and *Streptophyta* in healthy control subjects.[83] Although differences in the oral microbiome have been identified, additional studies should explore the roles that these differences may play in FA pathophysiology. It is proposed that the microbiome may influence immune function through the production of metabolites generated in the local immune environment.[84] It is known that varying reaction thresholds exist among individuals with peanut allergy. Differences in the oral and gut microbiome have been identified between children with OFC proven peanut allergy with low versus high thresholds for reactivity when exposed to peanut protein.[84]

## EXPOSOME

The hygiene hypothesis proposes that exposure to more sterile environments with less microbial diversity and load may actually increase risk for allergy development. Thus, early exposure to a farming environment has traditionally been thought of as protective of allergy development.[85] A study examining the prevalence of self-reported FA in the New York Old Order Mennonite community compared to the general US population found that the rates of self-reported FA were markedly lower in this single-family farming community.[86] Interestingly, this did not seem to be due to earlier oral introduction of allergenic foods into the diet.[86]

Environmental exposures are particularly relevant in the context of the dual allergen exposure hypothesis. In this hypothesis, oral exposure to food antigen is thought to be tolerance-promoting; however, cutaneous exposure to food antigen, particularly through a disrupted skin barrier, leads to skewing of the immunologic milieu such that sensitization and FA are promoted. Exposure to food allergen through dust in the home, school, or work environment may lead to the development of sensitization and FA, and when combined with other components found in house dust, like fungi and microbes, this tendency for pro-allergic skewing may be even more pronounced.[85,87]

Exposure to both indoor and outdoor air pollution has been associated with childhood food antigen sensitization, although few studies have explored well-defined FA outcomes.[85] However, a recent study exploring the association between living in a green environment during the first year of life and OFC proven FA found increased exposure to environmental greenness in the first year of life to be associated with FA.[88] Further studies comprehensively profiling internal and external exposures and their association with clearly defined FA outcomes are necessary to improve the understanding of the exposome and FA.

## INTEGRATION

Understanding how certain exposures or particular circulating metabolites may change gene expression or protein generation within a particular cellular compartment or entire tissue is an important aspect to consider in future omics studies focused on FA. The integration process will bring together the biological information dispersed across different layers of biological systems that influences the disease process (Fig. 1). Integration of omics data relies heavily on modeling and the analytic approach[89] which becomes more complex when clinical and epidemiologic data are being explored in the same dataset. Although integration remains an active area of research, the prospect of developing predictive models integrating omics, clinical, and epidemiologic data is exciting and would represent an advance towards more personalized medicine in FA.

Integration, however, does not come without some substantial challenges. The sheer quantity of data is vast and often requires specialized computers and storage systems for use.[90] The analytical approaches should account for the relationships and complex interactions between different layers of omics, such as gene expression, DNA methylation, microRNA expression, exposures, and others (Table 2). There are different technologies utilized to obtain omics data, which needs to be considered when performing analyses and/or when trying to merge similar data. Although the number of subjects enrolled in omics studies is often small, the quantity of variables for each individual is large, and managing these vast array of variables

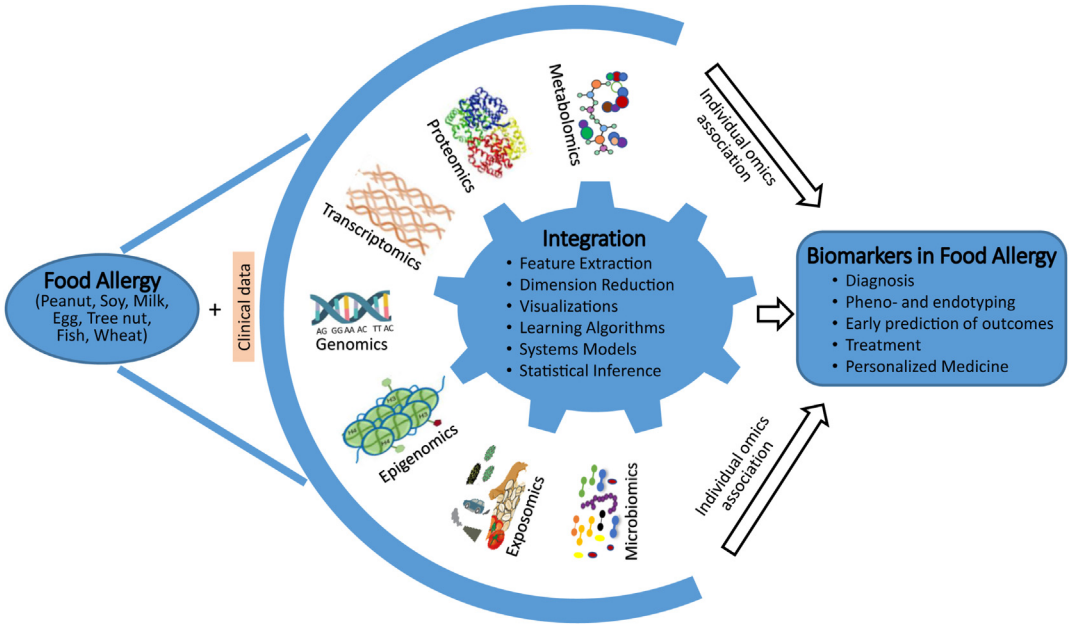


**Fig. 1** Integrative schema of multi-omics studies of food allergy for biomarker development

requires statistical expertise.[90] The high dimensionality of the omics data poses a major challenge for multi-omics integration. Dimension reductions and feature extraction techniques can be helpful to acquire the most informative features from individual omics data before the actual integration is performed.[91] Machine learning methods can then be used for statistical learning model development from the data in a supervised or unsupervised fashion.[92,93]

Additional challenges facing integration of omics and clinical data in the context of FA include variability in FA definitions. The quality and validity of omics studies depends to a large extent on accurate and consistent outcome definitions, which can be challenging, in the case of FA. Self-reported allergy to foods based on symptoms has been found to vastly overestimate the rate of FA.[94,95] Although evidence of sensitization to foods using SPT or serum IgE measurement is a strong FA predictor, not all individuals with food sensitization go on to develop FA. The gold standard for diagnosis of FA is the double-blind, placebo-controlled OFC conducted in a clinical setting. OFC is generally considered safe but requires emergency support to be immediately available and can be unpleasant for the patient in the case of a clinical reaction. Existing studies are

| Publication | Tool developed | Type of data integrated |
|---|---|---|
| Tibshirani, R. (1996)[101] | Lasso | Genomic and clinical data |
| Uppal, K. (2018)[102] | xMWAS | Data from biochemical assays and ≥2 omics platforms |
| Planell, N. (2021)[103] | STATegra, a pipeline of data integration | mRNA, miRNA, methylation |
| Mo, Q. (2013)[104] | iClusterPlus | ≥2 omics data |
| Yao, Q. (2015)[105] | MetPriCNet | Metabolomic, transcriptomics, and phenomics |
| Wu, D. (2015)[106] | LRAcluster | ≥2 omics data |

**Table 2.** Multi-omics data integration tools

highly heterogeneous with regard to outcome definitions; thus, standardized and accurate diagnostic outcome criteria for FA are needed in order to facilitate meta-analysis approaches.

Lastly, lack of diverse populations from different ancestral populations is a major challenge facing generalizability of current omics studies. For example, the current pool of samples in GWAS are predominantly representative single ancestral populations of the European ancestry. Broadening diversity of study populations will improve the discovery of risk variants that varies in allele frequency across ancestral populations.[96] When ancestry-specific effects are relevant, it is important to study the local ancestry variation using admixture mapping (AM). To date, no GWAS or AM of FA on African Americans or Latinos are conducted.

Through the past years, researchers have put a tremendous effort into finding biomarkers in "Omics" fields: genomics, transcriptomics, epigenomics, proteomics and metabolomics. This article reviewed the evolving field of multi-omics and its role in diagnosing FA.

## CONCLUSION

Exciting advancements have been made over the past several years in the omics of FA. Moving forward, multi-omics studies in diverse patient populations with consistent and well-defined clinical FA phenotypes are critical. These will allow for integration of these data within individuals, fostering more personalized data collection and insights regarding how omics may relate to clinical phenotype, natural history, and response to therapy. Although FA is a complex and multifactorial outcome, deep phenotyping of these patients using novel omics technologies will likely result in an improved understanding of underlying pathophysiology and disease heterogeneity.

### Abbreviations

CMA, cow's milk allergy; FA, food allergy; FoxP3, forkhead box protein P3; GO, Gene Ontology; GWAS, genome-wide association studies; OFC, oral food challenge; OIT, oral immunotherapy; SAM (syndrome), severe skin dermatitis, multiple allergies, and metabolic wasting; PBMC, peripheral blood monocellular cells; RNAseq, RNA-sequencing; SCFA, short chain fatty acids; SNPs, single nucleotide polymorphisms; TCR, T cell receptor.

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### Consent for publication

All authors have reviewed this manuscript and consent to its publication.

### Declaration of competing interest

The authors declare that they have no competing interests.

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